PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Flower Pollen Extract and its Effect for Prostate Health

Contents

A Critical Review of Graminex Flower pollen extract for Symptomatic Relief Of Lower Urinary Tract Symptoms (LUTS) in Men

Walter G. Chambliss, Ph.D.

National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences,
University of Mississippi, University, Ms. 38677
January 12, 2003

Objective

To review published data concerning the ability of a Graminex's Flower Pollen Extract to provide symptomatic relief in men suffering from lower urinary tract symptoms (LUTS).

Introduction

The National Institutes of Health (NIH) estimates 9 million men suffer from symptoms related to an enlarged prostate and 400,000 surgeries are conducted each year in the U.S.[1] The term lower urinary tract symptoms (LUTS) is used to describe symptomatology in men who are experiencing one or more symptoms on the International Prostate Symptom Score (IPSS) questionnaire that includes urgency, daytime and nighttime urinary frequency, hesitancy, intermittency, sensation of incomplete voiding, and force of urine stream.[2] LUTS is used to describe urinary tract disorders in men with benign prostate hyperplasia (BPH), prostatodynia, acute and chronic prostatitis caused by a bacterial infection and acute and chronic abacterial prostatitis.

Bruskewitz stated the primary aim of pharmacological treatment is to improve quality of life by relieving bothersome symptoms since serious complications from BPH are rare[3]. However, he reported the results of a study conducted in the U.S. that showed Urologists gave no treatment 77% of the time to men with mild symptoms. Prescription drugs were given 89% of the time and surgery was conducted on 1% of the time for men with moderate symptoms. The primary therapeutic treatment was alpha(1)-adrenoceptor antagonists such as terazosin hydrochloride (Hytrin®) that provides symptomatic relief but has not be shown to provide long-term effects on the incidence of surgery, acute urinary obstruction or other complications of BPH.[4] The need exists for safe, effective products that can be used by men to treat mild to moderate LUTS in lieu of or in addition to prescription drugs. This review focuses on the potential for flower pollen extract, a dietary supplement, to fill this therapeutic void.

Graminex Flower Pollen Extract is a standardized extract of rye pollen (*Secale cereale)*, corn pollen (*Zea mays)* and timothy pollen (*Phleum pratense)*. The extract contains a blend of water-soluble and lipid-soluble fractions and is available around the world under other brand names such as Cernitin, and in capsule and tablet forms as Cernilton. In vitro[5] and animal model studies[6] have shown that both fractions have anti-inflammatory properties through inhibition of

the prostaglandin and leukotrien synthesis. The water-soluble fraction has been shown to reduce the size of the ventral and dorsal prostate in the rat[7] and to inhibit testosterone-induced BPH in castrated animals[8]. Both fractions have been shown to relax the smooth muscle of the mouse and pig urethra, increase bladder muscle contractions[8] and reduce prostate size in mature Wistar rats[9].

Methods

Literature searches were conducted on Medline and the Cochrane Library. Secondary sources such as review articles and monographs in botanical reference books were included in the analysis. Open label and comparative trials were included in the assessment, although more weight was placed on placebo-controlled, double-blind studies. Emphasis was placed on subject ratings of symptoms in light of the potential for self-medication of this extract.

Results

Secondary Literature

Four reviews of the clinical efficacy and safety of flower pollen extract have been published in the past 8 years. Although each used their own criteria in selecting valid studies they all concluded that flower pollen extract was very safe with few or no side effects so summaries below are limited to efficacy.

Commission E, an expert committee established by the German government to evaluate the safety and efficacy of over 300 botanical and botanical combinations sold in Germany, concluded in 1994 that the combination extract of rye, corn and timothy pollen was useful in the treatment of "micturition difficulties associated with Alken stage I-II benign prostatic enlargement (BPH)".[10]

The Natural Medicines Comprehensive Database concluded that rye grass pollen extract (CerniltonÒ) was "possibly effective" for the management of BPH symptoms, for shrinking prostate size and when used for prostatitis and prostatodynia.[11]

McDonald et al concluded in reviews published in 1999[12] and 2000[13] that results from 4 double-blind studies (444 men in total, 2 studies with placebo; 2 with active controls) consistently showed a "modest" improvement in subjective symptoms and nocturia in the flower pollen extract groups compared to placebo, and 2 control products, Paraprost and Tadernan, although the authors called for additional studies to evaluate long-term effects.

Shoskes concluded that there was credible clinical and scientific evidence that treatment with flower pollen extract was efficacious for the majority of patients with nonbacterial prostatitis and prostadynia.[14]

Primary Literature

Flower pollen extract was well tolerated in all of the published studies with minimal reported side effects therefore the discussion will be limited to efficacy considerations.

Double-Blind, Placebo-Control Studies

Two double-blind, placebo-controlled studies have been published with a total of 149 subjects. Becker et al[15] reported data for 96 subjects with BPH in stages II or III according to the Vahlensieck. Subjects received 2 CerniltonÒ capsules or placebo three times daily for 12 weeks. The results showed significant improvement in nocturia (68.8% on CerniltonÒ versus 37.2% on placebo), daytime frequency (65.8% on CerniltonÒ versus 43.9% on placebo), freedom from daytime frequency (48.8% on CerniltonÒ versus 19.5% on placebo) and freedom from sensation of residual urine (37.1% on CerniltonÒ versus 7.7% on placebo). In addition there was significant improvement in global assessment scores of both the physicians

and patients. Physicians rated the overall response as very good or good for 68.1% on CerniltonÒ versus 13.7% on placebo. Patients rated the overall response as very good or good for 72.1% on CerniltonÒ versus 27.3% on placebo. There was no significant change in the size of the prostate as determined by palpitation.

Buck et al[16] reported data for 53 subjects awaiting operative treatment for outflow obstruction due to prostate enlargement. Patients were instructed to take 2 capsules of CerniltonÒ or placebo twice a day over a 6-month period. The results showed 60% of the subjects on CerniltonÒ had improve nocturia compared to 30% on placebo ($p < 0.063$), 57% showed improvement in bladder emptying compared to only 10% on placebo. There was a significant difference in overall improvement in subjective symptoms in the CerniltonÒ group (69%) versus placebo (29%). There was no significant change in peak urine flow rate or voided volume. Residual urine volume decreased significantly in the Cernilton Ò group compared to placebo.

Double-Blind, Active-Control Studies

Maekawa M., et al[17] conducted a double-blind study comparing CerniltonÒ, 2 capsules twice daily for 12 weeks to Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) in 159 patients with BPH. The two supplements were comparable in improving symptoms from baseline (55% for Cernilton Ò and 62% for Paraprost). There was a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the Cernilton Ò group versus Paraprost. Greater than moderate effectiveness rating was 49.1% for Cernilton Ò and 41.2% for Paraprost.

Open Label Studies

Eleven published open label studies with a total of 2291 subjects were reviewed. The results indicate significant beneficial effects in subjective LUTS when Cernilton Ò is used on average for 13.6 weeks.

Becker et al[18] continued the placebo-controlled study[15] described above with an open label study in which 92 subjects previously treated in the first phase of the study with Cernilton Ò (n=45) or placebo (n=47) were treated with Cernilton Ò for 12 weeks. Physicians were blinded as to whether the subjects received Cernilton Ò or placebo in the first phase. The results showed that the differences observed between the two groups in the first phase were eliminated in the 2nd phase. Subjects previously treated with placebo improved significantly when treated with Cernilton Ò. Significant improvements were observed in nocturia, frequency, feeling of incomplete emptying, palpable enlargement of the prostate and prostatic congestion.

Hayashi et al[19] treated 20 BPH patients with Cernilton Ò, 6 tablets a day for an average of 13.2 weeks. They reported improvements in sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%), and forceless urinary stream (53%). Overall subjective effectiveness was 80% and overall objective effectiveness was 54%. Overall effectiveness was rated 80%.

Yasumoto and colleagues[20] conducted an open label trial with 79 BPH patients. Patients were given 2 Cernilton Ò tablets 3 times a day for at least 12 weeks. The results showed that symptom scores improved significantly from baseline. Overall clinical efficacy was rated 85%. Clinical efficacy at 12 weeks was rated satisfactory or better in 85% of the patients.

Bach and Ebeling[21] reported the results from a large open label trial in Germany involving 208 physicians and 1798 evaluable patients with BPH. The patients were treated for 24 weeks with Cernilton Ò; 2 tablets 3 times daily. The patients were divided into 3 groups (stage 1, 2 and 3) for data analysis based on the severity of the BPH symptoms. Patients in stage 1 had the most improvement of the three groups in irritative symptoms whereas patients in stage 2 had significant improvement in both irritative and obstructive symptoms. Peak urine flow rate

increased significantly in all 3 groups. A continuing improvement in symptoms was noted when comparing the results after 12 and 24 weeks of treatment. Efficacy in stage 1 and 2 patients was judged to be satisfactory or better in 90% of the patients. Efficacy in stage 3 patients was judged to be satisfactory or better in 65% of the patients. The authors concluded that treatment with CerniltonÒ is justified even for stage 3 patients until surgery is performed.

Dutkiewicz[22] reported on a study in 51 patients with BPH were given CerniltonÒ, 2 capsules three times daily for 2 weeks then 1 capsule 3 times daily for an additional 14 weeks. Thirty-eight subjects were given Tadenan (Pygeum africanum extract) for 4 months. Significant improvement in subjective symptoms was reported for the CerniltonÒ group (78%) versus the Tadenan group (55%).

Horii et al[23] reported the results of 30 subjects with BPH who were given CerniltonÒ; 2 tablets, 3 times daily for at least 12 weeks. The overall clinical efficacy for subjective symptoms was rated at 80% and objective symptoms at 43%.

Ueda et al[24] treated 22 patients with stage I and II BPH with CerniltonÒ for over 4 weeks. Eighty-two percent of the patients were rated as moderately improved or better.

In a recently published study 24 patients with chronic prostatitis (NIH-category III) were treated with Cernilton Ò for at least 6 weeks. The results showed a significant decrease in the symptom scores at 4 and 6 weeks.[25]

In another open study, Buck et al[26] studied the effect Cernilton Ò, 2 tablets twice daily for up to 18 months on 15 patients with chronic, relapsing abacterial prostatitis and prostodynia. Seven patients became symptom-free, 6 patients were significantly improved and 2 patients failed to show improvement in symptoms. Improvement in symptomatology occurred for most patients after 3 months of treatment.

Jodai et al[27] reported the results of a study on 32 patients with chronic prostatitis given 6 tablets of Cernilton Ò daily for an average of 12 weeks. Subjective symptoms improved in 74.2% of the subjects and objective symptoms improved in 65.6%. The overall efficacy rate was 75%.

Rugendorff et al[28] reported the results of a study on 90 patients with abacterial prostadynia and chronic prostatitis. Subjects were given Cernilton Ò, 1 tablet 3 times daily for 6 months. Seven-two patients were identified as without complicating factors (such as bladder neck sclerosis, prostatic calculi or urethral stricture) and the remaining 18 with complicating factors. Seventy-eight percent of the patients without complications responded to the treatment with 36% of these becoming asymptomatic whereas only 6% of patients with complicating factors improved. Peak urine flow rate in the uncomplicated group increased significantly from 15.9 to 23.5 ml/s.

Discussion

A review of 2 placebo controlled trials and 11 open label studies indicate that flower pollen extract is a safe and effective therapy for the management of mild to moderate LUTS. The studies showed a consistent reduction in subjective symptoms and overall effectiveness ratings of 75% and greater. The extract reduces bothersome symptoms thereby improving quality of life. The two placebo-controlled, double-blind studies provide evidence that the extract is effective in reducing nocturia, daytime frequency and sensation of residual urine.

Potential Role of Combination Therapy

Although published clinical trials support the safety and efficacy of flower pollen extract in the relief of mild to moderate LUTS, a precedent exists to examine beneficial effects of combining flower pollen extract with other dietary supplement or pharmaceutical products. A recently completed clinical study sponsored by the National Institutes of Health concluded that the combination of 2 prescription drugs, finasteride and doxazosin were more effective that either treatment alone in preventing

progression of BPH.[1] This study demonstrates the therapeutic advantages of combining pharmacologically active constituents with different mechanisms of action.

Although the mechanism of action of flower pollen extract is not fully understood, it appears to work via an anti-inflammatory effect, therefore a combination with a botanical or prescription drug that works via a different mechanism may provide additional symptomatic relief. Two recently published trials on combinations with flower pollen extract are very encouraging. Preuss et al[29] reported on a double-blind, placebo controlled trial comparing a combination of flower pollen extract (378 mg), saw palmetto fruit standardized to 43% B-sitosterol (286mg) and vitamin E (100 IU). Seventy subjects completed the combination therapy and 57 subjects completed the placebo over a 90-day period. There was a significant reduction in nocturia, daytime frequency and overall symptomatology as measured by the American Urological Association Symptom Score. This combination therapy is logical since saw palmetto may have a different mechanism of action that flower pollen extract. It is generally believed that Saw Palmetto prevents the conversion of testosterone to dihydroxytestoterone, a potent androgen that stimulates enlargement of the prostate[30].

Aoki et al[31] conducted an open label trial to study tamsulosin hydrochloride (Flomax®), an alpha1A adrenoceptor antagonist, flower pollen extract and their combination in 243 patients with symptomatic BPH over a 12 week period. The results showed that whereas symptoms improved in each group, supporting the efficacy of flower pollen extract, the best results were obtained in the group that used the combination product.

Conclusions

Sufficient evidence exists in the primary and secondary literature to indicate that Graminex's Flower Pollen Extract is safe and effective for the treatment of mild to moderate LUTS. This dietary supplement ingredient has the potential to be used in combination with other dietary supplements or pharmaceuticals to provide relief of bothersome symptoms and improve quality of life for millions of men with this common condition.

References

1. National Institutes of Health, "Two-Drug Therapy is Best for Symptomatic Prostate Enlargement, Combination Should Change Clinical Practice", NIH News Release, May 28, 2002 (www.nih.gov/news/pr/may2002/niddk-28.htm).

2. Denis L.J., Editorial review of "Comparison of phytoptherapy (PermixonÒ) with finasteride in the treatment of benign prostates hyperplasia: A randomized international study of 1098 patients," Prostate 29:241-242, 1996.

3. Bruskewitz, R., "Management of symptomatic BPH in the US: who is treated and how?", Eur Urol 1999, 36, Suppl 3:7-13, 1999.

4. Hytrin® (terazosin hydrochloride) Capsules, 01G-501-0118-1 Master, February 2001, http://www.rxabbott.com/hy/hypi.htm; accessed on 11/22/02.

5. Loschen, G. and Ebeling, L., "Hemmung der Arachidons~ureKaskade durch emen Extrakt aus Roggenpollen. Arzneim-Forsch./Drug Rse.41:162-167, 1991.

6. Ito, R., Ishi, M., Yamashita, S., et al., "Cernitin™ pollen-extract (Cernilton®): Anti-prostatic hypertrophic action of Cernitin™ pollen extract", Pharmacometrics 31:214, 1986.

7. Hanamoto, M., Liao, M., Suzuki, H., et al., "Effect of Cernitin pollen-extract on the Sex-hormone-induced Nonbacterial Prostatitis in Rats", Jpn Pharmacol Ther., 11:65, 1998.

8. Kamijo, T., Sato, S. and Kitamura, T., "Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats", Prostate 49:122-131, 2001.

9. Bales G.T., Christiano A.P., Kirsh E.J., Gerber G.S., "Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Illinois", Urology, 54: 86-89, 1999.

10. Schulz, V., Hansel, R., Tyler, V.E., Rational Phytotherapy, A Physicians' Guide to Herbal Medicine, 3rd Edition, Springer, Berlin, 230-231, 1998.

11. Rye Grass Monograph, Natural Medicines Comprehensive Database, Therapeutic Research Faculty, Stockton, Ca., 919, 2000.

12. MacDonald, R., Ishani, A., Rutks, I., and Wilt, T.J., "A systematic review of Cernilton for the treatment of benign prostatic hyperplasia", BJU Int. 85:836-841, 1999.

13. Wilt, T., MacDonald, R., Ishani, A., Rutks, I., and Stark, G., "Cernilton for benign prostatic hyperplasia", Cochrane Database Syst Rev., (2), CD001042, 2000.

14. Shoskes, D.A., "Phytotherapy and other alternative forms of care for the patient with prostatitis", Curr Urol Rep 3(4):330-334, 2002.

15. Becker, H., and Ebeling, L., "Conservative treatment of benign prostatic hyperplasia (BPH) with CerniltonÒ. Results of a placebo-controlled double-blind study", Urologe(b) 28:301-306, 1988.

16. Buck, A.C., Cox, R., Rees, W.M., Ebeling, L., and John, A., "Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, CerniltonÒ. A double-blind, placebo-controlled study", Br. J. Urol. 66:398-404, 1990.

17. Maekawa, M., Kishimoto, T., Yasumoto, R., et al, "Clinical evaluation of Cernilton on benign prostatic hypertrophy – a multiple center double-blind study with Paraprost", Hinyo Kiyo, 36:495-516, 1990.

18. Becker, H., and Ebeling, L, "Phytotherapy of BPH with CerniltonÒ. Results of a controlled prospective study", Urologe (B) 31:113-116, 1991.

19. Hayashi J., Mitsui, H., Yamakawa, G., et al., "Clinical evaluation of CerniltonÒ in benign prostatic hypertrophy", Hinyo Kiyo, 32:135-141, 1986.

20. Yasumoto, R., Kawanishi H., Tsujino, T., et al, "Clinical evaluation of long-term treatment using CerniltonÒ pollen extract in patients with benign prostatic hyperplasia", Clin Ther 17:82-87, 1995.

21. Bach, D., and Ebeling, L., "Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH): Results of Treatment with CerniltonÒN for Stages 1-3 according to Alken (or II-IV according to Vahlensieck)", www.graminex.com/clinical_studies/study12_sum.php, unpublished report.

22. Dutkiewicz, S., "Usefulness of Cernilton in the treatment of benign prostatic hyperplasia", Int Urol Nephrol 28:49-53, 1996.

23. Horii, A., Iwai, S., Maekawa, M. and Tsujita, M., "Clinical evaluation of Cernilton in the treatment of the benign prostatic hypertrophy", Hinyo Kiyo 31:739-746, 1985.

24. Ueda, K., Kinno, H. and Tsujimura, S., "Clinical evaluation of Cernilton on benign prostatic hyperplasia", Hinyo Kiyo, 31:187-191, 1985.

25. Monden, K., Tsugawa, M., Ninomiya, Y., Ando, E., and Kumon, H., "A Japanese version of the National Institutes of Health Chronic Prostatis Symptom Index (NIH-CPSI: Okayama version) and the clinical evaluation of cernitin pollen extract for chronic non-bacterial prostatitis", Nippon Hinyo Gakkai Zasshi, 93:539-547, 2002.

26. Buck, A.C., Rees, R.W.M., and Ebeling, L., "Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract", Br J Urol 64:496-499, 1989.

27. Jodai, A., Maruta, N., Shimomae, E., et al, "A long-term therapeutic experience with Cernilton in chronic prostatitis", Hinyo Kiyo 34:561-568, 1988.

28. Rugendorff, E. W., Weidner, W., Ebeling, L., and Buck, A.C., "Results of Treatment with Pollen Extract (CerniltonÒ) in Prostatodynia and Chronic Prostatitis", Br J Urol, 71:433-438, 1993.

29. Preuss, H.G., Marcusen, C., Regan, J., et al, "Randomized trial of a combination of natural products (cernitin, saw palmetto, B-sitosteriol, vitamin E) on symptoms of benign prostatic hyperplasia (BPH)", Int. U. and Neph., 33:217-225, 2001.

30. Sultan, C., "Inhibition of androgen metabolism and binding by a liposterolic extract of *"Serenoa repens* B*"* in human foreskin fibroblasts". J. Steroid Biochem 20:515-519, 1984.

31. Aoki, A., Naito, K., Hashimoto, O., et al., "Clinical evaluation of the effect of tamsulosin hydrochloride and cernitin pollen extract on urinary disturbance associated with benign prostatic hyperplasia in a multicentered study", Hinyo Kiyo, 48:259-267, 2002.

A Critical Review of Cernitin for Symptomatic Relief Of Lower Urinary Tract Symptoms (LUTS) in Men

Harry G. Preuss[1]
Debasis Bagchi[2]
Walter G. Chambliss[3]

[1] Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, D.C. USA

[2] Department of Pharmacy Sciences, School of Pharmacy and Health Professions, Creighton University Medical Center, Omaha, NE. USA

[3] National Center for Natural Products Research, and Department of Pharmaceutics, University of Mississippi, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University, MS. USA

Objective

We reviewed published data concerning the ability of a defined flower pollen ex-tract derived from rye, corn, and timothy, commonly referred to as Cernitin to provide symptomatic relief in men suffering from lower urinary tract symptoms (LUTS). This same defined pollen extract has also been called Cernilton in other reports and is commercially available as Graminex Flower Pollen Extract. To maintain clarity, however, we will only use the term Cernitin to describe the defined pollen extract. In writing this review, our major goal is to present evidence concerning the therapeutic role of Cernitin in the management of mild to moderate LUTS. Nevertheless, we briefly describe prostatic perturbations in general and other natural therapeutic approaches to alleviate symptoms caused by them.

Introduction

It is estimated that 9-10 million men have lower urinary tract symptoms (LUTS) secondary to an enlarged prostate; and 400,000 surgeries are conducted each year in the U.S to alleviate such symptoms [1,2]. Although cancer might be a root cause, LUTS are more commonly found in men with non-cancerous conditions such as benign prostate hyperplasia (BPH), prostadynia, acute and chronic prostatitis caused by a bacterial infection, as well as chronic non-bacterial prostatitis. BPH, the most common cause of LUTS, does not distinguish between race and ethnic background, although African-American men are at a slightly greater risk [3]. It does not relate to sexual activity, since it can occur in celibate priests as well as the most sexually active of men [4]. Regardless of the etiology of the specific prostate-related disorders, health worries associated with prostatic enlargement are significant. Over $1 billion dollars are spent each year on treatment for prostatic enlargement, because LUTS can lead to more

serious health problems if not treated properly [5].

The term LUTS describes men experiencing one or more symptoms listed on the International Prostate Symptom Score (IPSS) questionnaire. Among the mentioned urinary symptoms are daytime and night time (nocturia) frequency, urgency, hesitancy, intermittency, sensation of incomplete voiding, and decreased force of urinary stream [2]. An individual often becomes aware of the problem when urination occurs more frequently than usual. He may eventually become the person who rarely can sit through a movie or concert -- the one that requests the aisle seat on an airplane so as not to disturb his fellow passengers on his frequent sojourns to the restroom. At night, the trips to the bathroom caused by nocturia steadily increase, and there is a definite impingement on sleep. Suffice it to say, any experiencing of such frequency should lead to suspicion of the disorder.

What do we know about this troublesome gland? The prostate gland is associated with the male reproductive system. Its major function is to produce and discharge a viscous, alkaline liquid that provides a major portion of the seminal fluid. The prostate makes and stores fluid almost continuously. Because of the environment afforded by the presence of prostatic fluid, sperms are protected, at least to some extent, and can survive longer after ejaculation. In addition, the prostatic fluid contains prostaglandins, which are fatty acids that, similar to hormones, affect smooth muscle fibers and blood vessel walls. Although the prostate plays no direct role in the functioning of the male urinary system, its location near the bladder and urethra cause many urinary perturbations when it expands via growth or response to chronic inflammation [6-8].

At birth, the gland is the size of a pea and grows slowly until puberty. Under the influence of sex hormones, the prostate grows at a faster pace. During the 20's and 30's, the gland is characteristically the size of a walnut and weighs roughly one ounce. The gland, made up of muscular and glandular tissue, is located in front of the rectum and below the urinary bladder. Importantly, the gland surrounds the urethra, a tube that carries urine from the bladder to the tip of the penis for expulsion. Obviously, this setting has the potential to cause problems and unfortunately does. Around the age of 45, cells in the majority of prostates began to multiply again and the gland can reach up to 10 times the normal adult size [3].

The prostate can be divided into various lobes, with the major problems of BPH lying in the small transitional zone. The transitional zone that lies within the so-called middle lobe is the sole site of BPH [9]. Interestingly, the small transition zone comprises only two per cent of the entire prostatic mass before enlargement. Obviously, enlargement of this area does not in itself increase the size of the prostate greatly. Because of this, the degree of urethral obstruction may not directly relate to the overall size of the prostate gland but instead to the direction of growth enlargement. Some men with greatly enlarged prostates may have no signs of obstruction, while those with relatively small prostates may have severe obstruction.

While the exact mechanism behind age-related enlargement of the prostate is uncertain, a highly active form of the male hormone, testosterone, called dihydrotestosterone (DHT), is considered a major factor behind prostatic enlargement [4]. Excessive levels of DHT have been found in men with enlarged glands, and high concentrations of DHT are also associated with an increased risk of prostate cancer. To make matters worse, the concentration of DHT within the prostate increases with age. A major factor in the rise is that the enzyme responsible for the conversion of testosterone to DHT, 5-alpha reductase, becomes more active over the lifespan. Therefore, it is not too surprising that 5-alpha reductase is an important focal point in the medical treatment of prostate enlargement. Nevertheless, it is equally important to be aware that other prostatic enzymes, such a 3

oxidoreductase, deficiency of minerals such as zinc, and inflammation may also play a role in the enlargement process.

Background of Treatment

Bruskewitz points out that since serious complications from BPH and related non-cancerous conditions are rare, the primary aim of pharmacological treatment is to improve quality of life by relieving the vexing symptoms [10]. Studies conducted in the U.S. showed that urologists provided no specific treatment 77% of the time to men with mild symptoms. With moderate symptoms, however, prescription drugs were given 89% of the time; and surgery was conducted 1% of the time. The primary therapeutic treatment was use of alpha (1)-adrenoceptor antagonists such as terazosin hydrochloride (Hytrin®) that provide symptomatic relief but have not been shown to influence the incidence of surgery, acute urinary obstruction, or other complications of BPH [11]. In the past, treatment options for significant prostate enlargement focused on surgery. In a given year, approximately 400,000 men are driven to undergo a procedure called a transurethral resection of the prostate (TURP). Even now, transurethral resection is the standard treatment for BPH, i.e., the gold standard by which all other procedures are measured [12]. Unfortunately, while many symptoms of obstruction are ameliorated, post urination dripping may continue and may even result in severe incontinence. Even worse, the operation may be followed by a decline in sexual function. This may also occur with the use of the common pharmaceuticals as well [2]. Accordingly, a need exists for safe, effective products that can be used to treat mild to moderate LUTS in lieu of or in addition to prescription drugs and major surgery. Natural products have been considered among the alternative therapies.

Natural Products to Treat LUTS

Saw Palmetto (Serenoa Repens)
Research carried out in Europe over the past 20 years shows that natural, fat-soluble extracts from specific plants effectively inhibit the function of 5-alpha-reductase, and block, at least in part, the formation of DHT [13-16]. The best-known and most extensively researched plant is saw palmetto. Saw palmetto is an extract of the pulp and seeds of a dwarf, scrubby palm tree native to the West Indies and the Atlantic coast of the United States. Saw palmetto works, for the most part, by the same mechanism as the pharmaceutical Proscar®, i.e., preventing the conversion of testosterone to DHT [16]. Additional benefits from plant extracts have also been found and may add to the good results found with their use. Some plant extracts not only lower the rate of DHT formation, but also block the ability of DHT to bind to cells, preventing the action of hormone [17,18]. In addition, they may prevent severe inflammatory responses. Saw palmetto, known to be popular in Europe, has recently become recognized in America. In one study using saw palmetto in 110 men, it decreased nighttime urination by 45 percent, increased urinary flow rate more than fifty percent, and reduced the amount of urine left in the bladder after urination by 42 per cent [19]. In other large trials, improvement in prostatic symptomatology was readily noted and saw palmetto even compared favorable with Hytrin and Proscar when they were compared head to head [20-24].

Pygeum Africanum

The powdered bark of the pygeum tree, a large tropical African evergreen, has been used for centuries to treat urinary disorders [25]. Pygeum contains phytoesterols, which have been purported to have anti-inflammatory properties. In addition, much benefit has been attributed to their ability to decrease prostatic swelling, to reduce harmful prostaglandins that induce inflammation, and to diminish circulating prolactin that decreases the prostate uptake of testosterone. When 263 German men were tested with Pygeum africanum, urinary symptoms improved in 66% compared to 31% in the placebo group [26]. Occasional gastrointestinal upset seems to be the major

adverse side effect.

Stinging Nettle (Urtical dioica)

Less research has been performed using the stinging nettle to ameliorate BPH. Laboratory studies have shown its ability to inhibit laboratory induced prostate growth in mice [27]. The results from one study suggest that the steroidal components of stinging nettle roots suppressed prostate cell growth [28].

Beta-sitosterol

Much attention has recently been focused on beta-sitosterol. In a randomized double blind study reported in the Lancet, 200 patients from eight private urological practices were treated for six months with either 20 mg of beta-sitosterol or placebo [29]. At the end of six months, modified Boyarsky scores decreased statistically in the beta-sitosterol treated group compared to placebo. The quality of life score improved, the peak urine flow increased, the mean voiding time and the urinary volume retention also improved from the initial scores in the verum group, whereas no changes were noted in the placebo group. Results were also positive in another randomized, double-blind and placebo-controlled study carried out in Germany [30].

Cernitin

Cernitin is a natural product recently introduced in the USA to be used to treat LUTS. However, it has actually been around a long time. In 1950, in a tiny Swedish village, a beekeeper found a way to collect pollen artificially [31]. Since it was good for bees, his hypothesis was that it would be good for humans. Initially, the flower pollen was used as a prophylactic agent against infections. Later the extraction process was modified so that the active pollen was released and was non allergenic. Found in the pollen are peptides, carbohydrates, fatty acids, vitamins, minerals, nucleic acids, and enzymes. Whatever the original hypothesis concerning overall health, the defined pollen extract called "Cernitin" proved specifically useful in treating BPH and other prostate conditions [2,32].

Cernitin is a standardized extract of rye pollen (*Secale cereale)*, corn pollen (*Zea mays),* and timothy pollen (*Phleum pratense).* From these combined pollens, two important, therapeutic extracts are derived -- a water-soluble fraction and a lipid-soluble fraction with different physiological functions. *In vitro* and *in vivo* animal studies [33,34] have shown that both fractions have anti-inflammatory properties emanating from inhibition of prostaglandin and leukotriene synthesis. The water-soluble fraction has been shown to reduce the size of the ventral and dorsal prostate in the rat [35] and to inhibit testosterone-induced BPH in castrated animals [8]. The combined extracts were shown to inhibit growth of transplanted human BPH tissue in an athymic nude mouse model (36). Both fractions have been shown to relax the smooth muscle of the mouse and pig urethra, increase bladder muscle contractions [34], and reduce prostate size in mature Wistar rats [37].

Cernitin extracts are also sold as Graminex Flower Pollen Extract and are available in the marketplace in tablet and capsule forms, usually contain 63 mg of a 20:1 ratio of water-soluble to lipid-soluble fractions. Cernitin is contained in products regulated as drugs in Switzerland, Germany, Austria, Japan, South Korea and South Africa. In the U.S., the use of botanicals for LUTS is relatively less. No botanicals are approved as prescription or over-the-counter drugs for LUTS or BPH in the U.S. Accordingly, they are sold as dietary supplements and are labeled with non-specific information, e.g., "maintains prostate health." In a study conducted in Chicago in 1997-1998 with 738 men having LUTS and/or prostate disease, Bales et al [38] found that 13% of the group had used botanicals for their condition (59% in combination with prescription drugs), 37% were aware of botanicals as an option but had never used them, and 50% were unaware of this treatment option. Such information prompted our review of Cernitin.

Methods

Literature searches were conducted on Medline and the Cochrane Library. Sources such as review articles and monographs in botanical reference books and other books referring to Cernitin were included in the analysis. Open label and comparative trials were included in the assessment, although more weight was given to placebo-controlled, double-blind studies. Emphasis was placed on subject ratings of symptoms in light of the potential for self-medication of this extract.

Results

Reviews, Books, and Monographs

Four reviews [39-43] and a number of books/monographs [2,44-46] dealing largely with the clinical efficacy and safety of Cernitin have been published in recent years. Each used its own criteria to select studies considered to be valid. Because all reviews concluded that Cernitin is very safe with few or no side effects, the summaries described below are essentially limited to efficacy.

In the first, Commission E, an expert committee established by the German government to evaluate the safety and efficacy of over 300 botanical and botanical combinations sold in Germany, concluded in 1994 that combining extracts of rye, corn, and timothy pollen was useful in the treatment of "micturition difficulties associated with Alken stage I-II benign prostatic enlargement (BPH)" [39]. In the second, the Natural Medicines Comprehensive Database concluded that rye grass pollen extract (Cernitin) was "possibly effective" for the management of BPH symptoms, for shrinking prostate size, and for prostatitis and prostadynia based on the information it gathered [40]. In the third source, the same group published reviews in 1999 and 2000 based upon results from 4 double-blind studies (444 men in total, 2 studies with placebo; 2 with active controls) [41,42]. Results consistently showed a "modest" improvement in subjective symptoms and nocturia in the Cernitin groups compared to placebo, Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) and Tadenan (Pygeum africanum extract). The authors called for additional studies to evaluate long-term effects. In the final review, Shoskes concluded that there was credible clinical and scientific evidence that treatment with Cernitin pollen extract was efficacious for the majority of patients with non-bacterial prostatitis and prostadynia [43]. The books/monographs largely corroborate the conclusions of the reviews [2,44-46].

Research Papers

Again, Cernitin was well tolerated in all of the published studies from primary literature with minimal reported side effects. Therefore, the discussion will continue to focus on efficacy.

In the 1960's, Leander [47] published results of a carefully controlled trial. He compared placebo with Cernitin pollen extract in 179 cases. Using pollen extract, Leander found a 60-80 per cent improvement over placebo in symptoms of obstruction, probably through elimination of inflammatory edema. Around the same time, much work was progressing in Japan. Inada et al [48] reported favorable effects in 12 patients suffering from prostatic hypertrophy. They reported that five cases had "effective" results; five showed "slightly effective" results and two reported "ineffective" results. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University, reported impressive results in 30 patients with prostatitis and/or urethritis [49]. Examining 14 patients receiving Cernitin, it was found that treatment was "successful" in 10, "slightly effective" in three, and "ineffective" in only one case. In 16 patients given placebo, seven found the treatment to be "effective" and nine reported "no change."

In 1981, Takeuchi [50] investigated both subjective and objective effects of Cernitin on 25 men with BPH. The efficiency rate for Cernitin

was reported as 64%. There was a 50% improvement for nocturnal micturation. Horii et al [51] reported the results of 30 subjects with BPH who were given Cernitin 2 tablets, 3 times daily for at least 12 weeks. The overall clinical efficacy for subjective symptoms was rated at 80% and objective symptoms at 43%. Ueda et al [52] treated 22 patients with stage I and II BPH with Cernitin for over 4 weeks. Eighty-two percent of the patients were rated as moderately improved or better. Hayashi et al [53] treated 20 BPH patients with Cernitin, 6 tablets a day for an average of 13.2 weeks. They reported improvements in sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%), and forceless urinary stream (53%). Overall subjective effectiveness was 80% and overall objective effectiveness was 54%.

In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [54]. They examined the effectiveness of Cernitin pollen extracts on chronic prostatitis and/or BPH. Improvement of symptoms was reported in 64 to 82%, in contrast to a low rate of adverse reaction found only in 2.9% of cases. In the same year [55], Brauer compared the effects of Cernitin and beta-sitosterol in 39 patients. A significant reduction in circulating levels of PSA with Cernitin therapy indicated a reduction of cell lesions in BPH. In contrast, no such change occurred with beta-sitosterol treatment. Although flower pollen extract proved superior to beta-sitosterol in many respects, the mean values for residual volume fell under 15 ml for both at the end of treatment. Subjective symptoms improved in 74.2% of the subjects as compared to 65.6% for objective symptoms. The overall efficacy rate was 75.0%.

In a double-blind, placebo-controlled study, Becker et al [57] reported data for 96 subjects with BPH in stages II or III according to the Vahlensieck. Subjects received two Cernitin capsules or placebo three times daily for 12 weeks. The results showed significant improvement in nocturia (68.8% on Cernitin versus 37.2% on placebo, $p = 0.005$), daytime frequency (65.8% on Cernitin versus 43.9% on placebo, $p = 0.076$), freedom from daytime frequency (48.8% on Cernitin versus 19.5% on placebo, $p = 0.010$) and freedom from sensation of residual urine (37.1% on Cernitin versus 7.7% on placebo, $p = 0.016$). In addition there was significant improvement in global assessment scores of both the physicians ($p = 0.001$) and patients ($p = 0.01$). Physicians rated the overall response as very good or good for 68.1% of patients taking Cernitin versus 13.7% taking placebo group. 72.1% of patients taking Cernitin rated their overall response as very good or good versus 27.3% in the placebo group. However, there was no significant change in the size of the prostate as determined by palpation.

In an open study, Buck et al [58] studied the effect Cernitin, 2 tablets twice daily for up to 18 months on 15 patients with chronic, relapsing non-bacterial prostatitis and prostadynia. Seven patients became symptom-free, 6 patients were significantly improved, and 2 patients failed to show improvement in symptoms. Improvement in symptomatology occurred for most patients after 3 months of treatment.

In a double-blind, placebo-controlled study, Buck et al [59] reported data for 53 subjects awaiting operative treatment for outflow obstruction due to prostate enlargement. Patients were instructed to take 2 capsules of Cernitin or placebo twice a day over a 6-month period. The results showed 60% of the subjects receiving Cernitin had less nocturia compared to 30% receiving placebo ($p < 0.063$), and 57% showed improvement in bladder emptying with Cernitin compared to only 10% taking placebo ($p < 0.004$). There was a significant difference ($p < 0.009$) in overall improvement in subjective symptoms in the Cernitin group (69%) versus placebo (29%). Despite no significant change in peak urinary flow rate or voided volume, residual urinary volume decreased significantly in the Cernitin group compared to placebo ($p < 0.025$).

In a double-blinded, active-control study,

Maekawa et al [60] conducted a double-blind study comparing Cernitin, 2 capsules twice daily for 12 weeks, to Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) in 159 patients with BPH. The two botanical preparations were comparable in improving symptoms (IPSS) from baseline (55% for Cernitin and 62% for Paraprost). There was a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the Cernitin group versus Paraprost. Greater than moderate effectiveness rating was 49.1% for Cernitin and 41.2% for Paraprost.

Becker et al [61] continued the placebo-controlled study described above [57] with an open label study in which 92 subjects previously treated in the first phase of the study with Cernitin (n=45) or placebo (n=47) were continued or now treated with Cernitin for 12 weeks. Physicians were blinded in this second phase as to whether the subjects received Cernitin or placebo in the first phase. The results showed that the differences observed between the two groups in the first phase were eliminated in the 2nd phase. Subjects previously treated with placebo improved significantly when treated with Cernitin. Significant improvements were observed in nocturia ($p = 0.051$), frequency ($p = 0.039$), feeling of incomplete emptying ($p =0.013$), palpable enlargement of the prostate ($p = 0.046$) and prostatic congestion ($p=0.03$).

Bach and Ebeling [62] reported the results from a large open-label trial in Germany involving 208 physicians and 1798 patients with BPH capable of being evaluated. The patients were treated for 24 weeks with Cernitin; 2 tablets 3 times daily. The patients were divided into 3 groups (stage 1, 2 and 3) for data analysis based on the severity of the BPH symptoms. Patients in stage 1 had the most improvement of the three groups in irritative symptoms whereas patients in stage 2 had significant improvement in both irritative and obstructive symptoms. Peak urinary flow rates increased significantly in all 3 groups. A continuing improvement in symptoms was noted when comparing the results after 12 and 24 weeks of treatment. Efficacy in stage 1 and 2 patients was judged to be satisfactory or better in 90% of the patients. Efficacy in stage 3 patients was judged to be satisfactory or better in 65% of the patients. The authors concluded that treatment with Cernitin is justified even for stage 3 patients until surgery is performed.

Rugendorff et al [63] reported the results of a study on 90 patients with non-bacterial prostadynia and chronic prostatitis. Subjects were given Cernitin, 1 tablet 3 times daily for 6 months. Seven-two patients were found to have complicating factors (such as bladder neck sclerosis, prostatic calculi or urethral stricture), while the remaining 18 possessed no complicating factors. Seventy-eight percent of the patients without complications responded to the treatment with 36% of these becoming asymptomatic. In contrast, only 6% of patients with complicating factors improved. Peak urine flow rate in the uncomplicated group increased significantly ($p < 0.001$) from 15.9 to 23.5 ml/s.

Braun and Peyer [64] in a 1993 double blind, placebo-controlled investigation on 44 patients with Grade I and II BPH assessed the validity of treatment with flower pollen extract on subjective and objective parameters. They found by using questionnaires, echography, and laboratory analysis of PSA that flower pollen extract had a clear benefit over placebo. In 25 patient receiving verum compared to 19 receiving placebo, there was a significant reduction in the mean number of both diurnal and nocturnal micturations with flower pollen extract ($p<0.05$). Using ultrasonic measures, the mean volume of the prostate decreased significantly more in the verum group (-29% vs. -8.8%, $p<0.05$). More reduction in residual urine volume and PSA levels were noted in the verum group.

Yasumoto and colleagues [65] conducted an open-label trial with 79 BPH patients. Patients were given 2 Cernitin tablets 3 times a day for at least 12 weeks. The results showed that symptom scores improved significantly from

baseline. Overall clinical efficacy was rated 85%. Clinical efficacy at 12 weeks was rated satisfactory or better in 85% of the patients. Dutkiewicz [66] gave Cernitin to 51 patients with BPH -- 2 capsules three times daily for 2 weeks then 1 capsule 3 times daily for an additional 14 weeks. Thirty-eight subjects were given Tadenan (Pygeum africanum extract) for 4 months. Significant improvement in subjective symptoms was reported for both -- Cernitin group (78%) and the Tadenan group (55%). In a recently published study, 24 patients with chronic prostatitis (NIH-category III) were treated with Cernitin for at least 6 weeks. The results showed a significant decrease in the symptom scores at 4 and 6 weeks [67].

Potential Role of Combination Therapy

Although published clinical trials support the efficacy of Cernitin in the relief of mild to moderate LUTS, a precedent exists to examine beneficial effects of combining Cernitin with other botanical products. A recently completed clinical study sponsored by the National Institutes of Health concluded that the combination of finasteride and doxazosin was more effective that either treatment alone in preventing progression of BPH [68]. This study demonstrates the therapeutic advantages of combining drugs with different mechanisms of action.

The precise mechanisms behind the therapeutic benefits of Cernitin are not fully understood, but it is generally accepted that anti-inflammatory and/or alpha adrenergic blocking effects are important. Therefore, combining Cernitin with a botanical and/or prescription drug with different mechanisms of action may provide additional symptomatic relief. Two recently published trials using combinations of agents with Cernitin support this theory.

Preuss et al [69] reported on a double-blind, placebo-controlled trial comparing a combination of Cernitin (378 mg); saw palmetto fruit standardized to 43% B-sitosterol (286mg) and vitamin E (100IU). Seventy subjects completed the combination therapy and 57 subjects completed the placebo over a 90-day period. There was a significant reduction in nocturia ($p < 0.001$), daytime frequency ($p < 0.04$) and overall symptomatology as measured by the American Urological Association Symptom Score. This combination therapy is logical, since saw palmetto may have different mechanisms of action than Cernitin. As an example, it is believed that saw palmetto compared to Cernitin prevents to a greater extent the conversion of testosterone to dihydroxytestoterone, a potent androgen that stimulates enlargement of the prostate [17,21,22].

Aoki et al [70] conducted an open label trial to study tamsulosin hydrochloride (Flomax®), an alpha1A adrenoceptor antagonist, Cernitin, and the combination in 243 patients with symptomatic BPH over a 12-week period. The results showed that whereas symptoms improved in each group, supporting the efficacy of Cernitin, the best results were obtained in the group that used the combination.

Discussion

A review of placebo-controlled trials, active-controlled and open-label studies indicate that Cernitin is a safe and effective therapy for the management of mild to moderate LUTS. By reducing bothersome symptoms, Cernitin improves quality of life. The placebo-controlled, double-blind studies with Cernitin alone [47,57,59,60] and combined with other natural products [69] especially provide evidence that Cernitin is effective in reducing nocturia, daytime frequency, and sensation of residual urine. The number of subjects in these studies was small relative to the studies conducted for prescription therapeutics such as Terazosin [11] (Hytrin, minimum of 430 subjects) and Doxazosin [71] (Cardura, minimum of 900 subjects), however the duration of the studies were comparable. Cernitin studies were generally conducted for 12 to 24 weeks, terazosin trials were conducted for 12 to 24 weeks, and doxazosin studies were

also conducted over a 14 to 16 week period.

Since the number of subjects studied in placebo-controlled trials is small, it was necessary to review open-label and active control studies as supporting data. Concerning the use of Cernitin alone, we report on 15 open label studies and 4 double-blind, placebo-controlled studies that showed consistent reduction in subjective symptoms and overall effectiveness ratings of 75% and greater. In addition, 1 double-blind, active-controlled study, 1 open-label study on a combination, and 1 double-blind, placebo-controlled study on a combination strengthen the conclusions on the therapeutic merits of Cernitin.

Conclusions

Sufficient evidence exists in the primary and secondary literature to indicate that a standardized flower pollen extract commonly referred to as Cernitin is safe and effective for the treatment of mild to moderate LUTS. This dietary supplement composed of pollen extracts from rye, corn, and timothy has the potential to be used in combination with other dietary supplements or pharmaceuticals to provide relief of bothersome symptoms and improve quality of life for millions of men

References

1. Jacobsen SJ, Girman CJ, Guess HA, Oesterling JE, Lieber MM: New diagnostic and treatment guidelines for benign prostatic hyperplasia. Potential impact in the United States. Arch Int Med 155:477-481, 1995.

2. Preuss HG, Adderly B: Benign prostatic hyperplasia: men's secret disease. In: The Prostate Cure. (eds) HG Preuss, B Adderly. Crown Publishing, Inc., New York, NY, pp 1-29, 1998.

3. Oesterling JE: Benign prostatic hyperplasia: a review of its histogenesis and natural history. The Prostate Supplement, 6:67-73, 1996.

4. Buttyan R, Chen M-W, Levin RM: Animal model of bladder outlet obstruction and molecular insights into the basis for the development of bladder dysfunction. European Urology 32(Suppl 1):32-39, 1997.

5. Knott MA, Bootman JL: The economics of benign prostatic hyperplasia treatment: a literature review. Clinical Therapeutics 18:1227-1241, 1995.

6. Salcedo H: The Prostate. Facts and Misconceptions. Birch Lane Press Book, New York, NY, 1993.

7. Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol 132:474-479, 1994.

8. Lytton B, Emery JM, Howard BM: The incidence of benign prostatic hy-pertrophy. J Urol 99:639-645, 1968.

9. Walsh PC, Worthington JF: The Prostate. A Guide for Men and the Women Who Love Them. Baltimore and London: The Johns Hopkins University Press, p 15, 1995.

10. Bruskewitz, R: Management of symptomatic BPH in the US: who is treated and how?, Eur Urol 36(Suppl 3):7-13, 1999.

11. Hytrin® (terazosin hydrochloride) Capsules, 01G-501-0118-1 Master, February 2001, http://www.rxabbott.com/hy/hypi.htm; accessed on 11/22/02.

12. Fowler FJ, Wenneberg JE, Timothy RP, et al: Symptom status and quality of life following prostatectomy. JAMA 259:3018-3022, 1988.

13. Breu W, Stadler F, Hagenlocher M, Wagner H: Der sabalfrucht-extrakt SG 291. Ein phytotherapeutikin zur behandlung der benignen prostatahyperplasie. Zeitschrift Fur Phytotherapie 13:107-115, 1992.

14. Breu W, Hagenlocher M, Redl K, et al: Antiphlogistische wirkung eines mit hyperkritischem kohiendixid gewonnenen sabalfrucht-extraktes. Arzneim Forsch Drug Research 42:547-551, 1992.

15. Stenger A, Tarayre JP, Carilla F: Etude pharmacologique et biochimique de l'extrait hexanique de serenoa repens. B: Gaz Med de France 89:2041-2048, 1982.

16. Rhodes L, Primka RL, Berman C et al: Comparison of finasteride (Proscar), a 5_ reductase inhibitor, and various commercial plant extracts in in vitro and in vivo 5_ reductase inhibition. The Prostate 22:43-51, 1993.

17. Sultan C, Terraza A, Divillier C: Inhibition of androgen metabolism and binding by a liposterolic extract of Serenoa repens B in human foreskin fibroblasts. J Steroid Biochem 20:515-521, 1984.

18. Carilla E, Briley M, Fauran F, Sultan C, Duvilliers C: Binding of Permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate. J Steroid Biochem 20:521-523, 1984.

19. Champault G, Patel JC, Bonnard AM: A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. Br J Clin Pharmacol 18:461-462, 1984.

20. Carraro JC, Raynaud JP, Koch G, et al: Comparison of phytotherapy (Permixon) with finasteride in the treatment of

benign prostate hyperplasia: a randomized international study of 1,098 patients. The Prostate. 29:231-240, 1996.

21. Posker GL, Brogden RN: Serenoa repens (Permixon). A review of it pharmacology and therapeutic efficacy in benign prostatic hyperplasia. Drug and Aging 9:379-395, 1996.

22. Denis LJ: Editorial review of Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. The Prostate 29:241-242, 1996.

23. Braeckman J: The extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a multicenter open study. Curr Therap Res 56:776-785, 1994.

24. Champault G, Bonnard AM, Cauquil J, Patel JC: Medical treatment of prostatic adenoma. Controlled trial PA 109 vs placebo in 110 patients. Ann Urol 18:407-410, 1984.

25. Steinman D: Enlarged prostate? Try tree bark. Natural Health 24:46-47, 1994.

26. Barlet A, Albrecht J, Aubert A, Fisher M, Grof F, Grothhuesmann HG, Masson JC, Mazeman E, Mermon R, Reichert H: Efficacy of Pygeum Africanum extract in the medical therapy of urination disorders due to benign prostatic hyperplasia: evaluation of objective and subjective parameters. A placebo-controlled double-blind multicenter study. Wiener Klinische Wochenschrift. 102:667-673, 1990.

27. Lichius JJ, Muth C: The inhibiting effects of Urtica dioica root extracts on experimentally induced prostatic hyperplasia in the mouse. Planta Medica 63:307-310, 1997.

28. Hirano T, Homma M, Oka K: Effects of stinging nettle roots and their steroidal components on the Na+, K+ ATPase of the benign prostatic hyperplasia. Planta Medica 60:30-33, 1994.

29. Berges RR, Windeler J, Trampisch HJ, et al: Randomized, placebo-controlled clinical trial of _-sitosterol in patients with benign prostatic hyperplasia. The Lancet 345:1529-1532, 1995.

30. Klippel KF, Hiltl DM, Schipp B: A multicenter, placebo-controlled, double-blind clinical trial of _-sitosterol (Phytosterol) for the treatment of benign prostatic hyperplasia. Br J Urol 80:427-432, 1997.

31. Asplund A: Searching for the source of life and vitality. Sanomin (SA) SDN, Singapore, p 36, 1991.

32. Meares Jr EM: Prostatitis and related disorders. In: Campbell's Urology, 6th edition. (ed) PC Walsh, Philadelphia, PA, pp 807-822, 1992.

33. Loschen, G, Ebeling L: Hemmung der Arachidons~ureKaskade durch emen Extrakt aus Roggenpollen. Arzneim-Forsch./Drug Rse 41:162-167, 1991.

34. Ito R, Ishi M, Yamashita S, et al: Cernitin pollen-extract (Cernilton®): Anti-prostatic hypertrophic action of Cernitin pollen extract Pharmacometrics 31:214, 1986.

35. Hanamoto M, Liao M, Suzuki H, et al: Effect of Cernitin pollen-extract on the sex-hormone-induced nonbacterial prostatitis in rats. Jpn Pharmacol Ther 11:65, 1998.

36. Wagner B, Otto H, Becker S, Schroder S, Klosterhalfen H: Experimental treatement studies with Cernilton N in human benign prostatic hyperplasia. In: Benign Prostatic Diseases. (eds) W Vahlensieck, G Rutishauser , Georg Thieme Verlag, Stuttgart, Germany and Thieme Medical Publishers, Inc. New York, NY, pp 123-127, 1992.

37. Kamijo T, Sato S, Kitamura T: Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats. Prostate 49:122-131, 2001.

38. Bales GT, Christiano AP, Kirsh EJ, Gerber GS: Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Illinois. Urology 54: 86-89, 1999.

39. Schulz, V, Hansel R, Tyler VE: Rational Phytotherapy, A Physicians' Guide to Herbal Medicine, 3rd Edition, Springer, Berlin, 230-231, 1998.

40. Rye Grass Monograph, Natural Medicines Comprehensive Database, Therapeutic Research Faculty, Stockton, Ca, p 919, 2000.

41. MacDonald R, Ishani A, Rutks I,Wilt TJ: A systematic review of Cernilton for the treatment of benign prostatic hyperplasia. BJU Int 85:836-841, 1999.

42. Wilt T, MacDonald R, Ishani A, Rutks I, Stark G: Cernilton for benign prostatic hyperplasia. Cochrane Database Syst Rev (2), CD001042, 2000.

43. Shoskes DA: Phytotherapy and other alternative forms of care for the patient with prostatitis. Curr Urol Rep 3:330-334, 2002.

44. Vahlensieck W, Rutishauser G (eds): Benign Prostatic Diseases. Georg Thieme Verlag, Stuttgart, Germany and Thieme Medical Publishers, Inc. New York, NY, pp 1-207, 1992.

45. Clouatre D: Pollen Extract for Prostate Health. Pax Publishing, San Francisco, CA, pp 1-30, 1997.

46. Stoffe JA, Clouatre D: The Prostate Miracle. Kensington Books, New York, NY, pp 1-261, 2000.

47. Leander G: A preliminary investigation on the therapeutic effect of Cernilton N in chronic prostatovesiculitis. Svenska Lakartidningen 59:3296, 1962.

48. Inada T, Kitagawa T, Miyakawa M: Use of Cernilton in patients with prostatic hypertrophy. Tobishi Pharmaceutical Co, Ltd. Tokyo, Japan, 1966.

49. Ohkoshi M, Kawamura N, Nagakubo I: Clinical evaluation of Cernitin in chronic prostatitis. Japanese Journal of Urology, 21:73-85, 1967.

50. Takeuchi H, Yamauchi A, Ueda T et al: Quantitative evaluation on the effectiveness of Cernilton on benign prostatic hypertrophy. Hinyoki Kiyo 27:326-327,1981.

51. Horii A, Iwai S, Maekawa M, Tsujita, M: Clinical evaluation of Cernilton in the treatment of the benign prostatic hypertrophy. Hinyo Kiyo 31:739-746, 1985.

52. Ueda K, Kinno H, Tsujimura S: Clinical evaluation of Cernilton on benign prostatic hyperplasia. Hinyo Kiyo, 31:187-191, 1985.

53. Hayashi J, Mitsui,H, Yamakawa G, et al: Clinical evaluation of Cernilton in benign prostatic hypertrophy. Hinyo Kiyo, 32:135-141, 1986.

54. Ebeling L: The therapeutic results of defined pollen extract in patients with chronic prostatitis. In: Schmiedt E, Alken JE, Bauer HW (eds). Therapy of Prostatitis. Zuckschwerdt Verlag, Munchen, pp 154-160, 1986.

55. Brauer H: The treatment of benign prostatic hyperplasia with phytopharmacia: a comparative study of Cernilton and beta sitosterol. Therapeiwoche 36: 1686-1696, 1986.

56. Jodai A, Maruta N, Shimomae E, et al: A long-term therapeutic experience with Cernilton in chronic prostatitis. Hinyo Kiyo 34:561-568, 1988.

57. Becker H, Ebeling, L: Conservative treatment of benign prostatic hyperplasia (BPH) with Cernilton. Results of a placebo-controlled double-blind study. Urologe(b) 28:301-306, 1988.

58. Buck AC, Rees RWM, Ebeling L: Treatment of chronic prostatitis and prostatodynia with pollen extract. Br J Urol 64:496-499, 1989.

59. Buck AC, Cox R, Rees, W, Ebeling L, and John A: Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernilton. A double-blind, placebo-controlled study. Br. J. Urol. 66:398-404, 1990.

60. Maekawa M, Kishimoto T, Yasumoto R, et al: Clinical evaluation of Cernilton on benign prostatic hypertrophy - a multiple center double-blind study with Paraprost. Hinyo Kiyo, 36:495-516, 1990.

61. Becker H, Ebeling L: Phytotherapy of BPH with Cernilton. Results of a controlled prospective study. Urologe (B) 31:113-116, 1991.

62. Bach D, Ebeling L: Possibilities and limitations of phytotherapy for benign prostatic hyperplasia (BPH): results of treatment with Cernilton N for stages I-III according to Alken (or II-IV according to Vahlensieck). In: Benign Prostatic Diseases. W Vahlensieck, G Rutishauser (eds). Georg Thieme Verlag, Stuttgart, Germany pp 180-187, 1992.

63. Rugendorff EW, Weidner W, Ebeling L, Buck AC: Results of treatment with pollen extract (Cernilton_) in prostatodynia and chronic prostatitis, Br J Urol 71:433-438, 1993.

64. Braun L, Peyer P, Ackermann, et al: A multicentre, placebo-controlled study on the efficacy and tolerability of adenoprostal in patients with benign prostatic hyperplasia (BPH). Tribuna Medica Ticinese, 1993.

65. Yasumoto R, Kawanishi H, Tsujino T, et al: Clinical evaluation of long-term treatment using Cernilton pollen extract in patients with benign prostatic hyperplasia. Clin Ther 17:82-87, 1995.

66. Dutkiewicz S: Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. Int Urol Nephrol 28:49-53, 1996.

67. Monden K, Tsugawa M, Ninomiya Y, Ando E, Kumon H: A Japanese version of the National Institutes of Health Chronic Prostatis Symptom Index (NIH-CPSI: Okayama version) and the clinical evaluation of cernitin pollen extract for chronic non-bacterial prostatitis. Nippon Hinyo Gakkai Zasshi 93:539-547, 2002.

68. National Institutes of Health, "Two-Drug Therapy is Best for Symptomatic Prostate Enlargement, Combination Should Change Clinical Practice", NIH News Release, May 28, 2002 (www.nih.gov/news/pr/may2002/niddk-28.htm).

69. Preuss HG, Marcusen C. Regan J, et al: Randomized trial of a combination of natural products (cernitin, saw palmetto, B-sitosteriol, vitamin E) on symptoms of benign prostatic hyperplasia (BPH). Int Urol and Neph 33:217-225, 2001.

70. Aoki A, Naito K, Hashimoto O, et al: Clinical evaluation of the effect of tamsulosin hydrochloride and cernitin pollen extract on urinary disturbance associated with benign prostatic hyperplasia in a multicentered study. Hinyo Kiyo, 48:259-267, 2002.

71. Cardura® (doxazosin mesylate) Tablets, 70-4538-00-8 www.pfizer.com/hml/pi's/cardurapi.pdf; accessed on 11/24/02.

Effects of pollen extract EA-10, P_5 on chronic prostatitis or infertility with chronic prostatitis

CHEN Hong-Jie [1] , WANG Zhi-Ping [2] , CHEN Yi-Rong, QIN Da-Shan, FU Sheng-Jun, MA Bao-Liang

[1] Now in *1st Renmin Hospital of Lanzhou, Lanzhou 730050, China.*

[2] Corr espondence to Prof WANG Zhi-Ping.

Received 2001- 12-24 Accepted 2002-08-03

Institute of Urology, 2nd Affiliated Hospital of Lanzhou medical College, Lanzhou 730030, China

KEY WORDS prostatitis; infertility; free radicals; pollen

ABSTRACT

AIM: To determine the drug action mechanism of pollen extract EA-10, P_5 on the treatment of chronic prostatitis (CP) or infertility with CP. **METHODS:** Malondiadehyde (MDA), super oxide dismutase (SOD), and nitrogen monoxide (NO) were measured by biochemical assay, and zinc content was assayed by atomical spectrophotography in the pre-treatment and post-treatment of CP or infertility with CP. **RESULTS:** Compared with control group, leukocytes in expressed prostatic secretion (LEPS), MDA, and NO were increased, and zinc content and SOD were decreased significantly in the pre-treatment of CP. After the treatment, LEPS was improved, and MDA and NO were reduced, while zinc content were increased apparently and the alteration of SOD was not evident *(*P>0.05). In the pre-treatment of infertility with CP, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and seminal plasma SOD, zinc content, and sperm motility were obviously lower than those in control group. After the treatment, LEPS, sperm motility, and sperm viability were improved, MDA, NO, and seminal leukocytes were decreased, SOD and zinc content were increased markedly. **CONCLUSION:** There was inter-correlation between oxygen free radicals (OFR) and occurrence, development, and recovery of CP; Change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP.

INTRODUCTION

Chronic prostatitis (CP) is one of t he most common diseases in andrology. Its therapeutic efficacy is not very satisfactory. Recent studies showed that CP might defect semen quality. Thus, it is significant to make an investigation of pathogenesis and medication of CP.

Oxygen free radical s (OFR) which causes tissue damage by lipid peroxidation (LPO)[1], includes mainly super oxide anion (O_2), hydrogen peroxide (H_2O_2), hydroxyl free radical (·OH), and nitrogen monoxide (NO). LPO has yielded several types of secondary free radicals and a large number of reactive compounds (including MDA), resulting in the destruction of cellular portion. Of course, cells are equipped with various antioxidants, such as vitamin E, vitamin C, glutathione (GSH), super oxide dismutase (SOD), catalase (CAT), and so on. These can scavenge supernumerary OFR and protect organism from cytotoxic effect of OFR[2,3]. In addition, there was apparent negative correlation between semen OFR level and semen quality, but with the increasing of semen OFR level and pro-longing of contact time between OFR and sperm, sperm vital force would obviously decrease [4,5]. Studies also showed seminal MDA might be increased apparently in chronic bacterial prostatitis, resulting in the influence of sperm vitality and sperm motility [6,7]. These data indicated that OFR played an important role in pathogenesis of CP and infertility.

EA-10, P_5 is regarded as a satisfactory drug in the treatment of CP. At present, it is still unknown that whether OFR, antioxidase, and zinc content in semen will be regulated in t he treatment of CP or infertility with CP by EA-10, P_5. Therefore, we investigated whether EA-10, P_5 could inhibit LPO, and thus to obtain the primary conclusion about drug action mechanism of EA-10, P_5 in our treatment.

MATERIALS AND METHODS

Population

All 68 cases of CP (group I) and 63 cases of infertility with CP (group II) were divided into two groups, which were then subdivided into three treatment subgroups respectively (group A: EA-10, P_5 + Roxithromycin, group B: EA-10, P_5 alone, and group C: Roxithromycin alone). Twenty cases who were normal healthy donors of proven fertility were used as control group. The treatment period was four weeks. Group A received EA-10, P_5 (product from Sweden Pharmacia Allergon AB, 375 mg/pill) and roxithromycin (150 mg/pill) twice daily. Group B-C received respectively EA-10, P_5 and Roxithromycin twice daily. During the treatment, all 131 cases were treated with sitzing bath in hot water and controlled diet (wine and pungent diet prohibited).

Semen samples and treatment

Semen samples were obtained from all cases by masturbation after 3 d of abstinence. Samples were incubated for 20 min in 37 ºC warm bath box. Firstly, regular semen analysis and seminal MDA content were analyzed after semen has been liquefied completely; Secondly, liquefied semen was centrifuged at 1000×*g* for 10 min, and seminal plasma was used to determine the content of NO and SOD. Finally, surplus seminal plasma was frozen at -20 ºC until further use for zinc content assay.

Determination of seminal MDA content and SOD activity

Seminal MDA content was determined by thiobarbituric acid (TBA) method [8]. SOD activity was measured as the inhibition of nitroblue tetrazolium reduction due to super oxide anion generation by xanthine plus xanthineoxidase [9].

Zinc and NO content in seminal plasma assay

Zinc content was assayed by a method based onatomical spectrophotography [10]. The NO concentration was estimated by a method based on nitrite salt response with sulfanilamide to from diazole, which could appear purplish red color reacting with naphthalene ethylenediamine in the acid conditions. The absorbance of 530 nm was measured [11].

Semen parameters

All semen analysis adopt with color quality analysis system of WLJY-9000, which was devised by skill-trade Company Weili Peking. All parameters were settled down to refer to standard of World Health Organization (WHO) [12].

Statistical

Date were expressed as mean ±SD and analyzed with *t*-test. Value of P<0.05 was considered to be statistically significant.

RESULTS

Changes in symptom and LEPS in CP or infertility with CP After the treatment by EA-10,

P_5 +Roxithromycin, EA-10, P_5 alone, and roxithromyc alone in CP or infertility with CP, remissive rate of symptom was 92 %, 66.67 %, 68.17 %, and 90 %, 61.91 %, 63.64 %, while effective rate of LEPS was 88 %, 57. 14 %, 59.09 %, and 85 %, 52. 38 %, 54. 55 %, respectively. Therapeutic efficacy in group A was significantly higher than that in group B or C *(*P<0. 01) (Tab 1, 2).

Tab 1. Changes in symptom and LEPS in different treated groups of CP. [b]P<0.05 *vs* EA-10, P_5+Roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved.	
		Efficiency	Percent/%	Efficiency	Percent/ %
EA-10, P_5+Roxithromycin	25	23	92	22	88
EA-10,P_5	21 1	4	66.67[b]	12	57.14[b]
Roxithromycin	22	15	68.17[b]	13	59.09[b]

Tab 2. Changes in the symptom and LEPS in different treated groups of infertility with CP. [b]P<0.05 *vs* EA-10, P_5 +roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/%
EA-10, P_5+roxithromycin	20	18	90	17	85

EA-10,P_5	21	13	61.91[b]	11	52.38[b]
Roxithromycin	22	14	63.64[b]	12	54.55[b]

Changes in LEPS, MDA, SOD, Zinc content, and NO in CP Compared with control group, LEPS, MDA, and NO were increased, while zinc content and SOD were decreased significantly in the pre-treatment *(*P<0.01). After the treatment, LEPS and zinc content were improved, while MDA and NO were decreased apparently *vs* pre-treatment *(*P<0.01), but there was no obvious alteration of SOD *(*P>0.05) (Tab 3).

Tab 3. Changes in LEPS, MDA, SOD, Zn $^{2+}$ content, and NO in different treated groups of CP. Mean ±SD. [b]P<0.05, [c]P<0. 01 *vs* control. [d]P>0.05, [f]P<0.01 *vs* pre-treatment at the same group. [h]P<0.05 *vs* EA-10, P_5+Roxithromycin group.

		EA-10,P_5+Roxithromycin					
				EA-10, P_5 *(*n=21)		Roxithromycin *(*n=22)	
	Control *(*n=20)	*(*n=25)					
		pre-treat	post-treat	pre- treat	post-treat	pre-treat	post-treat
LEPS /Hp	3.4±2.1	25±16[b]	5.0±2.8[f]	23±13[b]	7±4[f]	25±14[b]	7±4[f]
MDA/μmol-L^{-1}	4.1±1.1	8.3±1.9[c]	4.3±1.4[f]	8.3±1.7[c]	5.4±1.6[bf h]	8.4±1.8[c]	5.2±1.2[bf h]
Zn^{2+}/mmol-L^{-1}	2.3±0.6	1.2±0.4[b]	1.8±0.5[f]	1.2±0.5[b]	1.6±0.5[f]	1.2±0.4[b]	1.6±0.5[f]
SOD/kU-L^{-1}	20±119	850±118[b]	851±122[d]	838±110[b]	840±113[d]	829±120[b]	831±123[d]
NO/μmol-L^{-1}	4.6±1.6	63±20[c]	39±16[bf]	63±20[c]	45±18[bf]	63±21[c] 4	7±18[bf]

Changes in LEPS, MDA, SOD, Zinc content, NO, and semen parameters in infertility

with CP In the pre-treatment, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and SOD, zinc content, and sperm motility were obviously lower than those in controlled group *(*P<0.01). After the treatment, LEPS, SOD, zinc content, sperm motility, and sperm viability were improved and MDA, NO, and seminal leukocytes were decreased significantly (P<0.01). Compared with the pre-treatment, MDA levels and seminal leukocytes were reduced significantly in group A than these in group B or C in the post-treatment *(*P<0.01) (Tab 4).

Tab 4. Changes in LEPS, MDA, SOD, Zinc content, NO, and Semen parameters in different treated groups of infertility with CP. Mean±SD. [a]P>0.05, [b]P<0.05, [c]P<0.01 *vs* control. [d]P>0.05, [e]P<0.05, [f]P<0.01 *vs* pre- treatment at the same group. [h]P<0. 05 *vs* EA-10, P_5+Roxithromycin groups.

	Control	EA-10,P_5+Roxithromycin					
				EA-10,P_5 (n=21)	Roxithromycin (n=22)		
		(n=20)	(n=25)				
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS/Hp	3.4±2.1	23±13c	6±4f	23±12c	7±5f	23±12c	6±4f
MDA/μmol-L-1	4.1±1.1	9.2±1.6c	5.5±2.1f	9.1±1.9c	7.5±2.4beh	9.1±1.7c	7.2±2.5 bch
Zn2+/mmol-L-	1 2.3±0.6	1.1±0.4c	1.6±0.4bf	1.1±0.4c	1.5±0.4bf	1.1±0.3c	1.4±0.4bf
SOD/kU-L-1	920±119	653±115c	736±125bf	663±91c	727±104bf	660±97c	722±109b f
NO/μmol-L-1	4.6±1.6	78±20c	55±18bf	76±27c	63±27bf	77±25c	61±21bf
10-9 x Sperm density/L-1	76±24	82±49a	79±46ad	79±42a	77±41ad	80±41a	79±40ad
Sperm motility/%	75±12	37±14c	46±14bf	38±17c	43±19bf	37±16	43±18bf
Sperm viability/%	14±8	36±14c	24±10bf	34±14c	28±11bf	34±13c	28±11bf
10-9x Seminal leukocyte	0.5±0.3	1.6±0.9c	0.7±0.4af	1.6±0.8c	0.9±0.4bf	1.6±0.8c	0.9±0.5bf

DISCUSSION

In this test, we have used EA-10, P_5 and roxithromycin to treat CP and infertility with CP.

Roxithromycin has a good effect to chlamydia besides much of Gram-negative bacteria [13]. Therapeutic efficacy was lower in our works than that in literature. But our therapeutic efficacy was still satisfactory. We considered that the reason may be as follows: (1) Chronic bacterial prostatitis may be selected in all the chosen cases, which might influence therapeutic efficacy of EA-10, P_5.

(2) The treatment period was shorter compared with that illustrated in literature. In addition, we have found that therapeutic efficacy in group A was better than in group B or C. This indicated that EA-10, P_5 should be used together with effective antibiotic in the treatment of CP.

Some studies have proved that OFR was related to occurrence and development of CP[3- 4,14]. In our studies, MDA was higher and SOD was lower significantly in the pre-treatment of CP than those in the control group, which suggested that there be an increase of OFR, a decrease of antioxidation, and reinforce a of LPO. But MDA was decreased after the treatment, indicated that OFR was scavenged massively and LPO was obviously inhibited.

Similarly, MDA was higher and SOD was lower significantly in pre-treatment of infertility with CP than those in the control group, which suggested that oxidation be increased and antioxidation be decreased in semen. At the same time, we discovered that sperm motility was declined and sperm viability was raised significantly. But after the treatment, MDA was decreased and SOD was increased significantly than those in the pre-treatment (P<0.01), accompanying with improvement of sperm motility and sperm viability apparently. This indicated that LPO was inhibited andantioxidation was reinforced. From the result above, we believed that EA-10, P_5 could reduce LPO and enhance antioxidation in the treatment of CP or infertility with CP.

In our treatment, antibiotic and EA-10, P_5 were used not only to cure CP but also to improve semenquality. We found that EA-10, P_5 had an effect on weakening oxidative stress and increasing

antioxidation in prostatic secret ion and semen. This suggested that change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP. At present, it is known that ferulic acid was an antioxidant containing phenolic hydroxyl [15]; and P_5, one of valid portion in pollen extract EA-10, P_5, may have anti-oxidative effect owing to providing phenolic hydroxyl too. Nevertheless this view still needs to be confirmed by more investigation.

It was reported that zinc content in prostatic secretion and semen was higher than in other organand body fluid, which showed that zinc played an important role in keeping function of prostate and other accessory sex glands. Our studies showed that zinc content was increased accompanying with improvement of an illness state. EA-10, P_5 can enhance zinc content in seminal plasma, which may be related to improve local circumstance.

In summary, all these results could provide us with a possible therapeutics approach to treat infertility with CP. In order to improve therapeutic efficacy, anti-infection and anti-oxidation should be adopted in the treatment of CP or infertility with CP.

REFERENCES

1. Aitken RJ, Harkiss D, Buckingham DW. Analysis of lipid peroxidation mechanisms in human spermatozos. Mol Reprod Dev 1993; 35: 302-11.

2. de Lamirande E, Gagnon C. Human sperm hyperactivation in whole semen and its association with low super oxide scavenging capacity in seminal plasma. Fertil Steril 1993; 59: 1291-5.

3. Yu JH, Zhang YSH. Zinc and SOD activity in seminal plasma of chronic prostatitis patients. Chin J Urol 1992; 13: 181-3.

4. Mazzilli F, Rossi T, Marchesini M, Ronconi C, Dondero F. Superoxide anion in human semen related to seminal paramenters and clinical aspects. Fertil Steril 1994; 62: 862-8.

5. Zini A, Garrels K, Phang D. Antioxidant activity in the semen of fertile and infertile men. Urology 2000; 55: 922-6.

6. Chen GW, Zheng S, Wu YL, Qian XM, Leng J, Cao XR, *et a*l. The study of relationship between seminal leukocyte and sperm function. Chin J Androl 1998; 12: 82-5.

7. Pasqualotto FF, Sharma RK, Potts JM, Nelson DR, Thomas AJ, Aqarwal A. Seminal oxidative stress in patients with chronic prostatitis. Urology 2000; 55: 88-5.

8. Zheng RL, Zhang H. Effects of ferulic acid on fertile and asthenozoospermic infertile human sperm motility, viability, lipid peroxidation, and cyclic nucleotides. Free Radic Biol Med 1997; 22: 581-6.

9. Zhang JP, Meng QY, Zhang LJ, Mao YL, Sun ZX. Effect of smoking quality of infertile men in Shangdong, China. Asian J Androl 2000; 2: 143-6.

10.Kang LX. Treatment of chronic prostatitis with electric conduction of Zinc ion. Chin J Urol 1996; 17: 168-70.

11.Wang Q, editors. Experimental method of modern medicine. 1st ed. Beijing: People's Medical Publishing House; 1997. p 218-20.

12.WHO Laboratory manual for the examination of human semen and Sperm-cervical mucus interaction. 3rd ed. Cambridge: Cambridge University Press; 1992. p 8-9.

13.Nickel J C, Downey J, Clark J, Ceri H, Olson M. Antibiotic pharmacokinetics in the inflamed prostate. J Urol 1995; 153: 527-9.

14.Zhang H, Chen FY, Zheng RL. Sperm viability and sperm peroxidation in infertile patients and male fertile volunteers. Chin J Urol 1997; 18: 368-70.

15.Ju HS, Li XJ, Zhao BL, Hou JW, Han ZHW, Xin WJ. Scavenged effect of sodium and β-enoxolone to oxygen free radicals.81 Chin J pharmacol 1990; 11: 466-71.

Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats

Toshiyuki Kamijo,[1*] Shiegeru Sato, [2] and Tadaichi Kitamura[1]

[1] *Department of Urology, Faculty of Medicine, University of Tokyo, Japan*

[2] *Ohme Research Laboratories, Tobishi Pharmaceutical Co., Ltd., Tokyo, Japan*

BACKGROUND

The treatment for chronic nonbacterial prostatitis (NBP) has not been established. Cernitin pollen extract (CN-009) is reported to have therapeutic effects for NBP. The effects and mechanisms of CN-009 were investigated.

METHODS

Ten-month-old rats were used with administration of estradiol after castration, which were similar to human NBP histologically. Since CN-009 consists of T-60 and GBX, these drugs were administered, respectively. The prostate was evaluated histopathologically including glandular damage (epithelial score), stromal ratio and immunohistochemical assays for epithelial function (PAP), stromal evaluation (Vimentin), cell proliferation (PCNA) and apoptosis (deoxyuridine triphosphate biotin nick end-labeling (TUNEL)).

RESULTS

Controls revealed severe acinar gland atrophy and stromal proliferation. CN-009 showed diminished these damages. Epithelial score was better ($P<0.01$) and PAP positive materials were more abundant in CN-009 and GBX than in Controls. The stromal ratio was lower in CN-009 ($P<0.01$) and T-60 ($P<0.05$). There was no difference for PCNA positive cells in the epithelium and stroma, and TUNEL positive cells in the epithelium. While, the number of TUNEL positive cells in the stroma of CN-009 and T-60 increased ($P<0.01$).

CONCLUSIONS

These findings suggest that CN-009 protects acinar epithelial cells mainly by GBX and also inhibits stromal proliferation in association with enhanced apoptosis mainly by T-60. *Prostate 49: 122-131, 2001.*

KEY WORDS: Cernitin pollen-extract; apoptosis; chronic prostatitis; sex-hormone-induced prostatitis

INTRODUCTION

Three chronic prostatitis syndromes have been recognized; chronic bacterial prostatitis (CBP), chronic nonbacterial prostatitis (NBP) and prostatodynia. NBP is the most frequent disorder of 64% in these three diseases [1]. The etiology of NBP is unknown. A number of organisms or other factors have been reported to be the possible causes for NBP. They are *Trichomonas vaginalis*, *Chlamydia trachomatis*, genital mycoplasmas, staphylococci, coryneforms, genital viruses [2], biofilms [3], stagnation of prostatic secretion, autoimmune disease, allergy, disorder of sex hormone and psychological effects [4, 5]. For the treatment of CBP or NBP, antibiotics of new-quinolone or tetracycline have been administered.
However, many cases resist these treatments [6].

Cn-009 is a pollen extract, which contains 20:1 ratio of powdered aqueous and organic extract. It is essentially a microbial digest of a standardized mixture of eight plant species grown at the Scania area in southern Sweden. The active ingredients consist of water-soluble (t-60) and fat-soluble (GBX) fractions [7, 8]. It was reported that CN-009 showed urine discharge action [9.10], anti-prostatic hypertrophic action [7] and anti-inflammatory effects to the prostate [11] in a preliminary study. Since Ask-Upmark [12] Reported CN-009 showed an efficacy to prostatitis, it has been used for the treatment of chronic prostatitis with high therapeutic effects. However, the mechanisms for these effects remain unknown.

To assess the mechanisms of the anti-prostatitis effect by CN-009, the present study was performed using a nonbacterial prostatitis rat model [13, 14] induced by 17b -estradiol administrations and castration.

MATERIALS AND METHODS

Sex Hormone-Induced Nonbacterial

Table 1. The structure of the Experiment

Group	No. of animals	Inflammatory agent	Drug treatment
Sham-ope.	5	No-treatment	No-treatment
Control	6	17 b-estradiol 0.25 mg/kg (s.c.)	1% HCO-60 (p.o.)
CN-009 630	5	17 b-estradiol 0.25 mg/kg (s.c.)	CN-009 630 mg/kg (p.o.)
CN-009 1260	6	17 b-estradiol 0.25 mg/kg (s.c.)	CN-009 1260 mg/kg (p.o.)
T-60	5	17 b-estradiol 0.25 mg/kg (s.c.)	T-60 1200 mg/kg (p.o.)
GBX	6	17 b-estradiol 0.25 mg/kg (s.c.)	GBX 60 mg/kg (p.o.)
TS	5	17 b-estradiol 0.25 mg/kg (s.c.)	Testosterone 2.5 mg/kg (s.c)

Each parenthesis represents the route of administration. s.c, subcutaneous injection; p.o., oral administration

Prostatitis Model

Ten-month-old Wistar aged male rats were purchased from Japan Slc Co. (Tokyo, Japan).

The rats were housed in a climatised environment with a 12-hr light/dark cycle, 40-70% humidity. Food and water were supplied ad libitum. The rats were castrated under ether anesthesia, and then 17b-estradiol (Sigma, MI) 0.25 mg/ 2ml/kg diluted by sesame oil, as an inducer for prostatitis, was subcutaneously injected into the back of rats for 30 days from 1 day after castration [13,14].

Experimental Structure and Schedule

CN-009was suspended for 630 or 1,260 mg/5ml with 1% HCO-60 (Japan Surfactant, Tokyo, Japan). T-60 and GBX were similarly prepared for 1,200 and 60-mg/5 ml, respectively. Testosterone (TS) (Wako Chemicals, Tokyo, Japan), as a positive control, was diluted for 2.5-mg/2 ml with corn oil (Yuro Chemical, Tokyo, Japan).

The experimental structure is shown in Table I and the experimental schedule is illustrated in Figure 1. The rats were divided into seven groups consisting of Sham-operation (Sham-ope), Control, CN-009 630, CN-009 1260, T-60, GBX and TS with five or six animals in each group.

In the Sham-ope group, the rats were treated with only Sham-castration and without any drugs. In the Control group, the rats were injected subcutaneously environment with a 12-hr light/dark cycle, 40-70% humidity. Food and water were supplied ad libitum. The rats were castrated under ether anesthesia, and then 17b-estradiol (Sigma, MI) 0.25 mg/ 2ml/kg diluted by sesame oil, as an inducer for prostatitis, was subcutaneously injected into the back of rats for 30 days from 1 day after castration [13,14].

Experimental Structure and Schedule

CN-009 was suspended for 630 or 1,260 mg/5ml with 1% HCO-60 (Japan Surfactant, Tokyo, Japan). T-60 and GBX were similarly prepared for 1,200 and 60-mg/5 ml respectively. Testosterone (TS) (Wako Chemicals, Tokyo, Japan), as a positive control, was diluted for 2.5-mg/2 ml with corn oil (Yuro Chemical, Tokyo, Japan)

The experimental structure is shown in Table I and the experimental schedule is illustrated in Figure 1. The rats were divided into seven groups consisting of Sham-operation (Sham-ope), Control, CN-009 630, CN-009 1260, T-60, GBX and TS with five or six animals in each group.

In the Sham-ope group, the rats were treated with only Sham-castration and without any drugs. In the Control group, the rats were injected subcutaneously With 17b-estradiol for 30 days from the day following castration and administered orally with only 1% HCO- 60 5ml/kg for 14 days from Day 17. In the CN-009 630, CN-009 1260, T-60 1200 and GBX groups, similar protocols were performed with oral administration of CN-009 630, CN-009 1260, T-60 1200 and GBX 60 mg/kg, respectively. Also in the TS group, the rats were subconsciously with 17b-estradiol for 30 days from the next day of castration. After 14 days, TS 2.5 mg/kg was injected subconsciously for 14days. All studies were conducted in accordance with institutional guidelines of animal care in accordance with Japanese Governmental Animal Protection and Management Law.

Prostate Weights and Histopathological Evaluation

The rats were sacrificed on the day following the final administration. The prostate was extirpated and weighed. Relative prostatic weight was calculated from body weight and absolute weight.

After fixation in 10% neutral buffered formalin, each prostate was cut into coronal blocks. The tissue samples were dehydrated and embedded in paraffin. Sections (3-4 mm thickness) were stained with Hemotoxyline-Eosin (HE), Periodic acid Shiff (PAS) and Masson's tri-chrome. The specimens were evaluated histopathologically.

Immunohistochemistry

Immunohistochemical studies were performed with anti-prostatic cid phosphatase (PAP), and vimentin. PAP staining was performed for the evalutation of glandular epithelial function. In PAP stained specimens, anti-PAP polyclonal antibody (Chemicon International, New York, NY) was diluted by PBS including 0.1% BSA of a 1:100 ratio, and incubated for 2 hr at 37°C. Biotinylated anti-rabbit IgG and the avidin-biotin peroxidase complex (ABC) method were performed. Unitect rabbit Immunohistochemistry detection systems (Oncogene Science, New York, NY) were reacted by those methods. Vimentin staining was performed for the evaluation of stromal proliferation. An ImmunoCruz staining system (Santa Cruz BioTech, Santa Cruz, CA) for Vimentin Staining was used according tot eh manufacture's instructions.

Cell Proliferation and Apoptosis

Cell proliferation and apoptosis were investigated with proliferating cell nuclear antigen (PCNA) and terminal deoxynucleotidyl transferase mediated deoxyuridine tri phosphate biotin nick end-labeling (TNEL), respectively. PCNA staining was performed with PCNA staining kit (ZYMED Laboratories, South San Francisco, CA). TUNEL method was performed with ApoTag Peroxidase In Situ Apoptosis Detection kit (Intervene, New York, NY). In PCNA and TUNEL specimen, 5,000 cells were countedunder a microscope in glandular epithelial cells and stromal cells respectively.

Acinar Epithelial Score and Stromal Area Ratio

To evaluate glandular damage, acinar epithelial cells were classified and scored, as follows; columnar (2 points), cuboidal (1 point), squamous-like (0 point) shape. Three different pathologists without any information judged the score. Using this scoring evaluation, 20 acinar glands of each specimen were investigated. To assess stromal proliferation, all areas of the specimen and the glandular area were measured using a digitizer (Graph Tech, Tokyo, Japan) with photomicrographs. Using these findings, the stromal ratio was calculated.

Statistical Analysis

All experiments were repeated at least twice. Each value was demonstrated as the mean±SD. Dunnett's test if in equal variance, or non-parametric Dunnett's test if in unequal variance between treatment groups and Control group was performed after 1-way ANOVA followed by Bartlett variance analysis test. Mann-Whitney U test was performed between the Sham-ope and Control groups.

RESULTS

Body and Prostate Weights

(Fig. 2)

In the Sham-ope group, the prostate was larger than in other groups. Acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials. Acinar epithelial cells were cylindrical with a normally situated nucleus and the supranuclear spaces of these cells contained secretory materials, which were strongly stained with PAP antibody. A few fibrous tissues were found in the stroma (Figs. 3A and 4A). Vimentin positive cells were few, and the Vimentin positive was small (data not shown).

In the Control group, the prostate was atrophic acinar glands were irregularly shaped. The acinar lumen was poor with pale stained eosinophilic materials and filled with inflammatory cell infiltrations mainly characterized by neutrophils. Acinar epithelial cells were flattened similar to a squamos cell. A few secretory materials in the epithelial cells were poorly reacted with PAP antibody. The stroma showed severe proliferation with many lymphocyte and monocyte infiltrations and

marked fibrosis with fibroblasts (Figs. 3B and 4B). The stroma was stained very strongle with Vimentin. The Vimentin positive area was significantly increased (data not shown). In the CN-009 630 group, the findings were basically identical with the Control group (data not shown).

In the CN-009 1260 group, acinar glands were more roundly shaped than in the Control group. Acinar epithelial cells were cuboidal, and the supranuclear spaces contained secretory materials stained with anti-PAP that were much more abundant than the in control group. Inflammatory cell infiltrations into the acinar lumen were diminished. The stroma showed mild proliferation with few lymphocytes, monocytes, and mild fibrosis with fibroblasts (Figs. 3C and 4C). The Vimentin positive area was much less than that of the Control group (data not shown).

In the GBW group, acinar epithelial cells were more cuboidal than in the Control group. Epithelial cells contained secretory materials stained with anti-PAP, which was basically identical with the CN-009 1260 group. Diminished call infiltration into the lumen was found (Fig. 3E). However, the stroma showed a proliferative condition with many lymphocyte and monocyte infiltrations and marked fibrosis with many fibroblasts. The stroma was stained strongly with Vimentin, and the positive area was markedly increased (data not shown).

In the TS group, acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials with a few cell infiltrations. Acinar epithelial cells were cylindrical and the supranuclear spaces contained many secretory materials with reactive anti-PAP. However, the stroma was stained strongly with Vimentin and showed mild proliferation with fibroblasts (data not shown).

Cell Proliferation and Apoptosis

(PCNA and TUNEL Positive Cell Counts (Fig. 5))

No significant differences among the groups were observed in the PCNA positive cell counts in epithelial cells (Fig. 6) or in stromal calles (Fig. 7). In the Sham-ope group, a few TUNEL positive cells were found (Fig. 5A). The findings of the Control group were basically identical with the Sham-ope group (Fig. 5B). In the CN-009 1260 group, TUNEL positive cells in the stroma were more abundant than in the Sham-ope and Control groups (Fig. 5C). In the TUNEL positive cell counts, no significant differences were observed in acinar epithelial cells (Fig. 8). However, in the stroma, TUNEL positive cells were significantly ($P < 0.05$)

Fig. 3. HE staining of the prostate in the experimental nonbacterial prostatitis rat. (**A**) Sham-ope group: The acinar lumen is filled with eosinophilic materials without any cells. Acinar epithelial cells are cylindrical. A few fibrous tissues are found in the stroma. (**B**) Control group: The acinar lumen is filled with induced inflammatory cells mainly characterized by neutrophilis. Acinar epithelial cells are flattened similar to squamous cells. The stroma shows severe proliferation with many lymphocyte and monocyte infiltrations and remarkable fibrosis with fibroblasts. (**C**) CN-009 1260 group: Acinar epithelial cells are cuboidal. Inflammatory cell infiltrations into the acinar lumen are diminished. The stroma shows mild proliferation with a few lymphocytes, monocytes, and fibroblasts. (**D**) T-60 group: Stromal proliferation is relatively mild without severe inflammatory cells. (**E**) GBX group: Acinar epithelial cells are cuboidal, and diminished inflammatory cell infiltrations are shown. 400 The bar indicates 10 mm.

Increased in the CN-009 1260 group or T-60 group compared with the control group (Fig. 9).

Acinar Epithelial Score (Fig. 10)

In the Control group, acinar epithelial score was significantly lower ($P > 0.01$) than that of the

Sham-ope group. In comparison with the Control group (Fig. 10), the acinar epithelial score was significantly higher ($P < 0.01$) in the CN-009 1260, GBX and TS groups.

Stromal Area Ratio (Fig. 11)

In the Control group, the stroma area ratio was significantly higher ($P < 0.01$) than that of Sham-ope group.

Fig. 4. Immunohistochemical findings (PAP Staining) of the prostate in experimental nonbacterial prostatitis rats. (A) Sham-ope group: Supranuclear spaces of acinar epithelial cells contain secretory materials which are stained with anti-PAP. (B) Control group: Acinar epithelial cells are flattened similar to squamous cell. Secretory materials are poorly reactive with anti-PAP. (C) CN-009 1260 group: Supranuclear spaces contained secretory materials with PAP staining, which are significantly more abundant than in the Control group. ´400 the bar indicates 10 mm.

In comparison with the Control group (Fig. 11) the stromal area ratio of the CN-009 1260 was significantly ($P < 0.01$) lower. The T-60 group was also significantly ($P < 0.05$) lower than the Control group. However, there was no difference between other groups.

Fig. 5. Immunohisochemical findings (TUNEL) of the prostate in rats. (A) Sham-ope group: A few TUNEL positive cells are shown. (B) Control group: The findings are basically identical to these of the Sham-ope group. (C) CN-009 1260 group: TUNEL positive cells in the stroma are more abundant compared with the Sham-ope and Control groups. **´400 the bar indicates 10 mm**

Discussion

Although chronic prostatitis is a common disease, it is very difficult to treat effectively. Typical clinical findings are decreased potentia, perineal or scrotal pain, urethral discharge and lower urinary tract irritative symptoms. The prostate gland is irregularly indurated and the numbers of leukocytes in expressed prostatic secretion are increased [15]. Pathological findings of this disease are chronic inflammation characterized by aggregates of lymphocytes in the stroma and acute inflammation characterized by the presence of neutrphic polymorphonnuclear leukocytes in the lumen of acinar glands [15 – 17]. Pathological definition of chronic prostatitis is different from the clinical definition for the urologists. Clinical definition has been the combination of a clinical symptom and inflammatory cells in expressed prostatic secretion. The pathological inflammation of the prostate was repoted to be not frequent in the patients with symptoms of chronic prostatitis/chronic pelvic pain symdrome [16].

In experimental animals, Lewis, Wistar and Copenhagen rats have a high incidence of spontaneous nonbacterial prostatitis [14]. Administration of exogenous 17b-estradiol can induce 100% of the incidence on prostatitis in old Wistar rats [18] and castration also has a similar effect [13, 18]. Naslund et al. [13] reported that histopathological findings were very similar between spontaneous nonbacterial prostatitis and estradiol-induced prostatitis in rats [13]. These histopathological findings in rat spontaneous age-dependant prostatitis demonstrated several similarities to pathological defined chronic prostatitis in humans [19, 20]. These findings suggested that this rat model would be a useful model for the study of the treatment of human chronic prostatitis. Therefore, we decided to investigate the effects and mechanisms of CN-009 using a nonbacterial prostatitis rat model [13, 14] induced by 17b-estradiol injection and castration.

No differences in the prostate weight were found in CN-009 630, CN-009 1260, T-60 and GBX groups compared with the Control group. Since the weight of the prostate is mostly determined by the amount of residual secretory fluid, these

findings may indicate that CN-009 cannot prevent the reduction of secretory prostatic fluid.

In the CN-009 1260 group, we observed roundly shaped acinar glands, cuboidal acinar epithelial cells containing secretory materials with positive PAP staining and diminished cell infiltrations into the lumen compared with the Control group. The acinar epithelial score was significantly increased. CN-009 could protect acinar epithelial function and cell shape against nonbacterial inflammation. GBX had a similar effect to CN-009 in the acinar glands. T-60 was not effective in the acinar epithelial function of this rat model. Therefore, GBX may play a role for the protection of epithelial damage in NBP. The effect of GBX is discriminated from TS effect. In an in vitro study, GBX was reported to inhibit the cyclooxygenases and 5-lipooxygenases in the biosynthesis of the prostaglandins and leucotriens enhance inflammatory cell infiltrations, GBX may protect against inflammation into the acinar lumen by inhibition of these enzymes. Furthermore, CN-009 showed an inhibition on the heat-induced hemolysis, which is correlated to lysosomal membrane stability [11]. CN-009 appears to stabalize a lysosomal membrane, recover cell function and protect against degeneration of the acinar epithelium.

In addition, T-60 was shown to inhibit the growth of an immortal prostate cancer cell line in vitro [22]. However, their mechanisms are unknown. In the present study, the ratio of stromal area was significantly decreased in the CN-009 1260 and T-60 groups. Stromal TUNEL positive cell counts were increased in these groups. Therefore, CN-009 and T-60 may inhibit stromal cell proliferations by enhanced apoptosis. Although the exact mechanism of this process is unclear, several speculations are possible such as the direct effect by the apoptosis of fibroblast, and the indirect effect by the apoptosis of lymphocytes through the inhibition of several cytokines, such as several interleukins. Further laboratory studies are necessary to elucidate the exact mechanisms of this compund.

Since no toxicological effects have been shown even in long-term administration, CN-009 is thought to be a safe drug [6, 23]. Here we reported the effects and mechanisms of CN-009 on rat experimental nonbacterial prostatitis model. CN-009 will also be a safe and effective agent against human nonbacterial chronic prostatitis.

In conclusion, CN-009 can work as a potent anti-inflammatory agent against chronic prostatitis. These present findings suggest that GBX, a fat-soluble fraction of CN-009, protects the function and shape of acinar glandular epithelium and T-60, a water-soluble fraction of CN-009, inhibits stromal cell proliferations in association with enhanced apoptosis.

Acknowledgments

We thank M. Komukai, M. Ishii, F. Kimura and E. Higaki for their technical assistance.

References

1. Brunner H, Weinder W, Scheifer HG. Studies on the role of Ureaplasma urealyticum and Mycoplasma hominis in prostatitis. J Infect Dis 1983; 147:807-813.

2. Domingue GJ, Hellstrom WJ. Prostatitis. Clin Microbiol Rev 1998; 11:604-613.

3. Arakawa S, Matsui T, Gohji K, Okada H, Kamdono S. Prostatitis- the Japanese view point. Int J Antimicrob Agents 1999; 11:201-203.

4. Donovan DA, Nicholas PK. Prostatitis; diagnosis and treatment in primary care. Nurse Practitioner 1997; 22:144-156.

5. Pewitt EB, Schaeffer AJ. Urinary tract infection in urology; including acute and chronic prostatitis. Infect Dis Clin North Am 1997; 11:623-646.

6. Jodai A, Maruta N, Shimomae E, Sakuragi T, Shindo K, Saito Y. A long term therapeutic experience with Cernilton in chronic prostatitis. Acta Urol Jpn (Jpn.) 1988; 34:561-568.

7. Ito R, Ishii M, Yamashita S, Noguchi K, Ohkubo Y, Tsushima Y, Sato S, Akamatsu H, Antiprostatic hypertrophic action of Cernitin pollen-extract (Cernilton). Pharmacometrics (Jpn.) 1986; 31:1-11.

8. Shah PJR. The treatment of disorders of the prostate with the rye-grass extract Prostabrit. Comp Therp Med 1996;4:21-25.

9. Onodera S, Yoshinaga M, Takenaga K, Toyoshima A, Uchiyama T. Effects of Cernitin pollen extract (CN-009) on the isolated bladder smooth muscles and the intravesical pressure. Folia pharmacol Japon (Jpn.) 1991; 97:267-276.

10. Nakase K, Takenaga K, Hamanaka T, Kimura M. Inhibitory effect and synergism of Cernitin pollen extract on the urethral smooth muscle and diaphragm of the rat. Folia pharmacol Japon (Jpn.) 1988; 91:385-392.

11. Ito R, Noguchi K, Yamashita S, Namikata S, Takenaga K, Yosinaga M, Shimuzu K, Ishii M, Mori N. Anti-inflammatory effects of Cernitin pollen-extract (Cernilton). Pharmacometrics (Jpn.) 1984; 28:55-65.

12. Ask-Upmark E. On a new treatment of prostatitis. Grana Palynologica 1960; 2:115-118.

13. Naslund MJ, Strandburg JD, Coffey DS. The role of androgens and estrogens in the pathogenesis of experimental nonbacterial prostatitis. J Urol 1966; 96:519-533.

14. Robinette CL. Sex-hormone-induced inflammation and fibromuscular proliferation in the rat lateral prostate. The Prostate 1988; 12:271-286.

15. Schmidt JD, Patterson MC. Needle biopsy study of chronic prostatitis. J Urol 1966; 96:519-533.

16. True LD, Berger RE, Rothman I, Ross SO, Krieger JN. Prostate histopathology and the chronic prostatitis/ chronic pelvic pain syndrome: a prospective study. J Urol 1999; 162:2014-2018.

17. Aumüller G, Enderle-Scmitt U, Seitz J, Müntzig J, Chandler JA. Ultrastructure and immnohistochemistry of the lateral prostate on aged rats. The Prostate 1987; 10:245-256.

18. Seethalakshmi L, Bala RS, Malhotra RK, Austin-ritchie T, Miller-Graziano C, Menon M, Luber-Narod J. 17 β-Estradiol induced prostatitits in the rat is an autoimmune disease. J Urol 1996; 156:1838-1842.

19. Lundgren R, Holmquist B, Hesselvik M, Müntzig J. Treatment of prostatitis in the rat. The Prostate 1984; 5:277-284.

20. Müntzig J, Sufrin G, Murphy GP. Prostatitis in the rat. Scand J Urol Nephrol 1979; 13:17-22.

21. Loschen G, Ebeling L. Hemmung der Arachidonsaure-Kaskade durch einen Exrakt aus Roggenpollen. Arzneim-Forsch Drug Res 1991; 41:162-167.

22. Habib FK, Ross M, Buck AC, Ebeling L. Lewenstein: in vitro evaluation of the pollen extract, Cernitin T-60, in the regulation of prostate cell growth. Br J Urol 1990; 66:393-397.

23. Rugendorff EW, Weinder W, Ebeling L, Buck AC. Results of treatment with Pollen extract (Cernilton N) in chronic prostatitis and prostatodynia. Br J Urol 1993; 71:433-438.

Cheng HJ *et al* / Act a Pharmacol Sin 2002 Nov; 23 (11): 1035-1039

Ó2002, Act a Pharmacologica Si nica

ISSN 1671-4083

Shanghai Institute of Materia Medica

Chinese Academy of Sciences

http:/ /www.ChinaPhar.com

Phytotherapy in Chronic Prostatitis

Daniel A. Shoskes

Cleveland Clinic Florida, Weston, Florida, USA
Urology, Volume 60, Issue 6, Supplement 1, December 2002,

Abstract

Chronic prostatitis is a very common condition that is poorly understood and has a significant impact on quality of life. Given the lack of proven efficacy of conventional therapies, such as antibiotics, it is not surprising that patients have turned with increasing frequency to phytotherapy and other alternative treatments. Although alternative therapies are plentiful, few have been subjected to scientific scrutiny and prospective controlled clinical trials. This review will cover phytotherapies commonly used in prostatitis patients and focus in detail on those with published data. These treatments include zinc, cernilton (bee pollen), quercetin, and saw palmetto. Although many of these therapies appear promising in small preliminary studies, phytotherapy requires the same scientific criteria for validation and acceptance as do conventional medical therapies.

Article Outline

All prostatitis researchers can agree that patient and physician dissatisfaction over the management of this disease is high. It is not surprising, therefore, that patients often seek alternative forms of therapy. Phytotherapy, the use of plant-derived or "herbal" products, is gaining popularity in North America and is already the treatment of choice for many chronic conditions in Europe and Asia. Advantages of phytotherapy include (1) unique mechanisms of action, (2) typically low side-effect profiles, (3) low cost, and (4) a high level of acceptance by patients. A large disadvantage of phytotherapy in the United States is lack of US Food and Drug Administration (FDA) oversight, and indeed, consumer watchdog groups have found that many herbal preparations do not contain what is claimed on the label. Other disadvantages include (1) unknown drug interactions (sometimes leading to catastrophic results[1]), (2) no side-effect data collection, and (3) meaningless labels (to circumvent FDA regulations), such as "supports prostate health" or "promotes normal bladder function."

Alternative herbal-based therapies are prevalent and popular in urologic disease in general and prostatic disorders in particular. Typical herbal

therapies recommended for benign prostatic hypertrophy (BPH) with some clinical evidence of efficacy include saw palmetto (*Serenoa repens*), stinging nettle (*Urtica dioica*), and *Pygeum africanum*.[2] Bee pollen extract (cernilton) has also been used with less evidence of efficacy for BPH. [3] Given the overlap of lower urinary tract symptoms between BPH and chronic prostatitis, these agents, either alone or in combination in "prostatic health" formulations, have also been recommended for men with prostatitis.

In patients with documented recurrent bacterial prostatic infection (category II), prolonged antibiotics remain the mainstay of therapy. Prolonged antibiotic use can alter intestinal flora, and use of probiotics (live beneficial bacteria) may reduce the incidence of gastrointestinal side effects.[4] Many men with category II prostatitis have recurrent urinary tract infections, and there is considerable interest in cranberry juice to treat cystitis in women, although randomized placebo-controlled data are lacking. [5] Cranberry juice may reduce *Escherichia coli* adherence and biofilm load in uroepithelial cells.[6] There are no published data on the efficacy of cranberry juice in prostatic infections, however, and it is possible that the acidity of the product could actually exacerbate symptoms. Zinc was one of the first factors with an antimicrobial effect to be identified in seminal plasma. [7] The initial discovery that many men with chronic bacterial prostatitis have low levels of zinc in the semen has led to the long-standing recommendation for zinc supplements in men with all forms of prostatitis. Unfortunately, oral intake of zinc does not appear to increase zinc levels in semen. [8] There are no published clinical trials that demonstrate the efficacy of zinc supplements for either treating or preventing prostatitis.

Category III (chronic pelvic pain syndrome [CPPS]) is the most common and enigmatic prostatitis syndrome. In the absence of infection, there is evidence for an inflammatory or autoimmune component to CPPS in some patients. Even in the absence of visible white blood cells, expressed prostatic secretions and semen of men with CPPS have elevated levels of inflammatory cytokines and oxidative stress.[9, 10, 11 and 12] Phytotherapy has been used most commonly in this category of prostatitis, and evidence for efficacy is actually more compelling than for other standard therapies.

Cernilton, an extract of bee pollen, has been used in prostatic conditions for its presumed anti-inflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement.[13] In a larger more recent open-label study, 90 patients received 1 tablet of cernilton N 3 times daily for 6 months. [14] Patients with complicating factors (prostatic calculi, urethral stricture, bladder neck sclerosis) had minimal response, with only 1 of 18 showing improvement. In the "uncomplicated" patients, however, 36% were cured of their symptoms and 42% improved. Symptomatic improvement was typically associated with improved uroflow parameters, reduced inflammation, and a decrease in complement C3/coeruloplasmin in the ejaculate. Side effects in studies of cernilton for BPH and prostatitis have been negligible.

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea, and onions.[15] It has documented and anti-inflammatory properties and inhibits inflammatory cytokines implicated in the pathogenesis of CPPS, such as interleukin-8. [16] In a preliminary small open-label study, quercetin at 500 mg 2 times daily gave significant symptomatic improvement to most patients, particularly those with negative expressed prostatic secretions cultures. [17] This was followed by a prospective, double-blind, placebo-controlled trial of quercetin 500 mg 2 times daily for 4 weeks using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as the primary endpoint. [18] Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8, and

those taking quercetin had a mean improvement from 21.0 to 13.1 (P = 0.003). In all, 20% of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement in symptoms of $\geq$25%. A third group of patients received Prosta-Q (Farr Cabs, Santa Monica, CA), a commercial formulation containing quercetin with bromelain and papain, digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% had a significant improvement in symptoms.

Saw palmetto is the most commonly used phytochemical for lower urinary tract symptoms and BPH, and indeed, some of the clinical studies with entry criteria based on symptoms likely included patients with CPPS. There have been no published studies of saw palmetto use in CPPS. A poster presented at the 2001 American Urological Association meeting compared therapy with saw palmetto or finasteride in CPPS patients for 1 year.[19] Although there was some improvement seen in the finasteride group, there was no improvement in the saw palmetto group.

Traditional Chinese medicinal therapies typically use acupuncture and herbal preparations. There are some publications with English abstracts that suggest significant improvement with this approach, although it is difficult to interpret formulation composition, entry criteria, and endpoint measures.[20]

In summary, phytotherapy shows much promise for prostatitis patients. In category II, probiotics can reduce the gastrointestinal side effects of prolonged antibiotic use. In category III, cernilton and quercetin have documented effects in both patient-reported improvement and improvement in biochemical markers of inflammation. Zinc, saw palmetto, and other agents used in BPH, such as stinging nettle and *Pygeum africanum*, do not have evidence for efficacy in CPPS. It is important that these phytotherapeutic approaches, and others, such as traditional Chinese medicine, be evaluated in prospective, randomized placebo-controlled trials with defined entry criteria and validated endpoints.

References

1. F. Ruschitzka, P.J. Meier, M. Turina *et al.*, Acute heart transplant rejection due to Saint John's wort. *Lancet* **355** (2000), pp. 548–549.

2. T.J. Wilt, A. Ishani, I. Rutks *et al.*, Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr* **3** (2000), pp. 459–472.

3. Wilt T, Mac Donald R, Ishani A, *et al*: Cernilton for benign prostatic hyperplasia. Cochrane Database Syst Rev CD001042, 2000.

4. J.A. Vanderhoof , Probiotics: future directions. *Am J Clin Nutr* **73** (2001), pp. 1152S–1155S.

5. F.C. Lowe and E. Fagelman , Cranberry juice and urinary tract infections: what is the evidence?. *Urology* **57** (2001), pp. 407–413.

6. G. Reid, J. Hsiehl, P. Potter *et al.*, Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients. *Spinal Cord* **39** (2001), pp. 26–30.

7. P.A. Mardh and S. Colleen , Antimicrobial activity of human seminal fluid. *Scand J Urol Nephrol* **9** (1975), pp. 17–23.

8. W.R. Fair, J. Couch and N. Wehner , Prostatic antibacterial factor. Identity and significance. *Urology* **7** (1976), pp. 169–177.

9. R.B. Alexander, S. Ponniah, J. Hasday *et al.*, Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. *Urology* **52** (1998), pp. 744–749.

10. A.R. Shahed and D.A. Shoskes , Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response. *J Androl* **21** (2000), pp. 669–675.

11. R.B. Nadler, A.E. Koch, E.A. Calhoun *et al.*, IL-1beta and TNF-alpha in prostatic secretions are indicators in the evaluation of men with chronic prostatitis. *J Urol* **164** (2000), pp. 214–218.

12. W.W. Hochreiter, R.B. Nadler, A.E. Koch *et al.*, Evaluation of the cytokines interleukin 8 and epithelial neutrophil activating peptide 78 as indicators of inflammation in prostatic secretions. *Urology* **56** (2000), pp. 1025–1029.

13. A.C. Buck, R.W. Rees and L. Ebeling , Treatment of chronic prostatitis and prostatodynia with pollen extract. *Br J Urol* **64** (1989), pp. 496–499.

14. E.W. Rugendorff, W. Weidner, L. Ebeling *et al.*, Results of treatment with pollen extract (cernilton N) in chronic prostatitis and prostatodynia. *Br J Urol* **71** (1993), pp. 433–438.

15. P.C. Hollman and M.B. Katan , Bioavailability and health effects of dietary flavonols in man. *Arch Toxicol* **20** Suppl (1998), pp. 237–248.

16. M. Sato, T. Miyazaki, F. Kambe *et al.*, Quercetin, a bioflavonoid, inhibits the induction of interleukin 8 and monocyte chemoattractant protein-1 expression by tumor necrosis factor-alpha in cultured human synovial cells. *J Rheumatol* **24** (1997), pp. 1680–1684.

17. D. Shoskes , Use of the bioflavonoid quercetin in patients with long-standing chronic prostatitis. *J Am Neutraceut Assoc* **2** (1999), pp. 18–21.

18. D.A. Shoskes, S.I. Zeitlin, A. Shahed *et al.*, Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology* **54** (1999), pp. 960–963.

19. M.A. Volpe, M. Cabelin, A.E. Te *et al.*, A prospective trial using saw palmetto versus finasteride in the treatment of chronic nonbacterial prostatitis (CP). *J Urol* **165** (2001), pp. 27–28.

20. Y. Jia, Y. Li, J. Li *et al.*, Treatment of nonspecific chronic prostatitis with Qian Lie Xian Yan Suppository suppository in 104 cases. *J Tradit Chin Med* **21** (2001), pp. 90–92.

Praxisspiegel Urologe B

Urologe [B] (1991)31:113-116 Springer-Verlag 1991

Phytotherapeutic Agents in the Treatment of Benign Prostatic Hyperplasia

Dreikorn K.

Department of Urology, ZKH St.-Juergenstrasse, 28355 Bremen, Germany.

Curr Urol Rep. 2000 Aug;1(2):103-9.

The rationale and efficacy of phytotherapeutic agents in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) are continuously debated. While plant extracts are prescribed and reimbursable treatment options in Europe, they are officially classified merely as dietary supplements in the United States. The most commonly used preparations originate from the species Serenoa repens, Pygeum africanum, hypoxis rooperi, pinus, picea, urtica dioica, and secale cereale (rye pollen). Combination extracts derived from two or more plants are also used. Various components have been suggested to be active, and different mechanisms of action are being supposed. Open trials and some short-term randomized studies, suggesting safety and efficacy have been reported. However, if stringent criteria of evidence-based medicine are applied, the data are inconclusive. Therefore, the 4th International Consultation on BPH and the recent German guidelines have not (yet) recommended phytotherapy for the management of symptomatic BPH.

Publication Types:

- Review
- Review, Tutorial

PMID: 12084323 [PubMed - indexed for MEDLINE]

Phytotherapy for benign prostatic hyperplasia

Timothy J Wilt*, Areef Ishani, Indulis Rutks and Roderick MacDonald

Minneapolis VA Center for Chronic Diseases Outcomes Research, 1 Veterans Drive (111-0), Minneapolis, MN 55417, USA

Abstract

Objective

To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH).

Design

Randomized trials were identified searching MEDLINE (1966±1997), EMBASE Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic reparational one or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators.

Results

A total of 44 studies of six phytotherapeutic agents (Serenoa repens, Hypoxis rooperi, Secale cereale, Pygeum africanum, Urtica dioica, Curcubita pepo) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. Serenoa repens, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking Serenoa repens reported greater improvement of urinary tract symptoms and flow measures. Serenoa repens decreased nocturia (weighted mean difference .WMD. . 20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies) and improved peak urine flow.WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies). Men treated with Serenoa repens rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio

of improvement . 1:72; 95% CI . 1:21 to 2.44, n . 8 studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. Hypoxis rooperi (n . 4 studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was 24.9 IPSS points (95% CI . 26:3 to 23.5, n . 2 studies) and the WMD for peak urine flow was 3.91 ml s21 (95% CI . 0:91 to 6.90, n . 4 studies). Secale cereale (n . 4 studies, 444 men) was found to modestly improve overall urological symptoms. Pygeum africanum (n . 17 studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving Urtica dioica and Curcubita pepo are limited although these agents may be effective combined with other plant extracts such as Serenoa and Pygeum. Adverse events due to phytotherapies were reported to be generally mild and infrequent.

Conclusions: Randomized studies of Serenoa repens, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. Serenoa repens appears to be a useful option for improving lower urinary tract symptoms and flow measures. Hypoxis rooperi and Secale cereale also appear to improve BPH symptoms although the evidence is less strong for these products. Pygeum africanum has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of Urtica dioica or Curcubita pepo alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

Keywords:

Phytotherapy
Benign prostatic hyperplasia
Randomized controlled trials
Systematic reviews
Meta-analysis
Public Health Nutrition: 3(4A), 459±472 459

Phytotherapy or the use of plant extracts for treatment of lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH) was first described in Egypt in the 15th century BC1. Phytotherapy is common in Europe and is increasing in the Western Hemisphere. In1998, the sale of botanical medications in the United States was $1.5 billion per year and the use of phytotherapeutic compounds increased nearly 70% among US adults2,3. About 30 phytotherapeutic compounds are used for the treatment of BPH (Table 1). Phytotherapeutic agents represent nearly half the medications dispensed for treatment of BPH in Italy, compared with 5% for alphablockers and 5% for 5a-reductase inhibitors4. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate lower urinary tract symptoms and represents more than 90% of drugs prescribed for treatment of BPH. In the United States, phytotherapies for BPH are available as nonprescription dietary supplements. Nearly a quarter of men attending a United States urology clinic who had previously treated BPH indicated they had used phytotherapeutic agents for self-treatment of urinary tract symptoms 5.

Phytotherapies are often promoted to `maintain a healthy prostate' and as natural and harmless treatment of BPH symptoms. Despite their popularity with the public there has been reluctance among many practitioners to routinely recommend these products. This is because of uncertainty regarding their efficacy and safety6,7. Most phytotherapeutic compounds are unlicensed and do not require evidence of efficacy, safety or purity. There have been over 40 published randomized controlled trials evaluating the efficacy of phytotherapy for symptomatic BPH in approximately 5000 men. Many more trials are in progress and should provide needed evidence regarding the role of phytotherapeutic products.

Systematic reviews of the existing literature provide a systematic assembly of the results of primary investigations using strategies that limit bias and random error8. Systematic reviews efficiently integrate unmanageable amounts of information and provide results that allow for rational decision making. They can establish whether findings are consistent and generalized or whether findings vary by subsets. If clinically and statistically appropriate, a quantitative summary (meta-analysis) can be performed resulting in statistical pooling of results and enhancement of the estimates of therapeutic effects and risk estimates. This is especially helpful when a large number of small trials have been conducted or when results from comparable studies provide differing results. Systematic reviews also identify gaps in existing evidence and make recommendations for future research to close these scientific and clinical gaps. Phytotherapeutic compounds Serenoa repens (saw palmetto) Background The most widely used phytotherapeutic agent for BPH is the extract of the dried ripe fruit from the American dwarf palm plant, saw palmetto, Serenoa repens (also known by its botanical name as Sabal serrulata). Serenoa repens has been approved in France and Germany for treatment of BPH. Berries from saw palmetto were first used by the American Indians in the southeast United States in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation1. The medicinal value of Serenoa repens for relief of prostate gland swelling has been reported since the 1800s. The mechanism of action of Serenoa repens has been investigated in several in vitro or indirect in vivo studies and has not been definitively defined. The mechanism may include alteration of cholesterol metabolism, anti-oestrogenic, anti-androgenic (including 5a-reductase inhibitor activity), anti-inflammatory effects, and a decrease in available sex hormone binding globulin9±12.

Results of studies A systematic review and meta-analysis of randomized trials assessed the existing evidence regarding efficacy and safety of Serenoa repens in men with symptomatic BPH13. Studies were identified through a search of MEDLINE (1966±1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic BPH, the intervention was a preparation of Serenoa repens alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, therapy allocation and outcomes of the studies. A total of 18 studies involving almost 3000 men were identified and analysed14±31 (Tables 2±5). Many studies did not report results in a method that permitted quantitative meta-analysis. Sixteen trials were double blinded, 14 were placebo controlled and four involved Serenoa repens in combination with other phytotherapeutic agents. The average study duration was 9 weeks (range 4±48 weeks) and the average age of enrollees was 65 years. Baseline characteristics regarding prostate volume, urine flow rates and symptom scale scores were comparable with previous trials evaluating pharmacologic management of BPH. The available data indicate that Serenoa repens

(alone or in combination with other phytotherapeutic agents) improves urinary symptoms and flow measures (Figs 1± 3). Compared with placebo, saw palmetto improved urinary symptom scores by 28% and nocturia by 25% (the weighted mean difference .WMD. . 20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies). Peak urine flow was improved by 24% (WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies), mean urine flow by 28% (2.22 ml s21; data not shown), and residual urine volume by 43% (222.05 ml; data not shown). Men taking Serenoa repens were more likely to report improvement in urinary symptoms than men taking placebo (73.6% vs. 50.9%; risk ratio . 1:76). Adverse effects were generally mild and comparable with placebo. Compared with finasteride17,30, saw palmetto provided similar responses in urologic symptom scores (0.37 International Prostate Symptom Score (IPSS) points), nocturia (20.20 times per evening) and flow measures. Saw palmetto was associated with a lower rate of erectile dysfunction than finasteride (1.1% vs. 4.9%; P , 0:001) and reduced neither prostate size nor prostate specific antigen (PSA) levels. Critics have stated that comparing saw palmetto with finasteride might be showing equivalency to placebo. However, previous trials and meta-analyses have demonstrated that finasteride provides symptomatic improvement in men with prostate glands .40 g, a size comparable to those enrolled in this study32,33.

The treatment effect sizes noted with saw palmetto were comparable to effects reported with other pharmacologic agents, such as finasteride. However, the results should be viewed cautiously. Studies utilized different doses and preparations of Serenoa repens (including combination preparations). The most extensively investigated preparation of Serenoa repens is manufactured in France and sold as Permixon. The most commonly reported dosage was 160 mg twice per day. Many studies did not report outcome data in a consistent fashion. Only three studies reported validated urologic symptom scales. Trials were of short duration with only two studies having follow-up of at least Phytotherapy for benign prostatic hyperplasia 463 6 months' duration. Therefore, it is not known whether Serenoa repens prevents long-term complications of BPH such as acute urinary retention or the need for surgical intervention. The only trial comparing Serenoa repens with alpha-blockers lasted less than 3 weeks, making a comparison impossible. Finally, it is possible that study results were not reported if there were no improvements in symptoms or flow measures (publication bias). There are two placebo-controlled studies involving 298 men that were scheduled for completion in 1998. However, their results have not yet been reported. Summary Extracts from the saw palmetto plant, Serenoa repens, provide modest improvement in urinary symptoms and flow measures. Compared with finasteride Serenoa repens produces similar improvements in symptoms and flow measures, has fewer adverse treatment effects and costs less. The long-term safety and efficacy of Serenoa repens and its ability to prevent complications from BPH are not known. Standardized preparations are often not available. Publication of ongoing trials is encouraged and initiation of long term studies compared with alpha-blockers would be useful. Hypoxis rooperi (South African star grass, bsitosterol) Background Phytosterol extracts derived from the South African star grass, Hypoxis rooperi, are popular. The resumed active constituent is b-sitosterol. Beta-sitosterol contains a mixture of phytosterols, with smaller amounts of other sterols, bonded with glucosides1. Additionally, the quantity of bsitosterol- bD-glucoside is often reported. The product is sold under the trade names Harzol or Azuprostat. Although the mechanism of action of b-sitosterols is not known it may be related to cholesterol metabolism or anti-inflammatory effects (via interference with prostaglandin metabolism) 1.

Results of studies four randomized controlled trials evaluated b-sitosterol in 519 men with symptomatic BPH34±37 (Table 3). All were 464

TJ Wilt et al. double-blinded and lasted between 4 and 26 weeks. Three trials used non-glucosidic b-sitosterols in doses ranging from 30 mg to greater than 120 mg per day34,35,37. The other trial utilized a preparation that contained 100% bsitosteryl- b-D-glucoside (0.15 mg twice a day)36. The average age of participants was 65 years. Men had moderately severe BPH (mean baseline IPSS score . 15:2; peak urine flow . 10:2ml s21; prostate size . 49 cc.: Beta-sitosterol provided statistically significant improvements in urinary symptom scores and flow measures (Figs 4 and 5). In the two studies reporting the IPSS score, the WMD compared with placebo was 24.9 points (95% CI . 26:3 to 23.5, n . 2 studies) (35% improvement). The WMD for peak urine flow was 3.91 ml s21 (45% improvement) and for residual volume the WMD . 228:62 ml (95% CI . 0:91±6:90; n . 4 studies) (29% improvement). Betasitosterol did not reduce prostate size and the trial using 100% b-sitosteryl-b-D-glucoside (WA184) did not show improvement in urinary flow rates. Adverse events were infrequent and mild. Withdrawal rates were less than 10% and did not differ from placebo. Summary An extract from South African star grass, b-sitosterol, improved urologic symptoms and flow measures. However, the existing evidence is limited to trials of short duration, relatively few patients studied and lack of standardized b-sitosterol preparations. Their long term effectiveness, safety and ability to prevent BPH complications are not known. Secale cereale (rye-grass pollen) Background Rye pollen extract is prepared from the rye-grass, Secale cereale. It is used by millions of men worldwide and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina38. In the United States, Cernilton is used as a nutritional supplement by approximately 5000 men39. One dose contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction38. The acetone-soluble fraction was found to contain bsterols 40. In vitro studies suggest that Cernilton may have anti-androgenic effects, relax urethral smooth muscle tone and increase bladder muscle contraction, or may act on the alpha-adrenergic receptors and relax the internal and external sphincter muscles41±43.

Phytotherapy for benign prostatic hyperplasia 467 Results of studies A total of 444 men have been enrolled in two placebocontrolled .n . 163. and two comparative trials lasting from 12 to 24 weeks44±47 (Table 4). Three studies were double-blinded44,45,47. The mean age of participants was 69 years. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a meta-analysis. However, three studies reported symptom scores or measured symptom improvement45±47. Nocturia was reported in three studies44,45,47 and all studies reported peak urine flow and residual urine volume. Data from all studies were consistent with improvement in symptoms and urinary flow. Cernilton improved `self-rated urinary symptoms' versus placebo and Tadenan, an extract from Pygeum africanum 46. Almost 70% men taking Cernilton reported symptom improvement ompared with 29% taking placebo. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% with Tadenan. Cernilton reduced nocturia compared with placebo and Paraprost, a pharmacologic treatment used primarily in Japan containing 265 mg of L-glutamic acid, 100 mg of Lalanine and 45 mg of aminoacetic acid47. Versus placebo, there was a two-fold improvement in the percentage of men reporting improvement in nocturia (63% vs. 31%)44,45.

Compared with Paraprost, Cernilton reduced nocturia by 0.40 times per evening. The only adverse event reported was mild nausea. Although the results suggest that Cernilton provided modest benefit there are limitations to the evidence. The longest treatment duration was 24 weeks. Only one study reported results from a standardized and validated urologic symptom scale. While the manufacturer suggests two to four tablets or capsules daily,

the dosages and standardization of preparation were not usually reported. The most frequently reported amount was two Cernilton capsules three times per day.

Summary

The evidence suggests that an extract from rye-grass pollen, Cernilton, is well tolerated and modestly improves urologic symptoms. However, trials were of short duration, enrolled relatively few patients, and lacked standard product preparation. Additionally, there was infrequent use of validated symptom scale scores. It does not improve urinary flow measures and the long-term safety and effectiveness is not known.

Pygeum africanum (African plum)

Background

Traditionally, the bark of the African plum tree (Pygeum africanum) was collected and powdered, then drunk as a tea to improve genito-urinary symptoms. Purified bark extracts have been used throughout Europe for the past 30 years. The postulated active components include phytosterols, especially b-sitosterols, pentacyclic triterpenoids and esters of long-chain fatty alcohols. Pygeum africanum extract may suppress LUTS by reducing bladder hyperreactivity, decreasing inflammation, and protecting against abnormal prostate growth48. A 1995 review identified 12 double-blind, placebo controlled studies involving 717 men with BPH46,49±63 (Table 5). Most studies used a Pygeum extract under the trade name Tadenan with doses ranging from 75 to 200 mg day21. All studies were at least 16 weeks in duration. More than half the studies measured peak urinary flow and all but one measured urinary frequency. Standardized and validated symptom scores were not utilized and there was no pooled estimate of treatment effect size or adverse events. The majority of studies noted an improvement in nocturia compared with placebo. An ongoing double-blind placebo-controlled study is evaluating Tadenan (100 mg and 400 mg) in 750 men with symptomatic BPH. The primary endpoint is a mean reduction in the IPSS score between baseline and 6 months. However, the results have not been reported. In five small-scale studies involving 183 men, P. africanum was compared with active drug or therapy50,57,63. Two studies involved plant extracts (sitosterin and extract of Radix urticae urtae)50. The results Fig. 5 Effect of b-sitosterol on peak urine flow vs. placebo 468 TJ Wilt et al. indicate that Pygeum reduced nocturia more than comparators in the 3 studies reporting this endpoint. However, in two of these studies there were no statistical comparisons. Since the publication of this review there have been two additional trials utilizing Pygeum. One was a study utilizing a combination of Pygeum with Urtica and is discussed in the section on Urtica59. The other trial demonstrated that Pygeum was less effective than Cernilton in improving `self-rated urinary symptoms'46. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% in men taking Tadenan. Summary

Extracts from the African plum tree, Pygeum africanum may be a useful treatment option for BPH. However, inadequacies in the reporting of outcomes limit the ability to estimate its safety and efficacy. An ongoing trial should provide much needed information on the short-term effectiveness and tolerability of Pygeum africanum.

Urtica dioica (stinging nettle)

Background

Extracts from roots of the stinging nettle are often used in Germany for the treatment of BPH. The extracts contain a mixture of water- and alcohol-soluble compounds with extraction procedures varying from company to company. Proposed mechanisms of action include inhibition of prostatic growth factor including blocking the conversion of testosterone to dihydrostersterone1. Results of studies There have been five randomized trials evaluating

stinging nettle. Three of these involved combinations with other phytotherapeutic agents (Pygeum and Sabal), making it difficult to evaluate the efficacy of stinging nettle alone26,30,59. Furthermore, one of these studies merely compared two different doses of a combined extract of Urtica and Pygeum59. The report by Sokeland compared a combination of Sabal and Urtica (PRO 160/120) extract with finasteride and placebo30. This trial lasted 12 weeks and evaluated 543 men. Compared with finasteride there were no differences in IPSS scores (24.8 vs. 25.8 IPSS points), peak urine flow or residual urine volume. More adverse events were associated with finasteride, including more cases of erectile dysfunction, diminished ejaculation volume, and headaches. Compared with placebo, the combination of Sabal±Urtica (Prostagutt) improved IPSS scores by 17% (23.5 IPSS points)26. One placebo-controlled study lasting 3 months compared a liquid preparation of stinging nettle with placebo in 41 men with BPH64. An improvement in IPSS scores was noted in men taking stinging nettle. However, because of unacceptable taste this preparation has been removed from the market. Another placebo-controlled trial examined the effectiveness of Urticae extract capsules65. Although improvements in peak urine flow and total voided volume were reported, there was no difference in urologic symptoms. Additionally, 24% of men (6/25) taking Urticae withdrew from the study; half of them due to unspecified side effects.

Summary Evidence from randomized trials suggests combination preparations of Urticae appear to provide some benefit for treatment of lower urinary tract symptoms, although stinging nettle extracts alone do not appear to be beneficial. Additional randomized controlled trials need to be conducted before Urticae can be recommended as an effective option for the treatment of LUTS.

Curcubita pepo (pumpkin seed)

Results of studies

There has been only one small-scale randomized trial of short duration that has evaluated the efficacy of pumpkin seed extracts16. This study evaluated 55 men, lasted for 12 weeks and utilized a preparation that included pumpkin seed, Curcubita pepo, and Sabal serrulata (Curbicin 160 mg three times a day). Compared with placebo, Curbicin improved self-rating of urinary symptoms (85% noted improvement vs. 11% taking placebo) and nocturia. Residual urine volume was reduced by 31% (42.5 cc) compared with only 6.5% (7.6 cc) with placebo. Because the study utilized a combination preparation the reported improvement in urologic symptoms and flow measures cannot be clearly attributed to pumpkin seeds.

Summary

There is no convincing evidence that extracts of pumpkin seed alone improve urologic symptoms or flow measures. They may provide improvement in urinary symptoms and flow measures when used in combination with Sabal serrulata. Randomized controlled trials need to be conducted. Recommendations and conclusions Should physicians recommend plant extracts for treatment of BPH? Despite their popularity and the existence of over 40 randomized controlled trials involving nearly 5000 men, the available data do not yet provide clear evidence of efficacy for most phytotherapeutic products. Extracts of saw palmetto (Serenoa repens) (alone or in combination with other phytotherapeutic products) have the strongest evidence for efficacy and tolerability. They appear to be a useful option for improving lower urinary tract symptoms and flow measures. Rye-grass pollen (Secale cereale) and South African star grass (Hypoxis rooperi, b-sitosterol) also appear to improve symptoms and are well tolerated. However, the evidence is Phytotherapy for benign prostatic hyperplasia 469 less strong for these products. African plum tree bark (Pygeum africanum) has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no

convincing evidence supporting the use of pumpkin seed (Curcubita pepo) or stinging nettle (Urtica dioica) extracts alone for treatment of BPH. They may be effective in combination with other phytotherapeutic products. The widespread use of phytotherapy attests to the popularity of plant extracts for treatment of BPH symptoms. They cost less and are better tolerated, at least in the shortterm, than either alpha-blockers or finasteride. However, if the primary goal is to reduce symptoms, alpha-blockers such as doxazosin, tamsulosin, alfuzosin or terazosin seem to be a better choice than finasteride and probably phytotherapy. Additionally, plant extracts have not yet been demonstrated to reduce complications from BPH or the need for surgical intervention in comparison with interventions such as finasteride33. The Committee on Other Medical Therapies of the Fourth International Consultation on BPH concluded that: most plant extract preparations have different components; it is not known what mechanisms of action demonstrated in vitro might be responsible for clinical effects; short-term randomized studies suggest clinical efficacy for some preparations; and studies were usually inadequate due to the methodology utilized, small numbers and short duration of study. Of greatest importance is the completion of additional high quality studies of long duration to fully evaluate the efficacy and safety of phytotherapeutic products for treatment of BPH6. Until completion of these studies and/or regulation of these products the lack of universal definitions, practices, and standards within the supplement industry place the onus on the physician to judge product quality and efficacy. Manufacturers/companies of plant extracts often use different extraction processes. There is no evidence that the extract from one manufacturer is equivalent to that of another. Additionally, since the active ingredient(s) are not known, it is possible that one product might have clinical efficacy while another does not. Each company's product must be tested to evaluate clinical efficacy and bioactivity. The following recommendations have been made for assessing quality measures (these do not directly address clinical efficacy or safety) in selecting high-quality and reliable preparations of phytotherapeutic products manufactured in the United States66. 1. The manufacturer tests raw ingredients for purity and potency prior to inclusion in a product. 2. The product is manufactured in a pharmaceutically licensed facility registered with the Food and Drug Administration. 3. The product's ingredients meet the applicable United States Pharmacopoeia (USP) standards. 4. All finished products are analysed for purity and potency following production by an independent laboratory using established methods to ensure that the product meets label claims and is of good quality. In some cases, this information can be found on product labelling. All reputable manufacturers will keep certificates of laboratory results for each finished batch of product on file. These should be available to physicians and pharmacists on request.

References

1. Lowe FC, Ku JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. Urology 1996; 48: 12±20.

2. Int. Med. World Report, February 1998, Vol. 13, No. 3, 8 pp.

3. Ernst E. Harmless herbs? A review of the recent literature. Am. J. Med. 1998; 104: 170±8.

4. Di Silverio F, Flammia GP, Sciarra A, Caponera M, Mauro M, Buscarini M, et al. Plant extracts in benign prostatic hyperplasia. Minerva Urol. Nefrol. 1993; 45: 143±9.

5. Bales G, Christiano AP, Kirsh E, Gerber GS. Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Chicago. Urology 1999; 54: 86±89.

6. Lowe FC, Dreikorn K, Borkowski A, Braeckman J, Denis L, Ferrari P, et al. Review of recent placebo-controlled trials utilizing phytotherapeutic agents for treatment of BPH. Prostate 1998; 37: 187±93.

7. Fitzpatrick JM. Phytotherapy for treatment of benign prostatic hyperplasia: case not proven. Urology 1999; 53: 462±4.

8. Mulrow CD. Rationale for systematic reviews. BMJ 1994; 309: 597±9.

9. Dreikorn K, Richter R. Conservative nonhormonal treatment of patients with benign prostatic hyperplasia. In: Ackerman R, Schroeder FH, eds. New Developments in Biosciences 5, Prostatic Hyperplasia. Berlin: Walter de Gruyter & Co, 1989: 109±31.

10. Marwick C. Growing use of medicinal botanicals forces assessment by drug regulators. JAMA 1995; 273: 607±9.

11. McGuire E. Detrusor response to obstruction. NIH Publication No. 87-2881, Department of Health and Human Services, Rockville, MD, 1987: 221

12. Di Silverio F, D'Eramo G, Lubrano C, Flammia GP, Sciarra A, Palma E, et al. Evidence that Serenoa repens extract displays an antiestrogenic activity in prostatic tissue of benign prostatic hypertrophy patients. Eur. Urol. 1992; 2: 309±14.

13. Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. JAMA 1998; 280: 1604±9.

14. Boccafoschi C, Annoscia S. Confronto fra estratto di Serenoa repens e placebo mediate prova clinica controllata in pazienti con adenomatosi prostatica. Urologia 1983; 50: 1257±68.

15. Braeckman J, Denis L, de Lavel J, Keuppens F, Cornet A, De Bruyne R, et al. A double-blind, placebo-controlled study of the plant extract Serenoa repens in the treatment of benign hyperplasia of the prostate. Eur. J. Clin. Res. 1997; 9: 247±59.

16. Carbin BE, Larsson B, Lindahl O. Treatment of benign prostatic hyperplasia with phytosterols. Br. J. Urol. 1990; 66: 639±41.

17. Carraro JC, Raynaud JP, Koch G, Chisholm GD, Di Silverio F, Teillac P, et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1098 patients. Prostate 1996; 29: 231±40.

18. Champault G, Patel JC, Bonnard AM. A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. Br. J. Clin. Pharmacol. 1984; 18: 461±2. 470 TJ Wilt et al.

19. Cukier J, Ducassou J, Le Guillou M, Leriche A, Lobel B, Toubol J. Permixon versus placebo; resultats d'une eÂtude multicentrique. C. R. Therapeut. Pharmacol. Clin. 1985; 4: 15±21.

20. Descotes JL, Rambeaud JJ, Deschaseaux P, Faure G. Placebocontrolled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after the exclusion of placebo responders. Clin. Drug Invest. 1995; 5: 291±7.

21. Emili E, Lo Cigno M, Petrone U. Risultati clinici su un nuovo farmaco nella terapia dell'ipertofia della prostata (Permixon). Urologia 1983; 50: 1042±8.

22. Gabric V, Miskic H. Behandlung des benignen prostataadenoms und der chronischen prostatatitis. Therapiewoche 1987; 37: 1775±88.

23. Lobelenz J. Extractum Sabal fructus bei benigner prostatahyperplasie (BPH). Klinische prufung im stadium I und II. Therapeutikon 1992; 6: 34±7.

24. Mandressi S, Tarallo U, Maggioni A, Tombolini P, Rocco F, Quadraccia S. Terapia medica dell'adenoma prostatico: confronto della efficacia dell'estratto di Serenoa repens (Permixonw) versus l'estratto di Pygeum Africanum e placebo. Valutazione in doppio cieco. Urologia 1983; 50: 752±8.

25. Mattei FM, Capone M, Acconcia A. Medikamentose therapie der benignen prostatahyperplasie mit einem extrakt der sagepalme. TW Urol. Nephrol. 1990; 2: 346±50.

26. Metzker H, Kieser M, HoÈlscher U. Wirksamkeit eines Sabal± Urtica-kombinationspraÈparats bei der behandlung der benignen prostatahyperplasie (BPH). Urologe B 1996; 36: 292±300.

27. Pannunzio E, D'Ascenzo R, Giardinetti F, Civili P, Persichelli E. Serenoa repens vs. gestonorone caproato nel trattamento dell'ipertofia prostatica benigna: Studio randomizzato. Urologia 1986; 53: 696±705.

28. Reece Smith H, Memon A, Smart CJ, Dewbury K. The value of permixon in benign prostatic hypertrophy. Br. J. Urol. 1986; 58: 36±40.

29. Roveda S, Colombo P. Sperimentazione clinica controllata sulla bioequivalenza terapeutica e sulla tollerabilita dei prodotti a base di Serenoa repens in capsule da 160 mg o capsule rettali da 640 mg. Arch. Med. Intern. 1994; 46: 61±75.

30. Sokeland J, Albrecht J. Kombination aus Sabal und Urticaestrakt vs. finasterid bei BPH (Stad. I bis II nach Alken); Vergleich der therapeutischen wirksamkeit in einer einjahrigen doppelblindstudie. Urologe A 1997; 36: 327±33.

31. Tasca A, Barulli M, Cavazzana A, Zattoni F, Artibani W, Pagano F. Trattamento della sintomatologia ostruttiva da adenoma prostatico con estratto di Serenoa repens. Studio clinico in doppio cieco vs. placebo. Minerva Urol. Nefrol. 1985; 37: 87± 91.

32. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: A meta-analysis of randomized clinical trials. Urology 1996; 48: 398±405.

33. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe L, et al. The effect of finasteride on the

risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N. Engl. J. Med. 1998; 338: 557±63.

34. Berges RR, Windeler J, Trampisch HJ, Senge TH. Randomised, placebo-controlled, double-blind clinical trial of b-sitosterol in patients with benign prostatic hyperplasia. Lancet 1995; 345: 1529±32.

35. Fischer A, Jurincic-Winkler CD, Klippel KF. Conservative treatment of benign prostatic hyperplasia with high-dosage b-sitosterol (65 mg): results of a placebo-controlled doubleblind study. Uroscop 1993; 1: 12±20.

36. Kadow C, Abrams PH. A double-blind trial of the effect of beta-sitosteryl glucoside (WA184) in the treatment of benign prostatic hyperplasia. Eur. Urol. 1986; 12: 187±9.

37. Klippel KF, Hiltl DM, Schipp B. A multicentric, placebocontrolled, double-blind clinical trial of b-sitosterol (phytosterol) for the treatment of benign prostatic hyperplasia. Br. J. Urol. 1997; 80: 427±32.

38. AB Cernelle. Engleholm, Sweden.

39. Ruyan D, Cernitin American. Personal communication, 19 February 1999.

40. Buck AC. Phytotherapy for the prostate. Br. J. Urol. 1996; 78: 325±6.

41. Ito R, Ishii M, Yamashita S, et al. Antiprostatic hypertrophic action of Cernilton pollen-extract. Pharmacometrics 1986; 31: 1±11.

42. Kimura M, Kimura I, Nakase K, Sonobe T, Mori E. Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Med. 1986; 2: 148±51.

43. Nakase S, Takenaka K, Hamanaka T, Kimura M. Effects of Cernilton pollen-extract on the urethral smooth muscle and diaphragmatic neuromuscular specimen. Folio Pharmacol. Jpn. 1988; 91: 385±92.

44. Becker H, Ebeling L. Konservative therapie der benignen prostata-hyperplasie (BPH) mit CerniltonwN: ergebnisse einer plazebokontrollierten doppleblindstudie. Urologe B 1988; 28: 301±6.

45. Buck AC, Cox R, Rees RWM, Ebeling L, John A. Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen-extract, Cernilton: a double-blind, placebocontrolled study. Br. J. Urol. 1990; 66: 398±404.

46. Dutkiewicz S. Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. Int. Urol. Nephrol. 1984; 28: 49± 53.

47. Maekawa M, Kishimoto T, Yasumoto R, Wada S, Harada T, Ohara T, et al. Clinical evaluation of Cernilton on benign prostatic hypertrophy: a multiple center double-blind study with Paraprost. Hinyo Kiyo 1981; 27: 317±26.

48. Andro MC, Riffaud JP. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. Curr. Ther. Res. 1995; 56: 796±817.

49. Barlet A, Albrecht J, Aubert A, Fischer M, Grof F, Grothuesmann HG, et al. Efficacy of Pygeum africanum extract in the medical therapy of urination disorders due to benign prostatic hyperplasia: evaluation of objective and subjective parameters. A placebo-controlled double-blind multicenter study. Wien. Klin. Wochenschr. 1990; 102: 667±73.

50. Barth H. Non hormonal treatment of benign prostatic hypertrophy. Clinical evaluation of the active extract of Pygeum africanum. Proceedings of Symposium on Benign Prostatic Hypertrophy, Paris 1981: 45±8.

51. Bassi P, Artibani W, De Luca V, Zattoni F, Lembo A. Standardized extract of Pygeum africanum in the treatment of benign prostatic hypertrophy. Controlled clinical study versus placebo. Minerva Urol. Nefrol. 1987; 39: 45±50.

52. Blitz M, Garbit JL, Masson JC, et al. Etude controlee de l'efficacite d'un traitemente medical sur des sujets consultant pour la premiere fois pour un adenome de la prostate. Lyon Mediterr. Med. 1985; 21: 11.

53. Bongi G. Il Tadenan nella terapia dell'adenoma prostatico. Studio anatomo-clinico. Minerva Urol. 1972; 24: 124±38.

54. Donkervoort T, Sterling A, van Ness J, Donker PJ. A clinical and urodynamic study of Tadenan in the treatment of benign prostatic hypertrophy. Eur. Urol. 1977; 3: 218±25.

55. Dufour B, Choquenet C, Revol M, Faure G, Jorest R. Controlled study of the effects of Pygeum africanum extract on the functional symptoms of prostatic adenoma. Ann. Urol. 1984; 18: 193±5.

56. Frasseto G, Bertoglio S, Mancuso S, Ervo R, Mereta F. Studio sull'efficacia e sulla tollerabilita del Tadenan 50 in pazienti affeti da ipertrofia prostatica. Prog. Med. 1986; 42: 49±53.

57. Gagliardi V, Apicella F, Pino P, Falchi M. Terapia medica dell'ipertrofia prostatica. Sperimentazione clinica controllata. Arch. Ital. Urol. Nefrol. Andrologia 1983; 55: 51±69. Phytotherapy for benign prostatic hyperplasia 471

58. Giacobini S, von Heland M, de Natale G, Gentile V, Bracci U. Valutazione clinica e morfo-funzionale del trattamento a doppio cieco con placebo. Tadenan 50 e Tadenan 50 associato a Farlutal nei pazienti con ipertrofia prostatica benigna. Antologia Med. Ital. 1986; 6: 1±10.

59. Krzeski T, Kazon M, Borkowski A, Witeska A, Kuczera J. Combined extracts of Urtica dioica and Pygeum africanum in the treatment of benign prostatic hyperplasia: Double-blind comparison of two doses. Clin. Ther. 1993; 15: 1011±20.

60. Maver A. Medical treatment of fibroadenomatous hypertrophy of the prostate with a new plant substance. Minerva Med. 1972; 63: 2126±36.

61. Ranno S, Minaldi G, Viscusi G, Di Marco G, Consoli C. Efficacia e tollerabilita del trattamento dell' adenoma prostatico con Tadenan 50. Prog. Med. 1986; 42: 165±9.

62. Rigatti P, Zennaro F, Fraschini O, Oxilia A. L'impegio del Tadenan nell'adenoma prostatico. Ricerca clinica controllata. Atti Accad. Med. Lomb. 1983; 38: 1±4.

63. Rizzo M, Tosto A, Paoletti MC, Raugei A, Favini P, Nicolucci A, et al. Terapia medica dell'adenoma della prostata: Valutazione clinica comparativa tra estratto di Pygeum africanum ad alte dosi e placebo. Farmacia Terapia 1985; 2: 105±10.

64. Englemann U, Boos G, Kres H. Therapie der benignen Prostatahyperplasie mit Bazoton liquidum. Urologe B 1996; 36: 287±91.

65. Vontobel HP, Herzog R, Rutihauser G, Kres H. Results of a double-blind study on the effectiveness of ERU (extractum radicis Urticae) capsules in conservative treatment of benign prostatic hyperplasia. Urologe A 1985; 24: 49±51.

66. McKinney DE. Re: Saw palmetto for Benign Prostatic Hyperplasia. JAMA 1999; 281: 1699.

Usefulness of Cernilton in the treatment of benign prostatic hyperplasia

Int Urol Nephrol 1996; 28(1):49-53

Dutkiewicz S

A total of 89 patients with benign prostatic hyperplasia (BPH) were treated pharmacologically for 4 months: 51 received Cernilton and 38 Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan-treated patients. The obstructive and irritative symptoms responded best to the therapy. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH.

Identification of a prostate inhibitory substance in a pollen extract

Habib FK, Ross M, Lewenstein A, Zhang X, Jaton JC.

University Department of Surgery, Western General Hospital, Edinburgh, Scotland.

Prostate. 1995 Mar;26(3):133-9.

Recently, much attention has focused on the treatment of BPH with the pollen extract, Cernilton. The present investigation was designed to identify the active component in this agent which might be responsible for the symptomatic relief of BPH as previously reported. Sequential purification of the active component present in the pollen extract was carried out by a combination of dialysis, gel filtration, and reverse phase chromatography. To monitor the biological activity of each of the purified fractions, a biological assay employing the human prostate cancer cell line DU145 was undertaken. While we have identified a number of constituent components in the pollen extract, only one fraction designated V-7 (FV-7) maintained a strong inhibitory effect on the growth of DU145 cells. The inhibition was time- and dose-dependent, and the concentrations of FV-7 required to reduce the cell numbers by 50% (IC50) after 2 days of exposure was 5 micrograms/ml. FV-7 was also inhibitory towards the primary culture of prostate stroma and epithelial cells, with the stroma/fibroblast showing greater sensitivity towards the HPLC-purified component. However, it should be noted that this inhibitory activity measured in the primary culture cells was only achieved at higher concentrations of FV-7. Preliminary characterization of the active ingredient identified FV-7 as DIBOA which is a cyclic hydroxamic acid. FV-7 and DIBOA induce similar inhibitory effects on the growth of DU145 cells.

PMID: 7899151 [PubMed - indexed for MEDLINE]

Prostatitis

Results of Treatment with Pollen Extract (Cernilton ®) in Prostatodynia and Chronic Prostatitis

E. W. Rugendorff, W. Weidner, L. Ebeling, A. C. Buck

Introduction

The results of treatment in patients with symptoms of chronic prostatitis are often disappointing. This is partly due to controversy regarding the etiology and clinical significance of the different forms of the benign painful prostate (18), and in particular, a failure to use the diagnostic criteria and methods necessary for the differential diagnosis of the various forms of prostatic disease. However, even if a precise classification in chronic bacterial or non-bacterial prostatitis and prostatodynia has been reached, there is no treatment which will guarantee a lasting cure and many patients suffer for years or even decades from persisting symptoms (38).

Clinical investigations with a defined pollen extract (Cernilton ®**, A. B. Cernelle, Sweden) have provided evidence of symptomatic improvement in benign forms of prostatic disease (4,5,13,14,19). Here we report the results of a prospective study carried out in 90 patients to investigate the efficacy of Cernilton ® in respect to voiding dysfunction and inflammation in chronic prostatitis syndromes.

Patients and Methods

There were ninety patients, 19 to 90 years of age (median 45, mean 47.2±SD 17.6), with symptoms of prostatitis of at least one-year duration and no positive cultures localizing a bacterial pathogen to the prostate included in this case control study (trial center E. W. R.). Of these 90 patients 30 had a history of bacterial prostatitis and at least two previous episodes of confirmed urinary tract infection, but entered into the study in the infectionfree interval after anti-bacterial treatment. Patients with urinary tract infection, anogenital syndrome, or benign prostatic hyperplasia influencing the clinical conditions, and patients with concomitant therapy with muscle relaxants, alpha-adrenergic blockers, or diuretics were not included in this study.

The differential diagnostic investigation was based upon bacterial localization cultures from urine samples and expressed prostatic secretions (EPS) by the technique recommended by Meares and Stamey (32). Additionally, leucocyte counts in the first-voided 10ml of urine (VB 1), mid-stream urine (VB 2) and first-voided 10ml urine after prostatic massage (VB 3) were analyzed. Using the sediments in these different urine specimens the leucocyte count was performed with a counting chamber (MD-KovaSysteme) (40) calculating the number of leucocytes in VB 3 per µl.

Additional investigations (ultrasonography, voiding and/or retrograde cystourethrography, endoscopy) revealed complicating factors (CF) in 18 patients. The complicating factors were bladder neck sclerosis in ten, urethral strictures in five, and excessive prostatic calcifications in three cases. Eight patients had undergone a previous transurethral or open prostatectomy, seven for benign prostatic hyperplasia and one for chronic prostatitis.

There were 44 patients (48.9 %) who had received treatment with various drugs (antibiotics, anti-inflammatory agents, urological remedies, etc.) during the three-month period before commencement of the study; 37 of them had noted some, but unsatisfactory, improvement.

Treatment with Cernilton ® was given in a dosage of one tablet 3 times daily and in most cases continued for a period of six months.

The following parameters were recorded before treatment and after 3 months and 6 months of therapy: (i) symptoms [discomfort and pain scored in: absence of the symptom or in mild, moderate and severe intensity of the symptom; nocturia, frequency, and dysuria, scored according to Bojarsky et al. (10)1; (ii) findings on rectal palpation of the prostate (normal or enlarged prostate; normal, smooth, increased, or irregular consistency of the prostate); (iii) uroflow (voided volume, flow time, micturition time, mean flow rate, time to peak flow, peak flow rate); (iv) leucocyturia in VB 2 and VB 3; (v) bacteriuria; (vi) complement C3 and coeruloplasmin in the ejaculate [scored semiquantitatively, combining the values of complement C3/ coeruloplasmin per dl according to a modified scheme of Bloik and Hofstetter (8) as follows: 1 = < 1,5 mg / negative; 2 = 1,5 - < 2 mg / <0,5mg; 3=2-4mg/0,5mg-1mg; 4=3-8 mg/ 1-3mg].

Complement C3 and coeruloplasmin were determined in the ejaculate after liquefaction, centrifuged for five minutes at 11,266 U /min resp. at 10,500 g. The radial immunodiffusion of the supernatant sample was performed with LC-Partigen®-C3c and LC-Partigen® plates (Behringwerke AG, Marburg, Germany). In addition to the sample, a control from a calibrated standard serum was filled on the plates (dilution 1:20 for complement C3; dilution 1:11 for coeruloplasmin). The amount of complement C3 and coeruloplasmin was calculated from the diameter of the sample precipitate according to the calibration curve from calibrated standard serum of complement C3 and coeruloplasmin (Behringwerke AG, Marburg, Germany).

When assessing the therapeutic results, a complete response with normalization of all parameters was defined as "cure" an improvement in the parameters as "improvement," and persistence or deterioration of the parameters as "no improvement."

The biometrical evaluation was performed by descriptive analysis of the parameters before and after treatment, also in relation to the changes after 6 months of treatment as compared with the status after 3 months of treatment. The following tests were used: (i) the t-test for related samples for the comparison of the uroflow parameters; (ii) the Wilcoxon matched-pairs signed-ranks test using chi2 approximation for the comparison of the leucocytes in VB 3; (iii) the sign test for the scored complement C3 / coeruloplasmin in the

ejaculate; (iv) the Pawlik corrected contingency coefficient for qualitative, and the Spearman rank correlation coefficient for quantitative correspondence between the changes of leucocyturia in VB 3 and the peak urine flow rate.

Results

The clinical status at baseline is characterized mainly by mild to moderate symptoms. The prostate was enlarged in 55.6 % and tender in 94.4 % of the patients. Complement C3 in the ejaculate was above 1.5mg/dl in all cases. Due to significant differences of the parameters at baseline and in their courses the results of the treatment in patients without (N = 72) and with (N = 18) complicating factors [CF] are described separately.

Symptoms

Almost all of the patients complained of frequency of voiding and dysuria, while pain was present in about two-thirds. Patients with associated CF responded poorly, whereas in cases without CF the symptoms were reduced markedly after six months of treatment (Table 1).

Tab. 1 Symptom response to treatment in patients without complicating factors (N = 72)

Symptom	free	improved	N
Discomfort	67.9%	9.4%	53
Pain	69.4%	12.2%	49
Nocturia	55.5%	29.6%	54
Frequency	48.6%	26.4%	72
Dysuria	52.2%	11.6%	69

* Details: see "Patients and Methods".

Palpation of the prostate

In patients without CF the initially enlarged prostate returned to a normal size in 15 / 39 cases, the consistency of the prostate improved in 37 / 68 cases, and the prostate was no longer tender on palpation in 47 / 71 cases after treatment. The consistency and the tenderness worsened in five patients. The findings on palpation in the group with CF showed practically no change or deterioriation.

Uroflow

In contrast to the patients with CF, where all the uroflow parameters worsened, there was a definite improvement ($p < 0.05$) of the time to peak flow by increased voided volume in the cases without CF Micturition and flow time remained unchanged. The peak urine flow rate (PUFR, ml-/s) showed a slight decrease from 11.9±3.9 to 10.5±2.6 (-x±SD) in patients with CF. The mean urine flow rate (ml/s) in patients without CF increased from 7.4±2.7 (x-±SD) to 9.1±3.4 (x-±SD) after three ($p<0.001$) and to 10.8±4.5 (-x±SD) after six months of therapy ($p<0.001$; also comparing six vs. three months). The PUFR at baseline was 15.9±5.2 (x-±SD) in cases without CF and increased to 19.0±7.2 (x± SID) and 23.9±10.6 (x±SD) respectively, at the control after three ($p<0.001$) and six months of treatment, respectively ($p < 0.001$; also comparing six vs. three months).

Leucocyturia in VB 3 (L-VB 3)

In patients with CF, the L-VB 3 increased in the median from 80 to 185 leucocytes /µl ($p < 0.001$). Comparing the number of leucocytes before and after treatment in patients without CF, the L-VB 3 decreased in the median from 50 to 20 leucocytes / µl ($p < 0.001$). The mean (x ± SID) from 85.9 ± 89.9 at baseline decreased to 69.1±121.8 at the three-month ($p < 0.001$) and to 42.2 ± 62.6 at the six-month control ($p < 0.001$; also comparing six vs. three months). Figure 1 shows the individual changes, which are documented separately as pre-post-values

according to different levels (< 50, 50 - 99, 100 - 1000 leucocytes /µl) of baseline values.

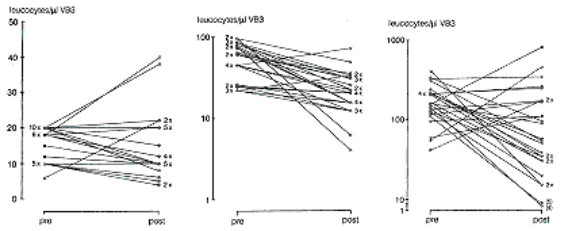


Fig. 1 Individual courses of the leucocyturia in VB 3 in patients without complicating factors (N = 72), separately plotted according to different baseline (pre: <50, 50-99, 100-1000 leucocytes/µ) or control (post) values. In brackets=two values of numbers of leucocytes (control). (Details: see "patients and Methods.")

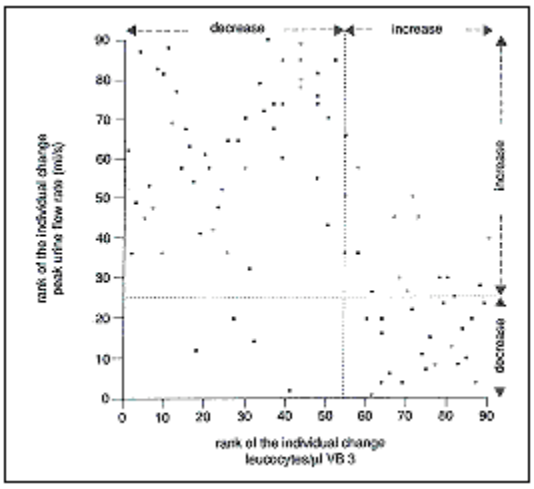


Fig. 2 Scattergram of the combined ranked individual changes of the leucocyturia in VB 3 (L-VB 3) and the peak urine flow rate (PUFR) in patients with chronic prostatitis syndromes (N = 90) comparing the values before and after treatment. High inverse qualitative (CCcorr= 0.720) and quantitative (rs = 0.565) correlation between the changes of L-VB 3 and PUFR. Rank 1 =strongest decrease, rank 90 =strongest increase, parallel lines to ordinates =no change (conversion point). (Details: see "Patients and Methods.")

L-VB 3 and PUFR

Comparing the changes of the L-VB 3 and the PUFR in patients without CF, the L-VB 3 decreased in three cases with a decreased PUFR and in 52 cases with an increased PUFR. An increase of the L-VB 3 was observed in eight cases with a decreased PUFR and in nine cases with an increased PUFR.

The inverse qualitative changes of the L-VB 3 and the PUFR were highly correlated (CCco, = 0.720). This correlation is confirmed by the inverse correspondence (rs = 0.565) between the quantitative changes of the L-VB 3 and the PUFR. Because of the extremely widespread pattern in the distribution of the leucocyte numbers in VB 3, the individual differences between the baseline value and the control value after treatment were separately ranked for L-VB 3 and PUFR according to the definition of rank 1 as strongest decrease and of rank 90 as strongest increase, and plotted as combined ranks of the individual changes for both parameters (Fig. 2).

Complement C3/coeruloplasmin

In correspondence with the changes of the L-VB 3, patients without CF showed a decrease of the inflammation parameters complement C3/coeruloplasmin in ejaculate after three ($p < 0.001$) and a further reduction after six months of treatment ($p<0.001$; $p= 0.005$ comparing six vs. three months), whereas an increase was documented in cases with CF ($p = 0.07$) (Table 2).

Tab. 2 Complement C3/coeruloplasmin per dl ejaculate before and after three ($p < 0.001$) and six months, respectively ($p < 0.001$; $p = 0.005$ comparing six vs. three months), of treatment in patients without complicating factors (CF) and before and after treatment in patients with CF ($p = 0.07$).

	no CF			with CF	
Complement C3/Coeruloplasmin	Pre N	3 months N	6 months N	pre N	post N
< 1,5 mg / negative	–	3	11	–	–
1,5 – < 2,0 mg / < 0,5 mg	8	36	40	4	–
2,0 – 4,0 mg / 0,5 – 1 mg	46	30	13	11	9
3,0 – 8,0 mg / > 1 – 3 mg	17	2	5	1	7
missing values	1	1	3	2	2

*Details: see "Patients and Methods".

Assessment of Efficacy

As therapeutic result in the cases without CF, 56 out of 72 patients (78 %) responded: 26 patients (36 %) were cured and 30 patients (42 %) were improved. In 16 cases (22 %) no improvement or deterioriation was registered. In patients with CF, only one responded (6 %) with improvement. The remaining 17 patients (94 %) did not improve or deteriorate.

Discontinuation of Treatment

Treatment was discontinued because of clinical deterioration or ineffective response in 12 patients. The most frequent cause of deterioration was symptomatic bacteriuria (83.3 %) to be treated with anti-bacterial therapy. CF were present in 66.7 % of all patients in whom treatment was discontinued.

Tolerance

In 96.7 %. of the patients the pollen extract showed a good tolerance. Unwanted events were registered as meteorism, heartburn, or nausea in three patients. These transient gastrointestinal symptoms were mild to moderate and did not require discontinuation of treatment.

Discussion

The chronic forms of bacterial prostatitis often relapse after therapy (17,22,38). Independent of the fact that new antibacterials such as fluoroquinolones show a good antibacterial efficacy (1,15,39,49), in the infection-free interval there are still many patients presenting prostatitic symptoms and signs despite negative urine and expressed prostatic secretion cultures.

In the so-called non-bacterial prostatitis three forms can be distinguished: patients with "Ureaplasma-associated" prostatitis, or with evidence of Chlamydia trachomatis infection, or without pathogens detectable in the EPS and/or in VB 3 (47). Although the possible etiological role of Ureaplasma and Chlamydia trachomatis remains controversial, and in spite of the culture problems due to contamination (20), there is increasing evidence of their role as pathogens (12,16,24,27, 29,34,35,48). However, anti-bacterial treatment is necessary in the case of a clearly established pathogen, but mostly, the EPS and the VB 3 are sterile.

A common observation in the condition defined as prostatodynia is the presence of reduced PUFR and increased maximum urethral closure pressure (MUCP) suggesting the use of relaxants and alpha-adrenergic blocking agents (3,7,31,36,37,46). The persistence of symptoms in these patients has even been ascribed to a psychosomatic element (11,41,43).

Thus, summarizing the therapeutic outcome in patients with chronic prostatitis syndromes, there is a need for conservative management which leads to symptomatic relief, to an improvement of the voiding disturbance, and to a reduction or even elimination of the inflammation in the prostate.

In this study the pollen extract, Cemilton®, was found to be effective in the treatment of prostatodynia and chronic prostatitis without positive cultures localizing a pathogen to the prostate, if no complicating factors such as bladder neck sclerosis, prostatic calculi, or urethral stricture were present. Practically no response to the treatment or deterioriation was observed in patients with these complicating factors.

Most of the patients without CF experienced partial or complete relief from their complaints, and the findings on palpation of the prostate improved. The pollen extract led to a significant reduction of the L-VB 3 and of the concentration of complement C3 and coeruloplasmin in the ejaculate. This anti-inflammatory effect corresponded with a significant increase of the PUFR. As revealed by the biometrical evaluation with CCcorr = 0.720 and rs = 0.565, there is a high qualitative and quantitative inverse

correlation between the changes of the L-VB 3 and the PUFR.

Analyzing the ranked individual changes of both parameters and the absolute changes of the individual L-VB 3, a high increase of the PUFR was registered together with high or very low decreases of the L-VB 3. This shows that also in patients with absent or minor inflammation in the prostate and thus with a small changing potential of the inflammatory parameter, the PUFR increased markedly.

Obviously, complicating factors play an important role in the failure of the therapy with the pollen extract. The baseline values of the PUFR were lower and those of the L-VB 3 were higher in these patients in comparison to the cases without CF, indicating a causal relationship with the presence of CF. Both parameters showed a deterioriation from control values after treatment. Practically no patient with CF responded to the therapy with pollen extract. From this it seems reasonable to recommend a careful search for bladder neck sclerosis, prostatic calculi, urethral strictures, or other complicating factors in patients who do not improve after three months of therapy with the pollen extract.

According to Blenk and Hofstetter (9), complement C3 in ejaculate is a very sensitive indicator of an inflammatory process in the prostate or adnexae. It may also represent inflammatory alterations with minor and / or focal pathological changes within the gland which do not lead to a marked increase of the number of leucocytes in the prostatic expressate or in the VB 3. The comparison of the baseline values of complement C3/coeruloplasmin and of the L-VB 3 showed also in patients with a low number of leucocytes in VB 3 an increased concentration of complement C3 in the ejaculate. The similar course of these parameters, i.e., their continuous decrease, in patients responding to the treatment with pollen extract suggests that edema or inflammation may also be present in prostatodynia, as has been indicated by studies of patients with prostatodynia and BPH by Vahlensieck and Dworak (45) and di Trapani et al. (44). Echodense areas as a result of inflammatory processes are seen predominantly in submucous periurethral, but also in outer parts of the prostate gland (6). Kohnen and Drach (28) described an incidence of 98.1 % of inflammation in resected hyperplastic prostates and Gorelick et al. (21) found in the tissue cultures of 200 patients undergoing prostatectomy a positive, single organism, bacterial growth in 21 %.

By video-pressure-flow-EMG urodynamic investigations in a prospective study of patients with prostatitis syndrome, Barbalias (2) showed an increased MUCP. A distal and proximal narrowing in the "pars prostatica urethrae" was observed in several patients, and a synchronous decrease in urinary flow rates was recorded in the majority of cases. Thus, this functional urethral obstruction represents a common characteristic of patients with prostatodynia or non-bacterial prostatitis.

Barbalias (2) posits that in patients with non-bacterial prostatitis local inflammation may irritate adrenergic endings and result in high MUCP. Our finding of the inverse correlation between inflammation and uroflow supports this hypothesis, but, furthermore, the observed decrease of complement C3 allows us to assume that this mechanism of local irritation may be responsible in patients with prostatodynia, too.

Takeuchi et al. (42) reported a significant decrease of the MUCP from 92±23cm H20 to 58 ±19 cm H20 (x ± SD) with a reduction of the prostatic profile length and of prostatic urethral resistance (from 28 ± 14 g / cm to 12 ± 3 g / cm; (-x ± SD) by pollen extract in patients with BPH. They concluded that this finding may be related to an elimination of edema or inflammation of the area in question.

It seems reasonable that the pathophysiology of voiding dysfunction due to an anatomical

enlargement cannot be influenced except by removing the obstruction, but functional obstruction in the proximal or distal part of the "pars prostatica urethrae" may be decreased by the pollen extract leading to a similar, although restricted, response pattern in BPH as in the case of chronic prostatitis syndromes.

Thus, a common characteristic of BPH, chronic prostatitis, and prostatodynia may be the presence of edema or inflammation in the prostate and a functional urethral obstruction, which may explain the clinical efficacy of the pollen extract in these different nosological entities.

Cernilton ® is an extract from several pollens and can be pharmacologically characterized by a dose-dependent inhibition of the cyclo-oxygenase and 5-lipoxygenase reducing the biosynthesis of prostaglandins and leucotriens in vitro (30). In urethral strips of mice, Kimura et al. (26) and in rat urethral smooth muscle, Nakase et al. (33) observed a dose-related inhibition of noradrenaline-induced contractions by pollen extract. Furthermore, Ito et al. (25) and Habib et al. (23) reported growth inhibition by pollen extract of the rat prostate and in prostate cell cultures. According to this broad spectrum of pharmacodynamic properties the precise mode of action is unknown.

However, the course of clinical symptoms and signs and of the urodynamic and laboratory parameters with further improvement comparing the results after three and six months of therapy in this study suggest an important role of the inflammation. This seems to be confirmed by the observation of Buck et al. (14), who indicate that patients with chronic prostatitis syndromes may need at least three months of therapy with pollen extract before a significant response is achieved.

Regarding the still unsatisfactory therapeutic outcome in prostatodynia, non-bacterial prostatitis, and chronic bacterial prostatitis in the infection-free interval, this study shows encouraging results for patients with chronic prostatitis syndromes. Further investigations are necessary to elucidate the precise urodynamic impact of the clinical mode of action of Cernilton ®.

Summary

The results of a prospective case control study with the pollen extract Cernilton ®** in the therapy of 90 patients with chronic prostatitis syndromes are reported. Cernilton ® was given in a dose of one tablet three times daily for a period of six months. The following parameters were documented before and after three and six months of treatment: symptoms, findings on rectal palpation of the prostate, uroflow, leucocyturia in the midstream, and the first-voided 10-ml specimen after prostatic massage (VB 3), bacteriuria, and complement C3 / coeruloplasmin in the ejaculate.

Favorable results were obtained in the group of patients without associated complicating factors (N = 72): a response was observed in 56 (78 %) patients; 26 (36 %) were cured, and 30 (42 %) improved, with an increase in peak urine flow rate (ml / s) from 15.9 ± 5.2 to 23.5 ± 10.7 (x± s; $p < 0.001$), a reduction of leucocyturia in VB 3 from 50 to 20 leucocytes /µl (median; $p < 0.001$), and a decrease of complement C3 / coeruloplasmin ($p < 0.001$) in the ejaculate. In cases with associated lower urinary tract pathology (N= 18), i.e., urethral strictures, prostatic calculi, bladder neck sclerosis, no response was observed with the exception of one patient who improved.

There was a strong qualitative (CCcorr = 0.720) and quantitative (rs= 0.565) inverse correlation between the changes in leucoyturia in VB 3 and peak urine flow rate.

Treatment was discontinued because of clinical deterioriation, mainly associated with symptomatic bacteriuria, or ineffective response in 13 (14,5 %) patients. The pollen extract was well tolerated in 96.7 % of cases. Three patients

noted mild or moderate gastrointestinal symptoms, which did not lead to discontinuation of the therapy.

Regarding the common types of prostatitis syndromes, Cernilton ® is considered to be most effective in prostatodynia and nonbacterial prostatitis in patients without complicating factors. The correlation between the therapeutic improvement of uroflow and inflammation suggests their functional relationship in the pathophysiology of the disease and a smooth muscle relexant (e.g., antiadrenergic) and / or anti-inflammatory mode of action of the pollen extract. Furthermore, if a patient fails to respond after three months of treatment with the pollen extract, a careful search for complicating factors is recommended.

Acknowledgements

We thank Dr. M. Luniper, Dr. C. Zippel, Dr. U. Groth and A. Helwig of the ambulatory laboratory in Giessen, Germany, for the determination of complement C3 and coeruloplasmin in the ejaculate samples.

We also thank Dr. J. Schnitker and his co-workers of the Institute for Applied Statistics, Dr. J. Schnitker GmbH, Bielefeld, Germany, for the biometrical evaluation of the data.

References

1. Andriole, V. T: Use of quinolones in treatment of prostatitis and lower urinary tract infections. Europ. J. clin. Microbiol. Infect. Dis. 10 (1991) 342-350.
2. Barbalias, G. A.: Prostatodynia or painful male urethral syndrom? Urology 36 (1990) 146-153.
3. Barbalias, G. A., E. M. Meares Jr., G. R. Sant: Prostatodynia: clinical and urodynamic characteristics. J. Urol. 130 (1983) 514-517.
4. Becker, H., L. Ebeling: Konservative Therapie der benig nen Prostata-Hyperplasie (BPH) mdt Cemilton 6 N -Ergebnisse einer plazebokontrollierten Doppelblind studie. Urologe B 28 (1988) 301-306.
5. Becker, H., L. Ebeling: Phytotherapie der BPH irdt Cernilton N - Ergebrilsse einer kontrollierten Verlaufsstudie. Urologe B 31 (1991) 113-116.
6. Bertermann, H., T Loch, H. Wirth et al.: Transrektale Sonographie der Prostata. Uro Imaging 1 (1991) 1-17.
7. Blacklock, N. J.: Urodynamic and psychometric observations and their implication in the management of prostatodynia. In Weidner, W, H. Brunner, W. Krause, C. F. Rothauge (eds.): Therapy of prostatifis. Klin. exp. Urol. 11 (1986) 201-206.
8. Blenk, H., A. Hofstetter: Quantitative Eiweifganalyse des Ejakulats. Laborbldtter 25 (1975) 166-173.
9. Blenk, H., A. Ho(stetter: Complement C 3, coeruloplasmin and PMN- elastase in the ejaculate in chronic prostato-adnexitis and their diagnostic value. Infection 19, Suppl. 3 (1991) 138-140.
10. Boyarsky, S., G. Jones, D. F Paulson et al.: A new look at bladder neck obstruction by the Food and Drug Administration regulators: guide lines for investigation of benign prostatic hypertrophy. Trans. Amer. Ass. gen.urin. Surgns 68 (1977) 29-33.
11. Braider, E., A. Brunner, Ch. Girshausen et al.: Psychosomatic and somatopsychological aspects of chronic prostatitis. In Weidner, W, H. Brunner, W. Krause, C. F. Rothauge (eds.): Therapy of prostatitis. Khn. exp. Urol. 11 (1986) 165-167.
12. Bruce, A. W, G. Reid: Prostatitis associated with Chlamyclia trachomatis in 6 patients. J. Urol. 142 (1989) 1006-1007.
13. Buck, A. C., R. Cox, R. W M. Rees et al.: Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernilton - a doubleblind placebo-controlled study. Brit. J. Urol. 66 (1990) 398-404.
14. Buck, A. C., R. W. M. Rees, L. Ebeling: Treatment of chronic prostatitis and prostatodynia with pollen extract. Brit. J. Urol. 64 (1989) 496-499.
15. Childs, S. J.: Ciprofloxacin in treatment of chronic bacterial prostatitis. Urology 35, Suppl. (1990) 15-18.
16. Doble, A., B. 1. Thornas: The role of Chlamydia trachomatis in chronic abacterial prostatitis: a study using ultrasound guided biopsy. J. Urol. 141 (1989) 332-333.

17. Drach, G. W: Prostatitis and prostatodynia. Their relationship to benign prostatic hypertrophy. Urol. Clin. N. Amer. 7 (1980) 79-88.

18. Drach, G. W, E. M. Meares Jr., W. R. Fair, T. A. Stamey: Classification of benign diseases associated with prostatic pain: prostatitis or prostatodynia? (Letter to the editor). J. Urol. 120 (1978) 266.

19. Ebeling, L.: Therapeutic results of defined pollen-extract in patients with chronic prostatitis or BPH accompanied by chronic prostatitis. In Weidner, W, H. Brunner, W. Krause, C. F. Rothauge (eds.): Therapy of prostatitis. Bain. exp. Urol. 11 (1986) 154-160.

20. Fowler, 1. E., Jr., M. Mariano: Difficulties in quantitating the contribution of urethral bacteria to prostatic fluid and seminal fluid cultures. J. Urol. 132 (1984) 471-473.

21. Gorelick, 1. L, B. S. Laurence, E. Darracott Vaughan Jr.: Quantitative bacterial tissue cultures from 209 prostatectomy specimens: findings and implications. J. Urol. 139 (1988) 57-60.

22. Greenberg, R. N., P. M. Reilly, K. L. Luppen et al.: Chronic prostatitis: comments on infectious etiologies and antimicrobial treatment. Prostate 6 (1985) 445-~8.

23. Habib, F K., A. C. Buck, M. Ross et al.: In vitro evaluation of the pollen extract, Cernitin ™ T-60, in the regulation of prostate cell growth. Brit. J. Urol. 66 (1990) 393-397.

24. Ireton, R. C., R. E. Berger: Prostatitis and epididymitis. Urol. Clin. N. Amer. 11 (1994) 83-94.

25. Ito, R., M. Ishii, S. Yamashita et al.: Cemitin pollen-extract (Cernilton); antiprostatic hypertrophic action of Cernitin ™ pollen-extract (Cemilton). Pharmacometrics (Jpn.) 31 (1986) 1-11.

26. Kimura, M., L Kimura, K. Nakase et al.: Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta med. 2 (1986) 148-151.

27. Kobayashi, T. K., L Sawaragi. Immunocytochemical detection of chlamydial antigen in both the urethral scraping and prostatic aspirate in a case of abacterial prostatitis (Letter to the Editors). Acta Cytol. 32 (1988) 270-272.

28. Kohnen, P. W, G. W. Drach: Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. J. Urol. 121 (1979) 755-760.

29. Kojima, H.: Chlamydial infection in urological field. Akt. Urol. 21 Suppl. (1980) 137-141.

30. Loschen, G., L. Ebeling. Hemmung der ArachidonsdureKaskade durch einen Extrakt aus Roggenpollen. Arzneim.-Forsch. /Drug. Res. 41 (1991) 162-167.

31. Meares, E. M., Jr.: Prostatodynia: clinical findings and rationale for treatment. In Weidner, W, H. Brunner, W. Krause, C. F. Rothauge(eds.); In Therapy of prostatitis. Klin. exp. Urol. 11 (1986) 207-212

32. Meares, E. M., T. A. Stamey: Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest. Urol. 5 (1968) 492-518.

33. Nakase, S., K. Takeraka, T. Hamanaka et al.: The effects of Cerriltin, pollenextract, on the urethral smooth muscle and diaphragmatic neuromuscular specimen. Folia pharmacol. jap. 91 (1988) 385-392.

34. O'Leary, W M.: Ureplasmas and human disease. Crit. Rev. Microbiol. 17 (1990) 161-168.

35. Oriel, 1. D.: Role of genital mycoplasmas in nongonococcal urethritis and prostatitis. Sex. transirdtt. Dis. 10 Suppl. (1983) 263-270.

36. Osborn, D. E.: Prostatodynia - clinical aspects. In George, N. J. R., J. A. Gosling (eds.): Sensory disorders of the bladder and urethra. Springer, Berlin 1986 (pp. 139143).

37. Osborn, D. E., N. 1. R. George, P. N. Rao et al.: Prostatodynia: physiological characteristics and their rational management with muscle relaxants. Brit. J. Urol. 53 (1981) 621-623.

38. Pfau, A.: Prostatitis. A continuing enigma. Urol. Clin. N. Amer. 13 (1986) 695-715.

39. Rugendorff, E. W: Low-close norfloxacin suppressive treatment of chronic bacterial prostatitis. J. Infect. Dis. 11 (1989) 789 (Abstract).

40. Sieck, R.: Quaht5tssicherung bei der Harnanalyse. In Haber, M. H. (Hrsg.): Farbatlas mikroskopische Harnanalytik. Urban & Schwarzenberg, Mimchen 1983 (S. 100-103).

41. Stuart, C. 1., 1. D. Jenkins, R. S. Lloyd: The painful prostate. Brit. J. Urol. 47 (1976) 861-869.

42. Takeuchi, H., A. Yantauchi, T. Ueda et al.: Quantitative evaluation of the effectiveness of Cernilton on benign prostatic hypertrophy. Acta Urol. jap. 27 (1981) 317326.

43. Thin, R. N., P. D. Simnons: Chronic bacterial and non bacterial prostatitis. Brit. J. Urol. 55 (1983) 513-518.

44. di Trapani, D., C. Pavone, V. Serretta et al.: Chronic prostatitis and prostatodynia: ultrasonographic alterations of the prostate, bladder neck, seminal vesicles and periprostatic venous plexus. Europ. Urol. 15 (1988) 230-234.

45. Vahlensieck, W, 0. Dzvorak Abgrenzung der rezidivierenden Prostatakongestion von der chronischen Prostatitis. Helv. chir. Acta 55 (1988) 293-296.

46. Weidner, W: Moderne Prostatitisdiagnostik. Min. exp. Urol. 7 (1984) 1-211.

47. Weidner, W: Neue Aspekte in der Therapie der infekti6sen Prostatitis mdt Gyrasehemmern. In Helpap, B., Th. Senge, W. Vahlensieck (Hrsg.): Die Prostata, Bd. 4. pmi Verlag, Frankfurt a.M. 1988 (S. 1-12).

48. Weidner, W, M. Arens, H. Krauss et al.: Chlamyclia trachomatis in'abacterial' prostatitis: n-dcrobiological, cytological and serological studies. Urol. int. 38 (1983) 146-149.

49. Weidner, W, H. G. Schiefer, A. Dalhoff. Treatment of chronic bacterial prostatitis with ciprofloxacin. Results of a one-year-follow-up study Amer. J. Med. 82, Suppl. 4A (1987).

* Submitted to Brit. J. Urol. 1992; with permission.
** Pharma Stroschein (licensed by Cernitin SA, CH-6903 Lugano) D-2000 Hamburg 61.

Phytotherapy of BPH with Cernilton® N

Results of a controlled clinical study

1. Becker1 and L. Ebeling2

Urology Department of the Marienkrankenhaus (Senior

Physician: Prof. Dr. H. Becker)

2. Medical Science/Clinical Research Department of Pharma

Stroschein GmbH (Head: L. Ebeling), Hamburg

Introduction

In a controlled clinical study in patients suffering from benign prostatic hyperplasia (BPH) the efficacy and the benefit/risk ratio of Cernilton® N is documented and its importance for the (long-term) treatment of this condition is discussed.

Treatment with phytopharmalogical reparations is well established in the therapeutic spectrum of benign prostatic hyperplasia and, on the basis of its high benefit/risk ratio, is recognized as a possible symptomatically oriented medication. Follow-up controls carried out within the framework of phytotherapy ensure that the indication for conservative treatment is regularly checked and, if necessary, revised. In view of the epidemiological knowledge concerning the comparatively rare indication of surgical intervention [2, 11] and the differentiated evaluation of TUR [7, 13], phytotherapeutic agents are used in BHP, preferably in the initial stages of the disease [2, 15,18].

Based on the positive therapeutic experience with Cernilton® N in benign prostatic diseases [6], we performed a clinical study in BHP patients in Stages II and III of the disease over a treatment period of 24 weeks, in which the standardized pollen-extract preparation Cernilton® N1 was investigated, according to a double-blind trial design, versus placebo, with separate follow-up phases for the two groups. The results of the double-blind phase have already been published [3].

This study, carried out in collaboration with 6 practising urologists in a representatve patient population, documents the therapeutic efficacy of Cernilton® N, which is attributed to the anticongestive and anti-inflammatory effects of the pollen extract.

Patients and method

With regard to the basic characterization of this clinical trial [3] it has to be established that the results of the double-blind study are confirmed in the trial population evaluated, and are therefore presented in the summarized pre/post comparison of Phase I. As an extension to the biometric methods, the variance analysis for the split-plot design of the time-points before the treatment, after Phase I and after Phase II is used.

The breakdown of BPH into Stages II and III was classified according to Vahlensieck [18] and the intensity of the disorders of miction according to the FDA recommendation [4]; the measurements of urinary flow are represented with reference to the urine volume, by means of the Uroflow Index [14].

Following the double-blind phase the active-drug and placebo groups were treated with Cernilton® N, according to an open trial design, whereby this follow-up phase also covers a 12-week study period. Due to discontinuation of the treatment (urine retention/TUR, lost capsules), premature withdrawal of the treatment (freedom from symptoms) in Phase I and non-inclusion of 7 patients in the follow-up phase, a total of 92 patients could be included in the biometric analysis. Of these, 45 patients were treated first with active drug and then with Cernilton® N, and 47 patients first with placebo and then with

Cernilton® N.

During Phase II neither the physicians nor the patients were informed which medication (placebo or active drug) had been given during Phase I, or with what general result, in order to avoid any subsequent effect on the trial results at the final control examination after 24 weeks. Deviations from the treatment plan occurred due to discontinuation or interruption of the treatment in three cases. The medication for concomitant diseases was changed in Phase II, in comparison with Phase 1, in one case.

Results

The comparative groups are homogeneous and their inclusion data correspond to those for the double-blind study [3]. The clinical symptomatology of BPH patients is determined by the leading symptom, nycturia, which was reported by almost all the patients. Concomitant diseases, mainly diseases of the cardiovascular system and metabolic diseases, were present in 54.3%, and concomitant medication, principally cardiovascular preparations and antidiabetics, was reported in 41.3% of the patients.

In the double-blind phase, statistically significant differences are documented in regard to nycturia, diuria (frequent urination during the day; pathological: >4 times a day), feeling of residual urine, volume of residual urine and overall assessment by the physician and the patient (Table 1).

Follow-up phase: Placebo - Cernilton® N

In comparison with the findings at the end of the double-blind and follow-up phases, after the change-over from the 12-week placebo medication to the also 12-week Cernilton® N therapy the following changes were observed.

The response, defined as asymptomatic or improved status following initially pronounced symptoms or findings, shows, for all the parameters studied, a marked increase in the number of patients in whom a regression of the symptomatology was recorded (Tables 2 and 3)

In the urodynamic parameters, a significant reduction of the residual urine volume (Fig. 1) and a further increase in the Uroflow Index values, from 0.79±0.27 to 0.97±0.25 (under placebo: from 0.70±0.31 to 0.79±0.27) were observed. Correspondingly, the overall assessment of the treatment as "very good" or

"good", by the physician and by the patient, is documented more frequently after the follow-up phase: in 63.8% and 66.0% of the cases, respectively (after the double-blind phase: 13.6% and 27.3%, respectively).

Follow-up phase: Active drug -Cernilton® N

In the patients treated firstly with active drug (Cernilton® N), the positive changes in the clinical symptoms, palpation findings and urodynamic test parameters observed after the subsequent 12-weeks treatment with Cernilton® N (Phase II), in comparison with the findings after Phase I, are slight when compared with the corresponding results in the placebo-Cernilton® N group (Fig. 1).

In the overall assessment of the treatment, after the active drug phase (Phase I) "very good" or "good" assessments by the physician and the patient were made in 58.1% and 72.1% of the cases, respectively, and after the subsequent Cernilton® N medication (Phase II) in 62.2% and 62.2% of the cases, respectively. The results after the total 24-week treatment period were assessed as poor by the patient in 4.4% of the cases and by the investigating physician in 13.3% of the cases.

Comparison of the treatment-groups

The findings concerning nycturia and volume of residual urine demonstrate that the therapeutic results under Cernilton® N in the placebo-Cernilton® N group correspond to those obtained under active drug (Fig. 1). In regard to the time-point of the effect on the following clinical symptoms and parameters, considerable differences were observed between the two treatment-groups: nycturia (P = 0.051), diuria (P = 0.039), feeling of residual urine (P = 0.013), enlargement of the prostate (P = 0.046) and congestion of the prostate (P = 0.030). In each case the earlier time-point was observed in the active drug-Cernilton® N group.

In Phase I the residual urine volume decreases significantly more markedly under active drug (P = 0.001); in Phase II there is a marked reduction (P = 0.002) in the placebo-Cernilton® N group. After Phase II the tolerability of Cernilton® N is assessed as "good" in 86 cases (93.5%) and as "satisfactory" in 6 cases (6.5%). Unwanted effects, given as pressure over the stomach and nausea, are recorded in 3 cases.

Discussion

The results of this controlled clinical study confirm the effectiveness of the pollen-extract preparation Cernilton® N in benign prostatic hyperplasia (BPH). Clear differences are demonstrated in favour of Cernilton® N for nycturia, diuria, feeling of residual urine and residual-urine volume and, in the comparison between the treatment-groups, also for enlargement of the prostate and congestion of the prostate. Also, in the comparison of the therapeutic results under active drug with those under Cernilton® N following initial placebo medication, an almost parallel course is to be observed. In regard to dysuria, pathological urge to urinate, malaise and the uroflow parameters, no statistically significant differences are to be observed.

In the patients treated with placebo in Phase I, marked improvement of miction is observed in the follow-up phase. In regard to certain of the parameters investigated, in particular diuria and feeling of residual urine, the continuous treatment with Cernilton® N leads to freedom from symptoms. For the leading symptom, nycturia, improvement is obtained in three-quarters of all the patients.

In regard to the urodynamic test parameters, the findings for the residual-urine volume show a stable course in the follow-up phase, after an initially marked reduction under active drug. The Uroflow Index also shows a continuous increase whereby, in spite of increased miction volume [8, 9, 14], the flow time and flow-increase time are reduced.

The continuous therapeutic efficacy of Cernilton® N inregard to the clinical symptomatology and the urodynamics, which also concurs with the results of a six-month, placebo-controlled, double-blind study with pollen extract in patients with comparatively advanced BPH [5], is reflected by the positive assessment of the treatment by the investigating physician and by the patient in over 80% and 90% of the cases, respectively.

The clinical relevance of changes in the congestion and inflammation of the prostate in BPH [2, 3, 12, 17, 18] is confirmed by the results of this clinical study, if a causal relationship with the irritative symptoms, and partly also with the obstructive symptoms, is assumed.

In this respect the differential diagnosis based on the urodynamics refers to the importance of the hyperactivity of the detrusor muscle, whereby the residual urine is also considered as a parameter of the performance of this muscle [9]. Assuming that the action of Cernilton® N is based on anti-oedematous effects, which lead to normalization of pathological changes in the neural supply, this is also suggested by the parallel improvements in the irritative symptoms and the residual-urine volume. Furthermore, an inhibitory effect of orally administered Cernilton® N on the hormonally stimulated growth of heterotransplants of BPH can be demonstrated in the nude-mouse model [19]. For a definitive evaluation of its clinical, human-pharmacolological relevance, more extensive studies are necessary.

Phytotherapy in BPH is characterized by a high benefit-risk ratio whereby, especially in disorders of frequency of miction, controlled long-term treatment is justified in view of the restrictive surgical indication [2, 7, 9, 11, 13, 18]. Although the clinical relevance of the treatment as an alternative to surgical intervention is not demonstrated [10], the main benefit is rather the improvement obtained in the subjectively experienced disturbance of miction. Therefore new drug developments [1, 16] need to be equally as effective as surgical intervention, unless tolerability equivalent to that of the phytotherapeutic agents is guaranteed.

Summary

In a controlled clinical study the efficacy and tolerability of the pollen-extract preparation, Cernilton® N, were studied in patients with BPH in Stages II and III (according to Vahlensieck) in 6 urology practices. In the 12-week Phase I of the trial Cernilton® N was studied according to a double-blind design versus placebo, and in the subsequent Phase II (follow-up), also of 12 weeks, according to an open trial design in the two comparative groups.

The evaluation, carried out in 92 patients, shows significant differences between active drug and placebo after the end of the double-blind phase, which level out at the end of the follow-up phase after the change-over to Cernilton® N in the group which received placebo during Phase I. The tolerability of Cernilton® N is assessed as "good" in 93.5% of the cases and as "satisfactory" in 6.5%. These results of a study in a representative patient population demonstrate the good efficacy of Cernilton® N in BPH in Stages II and III of the disease over a period of 24 weeks and documents the continuous therapeutic benefit of the pollen extract, which makes possible an effective long-term treatment of BPH.

Conclusions for medical practice

The continuous therapeutic efficacy of Cernilton® N makes low-risk long-term therapy possible. Antihormonally acting drugs have an equivalent benefit-risk ratio. Anticongestive therapy will continue to be the principal approach in the conservative treatment of BPH.

Acknowledgments: We thank our colleagues in Cologne, Dr. R.G. Kahrmann, Dr. J. Nuding, Dr. L. Pausch, Dr. G.-H. Rautenbach, Dr. J. Thissen and Dr. W.P. Winkler, and particularly their assistants, for their efforts in the realization of this study and for their excellent collaboration.

We also thank Dr. J. Schnitker and colleagues, of the Institute for Applied Statistics, Bielefeld, for the biometric evaluation, Intramed GmbH, Hamburg, for the presentation of the diagrams and Mrs. U. Bunke, for preparation of the manuscript.

Address of the author:
Prof. Dr. H. Becker
Urologische Abteilung
Marienkrankenhaus
Alfredstrasse 9
W-2000 Hamburg 76

Literature

1. Aumuller G., Enderle-Schmitt U, Seitz J (1988) 5alpha-Reduktase und Aromatase- Zielenzyme innovativer Therapieansatze der benignen Prostatahyperplasie. In: Helpap B, Senge T, Vahiensieck W (Hrsg) Prostataerkrankungen. pmi, Frankfurt/M, S 78-85

2. Bach D, Bruhl P (1989) Urologe [B] 29: 93

3. Becker H, Ebeling L (1988) Urologe [B] 28:301

4. Boyarsky S, Jones G, Paulson DF, Prout GR Jr (1977) Trans Am Assoc Urin Surg 68:29

5. Buck AC, Cox R, Rees RWM, Ebeling L, John A(1990)Br J Urol66:398

6. Buck AC, Rees RWM, Ebeling L (1989) Br J Urol 64:496

7. Chisholm GD (1983) Prostatectomy: Past and Present. In: Hinman F Jr (Ed) Benign prostatic hypertrophy. Springer, Berlin Heidelberg New York Tokyo, pp 35+

8. Drach GW, Steinbronn DV(1986) J Urol 135:737

9. Dreikorn K, Richter R (1988) Klin Exp Urol 19:89

10. Dreikorn K, Richter R, Schonhofer PS (1990) Urologe [A] 29:8

11. Glynn RJ, Campion EW, Bouchard GR, Silbert JE(1985)Am J Epidemiol 121:78

12. Helpap B (1989) Pathologie der ableitenden Harnwege und der Prostata. Springer, Berlin Heidelberg New York Tokyo

13. Malone PR, Cook A, Edmonson R, Gill MW, Shearer RJ (1988) Br J Urol 6l:234

14. Rohrborn C, Rugendorffew (1983) Z Urol Nephrol 76:721

15. Schilcher H, May P Sokeland J (1988) Urologe [B) 28:265

16. Schweikert H-U, Neumann F, Tunn UW (1989) Therapiewoche 39:1493

17. Sommerkamp H(1987)Klin Exp Uroll 4:52

18. Vahlensieck W (1985) Therapiewoche 36:4031

19. Wagner B, Otto U, Becker H, Schroder S, Klosterhalfen H (1991) Experimentelle Therapiestudien mit Cernilton® N an humaner benigner Prostatahyperplasie. Thieme, Stuttgart

Inhibition of the Arachidonic Acid Metabolism by an Extract from Rye Pollen

G. Loschen, L. Ebeling

Introduction

Clinical studies with a defined pollen extract preparation document its symptomatic efficacy in patients with benign prostatic diseases. In patients with benign prostatic hyperplasia (BPH) a significant reduction in nocturia and residual urine is observed (4,8). The continued improvement in symptoms (5) and a significant reduction in the anteriorposterior diameter of the prostate after six months of treatment (8) suggest a permanent pharmacological influence on pathophysiological alterations induced by the underlying disease. In patients with chronic non-bacterial prostatitis a significant improvement in symptoms or even a symptom-free status is achieved as it is in patients with prostatodynia. Furthermore, a reduction or even normalization of the white cell count in prostatic secretions has been documented (7).

Despite the fact that prostaglandins have been demonstrated for the first time in the prostate, and despite the fact that the entire group of substances received its name based on their increased presence in the prostate gland (10), little is known as of yet about their function in this particular organ. What is known, however, is that prostaglandins and leukotriens play an important role in inflammatory reactions (11). Furthermore, an etiologic role in the development of BPH has been suggested (1).

The majority of the known mediators of inflammation arise from the membranebound arachidonic acid. Their intracellular release by activation of phospholipases facilitates their enzymatic metabolism in a cascade of pharmocologically very potent reacation products. The biosynthesis of the eicosanoid-derived inflammatory mediators, which according to present pharmacological knowledge are of importance for the understanding of the pathologic alterations on a molecular level, is initiated by two enzymes: cyclo-oxygenase and 5-lipoxygenase.

The therapeutic effectiveness of many drugs can be explained by their interactions with enzyms that are responsible for individual steps in the metabolism of arachidonic acid (11). The clinical

effectiveness of the pollen extract in benign prostatic diseases therefore leads to the question, whether, and to what extent this extract influences the biosynthesis of prostaglandins and leukotriens in vitro.

Material

The examined pollen extract1 is produced by AB Cernelle, Engelholm (Sweden). It consists predominantly (greater than 90 %) of rye pollen (Secale cereale L.) as well as two other quantitatively relatively unimportant types of pollen. The exact composition can be obtained from the manufacturer. The pollen is extracted initially with water and thereafter with acetone. For the experiment discussed herein the water-soluble (wPE) and fatsoluble (fPE) fractions which were standardized for their content in a-amino-acids (18.3 % w/w) and for phytosterols (1.1 % w/w) were tested separately. The experiments were conducted in the research laboratories of Grünenthal GmbH, Aachen, Germany.

14C-marked arachidonic acid and the radioactive-marked metabolites of arachidonic acid (PGF2; PGE2; LTB4; 5-HETE) were purchased from Amersharn Buchler (Braunschweig, Germany). For the thinlayer chromatography, silica gel G 60 plates with fluorescent indicators and concentration zone were purchased from E. Merck, Darmstadt, Germany.

The thin-layer radiochromatography analyses were performed with the linear analyzer LB 2870, Berthold Company, Wildbad, Germany.

RBL-l cells (rat basophilic leukemia cells) were donated by Prof. P. Piper, Royal College of Surgeons, London. The medium for RBL-1 cells consisted of Eagles Medium, newborn calf serum, and fetal calf serum, L-glutamin, and a mixture of penicillin and streptomycin, and was purchased from Gibco, Karlsruhe, Germany. The cells were grown in spinner flasks (Bellco Glass Inc, Vineland, New Jersey, USA).

Lyophilized seminal vesicle microsomes were freshly obtained from slaughtered rams Oulius Kind OHG, Grevenbroich, Germany).

The Ca-Ionophor A 23 187 was purchased from Calbiochem, Frankfurt / Main, Germany. Indomethacin was purchased from Merck, Sharp and Dohme, Rahway, NJ (USA), and Naproxen from Syntex, Palo Alto, CA (USA).

All other solutions and reagents not described were either purchased from Boehringer Mannheim, Mannheim, E. Merck, Darmstadt, or Sigma, Miinchen, Germany.

Methods

Measurement of the Prostaglandin Biosynthesis (Cyclo-Oxygenase Activity)

25 µl lyophilized microsomes from ram seminal vesicle (1.8mg protein/m/d) are suspended in 975µl calcium phosphate buffer (50mmol/l, pH 7.5), and incubated in the presence of test substances together with 20 µmol/l 14C-arachidonic acid (150,000cpm/ml) for 10 minutes at room temperature.

The incubation reaction is stopped with 20 µl acetic acid and is extracted with 2ml of ethyl acetate. The extract is then compressed under N2 and separated on silica gel plates with a concentration zone in a solvent mixture of ether: hexan: acetic acid (50:50:1). This solvent is not suitable to separate the Prostaglandins but rather to quickly separate the non-metabolized arachidonic acid from its cyclo-oxygenase products. If a separation of the formed prostaglandins is desired, a solvent mixture of ether acetate: acetic acid = 99:1 (3 consecutive separations) is recommended.

The radioactivity distribution on the plate is measured thereafter using the TLC linear analyzer (Berthold Company). The radioactivity

of the formed cyclo-oxygenase products (starting peak) and the non-metabolized arachidonic acid (front peak) are calculated as a percentage of the total radioactivity.

Measurements are performed in triplicates and the means and standard deviations of the radioactive cyclo-oxygenase products are plotted against the logarithm of the test substance concentration. The concentration of test substance which leads after graphical interpolation to a 50% inhibition of the radioactive cyclo-oxygenase products is noted as IC50-value. Naproxen is used as a positive control of inhibition and is measured in each experiment to determine the IC50 value. The responding volume of the solvent for the test substances is used as blank (20 µl ethanol).

Measurement of Leukotrien Biosynthesis (5-Lipoxygenase Activity)

To search for inhibitors of the leukotrien biosynthesis, cell cultures of RBL-1 cells (rat basophilic leukemia cells) are particularly well suited.

RBL-1 cells are centrifuged for 20 minutes at 400 x g and are adjusted with potassium phosphate buffer (50mmol/ l; pH 7.4) to a cell count of 1.5 x 10 cells/ ml.

Indometacin (10µmol/l), the tested substance in various concentrations, 14C-arachidonic acid (20µmol/l cold plus approximately 100,000cpm radioactive arachidonic acid with a specific radioactivity of 56 mCi / mmol) and the Ca-Ionophor A 23 187 (20 µmol/l) are added to 1 ml of this cell suspension. After an incubation time of five minutes the assay is acidified with 20 µl of acetic acid and thereafter extracted twice with ethyl acetate. The extract is compressed under N2, then again resuspended with 20 µl ethyl acetate, and placed on silica gel thin-layer chromatography plates. The separation of the radioactive reaction products follows with two different solvents at 4 *C.

In the first solvent (ether: hexan: acetic acid=50:50:1) the plates are developed twice in immediate succession. In the second solvent (ethyl acetat:iso-octan: H20: acetic acid=110: 50:10:20; upper phase) the plates are only developed to approximately half the height of the plate. The radioactivity distribution is measured with the Berthold linear analyzer. 5-HETE and the LTB4-1somers (with a common peak) are separated by these two solvents from arachidonic acid, other monoHETEs (12-HETE and 15-HETE), and phospholipids and triglycerides. The 5-HETE peak and LTB4 peak (in the mixture of isomers of various LTB4 Isomers) are integrated with a TLC-Linear analyzer (Berthold Company) and are expressed as a percentage of the total radioactivity. Measurements are done in triplicate and means as well as standard deviations are plotted on semi-logarithmic paper against the inhibitor concentration. The IC50 value is graphically calculated by interpolation. In each experiment the IC50value for nordihydroguaiaretic acid (NDGA) is measured as a positive control. An equal volume of the used solvent for the test substances is used as blank.

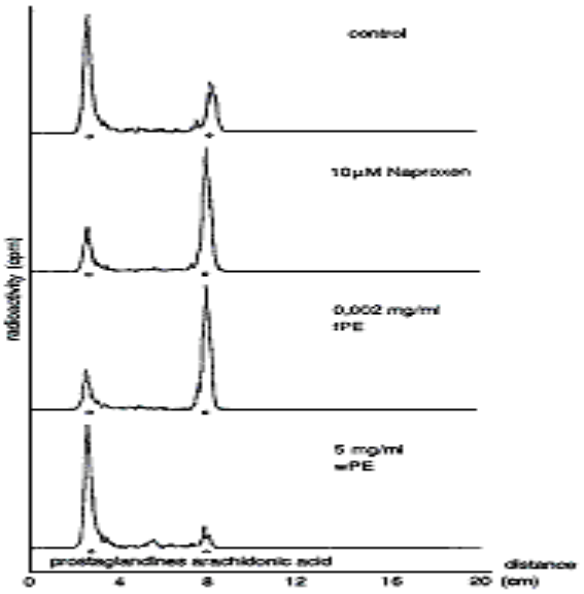


Fig. 1 Effect of the fat-soluble (fPE) and watersoluble (wPE) pollen extract fractions on the prostaglandin biosynthesis from radioactive-marked arachidonic acid in ram seminal vesicle microsomes in comparison to a non-steroidal anti-inflammatory agent (Naproxen).

Lyophilized microsomes from ram seminal vesicles are prepared according to the method of van der Ouderraa et al. (16). RBL-1 cells are grown in spinner flasks according to the instructions by Isersky et al. (12). The protein concentrations are measured according to the Lowry et al. method (13).

Results

The effect of both the fat-soluble (fPE) and water-soluble (wPE) pollen extract fractions on the biosynthesis of prostaglandins from radioactively marked arachidonic acid catalyzed by the cyclo-oxygenase in ram seminal vesicle microsomes is shown in Fig. 1.

Under identical conditions 14C-marked arachidonic acid was incubated in the presence of 5mg/ml water-soluble pollen extract (wPE, lowest chromatogram), 20µm/ ml fat-soluble pollen extract (fPE, second radio-chromatogram from bottom), 10 µmol / l Naproxen (non-steroidal anti-inflammatory agent and cyclo-oxygenase inhibitor), as well as 20 µl ethanol (solvent of the utilized test substances) and were incubated with ram seminal vesicles microsomes as the source for the enzyme.

After extraction of the radioactive reaction products and the subsequent thin-layer chromatography separation, two radioactive peaks are obtained. The starting peak contains the different cyclo-oxygenase products (Prostaglandin E2, F2, D2, G2, H2), which are not further separated with the chosen solvent. The front peak contains the rest of the non-metabolized arachidonic acid. A correlative comparison of the four radio-chromatograms shows that the fat-soluble pollen extract in a concentration of 20 µg/ml inhibits the biosynthesis of prostaglandins from arachidonic acid to approximately the same extent as the non-steroidal anti-inflammatory agent and cyclo-oxygenase inhibitor Naproxen in a concentration of 10 µmol/l.

The water-soluble pollen extract shows no significant inhibition of prostaglandin biosynthesis up to a contraction of 5 mg/ml in comparison to the control.

In a similar manner, the concentration-dependent inhibition of prostaglandin biosynthesis by the fat-soluble pollen extract was measured (Fig. 2).

Graphical interpolation resulted in an estimated 50 % inhibition of prostaglandin biosynthesis from arachidonic acid by the fat-soluble pollen extract at a concentration of only 5 µg/ml.

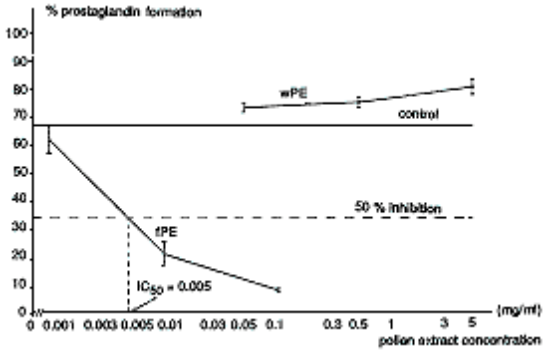
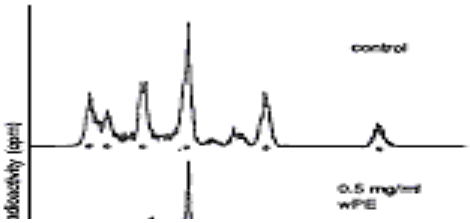


Fig. 2 Determination of the IC50-value for inhibition of prostaglandin biosynthesis (cyclo-oxygenase activity) from arachidonic acid (x ± SD) in ram seminal vesicle microsomes by the fat-soluble (fPE) pollen extract fraction (n = 3, related to the pollen extract concentration). 100% prostaglandin formation corresponds to a complete metabolism of 20µmol/ 1 14C-arachidonic acid.

In a similar fashion, the effect of both pollen extract fractions on the biosynthesis of leukotriens from arachidonic acid was investigated. We utilized cell cultures from rat basophilic leukemia cells (RBL-1 cells) as the source for the enzyme 5-lipoxygenase, which catalyzes the biosynthesis of leukotriens from arachidonic acid.



The effect of both pollen extract fractions on the leukotrien biosynthesis is initially again shown in the thin-layer radiochromatography (Fig. 3).

Under identical conditions RBL-1 cells were incubated in the presence of water-soluble (0.5 mg / ml) and fat soluble (0.2mg/ml) pollen extract together with the Ca-Ionophor A 23 187 and radioactive arachidonic acid. The three radio-chromatograms shown in Fig. 3 result after extraction of the radioactive reaction products and thin-layer chromatography separation. In the presence of fatsoluble pollen extract (fPE, bottom chromatogram) the enzymatic activity of 5-lipoxygenase is practically completely inhibited. The water-soluble pollen extract, however, shows no significant inhibition of the 5-lipoxygenase reaction (formation of 5-HETE and leukotrien B4-Isomers) in comparison to the control even if a 2.5-fold higher concentration (0.5 mg / ml) is utilized.

A 50 % inhibition of the leukotrien biosynthesis (5-lipoxygenase activity) is reached under these experimental conditions at a concentration of 0.08 mg / ml fat-soluble pollen extract (see Fig. 4). With the watersoluble pollen extract the leukotrien biosynthesis could not be inhibited in concentrations up to 5 mg / ml (data not shown). To judge the inhibitor effect of both pollen extract fractions on the prostaglandin and leukotrien biosynthesis in a therapeutic manner, the IC50-values for some known steroidal and non-steroidal anti-inflammatory agents were measured under the same conditions. Since the concentration of both pollen extract fractions cannot be expressed as a molar concentration, the concentration of the tested anti-inflammatory agents were converted from molarity to mg / ml to allow a better comparison of in vitro effectiveness. In Table 1 the IC50-values for the inhibition of leukotrien and prostaglandin biosynthesis are summarized. Table 1 demonstrates that the fat-soluble pollen extract fraction expressed as mg / ml inhibits the prostaglandin and leukotrien biosynthesis in vitro more than acetyl salicylic acid does, and equally as strongly as the non-steroidal anti-inflammatory agent diclofenac.

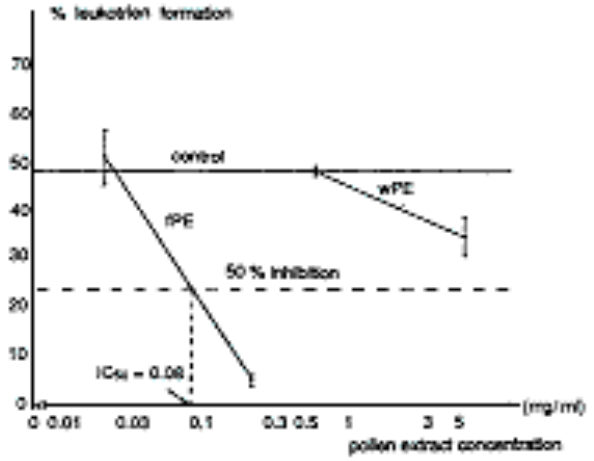


Fig. 4 Determination of the IC50-value for the inhibition of leukotrien biosynthesis (5-lipoxygenase activity) from arachidonic acid (-x ± SD) in rat basophilic leukemia cells (RBL-1 cells) by the fat-soluble (fPE) pollen extract fraction (n = 3, related to the pollen extract concentration). 100 % leukotrien formation corresponds to a complete metabolism of 20µmol/ 114 C- arachiclonic acid.

Discussion

The goal of this study was to test the effect of a defined pollen extract on the prostaglandin and leukotrien biosynthesis in vitro to develop a pharmacodynamically plausible hypothesis for its clinical effectiveness in patients with chronic prostatitis, BPH, and prostatodynia (also called prostate congestion [231]).

To determine prostaglandin and leukotrien biosynthesis, thin-layer chromatography was utilized and the radioactivity distribution of the formed cyclo-oxygenase and 5-lipoxygenase products as well as the non-metabolized arachidonic acid was investigated in ram seminal vesicles microsomes and RBL-1-cells.

The TLC documentation of the cyclo-oxygenase activity in this screening method is reliable and complete if influences on the metabolism of cyclo-oxygenase are tested.

Among the chemical-analytical methods of measurements for the influence on the 5-lipoxygenase pathway of the arachidonic acid cascade, thin-layer radiochromatography considers the sum of 5-HETE and the LTB4 isomers as representative for the 5-lipoxygenase products formed and does not capture peptidol leukotriens. This method is valuable in screening for 5-lipoxygenase in-hibitors if intact cultivated RBL-1 cells are utilized. To avoid the undesirable metabolism of arachidonic acid by the cyclo-oxygenase, indometacin is utilized in a sufficient inhibitory concentration. This does not affect the 5-lipoxygenase pathway.

The results document an inhibitory effect on the prostaglandin and leukotrien biosynthesis in vitro by the fat-soluble pollen extract. The inhibition of cyclo-oxygenase predominates. The inhibition of both cyclooxygenase and 5-lipoxygenase is dose dependent and the graphically determined IC50-values are approximately equal to those of diclofenac. The water-soluble pollen extract fraction, however, did not show a significant inhibitory effect on the arachidonic acid cascade in vitro.

Test substance	IC50-value 5-lipoxygenase (µmol/1)	(mg/ml)*	IC50-value Cclo-oxygenase (µmol/1)	(mg/ml)*
Pollen extract	-	0.08	-	0.005
Naproxen	215	0.0495	8	0.0018
Diclofenac	220	0.0623	26	.00074
Indometacin	240	0.0859	0.35	0.0002
Acetyl salicylic acid	>500	>0.090	375	0.0675
Paramethasone	>100	>0.053	>500	>0.267

* For better comparison of the inhibitory effects, the IC50-values of the anti-inflammatory agents were also expressed in mg/ml.

Tab. 1 Effect of the fat-soluble (fPE) pollen extract fraction on the prostaglandin and leukotrien biosynthesis in direct comparison with other anti-inflammatory agents.

Clinically the pollen extract has resulted in a reduction of pathologically increased white cell counts in prostatic secretions in patients with chronic non-bacterial prostatitis, with a concomitant decrease in dysuria and discomfort or pain in the inguinal, perineal, or genital area (7). In BPH and concomitant prostatic congestion, which also exhibits histological evidence for chronic inflammation and interstitial edema and the congestion of secretions in prostatic tissues (9,23), the symptomatic effect of the pollen extract leads to an improvement in the voiding dysfunction (4,5,7,8).

If the chronic inflammatory or congestive changes found in these benign prostatic conditions are considered as the pathophysiologically relevant substrate of the subjective complaints (5,23), the therapeutic effectiveness of the pollen extract could be the result of an intraprostatic inhibition of both the prostaglandin and leukotrien biosynthesis and a subsequent anti-edematous and antileukotactic effect of the fat-soluble fraction according to our in vitro results.

Furthermore, other effects, not primarily related to inflammation, are possibly relevant for the therapeutic mechanism of the pollen extract. The prostaglandin-modulated contraction of smooth muscle cells (19) resulting in coordinated voiding by bladder and urethral smooth muscle might also be influenced by an inhibition of the cyclo-oxygenase. Therefore a relaxation of the prostatic urethra could also explain urodynamic improvements after treatment with pollen extract such as the

reduction in residual urine and the improvement in average and peak urinary flow rate (4,5,7,8) (these parameters are found to be abnormal in patients with benign prostatic diseases (6,14,18)). Concerning the 5-lipoxygenase inhibition, no indications for a relaxation of the SRS-A (slow reacting substance of anaphylaxis)-induced contraction in vivo are available.

A further possible pharmacological effect of the pollen extract in patients with BPH could be a prophylactic or pathophysiologically relevant effect concerning hormonal or immunological metabolic processes in the prostate. Prostaglandins and leukotriens are suspected of being involved in the etiology and pathogenesis of BPH as a result of eicosanoid-dependent dysregulations (1, 17). A dose-dependent inhibition of the 5(a-reductase and the 3(a- and 3ß-hydroxysteroid-dehydrogenase which regulate the intraprostatic testosterone metabolism in the epithelium and stroma of BPH homogenates has been documented in vitro for the fatsoluble pollen extract fraction (M. Krieg, personal communication, publication in preparation). Whether and to what extent these results may be connected to our findings and to what extent these results are of pharmacological importance in humans has to be tested in further studies.

Treatment with ß-sitosterin, a phytosterol. also contained in rye pollen (21), has led to a decrease in the prostaglandin concentration in BPH tissue (24) and in the prostatic secretion of BPH patients (2). Concerning the discussed pharmacodynamical effects of the fatsoluble pollen extract fraction with a ß-sitosterin content of 8.3 % (w/w), these in vivo results do not allow any further conclusions since data concerning the above-mentioned metabolic parameters were not measured. The documentation of inhibition of the phospholipase A2 by free fatty acids (3), which are also contained in the fat-soluble pollen extract fraction (30 %; w/w) merely demonstrates that a pharmacological effect on the production of arachidonic acid from phosphatides with subsequently reduced substrate for cyclo-oxygenase and 5-lipoxygenase is possible.

Concerning the use of non-steroidal antiinflammatory agents for benign prostatic diseases, not much is known with the exception of an unsuccessful treatment of non-bacterial prostatitis with ibuprofen (400 mg po tid over 90 days) in a pilot study (22). Clinical experiences with the pollen extract in other typical indications for non-steroidal anti-inflammatory agents are also lacking. A comparison of desirable effects on the basis of in vivo studies is therefore not possible. Side effects associated with a generalized prostaglandin deficiency such as damage to the gastric mucosa (15), as it is characteristic for cyclo-oxygenase inhibition (11), has not been reported after the use of pollen extracts in humans. The side effects known to occur in humans after the use of non-steroidal anti-inflammatory agents are therefore not seen in the treatment with the pollen extract. Gastrointestinal complaints can occur (4, 5), however, but their incidence is rather rare and the intensity of these side effects is mild or moderate.

In drug extracts a number of different chemical compounds are contained some of which, in the case of the pollen extract, ß-sitosterin and free fatty acids, are pharmacologically effective. Therefore a clear determination of the clinical relevant substance or substances and their bioavailability is often not possible. This is particularly true for the pollen extract since even the water-soluble fraction has shown a significant growth inhibition of cultivated prostate cells in experimental studies (F K. Habib, Edinburgh, personal communication, publication in preparation). The possible explanations for the different side effect profiles of pollen extract and non-steroidal anti-inflammatory agents are therefore limited.

If identical conditions are assumed, the clinically utilized daily dosages of pollen extract (fat-soluble fraction) and diclofenac are 12 and 50

mg, respectively, which inhibit in vitro the prostaglandin and leukotrien biosynthesis in an equivalent fashion. Considering in addition the reduction of the production of arachidonic acid by the free fatty acid of the pollen extract, and the inverse relationship between orally taken dose and relative serum concentration as has been demonstrated for diclofenac (20), it is evident that the pharmacologically necessary dose of the pollen extract is comparatively low.

If one assumes a mechanism of action for the fat-soluble pollen extract fraction that is not completely or partially independent in relation to the eicosanoids, it seems reasonable to assume that the pollen extract in the usual dosage does not inhibit local prostagiandin biosynthesis in the mucosal cell layer of the gastrointestinal tract to an extent that it would cause undesirable side effects. At the same time, however, in the prostate and/ or periurethrally, a therapeutically necessary concentration may be reached. The chronic form of congestive and inflammatory processes in benign prostatic conditions which can be treated with a lower concentration of drugs in comparison to the acute inflammatory processes is another indicator for this hypothesis.

Our in vitro experiments concerning the influence of a pollen extract on the arachidonic acid cascade require animal experiments and pharmacological confirmation in humans to determine the value of the assumed therapeutic mechanisms of action, namely anti-congestive, anti-inflammatory, relaxant, and antiproliferative. This does not affect the possible relevance of the watersoluble pollen extract fraction for clinical effectiveness.

In summary we conclude that the in vitro inhibition of the prostaglandin and leukotrien biosynthesis by the fat-soluble pollen extract fraction offers a pharmacologically plausible explanation for the clinical effectiveness and the underlying mechanism in the therapy of benign prostatic conditions with the pollen extract.

Summary

A standardized extract mainly from rye pollen (Cemilton®) was tested in vitro on the inhibition of prostaglandin and leukotrien synthesis. The determination of the prostaglandin and leukotrien synthesis from labelled arachidonic acid was done in microsomes of ram seminal vesicles and in rat basophilic leukemia cells (RBL-1 cells). The water-soluble and fat-soluble extract fraction from the whole pollen extract were tested separately. The radio-TLC separation of the reaction metabolites showed a dose-dependent inhibition of the cyclo-oxygenase and the 5-lipoxygenase activity by the fat-soluble pollen extract fraction. The IC50-values of 0.005 mg/ml and 0.08 mg/ml, respectively, were similar to those of diclofenac, which was also tested. The water-soluble fraction showed no effect on this test system. According to these in vitro results and clinical experience with the pollen extract so far, its therapeutic efficacy on benign prostate diseases is best explained by the anticongestive, anti-inflammatory effect of the fat-soluble fraction. Due to the different actions of prostaglandins and leukotriens, relaxant and antiproliferative effects are also conceivable.

Acknowledgements

We wish to thank M. Urken, W Debarry and D. Dunkel for the experimental studies and the graphic illustrations.

References

1. Badi, D., H. Walker.- Urol. int. 37 (1982) 160.
2. Bach, D., H. Walker, H. P. Zahradnik: Therapiewoche 35 (1985) 4292.
3. Ballou, L. R., W. Y. Cheung: Proc. Natl. Acad. Sci. 82 (1985)371.
4. Becker, H., L. Ebeling: Urologe B 28 (1988) 301.
5. Becker, H., L. Ebeling: Urologe B (in press).
6. Blacklock, N. J.: Khn. exp. Urol. 11 (1986) 201.

7. Buck, A. C., R. W. M. Rees, L. Ebeling: Brit. J. Urol. 64 (1989)496.

8. Buck, A. C., R. Cox, R. W. M. Rees, L. Ebeling, A. john: Brit. J. Urol. 66 (1990) 398.

9. Dworak, 0., W. Vahlensieck: In Helpap, B., Th. Senge, W. Vahlensieck (eds.): Prostataerkrankungen. pmi-Verlag, Frankfurt/Main 1988 (S. 20).

10. von Eular, U. S.: J. Physiol. 84 (1935) 21.

11. Flohé, L., G. Loschen: Allergologie 5 (1982) 156.

12. Isersky, Ch., H. Metzger, D. N. 1. Buell: Exp. Med. 141 (1975) 1147.

13. Lowry, 0. H., N. J. Rosebrough, A. L. Farr, R. J. Randall: J. Biol. Chem. 193 (1951) 265.

14. Meares, E. M., Jr.: Min. exp. Urol. 11 (1986) 207.

15. Menassé-Gdynia, R., P. Krupp: Toxicol. Appl. Pharmacol. 29 (1974) 389.

16. van der Ouderraa, F. J., M. Buytenhock, D. H. Nugteren, D. A. van Dorp: Biochim. Biophys. Acta 487 (1977) 315.

17. Pegel, K. H., H. Walker: Extr. UroL 7 (1. Suppl.) (1984) 91.

18. Schäfer, W. In: Hinrnan, F., Jr. (ed.): Benign Prostatic Hypertrophy. Springer, New York 1983 (p. 450).

19. Schrör, K.: Prostaglandine und verwancite Verbindungen. Thieme, Stuttgart 1984.

20. Skoutakis, V. A., C. A. Carter, T. R. Mickle, V. H. Sinith, C. R. Arkin, 1. Alissandratos, D. E. Petty: Drug Intell. Clin. Pharm. 22 (1988) 850.

21. Stanley, R. G., H. F. Linskens: Pollen. Urs Freund Verlag, Greifenberg/Ammersee 1985.

22. Thin, R. N. T.: Min. exp. Urol. 11 (1986) 145.

23. Vahlensieck, W. In: Helpap, B., Th. Senge, W. Vahlensieck(eds.): Prostatakongestion und Prostatitis. pmi-Verlag, Frankfurt/Main 1985 (S. 1).

24. Zahradnik, H. R, R. Schillfahrt, R. Schoening, K. D. Ebbingliaus, U. Dunzendorfer. Fortschr. Med. 98 (1980) 69.

* Published in Arzneim.-Forsch./Drug Res. 41 (1), Nr. 2 (1991) 162-167.

[1] Cernilton®; composition: 23 mg pollen extract consisting of 20 mg water-soluble and 3 mg fat-soluble extract fractions. Pharma Stroschein (licensed by Cernitin ™ SA, Lugano, Switzerland), Hamburg.

Clinical evaluation of Cernilton on benign prostatic hypertrophy-a multiple center double-blind study with Paraprost

Maekawa M, Kishimoto T, Yasumoto R, Wada S, Harada T, Ohara T, Okajima E, Hirao Y, Ohzono S, Shimada K, et al

A multiple center double blind study was performed to study the effectiveness of Cernilton (CN) on benign prostatic hypertrophy in comparison to Paraprost (PP). Among a total of 192 patients, overall effect was studied on 159 patients, overall safety rate on 178 patients and rate of effectiveness on 159 patients. There were no differences between the two groups in the selected patients, criteria for exclusion and drop out cases or background data of the patients. Impression of patients and overall effect by committee and physician judgment were slightly higher in the CN group compared to the PP group, but there was no significant difference between the two groups.

For the improvement in subjective symptoms, the rate of moderate improvement or more after 4 weeks by committee judgement was higher in the CN group compared to the PP group. The rate of improvement in protracted miction, which is an effective marker of urinary disturbance, was also higher in the CN group compared to the PP group. An analysis of objective symptoms showed a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the CN group. A significant improvement in the phased change of residual urinary volume was also seen in the CN group. No side effects or abnormalities in clinical test levels were noted in the CN group. By committee judgment, the rate of more than moderate effectiveness was 49.1% in the CN group compared to 41.2% in the PP group, but there was no significant difference between the two groups.

By physician's judgment, the rate of more than moderate effectiveness was 49.4% in the CN group compared to 46.3% in the PP group, but there was also no significant difference between the two groups. These results suggested that Cernilton was an effective drug for benign prostatic hypertrophy.

Publication Types:
- Clinical trial
- Controlled clinical trial
- Multicenter study

PMID: 1696065, UI: 90334079
Department of Urology
Osaka City University, Medical School*Hinyokika Kiyo*
1990 Apr;36(4):495-51

Effects of Pollen-Extract Components, Diamines and Derivatives of Feruloylputrescine on Isolated Bladder and Urethral Smooth Muscles of Mice

Nakase K, Kimura I, Kimura M.

Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Japan.

Jpn J Pharmacol. 1990 Jun; 53(2):157-64.

The contracting or inhibitory effects of pollen-extract components, diamines and derivatives of feruloylputrescine (FP) were investigated on the isolated bladder or urethral smooth muscles of mice. Among the nine diamines (NH2.(CH2)n.NH2, n = 2-10) tested, five of them with shorter carbon chains (n = 2-6) (0.1-30.0 mM) only slightly contracted the bladder strips and to some extent inhibited the noradrenaline (NA, 1.77 microM)-induced contraction of urethral strips. 1,5-Diaminopentane (C5), a component of the pollen-extract, inhibited most effectively the NA-induced contraction of urethral strips with an IC50 value of 2.3 mM (95% confidence limit: 2.0-2.6 mM). FP, also a component of the pollen-extract, inhibited the NA-induced contraction of urethral strips in a non-competitive manner, producing 32.5 +/- 5.5% (N = 5) inhibition at 378 microM. Among the derivatives of FP, feruloylcadaverine inhibited urethral contraction most potently, producing 46.3 +/- 7.1% (N = 5) inhibition at 359 microM. These derivatives had no effect on bladder contraction. In contrast, four diamines with longer carbon chains (n = 7-10) contracted the bladder strips (3-30 mM) and potentiated the NA-induced contraction of urethral strips (10 microM-3 mM). Thus, the components of the pollen-extract, FP and C5, potently inhibited urethral contraction, which may facilitate the discharge of urine in vivo.

PMID: 2385002 [PubMed - indexed for MEDLINE]

In Vitro Evaluation of the Pollen Extract, Cernitin T-60, in the Regulation of Prostate Cell Growth

F.K. HABIB, MARGARET ROSS, A.C. BUCK, L. EBELING and A. LEWENSTEIN

University Department of Surgery (WGH), Western General Hospital, Edinburgh; Department of Urology, Royal Infirmary, Glasgow; Cernitin S.A., Lugano, Switzerland

Summary

Nine human-derived cancer and non-cancer continuous cell lines were employed to evaluate the relative in vitro activity of the pollen extract, Cernitin T-60. Responses of the cell lines to the drug were assessed by measuring growth and cell survival as determined by cell count. The results demonstrated that of the 9 continuous cell lines tested, only those derived from the human prostate were growth inhibited by the pollen extract, whereas the non-prostate derived cells exhibited variable degrees of resistance to the T-60. The selectivity of the drug for the prostate cell lines was even more pronounced on the hormone- independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells.

In spite of the considerable advances in our understanding of the processes leading to the growth and proliferation of the human prostate, the management of prostate, the management of prostate diseases still remains a major clinical problem (Chisholm, 1989). Cancer of the prostate is the second most common cause of death due to cancer in males in the United Kingdom (Cancer Research Campaign, Factsheet 10.1, 1988) and the death rate is increasing. Clearly, the traditional forms of treatment such as surgery at the primary site, orchiectomy, hormone treatment and radiation are not as effective as Huggins might have originally perceived (Huggins and Hodges, 1941) and there is now every reason to fond an alternative form of treatment.

Recently, there have been several reports suggesting that the pollen extract, Cernilton, is an effective agent in the treatment of prostate disease (Ito et al., 1986; Buck et al., 1989). The pollen extract is a preparation produced by AB Cernelle in Sweden and is essentially a microbial digestion of a mixture of pollens which have been extracted first in water and subsequently with an organic solvent (Kimura et al., 1986).

In an attempt to assess the selectivity and specificity of these pollen extracts, we undertook a number of experiments to compare the *in vitro* activity of Cernilton towards a wide range of human-derived cancerous and non-cancerous continuous cell lines of prostate and non-prostate origin. We confined our experiments to the water-soluble fraction T-60 component, which accounts for approximately 60% of the pollen extract. In addition, we also undertook a few experiment son benign hyperplastic prostates to test the impact of the pollen extract on testosterone metabolism and the binding of androgens to their receptors.

Materials and Methods

Chemicals

Cernitin T-60 was a gift from AB Cernelle, Helisingborg, Sweden.

Tissues

Specimens of benign prostatic hyperplasia (BPH), obtained by transurethral resection, were transferred to the laboratory and either used immediately or snap frozen in liquid nitrogen and stored at -70° C.

Cell cultures

The epithelial and fibroblastic cell lines were all derived from human cancerous and non-cancerous tissue and details of their sources are given in Table 1. Of the 3 human prostate cancer cell lines investigated, the LNCaP model is the only one which is hormonally responsive (Horosewicz et al., 1983), whereas the other 2 cell lines, the DU145 (Stone et al., 1978) and the 1013L (Williams, 1980) were all hormone-insensitive. All cell lines were maintained at 37° C under a humidified atmosphere at 5% CO2 and 95% air in 75cm2 tissue culture flasks (Corning, NewYork, USA). The culture medium used was RPMI-1640 (Gibco, Paisley) supplemented with 10% (v/v) fetal calf serum, 20 mM HEPES, penicillin (100 units/ml), streptomycin (100m g/ml) and 1% (v/v) L-glutamine. At each transplant, cells from the confluent monolayer were removed by trysinisation (trypsin 0.05%, EDTA 0.025%, Gibco) and suspended at 5x10 4 cells/ml in the growth medium.

Growth assays

Dose-response curves of Cernitin T-60 treatment were determined using the following method. Triplicate determinations for each treatment were performed in 24 well culture plates (Cell-Cult, Sterilin, Teddington). Each well was seeded with 5x10 4 cells and incubated overnight in the medium under incubation conditions as described above for routine cell culture. The following day, the T-60 stock solution was serially diluted in supplemented RPMI 1640 medium to yield concentrations of 1-4 mg/ml. Controlled cultures receive medium alone. For the dose-response curve studied, the cells were exposed to Cernitin T-60 for a total period of 4 days, with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 for 1, 2, 3, or 4 days. Experiments were terminated by the removal of cells from the monolayer by 2 successive trypsinisations and the pellets of harvested cells were subsequently suspended in 0.5 ml of Dulbecco A Medium (Oxoid Ltd, Basingstoke). The counting of cells was achieved on a haemocytometer slide after a 1-2 dilution with trypsin/ glutamine.

Nuclear androgen receptors

Method used for the preparation of nuclear fractions and measurements of androgen receptors followed those previously published (Habib et al., 1986). For androgen receptor

determinations, the competition binding assay was with 17a -methyl-3H-methyltrienolone (R1881) in the presence of triamcinolone acetonide. Dissociation constants (Kd) and number of binding sites were determined by the Scatchard (1949) method.

Assay for 5a -reductase activity

5a -reductase was assayed at 37° C by following the conversion of (3H) testosterone to (3H) dihydrotestosterone and (3H) 3a)b) androstanediol as previously detailed Habib et al., 1985).

Results

The effect of T-60 on cell growth

Table 1 Details of Cell Lines

Proliferation curves of the hormone-sensitive and hormone-insensitive prostate cell lines in the Absence and presence of increasing concentrations of T-60 for periods of up to 4 days are shown in Figure 1. Although the growth of each of these prostate cell lines was slowed following the addition of the pollen extract, the results show that the inhibition was much more marked in the case of the androgen-insensitive cell lines. Indeed, at 1mg/ml the pollen had no effect on the growth of the LNCaP cells, which exhibited an identical profile to that of the control, whereas the androgen-insensitive 1013L and DU145 cells demonstrated significant inhibition, particularly on day 4. By contrast, at the higher pollen concentrations (4mg/ml) the growth of all 3 prostate cell lines was arrested and the cell numbers were rapidly depleted with the time of exposure. After 4 days, cell counts had been reduced by an average of 94% compared with controls.

Parallel experiments on the non-prostate derived cell lines showed no response to pollen extract (1mg/ml) even after 4 days' exposure (Fig.2). However, at the higher concentrations (4mg/ml) the pollen induced some inhibition with the HEF and RT112 cells (P< 0.01) following a 4-day incubation (Fig. 2), although this was not as marked as in the prostate cells. Significantly, none of the other non-prostate derived cells showed any significant response (P> 0.5).

The effect of T-60 on androgen metabolism and steroid receptors

We also tested the impact of increasing concentrations of Cernitin T-60 (0-10mg/ml) on the 5a -reductase activity of tissue obtained from 6 separate BPH patients. As demonstrated in Table 2, there was no change in the activity of the enzyme with increase in T-60 even at concentrations as high a 10mg/ml.

Table 2 Effect of T-60 Concentrations on 5a -Reductase Activity of the Human Benign Prostate

Table 3 Effect of Cernitin T-60 (4mg/ml) on Nuclear Androgen Receptor Measurements in 6 BPH Specimens

In addition, we undertook several experiments to measure nuclear androgen receptor levels in the absence and presence of the pollen extract at 4mg/ml. The results summarized in table 3 indicate that there was no significant difference between the control and test groups with regard to the number of binding sites (P> 0.5) and dissociation constants (p> 0.5).

Fig 1 The effects of varying the concentrations of Cernitin T-60 on the growth of androgen-sensitive and androgen-insensitive prostate cell lines. Each point represents the mean ± SD of 3 separate experiments each run 6 times.

Fig. 2 The effect of Cernitin T-60 on the growth of 6 non-prostate derived cell lines after 4 days' exposure to the drug. Results are the mean ± SD of 3 separate experiments each run 6 times (P> 0.01).

Discussion

These data represent the first report of the in vitro evaluation of the water-soluble fraction of

the pollen extract, Cernitin T-60, using a panel of human prostate tumor-derived continuous cell lines. In addition, parallel in vitro experiments were also undertaken on 6 other cell lines derived from non-prostatic sources essentially to assess the specificity and efficacy of pollen extract.

Attempts to minimise variations between experiments were made by standardising experimental conditions with regard to the same medium, fetal calf serum concentrations, and narrow range of cell passages. Furthermore, we observed a little variation in drug response with repeated experiments for each particular cell line. Nonetheless, the results of this study suggest that the responses induced were varied and these were predominantly a function of the cell lines: high in the case of the prostate, low or non-existent in the non-prostate derived cells. Of interest also is the heterogeneity in responses of the prostate cell lines to the agent. The hormone-insensitive cells demonstrated a greater sensitivity to the pollen extract than the androgen-dependent line and this was particularly evident at the lower pollen concentrations.

We are not yet sure of the mechanism of action of this drug but quite obviously it is not mediated via the androgen delivery system of the cell, since the pollen had no effect on either the 5a - reductase activity of the tissues or its steroid receptors. There have also been reports suggesting that Cernilton might be a potent inhibitor of the cyclo-oxygenase and lipoxygenase enzymes which are needed for leucotrine and prostaglandin synthesis (Loschen, personal communication) but these reports have not been extended to the prostate and will require verification.

However, it is gratifying to note that the selectivity of the pollen extract for the prostate, as demonstrated in the present study, was also supported by the work carried out by Ito et al. (1986). Following an intake of Cernilton over a period of 21 days, the rats in the latter study showed significant reductions in the weight of the ventral and dorsal prostate but there was no change in any of the other major organs. Following these encouraging results, a double-blind trial was undertaken on a group of patients with BPH, the results of which are described by Buck et al. (1990).

References

Buck, A.C. Cox, R., Rees, R. W. M. et al. (1990). Treatment of outflow tract obstruction due to benign prostatic hypertrophy with the pollen extract, Cernilton.

A double-blind, placebocontrolled study. Br. J. Urol., 66, 398-404.

Buck, A.C., Rees R.W. M. and Ebeling, L. (1989). Treatment of chronic prostatitis and prostatodynia with pollen extract. Br. J. Urol., 64, 496-499.

Chisholm, G.D. (1989). Benign prostatic hyperplasia. The best treatment. Br. Med. J., 299, 215-216.

Habib, F.K., Odoma, S., Busuttil, A. et al. (1985). 5a - reductase activity in human prostate cancer is related to the histological differentiation of the tumour. Clin. Endocrinol., 23, 431-438.

Habib, F.K., Odoma, S., Busuttil, A. et al. (1986). Androgen receptors in cancer of the prostate, correlation with the stage and grade of the tumor. Cancer, 57, 2351-2356.

Horoszewicz, J. S., Leong, S. S., Kawinski, E. et al. (1983). LNCaP model of human prostatic carcinoma. Cancer Res., 43, 1809-1818.

Huggins, C. and Hodges, C.V. (1941). Studies on prostatic cancer. I. The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res., 1, 293-297.

Ito, R., Ishi, M., Yamashita, S. et al. (1986). Cernitin pollen extract (cernilton): antiprostatic, hypertrophic action of cernitin pollen extract. Pharmacometrics, 31, 2-14.

Kimura, M. Kimura, I., Nakese, K. et al. (1986). Micturition activity of pollen extract: contractile effects

on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Medica, 2, 148-151.

Scatchard, G. (1949). The attractions of proteins for small molecules and ions. Ann N.Y. Acad. Sci., 51, 660-672.

Stone, K.R., Mickey, D.D., Wunderli, H. et al. (1978). Isolation of a human prostate carcinoma cell line (DU145). Int. J. Cancer, 21, 274-281.

Williams, R.D. (1980). Human urologic cancer cell lines. Invest. Urol., 17, 359-363.

The Authors

F.K. Habib, PhD, Cchem, FRSC, Senior Lecturer in Biochemistry, University Department of Surgery, Western General Hospital, Edinburgh.

Margaret Ross, BSc, Research Technician, University Department of Surgery, Western General Hospital, Edinburgh.

A.C. Buck, PhD, FRSC, Consultant Urologist, Royal Infirmary, Glasgow.

L. Ebeling, MD, Medical Associate, Hamburg, Germany.

Lewenstein, PhD, General manager, Cernitin S.A., Lugano, Switzerland.

Requests for reprints to F.K. Habib, University department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

Treatment of Outflow Tract Obstruction Due To Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton ® - A Double-Blind, Placebo-Controlled Study

A. C. Buck, R. W. M. Rees, L. Ebeling, A. John

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; Habib et al., 1981; Stone et al., 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological.

More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symptoms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of "prostatism", interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade (Lancet, 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH (Takeuchi et al., 1981; Becker and Ebeling, 1988) prompted us to carry out a placebo-controlled, doubleblind study to evaluate its effect in patients with outflow obstruction due to BPH.

Patients and Methods

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean 68.6 ± SD 7.7). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules bd over a 6-month period.

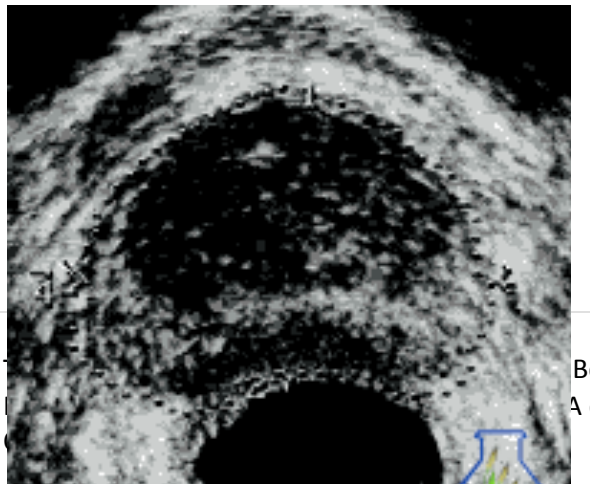
The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes < 150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was

scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling and dysuria, with a score of 0-3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) (Boyarsky et al., 1977).

In addition, a full haematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipo-proteins. All blood samples were obtained between 09.00 and 10.00 h, following an overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

Statistical Method and Analysis



The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of X2 tests for categorical data, X2 test with Yates' correction (4-fold tables) and Student's t test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the X2 test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anaemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight (P0.05).

Subjective Evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups (P = 0.66), but 60 % of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30 % of patients on placebo (P < 0.063). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10 % in the placebo group (P < 0.004). There were no significant differences in hesitancy (P= 0.48), urgency (P=0.157), intermittency (P= 0.5), terminal dribbling (P = 0.9) or dysuria (P = 1.0). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group (69 % of patients) compared with patients in the placebo group (29 %) (P < 0.009) (Table 1).

Tab. 1 Frequency of Symptom-free Findings following C and Placebo at 6

	Response Rate (%)		
Symptom	*Cernilton*	*Placebo*	*P value*
Frequency			
Daytime	37	47	0.664
Nocturia	60	30.4	0.063*
Hesitancy	47	29	0.480
Urgency	71	45	0.157
Intermittency	52	33	0.505
Incomplete emptying	57	10	0.004*
Terminal dribble	61	56	0.99
Dysuria	62	71	1.0

*Statistically significant. Some test results remained non-sig because of the small number of positive findings before the treatment.

Objective Evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume (slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving

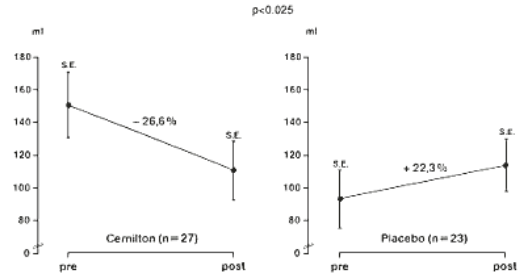


Fig.2 Residual urine volume.

Cernilton compared with the placebo group, in whom it increased (P < 0.025) (Fig. 2)

The results of ultrasound measurement of the parameters for prostate volume are shown in Table3. The A-P diameter was found to be significantly reduced after treatment with Cernilton at 6 months (P<0.025) (Fig. 3).

There were no significant changes in the haematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term,

whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms or retention (Fowler et al., 1988). Thus there may be a place for therapeutic compounds that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery.

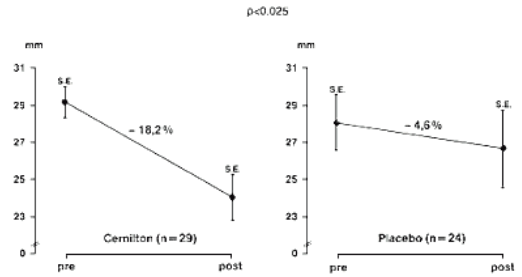


Fig.3 Prostate volume.

Several studies aimed at achieving androgen deprivation in BPH have been reported. These have included castration (Huggins and Stevens, 1940), oestrogens (Beacock et al., 1985), progestogens (Geller et al., 1965; Hald and From, 1972), anti-androgens (Caine et al., 1975) and, more recently, LH-RH agonists (Gabrilove et al., 1987; Peters and Walsh, 1987). With the introduction of selective xl adrenergic blockers, there has been renewed interest in their use for symptomatic relief (Caine, 1986; Kirby et al., 1987). The discovery of high concentrations of cholesterol in BPH has led to the use of cholesterol-lowering drugs such as candicidin, with variable results (Jensen and Madsen, 1983). However, none of these compounds has proved to be consistently effective and most have significant untoward side effects.

An interesting empirical approach to the non-adrenergic, non-hormonal treatment of symptomatic BPH has been the use of pharmacological compounds derived from plants, Donkervoort et al. (1977) evaluated Tandenan, an extract of African prunes, in a doubleblind study in 20 patients. Although the drug was harmless, it had no beneficial effect. An extract from the fruit of the American dwarf palm, Serenoa repens, reputed to have antiandrogenic activity, brought about a significant improvement in flow rate, residual urine and nocturia, although peak urine flow rates did not reach normal values in the large group of patients studied (5.35±SE 1.51 before and 8.05±SE 2.47 after treatment; n= 46)

Tab. 2 Results of Measurements before and afte Treatment

Parameter	*Time of examination*	*Cernilton* $\bar{x}$	*Cernilton* *SE*	*Placebo* $\bar{x}$	*Placebo* *SE*	*Analysis variance (P value*
Peak flow rate (ml/s)		(n = 26)		(n = 24)		
	Before treatment	10.3	5.2	11.8	6.4	0.92
	After treatment	10.5	5.1	12.1	5.1	
Volume voided (ml)		(n = 29)		(n = 24)		
	Before treatment	241.5	144	235	96.8	0.11
	After treatment	203.4	90.3	257	106.6	
Residual urine (ml)		(n = 28)		(n = 24)		
	Before treatment	145.4	107.5	93.4	91.4	0.025*
	After treatment	101.9	87.3	113.4	87.3	

* Statistically significant

(Champault et al., 1984).

The pollen extract, Cernilton, known to be effective in the treatment of chronic abacterial prostatitis and prostatodynia (Ohkoshi et al., 1967; Ebeling, 1986; Buck et al., 1989), has also been shown to provide symptomatic relief in patients with benign prostatic hyperplasia (Takeuchi et al., 1981; Becker and Ebeling, 1988). Cernilton is an extract of pollen derived from several different plants in southern Sweden. It is rendered free of allergens and its 2 principal active constituents are a water soluble fraction, T-60, and an acetone soluble fraction, GBX. The acetone-soluble fraction was found to consist of 3 B-sterols with a similarity on UV absorption spectra to oestrone and Stigmasterol (Kvanta, 1968). Cernilton produced a significant

decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals (Ito et al., 1986). Habib et al. (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice is significantly inhibited by Cernilton extract but no histological differences were observed between the treated and untreated groups (Otto, etal., 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) (0ckerman, personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Tab. 3 Measurements of Prostate Volume

Prostate size	*Time of examination*	*Cernilton* $\bar{X}$	*SE*	*Placebo* $\bar{X}$	*SE*	*Analysis of variance (P value)*
Circumference (mm)		(n = 29)		(n = 17)		
	Before treatment	169.6	26.3	163.2	16.2	0.446
	After treatment	153.4	27.5	150.5	21.6	
Transverse diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	56.4	8.3	53.8	8.1	0.753
	After treatment	52.2	9.7	50.3	8.1	
Anteroposterior diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	29.1	5.3	28.3	7.4	0.025*
	After treatment	23.8	7.0	26.7	9.1	

* Statistically significant

Kimura et al. (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase et al. (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cemilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronise the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

Acknowledgements

We thank Mr. Golding of Kretztechnik (UK) for his generous help in supplying the ultrasound equipment. Our thanks are also due to Dr. J. Schnitker and Dr. H.-F. Koch, of the Institut ffir

Angewandte Statistik Dr. J6rg Schnitker Gmbh, for statistical analysis of this work.

Summary

Whilst prostatectomy remains the "gold standard" for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment - if only for symptomatic relief - appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or the sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69 % of the patients) compared with placebo (30 %). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A-P) diameter of the prostate on ultrasound. However, differences in respect of flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect in BPH and may have a place in the treatment of patients with mild or moderate symptoms of outflow obstruction.

Appendix

Daytime Frequency
0- 1 to 4 times daily
1- 5 to 7 times daily
2- 8 to 12 times daily
3-13 or > times daily

Nocturia
0 - absence of symptoms
1 - subject awakened once each night because of the need to urinate
2 - subject awakened 2 to 3 times each night
3 - subject awakened 4 or > times each night

Hesitancy
0 -occasional hesitancy (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate hesitancy (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent hesitancy (occurs more than 50 % of subject's attempts to void)
3 - symptoms always present, lasts for 1 minute or longer

Urgency
0 - absence of symptoms
1 - occasionally difficult for subject to postpone urination
2 - frequently difficult (--nore than 50 % of the time) to postpone urination and may rarely loose urine
3 - always difficult to postpone urination and subject sometimes loses urine.

Intermittency
0 - occasional intermittency (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate intem-dttency (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent intermittency (occurs more than 50 % of the time, but not always, and may last up to 1 n-dnute)
3 - symptoms always present, lasts for 1 minute or longer

Incomplete Emptying
0 - absence of symptoms
1 - occasional sensation of incomplete emptying of bladder after voiding
2 - frequent (more than 50 % of the time) sensation of incomplete voiding
3 - constant and urgent sensation and no relief upon voiding

Terminal Dribbling
0 - occasional terminal dribble (occurs in 20 % or less of the subject's attempts at voiding)
1 - moderate terminal dribble (occurs in 20 to 50 % of subject's voiding)
2 - frequent terminal dribble (occurs in more than 50 % of the time but not always)
3 - symptom always present, dribbling lasts for 1 minute or more, or wets clothes

Dysuria
0 - absence of symptoms
1 - occasional burning sensation during urination
2 - frequent (more than 50 % of the time) burning sensation during urination
3 - frequent and painful burning sensation during urination

* Published in Brit.J. Urol. 66 (1990) 398-404

Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract

A. C. Buck, R. W. M. Rees, L. Ebeling

* Published in Brit.J. Urol. 64 (1989) 496-499

The treatment of chronic, relapsing nonbacterial prostatitis presents a formidable challenge to the clinician. It is also well recognized that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprapubic pain that mimic inflammatory disease in the prostate (3,13,15). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, a-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (10, 11). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (1,4,5,14). The aim of this study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9±SD 11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3±SD 2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, either persistent or intermittent, localized to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra / penis (3) or on ejaculation (2) (Table 1).

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including Chlamydia trachomatis, cultured from the EPS (expressed prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0-8.0) with >10 leucocytes and fat laden macrophages /high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH < 6.5; pus cells < 10 / HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (See Table 1 below). Only 1 patient, with a 12-month history of right testicular pain and urinary frequency, who had received 3 courses of antibiotics, with sterile urine and an EPS pH of 6.8 with < 5 leucocytes/HPF, was completely relieved of symptoms after 1 month's treatment with Cernilton. A second patient with a 5-month history of dysuria, frequency, back ache and sterile urine, but an EPS pH of 8 and > 20 pus cells/ HPF, was partially relieved of symptoms at 2 months and the pH of the EPS fell to 7.8, < 10 pus cells / HPF.

Two patients had a recurrence of symptoms after cessation of treatment. A 36 year old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells /HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a change in the alkalinity or leucocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with < 5 pus cells / HPF. On discontinuing treatment the symptoms recurred, with a return to leucocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Tab. 1 Details of Patients.

				Previous Therapy			
Name age (years)	Dur. of Symptoms (years)	Urinary symptoms	Pain site/ occurrence	Antibiotics	Relaxants/ aadrenergic blockade	Previous surgery	Response to Cernilton
TW 36	7	Dysuria	L. testis	Multiple		Epididymecytomy	Complete
DD 61	5	Dysuria	Suprapubic	None	Yes	TURP	Partial
FM 49	.05	Dysuria	Lumbosacral	None			Partial
GS 47	2	Dysuria	L. testis	Multiple			Partial
DB 33	1	Frequency	R. testis	Multiple			Complete

JG 46	2	Dysuria, frequency	Perineum, ejaculation	Multiple		Cystoscopy	None
MP 44	7	Dysuria	Groin	Multiple	Yes	Cystoscopy	Complete
PJ 29	1	Dysuria, Frequency	Perineum, penis	Multiple		Cystoscopy	Complete
DP 51	4	Dysuria	Perineum, testes	Multiple			Partial
HG 63	2	Frequency	Penile, on intercourse	Single	Yes	Cystoscopy	None
SC136	2	Dysuria	L. testis, groin	Multiple			Complete
DH 40	7	Dysuria	Perineum, testes	Multiple			Partial
JM 35	3	Dysuria	Testes, urethra	Single	Yes		Partial
RD123	3	Dysuria	Groins	Yes			Complete
AP 51	3	Frequency	Groins, perineum	Yes	Yes	Cystoscopy	Complete

1 Patients SC and RD relapsed when treatment was stopped and responded again to further treatment.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T/60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (7). The acetone-soluble fraction was found to consist of 3ß-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (9). More recently, in vitro studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (7). Kimura et al. (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis

(5,12). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The in vitro experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (2,10). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communication). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

Summary

Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that it has anti-inflammatory and antiandrogenic properties.

References

1. Ask-Upmark, E.: Die Behandlung der Prostatitis. Z. Urol. 56 (1963) 113-116.
2. Buck, A. C.: Disorders of micturition in bacterial prostatitis. Proc. roy. Soc. Med. 68 (1975) 4-7.
3. Buck, A. C., D. M. Crean, 1. L. Jenkins: Osteitis pubis as a mimic of prostatic pain. Brit. J. Urol. 54 (1982) 741 -744.
4. Denis, L. J.: Chronic prostatitis. Acta Urol. Belg. 34 (1966) 49-56.
5. Ebeling, L.: Therapeutic results of defined pollen-extract in patients with chronic prostatitis or BPH accompanied by chronic prostatitis. In Schmiedt, E., J. E. Alken, H. W. Bauer (eds.): Therapy of prostatitis. Zuckschwerdt Verlag, MiInchen 1986 (pp. 154-160).
6. Ito, R., A Ishii, S. Yamashita et al.: Cemitin pollen-extract (Cernilton). Antiprostatic hypertrophic action of Cernitin ™ pollen-extract (Cernilton). Pharmacometrics (Jpn.) 31 (1986) 1 - 11.
7. Ito, R. K. Noguchi, S. Yamashita et al.: Anti-inflammatory effects of cemitin pollen-extract (Cernilton). Pharmacometrics (Jpn.) 28 (1984) 55-65.
8. Kimura, M., I Kimura, K. Nakase et al.: Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Medica 2 (1986) 148-151.
9. Kvanta, E.: Sterols in pollen. Acta Chem. Scand. 22 (1968) 2161-2165.
10. Meares, E. M. Jr., G. A. Barbalias: Prostatitis: bacterial, non-bacterial and prostatodynia. semin. Urol. 1 (1983) 146-154.
11. Meares. E. M. Jr. t. A. Stamey: Bacterial localization patterns in bacterial prostatitis and urethritis. Invest. Urol. 5 (1986) 492-518.
12. Ohkoshi, M., N. Kawamura, I. Nagakubo: Clinical evaluation of Cernilton in chronic prostatitis. Jpn. J. Clin. Urol. 21 (1967) 73-81.
13. Osborn, D. E., N. J. R. George, P. N. Rao et al.: Prostatodynia-physiological characteristics and rational management

with muscle relaxants. Brit. J. Urol. 53 (1981) 621-623.
14. Saito, Y.: Diagnosis and treatment of chronic prostatitis. Clin. Exp. Med. 44 (1967) 2-15.
15. Segura, J. W., J. L. Opitz, L. F. Greene: Prostatosis, prostatitis or pelvic floor tension myalgia. J. Urol. 122 (1979) 168-17

Conservative Treatment of Benign Prostatic Hyperplasia (BPH) with Cernilton ® - Results of a Placebo-Controlled Double-Blind Study

H. Becker, L. Ebeling

Introduction

In view of the changing age structure and the rising average life expectancy of the male population the phytotherapeutic treatment of benign prostatic hyperplasia (BPH) will become increasingly more relevant. The justification and the need for such a drug therapy can be estimated on the basis of the available epidemiological data: the cumulative probability for a 40-year-old man to be operated on for a BPH until the age of eighty is p = 0.292, and to develop clinical symptoms and/or signs is p=0.777 (4). Consequently, for the treatment of BPH patients, a symptomatically oriented medication has priority. However, continuous observation of the course of the treatment rrvdst ensure that surgical measures are taken whenever they are indicated.

On the basis of our own positive experiences with the standardized pollen extract preparation (trade name, Cernilton ®1) in the treatment of BPH, a placebo-controlled, double-blind study of the efficacy and tolerance of this drug was initiated and carried out in collaboration with six practicing urologists.

An effect on the congestion of the prostate and on the chronic inflammatory changes occurring in BPH is to be suggested as the pharmacodynamic mechanism of action for the symptomatic therapeutic effectiveness of the pollen extract preparation, as clinically a normalization of the pathological parameters of inflammation has been demonstrated in the expressed prostatic secretions (leucocytosis, raised pH value) (2).

Patients and Methods

For this randomized, placebo-controlled, double-blind study in BPH patients in stages II and III according to Vahlensieck (12), a total of 103 patients could be included by six practicing urologists. Due to carcinoma in 1 case and antibiotic therapy for a concomitant urinary tract infection in 6 cases, a total of 96 patients were eligible for the statistical analysis. Further specific criteria for exclusion from the study were: (suspected) carcinoma of the prostate, residual urine volume more than 150ml, neurogenic disturbances of micturition, acute and/or chronic prostatitis/ prostatovesiculitis, malformation or postoperative status in the urogenital area with obstruction of the efferent urinary tract, and bladder stones. Previously treated BPH patients were subjected to a four-week washout phase. All the patients received

identical trial packs containing active drug or placebo capsules also of identical outward appearance. The treatment lasted 12 weeks, with control examinations on week 0, 6 and 12. The examination time 2 weeks after the start of the treatment, which was originally planned, proved to be impracticable. The dosage was 2

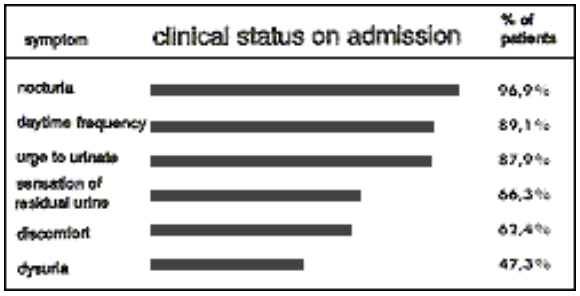


Fig. 1 Clinical status on admission to the study: incidence of the different symptoms in the total study population (n = 96).

capsules tid.

The control parameters investigated were symptoms like nocturia, daytime frequency, sensation of residual urine, dysuria, urge to urinate, discomfort in the inguinal, perineal and genital areas, palpation findings (enlargement, congestion of the prostate), uroflow, residual urine volume determined by ultrasound, and global assessment of the therapy by the physician and by the patient. In the laboratory examinations, SGOT, SGPT, PAP and creatinine in the serum were determined, as well as leucocytes, erythrocytes and germ count (if possible with identification of pathogens) in the sediment or in the urine culture.

Besides descriptive-statistical methods the following analytical procedures were used: chi-square test (with Yates' correction for 2 x 2-field tables) for testing the homogeneity of qualitative parameters, the comparison of the changes in the clinical symptoms at the end of the treatment versus the baseline findings, and for the comparison of the assessments of tolerance, the incidence of side effects and the global assessments by the physicians and by the patients, in both trial-groups; the t-test for independent samples in the homogeneity testing for age, height, body weight and urodynamic and quantitative laboratory parameters; the U-test in the homogeneity testing for the length of the disease and for the length of previous treatment of the BPH; variance analysis for the split-plot design for the evaluation of the course of the quantitative parameters. On account of the findings, the different levels of attendance at the appointed examination times and the practicability of the study, parameter-specific sample sizes were achieved which, in the evaluations of courses, are documented in the form of a reduced number of patients.

In accordance with the FDA recommendations, the disturbances of micturition were classified according to their intensity (1). The statistical comparison was based on the changes observed under the treatment, which were recorded as ‚symptom-free", ,,improved," unchanged," or ‚worsened." In patients with symptoms at the start of the study, response to the treatment is defined as a ‚symptom-free" or improved" status of the therapy. Quantitative parameters were evaluated for the course and the pre-treatment/post-treatment comparison. The parallelism of the mean levels of intensity was also tested. The uroflow findings were also based on the secondary parameter, uroflow index (10).

Tab. 1 Age distribution, BPH stage, duration of symptoms and previous treatment in the comparative groups. The BPH stages are according to the classification of W Vahlensieck.

Age distribution and baseline status			
Parameter	Value / Code	Cernilton ®	Placebo
Age (years)	Minimum	42	45

	Maximum	83	85
	Median	65	67
	Mean value	66.0	67.1
	Standard deviation	9.7	10.1
BPH Stage	II	23	22
	III	25	26
Duration of Symptoms (months)	Minimum	1	1
	Maximum	48	48
	Median	11.4	8.3
	Missing data	4	3
Previous Treatment	No	29	28
	Yes	19	20

Results

As regards medication and stage of the BPH, randomization gave a practically evenly distributed study population, with homogeneous baseline status in the two comparative groups. The age of the patients ranged from 42 to 85 years with a medium duration of the disease of 10 months; the BPH had been treated previously in 40.6 % of the cases (Table 1).

The initial clinical examination showed nocturia to be the leading symptom, occurring as a disturbance of micturition in 96.9 % of the patients (Fig. 1). In the total study population, examination by palpation showed enlargement of the prostate, with retained sulcus in 35.8 %, with obliterated sulcus in 55.8 % and with undefinable lateral lobes in 8.4 % of the patients.

On admission to the study, congestion of the prostate was palpable in 61.5 % of the cases, being classified as slight in 33.0 %, moderate in 17.5 % and severe in 11.0 %. The urodynamic status on admssion to the study also showed homogeneous baseline data in the two comparative groups, whereby the uroflow parameters are presented also according to the uroflow index (Table 2).

Tab. 2 Baseline urodynamic status: residual urine volume (ml) and uroflow index in the comparative groups. Homogeneous baseline status in both parameters (n = 96 and 86, respectively).

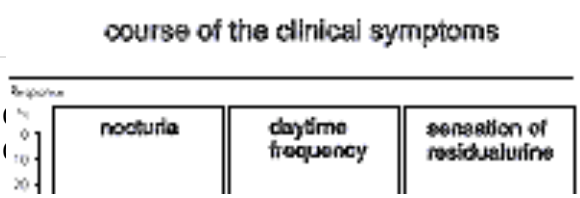
Urodynamic status at baseline					
Parameter	Value	Cernilton ®	Placebo	Total	Homogeneity P-value
Residual urine volume (ml)	Minimum	0	0	0	
	Maximum	100	120	120	
	Mean value	45.6	47.8	46.7	0.735
	Standard deviation	30.6	32.8	31.5	
Uroflow Index	Minimum	0.21	0.27	0.21	
	Maximum	1.43	1.76	1.76	
	Mean value	0.73	0.71	0.72	0.843
	Std dev	0.26	0.33	0.29	

Tab. 3 Statistically significant differences in favor of the

active treatment, in the symptoms nocturia, daytime frequency, and sensation of residual urine. The congestion of the prostate improved more frequently under the pollen extract.

Pre/post-treatment comparison of clinical symptomatology			
Symptom	Cernilton ®	Placebo	Significance P-value
		Response	
Nocturia	68.8%	32.2%	0.005
Daytime frequency	65.8%	43.9%	0.076
Sensation of residual urine	71.4%	48.1%	0.109
	Freedom from symptoms		
Nocturia	25.0%	16.3%	0.445
Daytime frequency	48.8%	19.5%	0.010
Sensation of residual urine	37.1%	7.7%	0.016
Palpation	Cernilton ®	Placebo	Significance P-value
		Response	
Enlargement of the prostate	17.4%	10.6%	0.522
Congestion of the prostate	88.5%	69.0%	0.155

Clinical Symptomatology



As regards the clinical symptornatology, the pre-treatment / post-treatment comparison shows clear differences between the treatment groups: under the pollen extract the nocturia improved significantly in 68.8 % of the patients compared with 37.2 % under the placebo medication. Freedom from the symptoms of daytime frequency and sensation of residual urine is found significantly more frequently under the active treatment (Table 3). For all the individual symptoms the examinations of the courses after 6 weeks and after 12 weeks of the study show higher rates of improvement or positive response course under the active treatment, with no change or deterioration under placebo. In the case of nocturia, daytime frequency, and sensation of residual urine, these differences are particularly pronounced (Fig. 2).

Enlargement and congestion of the prostate show higher response rates, in the sense of decrease in size and decongestion, under the active treatment (AT), whereby a striking trend is to be observed in comparison with placebo Pl (Table 3). In contrast to the course in regard to the enlargement of the prostate, where the response rate remained constant in both groups, in the case of the congestion the improvement rate after 12 weeks, at 86.7 %, was 20 % higher than that recorded after 6 weeks' treatment ' under the active preparation. In comparison, the response under placebo at these two examination times was 70.8 % and 70.9 %, respectively.

Urodynamics

Significant differences in favor of the pollen extract are also to be seen in regard to the urodynamic test parameters. For all the uroflow parameters the changes in the findings were similar in both treatment groups, whereby the differences before and after the treatment are not statistically significant. Taking into account the examination after 6 weeks, a continuous increase of the initially pathological uroflow index is to be observed, by an average of 0.18,

under the pollen extract. In the placebo group (x = + 0.10 after 12 weeks) the index value decreased in the second half of the study (Table 4, Fig.3). The peak urine flow rate increases by an average of 3.3 ml/sec in the pollen extract group and by 0.9 ml / sec in the placebo group.

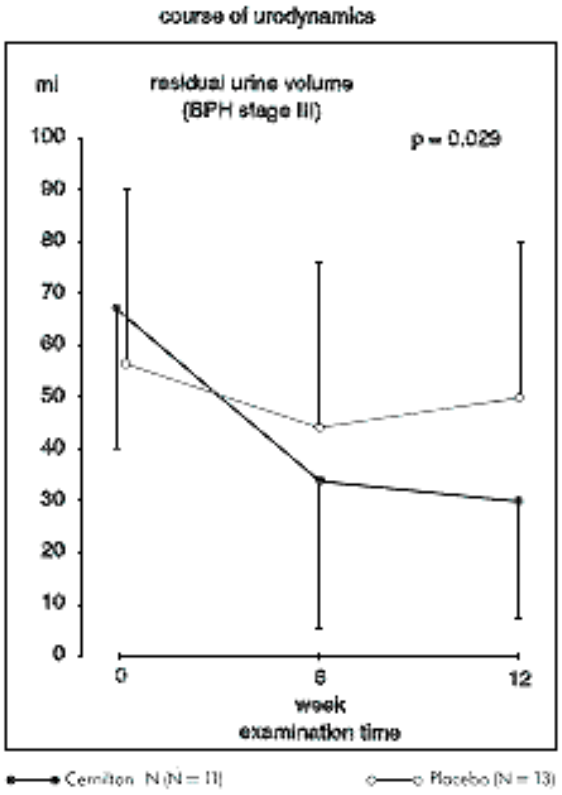


Fig. 4 Course of the residual urine volume (ml) in BPH stage III. Significantly different and continuous reduction of the residual urine volume under the pollen extract. Increase of the residual urine volume in the second half of the study period under placebo.

Pre/post-treatment comparison of the urodynamic findings

Parameter	Time of the control	Cernilton®N		Placebo		Variance analysis P-value
		$\bar{x}$	s	$\bar{x}$	s	
Residual urine volume (ml)	n	48		48		
	Before treatment	45.6	30.4	47.8	32.8	
	After treatment	22.5	20.9	37.0	28.9	0.032
Uroflow index	n	40		40		
	Before treatment	0.74	0.27	0.72	0.34	
	After treatment	0.86	0.25	0.82	0.31	0.747

Tab. 4 Residual urine volume (ml) and uroflow index before and after treatment in the two comparative groups. Statistically significantly greater reduction of the residual urine volume under the pollen extract.

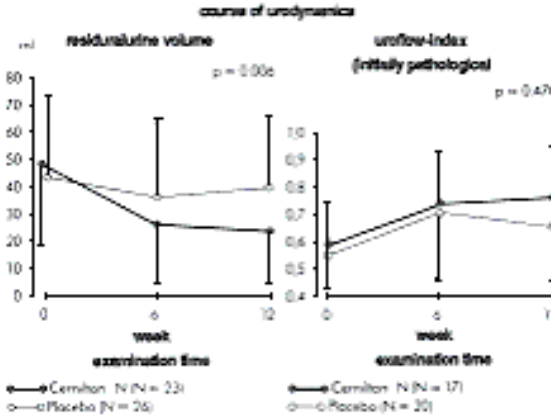


Fig. 3 Course of the residual urine volume (ml) and the uroflow index (initially pathological) in the comparative groups. Continuous reduction resp. increase of the two parameters, under the pollen extract. Unfavorable response of both parameters after 6 weeks under placebo.

The difference in the reduction of the residual urine volume in the course of the study was statistically significant (AT 24.3 ml / PI 3.7 ml, p = 0.006). The pollen extract leads to a continuous reduction, whereas in the placebo group there is a decrease after 6 weeks, compared with an increase in the residual urine volume after 12 weeks (Fig. 3). When BPH stage III is considered separately there is an average decrease of 36.9 ml under the active treatment, compared with 7.2 ml under placebo, whereby an increase in the residual urine volume is to be observed in the second of the two 6-week study periods in the placebo group (Fig. 4).

Global assessment

The laboratory parameters show no noteworthy changes. Unwanted drug effects in the form of

slight nausea are recorded in one case under the active treatment. The good tolerance of the treatment is documented in 95.8% of the patients. With regard to

the therapeutic efficacy, both investigator and patient assessed the result of the treatment as ,,very good" or ,good" significantly more frequently under the pollen extract (Fig. 5). A statistically significant difference of the assessment by the investigators was observed also in the patients with an initially pathological uroflow index (Table 5).

Discussion

The results of this study demonstrate the good efficacy of the pollen extract preparation in benign prostatic hyperplasia (BPH) in stages II and III. The superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both physician and patient.

The course of the characteristic disturbances of micturition is an important parameter for the assessment of therapeutic efficacy. Under the pollen extract the nocturia improved in the course of the 12-week study period in 68.8 % of the patients. In the placebo group, on the other hand, regression was observed in only 37.2 %. In the pre-treatment/post-treatment comparison this leading symptom of BPH showed a significant difference, which increased progressively in the course of the study, in favor of the active trial therapy. While under placebo the response rate remained practically constant, under the pollen extract medication, regression of the symptoms was observed in a further 21.3 % of the patients after the second 6-week period of the study. For the symptoms of daytime frequency and sensation of residual urine there are also clear differences in favor of the active treatment, whereby the differences as regards symptom-free status are statistically significant. For dysuria, urge to urinate, and discomfort no statistically significant differences are recorded on account of the high placebo-response rates. The irritative symptoms, which are predominant

Tab. 5 Significant better global assessment of the treatment by investigator in favor of pollen extract in patients with initially pathological uroflow index ($p < 0.001$).

Global Assessment of Treatment (Investigator) on Patients with Initially Pathological Uroflow Index		
	Cernilton ® (n = 29)	Placebo (n = 31)
Very good	17.3%	6.5%
Good	37.9%	6.5%
Satisfactory	41.4%	45.1%

in BPH, showed a particularly positive response to the active treatment. The obstructive components of the general disturbance of micturition were investigated on the basis of the urodynamic parameters, so that here an evaluation based on the symptoms themselves was not necessary.

As was to be expected, the size of the prostate, as determined by palpation, showed a low response rate, which remained constant in the course of the study.

Particularly striking is the change in the findings in regard to congestion of the prostate, which showed improvement in 69.0 % of the patients under placebo. Because of this high placebo-response rate, the response rate of 88.5 % under the active treatment is not statistically significant. The differences in the response rates observed in the course of the study, between the active treatment and placebo, in the clinical symptomatology and in the congestion of the prostate demonstrate the sustained therapeutic effect of the pollen extract on the intensity of the disturbance of micturition.

Because of the relation of the peak urine flow on the volume voided (3,10), the uroflow index was chosen for the evaluation of these parameters. An increase in this index is to be observed in both comparative groups, whereby the difference is not statistically significant. In the assessment over the course of the tudy a continuous increase is seen in the active-treatment group, while under placebo the index decreases in the second half of the study. The proportion of 35%, compared with 20% in the placebo group of initially pathological uroflow index values becoming borderline or normal after treatment, is to be evaluated as a trend in favor of the active treatment.

Clear differences are recorded in regard to the decrease in residual urine volume. Under both trial preparations a reduction is to be observed in the first 6 weeks, which in the active treatment group becomes even more pronounced in the second half of the study, whereas under placebo there is a deterioration of the value recorded after the first 6 weeks. As the separate evaluations according to the stage of the BPH demonstrate, the pollen extract leads to a more pronounced mean reduction in those cases with an initially high residual urine volume. The reduction in the residual urine volume in the patients with stage III BPH was 54.7 % under the active treatment and 12.5 % under placebo.

As a reflection of the therapeutic efficacy of the pollen extract there are clear differences between the active treatment and placebo in the global assessments of the therapy by the physicians and by the patients, especially in the patient group with an initially pathological uroflow index, where the assessment of efficacy by the urologists as ,,poor" was documented in 41.9 % of the patients under placebo. The fact that in 55.2 % of these patients the result of the treatment under the pollen extract was evaluated as ,very good" or ,good" is possibly an indication that the uroflow index is a relatively inaccurate parameter for detecting the more subtile urodynamic changes.

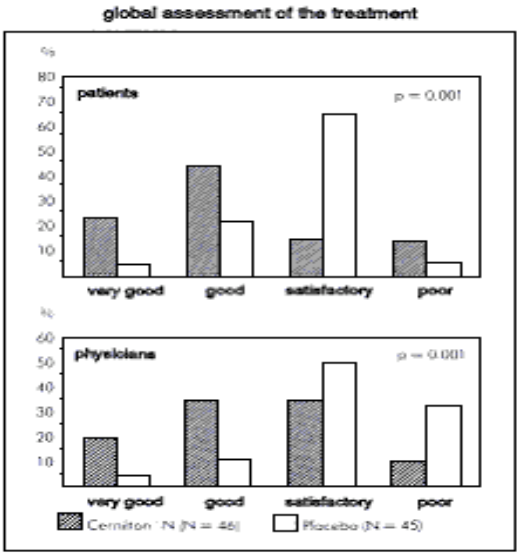


Fig. 5 Significantly better global assessment of the treatment by both physicians and patients in the pollen extract group.

In order to obtain a representative patient population for the investigation of the efficacy of a drug therapy, this study was carried out in collaboration with six practicing urologists. The consistency of the data confirms our view that in the case of conservative therapeutic measures which are used mainly on an ambulatory basis, the involvement of these aspects in the clinical research is both desirable and possible. However, the possible disadvantage that the number of patients attending the different control examinations can vary has to be taken into account.

The mechanism of action of the pollen extract may be its effect on the congestive and inflammatory changes occurring in BPH. Too little attention has been paid to the possible clinical relevance, particularly of the chronic inflammatory changes (9, 11), the incidence of which, in BPH, is given as up to 98.1 % (5-8). In the long term, changes can develop in the connective tissue, which then become pathological in the form of fibrosis and sclerosis. The congestion of the prostate caused by stasis of secretions or the formation of interstitial edema also has to be considered as a pathophysiological substrate of the disturbances of micturition occurring in BPH. It is to be assumed that these concomitant changes lead to alterations in the nerve supply in the prostate, influencing the clinical symptomatology and urodynamics.

The documented normalization of the parameters of inflammation in the expressed prostatic secretions with the pollen extract in patients with chronic prostatitis (2) can explain the therapeutic efficacy of this preparation, in the sense of its antiedematous and anti-inflammatory action, also in patients with BPH. In view of the antisclerotic properties of the pollen extract, a long-term pharmacological effect on the clinical symptomatology and urodynamics is conceivable with continuous application, so that surgical intervention, at least in certain cases, is not necessary (9).

Conclusion

The results of this study demonstrate the efficacy of the pollen extract preparation in BPH patients in stages II and III in regard to the clinical symptomatology, urodynamics, and global assessment. The pollen extract preparation is well tolerated and makes longterm treatment possible with a low risk of side effects. The use of Cernilton ® is recommended for the treatment of BPH stages II and III.

Summary

The efficacy
and tolerance
of the pollen
extract preparation, Cernilton ®, were investigated in a double-blind, placebo-controlled study carried out over a treatment period of 12 weeks in 6 urological practices, in a total of 103 patients suffering from benign prostatic hyperplasia (BPH) in stages II and III. The investigational parameters were the disturbances of micturition classified according

to the FDA recommendation, residual urine volume, palpation findings, uroflow as well as the global assessment of the therapy by the physician and by the patient. Under the pollen extract, nocturia, the principal symptom of BPH, improved in 68.8 % of the cases, compared with 37.2 % under the placebo medication ($p < 0.005$). Notable differences were observed in frequency and in sensation of residual urine, which were statistically significant as regards absence of these symptoms after the treatment, between the active treatment (AT) and placebo (Pl) ($p = 0.010$ and $p = 0.016$, respectively). Observation of the course of the symptoms after 6 weeks and 12 weeks showed higher rates of improvement under the active treatment, for all the individual symptoms. In the case of the urodynamic study parameters, similar changes were observed in the findings for all the uroflow parameters, whereby the differences between the comparative groups were unremarkable. At the control examination after 6 weeks a continuous increase in the peak urine flow rate was observed, averaging 3.3 ml / sec under active treatment and 0.9ml/sec under placebo ($p=0.060$). The difference in the average decrease in the residual urine volume in the course of the treatment was statistically significant (AT/Pl: 24.3 ml / 3.7 ml; $p = 0.006$). The pollen extract led to a continuous reduction, whereas in the placebo group the residual urine after 12 weeks had increased in comparison with the value recorded after 6 weeks. Significant differences in the residual urine volumes before and after the treatment, in favor of the pollen extract, were observed also in the patients in BPH stage III ($p = 0.042$). Prostate size and congestion showed higher response rates, in the sense of reduction in size and decongestion, as detected by palpation, under the active treatment, with a marked trend (AT/Pl: 88.5%/69.0%; $p=0.155$). Nausea was recorded under active treatment in one case. In accordance with their positive experiences with the treatment, the investigating physicians and the patients assessed the therapeutic result under the pollen extract as very good or good significantly more often than that obtained under placebo ($p = 0.001$). The results of the study prove the efficacy of the pollen extract in patients with BPH in stages II and III, in regard to clinical symptomatology, urodynamics and global assessment, and demonstrate the good tolerability of the drug, which permits long-term therapy with little risk of side effects.

Acknowledgements

For making this study possible and for their cooperation we would like to thank our colleagues in Cologne Dr. R. G. Kahnnann, Dr. 1. Nuding, Dr. L. Pausch, Dr. G.-H. Rautenbach, Dr. J. Thissen and Dr. W, P. Winkler as well as their office personnel.

Furthermore we would like to thank Dr. J. Schnitker and co-workers, Institute for Applied Statistics, Bielefeld, for the statistical analysis; Intramed GmbH, Hamburg, for the figures; Mrs. U. Bumke, Hamburg for typing.

References

1. Boyarsky, S., G. lones, D. F. Paulsoti, G. R. Prout Jr.: Trans.Amer. Ass. urin. Surg. 68 (1977) 29.
2. Buck, A. C., R. W. M. Rees, L. Ebeling: Treatment of chronic prostatitis and prostatodynia with pollen extract. Brit. J. Urol. 64 (1989) 496-499.
3. Drach, G. W., D. V Steinbronn: J. Urol. 135 (1986) 737.
4. Glynn, R. J., E. W. C ' anipion, G. R. Bouchard, J. E. Silbert:Amer. J. Epidemiol. 121 (1985) 78.
5. Helpap, B.: Morphologie der Prostatahyperplasie. In Helpap, B., T. Senge, W. Vahlensieck (Hrsg.): Prostatahyperplasie. PMI-Verlag, Frankfurt/M. 1983 (S. 3155).
6. Helpap, B.: Extr. Urol. 7 (1984) 435.
7. Helpap, B.: Zur Morphologie der Prostatitis. In Helpap, T. Senge, W. Vahlensieck (Hrsg.): Prostatakongestion und Prostatitis. PMI-Verlag, Frankfurt/M. 1985 (S. 27 48).

8. Kohnen, P. W., G. W. Drach: J. Urol. 121 (1979) 755.
9. Loy, V., H. W. Bauer. Klin. exp. Urol. 14 (1987) 1.
10. Rdhrborn, C., E. W. Rugendorff. Z. Urol. Nephrol. 76 (1983)721.
11. Sonimerkanip, H.: Klin. exp. Urol. 14 (1987) 52.
12. Vahlensieck, W.: Therapiewoche 36 (1985) 4031.
13. Vahlensieck, W.: Die Prostatakongestion. In: Helpap, B., T Senge, W. Vahlensieck: (I-Irsg.): Prostatakongestion und Prostatitis. PMI-Verlag, Frankfurt/M. 1985 (S. 19).

* Published in Urologe (B) 28 (1988) 301-306
[1]Pharmaceutical Company: Pharma Stroschein (licensed by Cernitin SA, 6903 Lugano, Switzerland) 2000 Hamburg, Germany

An Analytical Study on Fatty Acids in Pollen Extract

T. Seppanen and I. Laakso

Division of Pharmacognosy, School of Pharmacy, University of Helsinki, SF-00170 Helsinki, Finland

J. Wojcicki and L. Samochowiec

Institute of Pharmacology and Toxicology, Medical Academy, Powstancow Wielkopolskich 72, PL-70-11 Szczecin, Poland

Fatty acids in the fat-soluble fraction of pollen extract (Cernitin™ GBX™) were analyzed. Fatty acids were determined on a Dani 3860 PTV GC. Identification was based on the retention times of known mixtures of free fatty acids and their methyl esters in GC/MS. The major part of the fatty acid fraction was in free form. Bound fatty acids were characterized by a high content of α-linolenic acid (70%). The mechanism of antiatherosclerotic action of this pollen extract may be, at least in part, due to polyunsaturated fatty acids.

Keywords: Pollen extract, Fatty acids.

Introduction

Reports on the serum lipid-lowering effect of orally administered pollen extracts to rats (Samochowiec and Wojcicki, 1981; Wojcicki and Samochowiec, 1984) have been confirmed in humans (Wojcicki *et al.,*1983).

Pollen extracts-Cernitin™ T60™ and Cernitin™ GBX™ (AB Cernelle, Vegeholm, Sweden) were taken from six plant species: rye grass, maize, timothy grass, pine alder flower, and orchard grass. Cernitin™ T60™ contains water-soluble substances (6.0-9.2% of α-amino acids) while those in Cernitin™ GBX™ are mainly fat-soluble (10-16% phytosterols).

The chemical composition of pollen has been investigated (Kvanta, 1968; Nielson *et al.,* 1957; Lelson and Holmstrom, *1957).* Numerous chemical substances have been identified and isolated: 21 amino acids, all known vitamins, enzymes, coenzymes, sterols, minerals and trace elements.

This study was to analyze the fatty acids in the fat-soluble fraction of pollen extract (Cernitin™ GBX™) with regard to its proven antiatherosclerotic activity (Wojcicki *et al.,* 1986).

Materials and Methods

The fatty acid composition of the fat-soluble pollen extract (Cernitin™ GBX™) was analyzed by gas chromatography. Bound fatty acids were transesterified by modifying the method of Hiltunen *et al.,* (1979) as follows:

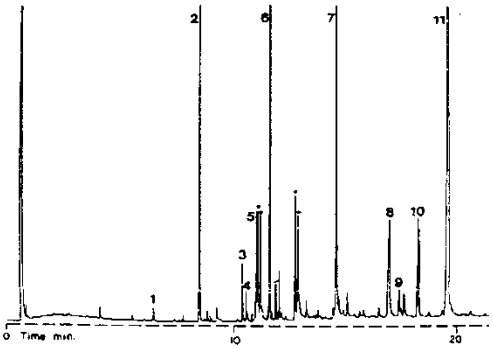
A sample (100 mg) of the fat-soluble pollen extract (batch No 759) was dissolved in 1mL petroleum spirit (b.p. 40-60^{0}C), transmethylated with 0.5mL 0.5 N NaOMe at 40^{0}C for 5 min and

neutralized with 1mL of 15% $NaHSO_4$. Petroleum spirit was added and 1μL taken from the upper layer for gas chromatography. Fatty acids were determined on a Dani 3860 PTV GC as follows: column OV-351 Nordion fused silica (25 m, 0.32 mm ID) oven programmed from 100^0C at 10^0/min to 225^0C, programmed temperature vaporizer (PTV)-injector from 70^0 to 250^0C, carrier gas (H_2) 0.8 bar, detector (FID) 250^0C, sampling mode split (40:1). Identification was based on the retention times of known mixtures of free fatty acids and their methyl esters. Analyses after transesterification of triolein confirmed that no free fatty acids were formed under the conditions used. Other constituents such as aliphatic hydrocarbons and alcohols were identified by GC/MS.

Results and Discussion

GLC analyses of the fat-soluble pollen extract revealed that the major part (more than 60%) of the fatty acid was in the free form (Table 1, Fig. 1). Bound fatty acids, which rather reflect the compositional profile of pollen, were characterized by a high content of α-linolenic acid (18: 3n-3, α-LLA) (70%) followed by small amounts of linoleic (18: 2n-6) and oleic acid (181n-9) only. Palmitic acid (16:0) was the most abundant saturated

Previous studies have revealed that the pollen extract has beneficial properties, lowering serum lipid levels, reducing atherosclerotic plaque intensity (Wojcicki *et al.,* 1986) and decreasing platelet aggregation both *in vitro* (Kosmider *et a1.,1983)* and *in vivo* (Wojcicki *et al.,* 1983). If fatty acids are involved in these effects, the role of α-linolenic acid as a precursor of eicosapentaenoic acid (20: 5n-3, EPA) is significant, since EPA is considered to be responsible for reduced platelet aggregation (Dyer-berg and Bang, 1979). EPA *in vivo* is incorporated into platelet phospholipids, to some extent replacing arachidonic acid and exerting an antithrombotic effect either by competing with remaining arachidonic acid for cylco-oxygenase and lipoxygenase or by being converted to less proagreggatory PGH_3 and TXA_3 (Moncada and



Vane, 1984). Studies in humans suggest that a diet supplemented with polyunsaturated Figure 1. GC chromatogram of pollen extract fatty acids on OV-351 column. Peak numbering as in Table 1. *Aljphatic hydrocarbons and/or alcohols.

Fatty acids decreases whole blood viscosity, and reduces triglyceride and cholesterol levels in patients with cardiovascular disease (Saynor et al., 1984). Recent clinical observations are in favour of a linolenic acid supply, leading to higher levels of phospholipid eicosapaentoic and docosahexaenoic acids (Jacotot et al., 1986). The metabolic conversion from α-LLA into EPA, which is known to occur in humans (Budowski et al., 1984; Sanders and Younger, 1983), would at least in part explain the mechanism of antiatherosclerotic action of pollen extract (Wojcicki *et al*, 1986).

Figure 1.

Table 1. Fatty acid composition of the fat-soluble pollen extract

Compound No		Relative amount (%)
Methyl esters		
1 14:0		0.21
2 16:0		7.64
3 18:0		0.98
4 18:1n-9		0.68
5 18:2n-6		1.85
6 18:3n-3		26.73
	Total	38.09
Free fatty acids		
7 16:0		17.44
8 18:0		1.20
9 18:1n-9		0.83
10 18:2n-6		3.50
11 18:3n-3		38.93
	Total	61.90

Peak numbers refer to constituents in Fig. 1.

Figure 2.

References

Budowski, P., Trostler, N., Lupo, M., Vaisman. N., and Elder, A. (1984). Effect of linseed oil ingestion on plasma lipid fatty acid composition and platelet aggregability in healthy volunteers. *Nutr. Res. 4, 343.*

Dyerberg, J., and Bang, H. 0. (1979). Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet* I,

433.

Hiltunen, R., Huhtikangas, A., and Hovinen, S. (1979). Breeding of a zero erucic spring turnip-rape cultivar, *Brassica campestds* L., adapted to Finnish climatic conditions. The use of glass capillary column gas chromatography in fatty acid analysis. *Acta Pharm. Fenn.* 88, 31.

Kosmider, K., Wojcicki, J.. Samochowiec, L.. Woyke, M., and Gornik, W. (1983). Effect of Cernilton® on platelet aggregation in *viva. Herba Polon.* 29, 237.

Jacotot, B., Lasserre, M., and Mendy, F. (1986). Effects of different diets rich in polyunsaturated fatty acids on plasma phospholipids in the human. *Prog. Lipid Res.* 25, 185.

Kvanta, E. (19681. Sterols in pollen. *Acta Chem. Scand. 22,* 1261.

Moncada, S., and Vane, J. R. (1984). Prostacyclin and its clinical applications. *An. Clin.* Res. 16, 241.

Nielson, N., Grommer, J., and Lunden, R. (19571. Investigations on the chemical composition of pollen from some plants. *Acta Chem. Scand.* 9,1672.

Nielson, N., and Holmstrom, B. (1957). On the occurrence of folic acid, folio acid conjugation and folic acid conjugases in pollen. *Acta Chem. Scand.* 11, 101.

Samochowiec, L, and Wojcicki, J. (1981). Effect of pollen on serum and liver lipids in rats fed on a high-lipid diet. *Herba Polon.* 27,333.

Sanders, T. A. B., and Younger, K. M. (19831. The effect of dietary supplements of 3-polyunsaturated fatty acids on the fatty acid composition of platelets and plasma choline phosphoglycerides. *Br.* J. *Nutr.* 45, 613.

Saynor, R., Verel, 0., and Gillot, T. (19841. The long-term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina. *Atherosclerosis* 50, 3.

Wojcicki, J., and Samochowiec, L. (1984). Further studies on Cernitin™s: screening of the hypolipidemic activitv in rats. *Herba Polon.* 30, 115.

Wojcicki, J., Samochowiec, L., Bartlomowicz, B., Hinek, A., Jaworska, M., and Gawronska-Szklarz, B. (1986). Effect of pollen extract on the development of experimental atherosclerosis in rabbits. *Atherosclerosis* 62, 39.

Wojcicki, J., Kosmider, K., Samochowiec, L., and Woyke, M. (1983). Clinical evaluation of Cernilton® as lipid-lowering agent. *Herba Polon. 29, 55.*

Received 15 September 1988. Accepted 1 November 1988.

Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract *

A. C. Buck, R. W. M. Rees, L. Ebeling

The treatment of chronic, relapsing nonbacterial prostatitis presents a formidable challenge to the clinician. It is also well recognized that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprapubic pain that mimic inflammatory disease in the prostate (3,13,15). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, a-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (10, 11). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (1,4,5,14). The aim of this study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9±SD 11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3±SD 2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, either persistent or intermittent, localized to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra / penis (3) or on ejaculation (2) (Table 1).

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including Chlamydia trachomatis, cultured from the EPS (expressed

prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0-8.0) with >10 leucocytes and fat laden macrophages /high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH < 6.5; pus cells < 10 / HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (See Table 1 below). Only 1 patient, with a 12-month history of right testicular pain and urinary frequency, who had received 3 courses of antibiotics, with sterile urine and an EPS pH of 6.8 with < 5 leucocytes/HPF, was completely relieved of symptoms after 1 month's treatment with Cernilton. A second patient with a 5-month history of dysuria, frequency, back ache and sterile urine, but an EPS pH of 8 and > 20 pus cells/ HPF, was partially relieved of symptoms at 2 months and the pH of the EPS fell to 7.8, < 10 pus cells / HPF.

Two patients had a recurrence of symptoms after cessation of treatment. A 36 year old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells /HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a change in the alkalinity or leucocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with < 5 pus cells / HPF. On discontinuing treatment the symptoms recurred, with a return to leucocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Tab. 1 Details of Patients.

Name age (years)	Dur. of Symptoms (years)	Urinary symptoms	Pain site/ occurrence	Previous Therapy: Antibiotics	Previous Therapy: Relaxants/ aadrenergic blockade	Previous Therapy: Previous surgery	Response to Cernilton
TW 36	7	Dysuria	L. testis	Multiple		Epididymecytomy	Complete
DD 61	5	Dysuria	Suprapubic	None	Yes	TURP	Partial
FM 49	.05	Dysuria	Lumbosacral	None			Partial
GS 47	2	Dysuria	L. testis	Multiple			Partial

DB 33	1	Frequency	R. testis	Multiple			Complete
JG 46	2	Dysuria, frequency	Perineum, ejaculation	Multiple		Cystoscopy	None
MP 44	7	Dysuria	Groin	Multiple	Yes	Cystoscopy	Complete
PJ 29	1	Dysuria, Frequency	Perineum, penis	Multiple		Cystoscopy	Complete
DP 51	4	Dysuria	Perineum, testes	Multiple			Partial
HG 63	2	Frequency	Penile, on intercourse	Single	Yes	Cystoscopy	None
SC[1] 36	2	Dysuria	L. testis, groin	Multiple			Complete
DH 40	7	Dysuria	Perineum, testes	Multiple			Partial
JM 35	3	Dysuria	Testes, urethra	Single	Yes		Partial
RD[1] 23	3	Dysuria	Groins	Yes			Complete
AP 51	3	Frequency	Groins, perineum	Yes	Yes	Cystoscopy	Complete

[1] Patients SC and RD relapsed when treatment was stopped and responded again to further treatment.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T/60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (7). The acetone-soluble fraction was found to consist of 3ß-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (9). More recently, in vitro studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (7). Kimura et al. (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis (5,12). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given

adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The in vitro experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (2,10). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communication). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

Summary

Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that it has anti-inflammatory and antiandrogenic properties.

References

1. Ask-Upmark, E.: Die Behandlung der Prostatitis. Z. Urol. 56 (1963) 113-116.
2. Buck, A. C.: Disorders of micturition in bacterial prostatitis. Proc. roy. Soc. Med. 68 (1975) 4-7.
3. Buck, A. C., D. M. Crean, 1. L. Jenkins: Osteitis pubis as a mimic of prostatic pain. Brit. J. Urol. 54 (1982) 741 -744.
4. Denis, L. J.: Chronic prostatitis. Acta Urol. Belg. 34 (1966) 49-56.
5. Ebeling, L.: Therapeutic results of defined pollen-extract in patients with chronic prostatitis or BPH accompanied by chronic prostatitis. In Schmiedt, E., J. E. Alken, H. W. Bauer (eds.): Therapy of prostatitis. Zuckschwerdt Verlag, MiInchen 1986 (pp. 154-160).
6. Ito, R., A Ishii, S. Yamashita et al.: Cemitin pollen-extract (Cernilton). Antiprostatic hypertrophic action of Cernitin pollen-extract (Cernilton). Pharmacometrics (Jpn.) 31 (1986) 1 - 11. Ito, R. K. Noguchi, S. Yamashita et al.: Anti-inflammatory effects of cemitin pollen-extract (Cernilton). Pharmacometrics (Jpn.) 28 (1984) 55-65.
7. Kimura, M., I Kimura, K. Nakase et al.: Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Medica 2 (1986) 148-151.
8. Kvanta, E.: Sterols in pollen. Acta Chem. Scand. 22 (1968) 2161-2165.
9. Meares, E. M. Jr., G. A. Barbalias: Prostatitis: bacterial, non-bacterial and prostatodynia. semin. Urol. 1 (1983) 146-154.
10. Meares. E. M. Jr. t. A. Stamey: Bacterial localization patterns in bacterial prostatitis and urethritis. Invest. Urol. 5 (1986) 492-518.
11. Ohkoshi, M., N. Kawamura, I. Nagakubo: Clinical evaluation of Cernilton in chronic prostatitis. Jpn. J. Clin. Urol. 21 (1967) 73-81.
12. Osborn, D. E., N. J. R. George, P. N. Rao et al.: Prostatodynia-physiological characteristics and rational management with muscle relaxants. Brit. J. Urol. 53 (1981) 621-623.
13. Saito, Y.: Diagnosis and treatment of chronic prostatitis. Clin. Exp. Med. 44 (1967) 2-15.
14. Segura, J. W., J. L. Opitz, L. F. Greene: Prostatosis, prostatitis or pelvic floor tension myalgia. J. Urol. 122 (1979) 168-171.

Cernilton

Cernilton, an extract of flower pollen, has been used to treat prostatitis and BPH in Europe for more than 35 years. It has been shown to be quite effective in several double-blind clinical studies in the treatment of BPH.

The overall success rate in patients with BPH is about 70%. Patients who respond typically have reductions of nocturia and diurnal frequency of around 70% as well as significant reductions in residual urine volume. The extract has been shown to exert some anti-inflammatory action and produce a contractile effect on the bladder while simultaneously relaxing the urethra. In addition, Cernilton contains a substance, which inhibits the growth of prostate cells.

In the most recent study, the clinical efficacy of Cernilton in the treatment of symptomatic BPH was examined over a 1-year period. Seventy-nine males of an average age of 68 years (range 62-89), with a mean baseline prostatic volume of 33.2 cm, were administered 63mg Cernilton pollen extract twice daily for 12 weeks. Average urine maximum flow rate increased from 5.1 to 6.0 ml/s. Average flow rate increased from 9.3 to 11 ml/s. Residual urine volume decreased from 54.2 ml to less than 30ml. Clinical efficacy, based on symptoms, was as follows:

- urgency or discomfort- improved by 76.9%
- dysuria- improved by 71.4%
- nocturia- improved by 56.8%
- incomplete emptying- improved by 66.2%
- prolonged voiding- improved by 64.1%
- delayed voiding- improved by 62.2%
- intermittency- improved by 60.6%
- post-void dribbling- improved by 42.7%
-

Overall, 85% of the test subjects experienced benefits.

11% reporting “excellent”, 39% reporting “good”, 20% reporting “satisfactor”’ and 15% reporting “poor”, as description of their outcome.

Reference: Specific Health Problems Pg. 1150

Cernitin™ - A microbiological digest

We often speak of Cernitin™ as a microbiological digest, and therefore it may be appropriate to explain what this expression means.

As you already know Cernitin™ is produced by extraction from the raw-material pollen. Hereby only type-pure pollen is used. Before the extraction it has been stabilized and purified through a special treatment. A number of selected plants give their pollen to the production of different Cernitin™ extracts. These plants have been chosen after animal experiments.

The extraction of the pollen grains presents certain problems. Each grain is a biological unit with a complete set of different substances necessary for the creation of new life. These substances are well protected by the sheath, which is very resistant and can stay unchanged for thousands of years even if the grains have fallen unprotected on the ground. However, the sheath is provided with hilums, germinal openings, covered by a membrane, which can be dissolved.

The lenient extraction method used by Cernelle can easiest be described as follows. After having removed the membrane with a solvent, the content of the grains is flushed out through the hilums. The solvent is then removed. This is done so carefully that the extract is never heated to more than 40^0C. The extract received is called Cernitin™. It is then microbiologically digested in doing which certain microbes ferment the extract under control. Through this treatment such substances that are toxic or harmful, e.g. allergens and other high-molecular substances, are broken down. Therefore, as a rule, our products can be used also by people otherwise allergic or hypersensitive to pollen.

This breaking down can easily be controlled with a gel-precipitation test according to Ouchterlony, at which the Cernitin™ extract is controlled against blood from rabbits treated with the pollen in question. During the fermentation high-molecular substances, that are difficult to absorb and often irritating, are reduced to low-molecular substances, i.e. each molecule contains less atoms, e.g. protein is reduced to peptides and amino acids. These low - molecular substances are harmless and can quickly be absorbed in the blood so that the body immediately can benefit by them. This is the reason for the quick effect of the Cernitin™ preparations and also an explanation to the fact that relatively small amounts are needed for a good effect.

Almost nothing gets lost, but the whole amount of Cernitin™ is active as distinguished from usual foodstuff or Synthetic substances of a more complicated composition. In those cases the body can sometimes have difficulties to utilize the substances, e.g. calcium and vitamin preparations. Even if large quantities are supplied, the body can have difficulties in utilizing necessary substances.

Some of the conditions determinative for the body's ability to utilize different substances are known. Thus, already more than 100 years ago, Justus von Liebig could phrase his classic "Minimum Law" in which he pronounced that very often a substance, from which is added too little, can be determining for how all added nourishment is absorbed. Thus it is possible to increase the body's ability to utilize supplied nourishment by providing for the body reasonable demands for nutrient substances of different kinds.

This can, however, many times be difficult, as we are creatures of habit and prefer to eat what we like, even if we thereby perhaps miss some substances that our body really need.

By a daily supply of Cernitin™ extract in Pollisport™ or Cernelle Special the body gets guaranteed all the substances necessary for life and it will also be possible for the body to utilize all nourishment in the food. The body can, thanks to Cernitin™, utilize vitamins and other important substances present in the daily food. In this way Cernitin™ normalizes the functions of the body and increases health and resistance against diseases.

Cernilton for Benign Prostatic Hyperplasia

Wilt T, Mac Donald R, Ishani A, Rutks I, Stark G.
General Internal Medicine, Department of Veterans Affairs Coordinating Center of the, One Veterans Drive, Minneapolis, Minnesota 55417, USA. wilt.timothy@minneapolis.va.gov

BACKGROUND: Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. Cernilton, prepared from the rye-grass pollen Secale cereale, is one of the several phytotherapeutic agents available for the treatment of BPH.

OBJECTIVES: This systematic review aims to assess the effects of Cernilton on urinary symptoms and flow measures in men with benign prostatic hyperplasia (BPH).

SEARCH STRATEGY: Trials were searched in computerized general and specialized databases (MEDLINE, EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting manufacturers and researchers.

SELECTION CRITERIA: Trials were eligible if they were: (1) randomized controlled trials or controlled clinical trials comparing Cernilton with placebo or other BPH medications in men with BPH; and (2) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements.

DATA COLLECTION AND ANALYSIS: Information on patients, interventions, and outcomes was extracted by at least two independent reviewers using a standard form. Main outcome measure for comparing the effects of Cernilton with placebo and standard BPH medications were the change in urologic symptoms scales. Secondary outcomes included changes in nocturia as well as urodynamic measures (peak and mean urine flow, residual volume, prostate size). Main outcome measure for side effects was the number of men reporting side effects. MAIN RESULTS: 444 men were enrolled in 2 placebo-controlled and 2 comparative trials lasting from 12 to 24 weeks. Three studies used a double-blind method although treatment allocation concealment was unclear in all. Cernilton improved "self rated urinary symptoms" (percent reporting satisfactory or improving symptoms) versus placebo and Tadenan. The weighted risk ratio (RR) for self-rated improvement versus placebo was 2.40 [95% CI = 1.21, 4. 75], and the weighted RR versus Tadenan was 1.42 [95% CI = 1.21, 4. 75]. Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted RR was 2.05 [95% CI = 1.41, 3.00], and versus Paraprost, the WMD was -0.40 times per evening [95% CI = -0. 73, -0.07]. Cernilton did not improve urinary flow rates, residual volume or prostate size compared to placebo or the comparative study agents. Adverse events were rare and mild. The withdrawal rate for Cernilton was 4.8% compared to 2.7% for placebo and 5.2% for Paraprost.

REVIEWER'S CONCLUSIONS: The Cernilton trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of the preparations utilized. The comparative trials lacked a proven active control. The available evidence suggests Cernilton is well tolerated and modestly improves overall urologic symptoms including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety

of Cernilton.
Publication Types:

- Review
- Review, Academic

PMID: 10796739 [PubMed - indexed for MEDLINE]

Effect of Cernitin pollen-extract (Cernilton®) on the Function of Urinary Bladder in Conscious Rats

Akiko Nagashima, Makoto Ishii, Masaichi Yoshinaga and Etsuji Higaki

Ome Research Laboratories, Tobishi Pharmaceutical Co., Ltd.,

7-1, 1-chome, Suehiro-cho, Ome-shi, Tokyo 198-0025, Japan

We studied the effect of Cernitin pollen-extract (Cernilton®, CN-009), a preparation made from eight kinds of pollen such as timothy, rye, and maize etc., on the function of urinary bladder in conscious rats using the method that reported previously by Kontani *et al*.

The surgical procedure was performed under ether anesthesia, and after the recovery, the rat was restricted in a Ballman cage during the experiment. The bladder contraction was induced by the constant infusion of physiological saline. The effect of CN-009 was evaluated by using the following parameters measured from the cystometrogram; number of micturition (NM, times/hr), micturition threshold pressure (MTP, cmH_2O) and peak pressure during bladder contraction (PP, cmH_2O).

The single administration of CN-009 (630 and 1260 mg/kg, i.d.) did not affect the three parameters mentioned above. On the other hand, administered CN-009 (630 or 1260 mg/kg, p.o. for 6 or 13 days and i.d. on the very day of the experiment) for 7 or 14 successive days increased PP in the dose-and time- dependent manners, and the PP was increased significantly (p<0.05-0.01) on the group administered high dose for long period compared to that of control group. CN-009 did not affect NM and MTP much.

These results suggested that CN-009 administered sub acutely enhanced PP and promoted the function of urinary bladder.

KEY WORDS

Cernitin pollen-extract, Cernilton, CN-009, Urinary bladder function,

Cystometrogram, Conscious rats

Clinical evaluation of the effect of tamsulosin hydrochloride and cernitin pollen extract on urinary disturbance associated with benign prostatic hyperplasia in a multicentered study

Aoki A, Naito K, Hashimoto O, Yamaguchi M, Hara Y, Baba Y, Wada T, Joko K, Nagao K, Yamakawa G, Suyama K, Nagata K, Matsuyama H, Hirao H, Shimizu Y, Hironaka H, Isoyama R, Takemoto M, Tuchida M, Shiraishi K, Kato M, Kamiryo Y, Harada H, Otsuka T, Mitsui H, Nasu T, Hayashida S, Jojima K, Sacho T, Koshido Y, Harada N.

Department of Urology, Yamaguchi University School of Medicine.

We evaluated the clinical efficacy and safety of tamsulosin hydrochloride and cernitin pollen extract in 243 patients with urinary disturbance associated with benign prostatic hyperplasia. They were assigned randomly to 3 groups, oral tamsulosin hydrochloride, cernitin pollen extract and their combination were administered for 12 weeks. The international prostate symptom score, post-voided residual urine and uroflowmetrogram were obtained before and after treatment. The international prostate symptom score improved in each group and then the maximum flow rate and average flow rate also increased significantly in the tamsulosin hydrochloride-administered groups. In conclusion, the administration of only tamsulosin hydrochloride and the combination of tamsulosin hydrochloride and cernitin pollen extract seemed more effective then the administration of only cernitin pollen extract in the treatment of urinary disturbance associated with benign prostatic hyperplasia.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 12094707 [PubMed - indexed for MEDLINE]

Clinical experience with Cerniltonby means of double blind test

By Yoshio Kai, M.D.

Department of Urology,

Showa University School of Medicine

TOBISHI PHARMACEUTICAL CO., LTD.

Tokyo, Japan

March 25, 1968

Basing on the clinical results obtained, the author has previously reported that CERNILTON is effective in the treatment of prostatic hypertrophy. However, as the criteria of evaluation used then were primarily based on improvement in subjective symptoms, he thought psychosomatic factors might have played a substantial role. For this reason he performed, as reported here, a double blind test, using 4 cases which showed favorable response in the previous experiment and 10 new cases.

The details of each case are as shown in Table. Cases 1-5 were responsive to CERNILTON but were then given placebos in the course of treatment. Placebos and CERNILTON were identical in appearance, though slightly differing in smelling. None of the patients, however, noticed the difference.

In cases 2 and 3 there were noted no specific changes in symptoms after administration of placebos. This can mean one or the other: either that the effect of CERNILTON was continuing or that the effectiveness of CERNILTON had a suggestive effect on the patients. If in the former, it means placebos were ineffective and, if in the latter, psychosomatic factors played a part.

In cases 1 and 4 the subjective symptoms became exacerbated after administration of placebos, showing ineffectiveness of the placebos. In other words, the effectiveness of CERNILTON was proved. Subsequently, however, suprapubic prostatectomy was carried out in case 1 at the request of the patient.

Cases 6-14 visited the Outpatient Clinic with chief complaints of pollakisuria and dysuria and were all diagnosed as having prostatic hypertrophy. To avoid the influence the drug or psychic suggestions, placebos were given first, 4 tablets daily, or 2 tablets each in the morning and

evening. As, however, there was obtained no improvement either in subjective or objective symptoms after 1-2 weeks' administration except in case 9, CERNILTON was given in place of placebos. In 2 weeks all the patients had good urination with marked improvement in subjective symptoms: residual urine decreased, too.

In case 9, with administration of placebos, the frequency of urination was decreased from 10 times to 5-6 times in the daytime and from 5-6 times to 1-2 times at night. Even after switching over to CERNILTON, the favorable clinical course continued.

In summary, while placebos exerted influence in 3 of 14 cases, no influence was noted at all in the other 11 cases. In other words, in 11 (78%) of 14 cases the effect was definitely due CERNILTON. It is obvious then that CERNILTON can be considerably effective in the treatment of dysuria associated with prostatic hypertrophy.

No.	Age	Chief Complaints	Residual Urine	Clinical Course
1	60	Pollakisuria	100	Cernilton was given in doses of 4 tablets for 4 weeks. No residual urine. Then placebos were given for 2 weeks. The symptoms were exacerbated and prostatectomy was performed.
2	63	Pollakisuria	50	With Cernilton, residual urine was 10cc and urination decreased in frequency. With placebos, no specific changes were noted in subjective symptoms.
3	75	Nocturnol Pollakisuria	80	With Cernilton, residual urine was 50cc. Placebos were given for two weeks but residual urine was not changed. Subjective symptoms were not exacerbated.
4	86	Dysuria	0	Urination improved with Cernilton. Placebos were given, but urination was again disturbed.
5	66	Anuria	600	Residual urine was 550cc after 7 days and 300cc after 14 days with Cernilton. Placebos were then given but the symptom was not improved.
6	74	Pollakisuria	50	Placebos were ineffective. Cernilton was given in doses of 4 tablets for two weeks. Frequency of urination decreased to 5-6 times in the daytime and one time at night. Residual urine was 20cc.
7	71	Imcomplete Anuria	150	Placebos were given in doses of 4 tablets for 7 days after catheterization without effect. With Cernilton, sensation of urinary retention disappeared and residual urine was not found.
8	70	Dysuria	0	The patient voided 10 times in the daytime and 4 to 5 times at night had complained of marked sensation of urinary retention. Placebos had no effect at all. With Cernilton, good urination ensued.
9	55	Pollakisuria	10	The patient complained of dysuria and voided 4 to 5 times at night. Placebos were first given. In one week the frequency of urination decreased to 5-6 time in the daytime and 1-2 times at night. Cernilton was then given, but no changes were noted.

10	75	Dysuria	130	The patient voided every one to two hours. With placebos, sensation of urinary retention became even worse. With Cernilton, the frequency of urination decreased to 4-5 times in the daytime and 1-2 times at night, and one month later urination was no longer disturbed.
11	74	Pollakisuria	30	The patient voided every 20 minutes in the daytime and had severe sensation of urinary retention. The symptoms were not changed at all with placebos. With Cernilton, sensation of retention disappeared and residual urine was 10cc.
12	75	Dysuria	50	No changes with placebo. After administration of Cernilton for two weeks, the frequency of urination was decreased from 4 times to 2 times at night.
13	63	Pollakisuria	0	The patient voided 8 times in the daytime and 3 times at night. Placebos were ineffective. Good urination with normal frequency was noted after administration of Cernilton.
14	71	Pollakisuria	100	The patient voided every 20 minutes in the daytime and 3 times at night. Placebos were ineffective. After administration of Cernilton, he voided every 3 hours and 2 times at night. Disturbance of urination was improved.

Effects of yanlieping formula on mice with chronic nonbacterial prostatitis
Xue CM, Zhu Q, Xu ZD.

Chinese Traditional Surgery Department, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200021, China.
OBJECTIVES: To study the mechanism of Yanlieping Formula in treating chronic nonbacterial prostatitis. METHODS: Thirty-two C57BL/6 mice were divided into Chinese Traditional Medicine group (Yanlieping group, 10 mice), treatment control group (Cernilton group, 10 mice), model group (6 mice) and normal group (6 mice). The animal model was created by using immunologic adjuvant, and Yanlieping (0.84 g per mouse), Cernilton (7.5 mg per mouse), distilled water (1.05 ml per mouse) and distilled water (0.5 ml per mouse) were respectively administered to the four groups every day for one month. The prostate weight, pathological changes, TNF-alpha and IL-2 in serum were observed. RESULTS: The prostate weight in Yanlieping group and Cernilton group became significantly lower than in the model group ($P < 0.05$). Pathologic sign of chronic inflammation became better significantly (Yanlieping group showed more significant improvement). The expression of IL-2 in Yanlieping group and Cernilton group were down regulated significantly. And the expression of TNF-alpha in Yanlieping group was higher than that of the model group and the normal group ($P < 0.05$). CONCLUSIONS: The mechanism of Yanlieping Formula in treating chronic prostatitis may lie in the max urethral close pressure reduction, anti-inflammation, local blood circulation improvement.

PMID: 12931379 [PubMed - in process]

Plant extracts in the medical management of benign prostatic hyperplasia: fact or fiction?

Mahoney JE.

Assistant Professor, Department of Urology, Wellesley Hospital, University of Toronto, Toronto, Ontario.

The objective of this study was to critically review the published literature on the role of phytotherapeutic agents and phytosterols (also referred to as plant extracts) in the medical management of benign prostatic hyperplasia. Data sources included a bibliographic database that was searched to retrieve articles on benign prostatic hyperplasia with a time constraint of 1985-1993. Indexing terms used included plant extracts, phytosterols, cernilton, paraprost and medical management. Studies selected were randomized trials incorporating plant extracts. English abstracts were reviewed for articles published in other languages and these reviews are noted. English articles were critically reviewed based on study design, patient selection, length of follow up, postulated mechanisms of action and benign prostatic hyperplasia subjective and objective outcome measures. A number of plant extracts are being used in the management of benign prostatic hyperplasia, predominantly in Europe. These plant extracts, which are biochemically heterogenous, have been found to act through a variety of mechanisms: an anti-inflammatory effect, a decrease in globulin, a direct cytotoxic effect, anti-prolactin activity and bladder compliance modification. More importantly, these plant extracts have not been associated with the side effects of chemical castration. Their alleged efficacy may be based upon a mechanism which is currently not understood and a combination of these extracts with accepted medications may have the potential of improving the overall efficacy of medical therapy in the treatment of benign prostatic hyperplasia. Despite the shortcomings of the published trials, there is enough evidence to warrant additional study in the form of randomized control trials using scientific validated outcome measures. Using validated scores with patients of mild to moderate symptomatology would help to further elucidate the relative efficacy of cernilton, curbicin and permixon.

PMID: 12803719 [PubMed]

Pollen - an interesting raw material

Each flower has its pollen, characteristic for that particular plant. The size, weight, shape, number of hila (germinal openings), ridges and hollows on the sheath makes it possible to differ pollen from different plants. Sometimes researchers refer to pollen as the plants' fingerprints. Within palynology (knowledge of pollen) (his character has created the modern pollen analysis, where Swedish researchers such as Lennart von Porat and Gunnar Erdtman are great names.

Palynologists can sift off the pollen grains from a sample of soil by treating the soil with strong acids, at which everything is dissolved except the pollen. the sheath of pollen grains is almost indestructible. Then the pollen grains are examined, and the identity of the plant in question can be established. In soil from an archaeological find it is thus possible to get a picture of the nature at that very time when the find was buried in the soil. If one knows what the vegetation was like in the past one can date the find rather exactly.

A pollen grain is very small. Of the ordinary pollens used in the production of Cernitin™ extracts, there is room for 100 in a row on one millimeter. There are, however, much smaller pollen: those from "Forget-me-not" are so small that there is room for 300 in a row on one millimeter.

The palynologists have in detail described pollen grains from a large number of plants, and this makes it possible for Cernelle to assort the pollen grains and then control the conformity to type. The conformity is received by treating the raw material in certain apparatus. Tests performed at the Palynological Laboratory in Stockholm have shown that the conformity of the Cernelle pollen raw material is so high, that the contents of foreign pollen grains in true-to-type material never exceed 1 %. As a rule one can find a total conformity. If foreign particles are present they only amount to some promille consisting of a few foreign pollen grains and perhaps also some grains of dust.

This conformity is necessary, as pollen is the raw material for a pharmaceutical product. Cernitin™ which must be controlled as to its effect and also possible side-effects. Bearing in mind the well-known fact that pollen as raw material contains substances that can give rise to side-effects of different kinds, such as allergies, one must test the pollen as raw material and compare their side-effects with those of the Cernitin™ extracted from pollen, in order to be sure that the Cernitin™ extracted from the pollen in question is harmless and can be used regularly and for a very long time without risk. This is very important and the absolutely first step to be taken in the production of products for human use.

In this connection we would like to point out the danger of using pollen raw material for human consumption. Pollen raw material has to be refined before use exactly as the sugar beet is refined to sugar. (The sugar-beet. however. is probably much more harmless to eat than pollen.)

The reason for mentioning these facts is that material containing pollen has of old been collected by apiarists to be given to weak bee colonies in the spring and thereby saving them from destruction. Such bee-feed has often been

sold among beekeepers at a fixed market price, after having been collected as follows:

A grating is placed on the beehive entrance; when the bees pass it the collected lumps of pollen and plant fibers are scraped off and fall down in a box covered with a net so that the bees cannot take it back. When the box is filled, the apiarist empties it. The bee-collected pollen lumps contain rather a high percentage of moist and make an excellent foundation for the growing of all kinds of bacteria and fungi, promoted by the warm summer air. Different insects search the pollen traps to lay their eggs there. The apiarists themselves grade the quality of their product by the content of worms. I.e. the amount of larvae found per 100g lump of the material, which evidently is not suitable for consumption by human beings. In spite of this fact unscrupulous businessmen buy this raw material, press it to tablets and sell this bee-feed for human consumption, of course with a very good profit.

The health authorities should demand control and analysis of such material and block the marketing thereof definitely.

Cernitin™ - a microbiological digest

By extraction from the pollen raw material by a special method a certain substance, Cernitin™ is won. Hereby only type-pure pollen is used, taken from selected plants, chosen after animal experiments and other tests of suitability. Before the extraction it is stabilized and purified through a special treatment.

The extraction of the pollen grains presents certain problems. Each grain is a biological unit with a complete set of different substances necessary for the creation of new life. These substances are well protected by the sheath, which is very resistant and can stay unchanged for thousands of years even if the grain has fallen unprotected on the ground. However, the sheath is provided with hila (germinal openings), covered by a membrane, which can be dissolved.

The special extraction method used by Cernelle can shortly be described as follows. After having removed the membrane with a solvent the contents of the grains are flushed out through the hila. The solvent is then removed. This operation is made so carefully that the extract is never heated to more than 40ºC, the extract is called Cernitin™. The Cernitin™ is then microbiologically digested in a process during which certain microbes ferment the extract under control. Through this treatment such substances that are toxic or harmful, e.g. allergens and other high-molecular substances, are broken down. Therefore, as a rule, Cernitin™ products can be used also by people otherwise allergic or hypersensitive to pollen.

This breaking down can easily be controlled with a gel precipitation test according to Ouchterlony, in which the Cernitin™ extract is controlled against blood from rabbits treated with the pollen in question. During the fermentation high-molecular substances, that are difficult to absorb and often irritating, are reduced to low-molecular substances: e.g. protein is reduced to pep-tides and amino acids. These low-molecular substances are harmless and can quickly be absorbed into the blood so that the body can benefit by them immediately. This is the reason for the quick effect of the Cernitin™ preparations and also an explanation of the fact that to attain a good effect relatively small quantities are needed.

Almost nothing gets lost: all of the Cernitin™ is active, therein different from usual foodstuff or synthetic substances of a more complicated composition. In those cases the body can sometimes have difficulties in utilizing substances as e. g. calcium and vitamin preparations, even if large quantities are supp-lied.

Some of the conditions determinative for the body's ability to utilize different substances are known. Thus, already more than 100 years ago, Justus von Liebig could phrase his classic "Minimum Law" in which he pronounced that sometimes a substance fed in too small quantities can be determining for how all the nourishment intake is absorbed. Thus it is possible to increase the body's ability to utilize supplied nourishment by providing the body with sufficient nutrient substances of different kinds. This can, however, many times be difficult, as we are creatures of habit and prefer to eat what we like, even if we thereby perhaps miss some substances that our body would really need.

By a daily supply of Cernitin™ extract the body will be guaranteed all the substances necessary for life and can fully utilize vitamins and other

important substances present in the daily food. In this way Cernitin™ normalizes the functions of the body and increases health and resistance against diseases.

Control of Cernelle products

The pollen raw material is collected by Cernelle itself, in a way guaranteeing type-pure pollen of low moisture. The pollen is stored in constant temperature and under controlled air humidity conditions.

The control starts immediately after the collection. The conformity to type of the raw material is established, and for security samples are also sent for control to the Palynological Laboratory in Stockholm.

The raw material is extracted under constant control, and the following fermentation of the extract controlled by gel precipitation test as well as spectrophotometric and chromatographic analyses. The extracted Cernitin™ is split into fractions with different qualities e.g. “Cernitin™ T60™ sicc.” “Cernitin™ GBX™$_1$”.

At the Cernelle control laboratory the Cernitin™ fractions are distinguished from each other by special analysis methods, which are also performed on the finished extracts. All finished products are also controlled. Samples are taken daily from each batch of preparations and the contents of active substances established. The Cernitin™ extracts also undergo toxicity control.

At last, also dissolving capacity of the tablet preparations and their resistibility against different air humidity and temperature during storage are controlled. Tablets with Cernitin™ extracts shall, as a rule, keep their active properties unchanged during almost unlimited storage time when kept in a dry and cool place. Tablets with vitamins added have a storage time of only ca. 2 year, as the activity of the vitamins will be reduced when stored for a longer period.

All constituents contained in the Cernelle preparations are also controlled at the arrival to correspond to the regulations of the pharmacopoeia.

The Treatment of Benign Prostatic Hyperplasia with Phytopharmata

A comparative study of Cernilton® vs. β-sitosterol

The conservative treatment of benign prostatic hyperplasia (BPH) has gained increasingly in significance in view of the increased life expectancy. In a controlled comparative study (n = 39) with Cernilton® and β-sitosterol the course of treatment was objectified by clinical-chemical findings. The results demonstrate the marked improvement of symptoms and signs, whereas the regression of complaints was more pronounced under Cernilton®. The significant decrease of PAP and PSA serum levels shows the reduction of cell lesions in BPH under the treatment with Cernilton®. A comparable effect of β-sitosterol could not be demonstrated. The relative lack of toxicity of both drugs can be confirmed by the biochemical data.

In the second half of the normal life-span the physiological process of aging leads to the appearance of an increasing number of diseases. One of these is benign prostatic hyperplasia (BPH), which sooner or later develops in practically all males. The data on the incidence of benign prostatic hyperplasia vary more than for almost any other condition.

Some authors assume that from the fourth decade of life almost 80%, and from the seventh decade almost 100% of all men show a more or less pronounced nodular hyperplasia of the prostate (2, 6). This means that the older a man becomes the more certain it is that he will be confronted with an alteration of his prostate and its consequences. The almost unbelievable increase in life expectancy which has been achieved through the diagnostic, therapeutic and prophylactic measures of modern medicine means that more and more men are reaching the critical age for prostate disease. In Sweden, the United Kingdom and Germany, for example more than 50% of the population is over the age of 65 years.

The figures published by the German Federal Statistics Office in Wiesbaden for 1983 show that 156,000 people in the Federal Republic were 90 years of age or over. Ten years earlier the corresponding figure was only 92,000. The trend is the same in all industrial countries and will continue. As a result, the incidence of the “old man’s disease”, prostatic hyperplasia, will also increase.

The aetiology and pathogenesis of benign prostatic hyperplasia are still unclear and are the subject of controversial discussion. Changes in enzyme activity in the prostate, shifts in various hormonal parameters (e.g. DHT) and, more recently, altered hormone-receptor conditions, are accepted as

possible triggering factors (1, 2, 4, 6, 7). It is established that the endocrine system influences the development of a prostatic hyperplasia.

Rationale of the study

The fact that only relatively few men are not affected by benign prostatic hyperplasia makes it almost impossible to find a healthy control group in the same ate-range, in order to obtain comparative clinico-chemical data, for reference. This is probably also the reason for the sometimes contradictory results reported in many publications.

In out study two phytopharmaca, Cernilton® (Stroschein, Hamberb and β-sitosterol, were compared and the course of the treatment with each preparation objected on the basis of clinico-chemical data.

Our investigations

Selection of patients

It was possible to carry out the study almost exclusively with trial subjects from a large old people's home, who always received food of the same type and composition, and to a certain extent the same amount. It was thus relatively easy to exclude changes attributable to nutritional factors in the parameters to be measured in the course of the study, in both groups.

With a predictable drop-out rate of 20%, 50 patients were taken into the study, in accordance with the defined criteria for exclusion an inclusion, in order to reach a total of at least 20 patients in each group, for the final evaluation. The patients were allocated to the two groups according to a strict randomization procedure. All the patients entered the study without any additional medication. In order to exclude possible uncheckable drug effects, a one-week wash-out period was included before the start of the treatment, in 4 cases. All the patients required treatment and had been receiving medical therapy for their prostatic symptomatology for more than 6 months. Because of unsatisfactory results of previous therapy they can be considered as a "simple-negative" patient selection.

Two patients were excluded from the initial patient population because of extreme obesity and a further seven because of the results of diagnostic laboratory investigations (malignant tumors, sever alcoholic liver disease and extreme electrolyte imbalances). One patient had to discontinue the study for private reasons. At the final evaluation one patient of Group A with residual urine values of over 130 ml and who had to be operated for anuria before the end of the study period, was excluded. Table 1 shows the mean values for age, height, and weight in the two groups, A and B. Tables 2a and 2b provide information on concomitant diseases and the general condition of the patients of Groups A and B, respectively.

Methodology

The patients of Group A (trial preparation: a specially prepared pollen extract (3). Cernilton® [1)] received, as did the patients of Group B (control preparation: β-sitosterol [2)] 2 tablets/capsules 3 times a day for the first week, and then 1 tablet/capsule 3 times a day for the first week, and then 1 tablet/capsule 3 times a day 3) from the 8th to the 42nd day.

The blood samples were taken in the morning, between 8:00 and 9:00 a.m., in the fasting state, by the Vacutainer system (Becton & Dickinson), centrifuged after maturation of the fibrin (1 hour at room temperature), separated by means of Seraclear filters and deep-frozen at -25º C and kept constantly at this temperature until the analytical processing. The clinico-chemical and haematological parameters were analyzed on a

Type determinations of prostatic acid phosphatase (PAP) and prostate-specific antigens (PSA) were carried out by radioimmunoassay (RIA), as double-blind determinations which were repeated if the results exceeded the normal values by more than 600 counts. The counting was carried out with a Y-counter system (MR-1032-W+W) of the Kontron Co.

The enzyme activities were measured at the normal physiological temperature of 37ºC. The reproducibility for these values and for the haematology is ±3%, and for the other clinico-chemical parameters ±1%.

1) One tablet contains: Stand. Extr. Pollin. Sicc. (Cernitin T60) 60 mg; Stand. Extr. Pollin. dialys (Cernitin GBX) 3 mg.

2) One capsule contains: 10 mg β-sitosterol.

3) The manufacturer's recommendation of a dosage of 2 capsule 3 times a day was not followed, in order to be able to compare the therapeutic effects of the two preparations.

The data of the clinical investigations were classified according to symptoms and complaints and recorded according to the degree of change at each examination. The residual urine was determined by catheterization, always performed by the same investigator. The bacterial examinations of the urine samples were performed by means of the classical culture methods. All the data have been documented in accordance with GLP 4) and processed according to standard biostatisical methods on an EDP unit (Olivetti L I M 40 ST).

Results

Changes in the clinical symptomatology

Subjective complaints

Comparison of the initial findings with those at the end of the study shows improvement in the clinical symptoms with both preparations, which were clearly more pronounced with the pollen extract preparation, according to both the investigating physician's impression and that of the patients and the observations of the treating physicians these data are supported, at least semi quantitatively, by Table 3. This table shows a clinically relevant rate of improvement in the subjective symptoms, painful micturition , changes in the urinary stream and pollakisuria, for both preparations, with Cernilton® proving better than β-sitosterol. For vesical tenesmus, polyuria, urinary dribbling, as well as for pain and a feeling of pressure there is also a marked regression of the symptomatology in both groups.

4) GLP = Good Laboratory Practice: recommendations of the German GLP Committee, according to the guidelines of the Food and Drug Administration.

Determination of residual urine

In the β-sitosterol group the residual urine volume was 35 ± 22.5 ml and in the pollen-extract group 28 ± 16.6 ml. In both groups the mean values had fallen to under 15 ml at the end of the treatment.

Urine examinations

Table 4 gives an overview of the changes in the cell-counts and the bacterial status during the treatment. With the improvement in the symptomatology the pathomorphological picture also improved.

Changes in the biochemical parameters under the medication

The parameters indicating disturbances of renal function, namely creatinine and blood urea

nitrogen, showed a clear decrease under both Cernilton® and β-sitosterol. The urea nitrogen fell from 19.5 mg/100 ml to below 18.5 mg/ 100ml and from 21.0 mg/100 ml to 20.2 mg/100 ml under the two medications, respectively. The creatinine also showed a trend towards a slight decrease in the plasma concentration, which can be interpreted as not statistically significant tendency to improvement. The uric acid concentration was not influenced by either of the two preparations. The electrolytes remained largely within the ranges of the baseline values. Only in the case of chloride was there slight regression, by about 1 mmol/l. Neither preparation has any effect on blood pressure.

Impressive are those enzyme values which indicate cellular lesions. The γ-GT, generally known as a cholestase-indicating enzyme in alcohol abuse, had its highest intracellular value in the renal parenchymal cells. The fall in the primarily intrarenal γ-GT was not only statistically significant but also clinically relevant, and was more pronounced in the Cernilton® group.

Although the alkaline phosphatase (AP) isoenzyme group is not particularly prostate-specific, an enzyme of this group is however to be found in a high concentration in the prostate tissue. During the course of the study there was a marked fall in the serum concentration of AP in both groups.

The PAP and PSA determinations in the serum show a clear difference in the effectiveness of the two preparations. Prostatic acid phosphatase (PAP) is a highly tissue-specific enzyme which is normally passed into the seminal fluid. All pathological changes of the prostate, whether carcinoma, benign hyperplasia or prostatitis, lead to an increase in the concentration of this enzyme in the peripheral blood. In group A the PAP concentration fell, the decrease being not only clinically relevant but also statistically significant ($p < 0.05$), from 3.5 to 2.7 ng/ml, i.e. the serum concentration reached the normal range, the upper limit of which, measured by the RIA method , is 2.8 ng/ml. Group B, with a high baseline value, showed a similar initial fall from 4.4 to 3.7 ng/ml, which remained at this level until the end of the study, and thus did not reach the normal range (Fig. 1).

The prostate-specific antigen (PSA) originates from the epithelium of the excretory ducts of the glandular complex and shows a maximum physiological concentration in the serum of 2.3 ng/ml. In benign prostatic hyperplasia concentrations of up to 12 ng/ml are reached. β-sitosterol lowered the serum concentration from the start to the end of the study by only 0.5 ng/ml (from 12.9 to 12.4 ng/ml). This value is not statistically significant and also there is no detectable trend. Statistically significant and also there is no detectable trend. Statistically significant ($p<0.01$), and in our opinion clinically relevant, on the other hand, is the fall in the PSA value in the pollen-extract group. Here the value fell from 8.25 to 5.8 ng/ml, i.e. a decrease of 2.45 ng/ml was obtained (Fig. 2).

For the other clinico-chemical parameters, namely iron, total protein, albumin, calcium, an organic phosphate, bilirubin, LDH, GPT (ALT), GOT (AST), triglycerides, cholesterol, cholinesterase, copper, magnesium and zinc, no significant changes were recorded, between the baseline and final values. Only in the values for leukocytes, erythrocytes, haematocrit, haemoglobin and CPK are there a trend towards a slight fall in both groups, so that on the basis of this spectrum of parameter the relative innocuity of both preparations can be confirmed.

Discussion

Prostatic acid phosphatase (PAP) is a glycoprotein with a relatively low carbohydrate content of only 6%. Under normal physiological conditions this enzyme is passed from the prostate to the seminal fluid in which, together

with hyaluronidase, it influences the fluidity of the semen (8). Because of secretory obstruction a benign prostatic hyperplasia is always accompanied by raised internal pressure in the glandular complex. This raised pressure leads to compressive cellular lesions and cytolysis, as a result of which the PAP concentration in the peripheral blood increases. During the course of the study the mean value of the PAP concentration in Group A fell below the upper limit of the normal rage (Fig. 1), while in Group B there was an initial improvement, but then no further change in the mean value for the rest of the period of the study.

In healthy subjects the prostate-specific antigen (PSA) is to be found in high concentrations only in the semen. In the peripheral blood it is normally present only in a very low concentration (up to 2.3 ng/ml) (%), but increases markedly (up to 12 ng/ml) in the presence of cellular lesions of the excretory ducts resulting form a benign prostatic hyperplasia. Like the PAP concentration, that of the PSA also shows a marked fall under pollen-extract therapy, from 8.25 ng/ml (Day 0) to 5.8 ng/ml (Day 42), while underβ-sitosterol therapy the values fall only slightly (Fig. 2).

The fall in the serum concentrations of these two highly prostate-specific markers (PAP and PSA) permits the conclusion to be drawn that the cellular lesions of the glandular tissue resulting from prostatic changes show marked improvement under treatment with pollen extract. Presumably the internal pressure in the glandular complex due to the secretory obstruction also subsides. The concentrations of the mediators of inflammation, of the prostaglandin and leukotriene types, are certainly also reduced. In this way the vicious circle of a self-perpetuating inflammatory process can be broken, since the excessive secretion of prostaglandin is always set in motion by cellular lesions and persists for as long as these lesions are present. Thus with these values it can be confirmed that Cernilton® exerts an anti-inflammatory effect.

On the basis of the measurement values presented here the use of Cernilton® can be recommended for the indication, “benign prostatic hyperplasia in Stages I and II”, provided the residual urinary volume is still under 100 ml. Cernilton® reduces the symptomatolofy of prostatic hyperplasia. The anti-inflammatory and micturition-improving effects are confirmed by the various measurement data. We consider very important the fact that the preparation is extremely well tolerated.

The conservative drug therapy of benign prostatic hyperplasia is also of great significance, both in the hospital environment and in general practice, in view of the fact that the proportion of the general population over the age of 50 will in future be even greater than it is today.

Keywords: Prostatic hyperplasia, benign, Cernilton®, β-sitosterol, Prostatic acid phosphatase, Prostate-specific antigen.

A Japanese version of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI, Okayama version) and the clinical evaluation of cernitin pollen extract for chronic non-bacterial prostatitis

Monden K, Tsugawa M, Ninomiya Y, Ando E, Kumon H.

Department of Urology, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan.

PURPOSE: The chronic prostatitis syndromes are common disorders in urologic practice and present various clinical symptoms. The development of a chronic prostatitis symptom index appropriate for judgment of therapeutic effects is awaited since the pathophysiology and appropriate treatment are not well defined so far. We developed a Japanese version of the National Institutes of Health Chronic Prostatitis Symptoms Index (NIH-CPSI, Okayama version), and examined its usefulness. In addition, we evaluated clinical effects of Cernilton for chronic nonbacterial prostatitis using this symptom index

SUBJECTS AND METHODS: A total of 87 patients including 34 patients with NIH chronic prostatitis category III, 35 patients with BPH and 18 patients for control group who visited the Department of Urology at Okayama University Medical School filled in the questionnaire of our Japanese version of the NIH-CPSI to compare the NIH-CPSI scores among three groups. Twenty-four patients with NIH chronic prostatitis category III (IIIa 16, IIIb 8) were treated with Cernilton and the NIH-CPSI scores were examined before and after its administration.

RESULTS: The pain/discomfort domain score was 9.79 (mean) in the chronic prostatitis group, 1.66 in the BPH group and 0.39 in the control group; that of the urinary symptom domain was 3.82, 3.29 and 0.72, respectively; and that of the quality of life (QOL) was 8.21, 4.17 and 1.39, respectively. The pain/discomfort domain score was significantly higher in the chronic prostatitis group than in the other groups; the QOL domain score was higher in the order of the chronic prostatitis group, the BPH group and the control group. In the chronic prostatitis group, there was a significant, positive correlation between the pain/discomfort domain score and that of the QOL, and between the urinary symptom domain score and that of the QOL. These results suggested the usefulness of our Japanese version of the NIH-CPSI as a parameter of the severity of chronic prostatitis. Examination of changes in the NIH-CPSI scores revealed that scores of the items in all domains were significantly lower 4 to 6 weeks after the start of administration of Cernilton than those obtained before the drug administration in patients with chronic prostatitis.

CONCLUSIONS: A Japanese version of NIH-CPSI (Okayama version) accurately reflects clinical symptoms and the QOL in patients with chronic prostatitis. It seemed to be a useful and appropriate system for scoring symptoms of chronic prostatitis, indicating further studies on translation, adaptation and validation of the NIH-CPSI in Japan.

Publication Types:
- Clinical Trial

- Controlled Clinical Trial
  PMID: 12056038 [PubMed - indexed for MEDLINE]

Alterations in the Intraprostatic Hormonal Metabolism by the Pollen Extract Cernilton ®

Sabine Tunn, M. Krieg

Introduction

A number of hypotheses have been implicated in the etiology of benign prostatic hyperplasia (BPH). The most important theories are: (1) an alteration of the androgen metabolism in BPH if compared to the normal prostate (NPR) leading to an accumulation of the biologically highly active androgen 5a-dihydrotestosterone (DHT) predominantly in the stroma; (2) a change in the androgen-estrogen ratio in favor of estrogens; (3) and an alteration in the intraprostatic interaction between stroma and epithelium [for an overview see (3)]. Such variable hypotheses do not allow a unified therapeutic concept for BPH. For the medical treatment of BPH a variety of substances are utilized such as GnRH analogues, which reduce peripheral androgen and estrogen concentration (5,8), 5(a-reductase inhibitors, which lower the intraprostatic DHT concentration (14), or aromatase inhibitors, which lower the peripheral estrogen concentration (12).

Besides these substances influencing the hormonal milieu, phytopharmaca are also utilized to treat patients with BPH who do not have indications for surgery. These drugs, such as the pollen extract Cernilton ®, lead to a subjective improvement in the patient's symptoms. The effect is supposedly based on an improvement in the inflammation or congestion of the prostate. To what extent these drugs influence the intraprostatic hormonal milieu is not known. We were interested in the question whether and to what degree phytopharmaca influence the intraprostatic androgen metabolism and may exert their effects by a change in the intraprostatic DHT content. To this end we characterized the main enzymes of the androgen metabolism (5a-reductase, 3a- and 3B-hydroxysteroid oxidoreductase) in the epithelium and stroma of the human prostate, and tested the in vitro influence of the phytopharmacon Cernilton ® on these enzymes.

Material and Methods

The activity of DHT-metabolizing enzymes (5(a-reductase, 3a-HSOred, 3ß-HSOR,,d) was detemined in mechanically separated epithelial and stromal fractions from 10 normal and 20 hyperplastic prostate glands. To this end aliquots of the tissue homogenates were incubated with at least 4 different concentrations of the individual substrates (either exclusively in 3H-labelled or 3H-labelled and unlabelled form: testosterone to measure the 5a-reductase in concentrations from 14 to 600 nM, DHT to measure 3a- and 3ß-HSORred in concentrations from 100 to 4860 nM). After addition of a co-factor NADPH-regenerating system (5 mM glucose-6-phosphate, 0.6 U glucose-6-phosphate dehydrogenase) the reaction was started with the co-factor NADPH (5a-reductase: 0.5 mM; 3a- and 3ß-HSORred: 1.5 mM) and the mixture incubated for 15 min at 37degrees C. To determine the effect of the pollen extract, epithelial and stromal fractions of three of the hyperplastic prostates were incubated with various concentrations (49;246;493µg/ml) of the water-soluble wPE) or fat-soluble fPE) fractions of the extract, mixed well and then submitted to the same procedure as described above. After

the reaction was stopped by the addition of ether, and following extraction, the steroids were separated by HPLC (reversed phase, stationary phase: Lichrosorb RP 18, mobile phase: acetonitrile: H20 = 50:50). Quantification was performed by measuring the radioactivity in the individual chromatographic fractions (substrate and various metabolites). The enzymatic activity was determined from the distribution of the radioactivity in these fractions. The specific activity of the labelled substrate, the ratio between labelled and unlabelled substrate, the incubation time, the protein concentration, and the blanks were utilized for the calculation. All assays were performed in duplicate.

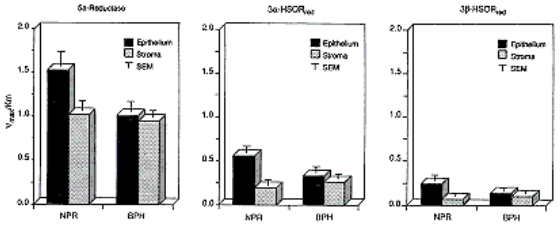


Fig. 1 Mean potential capacities (Vmax/Km) of 5a-reductase, 3a- and 3ß hydroxysteroid oxidoreductase (3a- and 3ß HSORred) in epithelium and stroma of 10 normal (NPR) and 20 hyperplastic (BPH) prostate glands.

Proteins were measured according to Lowry (6). The kinetic parameters Km and Vmax were calculated from the LineweaverBurk plot using regression analysis (least square method). The Student's t-test was utilized to determine significant differences between the means. P <.05 was considered significant.

Results and Discussion

In the human prostate many androgen-metabolizing enzymes are present (see Fig. 1 in the chapter, ‚Hormone Metabolism in the Human Prostate"). The potential capacities of these enzymes vary greatly as our own published (10,11) and unpublished results show. The DHT-forming 5a-reductase and the DHT-removing 3a- and 3ß-hydroxysteroid oxidoreductases (3a- and 3ß-HSORred) have the highest potential capacity and therefore the greatest biological significance. It can therefore be assumed that these three enzymes are mainly responsible in the regulation of the intraprostatic DHT level.

Androgen Metabolism in the Normal and Hyperplastic Human Prostate

The potential capacity of an enzyme is expressed by the ratio Vmax / Km (10). In Fig. 1 the mean potential capacities for 5a-reductase, 3a-HSORred and 3ß-HSORed in epithelium and stroma of normal and hyperplastic prostates are shown. The 5a.-reductase in the epithelium of normal prostate tissue has the highest potential capacity, where it is significantly higher than in the stroma, and also higher than in stroma or epithelium in hyperplastic prostate tissue. In the stroma there are no significant differences between NPR and BPH. The potential capacity of the 3a-HSORred is significantly lower than that of the 5a-reductase, and the capacity of the 3ß-HSORred is again significantly lower than that of the 3a-HSORred. Both DHT- removing enzymes have significantly higher capacities in the epithelium of normal prostate tissue than in the stroma, and than in the epithelium and stroma of BPH tissue. The potential capacity of the 3a-HSORred in NPR stroma is minimally lower, and that of the 3ß-HSORred even significantly lower than in BPH stroma.

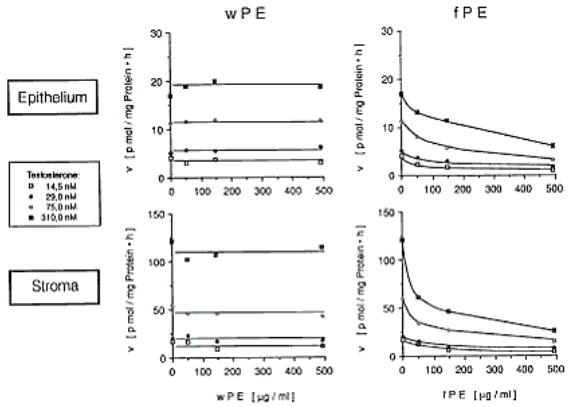


Fig. 2 Influence of the water-soluble fraction (wPE) of the pollen extract (left column) and the fat-soluble fraction (fPE) of the pollen extract (right column) on the enzyme activity (v). The activity of 5a-reductase in the epithelium (upper row) and stroma (lower row) is shown as an example. The enzyme activities were measured at different concentrations of the substrate testosterone (14.5-310W) and varying concentrations of wPE and f PE (49 - 493 µ/ ml incubation mixture). All measurements were done in duplicate.

A comparison of the potential capacities of the DHT-forming 5a-reductase and the DHTremoving 3a-HSORred and 3ß-HSORred allows the conclusion that there is no higher accumulation of DHT in BPH as compared to NPR. This conclusion is, however, only valid under the assumption of similar mean testosterone concentrations in men with normal and hyperplastic prostates. These results of the potential capacities therefore do not support the DHT accumulation hypothesis for BPH, but rather support the recently published data on DHT concentrations in normal prostate tissue (13,15) which demonstrated a higher concentration of DHT in normal prostate tissue removed immediately after death than in BPH tissue.

Alteration of the Intraprostatic Androgen Metabolism by the Pollen Extract Cernilton ®

To determine the effect of the pollen extract Cernilton ® on the enzymes of the intraprostatic androgen metabolism, the activities of the DHT-forming 5a-reductase and the DHTmetabolizing 3a-HSORred and 3ß-HSORred were measured in epithelium and stroma of three hyperplastic prostates with varying concentrations of substrates as well as different concentrations of the water-soluble (wPE) and fat-soluble fPE) fraction of the pollen extract. The activity of the 5a-reductase was not affected by wPE in a concentration range from 49 to 493 µg / ml incubation mixture in epithelium or stroma (Fig. 2). The activities of 3a-HSORred and 3ß-HSORred were similarly not affected by this substance within the same concentration range (data not shown). However, fPE demonstrated in epithelium and stroma an inhibitory effect on the 5(a-reductase (Fig. 2). The formation of DHT from testosterone is therefore significantly inhibited by the addition of fPE to the incubation mixture. Additionally, fPE also inhibited the activity of 3(a-HSORred and 3ß-HSOR,,d in epithelium and stroma (data not shown). Therefore the metabolism of DHT to 5(a-androstanediol is also diminished. The fatsoluble extract of another phytopharmacon (Serenoa repens B, Permixon®) was also found to inhibit the activity of 5a-reductase and 3a-HSORred in human foreskin fibroblasts (9). This would indicate that nonspecific acting ingredients of such fat-soluble extracts are responsible for the inhibition of the enzymes.

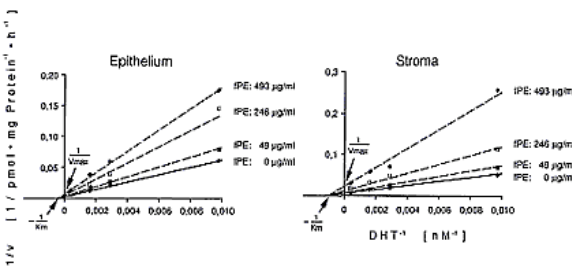


Fig. 3 Inhibition of the enzyme activity (v). The inhibition of the 3a-HSORred by different concentrations (49-493mg/ml incubation mixture) of the fat-soluble fraction (fPE) of the pollen extract as a function of the concentration of the substrate DHT in epithelium and stroma of a hyperplastic prostate is shown as an example (double logarithmic plot according to Lineweaver-Burk).

To determine the kinetic mechanisms of the inhibitory effect of fPE, the enzyme activities were plotted for the different substrate and inhibitor concentrations in a double-logarithmic plot according to Lineweaver-Burk as shown exemplarily for the 3a-HSORred in epithelium and stroma in Fig. 3. For all enzymes, 5a-reductase, 3a-HSORred and 3ßHSORred, it was found in epithelium and stroma that the presence of fPE in the incubation mixture of the tissue homogenate did not change the Km, but that the Vmax changed corresponding to the concentration. Therefore the fPE acts as a non-competitive inhibitor of these enzymes, or in other words, the ingredients of the fat-soluble fraction do not bind at the active center for testosterone or DHT, but at another location, thereby altering the turnover number.

In Fig. 4 the mean potential capacities (ratio Vmax/Km) for the three enzymes in epithelium and stroma of the three hyperplastic prostates are depicted without (Fig. 4 A) and with (Fig. 4 B) additional fPE (493µ ml incubation mixture). It is easily seen that the potential capacities of the 5a-reductase as well as the 3a- and 3ß-HSORred in epithelium and stroma are

drastically reduced, but that the inhibitory effect of the fPE on the three enzymes is different. The mean potential capacity of the 3a-HSORred is more inhibited in both compartments than that of

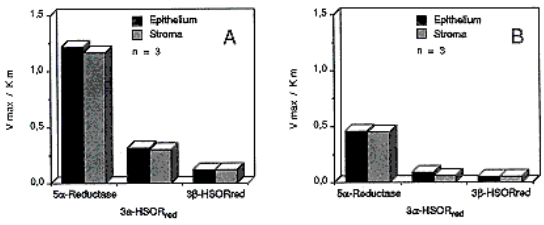


Fig. 4 Mean potential capacity (Vmax/Km) of 5a-reductase, 3a- and 3ß-HSORred in epithelium and stroma of three hyperplastic prostates without addition of fat-soluble fraction (fPE) of the pollen extract (A) and after addition of 493 µg fPE per ml of incubation mixture (B). All Vmax and Km values determined by Linewaver-Burk plots.

both 5a-reductase and 3ßHSORred.

To estimate the expected changes in DHT content after in vitro incubation with fPE, the mean potential capacities of the three enzymes without additional fPE were assumed to be 1.0, and the percent activity after addition of the highest concentration of fPE (493µg/ml incubation mixture) was calculated. The mean percentage activity of 5a-reductase after addition of fPE is shown next to the mean percentage activity of the DHT metabolizing enzymes 3a- and 3ß-HSORred (Fig. 5). It can be seen that the activity of the 3a-HSORred in particular in the stroma, but also in the epithelium is more inhibited than that of the 5a-reductase, while the inhibition of the 3ß-HSORred is similar to that of the 5a-reductase. The different reaction of the enzymes may be explained by the different intracellular localization. The 3a-HSORed is equally distributed between cytosol and cytosolic membranes, while the 3ß-HSORred is mainly membrane-bound (1). The 5a-reductase is exclusively found in the perinuclear and microsomal membranes (2,4,7). Although our studies were conducted in a cell-free milieu, the membrane-bound enzymes are probably surrounded by membrane particles and should be only minimally influenced by fat-soluble extract.

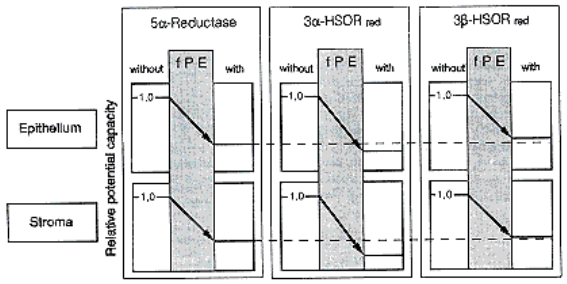


Fig. 5 Mean potential capacity (5a-reductase, 3a-HSORred and 3ß-HSORred) without (left columns) and after addition (right columns) of fat-soluble fraction (fPE) of the pollen extract in epithelium (upper row) and stroma (lower row) of three hyperplastic prostates. The potential capacities without additional fPE were assumed as 1.0, and the percentage remaining potential capacity after addition of fPE was calculated. The dotted lines indicate the relative potential capacities of the 5a-reductase in epithelium and stroma after addition of fPE.

Since these in vitro studies showed a stronger inhibition of the DHT catabolism compared to the DHT formation by the fatsoluble fraction of the phytopharmacon Cernilton@N, a lowering of the intraprostatic DHT level in tissue homogenates after fPE administration cannot be expected. On the contrary, an accumulation of DHT results, which should be similar to that in the normal prostate, however, at a generally lower activity level. This comparison is only valid under the condition that similar amounts of the fatsoluble extract are incorporated in the epithelial and stromal cells without being metabolized, and that these extracts reach the enzymes 5a-reductase, 3a- and 3ß-HSORred - which are located in different subcellular compartments - in similar concentrations. To make statements about the capacity of the pollen extract to influence androgen metabolism in vivo, further studies of androgen metabolism have to be conducted in prostate glands of patients who have been treated for a defined period of time with the pollen extract.

References

1. Abalain, 1. H., E. Queniener, J. L. Carre, B. Sinion, Y. Ainel, P. Mangin, H. H. Floch:

Metabolism of androgens in human hyperplastic prostate: Evidence for a differential localization of the enzymes involved in the metabolism. J. Steroid Biochem. 34 (1989) 467.
2. Bruchovsky, N., 1. D. Wilson: The conversion of testosterone to 5(x-androstan-17B-ol-3-one by rat prostate in vivo and in vitro. J. Biol. Chem. 243 (1968) 2012.
3. Coffey, D. S., S. 1. Berry, L. L. Ewing; An overview of current concepts in the study of benign prostatic hyperplasia. In: Rodgers, C. H., D. S. Coffql, G. Cunha, J. T. Grayhack~, F. Hininan, R. Horton (eds.): Benign prostatic hyperplasia. Vol If. NIH publication No 87-2881. Bethesda 1987 (p. 1).
4. Frederiksen, D. W, J. D. Wilson: Partial characterization of the nuclear reduced nicotinan-dde adenine dinucleotide phosphate: Delta 4-3 ketosteroid 5a-oxidoreductase of rat prostate. J. Biol. Chem. 246 (1971) 2584.
5. Gabrilove, J. L., A. C. Levine, A. Kirschenbawn, M. Droller: Effect of long-acting gonadotropin-releasing hormone analog (leuprohde) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. J. Clin. Endocrinol. Metab. 69 (1989) 629.
6. Lowry, 0. H., N. 1. Rosebrough, A. L. Farr, R. J. Randall: Protein measurement with Folin phenol reagent. J. Biol. Chem. 193 (1951) 265.
7. Nozu, K., B. I. Taniaoki: Testosterone metabolism in subcellular fractions of rat peostate. Acta Endocrinol. 73 (1973)585.
8. Peters, C. A., P. C. Walsh: The effect of nafaretin acetate a luteinizing-hormone-releasing hormone agonist on benign prostatic hyperplasia. New Engl. J. Med. 317 (1987)599.
9. Sultan, C., A. Terraza, C. Devillier, E. Carilla, M. Briley, C. Loire, B. Desconips: Inhibition of androgen metabolism and binding by a liposterolic extract of ‚Serenoa Repens B" in human foreskin fibroblasts. J. Steroid Biochem. 20 (1984) 515.
10. Twin, S., H. Hodistrate, L Grunwald, S. H. Fhichter, M. Krieg: Effect of aging on kinetic parameters of 5a-reductase in epithelium and stroma of normal and hyperplastic human prostate. J. Clin. Enclocrinol. Metab. 67 (1988) 979.
11. Tunn, S., R. Hatanann, J. Hey, S. H. FIfichter, M. Krieg: Effect of aging on kinetic parameters of 3a(p)hydroxysteroid oxidoreductases in epithelium and stroma of human normal and hyperplastic prostate. J. Clin. Endocrinol. Metab. 71 (1990) 732.
12. Tunn, U. W, P. Kaivers, H. U. Schweikert: Conservative treatment of human benign prostatic hyperplasia. In: Bruchovsky, N., A. Chapdelain, F Newnann (eds.): Regulation of androgen action. Congressdruck R. Brilckner. Berlin 1985 (p. 87).
13. Voigt, K. D., W. Bartsch: Intratissular androgens in benign prostatic hyperplasia and prostatic cancer. J. Steroid Biochem. 25 (1986) 749.
14. Vernieulen, A., V A. Giagulli, P. De Schepper, A. Buntinx, E. Stoner: Hormonal effects of an orally active 4-azasteroid inhibitor of 5a-reductase in humans. Prostate 14 (1989)45.
15. Walsh, R C., G. M. Hutchins, L. L. Ewing: Tissue content of dihydrotestosterone in human prostatic hyperplasia is not supranormal. J. clin. Invest. 72 (1983) 1772.

Regulation of Prostate Growth in Culture with the Pollen Extract, Cernitin ™ T60™, and the Impact of the Drug on the EGF Tissue Profiles

F. K. Habib

Introduction

A major difference between the prostate and other accessory reproductive glands is the susceptibility of the prostate to hyperplasia in aging men. Indeed, benign hyperplasia of the prostate (BPH) affects most males over 60 years of age and causes enlargement of the inner gland. When the urethra becomes constricted, treatment is required to relieve the kidney and circulating system of the damaging effects of back pressure.

Surgery in the form of transurethral resection still remains the "gold standard" for the treatment of outflow tract obstruction (1) but recently attention has also focussed on alternative forms of therapy, namely hormonal (2, 16), 5(ax-reductase inhibitors (11), and (ax-adrenergic blockers (5). However, the longterm prognosis for medical treatment has been poor and many of the endocrine and pharmacological agents presently in use have side effects (4). This has prompted the medical and scientific community to consider new lines of treatment of BPH. One recent development was the sudden and unexpected interest in phytotherapy, which was in part instigated by the encouraging results and the undoubted beneficial effects of the pollen extract, Cernilton ®, in the symptomatic relief of BPH (1).

The mechanism by which the pollen induces its effect on the hyperplastic prostate is not yet clear even though extensive experimentation has been undertaken by many workers (8,9, 10). Notably however, the bulk of the earlier research was focussed on experiments with animal tissue, which constitutes an unsatisfactory model for the human gland. Additionally, the few studies on the human prostate were carried out either on whole organ homogenates or on prostate epithelial cell lines (8), both of which ignore the potential heterogeneity of the cellular activity within the gland and the importance of stroma / epithelial interactions. Furthermore, the immortal cell lines represent a highly selective cell population which might have undergone phenotypic changes and may therefore be distinctive from the cells of origin.

In an attempt to overcome these earlier limitations, efforts in our laboratory have been directed towards developing primary culture of the human prostate and the serial culture of epithelial and fibroblast cells from BPH employing defined media. Initially, progress was slow and attempts to find the optimal concentration of ingredients to permit the growth of the cells and increase their plating efficiency were repeatedly frustrated. However, thanks to our collaboration with Dr. D. Chaproniere, to whom much of the credit for the earlier work goes (3), combined with the perseverance of my chief tissue culturist, Mrs. Margaret Ross, we managed to overcome many of the initial obstacles and finally establish a reliable technique for the serial culture of both prostate stroma. and epithelial cells in serum-free medium (manuscript in preparation). This model was subsequently adapted to our Cernilton ® studies in which the experiments were confined to the water-soluble Cernitin ™ T60™ fraction; this fraction accounts for approximately 60 % of the pollen extract. Details of the procedures followed and a summary of our findings on the characterization of the cultured cells along with the impact of the Cernitin ™ T60™ are described within.

This chapter also includes some preliminary data on growth factor profiles in prostate tissue specimen and in expressed prostate secretions (EPS) obtained from a group of BPH patients receiving the pollen extract. The relevance of growth factor peptides and particularly epidermal growth factor (EGF) to the prostate stems from their ability to maintain and regulate prostate growth either by acting in tandem with androgens or possibly even by by-passing the steroid hormones and imprinting their own characteristics on the gland (7,12). Recent reports on the preferential accumulation of EGF in BPH when compared to normal prostate tissue (6,14) supports the belief that this peptide might be implicated in the pathogenesis

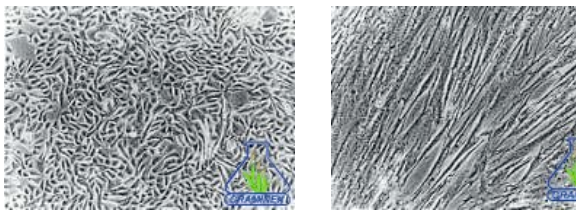
of this condition. Since the action of Cernilton ® in the prostate has been found not to be mediated via the androgen delivery system of the cell (8), we are now looking at the possibility of an association between the expression of some of these growth factors and their response to Cernilton ® in patients receiving the drug.

Serial Culture of Prostate Epithelial and Fibroblast Cells

BPH specimens obtained by transurethral resection were transported under sterile conditions to the laboratory in transport medium. Acini and fibroblast cells were released from prostate tissue by collagenase digestion and primary and sub-cultures were grown by plating onto plastic culture flasks and incubating at 37oC in a 95% air-5% C02 humidified atmosphere. By using this system it was possible to establish and serially culture pure populations of both epithelial (Fig 1 a) and fibroblasts (Fig I b) cells in well-defined media. For epithelial cells the WAJC404 medium (3) was serum free and was supplemented with insulin (2.5µg/ml), EGF (10µg /ml), dexamethasone (1µM), and choleratoxin (10µg/ml); this medium selects against the growth of the fibroblast cells. Four days after inoculation of the epithelial cells onto T-75 flasks, the acini demonstrated good spread, and confluence was usually reached by day five. Fibroblast cells were maintained in RPM11640 supplemented with fetal calf serum (10%) and penicillin and streptomycin (10µg/ml each). Fibroblast cells were initially slow in growing and confluence was reached usually after ten days.

Fig. 1 Phase-contrast micrograph of a primary culture of epithelium (1 a; x 100) and a serial culture of fibroblast (1 b; x 200) from a patient with benign prostatic hyperplasia.

a b



Verification of the culture as prostatic fibroblast and epithelial cells is accomplished by immunocytochemical staining employing a variety of antibodies including those for vimentin, desmin, prostatic-specific antigen (PSA), prostatic acid phosphatase (PAP), and cytokeratin. Assessment of the staining patterns and their intensities was always undertaken by an independent pathologist. A typical pattern of the staining profiles obtained is illustrated in Table 1.

In addition to the immunostaining (Table 1), the cells were also examined by phase contrast microscopy Analysis of the photomicrographs (Figs.1a and 1b) suggest that the resultant epithelial monolayers contain very little or no contaminants - any residual fibroblasts will be totally destroyed by the epithelium growth medium. Furthermore, the bulk of the epithelial cells appear to be of a secretory nature since PAP and PSA are strongly expressed (Table 1). The epithelial cells also stain uniformly for cytokeratin and recognize the antibody for the epidermal growth factor receptor. This confirms our earlier findings on the presence of EGF-receptors in epithelial cells of human prostate tissue (14).

Tab. 1 Immunocytochemical Staining of Epithelial and Fibro-blast Cells in Culture.

Markers used	Fibroblast cells	Epithelial cells
Prostatic acid phosphatase	-	++
Prostatic specific antigen	-	++
Epidermal growth factor receptor	-/+	++
Cytokeratin	-/+	++
Vimentin	++	-/+
Desmin	+	-
HMFG (Human Milk Fat Globulin)	-/+	++

Intensity of staining: (++) strongly positive; (+) moderately positive; (-/+) patchy; (-) negative.

In contrast, the fibroblast cells failed to stain for PAP and PSA but were positively labelled by antibodies for vimentin and desmin. Somewhat surprisingly, the fibroblast cells were also outlined by the antibodies for cytokeratin and for Human Milk Fat Globulin (HMFG), which are exclusively epithelial in nature. This raises the possibility that the fibroblast cells might contain small contaminants of a secondary cell. Closer examination of those fibroblastic cells by microscopy highlights the presence of small numbers of epithelial-like cells amongst the stromal monolayers. The secondary cells could be either non-secretory epithelial or endothelial cells which maintain an "epithelioid"-like appearance, but this needs to be confirmed. The presence of the fibroblast contaminants was also confirmed by flow cytometry and we are at present attempting to segregate the two cell populations employing a cell sorter. Interestingly, however, the "epitheloid"-like material appears not to multiply but remains constant throughout each passage and might merely act as a supportive matrix for the fibroblast.

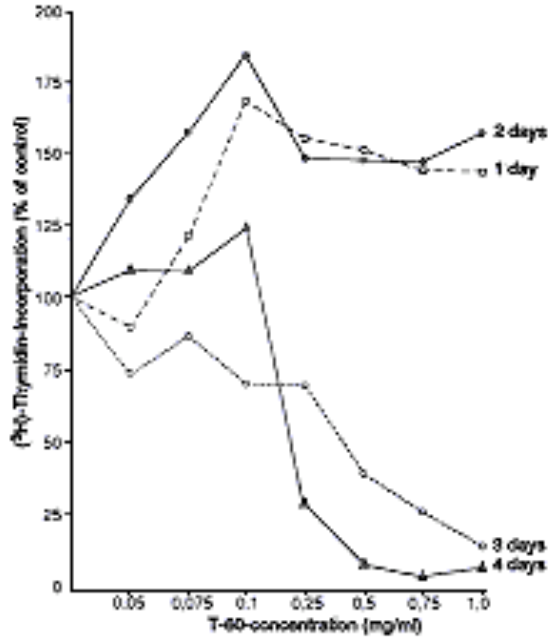


Fig. 2 Effect of T60™ concentration on fibroblast cell survival. Fibroblast cells (2.5 x 10 4 cells/well) were plated overnight in 96 well plates. Increasing concentrations of T60™ were added for varying times. (3 H)-thymidine was then added for 24 hours and the cells were trypsinized in 10 % TCA. The cells were then harvested onto filter mats, dried and counted in scintillation fluid. The data is normalized relative to the untreated control (100 %).

The Effect of T60™ on Epithelial and Stromal Cell Growth in vitro

Dose response curves of Cernitin ™ T60™ treat ment were determined using the following method: triplicate determinations for each treatment were performed in 96 well culture plates; each well was seeded with 2.5x104 cells and incubated overnight at 37C in the medium under defined incubation conditions. The following day, the Cernitin ™ T60™ stock solution was serially diluted in the defined medium to yield a concentration varying from 0.05-1 mg/ml. Controlled cultures received culture medium alone. For the dose response curve studies, the cells were exposed to Cernitin ™ T60™ for a total period up to 4 days with changes of freshly diluted T60™ in medium every 2 days. For the time course study, cells were treated in the presence and absence of T60™ a total period of 7 days. After the incubation periods, the cells were pulselabelled with radiolabelled thymidine whilst remaining in the defined medium for a further 24 hours.

For the determination of the rate of the DNA synthesis the cells were trypsinized and 10 % ice cold trichloroacetic acid was added for 2 hours. The cells were subsequently harvested onto filter mats ' dried at 60oC for 30 minutes and each disc of filter paper containing the precipitable material was then counted in scintillation fluid. The results illustrated in Fig. 2 (fibroblast cells) and Fig. 3 (epithelial cells) are expressed as the percentage of 3H-thymidine incorporated relative to the untreated control. These demonstrate that the effect of Cernitin ™ T60™ on stroma and epithelial cells is biphasic: initially and at the low concentrations of T60™ (up to approximately 0.1 mg / ml) we detect significant stimulation, particularly in the fibroblast cells which show after 2 days of exposure an increase of approximately 75 % in DNA synthesis. However, exposure to higher concentrations of the T60™ inhibits the uptake of thymidine and after 3-4 days exposure we do find that the concentrations of T60™ (P> 0.25 mg / ml) almost totally inhibit the fibroblast growth.

Although the epithelial cells do also show an inhibition in cell growth which is timeand concentration-dependent, it appears that the epithelial cells are slightly more resistant to the pollen extract than the fibroblast cells. Though

there is initially a minute stimulation in DNA synthesis of up to 25 % after 2 days of exposure (results not shown), this is rapidly reversed, and inhibition is observed at approximately the same concentrations of T60™ as those required to induce the same effect with the fibroblast but following longer periods of response to the Cernitin ™ T60™ (Fig. 3).

EGF Concentrations in Prostate Tissue and Prostate Secretions following Cernitin ™

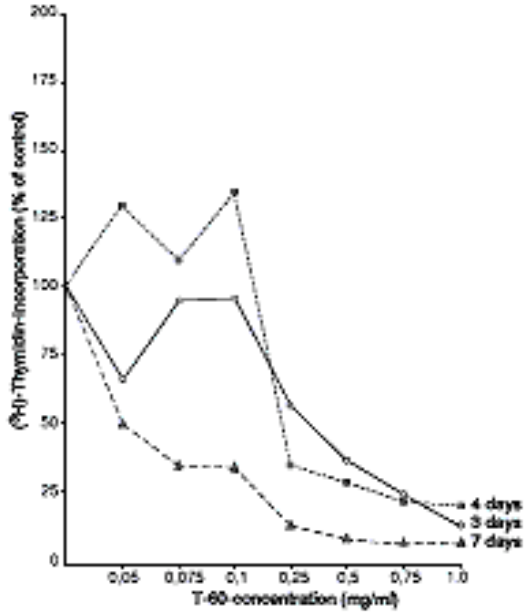


Fig. 3 Effect of T60™ concentration on epithelial cell survival. Details were identical to those followed for the fibroblast cells as detailed in legend to Fig. 2

Treatment

Prostate tissue was obtained at the time of the transurethral resection from 19 patients with BPH; the patients had been entered into a Cernilton ® double-blind placebo-controlled study over a six-month period. The tissue was transported immediately to the laboratory in iced saline, dry blotted, snap-frozen in liquid nitrogen and stored at - 70oC until analysis. Matching expressed prostatic secretions (EPS) were collected by transrectal massage before the commencement of the trial and at approximately three-month intervals with the last specimen obtained immediately prior to transurethral resection whilst the patient was under either regional or general anesthesia. The fluid was collected into 1-ml insulin syringes, frozen without delay, and stored at -70oC until needed.

Studies on EPS Specimens

Pre- and post-treatment samples of EPS were obtained from 8 patients in the Cernilton ® treatment group and 5 patients in the placebo group; the mean length of treatment with Cernilton ® was 147 ± 42 days. A comparison of EGF concentrations in both groups before commencement of treatment revealed no significant difference (P > 0.5; Fig. 4). Similarly, comparison of the EGF concentrations in samples before and after treatment also showed no significant difference (P > 0.5); these data are illustrated in Fig. 4. In addition we have also examined the changes in EGF concentrations of consecutive samples of EPS from individual participants in the doubleblind placebo-controlled study; the patterns obtained are illustrated in Fig.5. Clearly, there are no consistent patterns of change which could be of use for monitoring response to treatment.

Studies on Prostate Tissue

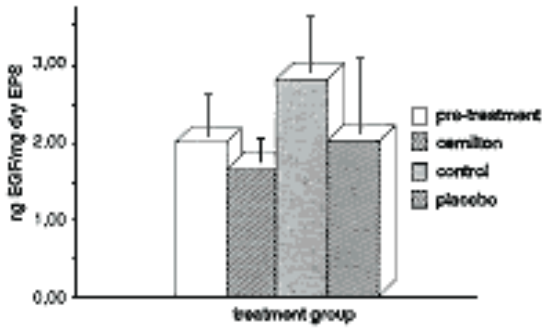


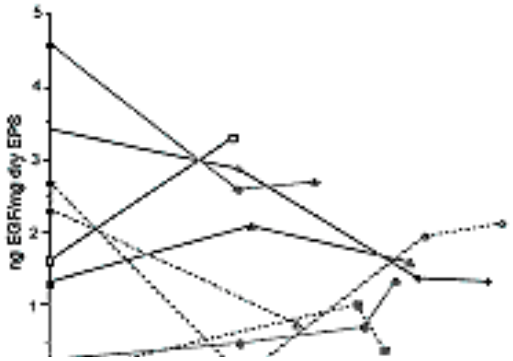
Fig. 4 EGF concentrations in expressed prostate fluid (EPS). Aliquots of EPS were taken from a group of patients who had entered the doubleblind placebo trial of Cemilton, and EGF was measured in samples taken at the start and towards the end of the trial. The concentrations in the treated group were compared to those on placebo. Results are expressed as mean ± SEM for 8 patients in the treated group and 5 patients on placebo. Bars show SEM.

In addition to the measurements undertaken on EPS, we have also measured the EGF concentrations in prostate tissue obtained from 15 BPH patients undergoing prostatectomy. These were compared to the concentrations

found in a parallel group of 7 patients who were taking Cernilton ® as part of the doubleblind placebo-controlled study. The data was expressed as ng EGF/mg protein in the tissue and the results obtained for the individual patients are outlined in Table 2. Although the levels of EGF in the treated group appeared to be considerably lower than those measured in the controlled group, the difference is not statistically different. However, it should be noted that the population receiving the Cernilton ® tablet is comparatively small and the results obtained might have been slightly biased by the fact that 2 out of 7 patients showed relatively high concentrations of EGF whereas the remainder of the population had levels considerably lower than those measured in any of the other individuals in the controlled group. We are at present extending this study to incorporate a further 20 patients on the drug in the hope that this might throw some light on the mechanism of action of Cernilton ® and whether the differences between the control and test groups are genuine and reflect actual changes in the metabolic pathways of the gland following treatment with the pollen extract.

Conclusion

The precise mode of action of Cernilton ® in BPH is not clearly understood even though many studies have been undertaken to elucidate the mechanism by which this pollen extract promotes symptomatic relief in patients with BPH. The earlier studies concentrated mainly on animal models and as reported by Ito et al. (9), Cernilton ® produced in mature Wistar rats a significant reduction in the size of the prostate as well as in PAP concentrations whilst also inducing a parallel increase in blood and tissue zinc concentrations. Additionally, Cernitin ™ T60™ produced relaxation of the smooth muscle of the mouse and increased the contraction of the bladder muscle in a concentration-dependent manner (10).



In view, however, of the specie differences in prostate anatomy and function, a fundamental distinction must be made between animal studies and experiments on human tissue. The attentions of this laboratory were therefore focussed initially on the immortal human prostate cell lines which demonstrated an inhibitory response following treatment with Cernitin ™ T60™ (7). Interestingly, the inhibitory effect was far more marked in the hormone unresponsive cell line when compared to the androgen-sensitive human prostate cells. Human cell lines derived from non-prostatic tissue failed to exhibit a similar sensitivity to the pollen extract (7).

Although the usage of immortal cell lines in our earlier studies was most helpful in identifying the specificity and selectivity of the drug, their use is somewhat limited because of: (a) the cancer nature of the continuous cells whilst Cernilton ® is prescribed purely for BPH; (b) immortal cells are identical clones and do not therefore take account of the morphological heterogeneity of the prostate; and (c) continuous cell lines may undergo phenotypic changes and this might render them distinctive from the cells of origin. In view of these limitations we have decided to continue our work on Cernitin ™ T60™ employing the well-established cultures of epithelial and fibroblast cells from human hyperplastic prostates (3,15). Those studies were facilitated by our ability to establish and serially culture pure populations of epithelial and fibroblast cells in a well-defined serum-free medium. By using this system the specific characteristics of Cernitin ™ T60™ could be assessed in a cohesive and systematic fashion.

Clearly, the data outlined in this report indicates that Cernitin ™ T60™ is a powerful mitogenic inhibitor of fibroblastic and epithelial proliferation. Although the mechanism involved is not as yet understood, we have evidence derived from our earlier studies (8) to indicate that these responses are not mediated via the androgenic pathways. We have therefore decided to look at the impact of Cernitin ™ T60™ on the expression of growth factors which have been implicated in the growth of the prostate cells. Though the results on the prostate fluid indicate little difference in EGF concentrations between the control and test groups, the evidence derived in this report suggests that there might be some impact on

the epidermal growth factor concentration of the tissue.

EGF is a well-established secretory product of the prostate and is retained in large concentrations by BPH when compared to the normal gland (6). This retention might be associated with the high concentrations of the EGF receptors found in BPH which must sequester the growth factor for internal use (14). We are not too clear on the mechanism responsible for this build-up of EGF receptors and whether it is a causal factor or merely a result of the development of hyperplasia. We are also not certain whether there is an association between these abnormal growth factor concentrations and the dihydrotestosterone levels which have previously been linked to the growth of the gland (17). Significantly however, our most recent studies reveal no correlation between EGF receptors and the endocrine status of the gland, suggesting that androgens do not modulate EGF-receptor expression in the prostate (13). Since the action of Cernilton ® on the prostate seems also to be independent of the endocrine functions of the gland, the impact of the pollen extract on the tissue EGF concentrations might be of significant importance, not only in controlling the abnormal growth of the gland but also in pinpointing new pathways relating to the pathogenesis of BPH.

Tab. 2 hEGF Concentrations in Prostate Tissue following Treatment With Cernilton ®.

Control Group	EGF concentration	Cernilton ® Group	EGF concentration
J. W.	1.50	W. F.	3.45
J. G.	1.35	C. F.	2.43
J. N.	2.09	C. S.	1.51
D. D.	1.61	K. B.	0.45
G. T.	2.07	A. S.	0.31
H. H.	1.20	T. S.	1.10
R. H.	2.84	R. H.	0.89
A. C.	3.98		
W. T.	3.67		
W. B.	4.38		
W. H.	1.50		
K. H.	3.40		
H. J.	2.57		
K. N.	3.00		

T. S.	1.76		

hEGF-Concentrations (mg/ EGF/mg Protein)

1.45 ± 1.31

Mean ± S.D. 2.39 ± 0.85

References

1. Buck-, A. C., R. Cox, R. W. M. Reese, L. Ebeling, A. John: Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernilton ®. A double-blind, placebo-controlled study. Brit. J. Urol. 66 (1990) 398-404.
2. Caine, M., S. Perlberg, R. Gordon: The treatment of benign prostatic hypertrophy with flutan-dde (SCH13521): A placebo controlled study. J. Urol. 114 (1975) 564-568.
3. Chaproniere, D. M., W. L. McKeelian: Serial culture of single adult human prostatic epithelial cells in serumfree medium containing low calcium and a new growth factor from bovine brain. Cancer Res. 46 (1986) 819-824.
4. Cliisliolm, G. D.: Benign prostatic hyperplasia: The best treatment. Brit. Med. J. 299 (1989) 215-216.
5. Gower, R., P. Wells: United Kingdom Indoramin Study Group. Low dose indoramin, an a-adrenoreceptor antagonist, in the management of benign prostatic hypertrophy Neurourol. Urodyn. 7 (1988) 216-217.
6. Gregory, H., I. R. Wiltshire, 1. P. Kavanagli, N. 1. Blacklock, S. Cliowderry, R. C. Richards: Urogastrone-epidermal growth factor concentrations in prostate fluid of normal individuals and patients with benign prostatic hypertrophy. Clin. Sci. 70 (1986) 359-363.
7. Habib, F. K.: Pepticle growth factors: A new frontier in prostate cancer. In Prostate Cancer and Testicular Cancer. EORTC Genito-Urinary Group Monograph. 7. (ed. Newling, D. W. W) Alan D. Liss, Inc. New York 1990 (pp. 107-115).
8. Habib, F. K., M. Ross, A. C. Buck, L. Ebeling, A. Lewenstein: In vitro evaluation of the pollen extract, Cernitin ™ T60™, in the regulation of prostate cell growth. Brit. J. Urol. 66 (1990) 393-397.
9. Ito, R., M. Ishi, S. Yamashita et al.: Cernitin ™ pollen-extract (Cernilton ®): Anti-prostatic hypertrophic action of Cernitin ™ pollen extract. Pharmacometrics 31 (1986) 214.
10. Kiniura, M., L Kitnura, K. Nakase et al.: Micturition activity of pollen extract: Contractfle effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Medica 2 (1986) 148-151.
11. McConnell, J. D., J. D. Wilson, F W. George et al.: An inhibitor of 5a-reductase, MK-906 suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J. Urol. 141 (1989) 239a.
12. MacDonald, A., G. D. Cidsliolm, F K. Habib: Production and response of a human prostatic cancer line to transforn-dng growth factor-like molecules. Brit. J. Cancer 62 (1990) 579-584.
13. MacDonald, A., F. K. Habib: Divergent responses to epidermal growth factor in hormone sensitive and insensitive human prostate cancer cell lines. (Submitted for publication) (1991).
14. Maddy, S. Q., G. D. CIfishohn, R. A. Hawkins, F K. Habib: Localization of epidermal growth factor receptors in the human prostate by biochemical and immunocytochemical methods. J. Endocrinol. 113 (1987) 147-153.
15. Peeld, D. M., T. A. Stainey; Growth responses of normal, benign hyperplastic and malignant human prostatic epithelial cells in vitro to cholera toxin, pituitary extract and hydrocortisone. Prostate 8 (1986) 51-61.
16. Peters, C. A., P. C. Walsli: The effect of nafarelin acetate, luteinising-hormone-releasing hormone agonist, on benign prostatic hyperplasia. New Engl. J. Med. 317 (1987) 599-604.
17. Wilson, J. D.: The pathogenesis of benign prostatic hyperplasia. Amer. J. Med. 68 (1980) 745-756.

Experimental Treatment Studies with Cernilton ® in Human Benign Prostatic Hyperplasia

B. Wagner, U. Otto, H. Becker, S. Schröder, H. Klosterhalfen

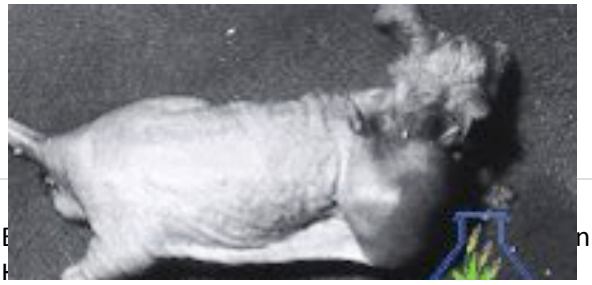
Introduction

Despite the high incidence of benign prostatic hyperplasia (BPH), so far a conservative treatment modality has not been established internationally (4,5). The reasons for this are the multifactorial etiology of the symptoms in patients with BPH (5) and the lack of suitable animal models to elucidate the pathogenesis of BPH (5,9). This makes the search for conservative therapies aimed at the underlying causes of the disease process difficult. Furthermore, all clinical trials in patients with BPH are complicated by a very strong placebo effect. Currently, patients with BPH up to stage III according to Vahlensieck are treated conservatively with phytotherapy in Germany (11,12).

To address some of the problems outlined above we established the heterotransplantation of human BPH tissue in nude mice as a model (Fig. 1) to evaluate the etiology of BPH and to facilitate the investigation of drug therapies and their mechanisms (8,13). In the context of these studies we utilized the phytopharmacon Cernilton ® (Extract. pollinis sicc.) since it had shown significant effects in placebo-controlled clinical trials (2,3). Our experimental studies were planned to address the question whether in the nude mice model a significant growth-inhibiting effect in hormonally stimulated human BPH was measurable.

Materials and Methods

The NMRI nu/nu mice were kept under sterile conditions at 27oC and a relative humidity of 55 %. They were fed a standard diet of Altromin (Lage, Germany) and water ad lib. Human BPH tissue was obtained by open transvesical prostatectomy from a patient with histologically proven BPH and divided in small pieces under sterile conditions after representative sections had been submitted for histology. Within one hour, 3 x 3 x 3-mm large pieces of tissue were transplanted subcutaneously on both sides of the thorax in 3-months-old male NMRI nu / nu mice which had been castrated the day before.



B n
H

Hormonal stimulation was affected by silicon implants containing 5 (x-dihydrotesterones DHT) and estradiol (E2) as described by van Steenbrugge (10). The animals were divided in three groups with 4 animals each (= 8 tumours). Groups II and III received the implants with DHT (serum levels of DHT 8 ng/ml) and E2 (serum level of E2 400 pg/ml) for hormonal stimulation, while group I served as controls (serum levels of DHT and E2 not measurable). The mice in group III were additionally treated with the pollen extract Cernilton ® (Extract. pollinis sicc., 2,5:1 which was given orally through a feeding tube as 10 mg / 25 g body weight twice weekly.

The tumor size was assessed by measuring the diameters and calculating the volume according to the following formula: length x width 2/2 (7).

After 6 weeks the animals were sacrificed and the tissue removed for histology. A semiquantitative determination of the human LDH isoenzymes (electrophoresis) was planned

6 weeks after transplantation to determine the human origin of the tissue.

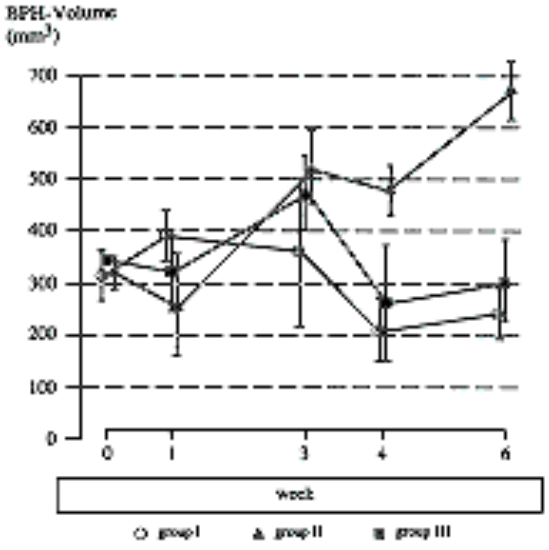


Fig. 2 Growth curves (x± s) of the human BPH transplants (nude mouse model) in the group without stimulation (1), with hormonal stimulation (11), and with hormonal stimulation and Cernilton ® treatment (I 11) (for details, see "Materials and Methods").

Statistical calculations were done to proof the experimental model, to test for homogeneity and for treatment effects. The t-test was used to compare mean values in two treatment groups, a one-way analysis of variance to compare mean values between all three groups, and an analysis of variance for the repeated measurement design. When all volume measurements were considered, the correlation between the two tissue pieces in each mouse showed a very strong correlation. Therefore the side related measurements were not considered an independent variable but interpreted as double measurements.

Results

The BPH tissue 6 weeks after transplantation is in all cases histologically vital and shows no sign of necrosis or rejection.

Immediately after transplantation the BPH tissue volumes are comparable in all groups (p =.605).

The growth curves of the BPH volumes are markedly different over the 6 weeks duration of follow-up (Fig. 2): in group I (control) the volume decreases according to the expectation, while in group II with hormonal stimulation by DHT and E2 an average increase in volume of 354.7mm3 is noted. A comparison between these two groups yields significant differences in particular at week 4 and 6 (Table 1). The validity of the animal model is therefore established.

In group III (hormonal stimulation with DHT and E2 and treatment with pollen extract) a slight decrease in volume in comparison to the starting volume is noted after 6 weeks, which is significantly different from the mean volume at week 6 in group II (control treated animals) (p =.003) (Table 2). At no time there are any significant differences between group III (Cernilton ®-treated and hormonally induced) and the control group I (Table 3). Analysis of variance reveals a significant difference of the mean at all four measurement points between the two hormonally treated groups (p =.007) demonstrating a growth inhibition of the pollen extract treated animals (group III).

Tab. 1 Volume differences (X±s) of the human BPH transplants (nude mouse model) in comparison with the starting volume in the groups without stimulation (1) and with hormonal stimulation (11). Statistical analysis demonstrated the effectiveness of the animal model (for details, see "Materials and Methods").

Time point of control	Group I $\bar{x}$	s	Group II $\bar{x}$	s	Validation of animal model p-value
1. week	74.5	95.3	−62.3	67.1	0.076
3. week	47.3	103.0	203.8	50.4	0.046
4. week	−102.1	106.1	161.5	57.2	0.008
6. week	−69.6	71.6	345.7	69.5	0.001

Tab. 2 Volumes (X±s) of the human BPH transplants (nude mouse model) in the groups with hormonal stimulation (11) and with hormonal stimulation and Cernilton ® treatment (111). Statistical analysis revealed a significant difference after 6 weeks in a time-related comparison between the two groups (for details, see "Materials and Methods").

Time point of control	Group II $\bar{x}$	s	Group III $\bar{x}$	s	Group III vs. Group II
before treatment	318.3	32.7	343.0	6.1	p-value
1. week	256.0	99.5	324.8	78.1	0.516
3. week	522.2	75.0	473.5	72.8	0.208
4. week	479.8	48.0	262.8	112.5	0.047
6. week	673.0	58.4	307.0	79.3	0.003

All examined specimens show histologically an epidermoid metaplasia (Fig. 3). There is no

histological difference between the two

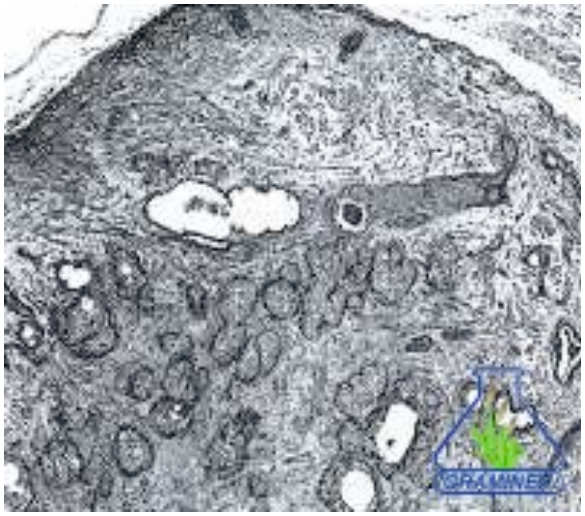


Fig. 3 BPH tissue 6 weeks after transplantation into the nude mouse and hormonal stimulation with DHT and E2 (for details, see "Materials and Methods") (HEx250)

treatment groups.

Discussion

The results of this study demonstrate a significant growth-inhibiting effect of orally administered Cernilton ® on heterotransplanted human BPH tissue in nude mice after 6 weeks of treatment under conditions of hormonal stimulation by DHT and E2. The model was validated and it can therefore be concluded that for the first time a growth-inhibiting effect of a phytopharmacon on human BPH tissue is demonstrated experimentally.

To what extent these results have clinical relevance as a therapeutic principle in patients with BPH cannot be answered definitely. Both stimulating hormones DHT and E2 are given in relatively high doses, and the amount of pollen extract given exceedes that usually given to patients by a factor of 50. While this is done to allow the effect to take place in the relative short time span of 6 weeks, extrapolation of the data obtained to other experimental or therapeutic in vivo situations is not possible.

The pollen extract group starts to show a significant difference from the also hormonally treated control group 11 after about 4 weeks. The clinically observed effects on voiding symptoms, residual urine and prostate volume (2,3) indicate positive changes within the first 6 weeks, and therefore there is no discrepancy between the human and the experimental data.

The mechanism of action cannot be determined from our observations since no histological differences were found between the treated groups. Since DHT and E2 were supplied, the growth inhibition cannot be the result of an inhibition of the 5ax-reductase or aromatase, which are target enzymes of innovative drug treatments for BPH (1). It is possible that the prostaglandin and leukotrienbiosynthesis in the prostate is influenced by the pollen extract (6).

Investigations in rats (10) and dogs (14) have contributed greatly to our understanding of the hormonal mechanisms involved in the etiology of BPH. However, it must be remembered that the rat does not develop spontaneous BPH and that dog BPH differs greatly in its histological characteristics from human BPH. Since in the nude mice model human BPH tissue retrieved at open prostatectomy is utilized, the observed effect caused by Cernilton ® may resemble the situation in humans more closely.

In summary, the nude mice model described here appears to be useful in experimental studies of the etiology of BPH as well as the mechanisms of effect of drug treatments for BPH. Further investigations utilizing the pollen extract in this model could serve to elucidate better its pharmacodynamic mechanism of action.

Tab. 3 Volumes (X ± s) of the human BPH transplants (nude mouse model) in the groups without stimulation (1) and with hormonal stimulation and Cernilton ® treatment (111). Statistical analysis revealed no signifiant differences after 6 weeks in a time-related comparison between the two groups (for details, see "Materials and Methods").

Time point of control	Group I $\bar{x}$	s	Group III $\bar{x}$	s	Group III vs. Group I
before treatment	315.9	48.7	343.0	6.1	p-value
1. week	390.4	50.8	324.8	78.1	0.231
3. week	363.1	141.9	473.5	72.8	0.255
4. week	213.8	63.7	262.8	112.5	0.809
6. week	246.3	54.0	307.0	79.3	0.595

Summary

The mechanism by which human BPH is induced is unresolved. As a result there is currently no established conservative treatment option available for patients with BPH. Up to stage III according to Valdensieck phytotherapy is commonly used as conservative treatment.

We established the heterotransplantation of human BPH tissue in athymic nude mice (NMRI nu / nu mice) as a model to investigate the etiology of BPH as well as the possible mechanisms of therapeutic approaches. The study presented here was designed to test whether the phytopharmacon Cernilton ® has a measurable effect on the volume of the transplanted BPH tissue in this model.

Human BPH tissue was grafted on NMRI nu/nu mice. The mice were stimulated by means of silicon implants containing dihydrotestosterone (DHT) and estradiol (E2). In comparison with the non-stimulated controls, a significant increase in volume was noted (p =.001). Cernilton ® was tested in this model and induced a significant growth inhibition of the BPH tissue in comparison to the hormonally stimulated control group (p = .007). There were no histological differences noted. In all cases the tissue was vital 6 weeks after transplantation.

References

1. Aumidler, G., U. Enderle-Schniitt, 1. Seitz: 5a-Reduktase und Aromatase-7-ielenzyme innovativer Therapieansdtze der benignen Prostatahyperplasie. In Helpap, B., T. Senge, W. Vahlensieck (Hrsg.): Prostataerkrankungen. pn-d-Verlag, Frankfurt/M. 1988 (S. 78-85).
2. Becker, H., L. Ebeling: Konservative Tberaple der benignen Prostatahyperplasie (BPH) mit Cernilton (D N. Urologe (B) 28 (1988) 301.
3. Buck, A. C., R. Cox, R. W M. Rees, L. Ebeling, A. john:Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cemilton. Brit. J. Urol. 66 (1990) 398.
4. Franks, L. M.: Benign nodular hyperplasia, of prostate: 12 review. Ann. R. Coll. Surg. (Engl.) 14 (1954) 92.
5. Lepor, H.: Nonoperative management of benign prostatic hyperplasia. 1. Urol. 141 (1989) 1283.
6. Loschen, G., L. Ebeling: Hemmung der Arachidons5ureKaskade clurch einen Extrakt aus Roggenpollen. Arzneim.-Forsch. 41 (1) (1991) 162.
7. Otto, U., G. Mjppel, H. P. Baisch: Transplantation of human renal cell carcinoma into NMRI nu/nu mice 1.14 Reliability of an experimental tumor model. J. Urol, 131 (19S4) 130.
8. Otto, U., B. Wagner, H. Becker, G. Kldppel: Transplantation of human prostate tissue into nude mice: can hormones influence its growth and structure? (in preparation, 1991).
9. Schroeder, F: Current models and their relation to human disease. In Hinnian jr-F. (ed.): Benign Prostatic Hypertrophy. Springer, New York 1983 (pp. 215 - 228).
10. Steenbrugge, G. J., M. Groen, F H. de Jong, F. SchrUder: The use of steroid containing silastic implants in male nude mice: plasma hormone levels and the effect of implantation on the weights of the ventral prostate and seminal vesicles. Prostate 5 (1984) 639.
11. Vahlensieck, W.: Konservative Behandlung von Prostata-Adenomen. Urologe (B) 12 (1972) 182.
12. Vahlensieck-, W.: Konservative Behandlung von Prostata-Adenomen. Urologe (B) 13 (1973) 176.
13. Wagner, B., U. Otto, H. Becker et al.: Kann die benigne Prostatahyperplasie hormonell induziert werden? Transplantation von menschlichern Prostatagewebe auf die NMRI nu/nu Maus. Verhandlungsbericht der Deutschen Ges. fdr Urologie. Springer, Berlin 1987 (S. 456-458).
14. Walsh, P., G. Wilson: The induction of prostate hypertrophy in the dog with androstandiol: J. din. Invest, 57 (1976) 1093.

Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH)

Results of Treatment with Cernilton ® for Stages 1-3 according to Alken (or II-IV according to Vahlensieck)

D. Bach, L. Ebeling

Introduction

Surgical treatment (transurethral resection or open surgical enucleation of the adenoma) of benign prostatic hyperplasia (BPH) is still the only curative therapy and therefore the "gold standard" for the treatment of BPH. Other treatment modalities have to be judged according to this standard. Despite all improvements in surgical technique and modem anesthesiology, a perioperative mortality rate of 0.2% and an increased delayed mortality due to cardiovascular diseases remains a significant risk factor (19). Furthermore, other possible complications of surgery such as urinary incontinence, erectile impotence, or retrograde ejaculation are not acceptable to some patients.

Despite extensive investigation into the endocrinological control of the growth of the prostate, the etiology of the pathological enlargement of this gland has not yet been definitely resolved. As a target organ for male steroid hormones, the prostate is under the influence of dihydrotestosterone and 17-ß-estradiol, which act in particular synergistically on the growth of the fibromuscular stroma. This explains why antiandrogens may be useful in the treatment of BPH (4,20). Because of the adverse effects of antiandrogens such as disturbances of libido and erectile function as well as gynecomastia, this therapeutic principle has thus far not been utilized widely, and is only used for certain patients such as those at prohibitive surgical risk. Other treatment attempts such as the inhibition of the enzyme 5alpha-Reductase require further studies concerning efficacy and adverse effects (14).

The importance of phytotherapeutic drugs with a low side effect profile has consequently increased in regard to the conservative treatment of BPH, which at least in Germany is mainly the responsibility of nonhospital-affiliated physicians. In recent years a standardized pollen extract (Cernilton ®1) has been investigated (5,6,9) and utilized. This pollen extract has also been utilized to treat prostatic congestion and/or prostatodynia and non-bacterial prostatitis without proven pathogens (8). The anticongestive effect of the pollen extract in the treatment of BPH should be considered as a clinically relevant therapeutic principle.

To examine the value of treatment of BPH with phytotherapeutic drugs in clinical practice, a study was conducted in BPH patients to determine efficacy and tolerance of the pollen extract in the various stages of the disease.

Patients and Methods

Patients

Over the course of one year, 208 practicing physicians documented their treatment experiences using Cernilton ® in 1,933 patients with BPH. Because of missing follow-up examinations or premature termination of either treatment or documentation not related to the

treatment with Cernilton ®, data on only 1,894 patients were available for analysis. An additional 96 cases which were not classified in regard to the stage of the disease were also excluded from the analysis. In seven of these patients treatment was terminated after the 12th week.

The patient material included therefore 1,798 patients with consecutive treatment over 24 weeks (2 tablets orally 3 times daily). In 1,661 patients pretreatment evaluations and evaluations after 12 and 24 weeks of treatment were available, while in 29 patients data were available for the pretreatment evaluation and after 24 weeks of treatment with Cernilton ®. In 51 patients the treatment was terminated because of symptomatic improvement (N = 11), lack of efficacy (N = 7), surgery (N = 27), untoward side effects (N = 4) or urinary tract infections (N = 2). In 57 cases treatment was terminated without a specified reason. Overall, therefore, 108/ 1,798 (6%) of the patients terminated treatment prematurely in the study population, as opposed to 115 / 1,894 (6.1 %) in the entire patient population.

The patients were staged according to Alken. Nine hundred and ten patients (50.6 %) were in stage 1, 770 patients (42.8 %) in stage 2, and 118 patients (6.6 %) in stage 3. The average age for these three groups was 60.0, 67.6, and 71.6 years, respectively. Overall, 59.1 % of patients had been pretreated, usually with other phytotherapeutic drugs used in BPH over an average duration of 21.2 (stage 1), 32.5 (stage 2), and 46.8 months (stage 3). This pretreatment was judged as "successful" in 52.0 % of stage 1 patients, 42.6 % of stage 2 patients and 30.4 % of stage 3 patients. Concomitant diseases existed in 812 (45.2 %) of the patients. Cardiovascular diseases (57.4%) endocrine and metabolic diseases (22.8%) and urological diseases (11.0 %) were most common. Among the urological diseases, prostatitis and bladder cancer were the most common.

To further describe the voiding disturbances, data such as age at the first manifestation, specific symptoms (irritative versus obstructive), intensity of the symptoms over time (constant versus variable, either increasing or decreasing), and incidence of episodes of acute urinary retention were documented.

Methods

Clinical evaluation was conducted prior to initiation of therapy as well as after 12 and 24 weeks of treatment. Irritative and obstructive symptoms (nocturia, frequency, feeling of incomplete emptying, urgency, delayed voiding, prolonged voiding time, weak urinary stream, and post-void dribbling) were classified as either mild, moderate, or severe.

Size and congestion of the prostate were evaluated by digital rectal examination (DRE). Residual urine volume was determined by ultrasonography. The documentation of residual urine was optional, and flow rate parameters were not documented at all since several of the participating physicians were family physicians and general practitioners who often did not have the means to perform residual urine or, in particular, flow rate measurements.

According to the design of the study, a statistical analysis was conducted using minimum, maximum, median, and mean values, standard deviation (STD), and frequency distributions. To compare frequency distribution across the various stages of BPH, the X2 test was used. For the comparison of means, a simple analysis of variance was employed, and for the comparison of mean time effectiveness profiles, split plot variance analysis was utilized.

Results

Voiding Disturbances and Findings on DRE

Tab. 1 Moderate to severe intensity of voiding symptoms and findings at digital rectal examinatioon (DRE) in 1,798 patients with BPH. [The frequency of symptoms and DRE findings differ significantly between the three stages. ($p<0.001$).]

Parameter	BPH 1 (N = 910)	BPH 2 (N = 770)	BPH 3 (N = 118)
Nocturia	43.6%	65.2%	79.8%
Frequency	53.8%	60.3%	77.9%
Feeling of incomplete emptying	20.9%	45.2%	69.8%
Urgency	26.4%	30.3%	49.5%
Delayed voiding	31.1%	62.3%	85.3%
Prolonged voiding	34.2%	70.1%	90.5%
Weak stream	38.7%	74.3%	88.8%
Postvoid dribbling	26.3%	44.0%	74.6%
Prostate enlargement	32.1%	86.1%	89.5%
Prostate congestion	28.1%	43.2%	63.0%

The distribution of obstructive and irritative voiding symptoms at the time of entry into the study is tabularized in Table 1. Data concerning age at first manifestation and type of voiding symptoms as well as their course are listed in Table 2. While in stage 1 BPH nocturia and frequency are the dominating symptoms, prolonged voiding time and a weak urinary stream are most common in stage 2, and in particular in stage 3 BPH. Post-void dribbling was of particular importance in patients with stage 3 BPH. Prostatic congestion increased significantly with increasing stages. As expected, a more pronounced enlargement of the prostate was found in patients with stages 2 and 3.

Of interest was the significantly different average age at the first manifestation of the voiding symptoms. In patients with stage 1, it was eight years earlier than in stage 3. If one takes the average age of the patient into account, symptoms have been present prior to treatment for 3.5 years in stage 1 patients, for 5.7 years in stage 2 patients, and for 7.1 years in stage 3 patients. If one excludes the possibility that the data obtained from older patients become relatively imprecise, these results can only be explained by an age-dependent dynamic course of progression of the disease process of BPH.

Irritative symptoms dominated in patients with stage 1, while in stages 2 and 3 obstructive symptoms were more common. However, in the advanced stages, often both irritative and obstructive symptoms were found equally common. Fluctuation of the intensity of the symptoms was particularly characteristic for patients with stage I BPH, while in patients with stages 2 and 3 a progression of the symptoms and a higher incidence of episodes of acute urinary retention was evident.

Tab. 2 Characteristic of voiding symptoms in the three stages of BPH.

Parameter		BPH 1	BPH 2	BPH 3	Comparison of Stages
Age at first manifestation (years)	$\bar{x}$	56.5	61.9	64.5	$p < 0.001$
	SD	10.2	8.7	8.0	
o not available		35	26	4	
Type of complaints					
o Mainly irritative		58.5%	29.7%	14.8%	
o Mainly obstructive		29.4%	42.5%	55.7%	$p < 0.001$
o Irritative and obstructive		11.8%	27.1%	28.7%	
o not available		8	10	3	
Clinical course (multiple listings)					
o Sometimes more, sometimes less		51.0%	32.5%	23.7%	$p < 0.001$
o Variable symptoms		47.8%	37.9%	22.0%	$p < 0.001$
o Increasing symptoms		31.9%	54.3%	73.7%	$p < 0.001$
o Episodes of retention		4.1%	9.9%	38.1%	$p < 0.001$
o not available		10	7	2	

In regard to the findings on DRE and the voiding symptoms, the treatment with Cernilton ® did not yield a significant difference in the response rates (range from 68% - 83%) between stages 1 and 2 (Table 3). However, if one compares the therapeutic efficacy in stages 1 and 2 with respect to the symptom-free status concerning nocturia and the obstructive voiding symptoms as well as the DRE concerning the prostatic size, a significant difference in favor of stage I was found (Table3). For patients with stage 3 BPH, a response rate between 28% and 63% was found, while a symptom-free status was found in 0 - 15% of patients (Table 3).

Unchanged positive symptoms and/or prostatic congestions (Non-responder) were found between 16.8% and 28.7% for patients with stage 1, 19.8% and 31.2% for patients with stage 2, and between 33.3% and 52.7% for patients with stage 3 BPH. Unchanged positive symptoms were found more commonly in the obstructive symptom category. Considering these findings, the comparison between the different stages yielded significant differences ($p < 0.001$) for all parameters, with a weaker effect in particular for stage 3 patients and in comparing stage I with stage 2. Worsening of the status in up to 6.4% of the patients was found particularly in patients with stage 3 BPH.

Tab. 3 Overall treatment response rates (R) and symptom-free or negative DRE status (S) after treatment with Cernilton ® in percent (rounded) of patients who initially had symptoms or findings on DRE.

Parameter	Patients (N) Stage 1/2/3	BPH 1 R (%)	BPH 1 S (%)	BPH 2 R (%)	BPH 2 S (%)	BPH 3 R (%)	BPH 3 S (%)
Nocturia	727/719/111	76	43	73	21	57	5
Frequency	746/693/108	82	48	89	34	63	12
Feeling of incomplete emptying	469/605/101	83	64	79	47	56	15
Urgency	449/454/ 83	79	60	79	56	59	33
Delayed voiding	645/701/111	72	46	73	27	54	5
Prolonged voiding	629/711/113	72	40	70	20	47	2
Weak stream	736/737/112	71	37	70	17	46	4
Postvoid dribbling	592/651/109	72	49	68	37	55	15
Prostatic enlargement	802/746/111	29	13	33	3	28	–
Prostatic congestion	504/495/ 74	75	55	68	38	51	16

An analysis of the time course showed for all parameters - with the exception of the size of the prostate - an increase in the rate of patients with a symptom-free status in regard to voiding symptoms and prostatic congestions at 24-week evaluation in comparison with the 12-week evaluation. The incremental rate of improvement between 12 and 24 weeks of treatment was 13

% to 24 % for stage 1, 10 % to. 25 % for stage 2, and 1 % to 17 % for stage 3. There was no principle difference detected between stages 1 and 2. Fig. I illustrates the time course of one of the symptoms (nocturia) for the different stages of the disease throughout the treatment period. The mean severity index for this symptom is shown.

Residual Urine

Significant improvements in the amount of residual urine were noted under treatment with Cernilton ® in patients with stages I and 2. A comparison between pre-treatment and post-treatment values in patients who had initially at least 20ml of residual urine revealed a mean decrease of 32.7ml (51 %) for stage 1, 43.1 ml (45 %) for stage 2, and 18.5 ml (13 %) for stage

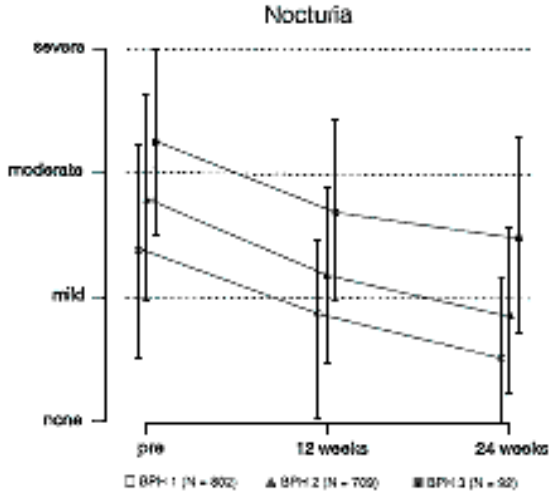


Fig.1 Nocturia (average intensity, X ± SA) during 24 weeks of treatment in patients with stages 1, 2 and 3 BPH with Cernilton ®. The intensity of the symptom decreases throughout the treatment in all three stages.

3.

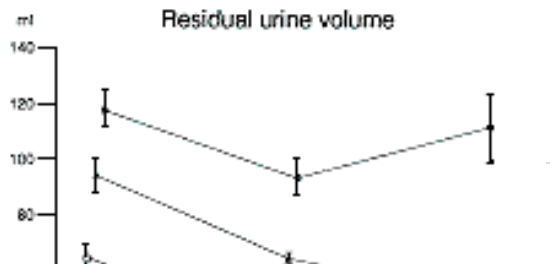
A time-course analysis in these patients showed for stages 1 and 2 a continuing decrease of the amount of residual urine under treatment. However, in patients with stage 3 BPH a worsening was noted at 24 weeks after an initial improvement (Fig.2). Analysis of variance revealed a significant difference when comparing the different stages of the disease (p=0.016). In patients with stage 2 BPH in comparison with stage 1, a more significant decrease of the residual urine volume was achieved after 24 weeks of treatment. In stage 1, 39.6 % of the patients with an initial residual urine volume of >20 ml had a residual urine volume of <20 ml at 24 weeks, while 25.0 % of patients with stage 2 achieved the same result. In patients with stage 3 BPH the residual urine volume was at the end of the treatment still significantly elevated. The degree of obstruction in this stage apparently does not allow a significant quantitative change of residual urine volume during treatment.

Adverse Effects

Adverse effects were noted in 15 patients for an incidence of 0.8 %. Except for two cases without specific documentation, the adverse effects were mainly gastrointestinal symptoms (stomach pain, pressure sensation, nausea, diarrhea, and indigestion). Treatment was terminated because of adverse effects after 12 weeks in four patients.

Global Assessment of Efficacy and Tolerance

Independent of the stage of the disease, tolerance was judged to be good in over 99 % of patients. There were statistically significant differences in the judgment of the treating physicians concerning the efficacy across the three stages (Fig. 3). The subjective assessment of the patients showed in principal a similar distribution of the results, but was overall somewhat more favorable when compared to the physicians' judgment. While the treatment result in patients with stages 1 and 2 BPH was judged as positive in over 90 %, it was judged as poor in 35 % of patients with stage 3. The main reasons for the treatment failure were advanced stage of the disease, need for surgery, psychogenic problems, bacterial prostatitis, and non-compliance of the patient.



Discussion

Reports in the urological literature document that several so-called conservative treatment options for BPH compete for both physicians and patients with BPH. Results following balloon dilation of the prostate, insertion of urethral spirals or stents made of surgical steel mesh in the prostatic urethra, thermotherapy, and drug treatment have been reported. Balloon dilation (15), insertion of spirals (11,18), or stents, (24), improved micturition only temporarily. Thermotherapy has apparently not yet reached practical applicability in the treatment of BPH (7,13,16,21).

If all these methods fail, oftentimes transurethral or suprapubic catheterization is a method of last resort. However, patients usually do not tolerate a permanent catheter over a long duration. This leaves the different drug treatments amongst which the low-risk phytotherapeutic drugs have a permanent place (2).

The use of these drugs is justified by good treatment results documented in case reports, open-label clinical studies, or prospective placebo-controlled double-blind studies. Criticism has been raised stating that the number of placebo-controlled studies is too low to prove the efficacy of the treatment (10). The placebo effect, which has to be taken into account with all drug treatments, is superimposed over the actual drug effect, and therefore no clear determination as to the efficacy of these drugs can be made.

However, concerning , the pollen extract preparation, Cernilton ®, experimental in vitro and in vivo data, and clinical documentation of effectiveness are available. An inhibition of the prostaglandin and leukotrien synthesis (17), an inhibition of the enzymes 5alpha-Reductase, 3alpha- and 3ß-Hydroxysteroid-dihydroxygenase (22), an anti-proliferative effect on BPH cells (12), as well as on BPH heterotransplants (23), and a significantly better efficacy of verum as compared to placebo in regard to nocturia, residual urine, and the global assessment of the treatment results have been reported (5,9). The following discussion therefore aims at the question of the clinical relevance and the indication for the use of phytopharmaca in the treatment of BPH.

The present report details the observation made by 208 practicing physicians during the treatment of 1,933 BPH patients with Cernilton ®. Under the conditions of routine clinical practice, it can be shown that irritative and obstructive voiding symptoms, prostatic congestion, and the residual urine volume are significantly improved, depending on the stage of the disease.

When comparing the results with those of controlled clinical trials, the response rates and the percentage of patients who achieve a symptom-free status or whose clinical findings become negative are higher in the present report. This may be explainable by the patient selection necessary for clinical studies. However, except for the symptom of frequency, which may be judged differently because of inconsistencies in its definition, there are no principal differences and therefore the data of the present study remain valid.

Concerning the symptoms, it is noted that the irritative symptoms show the largest margin of improvement, and patients with stage 1 BPH obtain the most benefit. Since irritative and obstructive symptoms are often equally common in patients with stage 2 BPH, these subjective voiding symptoms also improve significantly in patients with stage 2 BPH.

The clinical course of the voiding symptoms indicates that with the progression of the disease, obstructive symptoms increase and become more important in comparison to irritative symptoms. In regard to the therapeutic effect, this results in a lower percentage of patients achieving a symptom-free status in those men with stage 2 disease. In this group, prostatic congestion is also usually more pronounced.

In contrast to this, the residual urine volume decreases both absolutely and relatively more in patients with stage 2 disease than in patients with stage 1 disease. This may explain the relatively small differences in the global assessment of the therapeutic results stratified by these stages of the disease. The course over 24 weeks of treatment indicates that the residual urine decreases in particular in patients with stage 2 BPH between week 12 and 24. The percentage of patients with improved or

symptom-free status further increases during the second half of the treatment course. These results document therefore a relatively better efficacy of the treatment in stages 1 and 2 BPH during long-term therapy.

The clinical relevance of a therapeutic strategy is significantly impacted by the improvement of the quality of life as defined by the patient. The improvement of the voiding dysfunction is reflected in the overall global subjective assessment of the therapeutic result by the patient. If curative surgery is not medically indicated - this has to be decided for each individual patient - and an immediate surgical intervention independent of the stage of the disease is not necessary given the availability of continued monitoring of the patient (3), the results of the present study indicate that patients with stage 1 and 2 BPH according to Alken or stage II or III according to Vahlensieck represent a classical target group for the treatment with phytotherapeutic drugs. The impact of the treatment on prostatic congestion and associated inflammation is thereby the main focus of this treatment regimen (1).

The treatment of BPH with phytotherapeutic drugs is well tolerated and represents a treatment option with few risks. Therefore, a treatment trial may be justified even in patients with stage 3 BPH until the time of definite surgical treatment. In more than one-half of these patients some improvement in symptoms and a minor decrease in the amount of residual urine can be achieved. Phytotherapeutic drugs are not suitable for long-term treatment of patients at prohibitive surgical risk.

Summary

To examine the possibilities and limitations of phytotherapy for benign prostatic hyperplasia (BPH) a 24-week treatment trial using the pollen extract preparation Cernilton ® was conducted. Based on 1,798 cases a significant improvement in voiding symptoms, palpable prostatic congestion, and residual urine could be documented in stages 1 and 2. In patients with stage 3, the improvement in voiding symptoms was rather limited, as expected. When comparing the results after 12 and 24 weeks of treatment, a continuing improvement of all parameters during the second 12 weeks of treatment was noted. The drug was tolerated well in over 99% of patients. The efficacy in stages 1 and 2 was judged to be satisfactory, good or very good by over 90% of the patients. Because of the lack of conservative treatment alternatives for patients with BPH, treatment with phytotherapeutic drugs with their associated minimal risks is recommended as one of the prime treatment modalities for patients with BPH who are under continued medical care and monitoring. Until surgery, a treatment trial is also justified in patients with stage 3.

References

1. Bach, D., R. Schmidt, 1. Sdkeland: Entwicklung der benignen Prostatahyperplasie (BPH) - Pathogenese und moderne konservative Therapiem6ghchkeiten. Prakt. Arzt 25 (1988) 21-27.
2. Bach, D., P. Brfihl: Zur Frage der konservativen Behandlung bei benigner Prostatahyperplasie. Urologe B 29 (1989) 93-96.
3. Barry, M, I., A. G. Mulley Jr., F 1. Fowler, J. W. Wennberg: Watchful waiting vs immediate transurethral resection for symptomatic prostatism. J. Amer. med. Ass. 259 (1988) 3010-3017.
4. Bauer, H. W, D. Bach, U. Dunzendorfer, F. Pensel: Konservative Therapie der benignen Prostatahyperplasie (BPH) mit Flutan-dd. TW Urologie/Nephrologie 2 (1989) 259-269.
5. Becker, H,, L. Ebeling: Konservative Therapie der benignen Prostatahyperplasie (BPH) mdt Cernilton 0 N - Ergebriisse einer plazebokontrolherten Doppelblindstudie. Urologe B 28 (1988) 310-306.
6. Becker, H., L. Ebeling; Phytotherapie der BPH mdt Cernilton 0 N - Ergebnisse einer kontrollierten Verlaufsstudie. Urologe B 31 (1991) 113-116.
7. Bossche van den, M., 1. C, Noel, C. C. Schulman: Transurethral hyperthermia for benign prostatic hypertrophy. WId. J. Urol. 9 (1991) 2-6.
8. Buck, A. C., R. W. M. Rees, L. Ebeling: Treatment of chronic prostatitis and prostatodynia with pollen extract. Brit. J. Urol. 64 (1989) 496-499.
9. Buck, A. C., R. Cox, R. W. M. Rees, L. Ebeling, A. John: Treatment of outflow tract obstruction due to benign hyperplasia with the pollen extract Cemilton - A double-blind, placebo-controlled study. Brit. J. Urol. 66 (1990) 398-AO4.
10. Dreikorn, K., R. Richter, R S. Schdiih6fer. Konservative, nicht-hormonelle Behandlurig

der benignen Prostatahyperplasie. Urologe A 29 (1990) 8-16.
11. Fabian, K. M.: Der intraprostatische ‚partielle Katheter" (Urologische Spirale). Urologe A 19 (1980) 236238.
12. Habib, F. K.: Die Regulierung des Prostatawachstums in Kultur mit dern Pollenextrakt Cernitin ™ T60 und die Wirkung der Substariz auf die Verteflung von EGF im Gewebe. In Vahlensieck, W, G. Rutishauser (Hrsg.): Benigne Prostatopathien. Thierne, Stuttgart 1992 (in press).
13. Harzinann, R., D. Weckermann: Lokale Hyperthermie bei Prostataerkrankungen? Akt. Urol. 22 (1991) 10-14.
14. Kirby, R. S., T. Christmas: The potential value of 5-alpha- reductase-inhibition in the treatment of bladder outflow obstruction due to benign prostatic hyperplasia. Wld. J. Urol. 9 (1991) 41-44.
15. Klein, L. A.: Balloon dilatation of the prostate as compared with transurethral resection of the prostate for treatment of benign prostatic hypertrophy. Md. J. Urol. 9 (1991) 29-31.
16. Lindner, A., Z. Braf, A. Lev et al.: Local hyperthermia of the prostate gland for the treatment of benign prostatic hypertrophy and urinary retention. Brit. J. Urol. 65 (1990) 201-203.
17. Loschen, G., L. Ebeling: Hemmung der Arachidons~ureKaskade durch emen Extrakt aus Roggenpollen. Arzneim.-Forsch. /Drug Res. 41 (1991) 162-167.
18. Parker, C. J., B. R. P Birch, A. Conelly et al.: The Porges Urospiral: a reversible endoprostatic prostatic stent. Wld. J. Urol. 9 (1991) 22-25.
19. Roos, N. R, J. E. Wennberg, D. 1. Malenka et al.: Mortality and reoperation after open and transurethral resection of the prostate in benign prostatic hyperplasia. New Engl. J. Med. 320 (1989) 1120-1124.
20. Stone, N. N.: Flutan-dde in treatment of benign prostatic hypertrophy. Urology 34 (1989) 64-67.
21. Strohmaier, W, K. H. Bichler, M. Kaichtnaler et al.: Transrectal hyperthermia in benign prostatic hypertrophy. J. Endourol. 4 (1990) 134-136.
22. Tunn, S., M. Krieg: Beeinflussung des intraprostatischen Androgenstoffwechsels durch den Pollenextrakt Cernilton Q) N. In Vahlensieck, W, G. Rutishauser (Hrsg.): Benigne Prostatopathien. Thieme, Stuttgart (in press).
23. Wagner, B., U. Otto, H. Becker, S. Schroder, H. Klosterhalfen: Experimentelle Therapiestudien mit CerWIton@N an humaner benigner Prostatahyperplasie. In Vahlensieck, W, G. Rutishauser (Hrsg.): Benigne Prostatopathien. Thierne, Stuttgart 1992 (in press).
24. Williams, G.: Early experience of the use of permanently implanted prostatic stents for the treatment of bladder outflow obstruction. Wld. J. Urol. 9 (1991) 26-28.

[1]Pharma Stroschein GmbH, 2000 Hamburg 61 (licenced by Cernitin SA, CH-6903 Lugano)

Graminex™ Flower Pollen Extract - A microbiological digest

We often speak of Graminex™ Flower Pollen Extract as a microbiological digest, and therefore it may be appropriate to explain what this expression means.

As you already know Graminex™ Flower Pollen Extract is produced by extraction from the raw-material pollen using a non solvent manufacturing process. Graminex is currently the only manufacturer using non solvent technology to produce Flower Pollen Extracts eliminating residual solvents in the final product.

Hereby only type-pure pollen is used. Before the extraction it has been stabilized and purified through a special treatment. A number of selected plants give their pollen to the production of different Graminex™ extracts. These plants have been chosen after acute dermal, oral and genetic toxicology assay were completed.

The extraction of the pollen grains presents certain problems. Each grain is a biological unit with a complete set of different substances necessary for the creation of new life. These substances are well protected by the sheath, which is very resistant and can stay unchanged for thousands of years even if the grains have fallen unprotected on the ground. However, the sheath is provided with hilums, germinal openings, covered by a membrane, which can be dissolved.

The non solvent extraction method used by Graminex can easiest be described as follows. After having removed the membrane with a proprietary process using no solvents, the content of the grains is flushed out through the hilums. The husks are then removed. This is done so carefully that the extract is never heated to more than 400C. The extract received is called Graminex™ Flower Pollen Extract. Through this treatment such substances that are toxic or harmful, e.g. allergens and other high-molecular substances, are broken down .and eliminated Therefore, as a rule, our products can be used also by people otherwise allergic or hypersensitive to pollen.

During the processing high-molecular substances, that are difficult to absorb and often irritating, are reduced to low-molecular substances, i.e. each molecule contains less atoms, e.g. protein is reduced to peptides and amino acids. These low - molecular substances are harmless and can quickly be absorbed in the blood so that the body immediately can benefit by them. This is the reason for the quick effect of the Graminex™ preparations and also an explanation to the fact that relatively small amounts are needed for a good effect.

Almost nothing gets lost, but the whole amount of Graminex™ Flower Pollen Extract is active as distinguished from usual foodstuff or Synthetic substances of a more complicated composition. In those cases the body can sometimes have difficulties to utilize the substances, e.g. calcium and vitamin preparations. Even if large quantities are supplied, the body can have difficulties in utilizing necessary substances.

Some of the conditions determinative for the body's ability to utilize different substances are known. Thus, already more than 100 years ago, Justus von Liebig could phrase his classic "Minimum Law" in which he pronounced that very often a substance, from which is added too little, can be determining for how all added nourishment is absorbed. Thus it is possible to increase the body's ability to utilize supplied nourishment by providing for the body reasonable demands for nutrient substances of different kinds.

This can, however, many times be difficult, as we are creatures of habit and prefer to eat what we like, even if we thereby perhaps miss some substances that our body really need.

By a daily supply of Graminex™ Flower Pollen Extract in PollenAid™ or any of the Graminex products, the body gets guaranteed all the substances necessary for life and it will also be possible for the body to utilize all nourishment in the food. The body can, thanks to Graminex™ Flower Pollen Extract, utilize vitamins and other important substances present in the daily food. In this way Graminex™ Flower Pollen Extract normalizes the functions of the body and increases health and resistance against diseases.

A systematic review of Cernilton for the treatment of benign prostatic hyperplasia

R. MACDONALD, A. ISHANI, I. RUTKS and T.J. WILT

The DVA Coordinating Center of the Cochrane Collaborative Review Group in Prostatic Diseases and Urologic Malignancies.

Minneapolis VA Center for Chronic Diseases Outcomes Research, Minneapolis, USA

Objective To systematically review the evidence for the clinical effects and safety of the rye-grass pollen extract (Cernilton) in men with symptomatic benign prostatic hyperplasia (BPH). Methods Trials were identi®ed by searching Medline, specialized databases (EMBASE, Cochrane Library, Phytodok), bibliographies, and contacting relevant trialists and manufacturers. Randomized or controlled clinical trials were included if: men with symptomatic BPH were treated with Cernilton; a control group received either placebo or pharmacological therapy; the treatment duration was o30 days; and clinical outcomes were reported.

Results In all, 444 men were enrolled in two placebocontrolled and two comparative trials lasting 12± 24 weeks. Three studies used a double-blind method although the concealment of treatment allocation was unclear in all. Cernilton improved `self-rated urinary symptoms' (the proportion reporting satisfactory or improving symptoms) vs placebo and another plant product, Tadenan. The weighted mean (95% con- ®dence interval) risk ratio (RR) for self-rated improvement vs placebo was 2.40 (1.21±4.75) and the weighted RR vs Tadenan was 1.42 (1.21±4.75). Cernilton reduced nocturia compared with placebo or Paraprost (a mixture of amino acids); against placebo, the weighted RR was 2.05 (1.41±3.00), and against Paraprost the weighted mean difference for nocturia was ±0.40 times per evening (±0.73 to 0.07). Cernilton did not improve urinary ¯ow rates, residual volume or prostate size compared with placebo or the comparative study agents. Adverse events were rare and mild; the withdrawal rate for Cernilton was 4.8%, compared with 2.7% for placebo and 5.2% for Paraprost.

Conclusions The Cernilton trials analysed were limited by their short duration, limited number of enrolees, omissions in reported outcomes, and the unknown quality of the preparations used. The comparative trials had no con®rmed active control. The available evidence suggests that Cernilton is well tolerated and modestly improves overall urological symptoms, including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

Keywords Cernilton, plant extracts, benign prostatic hyperlasia, BPH, efficacy

Introduction

The LUTS associated with BPH are common in ageing adult men [1]; in the USA, population studies show that the frequency of moderate to severe LUTS is 8±31% among men in their ®fth decade and up to 44% among men in their seventh decade [2]. The cost of managing BPH is >$4 billion per year [3]. The primary aim of treatment in the vast majority of men is to relieve these bothersome obstructive and irritative symptoms. Treatment options for symptomatic BPH include lifestyle change, medical, device or surgical therapy [4]. Phytotherapy, i.e. the use of plant extracts, is becoming widely used to manage BPH [5]; the use of hytotherapeutic agents is common in Europe and increasing in the Western hemisphere. In Germany, phytotherapy is the primary treatment for mild to moderate urinary obstructive symptoms and represents >90% of all drugs prescribed for the treatment of BPH [6]. Phytotherapeutic agents are readily available in the USA as nonprescription dietary supplements and often recommended in `natural health-food' stores or books for the selftreatment of BPH symptoms [7]. Cernilton, prepared from the rye-grass pollen Secale cereale, is one of several phytotherapeutic agents available for the treatment of BPH. It is used by millions of men worldwide and is a registered pharmaceutical product throughout

Western Europe, Japan, Korea and Argentina (data from the manufacturer, AB Cernelle, Accepted for publication 10 August 1999 Engelholm, Sweden, 1999). In the USA, Cernilton is used as a nutritional supplement by <5000 men (D. Ruyan, Cernitin American, personal communication). One dose of Cernilton contains 60 mg of Cernitin T60, a watersoluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction (Cernelle AB). The acetone-soluble fraction contains b-sterols [8]. Several in vitro studies undertaken to investigate the mechanism of action suggest that Cernilton has antiandrogenic effects [9], may relax urethral smooth muscle tone and increase bladder muscle contraction [10], or may act on the a-adrenergic receptors and relax the internal and external sphincter muscles [11]. Despite many studies showing in vitro activity [9±11], the clinical effectiveness of Cernilton for the treatment of LUTS remains unclear. The objective of the present study was to systematically review the existing evidence for the clinical effectiveness and safety of Cernilton. Speci®cally, we assessed whether Cernilton is more effective than placebo or as effective as other pharmacological therapies in improving the obstructive and irritative urinary symptoms associated with BPH.

Methods

Inclusion criteria and the identi®cation of relevant trials Randomized (RCTs) or controlled clinical trials (CCTs) were included if men had symptomatic BPH; the treatment intervention was Cernilton (Cernitin) or a preparation of Secale cereale; a control group received either placebo or pharmacological therapy for BPH; and the treatment duration was o30 days. Medline (from 1966 to November 1998) was searched using a combination of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the medical subject headings `prostatic hyperplasia', `phytosterols', `plant extracts', `pollen', `sitosterols', Secale cereale,k `Cernilton.tw', and `Cernitin.tw' including all subheadings [12]. EMBASE was searched from 1974 to 1997 (performed in July 1997) in a similar approach to the one used for Medline. The private database hytodok (Munich, Germany) and the Cochrane Library, including the database of the Cochrane Prostate Group and the Cochrane Field for Complementary Medicine, were also searched similarly. The reference lists of all trials found were searched for additional trials. We attempted to solicit trialists identi®ed, asking them to identify any further published or unpublished trials; there were no language restrictions. Data extraction and study appraisal Study characteristics, demographic information, enrolment criteria and outcomes were extracted independently by two reviewers. Authors or sponsors of the trials were petitioned for required missing or additional information. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion. The number and age of enrolees, and dose and duration of treatment, were recorded. The main outcome was the ef®cacy of Cernilton vs placebo or control in improving urological symptom scores (e.g. the IPSS). The following secondary outcomes were also assessed: nocturia (times/evening); peak and mean urine ¯ow; postvoid residual urine volume (PVR); and prostate size. One study used the Uro¯ow Index, a formula developed to examine urinary ¯ow measurement based on maximum and mean ¯ow [13]. The number of and reason for men withdrawing from the trial or being lost to follow-up were assessed, as were treatment-related side-effects. The overall study quality was assessed according to the scale developed by Schulz et al. [14]. The quality of the concealment of treatment allocation is assigned a score from 1 to 3, (1 for the poorest quality and 3 the best). Trials in which concealment was inadequate (e.g. alternation or reference to case-record numbers or to dates of birth) were given a score of 1. Trials in which the authors either did not report their approach to allocation concealment or reported an approach that did not fall into one of the other categories were given a score of 2. Trials deemed to have taken adequate measures to conceal allocation, e.g. central randomization, were scored as 3. Statistical methods Summary treatment effect sizes were determined for Cernilton vs placebo and vs pharmacological therapies. Weighted mean differences (WMDs) and their 95% CI were calculated [15]. Heterogeneity was assessed using a chi-squared test; if there was evidence of heterogeneity then a random-effects model was used. For continuous measurements, a difference between treatment means and its correlated se of the difference were calculated using the methods of Lau [16] and Laird [17]. To assess the percentage of patients having an improvement in urological symptoms a modi®ed intention-to-treat analysis was conducted (i.e. men who withdrew or were lost to follow-up were considered to have had worsening symptoms) [18]. Chi-square tests were used to analyse bivariate comparisons.

Results

Four studies met the inclusion criteria from a total of six [19±24] identi®ed through the combined search strategy. Two trials were excluded because they had no control groups [23,24]. The concealment of treatment allocation was rated as unclear in the four studies reviewed, although two indicated randomization [19,22]. Three trials reported using a double-blind method [19,20,22]. Two studies were placebo-controlled [19,20] and two were `active-controlled' trials. The `active-controlled' trials included Tadenan, a phytotherapeutic extract

from the African plum plant, Pygeum africanum [21], and Paraprost (Nikken Kagakusha, Japan), a pharmacological treatment for BPH used primarily in Japan, and containing 265 mg of l-glutamic acid, 100 mg of lalanine and 45 mg of aminoacetic acid [22]. Atotal of444participants were enrolled in the four trials
(163 in the placebo-controlled and 281 in the `ativecontrolled' trials). Table 1 describes the participants, intervention, follow-up period, number of participants randomized, number who withdrew or were lost to followup, double-blind method status, and adverse effects. The mean (range) age of the enrolees was 69 (42±89) years and the duration of the trials was 12±24 weeks. The overall mean (range) rate of reported withdrawals or losses to follow-up was 6.3 (0±11.7)% (n = 28). Table 2 shows the summary of outcome data for urological symptoms scores, nocturia, peak urinary ¯ow rate and PVR. Three studies reported symptom scores or measured the symptom improvement, nocturia was reported in three, peak urinary ¯ow rate in four studies and four provided information related to PVR. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a quantitative meta-analysis. However, the results from all studies were consistent with an improvement in symptoms and urinary ¯ow measures, as described below.
Mean differences in outcomes Cernilton was comparable with both Paraprost and Tadenan in improving urological symptoms based on the IPSS (Paraprost) and two unde®ned symptom scales evaluating obstructive or irritative symptoms. For the IPSS, the mean (95% CI) difference (MD) was 0.90 (±0.43 to 2.23), with a percentage improvement from baseline of 55% for Cernilton and 62% for Paraprost [22]. For the trial comparing Cernilton with Tadenan, the MD for the obstructive scale score was ±0.70 (±1.78 to 0.40; % improvement from baseline, Cernilton 63%, Tadenan 46%) and for the irritative scale ±0.90 (±2.26 to 0.46; % improvement from baseline, Cernilton 68%, Tadenan 40%) [21]. Cernilton was better than placebo, Paraprost and Tadenan in the self-reported improvement of symptoms. The mean (95% CI) risk ratio (RR) vs placebo was 2.40 (1.21±4.75) (percentage of men reporting improvement, Cernilton 69%, placebo 29%) [20]. The RR vs Tadenan for a positive overall therapeutic response was 1.42 (1.21± 4.75; % of patients who reported improvement, Cernilton 78%, Tadenan 55%). Cernilton reduced nocturia compared with the controls (Table 3; 30.8% absolute improvement) [19,20] and against Paraprost, the MD was ±0.40 times per evening (±0.73 to ±0.07).

Table 1 The description of the individual studies
Study
Characteristic [19] [20] [21] [22]
Participants Symptomatic BPH Men with BOO from Men with BPH; assessed Men with BPH; global
Stage II±III (Vahlensieck)
BPH; modi®ed Boyarsky using authors' symptom physician assessment;
PVR >150 mL scale; ¯ow rate score; uro¯owmetry; US symptom score (graded
o150 mL/s; US estimate of PVR and prostate size 0±3 for nocturia,
of PVR and prostate size dysuria, hesitancy, etc.)
peak ¯ow 10 mL/s
(> 150 mL); PVR <50 mL
Mean (range) age (years) 66.6 (not reported) 68.6 (59±89) ? (50±68) 70 (54±68)
Intervention 1. Cernilton 2 caps 1. Cernilton 2 caps 1. Cernilton 2 caps 1. Cernilton (63 mg)
r 3/day; r 2/day; r 3/day for 2 weeks then 2 caps r 2/day;
2. Placebo 2. Placebo 1 cap r 3/day; 2. Tadenan
2 tabs r 2/day
Paraprost 6 g tab
2/day
Follow-up (weeks) 12 24 16 12
No. enrolled (withdrawals) 103 (7) 60 (7) 89 (0) 192 (14)*
Quality scale score{ 2 2 2 2
Double-blind method Yes Yes No Yes
Adverse events Mild nausea (1) None None None
*Ef®cacy was studied in only 159 patients. {Bbased on Schulz et al. [14]. US, ultrasonography.
838 R. MACDONALD et al.
2000 BJU International 85, 836±841

Urinary ¯ow measures were not significantly different between men treated with Cernilton and the placebo or active controls. The mean (95% CI) differences for peak urinary ¯ow and the Uro¯ow Index were 1.60 (±5.77 to 2.59) mL/s and 0.04 (±0.11 to 0.19) mL/s, respectively [19,20]. Against Paraprost, the MD was 0.37 (±1.90 to 2.64) mL/s for peak urinary ¯ow rate (4.6% absolute improvement) and 0.39 (±0.80 to 1.58) mL/s for the mean ¯ow rate [22]. Against Tadenan, the MD was 0.33 (±2.00 to 2.66) mL/s (8.7% absolute improvement) [21]. Cernilton modestly reduced the PVR in the two placebocontrolled studies (Table 3; 36.5% absolute improvement vs placebo) [19,20]. Cernilton was comparable with the control agents; the MD was ±5.00 (±14.98 to 4.98)mL vs Tadenan and 1.40 (±20.00 to 22.80) mL vs Paraprost [21,22]. No signi®cant differences in prostate size were evident when

compared with Tadenan, with a MD of ±2.09 (±10.21 to 7.97) mL, and Paraprost, with a MD of ±1.12 (±10.21 to 7.97) mL. One placebo-controlled study, reporting changes for three variables (circumference, transverse diameter and anteroposterior diameter) of the prostate, found a `statistically signi®cant reduction in the anteroposterior diameter' after treatment with Cernilton [20].

Table 2 The summary of the outcome data

Study	[19]	[20]	[21]	[22]				
Mean (SD) variable{	Cernilton	Control	Cernilton	Control	Cernilton	Control	Cernilton	Control
Symptom score or rating								
Baseline ± ±	`Overall improvement' +ve response		11.5 (3.5)	11.4 (4.0)				
Follow-up ± ±			5.2 (2.5)	4.3 (2.7)				
Difference ± ±	69%	29%{	78%	55%*	±6.3	±7.1		
Nocturia (times/night)								
Baseline	Improved ± ±		3.7 (0.5)	4.0 (0.8)				
Follow-up	`Improved' or symptom-free ± ±		2.8 (0.6)	3.2 (1.1)				
Difference	69%	37%{	60%	30%	± ± ±0.9	±0.8		
Peak urinary ¯ow rate (mL/s)								
Baseline	0.74 (0.27)	0.72 (0.34)	10.3 (5.2)	11.8 (6.4)	12.59 (3.0)	13.54 (3.2)	9.29 (4.99)	9.34 (4.86)
Follow-up	0.86 (0.25)	0.82 (0.31)	10.5 (5.1)	12.1 (5.1)	15.51 (4.3)	15.18 (4.5)	10.94 (5.09)	10.57 (4.82)
Difference	0.12	0.10	0.2	0.3	3.02	1.64	1.65	1.23
PVR (mL)								
Baseline	45.6 (30.4)	47.8 (32.8)	145.4 (107.5)	93.4 (91.4)	77.0 (15.7)	61.0 (14.1)	54.2 (78.84)	33.1 (40.06)
Follow-up	22.5 (20.9)	37.0 (28.9)	101.9 (87.3)	113.4 (87.3)	45.0 (21.0)	50.0 (15.8)	25.2 (28.22)	23.8 (28.59)
Difference	±23.1	±10.8*	±43.5	20.0*	±32.0	±11.0	±29.0	±9.26

*P<0.05; {P<0.01, otherwise not signi®cant. {Except for the values in [20], which are mean (sem).

Table 3 A comparison of Cernilton and placebo for nocturia and PVR in the two RCTs

Study			
Variable	[19]	[20]	Total
Reported improvement in nocturia			
Cernilton (n/N)	33/48	17/31	50/79
Placebo (n/N)	16/48	7/26	23/74
Weight (%)	67.8	32.2	100
Relative risk (95% CI ®xed)	2.06 (1.32±3.21)	2.04 (1.00±4.14)	2.05 (1.41±3.99)
PVR (mL)			
Cernilton (n)	48	28	76
Mean (SD)	22.5 (42.08)	101.9 (134.46) ±	
Placebo (n)	48	24	72
Mean (SD)	37.0 (41.08)	113.4 (124.48) ±	
Weight (%)	94.8	5.2	100
WMD (95% CI ®xed)	±14.5 (±30.94 to 1.94)	±11.5 (±81.93 to 58.93)	±14.35 (±30.35 to 1.66)

2000 BJU International 85, 836±841

Adverse effects In the short-term, Cernilton was well tolerated; the only reported adverse effect associated with the use of Cernilton was one case of mild nausea [20]. Withdrawal rates were Cernilton 4.8%, placebo 2.7% and Paraprost 5.2% (P = 0.26 for Cernilton vs placebo and P = 0.33 vs Paraprost).

Discussion

This is the ®rst systematic review summarizing the evidence from RCTs or CCTs about the ef®cacy and safety of Cernilton; the results suggest that Cernilton improved subjective symptoms and nocturia compared with placebo, Paraprost and Tadenan. Cernilton produced a similar response to the comparative study agents in improving urinary symptoms when evaluated by symptom scores. Only one adverse effect was reported, indicating that Cernilton was well tolerated; the withdrawal rate was <5%.

In contrast to the modest improvement in subjective symptom outcomes, Cernilton did not signi®cantly improve objective measures such as peak and mean urinary ¯ow rates when compared with placebo and the control study agents. Although Cernilton was analogous to Paraprost and Tadernan in improving peak ¯ow rates and reducing PVR and prostate size, these results were limited by the lack of con®rmed active controls to validate the comparisons.

Methodological issues

Although the results suggest that Cernilton provides modest benefit to men with BPH, the studies assessed for this review were limited by several factors. The concealment of treatment allocation was deemed unclear in all four trials and may be indicative of the questionable methodological quality of the studies meeting the inclusion criteria. Two of the studies reported random allocation with no detail of the method of concealment and three reported using a double-blind method. One trial did not report random allocation or a double-blind method [21]. Inadequate concealment of randomization and blinding are known to affect the sizes of the outcomes [25]. The treatment duration was short, with no studies lasting longer than 24 weeks. Cernilton dosages were not reported in three studies and whether a standardized preparation was used is also unknown. Additionally, fewer than 500 men were evaluated. Therefore, the longterm ef®cacy and safety of Cernilton, and its effectiveness in preventing complications of BPH such as acute urinary retention or the need for surgical interventions, is unknown. Only one study reported results from a standardized and validated urological symptom scale, the IPSS [22], although a modi®ed Boyarsky Scale was used in one [20], the others reporting various outcome variables. Therefore, the effect sizes should be interpreted with caution until future RCTs are conducted [26]. Such RCTs should be of suf®cient size and duration to detect important differences in outcome, including urological symptom scale scores (e.g. the IPSS), mean and peak urine ¯ow, voided volume, prostate size, PVR, and the development of acute urinary retention or need for surgical intervention. Studies are needed to compare Cernilton, a-blockers, 5a-reductase inhibitors and other phytotherapeutic agents, e.g. extracts of Serenoa repens (saw palmetto) [5,27]. Studies should also use standardized doses of Cernilton products that have been analysed for purity and potency by an independent laboratory to ensure the quality of the product. Additionally, cost-effectiveness studies should be conducted to evaluate the long-term cumulative costs associated with plant extracts, including the potential need for surgical intervention. The cost of a 90-day supply of Cernilton (three tablets/day, suggested use 2±4 tablets daily) is <US $40.00. In comparison, the cost of a 90-day supply of ®nasteride or terazosin (5 mg/day) is <$200 and $120, respectively. Alpha-blockers appear to be the preferred medical therapy for improving urological symptoms and urinary ¯ow [28]. However, the costs of the initial medication may not re¯ect the total charges incurred for the treatment of BPH-related conditions. Finasteride has been shown to reduce the need for surgical intervention in about 6% of men who have large prostates and moderate to severe symptoms [29]. The comparative total cumulative costs of medical or surgical management alone, and a combination of medicine and surgery caused by any failure of the initial medical management (mixed therapies), has been shown to depend on the age of the patient at onset of therapy and the avoidance of mixed therapies [30]. Medical management (including phytotherapeutic agents such as Cernilton) in younger patients appears to be costly over time unless it can also reduce urinary retention or the need for surgery. In men with mild to moderate symptoms of BPH that do not interfere with lifestyle watchful waiting remains a good initial option [31]. In conclusion, additional randomized placebo and active-controlled studies are needed to evaluate the clinical effectiveness of Cernilton. Until the results of such studies are available, the present systematic review provides the most complete assessment of the ef®cacy and safety of Cernilton in the treatment of mild to moderate BPH. The available evidence suggests that Cernilton is well tolerated and modestly improves subjective urological symptoms. Cernilton was not shown to improve urinary ¯ow measures compared with placebo. The long-term effectiveness and safety of Cernilton, and its ability to prevent complications from BPH, are unknown.

References

1 Berry SL, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132: 474±9

2 Bosch JL, Hop WC, Kirkels WJ et al. The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: Prevalence and correlation of symptoms with age, prostate volume, ¯ow rate and residual urine volume. Br J Urol 1995; 75: 622±30

3 Kortt MA, Bootman JL. The economics of benign prostatic hyperplasia: a literature review. Clin Ther 1996; 18: 1227± 41

4 Oesterling JE. Benign prostatic hyperplasia. Medical and minimally invasive treatment options. N Engl J Med 1995; 332: 99±109

5 Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. JAMA 1998; 280: 1604±9

6 Schmitz W. Urologika. In Schwabe U, Paffrath D, eds. Arzneimittel Verdungs ± Report 87, Stuttgart: Fischer G, 1987: 365±73

7 Marwick C. Growing use of medicinal botanicals forces assessment by drug regulators. JAMA 1995; 273: 607±9

8 Buck AC. Phytotherapy for the prostate. Br J Urol 1996; 78: 325±6

9 Ito R, Ishii M, Yamashita S et al. Antiprostatic hypertrophic action of Cernilton pollen-extract. Pharmacometrics 1986; 31: 1±11

10 Kimura M, Kimura I, Nakase K, Sonobe T, Mori E. Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Med 1986; 2: 148±51
11 Nakase S, Takenaka K, Hamanaka T, Kimura M. Effects of Cernilton pollen-extract on the urethral smooth muscle and diaphragmatic neuromuscular specimen. Folio Pharmacol Japan 1988; 91: 385±92
12 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. Br Med J 1996; 312: 944±7 13 Rohrborn C, Rugendorff EW. Uro¯ow index ± a formula for simplifying examination and the comparison of uro¯ow measurement curves in practice. Z Urol Nephrol 1983; 76: 721±4
14 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirica evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408±12
15 Update Software. RevMan, Version 3.0 For Windows Oxford: Update Software 1996
16 Lau J. Meta-Analyst, Version 0.99. Boston: New England Medical Center 1996
17 Laird N, Mosteller F. Some statistical methods for combining experiment results. Int J Tech Assess Health Care 1990; 6: 5± 30
18 Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? Neuropsychopharmacology 1992; 6: 39±63
19 Becker H, Ebeling L. Konservative therapie der benignen prostata-hyperplasie (BPH) mit CernitonÒN: ergebnisse einer plazebokontrollierten doppleblindstudie. Urologe B 1988; 28: 301±6
20 Buck AC, Cox R, Rees RWM, Ebeling L, John A. Treatment of out¯ow tract obstruction due to benign prostatic hyperplasia with the pollen-extract, Cernilton: a doubleblind, placebo-controlled study. Br J Urol 1990; 66: 398±04
21 Dutkiewicz S. Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. Int Urol Nephrol 1996; 28: 49±53
22 Maekawa M, Kishimoto T, Yasumoto R et al. Clinical evaluation of Cernilton on benign prostatic hypertrophy: a multiple center double-blind study with Paraprost. Hinyo Kiyo 1981; 27: 317±26
23 Hayashi J, Mitsui H, Yamakawa G et al. Clinical evaluation of Cernilton in benign prostatic hypertrophy. Hinyo Kiyo 1986; 32: 135±41
24 Yasumoto R, Kawanishi H, Tsujino T et al. Clinical evaluation of long-term treatment using Cernitin pollen extract with benign prostatic hyperplasia. Clin Ther 1995; 17: 82±7
25 Bero L, Drummond R. The Cochrane Collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. JAMA 1995; 274: 1935±8
26 Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of a randomized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials 1995; 16: 62±73
27 Wilt TJ, MacDonald R, Ishani A. b-sitosterol for treatment of benign prostatic hyperplasia: a systematic review. BJU Int 1999; 83: 976±83
28 Barry MJ. A 73 year-old man with symptomatic benign prostatic hyperplasia. JAMA 1997; 278: 2178±84
29 McConnell JD, Bruskewitz RC, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998; 338: 557±63
30 Chirikos T, Sanford E. Cost consequences of surveillance, medical management or surgery for benign prostatic hyperplasia. J Urol 1996; 155: 1311±6
31 Neal DE. Watchful waiting or drug therapy for benign prostatic hyperplasia? Lancet 1997; 350: 305±6

Authors

R. MacDonald, MS, Co-ordinator, VA Cochrane.
A. Ishani, MD, Resident.
I. Rutks, BS.
T.J. Wilt, MD, MPH, Associate Professor of Medicine.
Correspondence: R. MacDonald, Minneapolis VA Center for
Chronic Diseases Outcomes Research (111±0), 1 Veterans Drive, Minneapolis, MN 55417, USA.
e-mail: macdonald.roderick@minneapolis.va.gov

Clinical evaluation of long-term treatment using Cernitin ™ pollen extract in patients with benign prostatic hyperplasia

Yasumoto R, Kawanishi H, Tsujino T, Tsujita M, Nishisaka N, Horii A, Kishimoto T

Seventy-nine patients with benign prostatic hyperplasia (BPH) were treated with Cernitin ™ pollen extract. Patient ages ranged from 62 to 89 years (mean, 68 years). Mean baseline prostatic volume was 33.2 cm3. Cernitin ™ pollen extract was administered in a dosage of 126 mg (2 tablets, 63 mg each), three times a day, for more than 12 weeks. Symptom scores, based on a modified Boyarsky scoring scale, uroflowmetry, prostatic volume, residual urine volume, and urinalysis results were examined before and after administration of Cernitin ™ pollen extract. Symptom scores significantly decreased from baseline, and the favorable results continued during the treatment period. Urine maximum flow rate and average flow rate increased significantly from 9.3 mL/s to 11 mL/s and from 5.1 mL/s to 6 mL/s, respectively. Residual urine volume decreased significantly from 54.2 mL to less than 30 mL. There was no change in prostatic volume. However, 28 patients treated for more than 1 year showed a mean decrease of prostatic volume to 26.5 cm3. No adverse reactions were observed. Clinical efficacy at 12 weeks was rated excellent, good, satisfactory, and poor in 11%, 39%, 35%, and 15% of patients, respectively. Overall clinical efficacy was 85%. In conclusion, Cernitin ™ pollen extract showed a mild beneficial effect on prostatic volume and urination variables in patients with symptomatic BPH.

PMID: 7538904, UI: 95277792

Department of Urology and Andrology
Osaka Municipal Juso Citizens' Hospital, Japan

Clin Ther 1995 Jan-Feb;17(1):82-7

Treatment of chronic abacterial prostatitis: a review

Evans DT

Publication Types:

- Editorial
- Review
- Review, tutorial

PMID: 8061085, UI: 94339216

Int J STD AIDS 1994 May-Jun;5(3):157-64

Clinical effect of Cernilton in chronic prostatitis

Suzuki T, Kurokawa K, Mashimo T, Takezawa Y, Kobayashi D, Kawashima K, Totsuka Y, Shiono A, Imai K, Yamanaka H

Twenty-five patients with chronic prostatitis were given Cernilton tablets. Improvement of subjective symptoms and objective findings was noted in 96.0% and 76.0% of the cases. Sonographic findings in the prostate showed 33-100% improvement in four objective items. No side effects were observed in any case after Cernilton medication. Cernilton was judged to be an effective drug for chronic prostatitis.

PMID: 1529825, UI: 92411049

Department of Urology
Gunma University School of Medicine

Hinyokika Kiyo 1992 Apr;38(4):489-94

A long-term therapeutic experience with Cernilton in chronic prostatitis

Jodai A, Maruta N, Shimomae E, Sakuragi T, Shindo K, Saito Y

Thirty-two patients with chronic prostatitis were given 6 tables of Cernilton daily for 12.6 weeks on the average. Improvement of subjective symptoms and objective findings was noted in 74.2% and 65.6% of the cases, respectively. The effective rate was 75.0%. No subjective symptoms or abnormal changes in laboratory data were observed in any case after Cernilton medication.

PMID: 3389296, UI: 88267078

Department of Urology
Nagasaki University School of Medicine

Hinyokika Kiyo 1988 Mar;34(3):561-8

Clinical evaluation of Cernilton in benign prostatic hypertrophy

Hayashi J, Mitsui H, Yamakawa G, Suga A, Kai A, Shimabukuro T, Yanagi K, Fujisawa S, Takihara H, Kaneda Y, et al

Twenty patients with benign prostatic hypertrophy were treated with Cernilton, 6 tablets a day for an average of 13.2 weeks. Subjective effectiveness was observed in the improvement of sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%) and forceless urinary stream (53%). The overall subjective effectiveness was 80% of patients, and the overall objective effectiveness was 54% of patients. Night frequency, residual urine volume and tidal urine volume were improved significantly. The overall effectiveness was 80%. No side effects were observed.

PMID: 2421560, UI: 86183472

Hinyokika Kiyo 1986 Jan;32(1):135-41

Clinical evaluation of cernilton in the treatment of the benign prostatic hypertrophy

Horii A, Iwai S, Maekawa M, Tsujita M

Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

PMID: 2412423, UI: 85303710

Hinyokika Kiyo 1985 Apr;31(4):739-46

Clinical experience on treatment of chronic prostatitis with cernilton tablet

Kato T, Watanabe H, Takahashi H, Kaiho H, Shima M

PMID: 5463384, UI: 70208223

Hinyokika Kiyo 1970 Apr;16(4):192-5

Use of "Cernilton" in patients with prostatic hypertrophy

Inada T, Kitagawa T, Miyakawa M

PMID: 4170194, UI: 68131373

Hinyokika Kiyo 1967 Jun;13(6):466-9

REVIEW

Alternative medications for benign prostatic hyperplasia available on the Internet: a review of the evidence for their use

J.-P. MEYER and D.A. GILLATT
Bristol Urological Institute, Southmead Hospital, Bristol, UK

Introduction

The number of people seeking alternative medications to treat disease is increasing; indeed, this was the subject of a study conducted by Eisenberg et al. in 1993 [1] who reported that there were 425 million visits to providers of alternative treatment during 1992 in the USA. This number has probably increased since then. These alternative therapies are sold as nutritional supplements for numerous illnesses, ranging from treatments for the common cold to those for depression. As with other specialities, there is now an abundance of alternative therapies for urological conditions. It is estimated that in the USA 30–90% of patients seen by urologists for putative BPH may be taking some form of alternative therapy for the condition [2–4]. Access to these agents has become easier with the expansion of health-food shops, but more so with the increased use of the Internet by these patients. An Internet search using the words 'alternative treatments for BPH' as a search term revealed >1000 sites offering help and advice about BPH. On reviewing these sites there were several available alternative therapies, available via the Internet, for treating BPH:

· Seronoa repens (Saw palmetto berry extract); · Hypoxis rooperi (South African star grass); · Pygeum africaneum (African plum); · Cucurbita pepo (pumpkin seeds); · Urtica dioica (Stinging nettle);
· Secale cerale (Rye pollen); Flaxseed oil; · Lycopene; · zinc; · *b*-sitosterol; · selenium.

Each of these substances can be bought singly but much more common are the various combined 'prostate health' products. Some combination products list numerous ingredients, but the amount of each ingredient varies among products, and therefore if a combination product is selected the patient is required to undertake much painstaking reading of the labels. Despite the increased use of these products both in Europe and the USA, most urologists have little understanding or knowledge of them. There is also limited evidence of their efficacy [4]. In this article we review the evidence which supports their widespread use by current urological patients.

Serenoa repens (Saw palmetto berry extract)

This agent is derived from the olive-sized berries of the saw palmetto tree and is the most popular phytotherapeutic agent used in the treatment of BPH. The exact mechanism of its action has not been confirmed, although numerous mechanisms have been proposed. These include an anti-inflammatory effect, anti-androgenic activity, inhibitory effect on type 1 and 2 isoenzymes of 5a reductase, and inhibition of prolactin and growth factor-induced cell proliferation. The in vitro studies to determine its mechanism of action mainly used supraphysiological dosages, leaving the significance of these studies open to debate [4–6]. Lowe et al. [7] conducted a meta-analysis which set out to review all placebo-controlled trials using the 'Permixon' brand of saw palmetto. There were seven such studies, each of short duration, i.e. <3 months, reporting an improvement in symptoms, although the only symptom common to all of the studies was nocturia. There was also an improvement in urine flow when compared with placebo, although this was apparently limited.

The most widely quoted study of 'Permixon' saw Accepted for publication 9 February 2002 palmetto was a comparison with finasteride, a 5a reductase inhibitor, and involved 1098 patients in a 6-month double-blind, randomized controlled study. Both symptom scores and urinary peak flow rate were improved to a similar extent in both groups. The differences were significant when compared with baseline for both drugs. However, there was no placebo group in this trial and therefore the improvements reported might simply have been the result of a placebo effect.

Pygeum africanum (African plum)

In traditional African medicine a tea made from the powdered bark of this tall evergreen tree is drunk to control urinary disorders in men. Today, this supplement is commonly used in France, known more commonly under its trade name of Tadenan. It is frequently sold in combination with saw palmetto and other agents as part of pills for 'male health'. Tadenan has been shown to have several effects, including inhibition of fibroblast growth factors, antioestrogenic effects, inhibition of chemotactic leukotrienes and other 5 lipo-oxygenase metabolites [4,8]. Breza et al. [9] evaluated this agent in a recent 2-month open-label trial using a daily dosage of 100 mg.

Using the IPSS they reported a 40% reduction in scores and an improvement in mean peak urinary flow rates (10.97 mL/s at baseline to 13.07 mL/s at the end of the study). This was an uncontrolled study, only suggesting a benefit from Tadenan, and obviously no other conclusions can be made. Unfortunately, there are no recent placebo-controlled clinical studies using Tadenan.

Hypoxis rooperi (South African star grass)

This agent contains mainly b-sitosterol, which is thought to be the major active component, with other sterols being detected in lesser amounts [4,5]. The extract of star grass is marketed as Harzol. In vitro studies with Harzol show that it enhances the production and secretion of plasminogen activators in isolated epithelial cells. In prostate stromal cell cultures there are also increased levels of TGF-b1 when conditioned with b-sitosterol. TGF-b1 is a differentiation factor and induces apoptosis. These in vitro studies have not been verified in vivo and they have not been shown to be clinically relevant [4]. This drug has been studied in a double-blind placebocontrolled trial [10]; 200 patients were randomized to receive a placebo or a preparation of phytosterol. In both groups there were symptomatic improvements over baseline measurements and the difference was greater in the phytosterol group. These authors also reported a larger improvement (by 4.1 mL/s) in the peak urinary flow rate in those treated with Harzol than in the placebo group. At the 18-month follow-up the group initially given the placebo were given Harzol; they then had improvements which were comparable with the group initially treated with Harzol. Interestingly, the beneficial effect of Harzol continued over the next 12 months regardless of whether the patient stopped Harzol or was given the placebo [11].

Urtica dioica (stinging nettle)

There are at least 16 different preparations of this extract taken from the roots of the stinging nettle. The roots contain a mixture of lectins, phenols, sterols and lignins. Despite its widespread use in Germany for treating BPH there are limited clinical data about its efficacy for this condition. Two double-blind placebo-controlled studies were conducted >10 years ago, but with few patients and in trials of <3 months, the data produced were of little value.

Secale cerale (rye pollen)

The commercial preparation 'Cernilton' is a pollen prepared from several plants found growing in countries such as Sweden and Switzerland. This drug is available across Europe and is manufactured by microbial digestion of the pollen. As with many alternative medications the mechanism of action remains unclear.

Several mechanisms have been proposed, including an improvement in detrusor activity, inhibition of 5a reductase activity, and an influence on androgen metabolism in the prostate [5]. A study reported in 1996 [4] compared Cernilton with Tadenan over a 4-month period; there was no placebo group in the study. No conclusions can be drawn from this study as the efficacy of Tadenan has, as yet, not been confirmed. Despite this, the authors [4] reported a better response, in terms of symptom scores, residual volumes and peak flow rates, with Cernilton. Clearly, a double-blind placebo-controlled trial is required.

Soy

Environmental factors such as diet are thought to influence the causes of BPH. The underlying rationale for this comes from epidemiological data showing that the incidence of BPH is much lower in the Orient than in the Western world. This difference is not solely caused by genetic differences, as the incidence of BPH increases in those who migrate from the Orient to the USA [12]. When Western and Oriental diets are compared a major difference is the high intake of soybean products in the latter. Genistein is derived from soybean and is a major ingredient of tofu; it is also an active oestrogen, with a high affinity for the oestrogen receptor. Geller et al. [13] studied the effects of genistein on human BPH tissue in vitro, showing a dose-dependent decrease in the growth of this tissue. These promising results support a possible role for soy products in managing BPH, although further study is required.

Trace elements

Trace elements such as zinc and selenium are often marketed for their beneficial effects in the management of BPH. Although there is no evidence to support the efficacy of such trace elements they are still widely taken by patients.

Combination pills

Many of the above extracts are sold as combination pills. One such combination is 'Prostagutt forte', which is a combination of Serenoa repens and Urtica dioica; it is widely used although there are no data to support increased efficacy with combination products. This combination pill was compared with finasteride in 489 randomized patients in a 48-week trial; there were no statistically significant differences in the IPSS and peak urinary flow rates between the groups. Unfortunately, because there was no placebo group, no valid conclusions can be made from this study. Combination pills remain popular, although in many the amount of saw palmetto varies considerably, with some actually containing very little. Despite the lack of evidence for them, there is still widespread use of these products.

What advice should be given to patients?

Lowe et al. [4] reported that should a patient wish to try an alternative medication for BPH, then their advice would be for the patient to select the least expensive one available and trial it for 1 month. If the agent 'does not work', then they should try another brand for a month, even trying a third. Lowe et al. felt that if there was no change after 3 months then the patient would be best advised to take conventional medication. We concur with this advice and also suggest that the patient should be made aware that the alternative medications that they might be taking have not been subjected to the same rigorous clinical trials that 'conventional' drugs are, and that several of these alternative drugs remain 'unknown quantities'.

In summary, patients are now resorting to alternative medications for BPH with increasing frequency. One of the main reasons for this is the increasing public awareness of these previously 'unknown' products, through the expansion of health-food shops but particularly through the increasing use of the Internet by patients.
From this review it is apparent that although the use of these medications is increasing, understanding about them and the mechanisms of action are not increasing at the same rate. Although some of the studies cited here have shown promising results, randomized controlled trials containing many patients followed for long periods are needed. This will allow the initial results reported with these alternative medications to be validated or refuted. Only then will urologists be able to confidently and safely recommend these products to patients.

References

1 Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs and patterns of use. N Engl J Med 1993; 328: 246–52

2 Gerber GS, Bales G, Kirsh E, Christiano AP. Medicinal botanicals in the treatment of lower urinary tract symptoms (LUTS): a demographic analysis of awareness and use at the University of Chicago. J Urol 1998; 159: 334, A1282

3 Lowe FC, Ku JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. Urology 1996; 48: 12

4 Lowe FC, Fagelman E. Phytotherapy in treatment of BPH. An update. Urology 1999; 53: 671–8

5 Dreikon K. Other medical therapies. In Denis L, Griffiths K, Murphy G eds, Proceedings of the Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris July 2–5 1997. Plymouth, UK: Health Publication Ltd, 1998: 635–9

6 Buck AC. Phytotherapy for the prostate. Br J Urol 1996; 78: 325–36

7 Lowe FC, Roerhrborn CG, Robertson C, Boyle P. Metaanalysis of clinical trials of Permixon. J Urol 1998; 159: 257, A986

8 Lowe FC, Dreikorn K, Borkowski A, Braeckman J et al. Review of recent placebo controlled trials utilising phytotherapeutic agents for treatment of BPH. Prostate 1998; 37: 187–93

9 Breza J, Dzurny O, Borowka J et al. Efficacy and acceptability of Tadenan in the treatment of BPH. A multiculture trial in Central Europe. Current Med Res Opinion 1998; 14: 127–39

10 Berges RR, Windeler J, Trampisch H, Senge TH. Beta sitosterol in patients with benign prostatic hyperplasia. Lancet 1995; 345: 1529–32

11 Senge T, Windeler J, Berges RR et al. Wirksamkeit von B-sitosterin bei der behandlung von BPH. Urologe (a) 1995; 34: 130–1
ALTERNATIVE MEDICATIONS FOR BPH ON THE INTERNET 43 # 2002 BJU International 90, 41–44

12 Carro J, Raynaud JP, Koch G et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of BPH. A randomised international study of 1089 patients. Prostate 1996; 29: 231–40

13 Geller J, Sionit L, Partido C et al. Genistein inhibits the growth of human patient BPH and prostate cancer in histoculture. Prostate 1998; 34: 75–9

Authors

J.-P. Meyer, MRCS, Clinical Research Fellow.
D.A. Gillatt, ChM, FRCS, Consultant Urologist.
Correspondence: J.P. Meyer, Bristol Urological Institute,
Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK.
e-mail: jpmeyer@doctors.org.uk

Effect of Cernitin ™ pollen-extract on the Sex-hormone-induced Nonbacterial Prostatitis in Rats

Mitsue Hanamoto, Min Liao, Hajime Suzuki, Mitsuoki Ohba, Masato Honma, Akiko Nagashima, Syouhei Namikata, Shigeru Satoh, Makoto Ishii, Furnio Kimura and Etsuji Higaki

Ome Research Laboratories, Tobishi Pharmaceutical Co., Ltd.
7-1, 1-chome, Suehiro cho, Ome-shi, Tokyo 198-0025, Japan

Cernitin ™ pollen-extract (Cernilton ®, CN-009) is a preparation made from eight kinds of pollen. The active components are water-soluble (T-60) and fat-soluble (GBX) fractions. CN-009 has been used for the treatment of chronic prostatitis in Europe and Japan. To study the action of CN-009 on the prostatitis, we examined the effect of CN-009 on the sex-hormone-induced nonbacterial prostatitis in rats.

Aged Wistar rates (10 months old) were castrated and then injected 17b -estradiol (0.25 mg/kg, s.c.) for 30 days. These treatments reduced the weight of prostate and induced the inflammation and epithelial cell dysfunction of the lateral prostate lobe in the rats. Testosterone (2.5 mg/kg, s.c.) injected for the last 14 days of the treatment of 17b -estradiol to the rats restored markedly the estradiol-induced prostatitis. Those changes were similar to the findings reported by others. CN-009 was administered orally for the last 14 days of the treatment of 17b -estradiol to the rats. The administration of 378 mg/kg of CN-009 did not change in the prostatic histopathological findings, while 1260 mg/kg of CN-009 increased the number of intracellular secretory granules of epithelial cells and diminished weakly the invasion of inflammatory cells into the lumen or the stroma in the prostatic gland.

These results suggest that CN-009 may recover the prostatic epithelial cell dysfunction and have the mild anti-inflammatory properties.

KEY WORDS

Cernitin ™ pollen-extract, Cernilton, CN-009, Aged Wistar rat, Castration, Sex-hormone-induced nonbacterial prostatitis

Published in *Jpn Pharmacol Ther*, Vol. 26 No. 11 '98

Efficacy of Cernilton administration for infertile males associated with asymptomatic pyospermia

Tetsuya Arai, Shin Horiuchi, Kenichiro Yoshida
Department of Urology, Dokkyo University School of Medicine

Introduction

The cases, that white blood cell is significantly higher in semen, accounts for 16~17% of male infertility patients. Interestingly, it was common that no bacterial finding is presented in these cases, using standardized bacterial test, PCR methods for Chlamydia trachomatis (C. trachomatis), and semi-quantitative analysis for Ureaplasma urealyticum (U. urealyticum). Although these cases are classified in nonbacterial chronic prostatitis, it has been generally recognized to be associated with male infertility.

In present study, we reported that administration of Cernilton reduce PMN-elastase activity and to improve seminal findings in semen for 17 male infertility patients with no bacterial finding in semen.

Material and Methods

17 male infertility patients associated with nonbacterial asymptomatic pyospermia were treated with Cernilton 6 tablets daily over 12 weeks, then sperm density, progressively motile sperm ration, sperm motility and PMN-elastase activity in semen were measured.

Results

In all patients, progressively motile sperm ratio, sperm motility and PMN-elastase activity in seminar fluid were improved.

Conclusion

Administration of Cernilton is seemed to be effective in the treatment of infertile males associated with nonbacterial asymptomatic pyospermia.

Usefulness of Cernilton in the treatment of benign prostatic hyperplasia

Dutkiewicz S

A total of 89 patients with benign prostatic hyperplasia (BPH) were treated pharmacologically for 4 months: 51 received Cernilton and 38 Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan-treated patients. The obstructive and irritative symptoms responded best to the therapy. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH.

Publication Types:

- Clinical trial
- Controlled clinical trial

PMID: 8738619, UI: 96331567

Department of Urology
Central Clinical Hospital
Warsaw, Poland

Int Urol Nephrol 1996;28(1):49-53

Clinical evaluation of cernilton in the treatment of the benign prostatic hypertrophy

Horii A, Iwai S, Maekawa M, Tsujita M

Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

PMID: 2412423, UI: 85303710

Hinyokika Kiyo 1985 Apr;31(4):739-46

Findings on impairment of hepatic function through the "Pollen Extract G63" of Graminex Company

Hiromi Yokoyama Naofumi Suzuki Yoshimi Nishimura
(Kanda New Medical Clinic)

Pollen Extract, containing a rich source of nutrition (amino acids, minerals, and vitamins), represents the birth of the next generation of plant substances that should not be overlooked and is a substance with not yet known hidden effects. ED or andropause are modern-day diseases concomitant with impairment of liver function among male patients. Excessive alcohol consumption, nervous stress, and high calorie diets are mostly cited as the causes of a recurring vicious cycle. Protein, vitamins, and minerals are necessary for sufficient repair of hepatocytes (liver cells). In our report this time the effect of all that is contained in pollen extract was studied in terms of liver function impairment.

[Objective and Method]
At the Clinic, 5 patients which indicated for impairment of hepatic function were administered dosages of Pollen extract G63 over a period from 3 months to 5 months. The hepatic function was examined before administration started and after administration stopped (1 month~5 months afterward) and a determination made of the effect.
The pollen extract G63 used in the trial was produced by Graminex Company in Ohio, USA from the pollen of raw materials such as rye, corn, and timothy hay (referred to as Phlegm pratense in Japan) which were cultivated without using agrochemicals or genetically modified varieties. (However, a slight amount of pollen as weeds from timothy (referred to as Phleum pratense in Japan) was also included.) The pollen which has a double hull is not digested or absorbed even when ingested since it has strong resistance to acid and heat (cannot be destroyed even at 300 deg C).Graminex Company using a special technology is able to separately extract G60 (water soluble nutrition component) and GFX (lipid soluble component) and we received the product G63 which is a 20:1 combination G60 and GFX. The dosage was 6 tablets per day; three tablets each after breakfast and dinner. One 250 mg tablet contains 62.5 mg of pollen extract. (The daily quantity .... 375mg as pollen extract)

[Results]

Name	Gender	Age	Administration period	GOT	GPT	γ-GTP	T-cho	TG
N. Y	M	48	Before	67	186	119	244	197
			After 1 month	48	125	84	235	160
			After 2 months	31	60	76	239	174
			After 3 months	27	49	74	238	270
			After 5 months	35	65	76		
S. M	M	71	Before	61	56	144	183	126
			After 2 months	73	65	198	195	114
			After 4 months	48	47	164		
			After 5 months	46	49	135		
K. M	M	77	Before	47	47			
			After 2 months	26	29	152		
			After 3 months	26	29	178	136	161

K. M	M	48	Before	127	132	226	188	101
			After 1 month	69	79	220	187	135
			After 3 months	211	157	260	221	105
F. M	M	59	Before	119	360	241	169	153
			After 1 month	16	21	96		
			After 2 months	16	17	49		
			After 4 months	17	21	37		

[Results]
Among the 5 subjects all 5 experienced an improvement in GOT and GPT. However, the symptoms of medical case □ became wore after three months, although it can be considered that the reason for this was that alcohol consumption increased by the patient in response to the improvement achieved after one month. Medical case □ had hepatitis B, but improved dramatically from the first administration of pollen extract.

[Discussion]
Pollen extract is a substance that contains amino acids, and micro quantities of metal atoms (minerals) which have an antioxidant effect. It can be considered that blood flow is improved, fatigue is relieved, and the damage of the impaired hepatocytes is stopped and repaired at the smallest level.

[Safety]
Among the findings during the study, in particular there was no subject for which administration had to be stopped because of complaints of worsening condition. However, it is necessary to be cautious in the quantity of alcohol consumed as 2 individual complained that they did not drink to excess even though they drank alcohol.
4/19/2006

Findings on Prostatitis through the "Pollen Extract G63" of Graminex Company

Hiromi Yokoyama Naofumi Suzuki Yoshimi Nishimura
(Kanda New Medical Clinic)

Pollen, containing a rich source of nutrition (amino acids, minerals, and vitamins), represents the emergence of the next generation of plant substances with not yet fully understood hidden action that should not be overlooked. Pollen formulations have been used for the last 35 years in urology (enlargement of the prostate, prostatitis) treatment. This has been administered for a long time with peace of mind and without harmful effects as an alternative to pharmaceuticals for the improvement of both prostatitis and the associated indeterminate complaints. Moreover, this has seen as the welcome birth of supplements in improving associated symptoms. This time, we are reporting on study findings and the improvement effect obtained in the treatment of prostatitis with the supplement pollen extract.

[Objective and Method]
At this Clinic, 13 patients visiting the clinic for prostatitis treatment agreed to receive administration. The degree of improvement was determined based upon the IPSS score (International Prostate Symptom Score). The period of administration was from 1 month to three months. The pollen extract used in the trial was produced by Graminex Company in Ohio, USA from the pollen of raw materials such as rye, corn, and timothy hay (referred to as Phlegm pratense in Japan) which were cultivated without using agrochemicals or genetically modified varieties. However, a slight amount of pollen from timothy weeds (referred to as Phleum pratense in Japan) was also included. The pollen which has a double hull is not digested or absorbed even when ingested since it has strong resistance to acid and heat (cannot be destroyed even at 300°C).Graminex Company using a special technology is able to separately extract G60 (water soluble nutrition component) and GFX (lipid soluble component) and we received the product G63 which is a 20:1 combination of G60 andGFX.
The dosage was _ tablets per day; three tablets each after breakfast and dinner. One _ _ 0 mg tablet contains 62.5 mg of pollen extract. (The daily quantity .... 375mg as pollen extract)

[Results]
The trial study was stopped for 2 subjects among the 13 participants (one subject was stopped because his PSA value had increased prior to the start of administration and one was stopped because he was taking Gaster for epigastric distress before administration started but symptoms did not improve), and one other subject was eliminated from the effect determination since the IPSS was not filled in after administration.

Graminex Prostatitis Therapy Trials ... Prostatitis

Name	Age	Progress	IPSS	Perineal pain	Erection Ejaculation Difficult	Pain during urination	Change
S. K	56	Before	25	None	None	None	
		After 1 month	24	None	None	None	Morning erections increased.
S. T	73	Before	17	None	None	None	

		After 1 month	13	None	None	None	
I. Y	74	Before	12	None	occasionally	occasionally	
		With PSA - Therapy Trial stopped No related cause					
O. T	65	Before	8				
		After 3 months	3				Painful urination improved, did not have to go to the toilet at night
N. K	57	Before	11	None	Always	None	
		After 1 month	11	None	at times	None	Nocturia (night urination) (3~4 times)
		After 2 months	6	None	None	None	Nocturia (night urination) (2~3 times)
		After 3 months	9	None	None	None	Daytime urination, urinate freely
I. T	62	Before	10	pain at times	occasionally difficult	None	
		After 1 month	8	pain at times	occasionally difficult	None	A little improvement of perineal pain
		After 3 months	8	pain at times Difficult	occasionally	None	No particular change In symptoms, Watching the drop of of PSA
M. T	73	Before	18	None	None	None	
		After 1 month	14	None	None	None	
		After 3 months	14	None	None	None	
S. I	68	Before	7	None	None	None	
		After 1 month	5	None	None	None	Urination
S. M	61	Before	27				
		After 1 month		No IPPS record			improved a little,
T. M	71	Before	17	None	No Erection	None	Concomitant administration of Gastar (20)
				Reverse flow			Related cause unknown
U. T	62	Before	_ _ _	None	None	None	
		After 1 month	14	at times painful, At times difficult		None	
M. H	74	Before	15	None	None	None	
		After 1 month	6	None	None	None	rather improved
S. T	71	Before	24	None	always difficult	pain at times	
		After 1 month	17	None	difficult at times	pain at times	Pain is improving

[Conclusion]
The Average subject age was 66.1 ± 5.7, and 9 out of 10 patients saw improvement with a drop in IPSS score. The average IPSS was 15 before and administration, dropping to an IPSS average of 11 after administration. Additionally, improved patients evidenced an improving trend in their symptoms of perineal pain, erection, ejaculation difficulty, and pain during urination.

[Discussion]
Reshaping of the inflamed portion becomes necessary in the case of bacterial and non-bacterial inflammation of the prostrate occurring. Pollen extract makes possible rapid recovery since it contains plentiful amino acids and co-enzymes that work with the vitamins and mineral which are required for the repair of cells. Additionally, it is can be considered that the prostrate function also recovers since the zinc and selenium which are necessary for the Prostrate are also included in the extract.

[Safety]
There was an example of the medical trial being stopped for 2 subjects. As previously mentioned, the trial was stopped because of the high PSA value and treatment was changed to another method. And, the other case was stopped because Gaster was taken for epigastric distress before administration started but symptoms did not improve. Based upon examination by stomach camera, reflux esophagitis and erosive gastritis were evidenced and a causal relationship with pollen extract could not be recognized. There were no other symptoms of particular note and this supplement can be administered long term with peace of mind.

7/29/2005