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Successful Use of Oxandrolone in the Prophylaxis of Hereditary Angioedema: A Case Report

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ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant disorder typified by a deficiency or dysfunction of the C1-esterase inhibitor (C1-INH), and characterized clinically by swelling of the extremities, severe episodic abdominal pain and sometimes upper airway obstruction. This paper reports for the first time the successful use of oxandrolone in the prophylaxis of HAE in a 14-year-old girl. Oxandrolone has comparatively milder side effects and less potential for hepatotoxicity and virilization than other attenuated androgens used in the prophylaxis of this disease. We believe oxandrolone should be considered as an alternative androgen therapy for children and adults with HAE, particularly females experiencing untoward side effects from danazol or stanozolol, and patients who are not adequately controlled on maximum doses of androgens currently prescribed for HAE. (Pediatr Asthma Allergy Immunol 1999;13[4]:189–193.)

INTRODUCTION

HEREDITARY ANGIOEDEMA (HAE) is a rare autosomal dominant disorder typified by a deficiency or dysfunction of the C1-esterase inhibitor (C1-INH), an α-2-globulin synthesized in the liver. The disease is characterized by episodic swelling of the extremities, face, bowel wall, and upper airway. Long-term prophylaxis for symptoms of the disease has been successfully achieved by the use of the 17α alkylated androgens, danazol and stanozolol. There is currently no approved treatment for children with HAE. Additionally, many women experience untoward side effects from the androgens currently being used for HAE prophylaxis. The purpose of this article is to report the successful use of oxandrolone (17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one) for HAE prophylaxis in a 14-year-old girl with severe HAE symptoms, and to review treatment options for this disease.

CASE REPORT

The patient was a 14-year-old white girl who gave a history of episodic erythematous rash and mild swelling of the extremities since the age of 18 months. At age $3^1/_2$ years, she started to have attacks of episodic colicky abdominal pain associated with nausea and vomiting. The abdominal pain, which occurred every 2 weeks and lasted 24–72 h, was severe and excruciating, and it consistently followed the appear-

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ance of generalized erythema mottling by about 48 h. The pain and gastrointestinal symptoms did not respond to sedatives or antiemetics. There were no respiratory or laryngeal symptoms. Family history showed symptomatic HAE in the patient's father, paternal grandfather, a paternal uncle, and her father's paternal grandmother. Physical examination at age 14 years revealed a healthy-looking girl with a height of $66^1/_4$ in, weight 142 lb, blood pressure 120/70 mm Hg, and Tanner stage V development. Laboratory studies over the years revealed a C1-INH serum level of 4.7–5.1 mg/dl (normal 7.8–23.4 mg/dl) and a functional C1-INH of 7% to 41% (normal >67%). Complete blood count, liver and renal functions, and serum complement C3 an C4 were all normal.

At age 5 years, the patient was treated with danazol (200–400 mg) in a single dose as soon as the rash appeared. Danazol markedly reduced the frequency of abdominal pain and the occurrence of the rash. She tolerated the treatment well, and there was no evidence of virilization or adverse effects during that period.

Over the years, and in order to reduce the frequency and severity of attacks, the dose of danazol was increased gradually, and at age 9 years, it was given daily. At age 13 years, a dose of 2,000 mg/wk was associated with a weight gain of 20 lb over a period of 1 year. Her serum testosterone level went up from 21 mg/dl to 91 mg/dl, but she showed no evidence of clinical virilization. Reduction of the danazol dose resulted in the return of weekly episodes of severe abdominal pain. Treatment with epsilon aminocaproic acid (10 g/day) had no effect on the frequency and severity of symptoms. Fresh frozen plasma was administered and successfully resolved a particularly severe acute gastrointestinal attack that had lasted 5 days. At this time, the patient was given oxandrolone (0.1 mg/kg/day).

Oxandrolone had a remarkable effect on reducing the frequency and severity of the attacks, and throughout 12 months of therapy, her disease was better controlled than at any earlier time in her life. She experienced comparatively mild attacks less than once every 12–16 wk at an average dose of 8.5 mg/day. The bloated, puffy appearance and the weight gain that had accompanied danazol therapy disappeared. Her physical examination continued to be normal. Her testosterone levels dropped to a normal level of 20 mg/dl. Her adrenocorticotropic hormone, luteinizing hormone, cortisol, follicular stimulating hormone, and progesterone levels and the results of renal and hepatic function studies continued to be normal. Her C1-INH level persisted in the low range, at 3.9 mg/dl (normal 7.8–23.4 mg/dl).

DISCUSSION

Originally described by Osler in 1888, HAE is a rare autosomal dominant disorder, occurring in 1/10,000 to 1/50,000 individuals, and caused by a congenital defect of C1-INH, an α-2-globulin that is synthesized in the liver.[1,2] Our patient had low quantitative and functional C1-INH and a strong family history of HAE. Her father was shown to have a defect on his C1-INH gene, consisting of a single nucleotide insertion at 4460 (S198) leading to a stop signal 36 codons downstream, and resulting in a truncated nonfunctional C′ inhibitor protein. The normal C4 complement in this patient is not against the diagnosis of HAE.[2] Two types of the disease are known. Type I is characterized by low C1-INH levels and affects about 85% of patients, while type II affects the other 15% and is characterized by normal or elevated levels of the inhibitor that is functionally inactive. Clinically, the disease presents with episodic swelling of the extremities, face, bowel wall, and upper airways, and carries significant morbidity. The attacks may be spontaneous or may be triggered by physical trauma or emotional stress. While extremity swelling is a nuisance that most patients are able to tolerate, submucosal swelling of the gastrointestinal tract gives severe recurrent colicky abdominal pain in 75% to 90% of patients.[3] The abdominal pain is usually associated with nausea and vomiting and may mimic an acute surgical condition of the abdomen. Involvement of the upper airway results in dysphagia, hoarseness, and laryngeal obstruction, which may be life-threatening.

C1-INH is central to the regulation of the complement, coagulation, and contact (kinin-forming) systems. It is a member of the serine protease inhibitor (serpin) family and acts as a suicide protein by forming a stable bond with target proteases.[4] C1-INH inhibits C1r and C1s in the complement system, factor XII and kallikrein in the contact system, and factor XI in the coagulation system. Patients with HAE have low plasma levels of C4, which is the substrate of the C1r-C1s complex.[4] C1-INH deficiency results in an unrestricted activation of these systems and the release of vasoactive peptides that cause episodic attacks of

angioedema. The long-standing debate over which peptide is the primary mediator of HAE attacks—C2 kinin or bradykinin—may have been resolved in favor of bradykinin. Nussberger et al. reported plasma bradykinin levels up to 12 times higher than normal in patients experiencing an HAE attack.[5]

The treatment of choice for severely affected patients is prophylaxis with attenuated androgens, and danazol, a 17-α-ethinyltestosterone derivative, has been widely used since the mid-1970s.[6,7] The exact mechanism of action of danazol in this disease is not known; however, this medication produces a rise in C1-INH level in patients with hereditary HAE and usually results in the disappearance or improvement of their clinical symptoms.[8] Experience with danazol in children has been limited and was the subject of a previous article describing the same patient.[9] Danazol prophylaxis was successful and was well tolerated by our patient. However, after 8 years of treatment, severe weight gain and an elevated testosterone level occurred, necessitating discontinuation of the medicine and a search for other alternatives.

Although no longer widely used, antifibrinolytics are considered safe and in many patients resulted in a notable decrease in the frequency and severity of the angioedema, probably by inhibiting C1. This treatment may be considered in patients who are unable to take androgens.[10] Fresh frozen plasma (FFP) may serve as an alternative mode of treatment if antifibrinolytics are unsuccessful or are contraindicated. FFP has been shown to be effective for prophylaxis before surgical and dental procedures and has also been useful for the management of acute attacks.[11] Although concerns over the potential for viral transmission have limited the use of FFP, the recent availability of viral-inactivated FFP could result in more widespread use. FFP treatment of acute attacks, however, is controversial because of a theoretical risk that replenishing complement components could exacerbate an attack.[11]

C1-INH concentrate in a dose of 25 plasma units/kg intravenously has been shown to be a safe and effective therapy for acute attacks as well as for prophylaxis, and has been available in Europe for many years. C1-INH treatment resolves the angioedema in 30 min to 2 h, with complete remission in 24 h.[11,12] C1-INH has not yet been approved for use in the United States despite a double-blind randomized crossover study that concluded it was safe and effective for both prophylaxis and acute attack therapy.[13] A C1-INH concentrate phase 3 clinical trial is now under way.

Our patient responded to therapy with viral-inactivated FFP for an acute abdominal attack, but a trial with ϵ aminocaproic acid failed. At that time, we decided to try oxandrolone, which we assumed should be efficacious for HAE prophylaxis because other 17α alkylated androgens had been used successfully for almost two decades.[7] To our knowledge, the use of this medication in HAE has not been previously reported. Oxandrolone is 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one, almost identical to methyltestosterone, one of the first steroids shown to be effective in preventing HAE attacks. It has a long-standing safety record in treating Turner's syndrome in girls and constitutionally delayed growth and puberty in boys.[14] At recommended doses of <0.1 mg/kg body weight, oxandrolone has generally not been associated with inappropriate aging of bone, provided that treatment is withheld from boys and girls with a bone age of <8–9 years.[14]

Because of its weak androgenic properties, it appears that oxandrolone could be better tolerated than the other widely used prophylactic agents, particularly by women. Data compiled by the drug's US manufacturer indicate very few untoward side effects; out of >400 patients (both male and female) taking oxandrolone doses ranging from 5 to 10 mg/day, three reported acne and two showed signs of hirsutism. By contrast, long-term studies that evaluated danazol and stanozolol have reported a high incidence of side effects in women, including menstrual abnormalities, weight gain, myalgias, and transaminase elevations.

All of the 17α alkylated androgens carry warnings about hepatotoxicity, peliosis, and liver cell tumors. While the tumors are mostly benign, fatal malignant tumors have been reported. Withdrawal of the drug results in complete disappearance of the peliosis and regression or cessation of progression of benign tumors. It appears that these complications occur to a lesser extent with oxandrolone than with other drugs in the class, which are almost completely metabolized in the liver. By contrast, one third of oxandrolone is excreted unchanged in the urine, and the rest undergoes considerably less metabolic transformation in the liver.[15] Patients using long-term androgen therapy should receive the lowest dose possible and should have annual liver ultrasonography.

Androgens are contraindicated in patients with preexisting cardiac, renal, or hepatic disease. In children, careful monitoring is required because androgen therapy may accelerate bone maturation without produc-

ing a compensatory gain in linear growth. This adverse effect results in compromised adult height. Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization.

We know of another 38-year-old patient with type 2 HAE who was experiencing regular severe attacks of abdominal pain and extremity edema despite treatment with 800 mg/day of danazol. This patient was free of major attacks for 3 months while taking oxandrolone 20 mg/day, and she experienced no untoward side effects.

CONCLUSION

There is currently no approved treatment for children with severe HAE symptoms, although the literature indicates that antifibrinolytics should be the first therapy attempted. Long-term prophylaxis for patients with HAE has been successfully achieved by the use of danazol, antifibrinolytics, and FFP. In this article, we report the use of oxandrolone for the first time in the prophylaxis of HAE. In our opinion, oxandrolone could have a role in the prophylactic therapy of certain severely affected children and adults with HAE who cannot tolerate, or do not respond to, antifibrinolytics and other attenuated androgens. Oxandrolone has comparatively milder side effects and less potential for hepatotoxicity and virilization, even at doses as high as 20–40 mg/day, than other attenuated androgens.

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