EFFECTIVENESS OF NEDOCROMIL SODIUM 2% EYEDROPS ON CLINICAL SYMPTOMS AND TEAR FLUID CYTOLOGY OF PATIENTS WITH VERNAL CONJUNCTIVITIS

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SUMMARY

A double-masked, randomised, placebo-controlled study was conducted to evaluate the effectiveness of nedocromil 2% eyedrops, a mast cell stabiliser, in 20 symptomatic patients with vernal conjunctivitis. A 1-week baseline period was followed by 6 weeks of treatment. Clinical examination and cytological evaluation of tear fluid were performed weekly, and the patients recorded their subjective assessment on a daily diary card. The nedocromil group showed significantly less hyperaemia in the course of treatment than did the placebo group, and significantly less itching at all visits compared with baseline itching. In the nedocromil-treated group, but not in the placebo group, the number of neutrophils, eosinophils and lymphocytes in tears decreased significantly during some treatment weeks when compared with baseline. The overall assessment of treatment efficacy by both clinician and patient was significantly in favour of nedocromil treatment over placebo.

Vernal conjunctivitis is a recurrent inflammatory bilateral ocular disease. It occurs more frequently in children and shows clinical exacerbations every year at the beginning of spring. The disease is characterised by mild to severe ocular itching, redness and giant papillae on the upper tarsal conjunctiva. Eosinophils, basophils, neutrophils and lymphocytes infiltrate both the substantia propria and the conjunctival epithelium. The concomitant presence of itching and of eosinophils in the conjunctival epithelium is considered a pathogenetic hallmark of this disease.

Although substantial evidence suggests that a type I immediate hypersensitivity reaction plays an important role in the disease, the aetiological mechanisms are not completely understood, and other immune or non-immune mechanisms may also play a role.[1,2] The current goal of treatment is to inhibit the ocular signs and symptoms by the use of topical therapy.

Nedocromil sodium, the disodium salt of a pyranoquinoline dicarboxylic acid, was developed as an anti-allergic, anti-asthmatic agent. Although the mechanism of its action is not completely understood nedocromil seems more potent than cromolyn as a mast cell stabiliser.[3] Its clinical efficacy has been demonstrated in the treatment of allergic asthma and rhinitis by an improvement in symptoms and inhibition of inflammatory cell recruitment.[4-7] Preliminary studies reported the efficacy of nedocromil 2% eyedrops in the treatment of ocular hay fever.[8]

We report here the results of a double-masked, randomised, placebo-controlled study designed to evaluate the effectiveness of nedocromil sodium 2% ophthalmic solution in treating clinical symptoms and preventing inflammatory cell accumulation in the tear fluid of patients with vernal conjunctivitis.

PATIENTS AND METHODS

Twenty symptomatic patients with vernal conjunctivitis (15 males, 5 females) were included in the study. Their mean age was 11 years (range 7–33 years) (Table I). The diagnosis of vernal conjunctivitis was made on the basis of history, clinical examination, itching, and the presence of eosinophils in the tear fluid. Any additional eye disease, contact lens wear, pregnancy, or the requirement for systemic or topical anti-allergic agents were grounds for exclusion. After a week without treatment the patients received, in a randomised, double-masked, placebo-controlled study, either nedocromil 2% ophthalmic solution (Fisons, Loughborough, UK) or placebo in both eyes four times a day for 6 weeks. Treatment was formulated as

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Table I. Characteristics of 20 vernal conjunctivitis patients

Patient no., age (yr), sex	Duration (yr)	Family history of atopic disease	Patient history of atopic disease	Skin test of RAST sensitisation	Nedocromil (N) or placebo (P)
1, 11, M	4	–	+	–	N
2, 10, M	2	–	+	–	P
3, 13, M	2	+	+	–	N
4, 11, M	2	+	–	+	P
5, 11, M	4	+	+	+	P
6, 11, F	1	+	+	+	N
7, 15, M	8	–	+	–	P
8, 15, F	1	+	+	+	N
9, 10, F	3	–	–	+	P
10, 10, F	2	+	+	+	P
11, 9, F	2	+	–	+	N
12, 12, M	2	–	–	–	N
13, 33, F	20	–	+	+	N
14, 9, M	4	+	–	–	P
15, 10, M	1	+	–	–	P
16, 9, M	4	–	+	+	N
17, 7, M	1	–	–	–	P
18, 11, M	3	+	+	+	P
19, 11, M	1	+	+	–	P
20, 15, M	3	–	+	+	N

+, positive; –, negative; RAST, radio-allergosorbent test.
Patient no. 11 withdrew from the study; her data were excluded from the statistical analysis.

follows: 2% nedocromil sodium aqueous isotonic eyedrops containing 0.01% benzalkonium chloride and EDTA, and placebo eyedrops with the same concentration of preservative and EDTA in aqueous solution plus 0.005% riboflavine as the colorant. Signed informed consent was obtained from all patients or their parents. In two patients with severe symptoms of vernal conjunctivitis at the time of entering the study, treatment was started without the baseline week. Nevertheless, all patients were without treatment for at least 1 week before the study began. One non-compliant patient withdrew from the study because she moved outside the trial area; these data were excluded from the statistical analysis. Visit 1 occurred on admission to the study, visit 2 at the end of the baseline period, and visits 3 to 8 weekly during the treatment period. At all visits the physician's clinical assessment, the patients' diary cards, and the tear fluid cytology were evaluated. At the end of the study, patients' and clinicians' opinions of the efficacy of treatment were also evaluated.

Clinical Assessment

The following ocular signs were evaluated by the clinician: hyperaemia and chemosis of the conjunctiva, tearing, episcleral injection, and ciliary flush. The following ocular symptoms were evaluated by the patient in response to questioning by the clinician: itching, photophobia, burning, grittiness, sticky and watery discharge, and nasal congestion.

Each sign and symptom was scored on a scale of 0 (none) to 4 (very severe) for each eye separately. The mean score for the two eyes was calculated for each sign and symptom for each patient. An average severity score of 2 or more for the duration of the baseline period was required for a patient to be included in the study.

Diary Card Data

Diary cards were completed daily by the patient throughout the study. Itching, mucus, redness and tearing were scored on a scale of 0 (none) to 4 (very severe). For each symptom the weekly mean score was calculated for each patient for the baseline period and for each week during the 6-week treatment period.

Tear Fluid Cytology

Two microlitres of tears were collected with disposable micro-pipettes (Fisher Scientific, Pittsburgh, PA) from the inferior conjunctival fornix of each eye. Tears were spread from the capillary tubes onto a glass slide, which was allowed to dry at room temperature for 3–5 minutes. A modification of the Wright stain technique was performed to obtain an acid-fast Giemsa stain of all slides. All the cells observed on each slide (epithelial cells, neutrophils, eosinophils, lymphocytes, monocytes and basophils) were counted by light microscopy at ×100 magnification.

Since the amount of tears collected varied from 0.5 to 4 µl, all cell counts were adjusted to the corresponding value for 2 µl. The total count over both eyes was calculated for each cell type for each patient visit.

Opinions of Efficacy

At the end of the study the patients and the clinicians gave their opinions of the test treatment. The opinions were scored on a scale of 0 (no control) to 3 (full control) depending on how well the treatment or the placebo controlled the eye symptoms.

Statistical Analysis

A two-tailed non-parametric test (Mann–Whitney *U*-test) was used to analyse clinical sign and symptom scores, diary symptom scores, and cytology of the tear film. Two

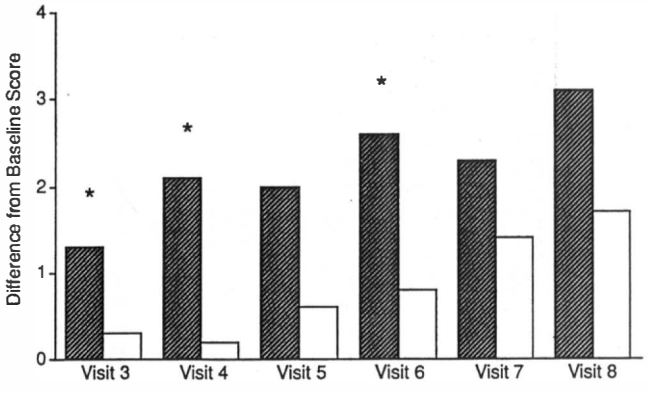

Fig. 1. *Difference from the baseline hyperaemia score at each treatment visit. Hatched bars, nedocromil group; open bars, placebo group. Note that the higher the bars, the greater was the reduction of hyperaemia during treatment. Significant differences (asterisks) in favour of nedocromil over placebo were observed at visits 3 and 4 ($p<0.02$) and visit 6 ($p<0.05$).*

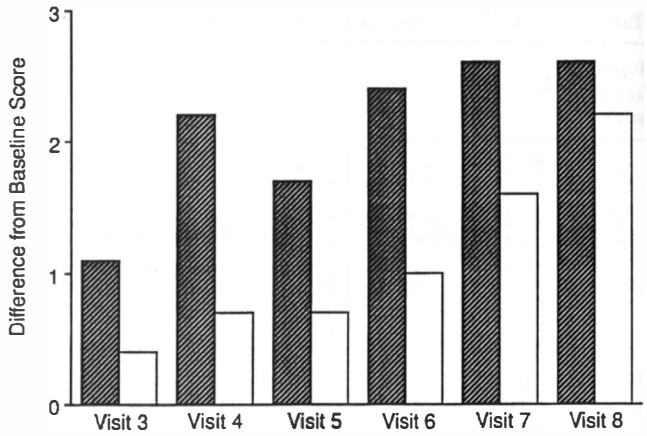

Fig. 2. *Difference from the baseline itching score at each treatment visit. Hatched bars, nedocromil group; open bars, placebo group. Itching was reduced after 1 week of treatment (visit 3) and continued to improve during treatment. Similar but smaller improvements were observed in the placebo-treated eyes.*

different statistical analyses were performed. First, the mean scores at baseline (visit 2) and the mean changes from baseline for the nedocromil and placebo groups were compared. Second, the mean clinical scores and the number of cells in the tear fluid (visits 3 to 8) for each group were compared with their respective baseline values.

The chi-squared test with Yates' correction was used to analyse patients' and clinicians' opinions of clinical control.

RESULTS

Data from 19 patients were included in the statistical analysis. There were 8 patients (5 males, 3 females) in the nedocromil group and 11 (10 males, 1 female) in the placebo group (Table I).

The signs and symptoms of the patients in the nedocromil group improved during the six treatment visits. There was a significant reduction of hyperaemia in the nedocromil group at visits 3 and 4 ($p<0.02$) and at visit 6 ($p<0.05$) when compared with the placebo group (Fig. 1). Itching was the clinical symptom most reduced in the nedocromil group; it decreased throughout the study. In three of the six treatment weeks the difference between the two groups was just short of statistical significance (Fig. 2). Moreover, itching in nedocromil-treated patients improved significantly at all visits compared with the baseline. In contrast, itching was reduced significantly at only two visits (7 and 8) in the placebo-treated group when compared with the baseline.

No significant differences between the two treatment groups were observed for the other signs and symptoms evaluated (Table II).

Although the mean number of cells in the tear fluid of the nedocromil-treated group decreased during treatment and was lower than in the placebo group, no significant differences between the two groups were observed for any type of cell counted. However, patients in the nedocromil group showed a significant reduction from baseline in the number of neutrophils at visits 6 ($p<0.05$) and 8 ($p<0.05$), of eosinophils at visit 8 ($p<0.05$), and of lymphocytes at visits 6 and 8 (both $p<0.05$) (Table III). No significant differences from baseline values were observed in the number of any cell type at any visit in the placebo-treated eyes. Statistical analysis was not per-

Table II. Mean scores of clinical symptoms of patients with vernal conjunctivitis at baseline (visit 2) and during treatment with nedocromil sodium 2% or placebo

Ocular symptom	Visit 2 (baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Nedocromil sodium 2% treatment group							
Itching	3.0	1.4	0.6	1.1	0.6	0.4	0.4
Hyperaemia	2.3	2.3	1.7	1.4	1.2	1.2	0.8
Burning	1.2	0.8	0.2	0.4	0.2	0.5	0.2
Photophobia	2.4	1.2	0.8	0.8	0.5	0.7	0.2
Grittiness	1.7	0.6	0.2	0.5	0.2	0.2	0.1
Tearing	2.3	2.1	1.4	1.8	1.1	1.2	0.6
Placebo treatment group							
Itching	2.5	2.1	1.9	1.8	1.5	0.8	0.4
Hyperaemia	2.0	2.3	2.0	1.6	1.7	1.4	1.2
Burning	1.0	1.2	1.0	0.6	1.0	0.2	0.4
Photophobia	1.9	1.2	0.6	0.2	0.4	0.2	0.2
Grittiness	1.5	1.5	0.6	0.8	0.8	0.2	0.1
Tearing	2.3	2.0	1.9	1.7	1.8	1.4	1.0

Table III. Mean (and range) of number of inflammatory cells in tear fluid of patients with vernal conjunctivitis during treatment with nedocromil and placebo

Inflammatory cells	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Nedocromil							
Eosinophils	33.7 (1–125.5)	15.5 (0–74)	37.7 (0–247.5)	18.1 (0–79)	9.7 (0–39)	18.3 (0–45)	9.6* (0–57.5)
Neutrophils	111 (19–282.5)	52.2 (2–213)	241.1 (0–1614)	45.3 (0–179.5)	19.6* (0–64)	87 (0–374)	13.6* (0–42)
Lymphocytes	23.5 (1.5–49.5)	4.7 (0–20)	10 (0–58.5)	8.8 (0–49.5)	8.5* (0–62.5)	11.8 (0–59.5)	2.8* (0–8.5)
Placebo							
Eosinophils	71 (0–650)	26.3 (0–154)	13.5 (0–57)	61.1 (0–401)	93.8 (0–800)	49.2 (0–415)	11.3 (0–46.5)
Neutrophils	89.5 (1.5–650)	39.3 (3.5–166)	27.4 (1–97)	69.6 (3–402)	223.9 (2–1138.5)	64.9 (0–428.5)	28.6 (0–115.5)
Lymphocytes	6.1 (0–37.5)	7.4 (0–44)	2.6 (0–10.5)	6.2 (0–48.5)	7.9 (0–50)	4.1 (0–28.5)	3.6 (0–27)

*Significant difference from baseline.

formed on the counts of basophils and monocytes because of their low numbers.

The diary cards showed that the patients in the nedocromil group had lower symptom scores throughout the study than those in the placebo group. The mean itching score for the first week of treatment calculated from the patient diary cards brought in at visit 3 was significantly reduced ($p<0.01$) in the nedocromil group compared with the placebo group. Tearing was diminished during the fourth ($p<0.05$) and sixth ($p<0.02$) treatment weeks (visits 6 and 8, respectively), and itching was reduced ($p<0.05$) at the fifth and sixth treatment weeks (visits 7 and 8, respectively) in the nedocromil-treated patients when compared with their baseline values. No significant difference was observed for either tearing or itching in the placebo-treated group compared with their baseline values. No significant differences were observed for mucus and redness between the two treatment groups. Redness improved at the sixth treatment week (visit 8) in both the nedocromil- and the placebo-treated groups compared with their respective baseline values.

The opinions of both the clinicians and the patients regarding control of symptoms were significantly in favour of nedocromil treatment ($p<0.05$).

No ocular side effects were observed by the clinicians or noted by any of the patients.

DISCUSSION

In our study nedocromil sodium 2% ophthalmic solution reduced both symptoms and signs of patients with vernal conjunctivitis. This agent significantly decreased hyperaemia and itching over the course of treatment. Nedocromil sodium is an anti-inflammatory, anti-allergic agent proven to be effective for the maintenance treatment of reversible obstructive airway disease. It reduces the bronchial constriction induced by a variety of allergic and non-allergic stimuli including allergen provocation, and it improves the clinical symptoms of patients with asthma.[9–12] Satisfactory results with the use of nedocromil sodium 2% in the treatment of seasonal ocular allergic diseases have been reported.[13–16]

Several clinical symptoms are commonly evaluated in clinical trials of patients with vernal conjunctivitis, but itching is the cardinal feature of this condition. It has been said that if there is no itch, there is no vernal.[17] In fact, the severe itching these patients suffer results in rubbing their eyes very often during the day. In the rat, eye rubbing causes degranulation of almost 50% of the mast cells and recruitment of neutrophils in the conjunctival epithelium.[18] The increased number of degranulated mast cells in the conjunctiva of patients with vernal conjunctivitis may perpetuate the ocular inflammation.

We found that nedocromil-treated eyes had significantly fewer inflammatory cells in the tear fluid than placebo-treated eyes compared with their respective baseline values. Nedocromil sodium has been shown to be more effective than cromolyn in reducing the quantity of inflammatory mediator release from mast cells and cell activation in bronchial disease.[7] Inflammatory cells, namely eosinophils, play an important role in the pathogenesis of vernal conjunctivitis. The presence of a high number of these cells in the conjunctival epithelium is pathognomonic of this disease.[17] Moreover, eosinophils and eosinophil-derived products contribute to conjunctival tissue damage.[19]

We observed a mild decrease of symptoms in the placebo-treated patients. Strictly controlled research in ocular allergies is difficult for several reasons. In fact, in many studies the application of a placebo serves also as a treatment in that irrigation is the first approach to the management of allergic eye conditions. Moreover, although vernal conjunctivitis is, by definition, a seasonal disease, symptoms are extremely variable the year round, and day-to-day variations frequently occur even without treatment. There are many possible reasons for this clinical feature: the presence of sensitising allergens, an individual conjunctival hyperresponsiveness, the influence of hormonal or climatic factors, or even minor modifications in the patient's environment. Ideally, to reduce bias, double-masked controlled clinical trials should begin at the same time of year with patients living in the same environment. Since this is not practicable, we evaluated

the individual responses by comparing the results after active treatment or placebo with their respective baseline values.

We found that patients' and clinicians' opinions significantly favoured active nedocromil treatment over placebo. In fact, active treatment improved clinical signs and symptoms after 1 week of treatment and continued to keep them lowered throughout the study.

Nedocromil 2% eyedrops administered twice a day was well tolerated by all patients. No ocular side effects occurred, and there was no need for additional therapy. Therefore, nedocromil 2% eyedrops can be used in the treatment of vernal conjunctivitis, possibly reducing the amount of corticosteroids needed by patients with severe symptoms.

Key words: Allergic conjunctivitis, Nedocromil sodium eye drops, Tear fluid cytology, Vernal conjunctivitis.

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