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A double-blind group comparative study of nedocromil sodium in the treatment of seasonal allergic rhinitis

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SUMMARY

Thirty-eight patients with seasonal rhinitis due to grass pollen allergy took part in this double-blind study comparing 1% nedocromil sodium and placebo. Treatment was allocated by randomised coding sheet and consisted of 1% nedocromil sodium nasal spray or placebo given four times daily for four weeks during the peak pollen season.

Highly significant ($p < 0.001$) differences in favour of nedocromil sodium were seen for all signs and symptoms recorded at clinical assessments, and for diary card assessments of symptoms.

In addition, time to effect and patient and clinician opinions of treatment significantly ($p < 0.001$) favoured nedocromil sodium. Laboratory data on blood and urine samples taken before and after treatment showed no significant effects, and both treatments were well tolerated.

Nedocromil sodium 1% nasal spray taken four times daily was shown to be an effective treatment for grass pollen rhinitis.

INTRODUCTION

Allergic rhinitis is characterised by an increase in the numbers of nasal mast cells and basophils (Hastie et al., 1979). Many pharmacological agents have been evaluated for their ability to prevent the release from cells of vasoactive, inflammatory mediators such as histamine and leukotrienes, which give rise to the symptoms of hayfever.

The first agent showing the potential to reduce allergen-induced nasal obstruction in allergic subjects was sodium cromoglycate (Taylor and Shivalkar, 1971), and this drug has subsequently been used with success against both seasonal and perennial rhinitis (Frostad, 1977; Chandra et al., 1982; Girard and Bertrand, 1975; Bellioni et al., 1984). However, some patients with nasal allergy are not completely protected by sodium

cromoglycate. This may be explained by the relatively poor activity of sodium cromoglycate on mast cells of the mucosal type (Eady et al., 1985), which have been shown to predominate in the nasal epithelium (Otsuka et al., 1985). Preclinical experiments have shown a new drug, nedocromil sodium to have a wider range of activity than sodium cromoglycate, protecting mucosal mast cells as well as connective tissue mast cells. Nedocromil sodium also appears to inhibit the activation of various cell types involved in secondary inflammatory responses, and its therapeutic efficacy has been demonstrated in clinical trials in asthmatic patients (Chu, 1987; Gonzales and Brogden, 1987; Carrasco and Sepulveda, 1986) and in rhinitic patients (Ruhno et al., 1988).

The present study was carried out to evaluate the effectiveness of nedocromil sodium 1% nasal spray (Tilarin®*) in the treatment of seasonal allergic rhinitis.

METHODS

Thirty-eight patients, 30 male and 8 female, aged between 5 and 58 years, were included in the study, which was carried out in accordance with the Helsinki Declaration of 1975. All subjects showed a positive skin test or RAST to grass pollen and had a history of rhinitis during the grass pollen seasons of at least the two previous years.

Patients were excluded from entry to the trial if they were pregnant or lactating, or if they had diseases of the nose not associated with grass pollen rhinitis. Also excluded were those currently receiving corticosteroids, nasal sodium cromoglycate or any drugs affecting the nasal mucosa, and patients who had received hyposensitisation therapy within the previous twelve months.

Test treatment was allocated using a randomised coding sheet, with 19 patients assigned to each group. The test medication was a metered-dose nasal spray containing a 1% aqueous solution of nedocromil sodium made isotonic with sodium chloride. The placebo spray contained physiological saline coloured yellow with riboflavin. Dosage was one spray per nostril four times daily for four weeks, and concomitant therapy during the study was restricted to antihistamines.

At the first clinic visit, the following subjective and objective parameters were recorded by the clinician, using a 0–4 scale running from "none" to "very severe": oedema of turbinates, mucosal hyperaemia, nasal obstruction, rhinorrhoea, sneezing and itching. There was then a flexible run-in period of about two weeks, during which each patient completed a daily diary card, recording nasal symptoms (itching, running, blocking, sneezing and general severity of condition) on a similar 0–4 scale. Once symptomatic, the patient was instructed to begin using the test medication for the next 28 days.

Throughout the four-week study period, diary cards were completed daily by the

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patients, recording severity of nasal symptoms and the use of antihistamines or any other medication in addition to the test medication.
At the second clinic visit, carried out after the first week of test treatment, the patient was asked to assess the speed at which the medication became effective. At the third (final) visit, both patient and clinician gave their assessment of its overall efficacy.
Blood and urine samples for laboratory analysis were collected at admission and at the final visit.
Local grass pollen counts were provided to cover the whole period of the trial and were high enough to cause significant symptoms in sensitive patients throughout the test treatment period (Figure 1).
Statistical analysis was carried out using the Mann Whitney U-test, and a probability level of 5% was taken to indicate significance.

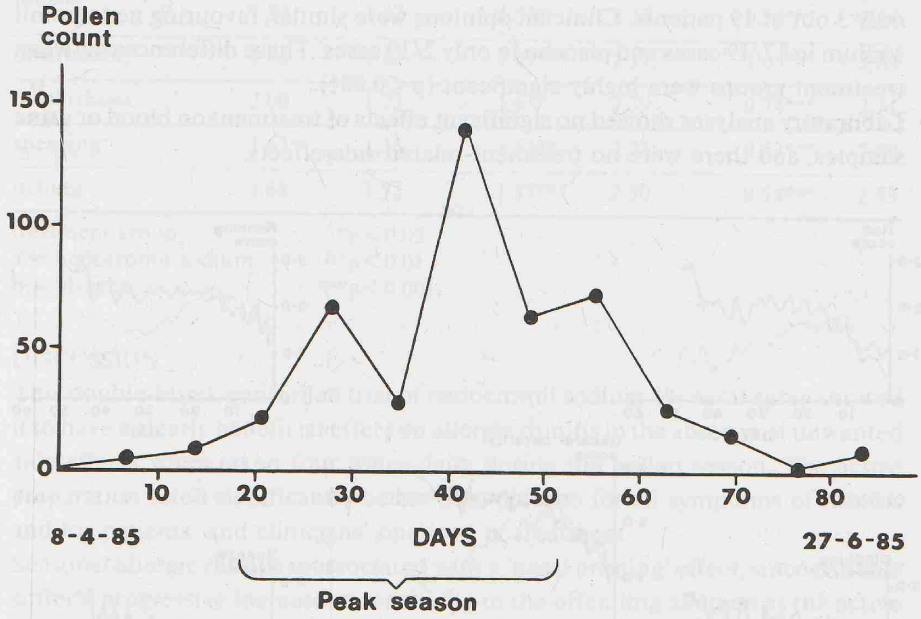

Figure 1. Grass Pollen Counts for Rome over the Period April-June 1985 (Weekly Average Pollen Grains per m^3), kindly provided by prof. G. Bruno, I[a] Clinica Medica, University "La Sapienza", Rome (Italy).

RESULTS

The mean daily symptom scores as recorded on patients' diary cards are shown in Figure 2. Patients began test treatments in two roughly equal blocks, on either 22nd or 29th April, coinciding with the onset of the pollen season. The peak pollen season was taken as running from 29th April to 26th May, when statistically significant differences ($p<0.001$) favouring nedocromil sodium were obtained for all diary card symptoms.

Clinical assessments found patients treated with placebo to show a deterioration of symptoms from baseline scores, while nedocromil sodium treated patients showed improvement from their previous condition at the second and third clinic visits. This difference between the two treatment groups was significantly in favour of nedocromil sodium ($p < 0.001$ throughout by visit 3) for oedema of turbinates, injection of mucosa, mucus, congestion and blockage, rhinorrhoea, sneezing and itching, whether taken as absolute values (Table 1) or as changes from baseline.

At the second visit, a significantly ($p < 0.001$) higher proportion of patients in the nedocromil sodium group (16/19) felt treatment was effective within seven days, compared to the placebo group where most patients (16/19) felt the treatment was ineffective after seven days.

At the end of the four-week treatment period, nedocromil sodium was considered effective by 17 out of 19 patients and placebo was considered effective by only 3 out of 19 patients. Clinician opinions were similar, favouring nedocromil sodium in 17/19 cases and placebo in only 2/19 cases. These differences between treatment groups were highly significant ($p < 0.001$).

Laboratory analyses showed no significant effects of treatment on blood or urine samples, and there were no treatment-related side-effects.

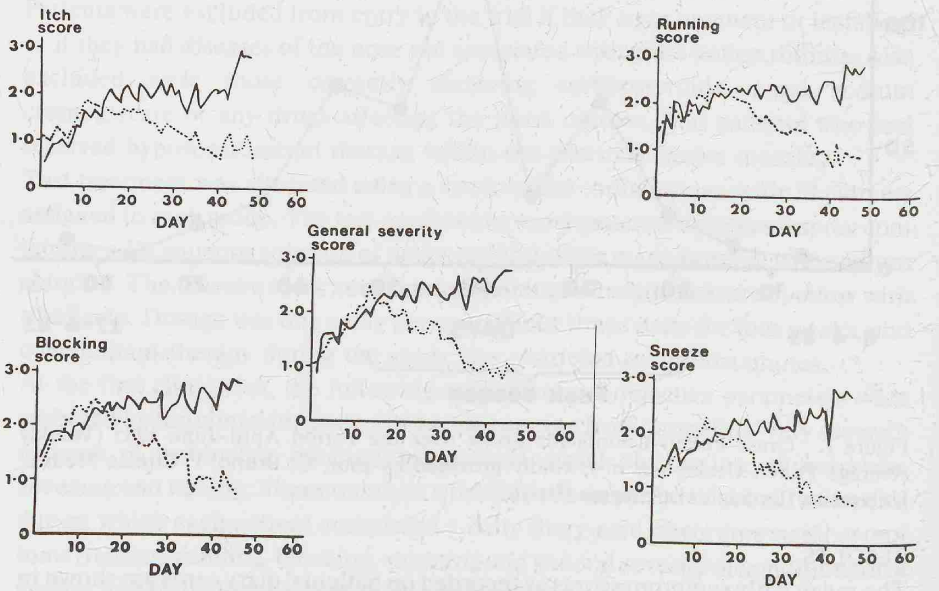

Figure 2. Daily Mean Diary Cards Symptom Scores (0 none, 1 mild, 2 moderate, 3 severe, 4 very severe) for Patients Treated with Nedocromil Sodium (.....) or Placebo (_____) from Day 14–21 onwards.

During the peak pollen season (days 20–50) the beneficial effect of nedocromil sodium was highly significant ($p < 0.001$) for all parameters.

Table 1. Clinician's Assessment of Nasal Symptoms: Mean Severity Scores at Clinic Visits
(0 none, 1 mild, 2 moderate, 3 severe, 4 very severe)

		visit					
		1 (8/15 Apr)		2 (29 Apr/6 May)		3 (20/27 May)	
		treatment group					
symptom	nostril	a	b	a	b	a	b
oedema of turbinates	L	1.57	1.42	1.42*	2.00	1.11***	2.47
	R	1.57	1.36	1.42**	2.06	0.95***	2.71
mucosal hyperaemia	L	2.00	1.36	1.42**	2.17	0.53***	2.59
	R	2.00	1.47	1.47*	2.06	0.68***	2.58
mucus	L	1.52	1.47	1.47**	2.17	0.58***	2.65
	R	1.84	1.47	1.53*	2.17	0.74***	2.64
obstruction		1.63	1.42	1.47***	2.17	1.05***	2.65
rhinorrhoea		2.00	1.73	1.63*	2.39	0.74***	2.71
sneezing		1.63	1.36	1.53**	2.22	0.53***	2.59
itching		1.68	1.52	1.37***	2.50	0.53***	2.53

treatment group
a = nedocromil sodium
b = placebo

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

DISCUSSION

This double-blind, controlled trial of nedocromil sodium 1% nasal spray showed it to have a clearly beneficial effect on allergic rhinitis in the absence of unwanted side-effects when taken four times daily during the pollen season. The active preparation rated significantly better than placebo for all symptoms of rhinitis and for patients' and clinicians' opinions of treatment.

Seasonal allergic rhinitis is associated with a 'nasal priming' effect, since patients suffer a progressive increase in sensitivity to the offending allergen as the active season progresses (Connell, 1969). A tendency toward worsening symptomatology can be seen in the results of the present study (Table 1, Figure 2), where the mean symptom scores of the placebo-treated patients continued to increase as the pollen season progressed. Nedocromil sodium not only prevented the occurrence of nasal priming, but all symptoms showed a decrease in severity to below the pre-season baseline levels after four weeks of treatment (Table 1).

The mode of action of nedocromil sodium has not yet been fully identified, but the compound appears to exert protective activity on a variety of cells involved in inflammatory reactions at the mucosal surface, as well as reducing responsiveness to both antigenic and irritant stimuli in the allergic lung (Chu, 1987). All

these factors could be involved in the activity of this new drug in seasonal allergic rhinitis.

It is interesting that nedocromil sodium, unlike sodium cromoglycate, has the ability to stabilise mucosal mast cells (Eady et al., 1985) since this cell type is the predominant metachromatic cell of the nasal mucosa. The number of mucosal mast cells in the nose has been found to show a significant correlation with the severity of rhinitis symptoms (Otsuka et al., 1985) and is also known to increase during the pollen season (Viegas et al., 1987), linking these cells with the development of nasal priming and suggesting one mechanism by which nedocromil sodium might show protective activity in the nose. This localised protective effect may well extend to other inflammatory cells. Nasal secretion eosinophilia is a characteristic feature of allergic rhinitis (Malmberg, 1979), and nedocromil sodium has been shown to inhibit secretion of granule proteins from human eosinophils in vitro (Spry et al., 1986).

This preventive type of action could be enhanced by other activities of the compound such as reduction of responsiveness to non-specific stimuli. Nasal priming has been shown to result in hyperreactivity of the nasal mucosa to agents such as histamine and acetylcholine (Konno et al., 1987) as well as specific allergen.

Nedocromil sodium appears to present a valid alternative treatment for seasonal allergic rhinitis in comparison to antihistamines, which have little influence on nasal obstruction (Munch et al., 1983), and topical corticosteroids which may lead to side-effects in the long-term. Further investigations will be necessary to evaluate fully the place of nedocromil sodium in nasal therapy.

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