

Comparative Therapeutic Studies with Tilavist

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Summary

Comparative clinical trials which include known therapies as well as placebos are essential in constructing a solid basis from which to 'launch' any new drug. This applies especially to eye drops for treatment of seasonal allergic conjunctivitis, where the symptomatology, already dependent on the vagaries of the natural pollen challenge season, is further influenced by a positive washing action of the placebo eye drops. Tilavist (2% nedocromil sodium ophthalmic solution) has therefore been compared with sodium cromoglycate eye drops and non-sedating antihistamine tablets, both mainstays in the treatment of seasonal allergy, in a series of double-masked, placebo-controlled, mainly multicentre studies. Nedocromil sodium, twice or four times daily, proved as effective overall as sodium cromoglycate (2% or 4% four times daily) in three seasonal trials, and was the more effective treatment in a study of patients with vernal keratoconjunctivitis. Its efficacy was most evident during peak periods of pollen challenge, when neither placebo nor sodium cromoglycate eye drops controlled breakthrough symptoms. Three further seasonal studies showed nedocromil sodium eye drops to be as effective as standard oral doses of astemizole and terfenadine, whilst a faster onset of action than terfenadine was reported in one multicentre study.

Introduction

New products in any area must be compared with existing 'bench mark' standards for a full assessment of their usefulness, and this certainly applies in the case of topical ocular therapies, where certain problems are inherent to the basic placebo-comparative clinical trials. In seasonal allergic conjunctivitis (SAC) studies, the difficulties are compounded by the reliance on natural forces, especially the pollen season. This may be early or late, it could be short-lasting, and the level of pollen allergen challenge can

vary from year to year and from place to place, adding to the problems of large multicentre trials. This is as true for the smaller countries in Europe¹ as it is for North America². If the pollen count is very high, it may be too much for the pre-selected trial dosage of the drug, whilst if too low, the symptoms can be so mild as to leave little room to demonstrate a clear therapeutic effect. A further problem, particularly in studies of ocular allergy, is the so-called 'placebo effect' of the negative (vehicle) control. In the eye, especially, the placebo solution is more likely to have a perceptible soothing effect by lubricating the surface and helping to wash away pollen grains and dilute the inflammatory mediators present in the tears.

It is therefore important to compare any new drug with established therapies which have a proven track record, by including a positive as well as a negative control group in some of the clinical trials. Nedocromil sodium 2% eye drops has been compared with two of the staple treatments for allergic conjunctivitis, namely topical sodium cromoglycate and oral antihistamines, in a total of 7 clinical trials – 6 in hayfever conjunctivitis and one in patients with vernal keratoconjunctivitis.

Discussion of methodology and results

Study details are summarised in Table 1: all were double-masked, placebo controlled group compara-

Table 1a. Summary of double-masked, placebo-controlled comparative therapeutic studies: sodium cromoglycate eye drops.

Trial design	Nedocromil sodium	Sodium cromoglycate
SAC ragweed 6 weeks Canada ²	2% one drop per eye 4X daily	2% one drop per eye 4X daily
SAC birch 4 weeks Finland ³	2% one drop per eye 2X daily single-dummy placebo	2% one drop per eye 4X daily
SAC ragweed 6 weeks USA ⁴	2% one drop per eye 2X daily single-dummy placebo	4% one drop per eye 4X daily
VKC 4 weeks Egypt ⁵	2% one drop per eye 4X daily	2% one drop per eye 4X daily

Table 1b. Summary of double-masked, placebo-controlled comparative therapeutic studies: antihistamine tablets.

Trial design	Nedocromil sodium	Oral H ₁ antihistamine
SAC ragweed 4 weeks Canada (page 27)	2% one drop per eye 2x daily double-dummy placebo	terfenadine 60 mg 2x daily
SAC grass 4 weeks UK (Fisons data on file)	2% one drop per eye 4x daily double-dummy placebo	terfenadine 60 mg 2x daily
SAC grass/weeds 4 weeks Italy ⁶	2% one drop per eye 4x daily double-dummy placebo	astemizole 10 mg 1x daily

tive trials. Data collection and treatment are described in the literature ²⁻⁶ and have been summarised by Kjellman and Stevens ⁷. In general, 2-tailed non-parametric statistical methods were used at the 5% level of significance, and data for the three treatment groups in multicentre studies were analysed for each centre separately and for all centres combined. Variables were compared using the Kruskal-Wallis test, with adjustments for centre (Mack-Skillings). If an overall significant difference occurred among the three treatment groups, pairwise comparisons were made using the Mann-Whitney U-test. Where pooled analyses were completed (for the antihistamine comparator studies) Mantel-Haenszel tests were carried out on patient and clinician opinions, comparing treatments in a pairwise fashion. Study centres having at least ten patients per treatment group were taken as the unit for analysis of eye itching and total symptoms during peak pollen, which was carried out using an analysis of variance with centre and treatment group as factors.

Sodium cromoglycate comparisons

Three SAC studies comparing nedocromil sodium with sodium cromoglycate ²⁻⁴ showed very little difference between the active treatments and no formal pooled analysis was carried out. Global opinions of treatment and the peak pollen mean severity scores for itching and total symptoms are shown in Table 2.

Table 2. Comparator studies with sodium cromoglycate in SAC: overall mean symptom scores during peak pollen and global opinions of treatment (% full/moderate control). (n=total patients).

	Nedocromil sodium (229)	Sodium cromoglycate (233)	Placebo (174)
Eye itching	1.12	1.18	1.30
Total symptoms	3.10	3.22	3.84
Patient opinion	79	75	70
Clinician opinion	76	76	67

Both the active treatments were consistently better than placebo, although the placebo effect itself was very marked in these studies, emphasising the importance of the positive comparator. Topical sodium cromoglycate is a well-established therapy for allergic conjunctivitis ^{8,9} and nedocromil sodium matched its performance both at the same four times daily (qd) dosage ² and when comparing twice-daily (bd) nedocromil sodium with qd 2% ³ or 4% ⁴ sodium cromoglycate. It should not be forgotten that the bd nedocromil sodium was accompanied by bd placebo eye drops, direct bd/qd comparison being impossible under double-masked conditions. However, in a similar single-dummy study, bd 4% sodium cromoglycate was found equivalent to qd 2% sodium cromoglycate ¹⁰, whilst the effect of qd cromoglycate was clearly related to drug concentration ⁸. This suggests only a minor influence of the bd single-dummy placebo in this design of study, adding to the impact of the bd 2% nedocromil sodium vs qd 4% sodium cromoglycate comparison ⁴.

When interpreting the results of seasonal studies, it is important to be realistic and to relate treatment effects to the prevailing pollen challenge conditions. The use of any 'rescue' therapy such as permitted antihistamines and artificial tears should also be taken into account as this can add to the apparent placebo effect ⁴. Because of the greatly varying conditions which can be found in multicentre trials, the picture may become clearer when looking at individual centres. As noted at Möller's centre in Sweden ^{1,7}, when symptoms increase in the placebo treated patients due to the relatively high pollen count, the therapeutic effect of the active treatment becomes more pronounced. This was also the case during the birch pollen season in Finland ³, where the 48 patients at Leino's Kuopio centre (representing 25% of the 7-centre total entry) demonstrated a lower than average placebo response. Fig. 1 shows these patients' opinions of their test treatment, which were recorded after week 1 as well as at the end of the 4-week study, and relates them to the progression of the local birch season. The advantage of nedocromil sodium over placebo ($p < 0.001$ throughout) appears most striking during peak pollen chal-

Table 3. Comparator studies with oral antihistamines in SAC: overall mean symptom scores during peak pollen and global opinions of treatment (% full/moderate control). (n=total patients).

	Nedocromil sodium (153)	Antihistamine (151)	Placebo (157)
Eye itching	0.98	1.10	1.09
Total symptoms	3.84	4.04	4.39
Patient opinion	66	68	58
Clinician opinion	66	64	56

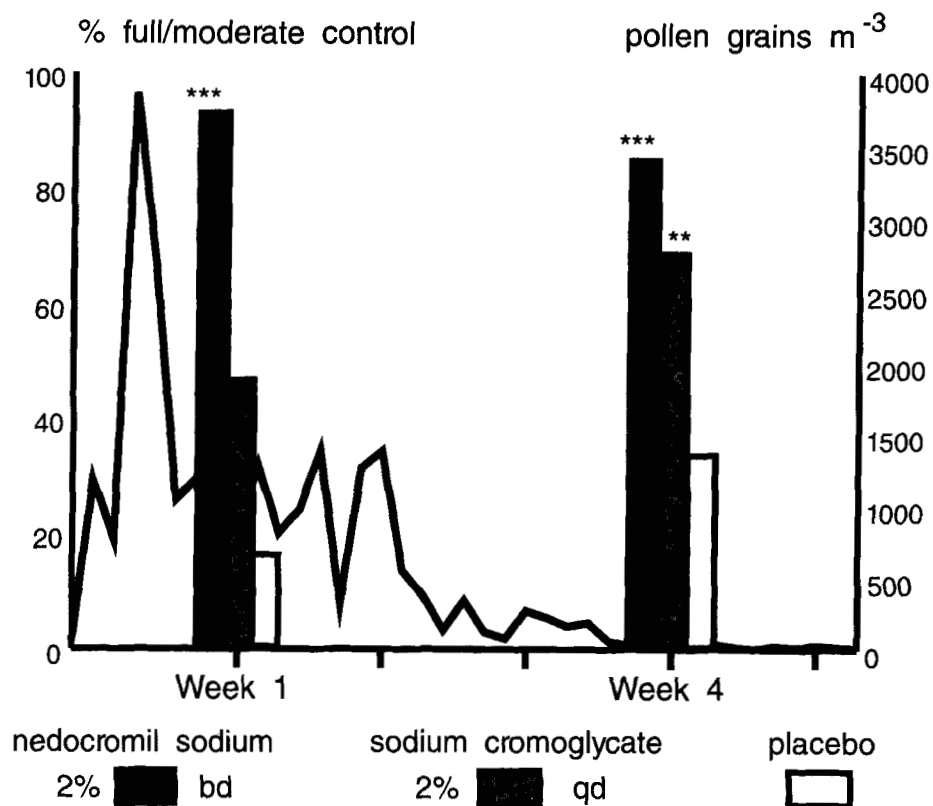


Fig. 1. Effect of the severity of pollen challenge on patients' opinions of topical treatment efficacy at one centre (Kuopio) during a multicentre, single-dummy placebo-controlled, double-masked comparison of bd 2% nedocromil sodium and qd 2% sodium cromoglycate, carried out during the birch pollen season in Finland³. ** $p < 0.01$ *** $p < 0.001$ vs placebo.

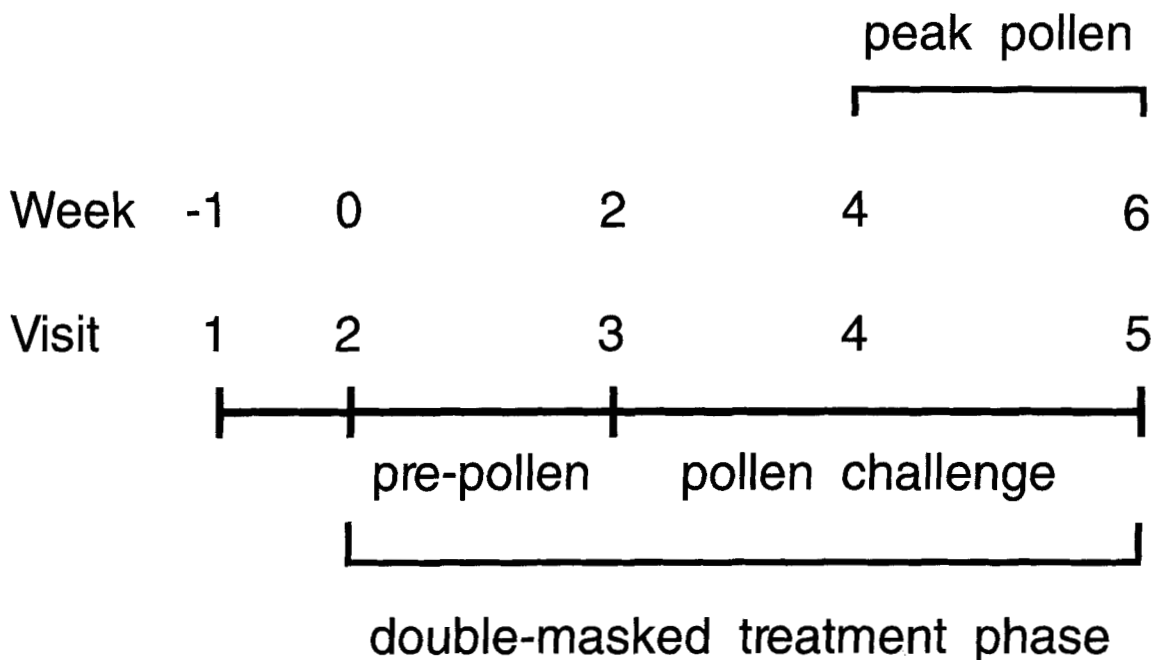


Fig. 2. Trial design for the Canadian multicentre study comparing qd 2% nedocromil sodium eye drops with qd 2% sodium cromoglycate eye drops and placebo in patients with SAC to ragweed pollen².

lenge, when sodium cromoglycate activity was mediocre and the patients on this treatment developed breakthrough symptoms. Taking the peak season activity into account may thus provide a more accurate impression than the 'global' opinions – often limited to the all-centres, end-of-treatment, result – and giving, in this case, 80%, 75% and 73% effective control for patient opinions of nedocromil sodium, sodium cromoglycate and placebo, respectively ³.

In North America, we have the advantage (from the trialist's point of view!) of the more prolonged but consistent ragweed pollen season. Ragweed is a small plant that has a foul odour. It exists both in the city and rural areas, and it generates millions of pollen grains during the late summer. Since the ragweed pollen season behaves quite predictably, it is possible to design clinical trials in a more structured way. The following is a brief summary of the Canadian trial in which I participated ². By including a 2-week pre-pollen treatment phase (Fig. 2) we made quite sure that for once the patients were not symptomatic at the start of test treatment, and also that the final opinions of treatment related to the period of peak pollen challenge, which occurred during the last two weeks of the study. This trial was actually

carried out at three centres (Alexander, Marshall, Greenbaum) and the full study will be reported elsewhere, but we also encountered some regional variations between rural and industrialised areas, and in order to avoid this complication I shall present my own results from Niagara Falls.

Patients were recruited who had a minimum 2-year history of ragweed SAC requiring topical and/or systemic medication; any concurrent immunotherapy was to remain unchanged. All subjects had a positive ragweed skin test at trial entry, but were asymptomatic to other allergens likely to affect the eyes during August/September. After the baseline week, the patients, who were aged from 7-54 with a mean of 27.6 years, were randomised to test treatment: one drop per eye qd, with 2% nedocromil sodium (27), 2% sodium cromoglycate (25) or placebo (27) for the 6-week double-masked phase. Both the sodium cromoglycate and placebo eye drops were colour-matched to the pale yellow of 2% nedocromil sodium by the addition of 0.0005% riboflavin.

Clinical assessments were made every 2 weeks during treatment, and whereas symptom severity increased beyond the baseline in patients treated with either placebo or sodium cromoglycate, scores for the major symptoms of eye itching and hyperaemia

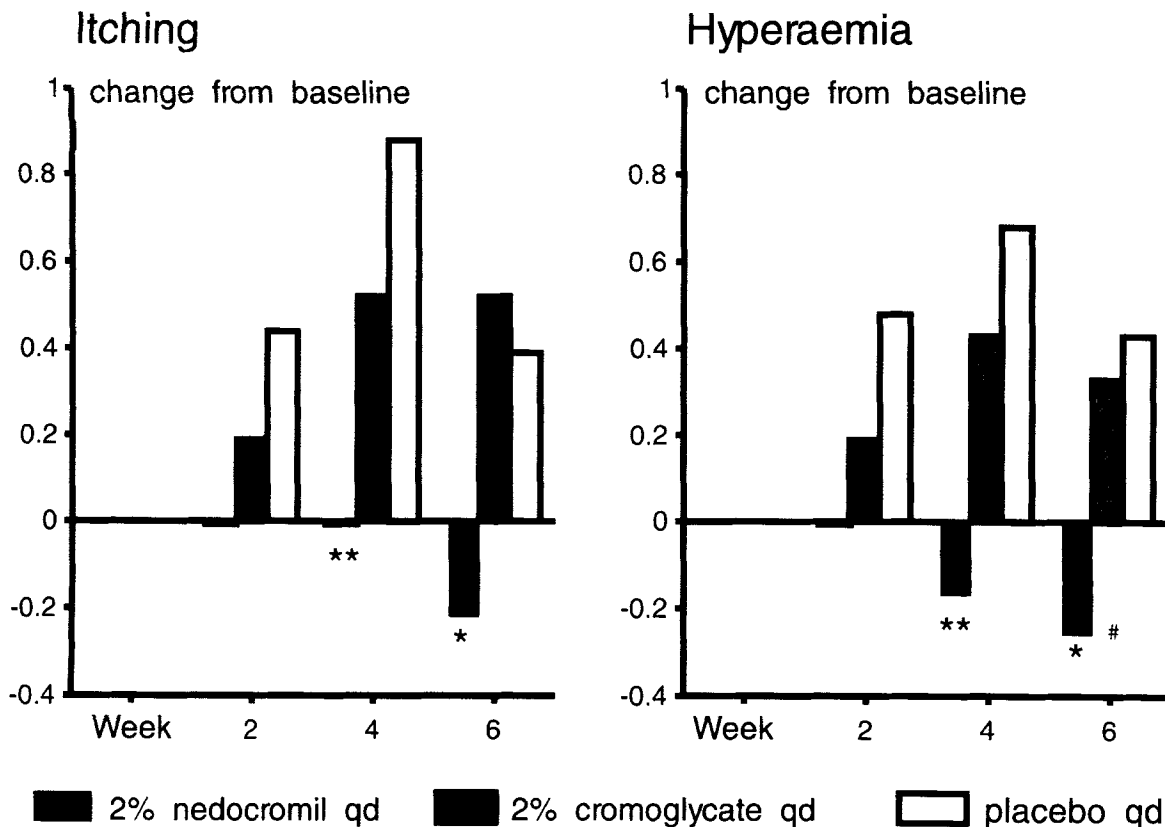


Fig. 3. Clinical assessments of eye itching and hyperaemia due to SAC during the course of the ragweed pollen season at the Niagara Falls centre, in patients treated qd with 2% nedocromil sodium, 2% sodium cromoglycate, or placebo eye drops ². * $p < 0.05$ ** $p < 0.01$ nedocromil sodium vs placebo; # $p < 0.05$ nedocromil sodium vs sodium cromoglycate.

were actually reduced by nedocromil sodium (Fig. 3). Patient diary card symptom scores recorded during weeks 4-6 again showed significantly less itching and redness with nedocromil sodium treatment than with either placebo or sodium cromoglycate ($p < 0.05$ - $p < 0.01$). Fig. 4 shows the daily total symptom scores recorded during peak pollen at Niagara Falls, and it is quite clear that with the onset of an extraordinarily high burst of pollen on September 4th, there was an immediate breakthrough of symptoms in patients receiving placebo or sodium cromoglycate: neither of these groups was well-covered. Nedocromil sodium, on the other hand, controlled symptoms extremely well during this peak challenge period. This increased ability of nedocromil sodium to control symptoms of SAC echoes its comparative activity in the VKC study⁵, in which nedocromil sodium demonstrated a stronger effect in general than sodium cromoglycate and was significantly better ($p < 0.05$) at reducing conjunctival swelling, or chemosis.

Oral H_1 -antihistamine comparisons

Regarding the oral antihistamine comparator studies in SAC (Table 1b), it should be borne in mind

that the inclusion of a double-dummy placebo will tend to bias the result in favour of the antihistamine. This is because the 'placebo effect' is less from a dummy tablet, as received by the nedocromil sodium group of patients, than from the eye drops, which do have a physical effect. In spite of this, patients' final opinions from these three studies demonstrated no preference for either astemizole or terfenadine over nedocromil sodium, which proved as effective as the standard-dose antihistamines for peak pollen eye itching and total symptoms. The impact of a high placebo effect was again diminished by the evidence of a known therapeutic comparator. Furthermore, as for Kuopio, patient opinions of treatment in the astemizole study⁶ were more relevant during peak pollen challenge (week 2), when symptoms were significantly reduced by each of the active treatments, than they were at the end of the 4-week trial.

The Canadian terfenadine comparison (Table 1b) also showed no differences in patient opinions of treatment after four weeks, when 60% experienced good control of symptoms in each group. The group size was about 85 at this time, my own patients at Niagara Falls accounting for one-quarter of the total entry into this 4-centre study (Alexander, Dolovich, Rosen, Yang/Drouin). On this occasion, the double

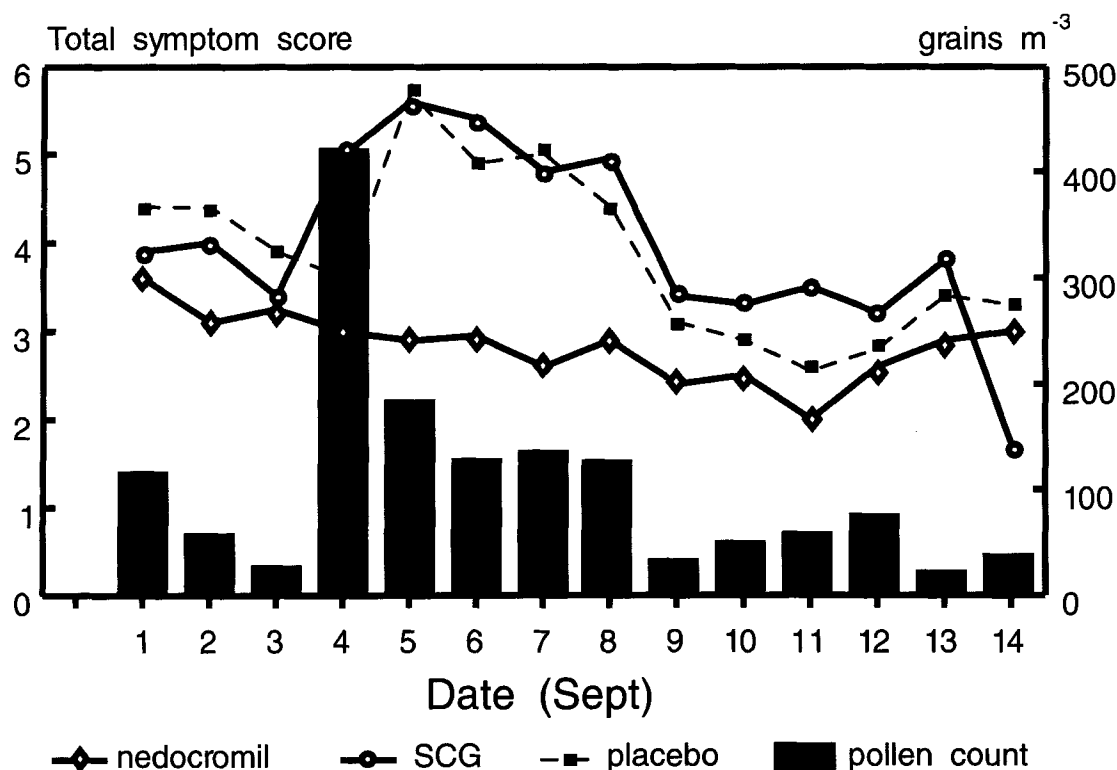


Fig. 4. Diary card total symptoms during the peak ragweed pollen period at the Niagara Falls centre, in patients treated qd with 2% nedocromil sodium, 2% sodium cromoglycate, or placebo eye drops². Mean daily total symptom scores for the whole peak pollen period were, respectively, 2.71, 4.14 and 4.13 ($p = 0.03$ by Kruskal-Wallis test). Pairwise comparisons (Mann-Whitney U-test): $p = 0.011$ nedocromil sodium vs sodium cromoglycate; $p = 0.055$ nedocromil sodium vs placebo; $p = 0.55$ sodium cromoglycate vs placebo.

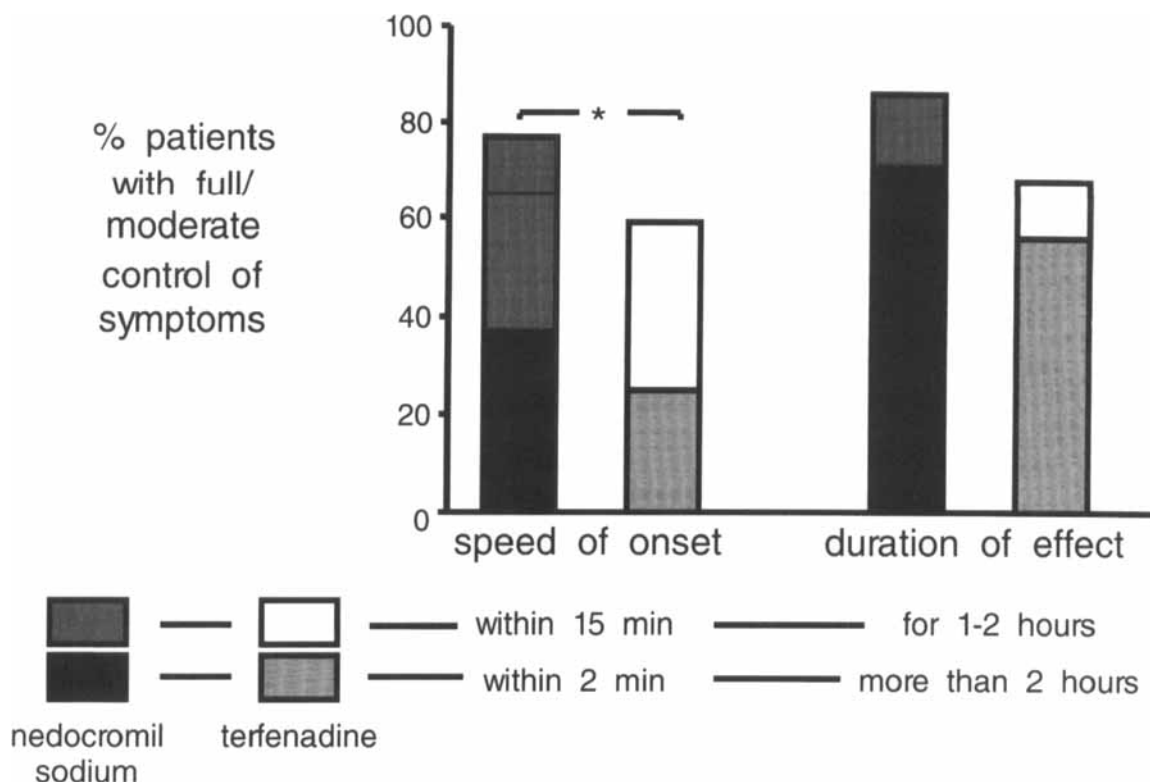


Fig. 5. 2% nedocromil sodium eye drops (bd) compared with terfenadine (60 mg tablet bd) in a double-dummy placebo-controlled multicentre Canadian study carried out in patients with SAC due to ragweed pollen: speed of onset of action and duration of effect of test treatment. * $p = 0.014$ nedocromil sodium vs terfenadine.

masked (bd) treatment period was timed to start alongside the ragweed season, and patient opinions recorded at week 2 – during the peak pollen count – already showed a strong placebo effect: patients with full/moderate control of symptoms represented 53% of the placebo group, as compared to 59% of the nedocromil sodium group and 50% of the terfenadine group, with no significant differences between treatments.

The major difference between the three groups in this study was in the speed of onset of the treatment effect, ascertained at the final, week 4 visit (Fig. 5). Terfenadine (+ placebo eye drops) proved similar to the double-dummy placebo treatment in that, respectively, 25% and 29% of patients experienced relief of symptoms within two minutes of administration, rising to 59% and 56% after 15 minutes. In contrast, 37% of the patients receiving nedocromil sodium eye drops (+ placebo tablet) experienced control of symptoms within 2 minutes, rising to 78% within 15 minutes. The speed of action of nedocromil sodium was statistically significantly better than either placebo ($p = 0.037$) or terfenadine ($p = 0.014$) whereas terfenadine was not significantly different from placebo.

The other question patients really are concerned about is, 'How long does the morning dose protect

against eye symptoms?' In answer to this, at the final clinic visit, 71% of the patients on nedocromil sodium reported a prolonged duration of action of more than two hours. Although the difference was not statistically significant, this compared favourably with 56% of patients in the terfenadine treatment group (Fig. 5).

Conclusion

On the evidence of the comparative SAC studies discussed here, in which the various therapies were equally well accepted by the patients, nedocromil sodium 2% eye drops can be used with confidence as a first line topical treatment for allergic eye disease. The compound is known to have potent anti-allergic and anti-inflammatory effects, combined with a good safety and tolerability profile. As a topical treatment for SAC, nedocromil sodium can be used twice daily, it has a very rapid onset of action, and it is at least as effective as four times daily sodium cromoglycate and the oral antihistamines terfenadine and astemizole. The use of nedocromil sodium reduces the need for concomitant antiallergic therapy and the 2% eye drops are well tolerated with minimal side effects.

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