

Clinical Experience with Tilavist: An Overview of Efficacy and Safety

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Summary

A programme of clinical studies was carried out to determine the basic efficacy and safety of 2% nedocromil sodium eye drops (Tilavist) in treating allergic conjunctivitis, in 2,905 patients from 3-76 years of age. Results of all the double-masked placebo comparative studies completed to date – five in vernal keratoconjunctivitis (VKC), five in perennial (PAC) and 16 in seasonal allergic conjunctivitis (SAC) – have been assessed in a statistical overview analysis. Nedocromil sodium, administered four times daily to 153 patients with VKC, was significantly more effective than placebo (155 patients) and in the clinicians' opinion gave good control in 76% of cases, compared with 46% for placebo ($p < 0.001$). Patients with chronic symptoms of PAC also responded better to nedocromil sodium given four times daily ($n = 146$) rather than twice daily ($n = 86$), and significantly more patients ($p < 0.001$) were effectively controlled by four times daily treatment with nedocromil sodium (72%) than with placebo (47%; $n = 156$). Twice-daily dosage with nedocromil sodium ($n = 677$) was adequate for SAC, however, and the treatment was statistically better than placebo ($p < 0.01$ – $p < 0.001$) whether dosed twice or four times daily. Speed of action was assessed in seven SAC studies in which 79% of all patients ($n = 295$) using nedocromil sodium had experienced relief of symptoms when questioned, half of them within 15 minutes and 74% during the first hour after dosing. Test treatments were well-accepted by both adults and children, and there were no major adverse events. Minor irritations reported more frequently with nedocromil sodium than placebo were stinging or burning of the eyes on application of the drops and a distinctive taste, noted by 5% of the active treatment group ($n = 1,552$).

Introduction

Nedocromil sodium is a non-toxic pyranoquinoline dicarboxylate compound which has wide-ranging but specific antiallergic and antiinflammatory properties, including stabilisation of mast cell subsets¹, inhibition of activated inflammatory cells such as eosinophils² and macrophages³, and modulation of neurogenic inflammation⁴. Developed initially as a treatment for bronchial asthma, the topical action of nedocromil sodium on mucosal inflammation soon extended its therapeutic potential to include allergic rhinitis and conjunctivitis^{5, 6}.

A programme of clinical studies was carried out during the period 1986-1991, in order to establish the basic efficacy and safety of a 2% ophthalmic formulation of nedocromil sodium (Tilavist). This overview does not merely present a selection of published studies, but includes *all* the placebo-controlled, double-masked clinical trials of Tilavist completed to date in patients with vernal, seasonal or non-seasonal (perennial) allergic conjunctivitis. Details and personal experiences from some of the published studies are additionally used to support the formal statistical analysis of the overall efficacy and safety of the eye drops.

Statistical methods

Severity of symptoms and signs of allergic conjunctivitis was assessed on a 5-point scale, scored as 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe, by both the clinicians (at visits) and the patients (on daily diary cards). Mean values were taken over both eyes for the analysis of clinical efficacy. Global opinions of treatment (full, moderate, slight, or no control of symptoms) were recorded at the final clinic visit, or in some studies at the end of the peak pollen period; patients withdrawn due to treatment failure were classed as 'no control'. Any problems during test treatment were discussed and recorded by the clinician at each visit.

Vernal keratoconjunctivitis

Clinical scores for symptoms (sticky and watery discharge, grittiness, itching and soreness) and con-

junctional signs (hyperaemia, chemosis, papillae and follicles) were analysed using the pre-treatment baseline and end-of-treatment change from baseline. An analysis of variance (ANOVA) with study, treatment and their interaction was carried out to test the consistency of treatment effect across studies. Since the interaction was not significant, a reduced model with treatment and centre only was used to test for treatment effect. A non-parametric test (Mack-Skillings) allowing for study as a blocking factor, was then used for confirmatory purposes to test the treatment effect and produced the same conclusions as the parametric ANOVA. Global opinions were also used to assess treatment efficacy: for patient and clinician opinions of test treatments, the number of patients showing a good effect (full/moderate control of symptoms) was calculated. A Mantel Haenszel test was carried out for patient and clinician opinions separately, adjusting for study, to compare the two test treatments.

Seasonal and non-seasonal (perennial) allergic conjunctivitis

Differences between centres are a major source of variation, and since many of these trials were multicentre studies, the 'centre' (having a minimum of ten patients per treatment group) was taken as a valid unit for unbiased estimation of the difference between treatments. Centres falling below this minimum were combined with the next smallest centre within the same trial. Under the null hypothesis that the two treatments have the same effect, there should then be no statistical difference between treatments over all the within-centre estimates. Taking account of all the seasonal studies provided a total of 34 centres dosed twice daily (bd) and eight centres dosed four times daily (qd), whilst the non-seasonal studies had four bd and six qd centres; the two dosage regimens were considered separately and in combination. Itching of the eye was taken as the primary symptom for analysis, together with the total diary symptom score (incorporating itching, soreness, grittiness, watering, redness and photophobia) as an overall measure of eye condition. Using paired t-tests to compare nedocromil sodium and placebo for each symptom, mean score values during the peak pollen period were considered for seasonal studies, and mean scores during a defined evaluation period (such as the last four weeks of treatment, or between the final two clinic visits) for perennial studies. To assess global opinions of treatment, the number of patients showing a good effect (full/moderate control of symptoms) was calculated for nedocromil sodium and placebo. A Mantel Haenszel test was carried out for patient and clinician opinions separately, adjusting for centre, to compare the two test

treatments. All tests were two-tailed and at the 5% significance level.

Efficacy

Vernal conjunctivitis (VKC)

Nedocromil sodium has been compared with placebo in five VKC studies, at a dosage of one drop per eye, four times daily. A total of 356 patients, (aged from 3-40 years) took part, 153 receiving nedocromil sodium and 155 placebo, for periods of 4-12 weeks; (one study⁷ included a sodium cromoglycate treatment group of 48 patients). As VKC is a disease with considerable problems occurring all the time, the signs and symptoms assessed by the clinician at the final clinic visit have been compared as changes from baseline severity in the efficacy analysis. Nedocromil sodium was significantly ($p < 0.05$ - $p < 0.01$) more effective than placebo for overall reduction of tarsal and bulbar conjunctival hyperaemia, bulbar chemosis, papillae and follicles, and watery discharge, whilst other symptoms showed a similar non-significant trend (Table 1). Global opinions of treatment reinforced these findings (Fig.1). The clinicians were clearly in favour of nedocromil sodium and considered 76% of VKC patients to be well-controlled by this treatment, as compared to 46% for placebo ($p = 0.0004$); the patients' own opinion was similar for the active treatment (75%) but showed rather less of a difference from placebo (58%; $p = 0.059$). In one of these group-comparative studies (Fig.2) eye itching – the *sine qua non* of VKC – was reduced by placebo ($n = 11$) but, compared to the group baseline, this effect became significant only after five weeks. In nedocromil sodium treated patients ($n = 8$) the

Table 1. Mean reduction in severity of signs and symptoms following treatment with nedocromil sodium or placebo in five VKC studies. (n =patients). (significance: * $p < 0.05$ ** $p < 0.01$)

		Change from baseline		
Sign or symptom		Nedocromil sodium	Placebo	P-value
<i>Tarsal</i>	hyperaemia	-1.10 (136)	-0.77 (132)	0.0059**
	chemosis	-0.80 (75)	-0.64 (74)	0.40
	papillae	-0.83 (129)	-0.68 (124)	0.16
	follicles	-0.16 (68)	+0.12 (70)	0.088
<i>Bulbar</i>	hyperaemia	-1.35 (136)	-1.07 (132)	0.034*
	chemosis	-0.95 (75)	-0.54 (74)	0.0069**
	papillae	-0.69 (129)	-0.41 (123)	0.019*
	follicles	-0.53 (82)	-0.13 (81)	0.014*
<i>Symptoms</i>	itching	-1.63 (145)	-1.35 (151)	0.11
	grittiness	-1.20 (143)	-0.97 (149)	0.64
	soreness	-1.12 (130)	-1.04 (129)	0.77
	discharge	-0.97 (145)	-0.79 (151)	0.29
	watery discharge	-1.81 (82)	-1.30 (87)	0.048*
	sticky discharge	-1.21 (82)	-0.92 (87)	0.30

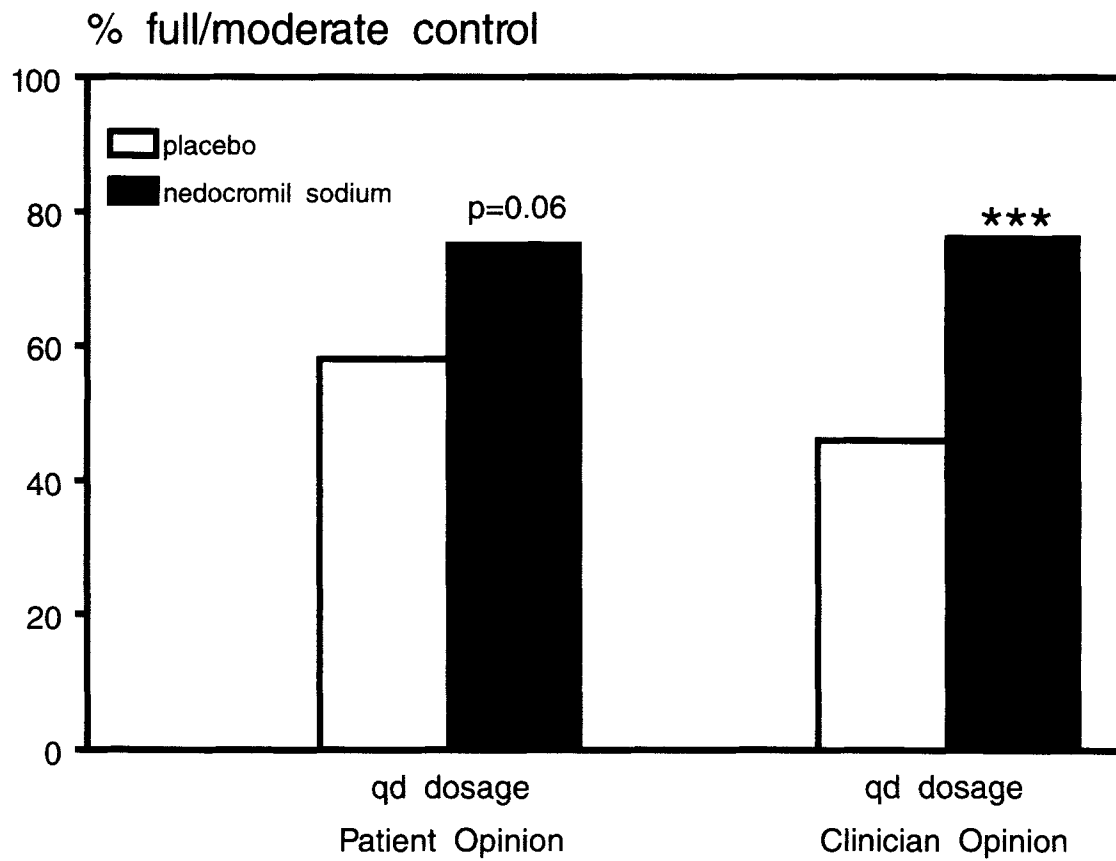


Fig. 1. Global opinions of treatment efficacy in five studies of VKC: percentage of patients with good control of symptoms. (***) $p < 0.001$

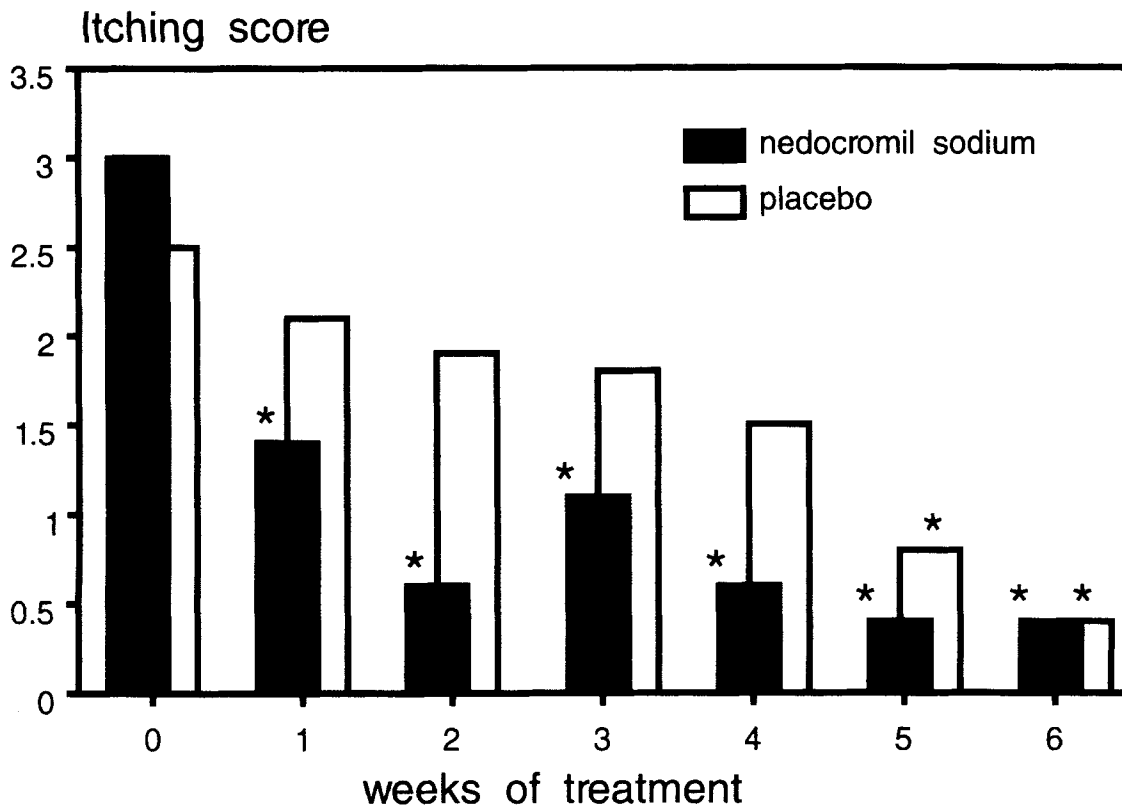


Fig. 2. Reduction of eye itching in VKC patients treated four times daily with nedocromil sodium ($n = 8$) or placebo ($n = 11$). (*) $p < 0.05$ vs baseline (adapted from Bonini et al, 1992⁸, with permission)

Table 2. Mean reduction in symptom severity from baseline, following treatment with nedocromil sodium or placebo, twice or four times daily, in five PAC studies. (n=centres).

	Itching		Total symptoms	
	4 x daily	All studies	4 x daily	All studies
Nedocromil sodium	-1.00 (6)	-0.89 (7)	-4.97 (6)	-4.33 (7)
Placebo	-0.38 (6)	-0.34 (7)	-2.32 (6)	-2.14 (7)
P-value	0.12	0.064	0.23	0.16
Difference	0.62	0.54	2.65	2.19
95% confidence limits	-0.23, 1.47	-0.04, 1.13	-2.33, 7.63	-1.13, 5.50

within-group reduction in itching was significant from the first week onwards, and was associated with significant decreases in the numbers of inflammatory cells (eosinophils, neutrophils and lymphocytes) found in tear fluid samples⁸.

Non-seasonal or perennial allergic conjunctivitis (PAC)

A further five studies have been completed in 388 patients with perennial allergic conjunctivitis, the majority being sensitive to housedust mites in addition to other allergens. The patients, aged from 6-74

years, were treated for periods of 3-12 weeks with either nedocromil sodium (n = 232) or placebo (n = 156). Dosage was one drop per eye, administered four times daily at 6 centres (146 patients received nedocromil sodium) and twice daily at 4 centres (86 patients received nedocromil sodium). One of the studies⁹ compared the active treatment at both dose frequencies, using a single-dummy placebo with the twice-daily nedocromil sodium, in addition to the four times daily placebo group, in order to maintain double-masked conditions. As this is again a troublesome disease all year round, changes from baseline severity scores (during the specified evaluation period) were compared for eye itching and total symptoms. As seen in Table 2, the reduction in mean severity scores was greater in nedocromil sodium treated patients, although statistical significance was not found in this overall analysis. The global evaluation, on the other hand (Fig.3), showed that significantly more patients ($p < 0.001$) were effectively controlled by four times daily treatment with nedocromil sodium (72%) than with placebo (47%). Under trial conditions, twice-daily dosage appeared less effective against the chronic symptoms of PAC, and this was demonstrated by the dose-frequency study⁹.

None of the PAC studies included active com-

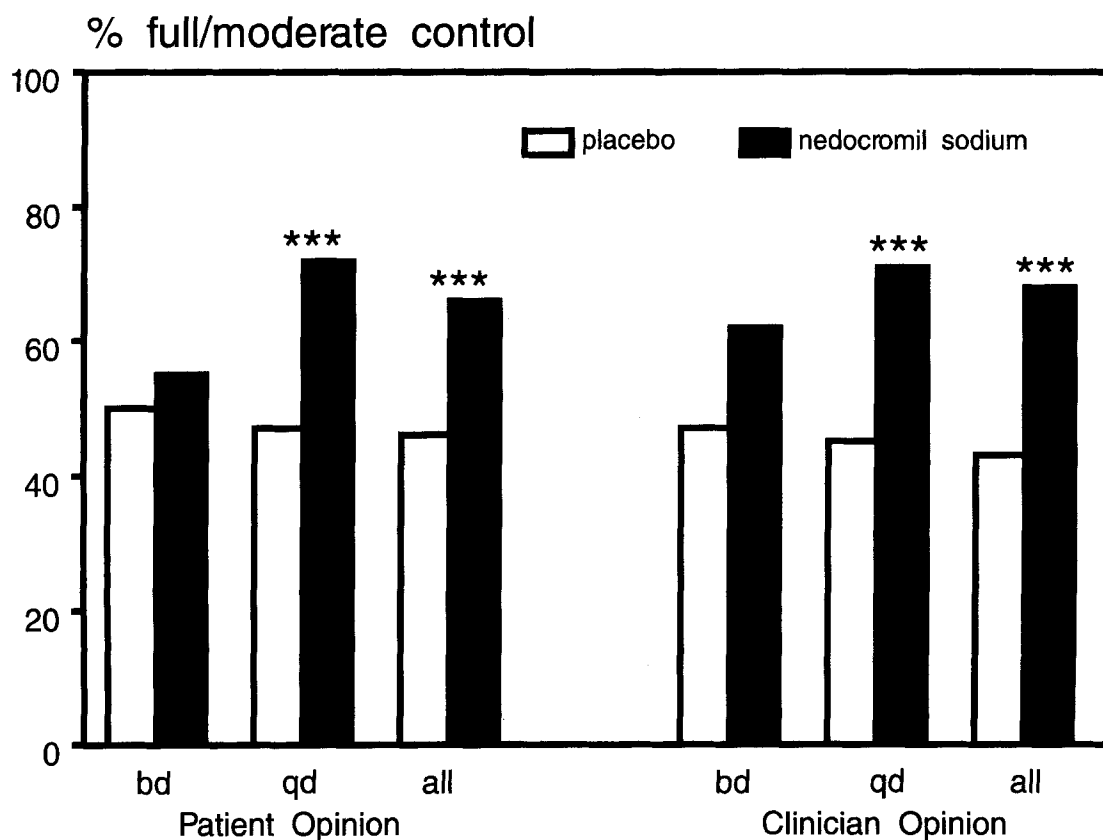


Fig. 3. Global opinions of treatment efficacy in five studies of PAC: percentage of patients with good control of symptoms. (***) $p < 0.001$

parator treatment groups, however van Bijsterveld et al¹⁰ selected for their study group only patients who were not responding well to sodium cromoglycate. After a further 1-week baseline when they received only sodium cromoglycate (2% eyedrops four times daily) patients remaining symptomatic were randomised to six weeks of treatment with either nedocromil sodium, four times daily, or placebo. Symptoms were not helped by the placebo treatment, whereas nedocromil sodium produced a steady improvement, which became statistically significant ($p < 0.05$) with respect to placebo during weeks five and six (Fig. 4).

Seasonal allergic conjunctivitis (SAC)

The greatest number of patients investigated has been in the area of SAC. So far, 2,242, ranging from 4-76 years of age, have been analysed in a total of 16 studies. Three studies included sodium cromoglycate as an active comparator treatment, and another three included an oral antihistamine and double-dummy placebo. Test treatment was used for 4-8 weeks, which always included the peak pollen season. In the overall analysis, 34 centres used a twice-daily dosage (677 patients received nedocromil sodium) and eight centres a four-times daily dosage (304 received nedocromil sodium). These results are

Table 3. Overall mean severity scores for eye itching during the peak pollen period in 16 SAC studies: nedocromil sodium, twice or four times daily, compared with placebo eye drops (n=centres). (significance: ** $p < 0.01$ *** $p < 0.001$)

	2X daily	4X daily	All studies
Nedocromil sodium	1.15 (34)	0.76 (7)	1.09 (41)
Placebo	1.35 (34)	1.03 (7)	1.30 (41)
P-value	0.0011**	0.006**	0.0001***
Difference	0.20	0.27	0.21
95% confidence limits	0.09,0.31	0.11,0.43	0.12,0.30

summarised in Table 3 and Fig. 5. During the peak pollen period, in spite of the inevitable differences in conditions prevailing from study to study, the major diary card symptom – eyes itching – showed significant effects for nedocromil sodium over placebo, whether dosing twice-daily ($p < 0.01$) or four times daily ($p < 0.01$), or for all centres ($p < 0.001$). The overall opinions of treatment effectiveness in SAC studies (Fig.5) showed statistically significant differences ($p < 0.01$ - $p < 0.001$) in favour of nedocromil sodium for both patient and clinician opinion. The high placebo response rate of 50-60% appears typical of this type of clinical trial and similar levels of symptom control with placebo eye drops have been reported in other drug studies¹¹. Nevertheless, the significant therapeutic effects of nedocromil sodium

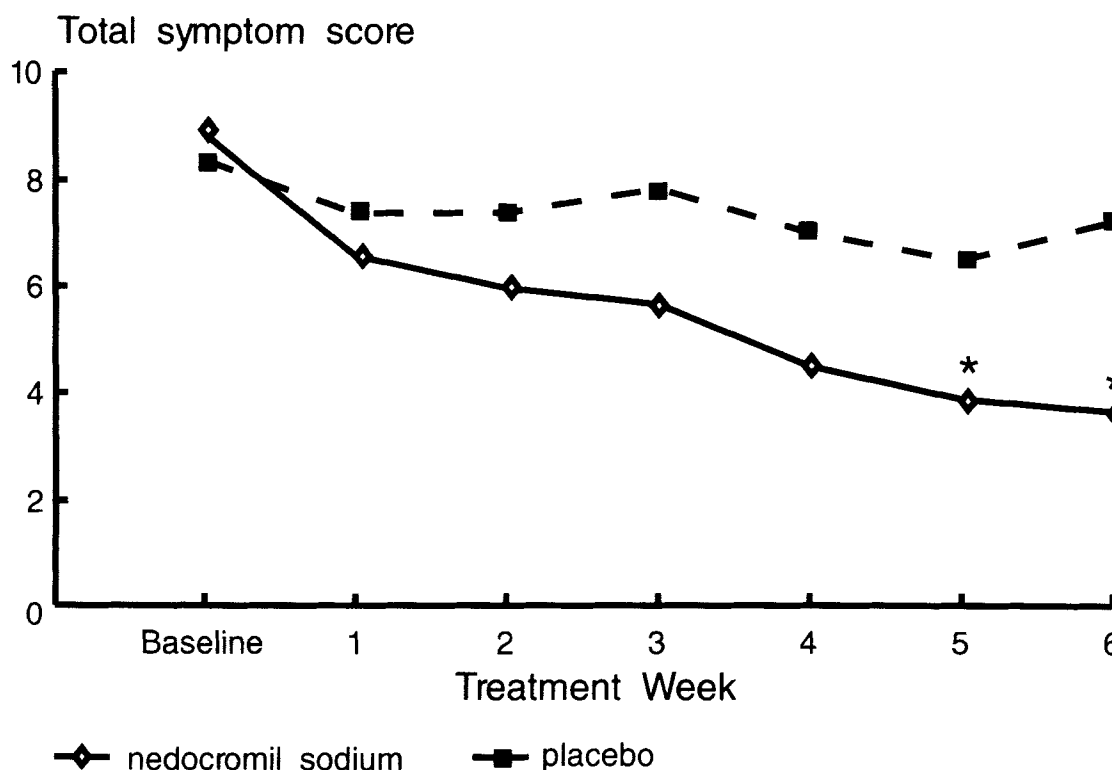


Fig. 4. Reduction in diary card symptoms of PAC, in patients not fully controlled by sodium cromoglycate, during six weeks of nedocromil sodium treatment. (* $p < 0.05$ nedocromil sodium vs placebo) (from van Bijsterveld et al, 1994¹⁰, with permission; copyright Aeolus Press)

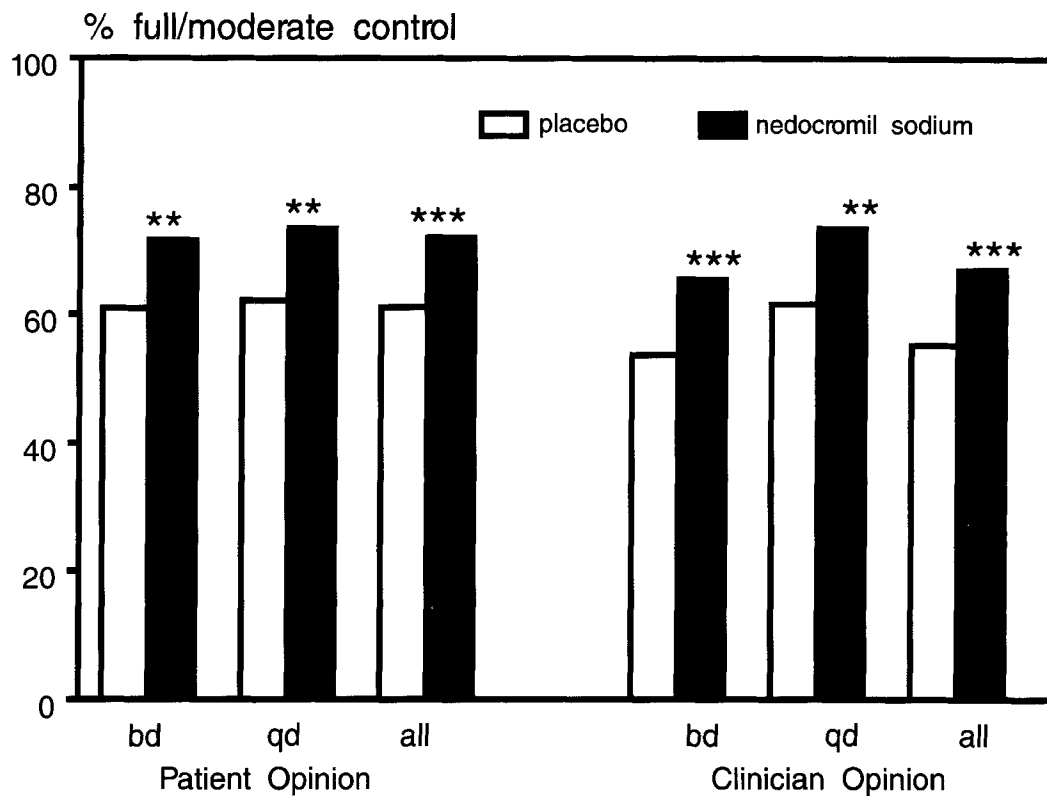


Fig. 5. Global opinions of treatment efficacy in 16 studies of SAC: percentage of patients with good control of symptoms. (** $p < 0.01$ *** $p < 0.001$)

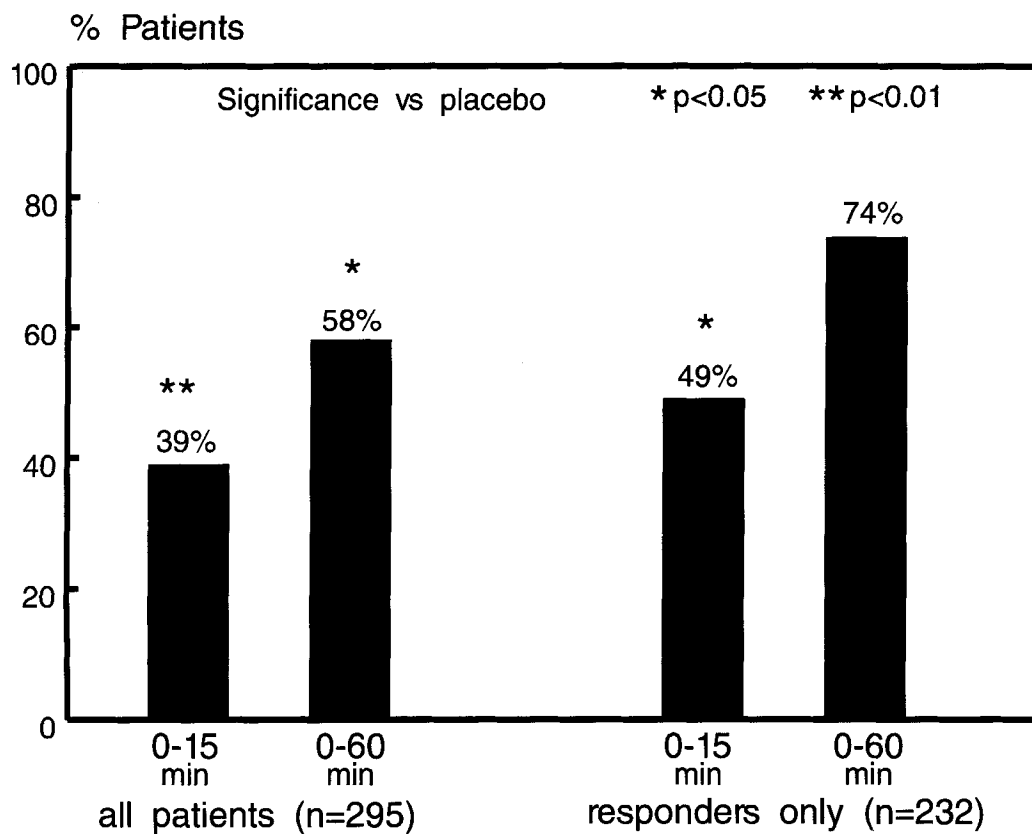


Fig. 6. Overall speed of onset of action of nedocromil sodium 2% eye drops in seven SAC studies. (79% of all patients had experienced relief of symptoms.)

were clearly demonstrated, whether for the isolated twice-daily or four times daily schedules, or for all the results combined.

Speed of onset of action in SAC

In seven of the seasonal studies, a total of 295 patients receiving nedocromil sodium and 307 receiving placebo were asked how quickly the test treatment worked during the 24 hours after dosing. This question was usually asked at the end of the first week of treatment, when eight out of ten patients on nedocromil sodium said they had experienced relief of symptoms: 49% within 15 minutes ($p < 0.05$ compared with placebo responders) and 74% within the first hour after using the eye drops (Fig. 6). Taking non-responders into account, the proportion of all patients that responded to nedocromil sodium within 15 minutes was 39% ($p < 0.01$ vs placebo) and within one hour was 58% ($p < 0.05$ vs placebo). It seems clear from this evidence that nedocromil sodium eye drops are active against ongoing conjunctivitis symptoms and can show this effect quite rapidly.

Experience with nedocromil sodium in a paediatric SAC study¹²

In clinical trials of nedocromil sodium eye drops in patients with SAC, most studies were designed so that the beginning of test treatment, after a 1-week baseline, coincided with the expected onset of the pollen season. This plan was followed in a study by Möller et al¹², carried out at four Swedish centres, in 149 children (aged 6-16) who had SAC due to birch pollen. As seen in Fig. 7, the largest centre (Umeå) is in the sub-arctic region, whereas the other three are more central. Local pollen counts were used to define the peak birch season, which always occurred during the first three weeks of treatment but was later, and heavier, in the north (15-28 May; mean 995 grains m^{-3}) than it was around Stockholm (24 April-10 May; mean 629 grains m^{-3}). Double-masked test treatment (2% nedocromil sodium or placebo) was administered, one drop per eye twice daily, for a period of four weeks and was well-tolerated by most of the young patients. All-centres diary card symptoms including eye itching

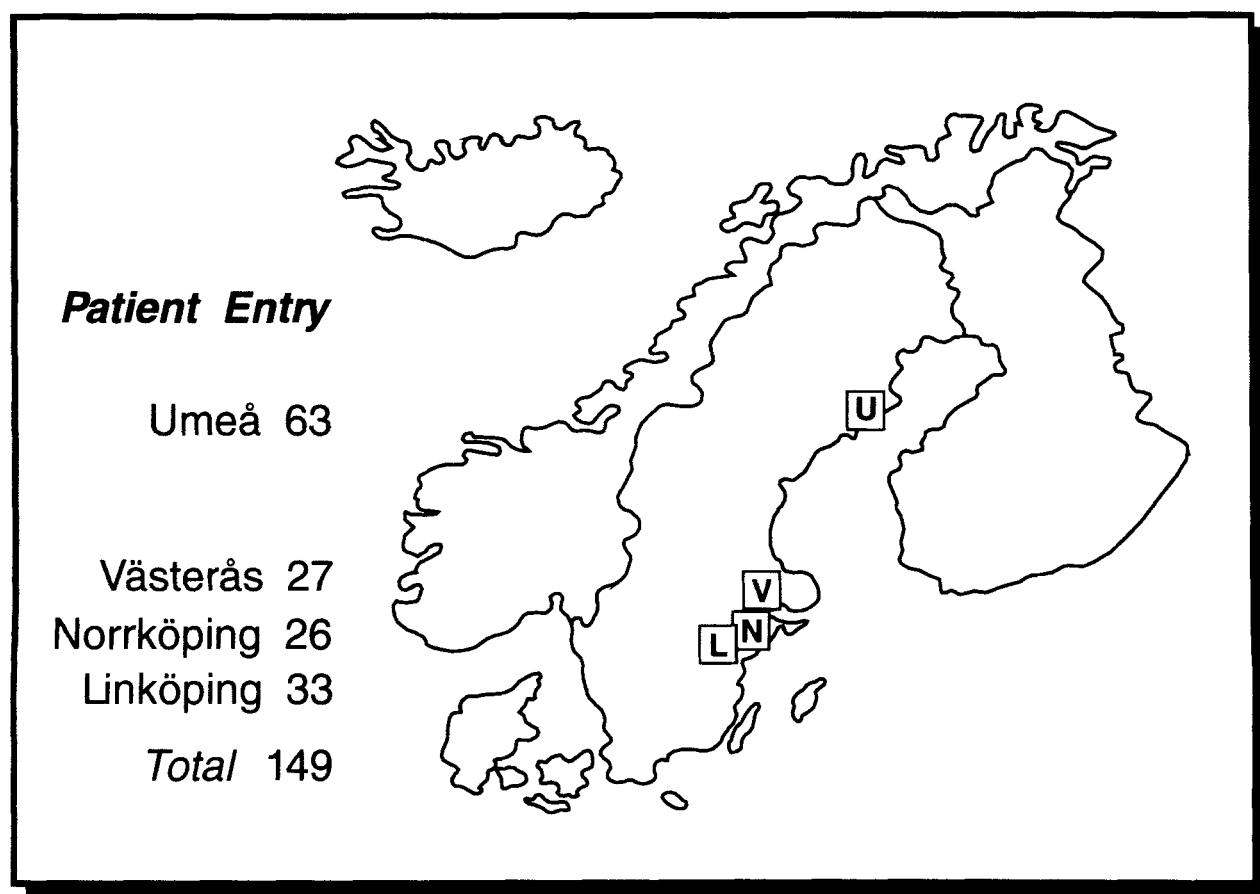


Fig. 7. Geographical distribution of patients in the Swedish paediatric SAC study¹².

Table 4. Reduction of conjunctivitis symptoms by twice-daily nedocromil sodium during peak pollen challenge in the Swedish paediatric SAC study¹². Mean severity scores are shown for all four centres and for the Umeå centre, which had the heaviest birch pollen season. (n=patients). (significance: * p<0.05 ** p<0.01)

	Itching		Total symptoms	
	All centres	Umeå	All centres	Umeå
Nedocromil sodium	0.9 (75)	0.8 (31)	2.8 (74)	2.8 (30)
Placebo	1.4 (72)	1.6 (31)	4.3 (71)	5.4 (30)
Mann-Whitney U-value	1967.0	281.0	1973.5	282.5
P-value	0.004**	0.005**	0.0097**	0.013*

and total symptom scores were reduced significantly by nedocromil sodium during the peak pollen season, and this effect was intensified at Umeå, where the more severe pollen challenge overcame the washing effect of the placebo but did not reduce the activity of nedocromil sodium (Table 4).

Safety & tolerability

During the entire Tilavist trial programme, more than 1,500 patients have received treatment with 2% nedocromil sodium eye drops. Headache was the most frequently reported event, but occurred equally often with placebo treatment (in about 10% of patients); other symptoms reported by more than 1% of patients were largely due to minor eye irritation (Table 5). The incidence of eye burning and stinging on application of the active eye drops was roughly twice that of the placebo, and about 5% of patients commented on the taste of nedocromil sodium draining through the nasolacrimal duct.

Table 5. Overview of safety and tolerability of nedocromil sodium 2% ophthalmic solution during the clinical trials programme: percentage of patients (n) reporting adverse events (frequencies > 1.0%).

Event reported	Nedocromil sodium (1,552)	Placebo (1,353)
Headache	10.8	9.3
Eye burning	7.3	4.2
Eye stinging	5.9	3.1
Distinctive taste	5.4	0.6
Eye redness	2.3	1.9
Eye itching	2.3	3.3
Eye watering	1.7	1.6
Eye soreness	1.7	0.9
Pharyngitis	1.6	1.2
Upper respiratory tract infection	1.6	1.1
Photophobia	1.2	1.1

Conclusions

This programme of clinical trials has shown Tilavist to be significantly more effective than placebo in treating allergic eye disease. In seasonal allergy, it works fast to relieve conjunctivitis symptoms, it is effective at a twice daily dosage, and it continues to protect the patient during high pollen exposure. In non-seasonal allergic conjunctivitis, four times daily dosage is more effective initially, in order to bring chronic symptoms under control, and nedocromil sodium can improve the situation for PAC patients not responding to sodium cromoglycate. Finally, for patients with VKC, four times daily treatment with nedocromil sodium is recommended to control symptoms and signs, by reducing the activity of inflammatory cells such as eosinophils and mucosal mast cells. The experience of the many trialists taking part in this programme has proved nedocromil sodium 2% eye drops to be a safe treatment which is well-tolerated by both adults and children.

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