

asks the prescribing physician to report back on any unusual symptoms or events that have occurred since the prescription was dispensed. More than 14,000 patient reports on nedocromil sodium have been gathered from the United Kingdom with the use of this method. These reports have generated no new or unexpected findings. The only features reported with any incidence are unpleasant taste, occasional headache, and nausea. Similar findings also come from spontaneous adverse event reports from other countries where the drug is marketed.

In summary, laboratory tests, clinical trials, and postmarket experience show that nedocromil sodium is well tolerated by most patients. Adverse

events are generally mild, and the incidence of severe reaction is extremely uncommon. These data indicate that nedocromil sodium has an excellent safety profile, a feature of major importance in the decision to prescribe this drug.

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Highlights of the nedocromil sodium clinical study presentations

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Nedocromil sodium (Tilade) is a new compound for the treatment of asthma: an antiinflammatory pyranoquinoline. It is chemically distinct from β_2 -agonists, corticosteroids, theophylline, and cromolyn sodium, the other agents commonly used to treat asthma patients.

Nedocromil sodium has been studied in placebo-controlled clinical trials at both four times and twice daily dosages. Some of the studies included in the worldwide clinical program assessing the efficacy and safety of nedocromil sodium are described below.

THE NORTH AMERICAN TILADE STUDY GROUP

The U.S. program to assess the clinical efficacy of nedocromil sodium has focused on patients

Abbreviation used

FEV₁: Forced expiratory volume in
1 second

with asthma of mild-to-moderate severity who regularly use theophylline or oral or inhaled β_2 -agonist drugs to control their asthma symptoms. These are the patients who are seen most frequently by clinicians who treat asthma.

The North American Tilade Study¹ was a multicenter, double-blinded trial in which 127 patients with mild-to-moderate asthma who had been maintained on slow-release theophylline and β_2 -adrenergic bronchodilators were randomly assigned to receive either nedocromil sodium or placebo four times a day for 14 weeks. Patients were started on treatment after a 2-week baseline period. Slow-release theophylline was withdrawn after 2 weeks of treatment and regularly used oral β_2 -adrenergic agents were discontinued at the sixth week of treatment. In this study patients on nedocromil sodium showed statistically significant reductions in their daytime and nighttime symp-

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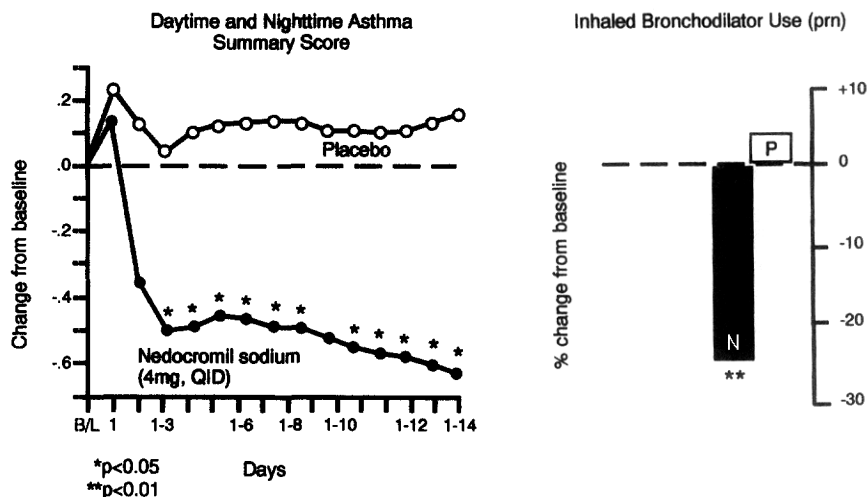


FIG. 1. Change from baseline of cumulative mean asthma symptom summary scores and, as required inhaled bronchodilator use for treatment weeks 1 and 2 (when nedocromil sodium was added to maintenance bronchodilator therapy). After a 2-week baseline period, patients maintained on sustained-release theophylline or oral β_2 -agonist bronchodilators were randomized to receive 4 mg nedocromil sodium ($n = 60$) or placebo ($n = 61$), four times a day, for 16 weeks. Closed circles indicate nedocromil sodium (N); open circles indicate placebo (P). Statistically significant differences (* $p < 0.05$, ** $p < 0.01$) favoring nedocromil sodium were determined from days 1 to 3 onward. The use of as-required inhaled bronchodilator decreased in the nedocromil sodium group and increased slightly in the placebo group during the 2-week analysis period. Data in Figs. 1 through 3 were obtained from the same subjects. (Modified from Cherniack RM, et al. Chest 1990;97:1299-306.)

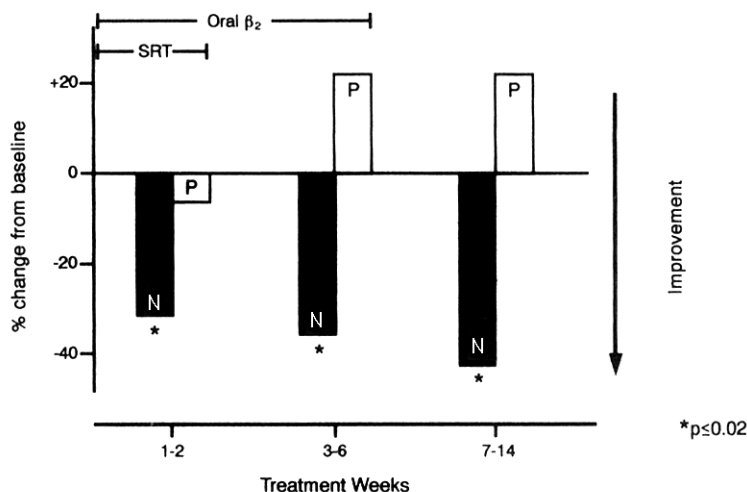


FIG. 2. Bar graph of daily diary card symptom severity scores for asthmatic cough represented as a mean value for each period of assessment (baseline, treatment weeks 1 and 2, 3 to 6, and 7 to 14). Data shown are for patients who recorded cough during baseline (nedocromil sodium, $n = 42$; placebo, $n = 35$). The withdrawal of sustained release theophylline (SRT) at treatment week 2 and oral β_2 -agonist bronchodilators at treatment week 6 did not cause an increase in cough symptoms. All differences are statistically significant in favor of nedocromil sodium (* $p \leq 0.02$). (Modified from Cherniack RM, et al. Chest 1990;97:1299-306.)

tom summary scores within 3 days of the start of treatment (Fig. 1). This improvement in the symptom summary scores occurred concomitantly with a decrease in as-needed aerosol bronchodilator

use (Fig. 1). This onset of action was not expected and had not been predicted on the basis of the action of other nonsteroid antiinflammatory agents for asthma. The improvement in asthma

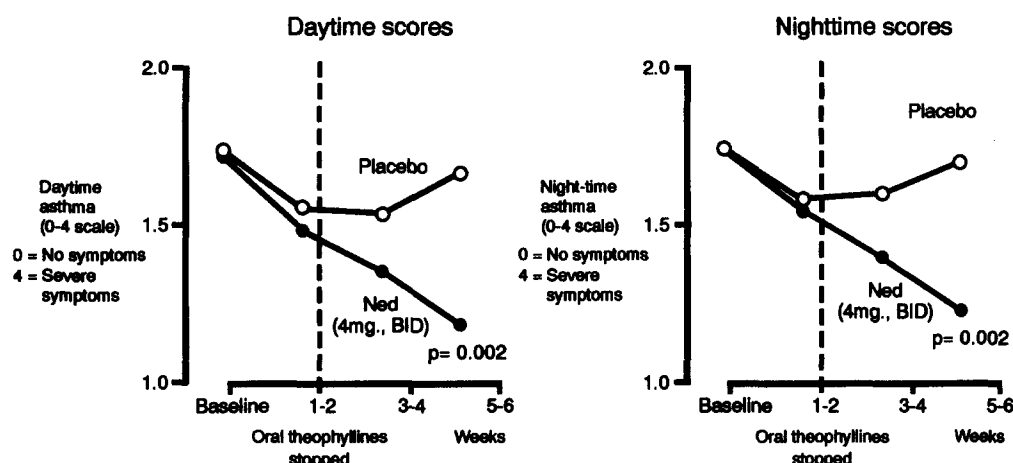


FIG. 3. Mean daily diary card scores for daytime and nighttime asthma symptoms after twice daily treatment with either 4 mg nedocromil sodium (N) or placebo (P). Eighty-seven patients with asthma (N: 45; P: 42) maintained on sustained-release theophylline (SRT) were randomized to treatment for 6 weeks. Diary card scores decreased in both groups during the first 2 weeks when treatment was added to maintenance SRT. After withdrawal of SRT, patients treated with nedocromil sodium continued to improve whereas placebo-treated patients showed an increased level of symptoms. Between-group differences were statistically significant at 6 weeks ($p = 0.002$). (Modified from van As A, et al. Eur J Respir Dis 1986;69:143-8.)

TABLE I. Improved symptoms and pulmonary function with twice daily nedocromil in 37 patients with moderate asthma*

Treatment week	2	4†	6‡	8
Daytime asthma	0.001	0.001	0.001	0.001
Nighttime asthma	0.001	0.001	0.001	0.001
Cough	0.05	0.01	0.001	0.001
Morning PEF _R	0.001	0.001	0.001	0.001
Evening PEF _R	0.001	0.001	0.001	0.01
As required bronchodilator				
Morning	0.001	0.001	0.001	0.01
Evening	NS	0.05	0.001	0.001
FEV ₁	0.05	0.05	0.05	0.01

Modified from Callaghan B, et al. Chest 1992;101:787.

PEFR, Peak expiratory flow rate; NS, not significant.

*Efficacy analysis of the addition of nedocromil sodium aerosol (4 mg twice daily) to sustained-release theophylline therapy (dose range, 400 to 800 mg daily) in 37 adult patients with chronic asthma. Patients were randomly assigned to 8 weeks of treatment with either nedocromil sodium or placebo after a 2-week baseline. Theophylline dose was reduced by one half or one third after treatment week 4 and stopped after week 6. The Mann-Whitney U test was used in the analysis of diary card symptom scores, and the Student *t* test was used in the analysis of pulmonary function measurements. Significance levels for treatment group differences are shown.

†Reduce sustained-release theophylline.

‡Stop sustained-release theophylline.

symptoms was maintained throughout the trial period despite the withdrawal of both theophylline and β_2 -agonist bronchodilators.

Of particular interest in this study was the effect of nedocromil sodium on asthmatic cough. Patients who had cough during the run-in phase showed marked and statistically significant improvements when treated with nedocromil sodium, even after the withdrawal of slow-release theophylline and maintenance β_2 -agonist bronchodilators (Fig. 2).

Patients treated with nedocromil sodium also showed statistically significant increases in pulmonary function measurements (forced expiratory volume in 1 second [FEV₁], forced vital capacity, and forced expiratory flow at 25% to 75% of forced vital capacity) throughout the trial.

The conclusion reached by the investigators was that the concurrent use of nedocromil sodium and inhaled as required β_2 -adrenergic bronchodilators provides a safe, well-tolerated, and effective maintenance regimen that is at least equivalent to the concurrent use of sustained release theophylline and inhaled β_2 -agonists.

TWICE DAILY DOSING

Twice daily studies with nedocromil sodium have also shown improvements in symptom scores, with differences favoring nedocromil sodium within the first 2 weeks of treatment. In one randomized parallel study, 80 patients with

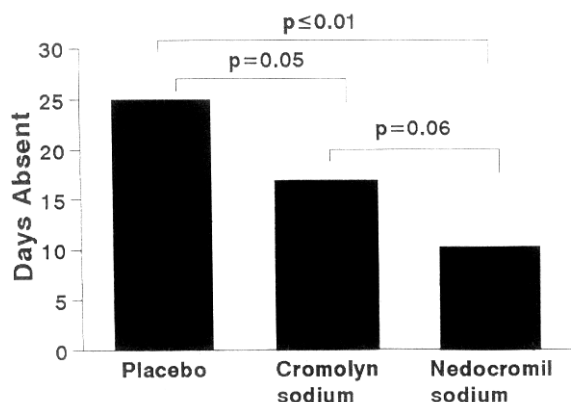


FIG. 4. Effect of treatment on patient days lost from work and school because of asthma. Nedocromil sodium (4 mg, M) was compared with cromolyn sodium (2 mg, C) and placebo (P), four times a day, in the treatment of 306 patients with mild to moderate allergic asthma (N: 103; P: 99; C: 104). All patients required daily use of sustained-release theophylline that was withdrawn during a 2-week baseline period. During the 14-week treatment period, patients treated with nedocromil sodium reported missing fewer days of work or school because of their asthma than patients in the other two treatment groups.

asthma (39 nedocromil sodium, 41 placebo) received treatment at a dosage of four times a day and 87 patients (45 nedocromil sodium, 42 placebo) received treatment twice a day for 6 weeks.² Slow-release theophylline was withdrawn after 2 weeks of treatment.

Compared with placebo, overall asthma severity showed a marked improvement in the nedocromil sodium group within the first 2 weeks of treatment regardless of the dosage regimen, and the improvement was maintained after the withdrawal of theophylline. The twice daily data were particularly impressive, a finding that may reflect improved patient compliance with trial drug treatment. As shown in Fig. 3, scores for nighttime and daytime asthma symptoms showed a steady and continual downward trend in the patient group that received twice daily nedocromil sodium, reaching statistical significance in this study by treatment week 6. Wheezing assessed by auscultation during clinic visits also showed statistically significant between-group differences favoring nedocromil sodium. The recommended starting dosage of nedocromil sodium for symptomatic adults and children (12 years of age and older) is two inhalations four times daily to provide 14 mg*

*Each 2 mg inhalation ex-valve provides 1.75 mg from the mouthpiece.

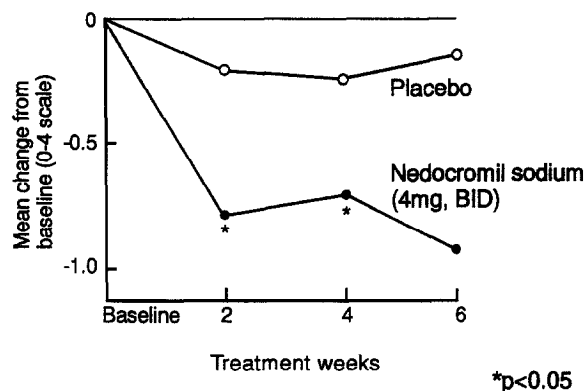


FIG. 5. Mean changes from baseline values in clinic assessments of asthma severity for nedocromil sodium (4 mg, closed circles) and placebo (open circles) given twice daily in addition to maintenance and as-needed bronchodilator therapy. Asthma severity was judged on a scale of 0 = no symptoms to 4 = very severe. Mean baseline values for nedocromil sodium and placebo groups were 2.4 and 2.0, respectively. Clinic visits were made at 2-week intervals. The difference in favor of nedocromil sodium over placebo was statistically significant (* $p < 0.05$) for all visits. (Modified from Grief J, et al. Chest 1989;96: 583-8.)

of nedocromil sodium per day. When the patient's asthma is determined to be under good control, the dose can be reduced first to a three times daily regimen and then, after several weeks on good control, to twice a day.

Similar findings with twice daily nedocromil sodium were recently reported by Callaghan et al.³ (Table I).

ABSENCES FROM WORK AND SCHOOL

One U.S. clinical efficacy study⁴ compared nedocromil sodium (4 mg four times a day) to placebo and cromolyn sodium (2 mg four times a day). The subjects were patients with mild-to-moderate allergic asthma who were expected to respond well to treatment with cromolyn sodium. All patients had been maintained on oral and inhaled β_2 -agonist bronchodilators or sustained release theophylline and were destabilized by removing maintenance medications before the start of the treatment period. As expected on the basis of the patient population, both active treatment groups showed statistically significant improvements in asthma symptoms, the asthma summary score, and pulmonary function measurements during the course of the trial despite decreased use of as required inhaled β_2 -agonist bronchodilators. One symptom parameter

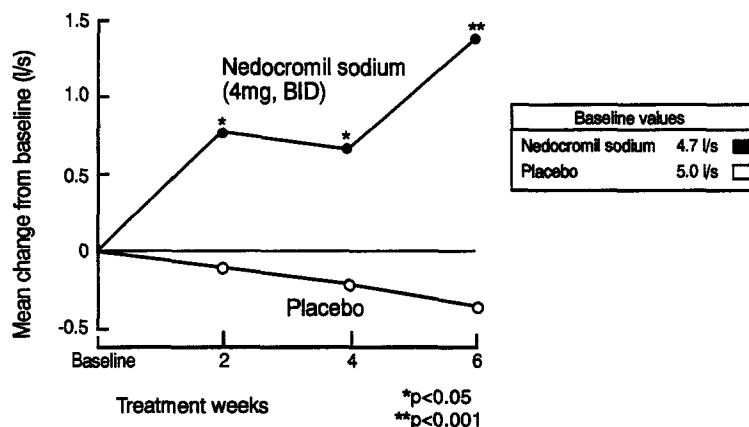


FIG. 6. Mean changes from baseline values in clinic measurements of clinic peak flow rates (PEFR) measured as liters per second for nedocromil sodium (4 mg, closed circles) and placebo (open circles) given twice daily in addition to maintenance and as-needed bronchodilator therapy. Mean baseline values for nedocromil sodium and placebo groups were 4.7 L/sec and 5.0 L/sec, respectively. Clinic visits were made at 2-week intervals. The difference in favor of nedocromil sodium over placebo was statistically significant (* $p < 0.05$; ** $p < 0.001$) for all visits. (Modified from Grief J, et al. *Chest* 1989;96:583-8.)

(nighttime asthma) and one measure of lung function (FEV_1) showed statistically significantly greater improvement in the cromolyn sodium group during the protocol-defined primary time period (treatment weeks 3 to 8). Among the other secondary variables, only the number of days lost from work or school due to asthma approached statistical significance for the two active treatments ($p = 0.06$, nedocromil sodium, Fig. 4).

BECLOMETHASONE DIPROPIONATE

A direct placebo-controlled comparison between nedocromil sodium (4 mg four times a day) and beclomethasone dipropionate (0.1 mg four times a day) was reported by Bergmann et al.⁵ These investigators studied 202 adult patients with mild-to-moderate asthma. Compared with placebo, both active treatments produced statistically significant improvements in pulmonary function, asthma severity, and asthma symptoms. No significant differences were determined between the two active drugs at these doses in this group of patients with mild-to-moderate asthma.

ADDED TO MAINTENANCE THERAPY

The results of worldwide clinical studies indicate that nedocromil sodium can safely be added to other treatment regimens. Clinical studies are available showing added benefit when nedocromil sodium is coadministered with theophylline, β_2 -adrenergic agonists, and inhaled corticosteroids. In some cases mild-to-moderately severe patients may be taken off their maintenance regimens; in

other cases, patients with moderate-to-severe disease may be able to reduce their use of inhaled corticosteroids.

In a study performed by Bianco et al.,⁶ nedocromil sodium (4 mg four times a day) or placebo was added to the maintenance therapies of 117 patients with moderately severe asthma. The established medications included inhaled bronchodilators (72 patients), oral bronchodilators (51 patients), and inhaled corticosteroids (25 patients). After 4 weeks of treatment the patients treated with nedocromil sodium showed statistically significant reductions in symptom scores for nocturnal asthma, morning tightness, daytime asthma, cough, and for as required use of bronchodilators. These patients also had statistically significant improvements in daily diary card peak expiratory flow rate measurements and in the physician's assessment of asthma severity. The investigators concluded that the addition of nedocromil sodium to the existing maintenance therapy of patients with moderately severe bronchial asthma was of significant clinical benefit.

Another study assessed the addition of nedocromil sodium (4 mg four times a day) to the maintenance therapy of 89 adults with moderately severe asthma who were receiving inhaled corticosteroid and bronchodilator treatment.⁷ Before the treatment phase, corticosteroid treatment was reduced to produce a statistically measurable level of symptoms. During the 4-week treatment phase, patients treated with nedocromil sodium showed steady improvements in symptom scores

and peak flow rates despite significant reductions in as required bronchodilator use. In this study nedocromil sodium did not completely replace inhaled corticosteroids but did reverse the symptoms produced by reducing maintenance therapy in patients dependent on inhaled corticosteroids.

A similar study looked at twice daily nedocromil sodium (4 mg) or placebo added to maintenance theophylline in 69 patients who had been maintained on inhaled corticosteroids.⁸ In this trial, patients were carefully withdrawn from their inhaled corticosteroids before the start of the treatment period. As shown in Fig. 5, there was a marked drop in asthma severity in the nedocromil sodium group compared with placebo, reaching statistical significance by treatment week 2. Furthermore, peak flow rates steadily increased in the nedocromil sodium group compared with the placebo group, whose peak flow rates deteriorated once the inhaled corticosteroids were removed (Fig. 6).*

In a Canadian double-blind group-comparative study, 188 steroid-dependent patients with asthma received either nedocromil sodium (4 mg four times a day) or placebo in addition to their regular corticosteroid therapy.⁹ Statistically significant between-group differences favoring nedocromil sodium were reported for morning and evening peak flow measurements, as required β_2 -agonist bronchodilator use, daytime and nighttime asthma symptoms, and morning chest tightness. The frequency of asthma symptom days recorded on daily diary cards decreased in the nedocromil sodium group, reaching statistical significance by treatment week 4. In contrast to studies with cromolyn sodium,¹⁰⁻¹³ this Canadian study showed that nedocromil sodium provided benefit in a group of steroid-dependent patients with stable asthma who were believed to be receiving appropriate maintenance therapy.

CONCLUSION

As described earlier,¹⁴ nedocromil sodium is associated with very few adverse effects. This is important at a time when questions are being raised about the safety of theophylline, β_2 -agonists (as maintenance drugs), and inhaled corticosteroids. A safe, inhaled nonsteroid antiinflamma-

tory agent deserves careful consideration as a first-line maintenance antiasthmatic therapy. The above studies show that nedocromil sodium not only reduces asthma symptoms and improves pulmonary function but decreases the incidence of breakthrough symptoms as measured by reductions in the use of rescue medication.

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*If systemic or inhaled steroid therapy is reduced, patients must be monitored carefully. Nedocromil sodium has not been shown to be able to substitute for the total dose of steroids.