A review of some recent clinical studies with nedocromil sodium

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Once efficacy and safety have been established in a clinical trial program, the next question to be addressed is how the new drug compares with medications currently available in the marketplace. Nedocromil sodium is an antiinflammatory agent intended for maintenance therapy in patients who have asthma of mild-to-moderate severity. This article briefly reviews recent studies, which have directly compared nedocromil sodium with inhaled corticosteroids, theophylline, β_2-agonists, and cromolyn sodium as maintenance therapy in asthma.

Abbreviations used
BDP: Beclomethasone dipropionate
FEV_1: Forced expiratory volume in 1 second
MDI: Metered dose inhaler
PEFR: Peak expiratory flow rate

INHALED CORTICOSTEROIDS

As presented earlier in this meeting, Bergmann et al.[1] have shown that 4 mg of nedocromil sodium and 100 μg beclomethasone diproprionate (BDP) both produced statistically significant improvements in asthma symptoms and overall asthma severity when given four times daily to adult asthmatic patients with moderate disease severity. In this study no statistically significant between-treatment differences were determined. Similar results were reported by Harper et al.,[2] who compared the two drugs in 17 adults with moderate asthma with use of a double-blind crossover protocol. Both nedocromil sodium (4 mg) and BDP (100 μg) given four times daily improved asthma control as shown by reduced symptom scores, increased pulmonary function, and less reliance on as-needed inhaled bronchodilators. Compared with baseline, both active treatments produced statistically significant improvements in daytime and nighttime asthma symptoms ($p < 0.001$, Fig. 1), morning tightness ($p < 0.001$), cough ($p < 0.001$), and morning and evening peak flow rates ($p < 0.05$). Pulmonary function measurements increased over baseline values with both nedocromil sodium and BDP but only reached statistical significance with nedocromil sodium. These changes occurred despite significant reductions in the use of as-needed β_2-agonist in both treatment groups, and the overall subjective severity assessment at the end of each treatment period decreased from "moderate" to "mild to moderate." The investigators concluded that "both inhaled nedocromil and beclomethasone give a significant improvement over baseline for all measured parameters of asthma . . . despite a simultaneous marked reduction in β-agonist inhaler use."

Hyperresponsiveness to a variety of stimuli is a hallmark of the asthmatic airway, and increased bronchial reactivity has been linked to airway inflammation in both normal and asthmatic subjects.[3-6] Bel et al.[7] compared the effects of four times daily treatment with the corticosteroid, BDP (100 μg), and the nonsteroid antiinflammatory agent, nedocromil sodium (4 mg), on airway responsiveness to inhaled methacholine in 25 non-steroid-dependent, nonatopic asthmatic subjects. Compared with placebo, the PC_{20} FEV_1 values increased with both antiinflammatory drugs during the 16-week treatment period. Maximal significant effects were observed at treatment week 8 ($p < 0.001$) for both nedocromil sodium and BDP. As reported for the other comparative studies, asthma symptoms improved in both active treatment groups and reached statistical significance at treatment week 4 for both nedocromil sodium ($p = 0.02$) and BDP ($p = 0.04$). The au-

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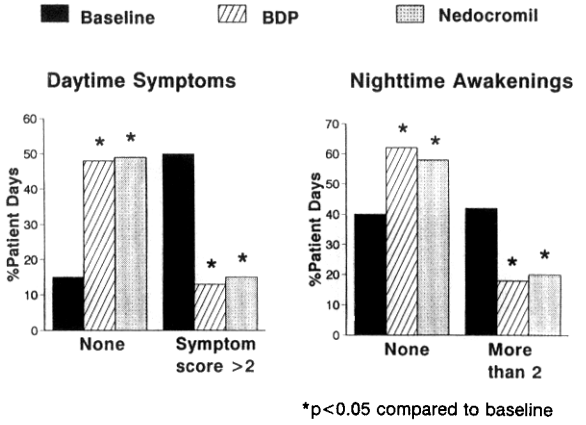

FIG. 1. Effects of inhaled BDP and inhaled nedocromil sodium on nocturnal awakenings and daytime asthma symptoms in adults with asthma not fully controlled by maintenance bronchodilator therapy. After a 2-week baseline period, 17 patients entered a double-blind crossover study consisting of two 8-week periods of four times daily treatment with either nedocromil sodium (4 mg) or BDP (100 μg). Both drugs produced statistically significant (*$p < 0.05$) improvements in daytime asthma symptom scores shown here as an increase in the percentage of patient days with no reported daytime symptoms and a decrease in the number of days with symptom scores greater than 2. Nedocromil sodium and BDP also produced statistically significant (*$p < 0.05$) improvements in sleep disturbances caused by asthma shown here *(right side)* as an increase in the percentage of patient days with no nocturnal awakenings caused by asthma and a decrease in the percentage of days with more than two awakenings reported. (Data from Harper GD, et al. Respir Med 1990;84:463-9.)

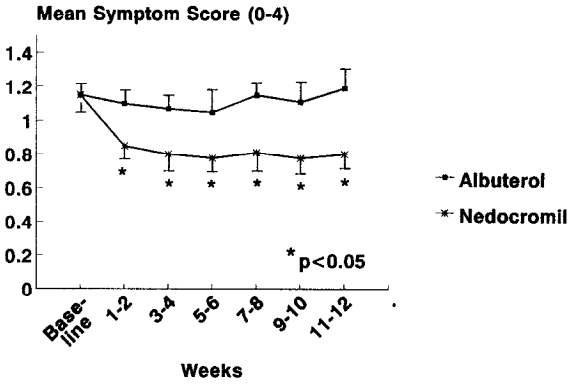

FIG. 2. Comparison of maintenance therapy with nedocromil sodium (*N*, 4 mg) and albuterol (*A*, 180 μg), four times daily, on nighttime asthma symptoms. Patients (*N*, 117; *A*, 118) whose asthma symptoms were not fully controlled with as-needed inhaled bronchodilators alone were randomly assigned to receive either nedocromil sodium or albuterol for 12 weeks. Mean symptom scores for nighttime asthma decreased throughout the trial for the albuterol group but remained stable in the nedocromil sodium group. All differences are statistically significant in favor of nedocromil sodium (*$p < 0.05$). Data in Figs. 2 and 3 were obtained from the same subjects. (Modified from Marcoux JP, et al. Ann Allergy 1992;68:110, with permission.)

thors concluded that long-term treatment with either nedocromil sodium or BDP decreased airway reactivity in nonatopic adults but suggested that these agents exert their effects through different mechanisms.

These head-to-head comparisons of 4 mg of nedocromil sodium and 100 μg of beclomethasone dipropionate administered four times daily did not specifically address adverse effects. According to the International Consensus Report on the Diagnosis and Management of Asthma,[8] nedocromil sodium is a novel antiinflammatory pyranoquinoline that "... is not associated with any significant adverse effects." However, the same document cautions that because of individual patient differences in drug metabolism, inhaled corticosteroids may be associated with systemic effects.

THEOPHYLLINE

Several controlled clinical studies have shown that nedocromil sodium (4 mg), twice daily and four times daily, was effective in patients who had been maintained on theophylline.[9-12] Crimi et al.[13] conducted a direct head-to-head comparative study of nedocromil sodium and theophylline in 105 asthmatic patients. During the 6-week treatment period, patients were randomly assigned to receive either nedocromil sodium (4 mg, four times daily) and placebo capsules, twice daily, or placebo aerosol four times daily and theophylline at a dose of 250 mg, twice daily, for the first 4 days followed by 350 mg, twice daily thereafter. All patients showed improvement in symptom scores (daytime asthma, nighttime asthma, morning tightness, and cough) and PEFRs; as-needed bronchodilator usage decreased with each treatment. No between-group differences were determined for efficacy variables. However, theophylline was associated with a statistically significant increase in reported adverse effects (Table I). A total of four patients receiving nedocromil sodium and 16 patients receiving theophylline ($p < 0.045$) reported gastric and abdominal pain, nausea, and vomiting; two patients using nedocromil sodium and 16 receiving theophylline ($p = 0.007$) reported agitation, headache, insomnia, and tremor. Twenty-six patients receiving

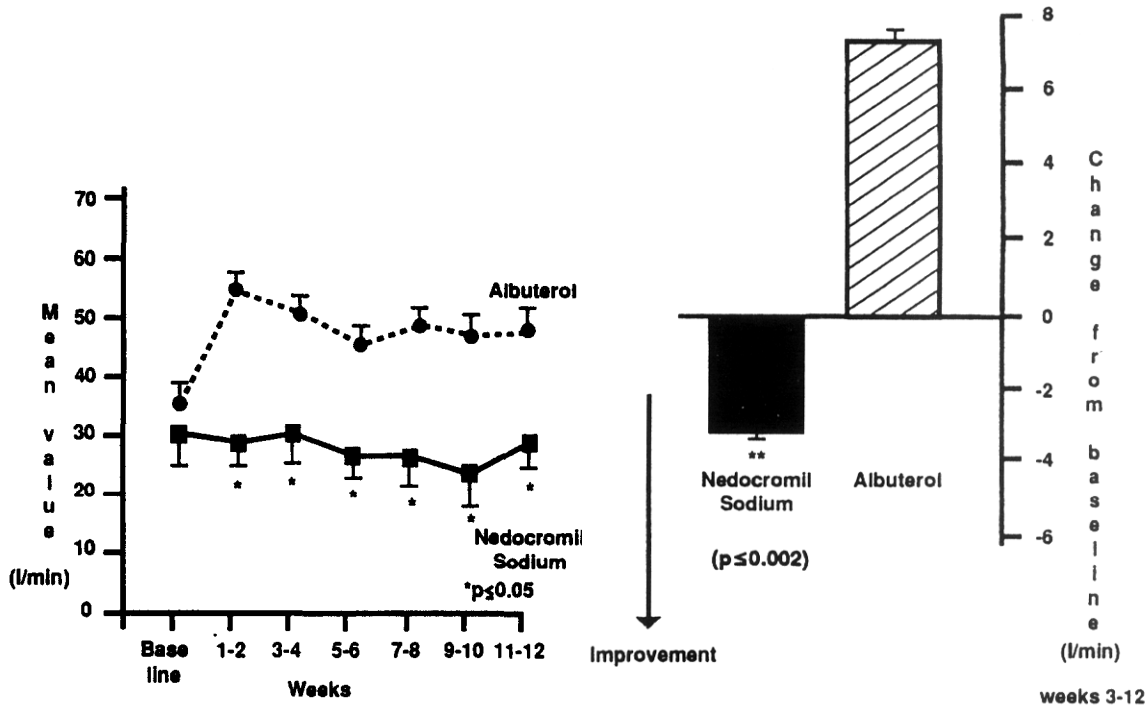

FIG. 3. The diurnal variation in PEFRs was determined from the mean diary card recordings of morning and evening PEFRs. Compared with the baseline period when the patients only used as-needed inhaled bronchodilators, diurnal variation increased with albuterol treatment and showed a slight but statistically significant decrease (**$p < 0.002$) with nedocromil sodium (bar graph on *right*). Between-group differences were statistically significant (*$p < 0.05$) throughout the trial favoring nedocromil sodium (graph on *left*). (Modified from Marcoux JP, et al. Ann Allergy 1992;68:110, with permisision.)

theophylline withdrew from treatment because of excessive variability in theophylline serum levels. The investigators concluded that nedocromil sodium MDI has a role in the safe management of asthmatic patients.

INHALED β_2-ADRENERGIC AGONISTS

Maintenance therapy with nedocromil sodium (4 mg, four times daily) was compared with maintenance therapy with inhaled albuterol (180 μg, four times daily) in a multicenter study involving 237 adult asthmatic patients who were poorly controlled on as-needed bronchodilators alone.[14]

Compared with baseline, patients treated with nedocromil sodium showed improvements in all symptoms (daytime asthma, nighttime asthma, morning tightness, and cough) and reduced bronchial reactivity as measured by the diurnal variation in PEFRs. Patients treated with albuterol had little change in their daytime asthma and morning tightness scores, and deterioration in asthma control was suggested by higher nighttime asthma scores (Fig. 2) and greater PEFR variability (Fig. 3). Between-group differences were statistically significant in favor of nedocromil for daytime asthma, nighttime asthma, morning tightness, and PEFR diurnal variability. Similar findings were reported in a crossover comparison of nedocromil sodium (4 mg, four times daily) and albuterol (200 μg, four times daily) in 32 atopic asthmatic patients.[15] Significant treatment differences ($p < 0.05$) favored nedocromil sodium for daytime asthma, nighttime asthma, wheeze, shortness of breath, morning PEFRs, overall asthma severity, and opinion of treatment effectiveness (patient: $p \leq 0.01$; clinician: $p \leq 0.05$). Nedocromil sodium also produced statistically significant reductions in bronchial responsiveness ($p < 0.02$) measured by propranolol inhalation challenge. Albuterol treatment resulted in increased responsiveness measured as a statistically significant reduction in the PC_{20} propranolol ($p = 0.003$ and $p = 0.02$, respectively, after 3 and 6 weeks of treatment).

Both national and international guidelines for the diagnosis and management of asthma now

TABLE I. Adverse effects of nedocromil sodium compared with theophylline*

Patients reporting	Nedocromil (n = 11; 26%)	Theophylline (n = 28; 45%)
Gastrointestinal/abdominal pain	2	11
Tremor	0	11
Nausea/vomiting	2	9
Headache	0	9
Agitation	2	5
Insomnia	0	5
Unpleasant taste	4	1
Tachycardia	1	2
Others	5	6
TOTAL	16	59

Modified from Crimi E, et al. Allergy Clin Immunol News Suppl 1991;1:328.

*Adverse events reported by asthmatic patients treated with either nedocromil sodium (n = 43) or theophylline (n = 62). After a 2-week baseline period, patients were randomly assigned to receive either nedocromil sodium aerosol (4 mg, four times daily) or theophylline (250 mg twice daily for the first 4 days; 350 mg twice daily thereafter) for 6 weeks. All patients showed improvements in symptoms scores and PEFRs, with no statistically significant between-group differences.

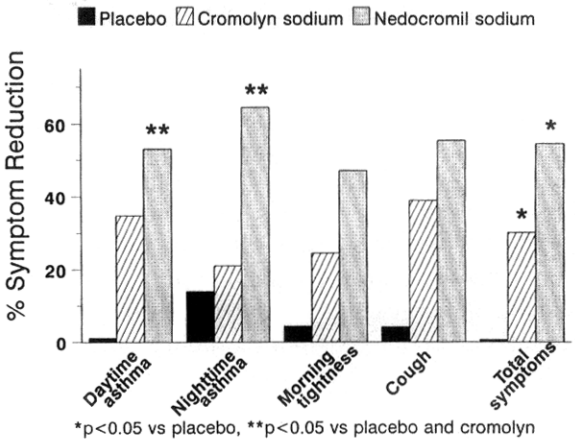

FIG. 4. Nedocromil sodium (4 mg) was compared with cromolyn sodium (2 mg) and placebo, four times daily, in the treatment of patients with moderately severe asthma maintained on inhaled corticosteroids. During a 4-week run-in period, the dose of inhaled corticosteroids was reduced by 50%. Patients treated with nedocromil sodium showed the greatest reductions in diary card symptom scores during the 6-week treatment period. Statistically significant (**$p < 0.05$) between-group differences favoring nedocromil sodium over cromolyn sodium and placebo were determined for daytime asthma and nighttime asthma symptoms and for nighttime as-needed bronchodilator use (not shown). Statistically significant (*$p < 0.05$) between-group differences favoring nedocromil sodium over placebo were determined for total symptom summary score as well as daytime and nighttime asthma symptoms and daytime and nighttime as-needed bronchodilator use (not shown). By the end of the treatment period, placebo-treated patients had increased their corticosteroid intake by 20%, a factor that may have confounded some of the statistical analyses. (Data on file, Fisons Pharmaceuticals.)

recommend that β_2-adrenergic agonists be used only for the relief of occasional breakthrough asthma symptoms and for acute severe exacerbations and not for the maintenance treatment of asthma.[8, 16] The results of these two studies support this recommendation

CROMOLYN SODIUM

Pretreatment with either nedocromil sodium or cromolyn sodium has been found to block the bronchospasm produced by both immunologic and nonimmunologic stimuli. While the two drugs are similar against antigen challenge or situations involving the participation of mast cell–related mechanisms, different results have been obtained in studies of "nonspecific" inhalational challenges.[17] Of 10 clinical pharmacology studies involving challenges with adenosine,[18-20] sulfur dioxide,[21, 22] bradykinin,[23] sodium metabisulfite,[24, 25] and cold air,[26, 27] two[23, 27] have shown the two drugs to be comparable and eight have shown nedocromil sodium to block the ensuing bronchoconstriction at a significantly lower dose than cromolyn sodium. No studies involving nonimmunologic inhalational challenges have shown cromolyn sodium to block bronchospasm at a significantly lower dose than nedocromil sodium. Therapeutic studies to assess the clinical relevance of these findings have not been carried out.

Two multicenter, placebo-controlled comparisons of nedocromil sodium and cromolyn sodium have been conducted. The results of one such study in mild-to-moderate allergic asthmatic patients were reported earlier.[28] A 6-week multicenter study of nedocromil sodium (4 mg), cromolyn sodium (2 mg), and placebo four times daily involved 132 moderately severe asthma patients who had previously been maintained on inhaled β_2-agonists and inhaled corticosteroids.[29] Approximately 66% of these patients were nonallergic asthmatics. Before the start of the treatment period, the dose of inhaled corticosteroid was reduced by up to 50% to produce a statistically and clinically important increase in asthma symptoms.

Compared with placebo, both cromolyn sodium

and nedocromil sodium showed beneficial effects on symptoms (Fig. 3). Statistically significant ($p < 0.05$) between-group differences favored nedocromil sodium over cromolyn sodium for reductions in daytime asthma symptoms, nighttime asthma symptoms, and nighttime as-needed bronchodilator use. In this study no statistically significant between-group differences were determined favoring cromolyn sodium over nedocromil sodium. The presently available data on the relative efficacies of nedocromil sodium and cromolyn sodium are inconclusive.

SUMMARY

Clinical trials reported in these proceedings have shown that nedocromil sodium is an effective antiasthmatic agent. Preclinical studies and the results of the worldwide clinical study program have also shown that nedocromil sodium is a very safe drug.

Although it is anticipated that a new drug will perform better than placebo, perhaps a more critical assessment of efficacy is how the drug compares with other currently used agents. Nedocromil sodium has been directly compared with all of the antiasthmatic medications currently used in the United States including theophylline, β-adrenergic agents, inhaled corticosteroids, and cromolyn sodium. The results of these studies indicate that for the treatment of mild-to-moderate asthma, nedocromil sodium provides a safe and clinically effective antiinflammatory addition to the physician's armamentarium of antiasthma drugs.

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