

Asthma symptoms and airway hyperresponsiveness are lower during treatment with nedocromil sodium than during treatment with regular inhaled albuterol

Stephen I. Wasserman, MD, Clifton T. Furukawa, MD,
Stuart I. Henochowicz, MD, J. Paul Marcoux, MD, Bruce M. Prenner, MD,
Steven R. Findlay, MD, Garry N. Gross, MD, Leonard D. Hudson, MD,
Debra J. Myers, MD, and Paul Steinberg, MD *San Diego, Calif.,
Rochester and Minneapolis, Minn., and Seattle, Wash.*

In a double-blind, double-dummy, multicenter study, 212 patients with asthma whose symptoms were not controlled by as-needed use of inhaled bronchodilators were randomized to receive either 4 mg of nedocromil sodium or 180 µg of albuterol four times daily for 12 weeks. Asthma symptom scores (daytime asthma, nighttime asthma, morning chest tightness, and cough) and peak expiratory flow rate were recorded daily on diary cards. Bronchial hyperresponsiveness was assessed by changes in diurnal variation in peak expiratory flow rate and by methacholine inhalation challenge. Statistically significant differences were found between groups favoring nedocromil sodium for relief of day and nighttime asthma and morning chest tightness. Patients treated with nedocromil sodium also had significantly lower diurnal variation in peak expiratory flow rate compared with patients treated with albuterol. Compared with patients treated with albuterol, patients treated with nedocromil sodium showed a greater improvement in cough and a decreased sensitivity to methacholine challenge. Patients in both groups reduced their as-needed albuterol use. Regular treatment with nedocromil sodium therefore led to greater asthma symptom control and reduced bronchial responsiveness compared with regular treatment with albuterol. The study also showed that more frequent use of a β_2 -agonist (for symptom relief or not) did not improve asthma control. Both drugs were well tolerated. (J ALLERGY CLIN IMMUNOL 1995;95:541-7.)

Key words: Nedocromil sodium, antiinflammatory, albuterol, asthma

Asthma management is under scrutiny for several reasons; most notable are the increasing trends in morbidity and mortality rates and the controversial studies recently published implicat-

From the Division of Allergy, Department of Medicine, University of California San Diego Medical Center; the Department of Internal Medicine/Allergic Diseases, The Mayo Clinic, Rochester; Pulmonary and Critical Care Medicine, Harborview Medical Center, Seattle; and Hennepin County Medical Center, Minneapolis.

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Reprint requests: Stephen Wasserman, MD, Department of Medicine, University of California, San Diego Medical Center, 402 W. Dickinson St., San Diego, CA 92103-9981.

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Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
IRT:	Immediate-release theophylline
PD ₂₀ :	Provocative dose (of methacholine) causing a 20% fall in FEV ₁
PEFR:	Peak expiratory flow rate
p.r.n.:	As needed

ing regular inhaled β_2 -bronchodilator use in the deterioration of symptom control.^{1,2} These reports suggested the need for a re-evaluation of regular therapy with inhaled β_2 -agonist bronchodilators. The International Guidelines, published by the National Heart Lung and Blood Institute,³ have acknowledged the increasing evidence that airway

inflammation is present in patients, even when asthma is mild. Thus antiinflammatory therapy should be available to all patients who require more than occasional bronchodilator therapy.³

Nedocromil sodium (Tilade) is a pyranoquinoline derivative, a new chemical entity developed for the treatment of asthma. Laboratory studies have demonstrated that it prevents the release of inflammatory, chemotactic, and smooth muscle-contracting mediators from a variety of cells implicated in the pathogenesis of asthma.⁴ Clinical trials⁵⁻⁷ have shown that therapy with nedocromil sodium reduces asthma symptoms in both atopic and nonatopic patients, and long-term treatment decreases nonspecific airway reactivity, which is believed to reflect asthmatic airway inflammation.⁸⁻¹⁰

In the light of current thinking on treatment strategies for optimal patient management, this study was designed to compare an antiinflammatory agent with regular inhaled bronchodilator therapy for symptom control and changes in bronchial responsiveness. The beneficial effects of instituting regular therapy with either nedocromil sodium (4 mg) or albuterol (180 μ g) four times daily were studied in patients whose asthma symptoms were not well controlled with as-needed (p.r.n.) bronchodilator treatment.

METHODS

Protocol

The study used a multicenter, randomized, double-blind, double-dummy, parallel group design. Patients were assigned by means of a randomized code to receive nedocromil sodium (2×2 mg/actuation, four times daily) plus placebo albuterol, or albuterol (2×90 μ g/actuation, four times daily) plus placebo nedocromil sodium. A 2-week baseline period was followed by 12 weeks of study treatments. Six clinic visits were scheduled for each patient: a prebaseline screening visit, an end-of-baseline visit, and visits after 2, 4, 8, and 12 weeks of study treatments. All patients provided written informed consent, and institutional review board approval was obtained at each center.

Patients recorded the severity of daytime asthma, nighttime asthma, morning chest tightness, and cough with a 5-point severity scale (0 = none to 4 = severe) and morning and evening peak expiratory flow rates (PEFRs) on a daily diary card. PEFR was always measured with a mini-Wright peak flow meter (Ferraris Medical, Inc., Holland, N.Y.) before study medication was administered, and the highest of three readings was recorded.

The use of all medications (whether prescription, over-the-counter, emergency, or study drug) was recorded daily by the patient. The primary rescue medication was the inhaled β_2 -agonist, albuterol. Patients were also allowed to use immediate-release theophylline (IRT) up to every 6

hours for relief of symptoms that were not responsive to inhaled albuterol. Both medications were to be used on a p.r.n. basis. Study treatments and concomitant medication were weighed before they were dispensed (IRT tablets were counted). Used supplies were collected and reweighed at subsequent clinic visits when new supplies were dispensed. At all clinic visits patients demonstrated their inhaler technique and were reminded to use concomitant medication on a p.r.n. basis.

Bronchial responsiveness was assessed at the second and final clinic visits by methacholine inhalation challenge and was expressed as the provocative dose of methacholine causing a 20% fall in forced expiratory volume in 1 second (FEV_1) (PD_{20}).¹¹ FEV_1 was measured before and 3 minutes after five breaths of saline diluent (DeVilbiss 646 nebulizer; DeVilbiss Health Care, Inc., Somerset, Pa.) and 3 minutes after five breaths of each methacholine inhalation (doubling concentrations from 0.075 to 10.0 mg/ml, 15 and 25 mg/ml) until a 20% fall in FEV_1 from the saline baseline occurred or the maximum concentration had been given. Albuterol was withheld for 6 hours before measurement. PD_{20} values were obtained by linear interpolation between the final two points on a log concentration/percent fall in FEV_1 curve.

Patients were screened for a diagnosis of asthma, a record of 15% or greater reversibility in FEV_1 after a standard dose of inhaled β_2 -bronchodilator, and current symptomatic use of an inhaled bronchodilator with or without IRT. Patients receiving immunotherapy were allowed to take part in the study, providing that no change in dose occurred. Patients had to show a minimum level of symptoms (score of at least 2 for an individual symptom on 7 of the 14 baseline days) plus a positive response to methacholine challenge (defined as a 20% fall in FEV_1 from baseline at 5 mg/ml or less of methacholine) to be eligible for the treatment phase.

Pulmonary function (FEV_1 , forced vital capacity, forced expiratory flow, and PEFR) was measured at each clinic visit. IRT was withheld for 12 hours and albuterol for 6 hours before measurement. The physician also evaluated the patient's asthma severity with a 5-point scale (0 = no symptoms to 4 = very severe symptoms). At the final visit, patients and physicians rated the overall effectiveness of study treatment with a 5-point scale (1 = very effective to 5 = made asthma worse).

During clinic visits, patients were questioned about adverse experiences, irrespective of their association with a study drug. During the screening and final clinic visits, blood and urine samples were obtained for complete blood counts, blood chemistry, and routine urinalysis.

Statistical analysis

Fisher's exact and Mantel-Haenszel tests (for binary type variables, e.g., sex), two-sample *t* tests, and two-way main effects (clinic by treatment) analysis of variance (for continuous type variables, e.g., age), and the Wilcoxon rank sum test and Cochran-Mantel-Haenszel

TABLE I. Patient characteristics*

	Nedocromil sodium group	Albuterol group	<i>p</i> Value
Number	117	118	
Age (yr)	33.4 (12-69)	33.7 (12-69)	0.89
Sex (M/F)	91/26	94/24	0.72
Duration of asthma (yr)	19.2 (1-65)	20.7 (2-60)	0.47
Asthma severity	2.03	2.03	0.98
	13/89/14/1†	8/99/11/0†	
PD ₂₀ (mg/ml)	2.41 (0.42)	2.14 (0.40)	0.57
Albuterol (actuations/day)	3.92 (0.15-12.2)	4.35 (0.29-12.8)	0.26
FEV ₁ (L)	2.93 (1.09-5.11)	2.86 (1.07-5.40)	0.55

*Data expressed as mean (range) or mean (SEM).

†Mild/moderate/severe/very severe.

analysis¹² (for ordinal data, e.g., disease assessment) were used to assess pretrial comparability between the two treatment groups. Tests were conducted within and across centers, respectively.

The primary between-treatment analysis used the method of Koch et al.¹³ for stratified, randomized covariance analysis of ranks and was based on changes from baseline. Because cough is not uniformly present in patients with asthma, only patients with a mean baseline score 0.5 or greater, (nedocromil sodium, *n* = 76; albuterol, *n* = 74) were included in the analysis of cough.

Diary card data were analyzed as biweekly means over the final 10 weeks of treatment (weeks 3 to 12). During the treatment phase, Fisher's exact test was used across centers to compare reports by patients of adverse effects.

Statistical significance was determined at the 5% level.

RESULTS

Patients

Ten centers screened 321 patients with asthma for entry into the study: 237 patients were randomized to treatment. One patient from each treatment group was excluded because of failure to receive treatment; hence, there were 117 and 118 patients in the nedocromil sodium and albuterol groups, respectively. The patients had mainly mild to moderate atopic and nonatopic asthma and were between the ages of 12 and 69 years (Table I). There were no significant differences in admission characteristics and baseline variables between the two treatment groups.

Twenty-five patients (9 in the nedocromil sodium group and 16 in the albuterol group) withdrew during the treatment period. The most common reasons for withdrawal were intercurrent illness and intolerance to or lack of effectiveness of study medication (Table II).

TABLE II. Reasons for patient withdrawal from the study

Reason	Nedocromil sodium group	Albuterol group
Intolerance to study drug	3	2
Intercurrent illness	1	3
Study medication ineffective	1	3
Moved outside the study area	1	2
Protocol violation	1	1
Adverse event	1	1
Noncompliance	0	1
Hospitalization	0	1
Lost to follow-up	0	1
Other	1	1
Total	9	16

Efficacy

Statistically significant differences between the two treatment groups were noted as early as weeks 1 to 2 for several diary card variables (Fig. 1).

Patients treated with nedocromil sodium had lower daytime symptom scores throughout the study, with statistically significant differences between the treatment groups during weeks 3 to 4, 7 to 8, and 11 to 12 (Fig. 1, *A*). During the final 10 weeks of the study, patients in the nedocromil sodium group had a significantly lower mean daytime asthma symptom score compared with patients receiving regular albuterol. The same pattern was observed for nighttime asthma (final 10 weeks, *p* < 0.001), with statistically significant differences in favor of nedocromil sodium treatment for all 6 biweekly intervals (Fig. 1, *B*).

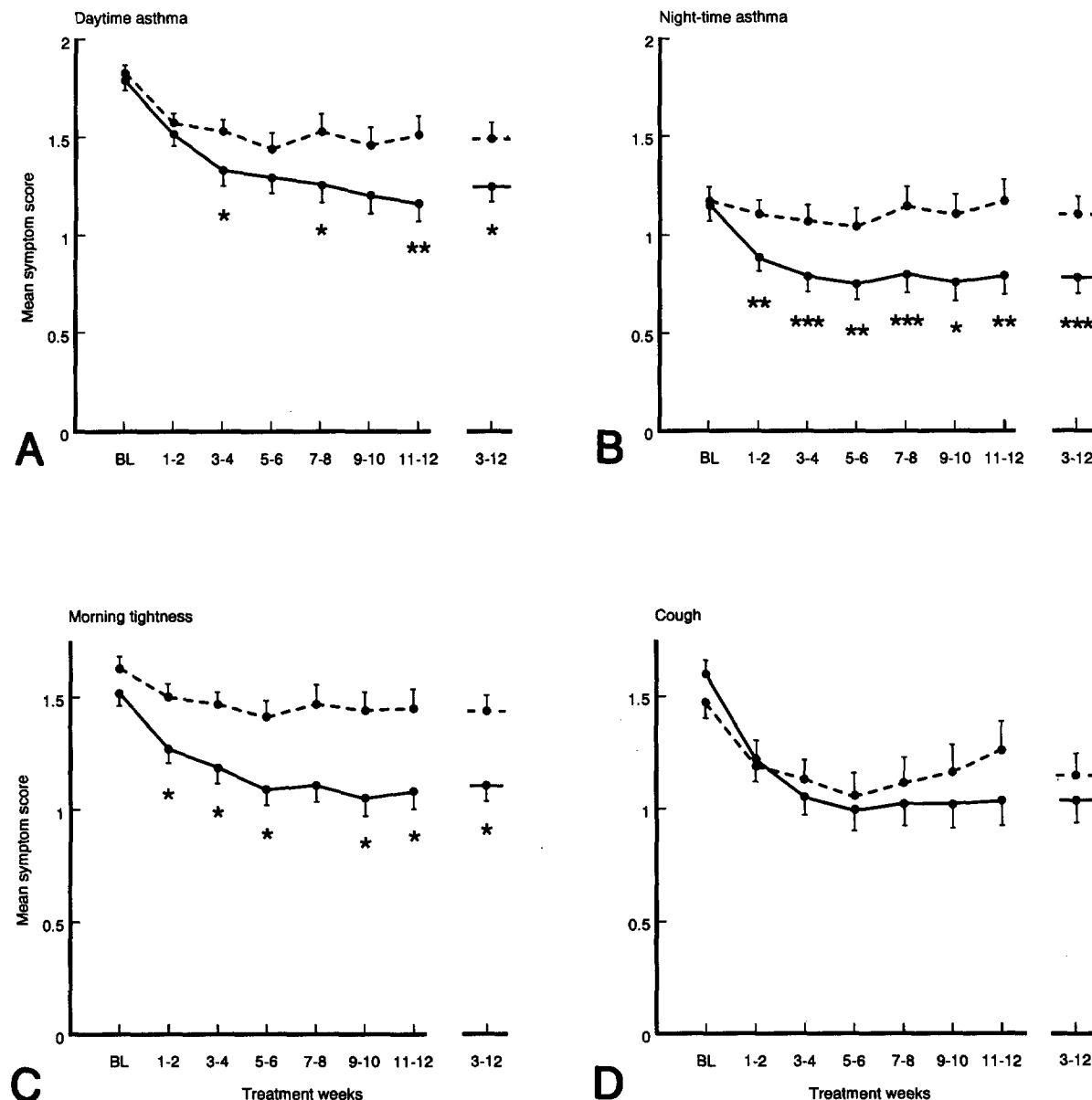


FIG. 1. Mean asthma symptom scores ($\pm$ SEM) during 12 weeks of treatment with nedocromil sodium (solid line) and albuterol (dashed line). Mean symptom scores over the final 10 weeks of treatment (weeks 3 to 12) are also shown. BL, Baseline. Significant between-treatment differences have been marked: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Morning chest tightness was statistically significantly improved in the nedocromil sodium treatment group for all except one biweekly analysis and for the final 10 weeks compared with that of patients treated with regular albuterol (Fig. 1, C).

Treatment decreased cough severity in both groups. Although cough improved to a greater extent in the nedocromil sodium-treated group, there were no significant treatment differences (Fig. 1, D).

There were no statistically significant differences between the treatments for morning and evening PEFr (Fig. 2, A and B). Morning PEFr improved to a greater extent in the nedocromil sodium group than in the albuterol group. Changes in evening PEFrs were comparable between the two treatment groups. Diurnal variation in peak flow showed a significant difference ($p < 0.05$) in favor of nedocromil sodium throughout the treatment period (Fig. 2, C).

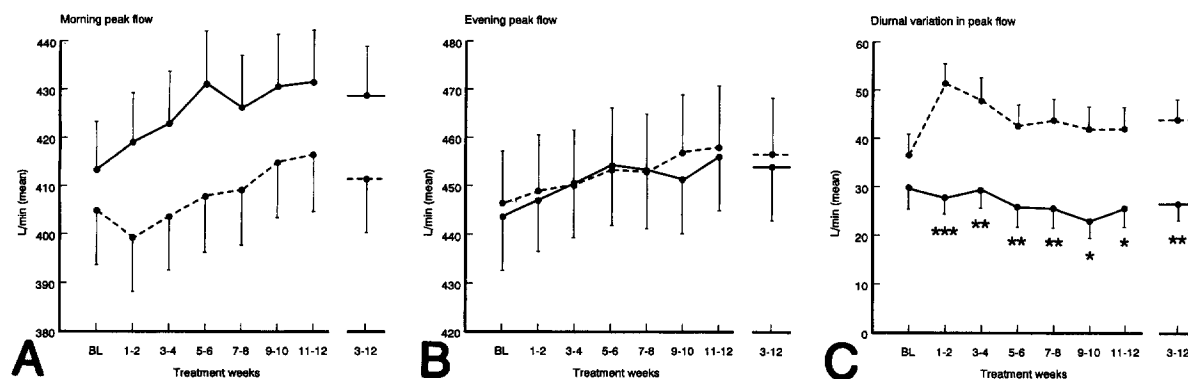


FIG. 2. Mean morning, evening, and diurnal variation in PEFR ($\pm$ SEM) during 12 weeks of treatment with nedocromil sodium (solid line) and albuterol (dashed line). Mean values over the final 10 weeks of treatment (weeks 3 to 12) are also shown. BL, Baseline. Significant between-treatment differences have been marked: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

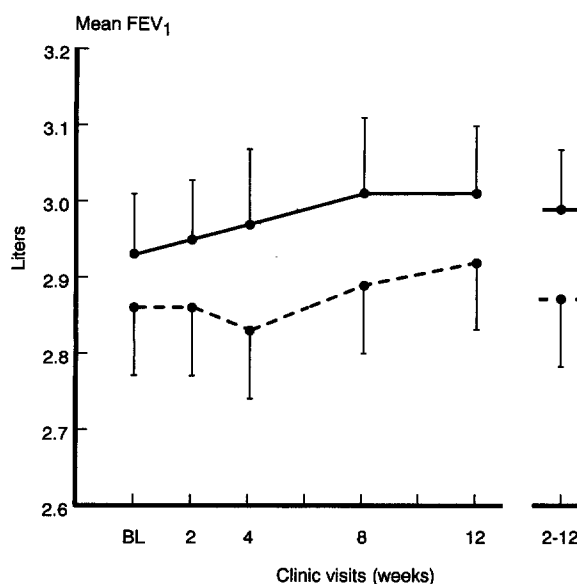


FIG. 3. Mean clinic measurement of FEV₁ ($\pm$ SEM) during 12 weeks of treatment with nedocromil sodium (solid line) and albuterol (dashed line). Mean FEV₁ over the final four clinic visits (10 weeks of treatment) is also shown. BL, Baseline. There were no significant between-treatment differences.

Compared with baseline values, patients receiving nedocromil sodium demonstrated an 11% decrease in diurnal variation compared with a 20% increase in the patients treated with albuterol for the final 10 weeks. The difference between treatments was statistically significantly ($p < 0.01$) in favor of nedocromil sodium.

Methacholine sensitivity improved in both treatment groups, and to a greater extent in the nedocromil sodium group. Mean PD₂₀ values $\pm$ SEM during week 12 were 4.85 ± 0.91 mg/ml and

3.32 ± 0.56 mg/ml for nedocromil sodium and albuterol, respectively. No between-group differences were observed. Clinic pulmonary function improved during the study, but there were no statistically significant differences between the two treatments (e.g., FEV₁, Fig. 3).

No statistically significant differences were found in the amount of p.r.n. albuterol or IRT therapy required by either treatment group. Patients in both treatment groups required a daily average of 1.5 inhalations of albuterol for

TABLE III. Adverse events probably related to test treatment use

Event	Nedocromil sodium group		Albuterol group	
	No.	%	No.	%
Headache	6	5	2	2
Unpleasant taste	6	5	2	2
Pharyngitis	4	3	2	2
Bronchospasm	2	2	2	2
Chest pain	2	2	2	2
Coughing	3	3	1	1
Bronchospasm aggravated	0		2	2
Other	5	4	8	7
Total	28		21	

control of breakthrough symptoms. During the baseline, mean p.r.n. albuterol use was 3.9 and 4.4 inhalations per day for the nedocromil sodium and albuterol groups, respectively. Both treatment groups therefore reduced p.r.n. albuterol use by approximately 60% (nedocromil sodium, 62%; albuterol, 66%). Patients in the nedocromil sodium group, however, demonstrated better asthma symptom control.

Both groups recorded improvements in physician assessment of asthma severity (15% and 7% reduction in severity score in the nedocromil sodium and albuterol groups, respectively). The difference between the two groups was not statistically significant.

In the opinion of the physicians, 73% of the patients treated with nedocromil sodium responded to treatment, compared with 68% of the patients treated with albuterol. In the opinion of the patients, 78% who were treated with nedocromil sodium responded to treatment compared with 77% of those treated with albuterol. Opinions of drug efficacy were not significantly different between treatments (physicians, $p = 0.94$; patients, $p = 0.56$).

Tolerability

Table III summarizes the list of adverse events judged to be probably related to test treatment. In total, 40 patients reported at least one adverse event during the course of the study: 23 in the nedocromil sodium group and 17 in the albuterol group. Headache and unpleasant taste were the two most common adverse events. There were no significant differences between the two treatment groups in the reporting of events.

The results of the laboratory data indicated that the two groups were comparable for almost all variables analyzed. Both drugs proved to be well tolerated throughout the course of the trial.

DISCUSSION

This study has compared the effects of regular, four-times-daily therapy with 4 mg of nedocromil sodium and 180 μ g of the β_2 -agonist albuterol in patients with mild to moderate asthma not fully controlled by p.r.n. use of bronchodilators.

The results show that regular treatment with nedocromil sodium provides a greater level of asthma symptom control than regular treatment with albuterol: patients treated with nedocromil sodium showed statistically significant improvements in daytime and nighttime asthma and morning chest tightness and a modest improvement in diurnal variation of PEFR compared with patients treated with albuterol. Differences in asthma symptom control were evident from the first period of evaluation. Although cough did not improve to the same extent, other studies—particularly those in which patients received maintenance bronchodilator therapy^{6,7}—have shown very positive effects of nedocromil sodium on asthmatic cough.

The significant improvements in symptom severity and diurnal variation in PEFR in the nedocromil sodium group were achieved despite a 60% reduction in p.r.n. use of albuterol. Because neither p.r.n. use of albuterol nor theophylline use differed between treatment groups, the regular use of the β_2 -agonist (whether needed for symptom relief or not) did not provide an improvement in asthma control comparable to that provided by regular use of an antiinflammatory agent. It also led to an increase in diurnal PEFR variability. These findings support results from previous studies comparing p.r.n. use with regular use of β_2 -agonists, which suggest that a regular regimen offers no advantages and may be detrimental.^{1, 14, 15}

Contrary to previous research on β_2 -agonists,¹⁶⁻¹⁸ the patients receiving albuterol regularly showed improved methacholine sensitivity. Our results therefore do not appear to support the conclusion that regular use of β_2 -adrenoceptor agonists necessarily increases airway responsiveness. We would caution against this interpretation, however, because the bronchodilator activity of albuterol (methacholine challenge was undertaken a minimum of 6 hours after the last dose of albuterol) may have influenced PD₂₀ values. Vathenen et al.¹⁹ have shown that 6 hours after a final terbutaline dose, which had been taken four times

daily for 2 weeks, the PC₂₀ remained artificially high when compared with assessments made 12 hours and even 23 hours after the final dose.

The results from this study indicate that the antiinflammatory agent nedocromil sodium is more effective than regular use of albuterol for asthma symptom control. The clinical significance of these results has an impact on recent concerns regarding the possible relationship between increased use of β_2 -agonists and rising asthma morbidity and mortality rates.

Many specialists in the field of asthma support the need for physicians to revise their current prescribing habits. With regular use of antiinflammatory agents, current guidelines recommend that use of β_2 -agonists should be reduced to an infrequent (p.r.n.) therapy regimen, thereby serving as symptom relievers or rescue therapy.³ Our observations indicate that the regular use of a safe antiinflammatory agent, such as nedocromil sodium, can significantly reduce both asthma symptoms and bronchial hyperresponsiveness while simultaneously decreasing total daily load of inhaled β_2 -bronchodilator.

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