

Section V: Clinical Effects of Nedocromil Sodium

Clinical effects of nedocromil sodium on allergen-related mechanisms

Eugene R. Bleecker, MD, Pamela L. Mason, BS, and Wendy C. Moore, MD
Baltimore, Md.

Many studies have demonstrated the ability of nedocromil sodium to block the acute response to allergen in persons who are sensitive to allergen. One study with subjects sensitive to ragweed showed a significant protective effect after a single 4 mg dose of nedocromil sodium, with no further protection achieved at higher doses. Numerous studies have also shown the ability of the drug to reduce or abolish the late asthmatic response in sensitive subjects when it was given before allergen challenge. Nedocromil sodium has also been shown to prevent the subsequent development of bronchial hyperresponsiveness. In addition, nedocromil sodium prevented the late asthmatic response when given after allergen challenge and an intact early response. These findings suggest that nedocromil sodium may be preventing the inflammatory events initiated by mast cell mediator and cytokine release. (J Allergy Clin Immunol 1996;98:S118-23.)

Key words: Allergen challenge, nedocromil sodium, ragweed antigen

Nedocromil sodium is an effective antiasthma drug with the ability to inhibit activation and mediator release from a wide range of cells involved in the inflammatory processes underlying asthma.^{1,2} Nedocromil sodium has also been shown to inhibit acute bronchospasm after subjects have been exposed to a variety of stimuli including allergen, exercise, sulfur dioxide, cold air, fog, and substance P. This review will examine the clinical effects of nedocromil sodium on responses to allergen exposure in the laboratory. In addition to reviewing the extensive literature on clinical allergen challenge, this article will focus in more detail on several studies of the effects of nedocromil sodium on allergen-induced responses.

Allergen challenge in the laboratory is a useful and clinically relevant tool for investigating pharmacologic effects. Short-term studies include single-dose allergen challenge and allergen dose-response protocols in which the dose of allergen is increased and the pharmacologically induced shift in that response can be measured. The approach is

similar to the standard methodology used for methacholine and histamine bronchial challenges. The single-dose allergen challenge, however, does not permit determination of the degree of protection afforded by a therapeutic intervention. In longer term clinical trials, allergen exposure can be used to assess the therapeutic effects of chronic drug therapy on bronchial hyperresponsiveness to allergen. However, one must weigh the drawback of potential sensitization resulting from repeated allergen exposure, especially in the unprotected placebo group. More recently, there has been increased interest in studying the delayed bronchospastic changes and other inflammatory responses to allergen exposure. The delayed response is thought to mimic some of the subacute and chronic changes that occur in the airways of patients with asthma. In addition, changes in nonspecific airways hyperresponsiveness to methacholine and histamine after allergen exposure can also be studied. Delayed response studies are affected by the ability of the intervention to reduce the acute response to allergen. If an agent does not alter the acute response, the challenge can easily be matched to a predose or placebo allergen exposure. If the intervention alters the acute response, there are two possible approaches: either to use the same dose of antigen that was used in the control challenge or to vary the dose of allergen to reproduce the acute

From the Division of Pulmonary Medicine, University of Maryland School of Medicine.

Reprint requests: Eugene R. Bleecker, MD, Division of Pulmonary Medicine, University of Maryland School of Medicine, 10 South Pine St., Baltimore, MD 21210.

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decrease in lung function. Allergen exposure can also be coupled with investigative bronchoscopy and segmental allergen challenge to measure physiologic events, mediator release, and cellular responses in bronchoalveolar fluid or bronchial biopsy material to determine the ability of an intervention to alter airway inflammatory responses.³

The advantage of the laboratory allergen exposure model is that this test can be performed in humans and is not an animal "model" or an *in vitro* cellular system. The type of allergen that is used is often relevant to clinical disease and the responses that are measured, including pulmonary function and other inflammatory changes, should be relevant to the pathophysiologic processes in asthma. However, in the laboratory the dose and deposition of allergen may differ dramatically from "usual" environmental exposure. If repetitive allergen exposures are performed, there is also the potential of adverse side effects in experimental subjects that potentially could sensitize them to allergen and worsen their disease.

The importance of laboratory allergen exposure as a model of asthma depends on two basic hypotheses. The first hypothesis is that natural or environmental allergen exposure is an important cause of acute asthma symptoms and subacute and chronic bronchial inflammation that increases airway responsiveness and asthma severity. The second hypothesis is that laboratory allergen exposure is a relevant system for investigating pathophysiologic mechanisms in asthma and therapeutic responses in humans. Another important question is whether the results of laboratory allergen exposure accurately reflect clinical asthmatic responses and predict the clinical efficacy of pharmacologic interventions. While these are relevant questions, responses to allergen have proved to be a useful model in the initial evaluation of new pharmacologic agents, have provided important information about dose-response relationships, and are a useful mechanism for studying inflammatory changes in the lower airways in asthma.

ACUTE RESPONSES

A large number of studies have demonstrated the ability of nedocromil sodium to partially or completely block the acute response to allergen in persons sensitive to allergen.⁴⁻¹³ The magnitude of this response is illustrated in the following study, which will be presented in detail. The purpose of this study was to investigate the effects of 4 and 8 mg doses of nedocromil sodium on the acute bronchoconstrictor response to inhaled ragweed antigen to evaluate its protective effects on bron-

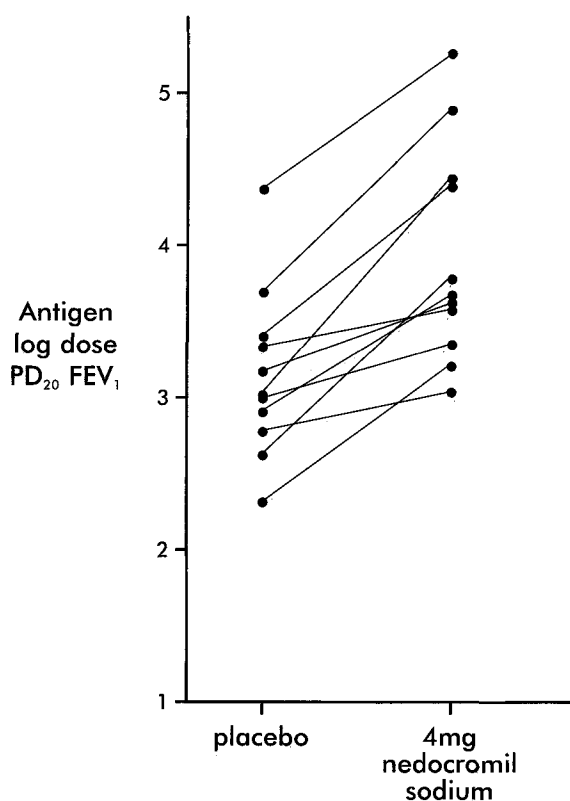


FIG. 1. Protective effects of nedocromil sodium 4 mg on the log dose of antigen required to produce a 20% fall in FEV₁. Each of the 11 patients with asthma required an increase in the cumulative ragweed antigen dose to produce PD₂₀.

chomotor tone and to determine whether there was a dose-response relationship.¹⁴ This study was a randomized, double-blind, placebo-controlled trial of 11 subjects with asymptomatic allergic asthma who ranged in age from 19 to 46 years. These subjects were known to respond to inhaled ragweed antigen. In brief, the study consisted of a control day, when baseline ragweed challenge was performed, followed by 3 double-blind challenge days, 5 to 10 days apart, in which ragweed antigen challenge was performed 30 minutes after the subjects took a single dose of either nedocromil sodium (4 mg or 8 mg) or placebo. Challenges were performed at the same time of day. Each study day fell outside the season for the allergens to which the patient was sensitive. Using standard techniques, antigen challenge was performed with use of incremental doses of ragweed antigen administered every 10 minutes until FEV₁ fell at least 20%. Baseline FEV₁ before and after drug administration did not differ significantly between the study days. The 4 mg dose of nedocromil sodium shifted the antigen response in each of the 11

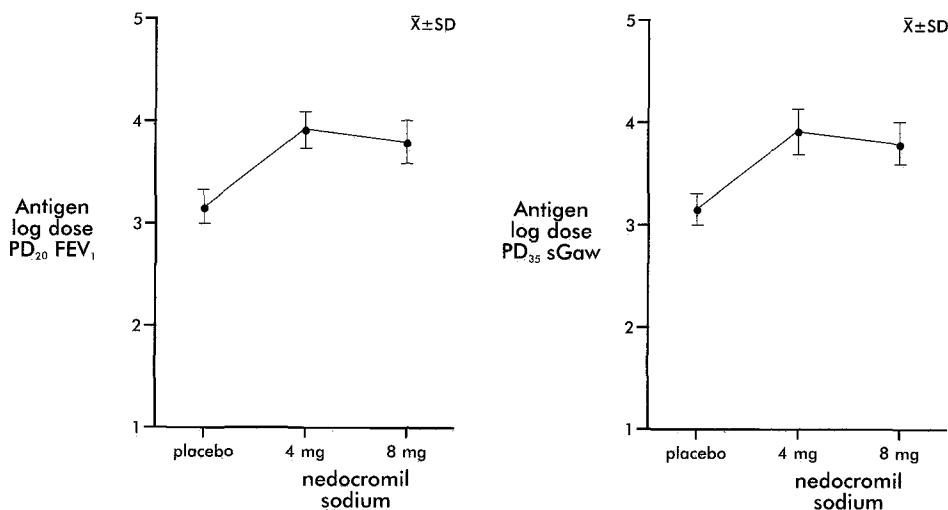


FIG. 2. Geometric mean data show the log dose of antigen that produced a 20% fall in FEV₁ in 11 patients with asthma. Whereas pretreatment with nedocromil sodium at both the 4 mg and 8 mg doses decreased antigen responsiveness, there was no incremental effect at the higher dose.

subjects with allergic asthma (Fig. 1). The geometric mean $\pm$ SD for the log PD₂₀ was 3.16 ± 0.56 on the placebo day, 3.95 ± 0.07 on the 4 mg dose day, and 3.84 ± 0.7 on the 8 mg dose day (Fig. 2). The log provocative dose causing a 35% increase in specific airways resistance was 3.10 ± 0.49 for placebo, 3.93 ± 0.71 for the 4 mg dose of nedocromil sodium, and 3.79 ± 0.66 for the 8 mg dose of nedocromil sodium. Statistical analysis indicated that the two doses of nedocromil sodium were significantly different from placebo ($p < 0.01$) but were not significantly different from one another. The mean shift in allergen response as measured by the PD₂₀ was approximately sevenfold, thus supporting the ability of nedocromil sodium to alter acute allergen responses. These shifts are greater than those reported for theophylline and the newer antileukotriene class of therapies.^{15, 16}

LONG-TERM THERAPEUTIC RESPONSES

The usual approach to assessing the effects of an antiasthma therapy on bronchial responsiveness is to evaluate its effects against nonspecific, direct-acting agents such as histamine or methacholine rather than against allergen. However, Orefice et al.¹⁷ studied the effects of chronic therapy with nedocromil sodium on airway hyperresponsiveness to allergen and the late asthmatic reaction. They showed that 4 mg of nedocromil sodium significantly protected against delayed reactions to house dust mite allergen exposure in 38 subjects. Cro-

molyn sodium, an agent with antiallergic properties similar to those of nedocromil sodium, has also been evaluated. The ability of cromolyn sodium to alter allergen responses during a natural environmental exposure to ragweed was studied in 11 subjects with allergic asthma.¹⁸ The subjects were randomly assigned to receive either placebo or cromolyn sodium during the late summer and early fall ragweed season. In this study, cromolyn sodium significantly and progressively decreased the response to inhaled allergen, whereas the placebo group showed worsening of their response with increased sensitivity to inhaled ragweed allergen (Fig. 3). These responses were associated with improved symptom control in the cromolyn sodium group. However, neither the placebo nor the cromolyn sodium group had any change in responsiveness to inhaled methacholine. The lack of effect of cromolyn sodium is in contrast to that of nedocromil sodium, which decreases both allergen and methacholine responsiveness.¹⁹

DELAYED RESPONSES TO INHALED ALLERGEN

Nedocromil sodium shows significant effects in reducing or abolishing the delayed response to inhaled allergen in asthma, as well as reducing the associated increase in nonspecific airway responsiveness.¹⁹⁻³⁰ This effect on the delayed reaction is important for several reasons; it implies that nedocromil sodium can reduce some of the long-term events that are associated with immunologic

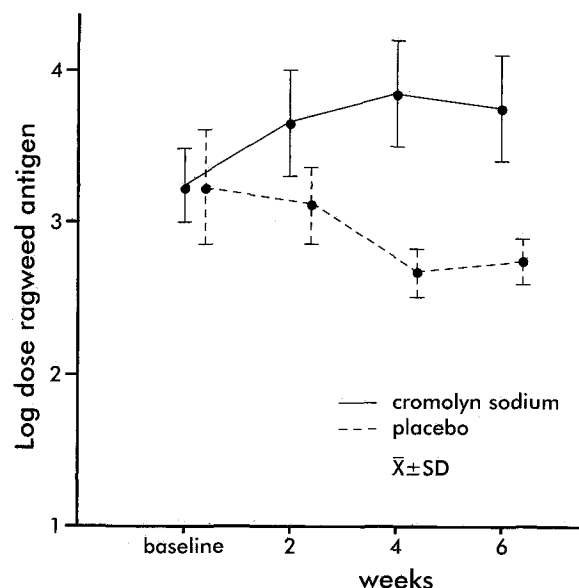


FIG. 3. Geometric mean ($\pm$ SE) for the log dose of ragweed antigen that caused a 20% fall in FEV₁. Eleven subjects were randomly assigned to receive cromolyn sodium ($n = 6$) or nedocromil sodium ($n = 5$) during the late summer and autumn ragweed season. Increased antigen responsiveness was observed in the placebo group while a progressive decrease in response was observed in the subjects receiving cromolyn sodium during the ragweed season.

inflammation in asthma, not only providing symptomatic relief from an antigen exposure but also altering the long-term pathophysiologic processes associated with asthma. The ability of nedocromil sodium to alter the acute and delayed responses is illustrated in Fig. 4, in which 2 mg of nedocromil sodium or a placebo was administered 30 minutes before allergen exposure. In this example, both the acute and delayed responses to allergen were nearly abolished. Interestingly, nedocromil sodium is also able to reduce or abolish the delayed responses to allergen when it is administered after the acute response is over,²⁵ supporting the hypothesis that it has widespread effects on mediator release. Nedocromil sodium may not only affect the acute release of mediators from cellular elements such as mast cells but may also modulate some of the other prolonged cellular inflammatory responses in asthma.

INFLAMMATORY MECHANISMS

Several studies have shown that nedocromil sodium administration reduces inflammatory responses after allergen exposure.³¹⁻³³ For example, Twentyman et al.³¹ investigated the effects of inhaled nedocromil sodium and albuterol, admin-

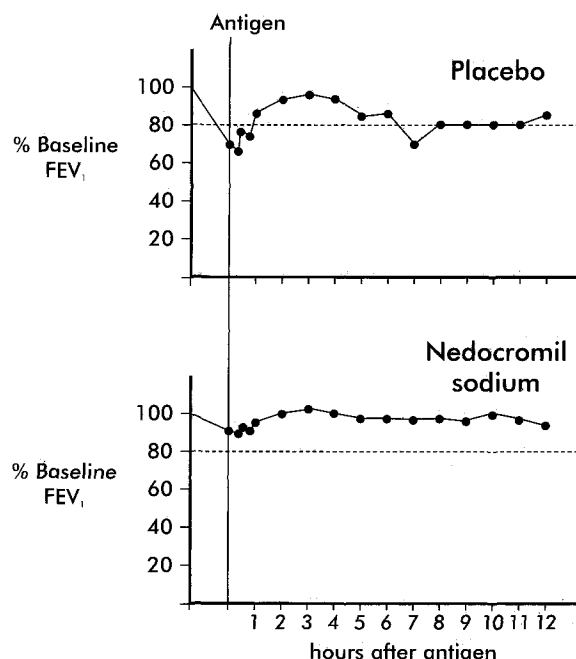


FIG. 4. Effect of pretreatment with nedocromil sodium on the acute and delayed responses to inhaled ragweed antigen.

istered before allergen challenge, on the late asthmatic response and circulating cells in a double-blind, placebo-controlled study. An additional control day without allergen exposure was included to determine diurnal variation. On the control day no changes in airway caliber occurred but a diurnal increase in the numbers of all circulating leukocytes except basophils was observed. Placebo treatment followed by allergen challenge caused both early and late asthmatic responses. Following allergen challenge in the placebo group the diurnal increase in eosinophils at 8 hours was abolished and elevated eosinophil and basophil counts were observed at 24 hours. Nedocromil sodium attenuated both the early and late asthmatic responses and restored the eosinophil and basophil responses toward normal. Albuterol, on the other hand, abolished the early asthmatic response and attenuated the late asthmatic 24-hour increase in circulating basophils. No changes in lymphocyte subpopulations were seen. These results indicate that during the late asthmatic response there is entrapment of eosinophils within the lung with a subsequent bone marrow response increasing peripheral populations of eosinophils and basophils. Nedocromil sodium may act by inhibiting the recruitment to the airways of inflammatory cells, particularly eosinophils, possibly by

affecting the generation of cytokines and the expression of leukocyte-specific adhesion molecules. Other studies have shown that nedocromil sodium reduces the rise in peripheral heat-stable neutrophil chemotactic activity³³ as well as decreasing responsiveness to cyclic adenosine 5'-monophosphate at 3 hours after allergen challenge.³⁴ The effects of nedocromil sodium on lower airway inflammatory events have been reviewed in earlier articles in this supplement.

SUMMARY

Modulation of the acute and delayed responses to laboratory allergen exposure and the effects of allergen exposure on airway hyperresponsiveness and inflammatory mediators are important methods for the evaluation of antiasthma medication such as nedocromil sodium. It is clear from the extensive literature that nedocromil sodium modulates both the acute and delayed responses to inhaled allergen. These data support the importance of nedocromil sodium as an effective antiinflammatory agent in the treatment of asthma.

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