

Chairman's Summary

A rationale for the use of nedocromil sodium in the treatment of asthma

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One of the aspects of asthma that has become increasingly evident in our discussions at this meeting is that, like other chronic inflammatory disorders, the disease appears to evolve. In very early childhood, viruses are a particularly important trigger, whereas in the school years and early teens, allergens play an increasing role as the immune response translates itself into atopy expressed in the form of asthma. Asthma may then emerge as a persistent disorder with episodes of exacerbation superimposed on a background level of inflammation. The triggers for these exacerbations may vary as the asthma progresses. As the disease becomes more severe and chronic it appears to acquire an increasing "intrinsic" component, in the sense that it becomes less dependent on common environmental agents. Moving into chronic persistent asthma in adulthood, it is possible to see how the T-cell repertoire of cytokines can take over and drive the progression of the disease and enroll the constitutive cells to bring about irreversible structural changes. By elucidating this evolution, we can explore the possibility of preventing that transition into a disease that is difficult to treat and manage.

Numerous lines of evidence support a primary role for the mast cell early in the development of asthma. Mast cells, along with eosinophils and lymphocytes, are present in increased numbers in the airways of patients with asthma. Mast cell mediators are also increased in persons with allergies, with the concentrations of histamine, tryptase, and prostaglandin D₂ proportional to the degree of airway obstruction and bronchial hyperresponsiveness (BHR). Increased numbers of activated mast cells and eosinophils (but not T cells or macrophages) have also been found in

bronchoalveolar lavage fluid of children. The mast cell is known to release a range of cytokines (e.g., tumor necrosis factor- α [TNF α] and IL-4) that have various important functions relevant to the allergic time response, including upregulation of the endothelial adhesion molecules that are responsible for eosinophil recruitment from the microvascular circulation into the airways and subsequent activation. Indeed, mast cell staining for secreted IL-4 was found to be proportional to the infiltration of eosinophils and lower airway symptoms in patients with seasonal asthma, which is compatible with the concept that mast cells can sustain the allergic inflammatory response. The proteases chymase and tryptase are also important for eosinophil recruitment and activation and increase of mucus secretion and microvascular permeability. The efficacy of nedocromil sodium in chronic mild to moderate asthma also supports the prominence of the mast cell in initiating and maintaining the inflammatory response.

In contrast, disease severity in patients with severe asthma has a highly significant correlation with numbers of activated (CD25+) T cells. These patients also showed increased expression for the cytokines IL-5 and IL-13, which, in severe disease, are likely to derive from activated T cells.

ANTIINFLAMMATORY EFFECT OF NEDOCROMIL SODIUM

Through cytokine release, it is possible to see how the mast cell could account for much of the late-phase inflammatory response that occurs after allergen exposure and for orchestration of the BHR that may persist for several days afterward. Because nedocromil sodium can inhibit tumor necrosis factor- α release from rodent mast cells, it seems likely that the suppression by this drug of the late asthmatic reaction and the acquired BHR after allergen provocation may be the result of inhibition of mast cell cytokine release. This has been demonstrated in terms of lung function in numerous clinical pharmacology studies, and Calhoun and colleagues have now shown that the

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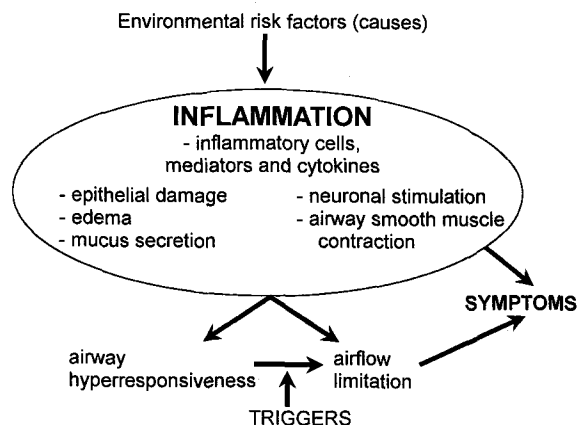


FIG 1. The interrelationship between airway inflammation and the development of symptoms, airway hyperresponsiveness, and airflow limitation.

effect is mediated through mast cells. With use of a technique in which antigen is instilled directly into the airways, nedocromil sodium pretreatment prevented the immediate (at 5 minutes) increase in levels of histamine and tryptase. Moreover, the degree of histamine reduction at 5 minutes correlated significantly with a reduction in eosinophil influx at 48 hours suggesting a connection between the two events.

The eosinophil plays a major role in causing the epithelial dysfunction and damage that are typically found in inflamed asthmatic airways. Epithelial cells are not just a physical barrier but can be activated by noxious substances such as atmospheric pollutants to release cytokines and adhesion molecules that aid in the recruitment of eosinophils. Nedocromil sodium has been shown to inhibit the increase in eosinophil chemotaxis and adhesion produced by a culture medium containing the products released from activated epithelial cells and prevent ozone-induced cytokine (IL-8) release from epithelial cells. The effect of nedocromil sodium on eosinophils was demonstrated not only by blocking the release of eosinophil cationic protein (implicated in epithelial cell damage) from eosinophils, but also by preventing the dysfunction of epithelial cells induced by the presence of activated eosinophils. This *in vitro* work by Davies' group was reflected in their study in patients with asthma who, after nedocromil sodium treatment, had a decreased number of total and activated eosinophils in bronchial biopsy samples (this decrease was significant compared with salbutamol treatment but not against placebo).

Similar results have been reported by Dr. Laitinen's group, again just escaping statistical significance, have suggested the need for larger sample sizes, because a common trend is clear.

This range of studies implies that nedocromil sodium is exerting subtle anti-inflammatory effects on, at least, mast cells, eosinophils, and epithelial cells, which together account for the release of an enormous range of mediators, cytokines, and enzymes. Airway inflammation is manifested clinically in an impairment of baseline lung function (with diurnal variation), BHR, and persistent symptoms. In clinical trials, nedocromil sodium has performed well against these variables, and it would be difficult to explain these effects, especially against BHR, without recourse to anti-inflammatory activity. Nedocromil sodium appears to be most effective at the milder end of the disease spectrum, which may well reflect the differing constituents of the disease through its various evolutionary phases.

ASTHMA SYMPTOMS AND THE EFFECT OF NEDOCROMIL SODIUM

The symptoms of asthma cannot be viewed or treated in isolation. Whereas acute bronchoconstriction in response to external stimuli, or triggers, can be observed in animals and volunteers, a patient with asthma is hyperresponsive to these triggers as a result of the underlying inflammatory process (Fig. 1). Wheezing and chest tightness are a manifestation of airflow limitation, principally in the form of acute bronchoconstriction, but with added components from the chronic inflammatory changes of edema of the airway wall, mucus plugging, and, with longstanding and severe asthma, irreversible structural changes implicit in airway wall remodeling. Dyspnea may reflect a decrease in airway compliance and a neuronal component. Cough is probably caused by stimulation of sensory nerves and exacerbated by inflammatory mediators; it is an important symptom, particularly in children. Triggers may include allergens, air pollutants, exercise and hyperventilation, cold air, sulfur dioxide, food additives, and many other conditions and substances. Exposure of the patient with asthma to triggers such as allergen not only causes acute symptoms but also may induce an increase in inflammation and exacerbate the asthma for a period of days. Asthmatic reactions induced in the laboratory by allergens and chemical stimuli can be used as a model of both acute symptoms and asthma exacerbations, because the immediate symptoms may be followed by a sus-

tained increase in inflammatory indices and airway responsiveness.

The inhibitory effect of nedocromil sodium on histamine release from mast cells can account for its efficacy in preventing the acute bronchoconstrictor response to allergen, exercise, and other natural and experimental (e.g., adenosine and hyperosmolar saline solution) stimuli. This response is manifested clinically as the symptom of wheeze. Symptoms with a neuronal component depend on reflexes involving sensory nerve stimulation and the subsequent release of active neuropeptides, which are also important in causing microvascular leakage and mucus secretion. Such provocative responses include the release of tachykinins substance P and bradykinin, which are also used in the laboratory, along with chemical stimuli such as sulfur dioxide and sodium metabisulfite, to investigate the effect of treatment on these neuronally driven symptoms. The efficacy of a single dose of nedocromil sodium in preventing neuronally mediated bronchoconstriction is likely to be caused by a direct effect on sensory nerves, although long-term antiinflammatory treatment would also remove the factors such as cytokines that stimulate increased neuropeptide synthesis.

In animal studies, nedocromil sodium has been shown to have a protective effect against a range of stimuli that invoke neuronal responses, for example, nonadrenergic noncholinergic bronchoconstriction, cigarette smoke, bradykinin, and sulfur dioxide. These effects may be explained by the inhibition of sensory nerve activation and the consequent prevention of tachykinin release. The beneficial effect of nedocromil sodium on asthma may also relate to its effects on sensory nerves, with inhibition of cough, airway microvascular leakage, and the sensation of chest tightness and wheeze that may result from sensory nerve activation through local axon reflexes.

Coughing can affect the life of a patient with asthma to a surprisingly large degree, and the symptom may persist despite adequate control of asthma exacerbations with inhaled or oral corticosteroids. Evidence points toward the rapidly adapting stretch receptors as the main sensory complex responsible for cough, but the picture is not clear-cut. The sensitivity of the cough reflex is heightened in asthma, probably as a result of the presence of endogenous inflammatory mediators in the airways. Because abolition of the normal cough response is not desirable, it is relevant that with use of a single-fiber recording technique, Myers

et al. found that nedocromil sodium reduced by 50% the generation of action potentials in C fibers in response to stimulation by capsaicin. Nedocromil sodium did not have a generalized inhibitory effect on afferent excitability (because it did not affect the sensitivity to electrical or mechanical stimuli). Thus, as opposed to studies in animals or volunteers, in whom the cough reflex is a normal and important defense mechanism, it would be more appropriate to test nedocromil sodium in models of enhanced cough reflex and in patients with asthma. Therapeutic studies confirm that nedocromil sodium can reduce the severity of asthmatic cough.

A potential barrier to compliance with anti-inflammatory or controller medication is concern that the patient may not perceive an immediate benefit and thus adherence to the daily regimen may drop off. In addition to controlling the inflammatory components of the disease, a rapid effect of a controller medication on the symptoms of asthma would be of additional benefit to both patient and physician. In therapeutic trials, nedocromil sodium has been shown to significantly reduce daytime and nighttime asthma symptoms as early as the third day of treatment, with a clinically useful reduction in cough severity within the same time frame. An analysis of studies carried out in patients with mild to moderate asthma demonstrated a statistically significant improvement in cough on the first day of treatment.

MECHANISM OF ACTION

The common pathway through which nedocromil sodium modulates inflammatory cells and sensory nerves is now thought to be the chloride channel. The findings presented have greatly furthered our understanding of the mechanism of action of nedocromil sodium and cromolyn sodium, a problem that has taxed researchers for many years. In the simplest terms, the accumulation of calcium ions within cells (which is necessary for cell activation and mediator secretion) is facilitated by an inward flow of chloride ions through the chloride channel. Although the properties of chloride channels differ between cell types, this is likely to be the mechanism in mast cells, because antigen-induced mediator release was reduced by removing extracellular chloride ions. Nedocromil sodium has been found to block an intermediate conductance chloride channel in cultured mucosal mast cells. Cells are also influenced by the tonicity, or solute concentration, of their environment: in conditions of hypotonicity,

water would pass into the cell to equilibrate the concentrations on either side of the cell membrane. Cells cannot be allowed to swell unchecked, and chloride currents are believed to be involved in regulation of cell volume. Nedocromil sodium was shown to inhibit the swelling-induced chloride current in a variety of cells. Chloride ion transport also operates on sensory nerves to facilitate depolarization and generation of action potentials. In an isolated vagus nerve preparation, nedocromil sodium produced an initial spike (transient opening of the chloride channel) followed by a refractory period during which further action potentials could not be generated (i.e., chloride channel closed). The fact that nedocromil sodium is acting on a mechanism that is operative only when the cell is activated may help explain the relative lack

of toxicity of this class of compounds. In other words, it increases the threshold of which a variety of cells will respond to stimulation.

The profile of anti-inflammatory effects of nedocromil sodium—its clinical efficacy and rapid effect on symptoms, with an absence of known long-term side effects—taken together provide a convincing argument to position this drug in current asthma management guidelines as a suitable choice for treating mild, persistent asthma when daily controller medication is instituted. In addition, depending on what we will learn about the underlying pathology of very early, intermittent asthma, the benefit:risk ratio of nedocromil sodium would make it an attractive candidate for investigating the outcome of therapeutic intervention at this point.