

did not differ significantly from one another. However, tests for both linear and quadratic trends in the data were significant ($p = 0.0004$ and $p = 0.04$, respectively). Further analysis indicated that the data best fit a quadratic regression curve (Fig. 2); that is, the increase in mean PC_8 for each increment in dose changes progressively and becomes smaller as the dose increases.

The lack of significant differences among the three doses of nedocromil sodium and the comparability of their mean responses suggest that no substantial advantage exists to any one of the three doses tested. However, one of the limitations of the study was that many patients did not have a true PC_8 (as computed by an increase in SR_{aw} of 8 units from baseline after administration of 8 ppm SO_2). With this limitation in mind, it is possible that differences among the three active

doses may be underestimated, although it is not possible to say to what degree.

We conclude that doses of nedocromil sodium as low as 2 mg are effective in inhibiting SO_2 -induced bronchospasm.

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Effect of nedocromil sodium on microvascular leakage

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The recognition that asthma is a chronic inflammatory disease has focused attention on microvascular leakage, which is a component of the inflammatory process. Epithelial shedding, airway edema, increased airway resistance, and airway hyperresponsiveness can result from the plasma extravasation caused by leakage. The chain of inflammatory events set off by microvascular leakage may contribute to the development of the late-phase asthmatic response. Thus the search for drugs that ameliorate this leakage continues. Intravenous nedocromil sodium in a dose of 100 μ g/kg is effective in blocking microvascular leakage induced by intravenous allergen in sensitized guinea pigs but has no effect on leakage induced by either intravenous histamine or platelet-activating factor, which suggests that it acts predominantly on mediator release. Studies in hamsters, however, have demonstrated that nedocromil sodium is effective in blocking leakage induced by histamine, which acts directly on endothelial cells. The ability of nedocromil sodium to reduce microvascular leakage may contribute to its effectiveness in preventing the late-phase response, but the mechanism by which this reduction occurs is not completely understood. (J ALLERGY CLIN IMMUNOL 1993;92:197-9.)

Microvascular leakage and edema are important components of the inflammatory response and may be important factors in the action of antiinflammatory therapies. The potential impor-

tance of microvascular leakage in airways has recently been highlighted by the recognition that asthma is a chronic inflammatory disease.

AIRWAY MICROVASCULAR LEAKAGE AND ASTHMA

Because microvascular leakage is an essential component of the inflammatory response, it is not surprising that there is evidence of plasma extravasation in asthma.¹ Bronchoalveolar lavage of

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patients who have asthma, particularly with "bronchial" washes, reveals a higher than normal concentration of albumin.² Patients with asthma are also known to have increased albumin in their sputum.³ Moreover, a major component of the sputum plugs that occlude the airways in severe asthma is derived from plasma.

Plasma exudation may have important pathogenic consequences in asthmatic airways. Exuded plasma contains precursors for several highly active mediators, including C_{5a} formed from complement. This particular substance is chemoattractive to neutrophils and activates several types of inflammatory cells.⁴ High molecular weight kininogens in plasma give rise to bradykinin and Lys-bradykinin after contact with the enzyme kininogenase that is released from various inflammatory cells.⁵ Bradykinin has several effects on airways in general and is a potent constrictor of asthmatic airways in particular.⁶ Plasma also may contain factors that inhibit mucociliary clearance, a common feature of asthma.⁷

The exudation of plasma stretches the basement membrane and may contribute to the epithelial shedding that is characteristic of asthmatic airways. In addition, microvascular leakage results in edema and submucosal swelling, physiologic components of airway narrowing in asthma. Even a small increase in mucosal thickness may result in a marked increase in airway resistance that is geometrically related to smooth muscle contraction.⁸ This submucosal thickening could in turn contribute to the development of airway hyperresponsiveness and to the loss of the plateau in the dose-response curve of a bronchoconstrictor. Furthermore, it is possible that microvascular leakage contributes to the late response that follows exposure to inhaled allergens in some patients because this late response cannot readily be reversed by bronchodilators.

Many of the mediators implicated in asthma (e.g., histamine, sulfidopeptide leukotrienes, bradykinin, and substance P) have been shown to cause microvascular leakage.⁹⁻¹¹ The most potent of these is platelet-activating factor, which causes leakage in all airways and appears to act directly on endothelial cells via specific receptors.¹² Depending on airway size, mediators have varying effects. For example, histamine appears primarily to cause leakage in central airways, whereas leukotrienes have a more pronounced effect on peripheral airways.¹³

Exposure to an allergen in sensitized guinea pigs causes airway microvascular leakage that can

be reduced by antihistamine, which exerts its major effect in large airways, and by a leukotriene antagonist or lipoxygenase inhibitor.^{14, 15}

EFFECT OF ANTI-ASTHMA DRUGS

Several antiasthma drugs inhibit microvascular leakage in the airways. Epinephrine is particularly effective and inhibits leakage by activating α_1 -adrenoceptors. Presumably, it does so by constricting precapillary arterioles, a process that prevents drug delivery to the leaky postcapillary venules.¹⁶ There is some debate about the effectiveness of β_2 -agonists. β_2 -Agonists are not effective when given intravenously¹⁵ but inhibit leakage when given by inhalation, which suggests that high local concentrations are needed to inhibit plasma exudation.^{17, 18} Corticosteroids are effective in inhibiting leakage as part of their antiinflammatory effect.^{17, 19}

EFFECT OF NEDOCROMIL SODIUM ON MICROVASCULAR LEAKAGE

Intravenous nedocromil sodium, in a dose of 100 $\mu\text{g/kg}$, is effective in blocking microvascular leakage induced by intravenous allergen in sensitized guinea pigs at all airway levels.¹⁴ This blockage was comparable with the effects of antihistamine in large airways. In more peripheral airways, the effects of nedocromil were comparable with that of leukotriene antagonist.

The inhibitory action of nedocromil on microvascular leakage could be the result of the release of inflammatory mediators from perivascular mast cells and other inflammatory cells.¹⁹ Alternatively, it is possible that nedocromil exerts an inhibitory effect on mediators that otherwise act on postcapillary venular endothelial cells. That nedocromil sodium had no significant effect on microvascular leakage induced by either intravenous histamine or platelet-activating factor in guinea pigs suggests that the predominant effect was on mediator release.²⁰ In contrast, studies of the cheek pouches of hamsters have found that nedocromil is active both in reducing the number of allergen-induced leakage sites and in reducing the leakage induced by histamine (which acts directly on endothelial cells) and leukotriene B₄ (which is leukocyte-dependent).²¹ Interestingly, nedocromil was effective against histamine-induced leakage only when given systemically.

These results suggest that nedocromil sodium reduces microvascular leakage in allergen-induced airway reactions. This effect may contrib-

ute to the effectiveness of nedocromil in preventing the allergen-induced late response. Further studies are needed to determine whether this agent has direct effects on airway vascular endothelial cells in addition to inflammatory cells.

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