Corticosteroids and Cromolyn Sodium as Modulators of Airway Inflammation*

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Heightened airway reactivity is a cardinal feature of asthma and correlates with many clinical features of the illness, such as the acute response to bronchodilator drugs, the magnitude of diurnal fluctuations in lung function, and the amount of therapy required to control symptoms. Data have accumulated indicating that a reduction in airway reactivity can decrease asthma morbidity, and many advocate treating asthmatic patients prophylactically to prevent acute exacerbations from developing, rather than responding to them after they have occurred. This approach is particularly effective if it is used when the airways are being exposed to stimuli to which they are sensitive. A number of drugs have been purported to reduce airway reactivity, but the most convincing evidence supports the effects of cromolyn and inhaled oral steroids. Although each type of drug has its own advantages and disadvantages and different modes of action, the common denominator is believed to be a reduction in the state of airway inflammation.

It is now widely recognized that heightened airway responsiveness is the cardinal feature of asthma and that its waxing and waning is associated with changes in the clinical manifestations of this illness. When airway reactivity is high, symptoms are more severe and persistent, the acute response to bronchodilator drugs is greater, and the amount of therapy required to control the patient's complaints increases. In addition, the magnitude of diurnal fluctuations in lung function becomes greater and the patient tends to awaken at night or in the early morning with breathlessness.

In both normal and asthmatic subjects, airway reactivity is known to rise following viral respiratory tract infections, and exposure to oxidative air pollutants such as ozone and nitrogen dioxide. Interestingly, sulfur dioxide does not appear to have this effect. With virus, airway responsivity can remain elevated for six to eight weeks while following exposure to ozone reactivity remains high only a few days. In asthmatic patients, the inhalation of specific antigen is a potent stimulus to increase reactivity. Recent data indicate that following exposure to immunologic active substances, airway responsiveness will begin to rise within minutes, and can remain elevated for weeks. If the dose of antigen is high enough, acute episodes of obstruction may occur daily for a prolonged period following a single exposure.

Multiple causes have been postulated for the heightened airway reactivity of asthma, but the basic mechanism remains unknown. Some have suggested that there is an acquired or congenital increase in the basic contractivity of the airway smooth muscle; however, physiologic examination of the bronchial smooth muscle of asthmatic patients taken at surgery does not support this concept. Goldie et al found that the in vitro responsivity of airway muscle of asthmatic patients to be no more reactive to carbachol or histamine than muscle removed from normal individuals.

The most popular hypothesis at present is that of airway inflammation. Following exposure to an initiating stimulus, mast cells, basophils, and macrophages can be activated to release a variety of mediators which produce direct effects on airway smooth muscle and capillary permeability, thereby evoking an intense local reaction which can then be followed by a more chronic one. The latter may be brought about by the release of chemotactic factors which recruit eosinophils, platelets and polymorphonuclear leukocytes to the site of injury. In addition, it is thought that the acute and chronic effects of mediator release and cellular infiltration may result in epithelial damage with involvement of neural endings within the airways and the activation of an axon reflex. In this fashion, an essentially local phenomenon can be amplified to have widespread effects throughout the tracheobronchial tree.

As the origin of airway hyperreactivity may reside with multiple cell types, a series of interactions between a multitude of chemical mediators may also be required. One group of substances that may be particularly important in this regard are the metabolites of arachidonic acid. The approximately 40 cell types that are resident in normal lungs, as well as the inflammatory leukocytes that can infiltrate the airways and parenchyma in airway diseases, all contain phos-
pholipids as a major component of their plasma membrane which are precursors of arachidonic acid. When stimulated appropriately with immunologic or nonimmunologic events, each cell type can release arachidonic acid and oxidatively metabolize it to prostaglandins, thromboxanes, hydroxyeicosatetraenoic acids, platelet activating factor and leukotrienes. These metabolic products are potent inflammatory mediators which can produce the majority of the physiologic effects seen in acute and chronic asthma. They also have the ability to modulate the capacities of target cells to produce additional mediators of inflammation. In addition, platelet activating factor has also been shown to increase airway reactivity in normal subjects, a phenomenon not previously observed with any other mediator.

A number of drugs have been employed in an attempt to reduce airway reactivity and data are available regarding the effectiveness of sympathomimetics, methylxanthenes, anticholinergics, alpha blockers, antihistamines, cromolyn, and glucocorticoids. In order to gain a perspective on the significance of these studies, one must differentiate between a simple bronchodilator effect with an acute reduction in airway responsiveness to a constrictor stimuli and a diminution in baseline airway reactivity. With bronchodilator drugs, the former predominates. For example, investigations employing single or multiple doses of beta agonists, theophylline or anticholinergics have shown that all of these agents acutely diminish airway responsiveness as measured by provocations with histamine, methacholine, exercise, or hyperventilation. Generally, the magnitude of the reduction in bronchial responsiveness appears to be related to the dose of drug used. However, most studies demonstrate that when the acute bronchodilator effect wears off, the responsivity again returns to its pretreatment state indicating that the underlying airway reactivity has not been altered.

Three well-controlled trials using various beta agonists show the above phenomenon quite nicely, and clearly demonstrate that the protective effect of bronchodilators is due only to an acute diminution in airway tone with a reduction in the response to constrictor stimuli. Peel and Gibson treated a group of asthmatic patients for four weeks with salbutamol daily by aerosol. Histamine bronchoprovocations were performed at the beginning and the end of the treatment. Despite an increase in airway caliber in this study there was no change in the inherent sensitivity to the constrictor. Similar findings were reported by Harvey and Tattersfield. Salome et al extended these observations by demonstrating that sympathomimetic drugs merely shift the stimulus response curves to methacholine or histamine to the right so that it takes more stimulus to produce an effect, but the intrinsic reactivity remains unchanged.

One drug with a proven ability to reduce airway reactivity has been cromolyn sodium. This agent has no significant smooth muscle relaxant properties and so its effect on reactivity is not dependent upon changes in bronchial tone. The major action of cromolyn appears to be stabilization of cell membranes, particularly mast cells, with the inhibition of the release of mediators of immediate hypersensitivity, but it may also limit damage to epithelial membranes as well. This protective effect is seen whether cells are activated with immunologic or non-immunologic stimuli, and may involve an effect on cytoplasmic control of calcium influx into the cell.

A number of studies have shown that the administration of cromolyn to asthmatic patients will substantially reduce the response of their airways both to specific and nonspecific stimuli. Not all studies have shown equal effects with all stimuli, but overall the data in the literature indicate that airway lability falls with this drug. Because of this, patients tend to have more symptom-free days and require less medication. When cromolyn is discontinued, responsiveness once again increases. An excellent example of the effects of cromolyn in the recent literature is the study of Lowhagen and Rak. These investigators performed repeated histamine challenges in 22 patients before, during and after the birch pollen season in a randomized double-blinded trial in which cromolyn was compared with placebo. Cromolyn prevented the rise in airway reactivity seen with placebo and diminished the patients' symptoms and need for bronchodilators.

It is important to emphasize that to produce its beneficial effect cromolyn must be given at a time when the airways are being exposed to repetitive or chronic stimuli, and that the drug must be administered for more than two weeks. When given out of season, for example, or for short periods, little, or no, response is seen. An exception to this phenomenon is the person who is episodically exposed to an antigen. In this situation, prophylactic treatment on an as-needed basis will prevent both the acute obstructive response to the antigen, as well as subsequent increases in reactivity. Recent data suggest that it may be possible to use cromolyn successfully even after antigen exposure. Mattoli et al have shown that the administration of cromolyn after an antigen bronchoprovocation will prevent the subsequent increases in airway reactivity, even though it does not inhibit the development of the late response. Interestingly, there are data that indicate that cromolyn also reduces the cough of cigarette smokers and the elevated reactivity seen in some individuals with chronic bronchitis.

Other agents, such as glucocorticoids, that are active against the inflammatory process within the tracheobronchial tree can also reduce airway reactivity. Cor-
ticosteroids reduce mediator release from certain cell
types, regulate eicosanoid production, inhibit the
formation of edema and reduce mucous production.
Hence, in theory they should be quite effective in
lowering airway lability. Most, but not all, studies
suggest that this is the case. Easton treated a small
group of asthmatic patients with beclomethasone for
four months and did not find any change in the
response to methacholine, and Arkans and associates
actually noted reactivity to rise after a two-week course
of corticosteroids. Subsequent studies, however, have
all found positive effects. One of the earliest studies
was by Juniper et al in which the long-term stability
of bronchial responsiveness to histamine was being
examined in a group of 35 adult asthmatic patients.
Bronchoprovocations were carried out on two occa-
sions separated by 10 to 30 months. Airway reac-
tiveness was found not to change in those who did not
require medication or who only used inhaled salbuta-
mol to control their symptoms. However, reactivity
was significantly improved in those treated with both
beclomethasone and salbutamol. Kerrebijn and
extended these observations by contrasting the
long-term effect of treatment with inhaled corti-
costeroids and beta agonists on bronchial responsiv-
ness in children with asthma. In this study, 12 patients
were treated with budesonide, and seven with terbu-
taline for six months. Bronchial reactivity decreased
in the patients receiving the inhaled steroid, but in
none of those receiving the sympathomimetic agents.
Similar results have been observed with beclometha-
sone and theophylline. In a double blind cross-over
study involving 26 patients with asthma, only the
corticosteroid medication reduced reactivity; the
methylnitethanine did not.

The effects of steroids may be dose and time
dependent. Kraan and associates administered either
200 or 800 μg of budesonide per day for eight weeks
to two parallel groups of asthmatic patients and found
that the higher dose was more effective in reducing
reactivity. They also noted that for each dose of drug,
reactivity fell as treatment progressed.

The relative effectiveness of cromolyn and inhaled
steroids is unknown. Unlike cromolyn, glucocorticoids
appear to reduce reactivity at times when the airways
are not being stimulated exogenously. Svendsen and
colleagues, in a cross-over study, administered bec-
athomethasone and cromolyn sodium to 38 atopic asth-
matic patients for eight weeks. This study was per-
formed out-of-season and only the beclomethasone
was found to reduce airway reactivity. In acute single-
dose studies, however, both drugs appear to protect
equally well against antigen-induced bronchial hyper-
responsiveness to histamine. In this situation, crom-
olyn has the advantage in that it inhibits both the
initial and late obstructive response, whereas beclo-
methasone only modulates the latter.

There are few data on what to expect when the two
drugs are used together. Toogood and associates gave
cromolyn sodium or placebo to 30 asthmatic patients
who required high-dose beclomethasone to control
their symptoms. In this investigation, subsequent
attempts to reduce the inhaled glucocorticoids
resulted in an increase in asthma intensity. On the
surface, these results suggest that cromolyn and beclo-
methasone do not act synergistically in the treatment
of asthma; however, their work is difficult to interpret
because a significant number of subjects had previously
failed to respond to cromolyn therapy before
entering the trial. A study examining the effects of
each agent alone and then in combination in sensitive
patients would be of great interest.

In summary, although bronchodilator drugs of various
types will protect patients with heightened airway
reactivity from the effects of acute exposure to con-
strictor stimuli, they do not appear to modify the
intrinsic responsiveness of the tracheobronchial tree.
To achieve the latter effect, one must employ agents such
as cromolyn or the glucocorticoids.

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