The Use of Corticosteroids in the Treatment of Asthma

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When corticosteroids were first introduced for the treatment of asthma, they were hailed as miracle drugs. As experience was extended, so was the appreciation of the myriad side effects. Advances in our understanding of the physiologic properties of oral agents has led to the discovery of methods for avoiding adverse effects. Additionally, new compounds and improved delivery by the aerosol route have mitigated side effects. Even with the new knowledge gained, systemic corticosteroids remain one of the most misunderstood medications utilized in the treatment of asthma and other pulmonary diseases. Physicians have been criticized for failure to use the drugs in patients dying during an attack of asthma, yet their utilization during status asthmaticus has been questioned repeatedly.6,7

Postulated Mode of Action

Corticosteroids have several immunologic and anti-inflammatory actions.4 Among the reasons postulated for corticosteroid effectiveness in obstructive lung disease are: (1) inhibition of synthesis or release of chemical mediators; (2) inhibition of cholinergic mechanisms (both probably act through changes in cyclic AMP and/or cyclic GMP); (3) a direct effect of corticosteroids on smooth muscle relaxation; (4) enhanced restoration of the effect of β-adrenergic bronchodilators; and (5) alteration of immune mechanisms and/or mediators of inflammation such as arachidonic acid.8

One of the most important actions of corticosteroids is their effect on metabolites of arachidonic acid. Macrocortin6 and lipomodulin6 are newly synthesized in the presence of corticosteroids. By inhibiting phosphodiesterase A, they prevent the formation of leukotrienes, prostaglandins, thromboxanes, and other metabolites of arachidonic acid.

Corticosteroids influence the migration and function of leukocytes. Neutrophils, which are normally marginated on the endothelium of capillary and other vessels throughout the body, including the lungs, reenter the circulation, whereas monocytes, eosinophils, and lymphocytes, particularly thymus-derived lymphocytes, disappear from the circulation. Although large daily doses of corticosteroids added to in vitro preparations may inhibit mononuclear leukocyte chemotaxis, phagocytosis, and killing, the high concentrations required to show these effects do not result from treatment within the usual dosage range for asthma or COPD. In fact, when we studied monocyte cellular function in asthmatic patients receiving alternate-day steroid therapy, we found no significant alteration in monocyte chemotaxis, bacterial killing, or phagocytosis.8

Corticosteroids interfere with lymphocyte proliferation, which may explain their suppressive effect on delayed-type hypersensitivity measurements such as tuberculin reactivity. However, in humans, unlike other species which are more steroid sensitive, the usual doses of corticosteroids do not interfere with antibody production.9 Although dose and timing of corticosteroid administration is important, steroids alter delayed-type hypersensitivity skin tests, but do not interfere with immediate (IgE-mediated) skin test reactivity.10

Even though tuberculin reactivity, for example, might be altered by steroids, the test should nevertheless be performed, since valuable information might be gained from a positive test. Additionally, small dose, alternate day steroids have a minimal inhibitory capacity.

Corticosteroids and catecholamines act synergistically to potentiate cyclic AMP action and to replenish β-receptors in cells. The action has been demonstrated in various clinical studies11,13 and with the use of various in vitro techniques.14

Table 1 summarizes the most important postulated mechanisms of action for corticosteroids.

**USE IN STATUS ASTHMATICUS**

Although there is general agreement that corticosteroids are beneficial in the management of chronic asthma, their use in the management of status asthmaticus has been challenged. In a randomized, double-blind study of 38 young patients in status asthmaticus, McFadden and co-workers9 administered either 0.85, 0.50, or 1.0 g of hydrocortisone hemisuccinate or placebo intravenously (IV), followed by isoproterenol, given at hourly intervals for a minimum of 6 hours. Results showed no statistical differences in any physiologic or clinical variable studied. The authors concluded that hydrocortisone provided no specific benefit during the 6-hour period of observation. Furthermore, Lukaza8 stated that steroids are ineffective once severe asthma is established and may have contributed to the epidemic of asthma deaths in the mid-1960s, possibly by enhancing the cardiotoxicity of isoprenaline (isoproterenol).

Kattan et al10 studied 19 children in status asthmaticus who had not received corticosteroids prior to hospitalization. Patients were randomized into 2 groups, each of which received albuterol inhalations and IV aminophylline. Additionally, one group received 7 mg/kg of hydrocortisone IV.

Table 1—Proposed Mechanisms of Action of Corticosteroids

| Direct relaxation of bronchial smooth muscle |
| Congenital abnormalities |
| Inhibition of synthesis and release of chemical mediators including histamine and arachidonic acid products |
| Stimulation of lipomodulin and/or macrocortin, which are inhibitors of phosphodiesterase A |
| Decrease in late-phase inflammatory response |
| Stimulation of cAMP |
| Altered vascular permeability and vasoconstriction |
| Inhibition of cholinergic mechanisms |
| Inhibition of cyclic guanosine monophosphate |
| Stabilization of lysosomes |
| Influence on the migration and function of leukocytes |
| Neutrophils reenter the circulation |
| Monocytes, eosinophils, and lymphocytes leave the circulation |
| Improved mucociliary clearance and decreased mucus formation |
| Enhanced response to catecholamines |
| Increased synthesis and restoration of β-adrenergic receptors |

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over 6 hours, while the other served as a control. Subsequent pulmonary function studies for 36 hours indicated no difference between the 2 groups. Thus, in these children corticosteroids did not appear to hasten the recovery or increase the responsiveness of airways to aminophylline or albuterol. It can be argued that Kattan and co-workers did not find a beneficial effect with steroids because the greater bronchodilatation produced by theophylline and the β-agonists unmasked any effect induced by the steroids.

When the McFadden group designed a subsequent emergency room study with the use of corticosteroids, they reported different results. Twenty asthmatic subjects were selected because of their refractoriness to 8 hours of conventional therapy. Eleven patients received hydrocortisone (2 mg/kg bolus; then 0.5 mg/kg/hour for 24 hours) and 9 received saline solution as a control. All were given identical bronchodilator treatment during the study. At the end of 24 hours, the subjects given glucocorticosteroids had a significantly greater resolution of their airway obstruction than did those given placebo.

Although most investigators have looked at pulmonary function studies, Pierson et al monitored changes in blood gas measurements. In a double-blind, placebo-controlled study, they evaluated the effects of corticosteroids in 45 asthmatic patients who failed to respond to 1:1000 aqueous epinephrine (0.2 to 0.5 ml/second) administered 3 times at 15-minute intervals. The group who received steroids had a significantly greater improvement in Po2 (p<0.005) than the control group after 24 hours of therapy.

Fiel and co-workers followed up a randomly assigned corticosteroid treated group or placebo group 7 to 10 days after emergency room treatment. Those patients who received corticosteroids had a decreased need for emergency care (5.9 percent vs 21 percent for placebo) and fewer respiratory symptoms (15.6 percent vs 36.4 percent for placebo).

Thus, the duration of observation may also be important in judging the effects of corticosteroids. Shenfield and co-workers suggested that objective changes in pulmonary function do not occur for at least 6 hours after steroid administration, and maximal improvement might require as long as 6 days of therapy. One of the 12 patients required 36 hours to show any demonstrable improvement.

McFadden and co-workers also emphasized the long time, even with vigorous therapy, that it takes to demonstrate physiologic recovery after an asthmatic attack.

In summary, various factors may influence an investigator's conclusions regarding the usefulness of corticosteroids. They include patient selection criteria, such as asthma severity, age, and prior medication, as well as the timing, type, and measurements selected.

It is important to remember that the time to treat status asthmaticus is "3 days before it happens." Give corticosteroids if the patient's disease is severe enough to merit hospitalization, or if the patient is having a severe bout of asthma and has been receiving corticosteroids within the preceding year.

Although there is no agreement as to the proper dosage, in my experience 4 to 8 mg/kg of hydrocortisone hemisuccinate IV or an equivalent should be given every 4 to 6 hours. In adults in whom salt retention may be a problem, 40 to 80 mg of methylprednisolone sodium succinate every 4 to 6 hours has proved useful.

I have no doubt that the potential benefits of corticosteroids, given during a severe asthmatic attack, greatly outweigh the unfounded concern regarding side effects, especially when corticosteroids are not given on a prolonged basis. There is no evidence that short-term therapy will induce a state of steroid dependency. Additionally, steroids absolutely should be used during episodes of stress (such as status asthmaticus) if they have been employed during the previous year.

**MAINTENANCE STEROID THERAPY**

Corticosteroids produce marked symptomatic relief in almost all patients with chronic asthma. Nevertheless, they are the last to be added to a medical program and, when possible, the first to be removed. This implies that maximally tolerated doses of various bronchodilators have been inadequate to control symptoms. In this respect, there are reviews of bronchodilator therapy that should be consulted.

It is important for the physician to explain the benefits as well as the potential side effects to the patient prior to initiation of steroid therapy, especially since these drugs are among the medications most poorly understood by patients (and even by some physicians) today.

Patients are often very much aware and fearful of the side effects of corticosteroids from sources such as newspapers, magazine articles, and even the PDR, which they might have in their possession.

Incidentally, we found a surprising relationship between corticosteroid administration and EEG patterns in asthmatic patients taking various asthma medications. The EEG abnormalities were greatest in those patients receiving the largest doses of theophylline and a combination of theophylline and ephedrine. Even though use of corticosteroids may represent an index of asthma severity—ie, corticosteroids are generally given to asthmatic patients whose symptoms are difficult to control with theophylline and β-agonists—significantly fewer patients receiving corticosteroids showed EEG abnormalities as compared to those patients who were not receiving steroids. These findings support the notion that theophylline can lead to CNS disturbances in certain individuals, but steroids may offer some protection against such theophylline-related CNS disturbances.

An important point is that side effects vary with the duration and timing of the administration as well as the type of steroid preparation used. The first choice would be to administer short courses of systemic corticosteroids with intervals of several weeks or months without steroid treatment. Alternate-day therapy, ie, a single morning dose every other day, is the next preferable program; with minimal doses, side effects can essentially be avoided. Compared to

<table>
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<tr>
<th>Table 2—Advantages of Alternate-day Early Morning Steroids</th>
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<td>Fewer or no pituitary-adrenal suppression and other side effects, eg, linear growth retardation</td>
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<tr>
<td>Less (no) suppression of fever</td>
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<tr>
<td>Less (no) suppression of WBC count</td>
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<tr>
<td>Less (no) suppression of delayed-type hypersensitivity skin tests, eg, tuberculin tests</td>
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daily steroids, there are many advantages (Table 2). There is minimal, if any, suppression of fever or of the WBC count or delayed-type hypersensitivity skin tests.

The third preference is daily therapy given as a single morning dose. And last, if the above methods are not successful, multiple doses can be given throughout the day. This therapy is most commonly employed during exacerbations of asthma.

Long-acting corticosteroids, such as triamcinolone acetonide, dexamethasone, or betamethasone, should not be given to asthmatic patients in whom alternate-day therapy will eventually be recommended. Prednisone, prednisolone, and methylprednisolone are among those short-acting preparations that are appropriate for alternate-day therapy.

Should a physician want to change a daily dosage schedule to an alternate-day program, 3 to 4 times the normal daily dose may be required initially. During an upper respiratory infection or other stress, such as surgery, a large amount of prednisone or methylprednisolone can be administered for a few days, followed by a resumption of the alternate-day schedule.

Although side effects during these short-term boosts are usually minimal and temporary, some individuals may require a tapering of the dosage of corticosteroids to avoid the so-called steroid withdrawal syndrome. This syndrome consists of joint pain, muscle aches, headaches, and even fever. Apparently, the steroid withdrawal syndrome is not related to the state of the hypothalamic-pituitary-adrenal (HPA) axis or the dose of steroid administered. For reasons not understood, it occurs most commonly in elderly asthmatic patients.

While the use of adrenocorticotropic hormone (ACTH) has been suggested to stimulate the adrenal gland and speed recovery after long-term corticosteroid therapy, there is no proved advantage, and often there are disadvantages in its use. An increase in HPA suppression might result, and anaphylaxis has been described.

Patients with possible adrenal suppression must be given supplemental systemic corticosteroids in the event of an acute stressful situation. Even certain individuals receiving large doses of topically active steroids may exhibit suppression of the HPA axis. Therefore, it is appropriate to give corticosteroids during stress or if there is any doubt about the function of the HPA axis.

The asthmatic patient taking corticosteroids who requires surgery demands special consideration. If possible, large enough doses of corticosteroids must be given to maintain a symptom-free clinical picture before surgery. Corticosteroids should be given the day before, the day of, and the day after surgery. Some surgeons, due to lack of knowledge about the benefits of corticosteroids in the asthmatic patient, have refused to perform surgery on asthmatic subjects for fear of delayed wound healing or of a severe asthmatic attack.

The treatment of asthma in a pregnant patient differs little from that of the nonpregnant. Ideally, while all medications that might affect the fetus should be excluded, this is seldom possible. Corticosteroid administration in pregnancy seems to present little risk to the mother. In human subjects, there is probably no increase in fetal malformations, although one study found a significantly lowered birth weight in infants of mothers taking prednisone for treatment of infertility. Alternative-day steroids provide stabilization to the pregnant asthmatic patient. They probably can be used without much risk to the mother or unborn fetus.

The relative merits of aerosolized corticosteroids vs alternative-day corticosteroids have recently been debated. Both beclomethasone dipropionate and alternate-day corticosteroids in large enough doses can suppress the HPA axis.77 A decision as to which is better in various situations, such as childhood asthma or pregnancy, awaits further studies of long-term side effects comparing these two useful therapies. Subcapsular lenticular opacities have been reported with alternate-day administration of steroids.88 If administration of topically active corticosteroids could avoid such side effects, it would be a strong argument for their use in preference to alternate-day corticosteroids. More data such as these are needed.

There are certain situations in which oral corticosteroids might be preferable to topically active aerosolized corticosteroids. Certain individuals may have adequate control of their asthma when their therapy is switched to aerosolized steroids, but marked sinus, nasal, or ocular discomfort may occur from other atopic diseases. A reduction in oral corticosteroids or a switch to an aerosolized corticosteroid may adequately control asthma symptoms, but the patient might actually prefer alternate-day therapy for better control of organs other than the lung.

Of course, there is no place for aerosolized corticosteroids during an acute asthmatic attack.

Although articles have been written about the metabolic conditions or drugs that interact with theophylline, there are fewer data regarding alteration of the rate of steroid degradation due to these factors. Nevertheless, hyperthyroidism can increase the clearance of corticosteroids, while hypothyroidism can slow steroid clearance (Table 3). Liver disease and the antibiotic troleandomycin can also alter steroid metabolism. Individual differences in clearance have led to the concept of possible steroid resistance. Troleandomycin and erythromycin were found to have "steroid-sparing" properties; ie, they allowed for substantial steroid reduction when used with methylprednisolone.89 Responders also improved in sputum production, pulmonary function measurements, the need for aerosolized bronchodilators, and subjective evaluations.

Although the mechanism of action is unknown, 11 of 14 marked responders raised their threshold dose of methacholine required to produce a 20 percent fall in FEV1. Transient changes in hepatic enzymes occurred in some patients, but these changes did not explain the beneficial effect of troleandomycin and were not present in most of the responders.

Subsequent studies showed that troleandomycin inhibited methylprednisolone elimination, suppressed lymphocyte proliferation in vitro, and delayed theophylline clearance.30-33

Table 3—Factors that Affect Steroid Clearance*

<table>
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<tr>
<th>Increased</th>
<th>Decreased</th>
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<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
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<tr>
<td>Phenobarbital</td>
<td>Liver disease</td>
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<tr>
<td>Diphenylhydantoin</td>
<td>Antibiotics</td>
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<tr>
<td>Ephetidine</td>
<td>(troleandomycin,</td>
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<tr>
<td>Rifampin</td>
<td>erythromycin)</td>
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*In addition to individual variation.
These properties alone are not thought to explain the beneficial effects of troleandomycin.

TREATMENT OF COPD

A review of this subject has been published elsewhere. A Some principles are mentioned in Table 4 and are included, since the chest physician often calls "COPD" what an allergist calls "intrinsic asthma."

INHALED CORTICOSTEROIDS IN ASTHMA

Aerosolized corticosteroids, which have certain advantages and limitations, may serve as useful alternatives to oral steroids in the therapy of many asthmatic patients. Beclomethasone has served as the prototype; however, triamcinolone recently has been introduced commercially in the United States. We have studied both products in severely asthmatic subjects.43

Beclomethasone Dipropionate

Both European and American investigators have confirmed the beneficial and sometimes dramatic effects of beclomethasone. While at an asthma referral center in Denver, we treated some of the most severely asthmatic patients in the country with a dose of 800 μg/day and compared it to the vehicle alone.43 Not only were a significant number of patients taking the active aerosol changed from daily steroids to an alternate-day program (or a reduced alternate-day program if they had already been receiving alternate-day steroid therapy), but also objective and subjective parameters of improvement accompanied the decrease in oral steroids. Thus, there was a significant improvement in pulmonary function, asthma symptom scores for wheezing, tightness, and cough, and patient and physician evaluations favoring beclomethasone over placebo.

At long-term follow-up visits there was a significant increase in mean plasma cortisol levels beginning at two months (p<0.05) and becoming more significant at 7 months (p<0.01). Repsher et al29 reported that 400 μg/day of beclomethasone dipropionate aerosol was significantly more effective than placebo aerosol in controlling steroid-dependent bronchial asthma. In subsequent studies, corticosteroid-independent asthmatic patients responded to 400 μg as well.

Pediatric studies in the United States have not differed from the adult studies in their findings of marked improvement in a large number of patients tested. Long-term studies have confirmed the drug's continued benefit. It has been suggested that further benefit could be derived from an adrenergic aerosol when beclomethasone treatment was instituted.

Important observations in pediatric patients were that beclomethasone aerosol does not retard growth or skeletal maturation, and that even infants can be taught to use it with the use of special adaptors. Side effects such as Candida infection or growth failure were not observed in the pediatric age group.

Dosage Schedule: According to the package insert, the maximal daily intake should not exceed 20 inhalations (1,000 μg) in adults and half this dose in children 6 to 12 years of age.

Toogood et al27 have advocated using substantially higher doses than those officially recommended. They feel that the therapeutic benefit of such doses outweighs the risk of increased pituitary adrenal suppression and oral candidiasis.

In the second report from the Brompton Hospital,30 the investigators also did not notice much improvement when patients were switched from 400 to 800 μg of beclomethasone aerosol. The Brompton group confirmed their previously reported findings29 of a high incidence of thrush, greater in the 800-μg group than in the 400-μg group.

When we studied twice-daily therapy compared to a 4-times/day program, all criteria used in assessing control of asthma showed no significant differences. The advantage of the twice-daily regimen, however, was improved compliance and patient preference.

Beclomethasone aerosol has been compared with a dry powder of beclomethasone, not yet commercially available, and the 2 forms appear equally effective.

The mechanisms responsible for the anti-inflammatory, anti-asthma action of beclomethasone aerosol are unknown. Unlike other steroid-sparing substances, beclomethasone aerosol does not change methacholine reactivity.

Indications and precautions: Although the manufacturer recommends beclomethasone aerosol for patients who require long-term treatment with corticosteroids to control symptoms of bronchial asthma, in actual practice many physicians administer the corticosteroid aerosol to those patients in whom the usual bronchodilator program is failing even before oral corticosteroids have been tried. The relative effectiveness of the steroid aerosols, compared with an alternate-day, low-dose oral corticosteroid regimen, is still controversial and awaits long-term studies of adverse side effects. I have been impressed with the benefit of these aerosols in patients requiring daily corticosteroids.

In some instances, investigators have noted such dramatic clinical effectiveness as to discontinue oral corticosteroids too rapidly, leading to adrenal insufficiency. Like cromolyn sodium, these agents provide no benefit during an acute attack and probably should be discontinued should severe asthma develop, since the aerosol might exacerbate symptoms and may not penetrate deeply into the tracheobronchial tree, where it presumably has its best action. Should an upper respiratory infection or other problem develop, a short course of daily prednisone (Deltasone, Metrocorten) should be attempted, with reversion to aerosolized corticosteroids. Concurrent administration of the nasal steroid aerosol fluinusolide in patients with both rhinitis and asthma has not been associated with an additive effect on plasma cortisol levels or an increased incidence of overgrowth of Candida.44,45

Side effects and complications: The single most important side effect is oral candidiasis, i.e., thrush. In the literature, its occurrence varies from 0 to 77 percent. Increased risk factors for the development of oral thrush include concomitant antibacterial use, diabetes, large oral doses of corticosteroids, and

Table 4—Corticosteroids in Chronic Bronchitis

Steroids can benefit COPD patients with acute respiratory insufficiency
If patients who respond to steroids also respond to inhaled β-agonists may have been maximally bronchodilated, it is difficult to demonstrate improvement
Sputum eosinophilia may or may not predict favorable response
Even a few so-called emphysema patients might get objective improvement
poor dental hygiene. Approximately 60 percent of normal persons will have growth of Candida from a fungal culture of sputum, and it appears that asthmatic patients with the greatest risk for developing thrush are those who have had Candida in their sputum prior to the initiation of beclomethasone.45

Patients should be instructed to rinse their mouths after each treatment, with either a mouthwash containing alcohol or with water. Spacer devices might also minimize the development of thrush. The oral candidiasis is usually not sufficiently troublesome to necessitate stopping the steroid aerosol therapy. However, an antifungal mouthwash such as nystatin (Mycostatin, Nilstat) will usually eradicate the oral candidiasis.

Associated phenomena, which are not truly side effects, include the appearance of adrenal insufficiency associated with too-rapid tapering of oral corticosteroids and exacerbation of eczema, rhinitis, and sinusitis if these symptoms were previously suppressed by oral corticosteroids. Such exacerbations have led to new products for a specific organ, such as halogenated corticosteroids for nasal or ocular use. We have not found the corticosteroid aerosols to penetrate the lungs sufficiently enough to improve pulmonary eosinophilia.46

Other workers have reported that patients with chronic asthma might have eosinophilia after oral prednisolone has been withdrawn and beclomethasone aerosol introduced.47 Although we noted one patient who had tuberculosis while using the aerosol but not an oral preparation, this has not proved to be common and may have been an incidental finding.48 No increase in bacterial infections has been reported, although a significant decrease in serum IgG might occur.49 Hoarseness is not uncommon and does not appear to be dose-related.45 Although isolated reports of Candida or herpetic esophagitis have been reported, it is not clear if a normal immunologic status was present in such patients.50

Triamcinolone Acetonide

Triamcinolone acetonide (TAA) is a water-soluble fluorinated corticosteroid that has also undergone clinical trials in asthmatic patients. The manufacturer has emphasized its advantageous delivery system. A Freon aerosol is used as a propellant, but the adaptor was specifically designed to minimize deposition in the oral cavity, with 90 percent of the particles being smaller than 5 μ in diameter. One puff of aerosol delivers about 50 μg of triamcinolone to the airways. It has been used in doses of 400 to 2,000 μg per day. Like beclomethasone, it has proved to be an effective therapy for asthma.

In a multicentered study, triamcinolone was compared with placebo in a 6-week, double-blind study.50 Ninety-six steroid-independent asthmatic patients were randomized into 2 parallel groups, and those given triamcinolone showed highly significant improvement in pulmonary function tests, asthmatic symptoms, and subjective assessment by physician and patient. In an open, long-term study, triamcinolone continued to be safe and effective.

Kriz et al48 studied 25 steroid-dependent severely asthmatic patients in whom triamcinolone proved to be an effective substitute for large oral doses of steroids. During their study, none of the patients demonstrated a definite return of adrenal function while they received a 1,200-μg daily dose. By contrast, Falliers et al51 in an open study gave 8 to 28 inhalations (400 to 1,400 μg/day of triamcinolone) and found that adrenocortical function returned to normal or near normal in almost all of the 25 adult asthmatic patients who had required oral corticosteroid therapy daily for several years to control their asthma. Side effects have been similar to other steroid preparations, with mild sore throat and hoarseness described,52 but a relatively low incidence of thrush. Currently, it is not known whether the delivery system of triamcinolone is a substantial advantage over that of beclomethasone aerosol, and if so, whether a simple extension device, such as are now commercially available, would improve the beclomethasone aerosol delivery.

Other inhaled corticosteroids currently available or under study include flunisolide, flucortin butyl, betamethasone valerate, and budesonide. Data presently are not available regarding a possible benefit of one over another. In fact, comparative trials are difficult to design, since canisters often differ in size and delivery.

We had the occasion to compare 250 μg of flunisolide 4 times daily and 100 μg of beclomethasone aerosol 4 times daily (the recommended starting doses for each product) in a double-blind crossover study with 2 weeks' baseline observation and 4 weeks of each medication. There was no significant difference between the 2 aerosols in the 30 patients studied. Certain individuals preferred 1 aerosol preparation over another, which corresponded to objective findings implying that a switch from 1 preparation to another might be indicated if improvement is not noted upon initial aerosol treatment. Although there was no statistical difference between the 2 preparations, flunisolide and beclomethasone dipropionate aerosol, there also was a trend toward suppression of the pituitary-adrenal axis in the flunisolide group.

Thus, corticosteroid aerosols have proved to be a welcome addition to the physician's armamentarium in the treatment of asthma. Present data suggest that the benefit of aerosolized corticosteroids greatly outweighs the risk of side effects. The most commonly described side effect is oral thrush, which is easily controlled with medical management. More studies should be done to compare low-dose alternate-day corticosteroids with aerosolized corticosteroids for potential long-term side effects or for their use as first-line medications for nocturnal asthma instead of cromolyn or theophylline, as has been suggested by some Europeans. The safety record for aerosolized steroids has been good until the present. Although there are responders and nonresponders to these medications, as well as others in the treatment of asthma, the improvement seen in most patients justifies the initial enthusiasm shown for these corticosteroid aerosols.

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Newer Drugs in Management*
Calcium Antagonists

Elliott Middleton, Jr., M.D.

Any discussion of new drug therapy of asthma must take into consideration any fresh thinking about the fundamental mechanisms involved in the pathogenesis of asthma. One new line of thought considers the importance of Ca²⁺ ion translocations in the cells involved in the pathogenesis of this disorder;¹² i.e., pulmonary mast cells, mucous glands, blood vessels, vagus nerves, and inflammatory cells that collect in the airways such as eosinophils and neutrophils.

Ca²⁺ Ions and Cell Function

It is well recognized that mast cell mediator secretion, mucous gland secretion, smooth muscle contraction, the initiation and conduction of nerve impulses (the vagal bronchoconstrictor reflex), and movement of inflammatory cells are all Ca²⁺-dependent phenomena which require an increase in the intracellular concentration of free Ca²⁺ ions to take place. Therefore, any proximate stimulus to bronchoconstriction, whether it be an allergic reaction, a respiratory viral infection, cold air, or exercise, must be associated with an increase in the free Ca²⁺ ion concentration within the cytoplasm of the relevant cell types. It follows, then, that any effective antianaphylactic drug therapy must ultimately act by reducing the availability of Ca²⁺ ions to the secretory, contractile, nerve-related, and inflammatory cell motility-related functions of the involved cell types. Indeed, there is evidence that the β-agonists decrease intracellular Ca²⁺ concentrations.¹³,¹⁴

Under normal resting conditions, the intracellular concentration of free Ca²⁺ ions is approximately 10⁻⁷ M, while the extracellular concentration is 10⁻³ M, an extraordinary concentration gradient representing a 10,000-fold difference between inside and outside. Clearly, there exist powerful mechanisms to maintain this concentration gradient. The Ca²⁺-ATPase extrusion pump, the Na⁺-Ca²⁺ exchange mechanism, and binding Ca²⁺ ions to plasma membrane and to subcellular organelles, such as endoplasmic reticulum, mitochondria, and Ca²⁺-binding cytoplasmic proteins, are important in maintaining the low cytosolic concentration of Ca²⁺ ions.

When a cell is stimulated to perform a particular secretory (mast cell, mucous glands) or contractile (smooth muscle) function, the intracellular concentration of Ca²⁺ increases to approximately 5 × 10⁻⁵ M to subserve Ca²⁺-dependent stimulus-secretion coupling or excitation-contraction coupling until intrinsic regulatory mechanisms cause a fall to resting cytosolic concentrations. In secretory cells and smooth muscle, the sources of activator Ca²⁺ ions include the extracellular medium and Ca²⁺ bound to the plasma membrane or subcellular organelles; several of these sources may be employed in mast cell-mediated secretion and smooth muscle contraction.

In stimulated cells extracellular Ca²⁺ enters the cytosol through so-called Ca²⁺ channels. The Ca²⁺ channels are of 2 types: potential dependent channels (PDC), activation of which is associated with action potential generation, and receptor operated channels (ROC), which are activated ("opened") by neurotransmitters and autacoids such as histamine.

Ca²⁺ Antagonists

The Ca²⁺ antagonists are drugs that interfere with Ca²⁺-dependent functions. These compounds fall into two classes: the familiar Ca²⁺ entry blockers, nifedipine, verapamil, and diltiazem, and calmodulin-active compounds of which trifluoperazine is the prototype. The Ca²⁺ entry blockers competitively antagonize the entry of Ca²⁺ through Ca²⁺ channels, particularly the PDC.¹ The remarkable structural diversity of currently available and experimental Ca²⁺ blockers argues strongly for an equally remarkable structural heterogeneity of Ca²⁺ channels.⁷ Calmodulin-active compounds, on the other hand, interact with calmodulin, the ubiquitous Ca²⁺-dependent regulator protein, to inhibit its essential function in the activation of many Ca²⁺-dependent enzymes including several involved in contractile and secretory events.¹ Interesting, amitriptyline, a tricyclic antidepressant, was found to be a moderately effective antiasthmatic medication.⁶ Of course, the Ca²⁺ entry blockers mentioned above have found a valuable place in the management of angina, hypertension, and certain arrhythmias and other cardiovascular disease states.¹⁰,¹¹

Clinical Effects of Ca²⁺ Blockers

On this background, it was not surprising that many investigators decided to test the effect of Ca²⁺ entry blockers on Ca²⁺-dependent processes in cell types involved in the pathogenesis of asthma, such as airway smooth muscle and mast cells. Several examples of these investigations will be presented.

Weiss et al.¹⁰ demonstrated that verapamil had an antianaphylactic effect on smooth muscle tension developed in sensitized guinea pig lung exposed to antigen. However, no effect of verapamil was found on antigen-induced histamine release.

Fanta and co-workers¹⁰ examined the effect of nifedipine on guinea pig airway smooth muscle contraction stimulated by histamine. They found a concentration-dependent shift of the dose-response curve to the right, indicating that nifedipine had a modest effect to inhibit histamine-induced