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# BRONCHODILATORS AND CORTICOSTEROIDS IN THE TREATMENT OF ASTHMA

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**Summary**

Despite advancements in treatment, the incidence of asthma, asthma-related deaths and hospitalizations for asthma have increased significantly during the past decade. Although asthma mortality may now be decreasing, reasons for the worsening of morbidity and mortality in asthma remain unclear. These unexpected changes in asthma severity have sparked renewed interest in research into the pathogenesis and treatment of the condition.

$\beta_2$-Adrenergic agonists are the most commonly used class of drugs for the treatment of asthma. Recent concerns about safety issues for β-agonists caused reevaluation of prescribing practices, and using them on an as-needed basis is now more frequently accepted and recommended. In acute asthma, a $\beta_2$-adrenergic agonist is still the medication of choice. Long-acting salmeterol and formoterol, administered only twice daily, can decrease symptoms of asthma during day and nighttime. On the other hand, the role of tolerance to their bronchodilator and bronchoprotective effects is still to be determined in the treatment of asthma.

Theophylline, whose use has been limited by the potential for serious toxicity, may regain an important position in asthma treatment with the development of the knowledge about its antiinflammatory actions. Dosing theophylline on a time-related basis also improves the risk/benefit ratio and makes it a useful drug for nocturnal asthma.

Ipratropium bromide, an anticholinergic drug, still awaits a defined role in the treatment of asthma. Studies on its use for acute asthma have not achieved consensus and, for nocturnal asthma, the short duration of effect limits the benefits.

Corticosteroids, including inhaled steroids, have measurable effects on symptoms, lung function, bronchial responsiveness and inflammation associated with asthma. Side effects of chronic use limit systemic, but not inhaled administration.

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Newer preparations, like budesonide, flunisolide and fluticasone, decrease the incidence of possible side effects related to inhaled steroids by having better ratio of topical to systemic potency. Daily doses up to 1600 μg of beclomethasone (or equivalent) are considered safe and higher doses should be reserved for patients with moderate to severe asthma. Although future trials are necessary to clarify many issues related to dosing of inhaled steroids, chronotherapy studies have shown that single administration between 3 and 5:30 p.m. may be as effective as 4 times a day dosing.

**Introduction**

Despite advancements in treatment, the incidence of asthma, asthma-related deaths and hospitalizations for asthma have increased significantly during the past decade. Although asthma mortality may now be decreasing, reasons for the worsening of morbidity and mortality in asthma remain unclear. These unexpected changes in asthma severity have sparked renewed interest in research into the pathogenesis and treatment of the condition.

In recent years, experimental evidence has accumulated pointing to a potentially important role of airway inflammation in the pathogenesis of asthma and, as a result, has led to increased emphasis on the importance of the early use of antiinflammatory agents in the treatment of moderate and severe asthmatic patients. This article focuses primarily on the use of bronchodilators and steroids in asthma, including basic and controversial aspects of these drugs in chronic and acute asthma.

**Bronchodilators**

*$\beta_2$-Adrenergic agonists*

The $\beta_2$-adrenergic agonists are the most prescribed class of drugs for asthma treatment and, generally, are preferred both for the rapid relief of symptoms and for the level of bronchodilation achieved in patients with bronchial asthma (1). These drugs produce their effects through stimulation of specific $\beta_2$-adrenergic receptors located in the plasma membrane, resulting in alterations in adenylyl cyclase and elevations in intracellular cyclic adenosine monophosphate (AMP). Cyclic AMP is responsible for the physiologic response, which is, in the bronchi, relaxation of smooth muscle with bronchodilation, increased ciliary beat frequency and a reduction in mucus viscosity (2).

Long-acting $\beta_2$-adrenergic agonists, whose bronchodilator effect lasts for 12 hours, have different binding to the $\beta_2$-receptor, which is thought to produce persistent functional agonism. Salmeterol and formoterol, long-acting $\beta_2$-adrenergic agonists, are highly lipophilic and have a high affinity for the receptor by different mechanisms. The side chain of salmeterol (Fig. 1) binds to a specific site within the $\beta_2$-adrenergic receptor that allows prolonged activation of this receptor (3). Formoterol, on the other hand, appears to enter the plasmalemma lipid bilayer from which it gradually leaches out and is thus available over a prolonged period to stimulate the receptor (4).

The prolonged agonism in bronchial smooth muscle and other locations by salmeterol and formoterol leads to a substantially longer-lasting bronchodilation. Anderson *et al.* found that at 6.5 hours after administration, salmeterol was still providing relief of exercise-induced asthma, but albuterol was beginning to wear off (5). Pearlman *et al.* compared the same drugs in 234 patients with asthma and found that the mean area under the curve for the forced expiratory volume in the first second ($FEV_1$) was consistently greater in patients treated with salmeterol, one dose of which produced 12 hours of steady bronchodilation (6).

The $\beta_2$ selectivity and the prolonged action of salmeterol and formoterol represent a great advance in asthma therapy, for example, in the treatment of asthmatics with nocturnal exacerbations. However, some problems still persist and limit the benefits of this class of drugs. Some adverse reactions result from the expected pharmacological actions of the drugs. Because of the widespread distribution of $\beta_2$-adrenergic receptors, a number of undesired responses result when $\beta_2$-adrenergic bronchodilators are absorbed into systemic circulation. The ability to avert these side effects by reducing plasma drug concentrations is one of the advantages of administering β-agonists by inhalation (7).

Table I shows the side effects and mechanisms of $\beta_2$-adrenergic agonists (8-16). Tremor is the most common side effect. Most of the side effects tend to disappear with continuing drug use and do not have any long-term health implications. The toxic effects of greatest concern are those that have impact on heart, although myocardial side effects have not been shown to be a major clinical problem in multicenter clinical trials (17, 18). The

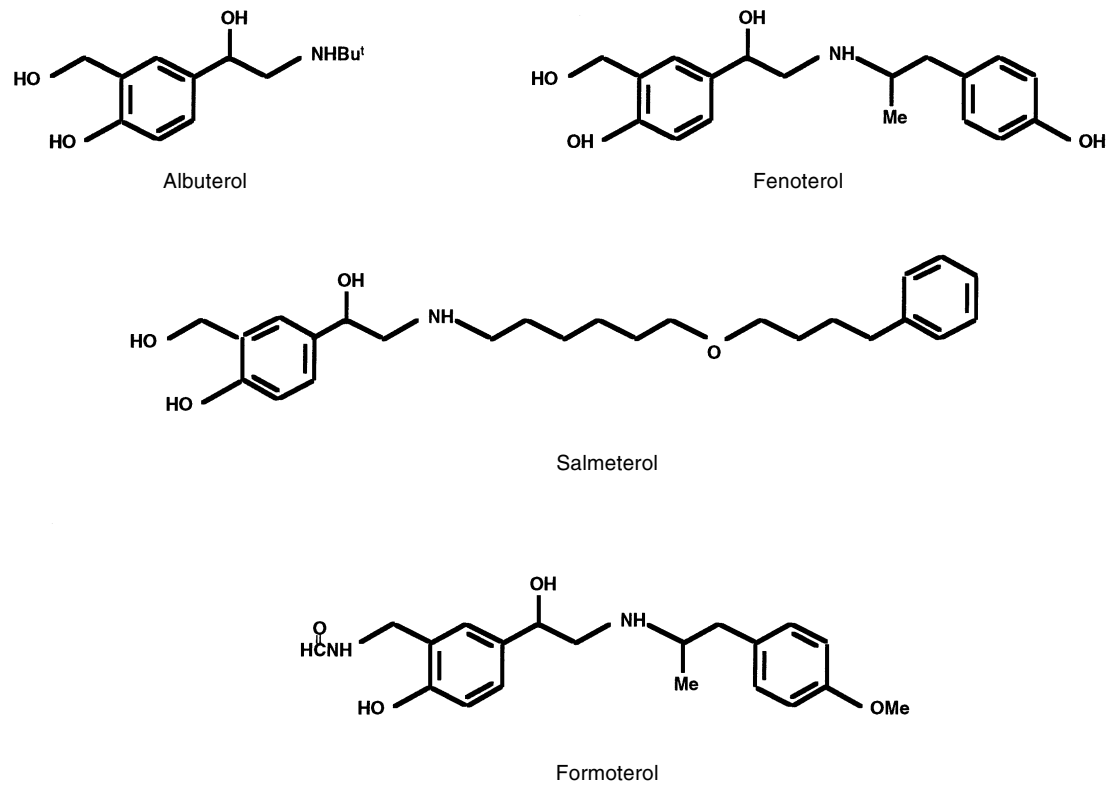


Fig. 1. Structures of albuterol and fenoterol, $\beta_2$-adrenergic agonists, and salmeterol and formoterol, long-acting $\beta_2$-adrenergic agonists.

potential adverse reactions to $\beta_2$-adrenergic agonists in addition to the standard toxicity that should be mentioned are tolerance to bronchodilator effects, tolerance to bronchoprotective effects, heightened airway reactivity and increased mortality rate.

Tolerance (tachyphylaxis) to the untoward effects is a well-recognized positive consequence of regular administration of $\beta_2$-adrenergic agonists (19). On the other hand, lessening of bronchodilator response also occurs with continuous dosing (20). For instance, Repsher and coworkers found tachyphylaxis to occur within 8 weeks of therapy with regard to duration, but not magnitude, of the acute bronchodilating effect of albuterol administered on a regular basis (21). However, others have found decreases in lung function of patients taking regular doses of inhaled albuterol (600-2000 μg/day) over periods of 3-5 weeks (22-24) and terbutaline (2000 μg/day) during 4 weeks (25).

*Table I: Side effects of $\beta_2$-adrenergic agonists.*

| Side effects | Mechanisms |
|---|---|
| Tremor | Stimulation of $\beta_2$-receptor in skeletal muscle (8, 9) |
| Increased heart rate, tachyarrhythmias | Vasodilation with reflex tachycardia and stimulation of $\beta_2$-receptor in heart (10, 11) |
| Decrease in arterial oxygen tension | Vasodilation in areas of compensatory pulmonary vasoconstriction, aggravating ventilation-perfusion imbalance (12, 13) |
| Hyperglycemia, hypokalemia | Glycolysis and insulin release with a shift of potassium to the intracellular space (14-16) |

Tolerance to β-agonists has been attributed not only to routine administration but also to overuse and has also been associated with long-acting $\beta_2$-adrenergic agonists (26).

The ability to protect against allergic-, chemical- or exercise-induced bronchoconstriction is an important therapeutic advantage of these bronchodilators and is more susceptible to tachyphylaxis. Cheung *et al.* showed that regular treatment with salmeterol led to a reduction in the protective effects against methacholine-induced bronchoconstriction within 4-8 weeks (27). Impaired protection against bronchoconstrictors due to regular use of salmeterol or albuterol has been reported by others (28-31). Tolerance to the protective effects of the short-acting $\beta_2$-adrenergic agonist terbutaline against methacholine and the indirect bronchoconstrictor adenosine monophosphate over 7 days of treatment was reported by O'Connor *et al.* The bronchodilator response was, however, unchanged (32). These observations suggest that different intracellular events may regulate the functions of bronchodilation and the protection against bronchoconstrictors.

Mechanistically, tolerance may reflect the desensitization of $\beta_2$-receptors in the airways. Desensitization is a complex multistep process that may involve the uncoupling, sequestration, and, ultimately, the downregulation of receptors (33). A considerable body of indirect evidence suggests that prolonged exposure of $\beta_2$-receptors to agonists can lead to hyporesponsiveness and/or receptor loss both *in vitro* in human airways smooth muscle preparation (34, 35) and in white blood cells isolated from subjects receiving β-agonists (36).

Steroids have been shown to reverse tolerance to β-agonists in nonasthmatic volunteers (37), and a large number of *in vitro* studies have shown that steroids can reverse β-receptor downregulation (34, 38-40). A recent report has shown that exposure of human lung tissue to dexamethasone caused both an increase in β-receptor mRNA and elevations in the number of $\beta_2$-receptors in the tissue (41). However, the situation regarding the effects of systemic or inhaled corticosteroids on modulating $\beta_2$-adrenergic responses in asthmatics is less clear (42). There is some evidence to suggest that inhaled corticosteroids are unable to prevent tolerance to long-acting $\beta_2$-adrenergic agonists (43, 44).

The tolerance to bronchodilation, once established, is stable even with further continuation of treatment. This self-limitation questions the clinical relevance of this tachyphylaxis. In contrast, there may be a complete loss of the bronchoprotective effects within days of initiation of treatment which is not prevented by use of inhaled corticosteroids, mainly in the case of long-acting β-agonists. These findings suggest that long-acting $\beta_2$-agonists should be prescribed with caution, watching for evidence of tachyphylaxis suggested by reduced protection to triggers or increasing need for short-acting β-agonists (44).

Although more controversial, the effects of $\beta_2$-agonists on increasing bronchial responsiveness and mortality rate of asthmatics may be more important than the tachyphylaxis and pharmacological toxicity because, if confirmed, they would be contrary to the aims of asthma therapy. In some animal studies, chronic administration of $\beta_2$-adrenergic agonists increased airway reactivity without changing the bronchorelaxant effect (45, 46). In humans, there have been reports showing a rebound effect (23, 47), reports showing increased bronchial hyperreponsiveness (BHR) by chronic use, and reports not showing it. In a study by Vathenen *et al.*, repeated doses of terbutaline daily for 14 days led to a 40% reduction in protection against histamine-induced bronchoconstriction in the morning and 82% reduction in the afternoon. On day 15, the first day without terbutaline, histamine responsiveness increased to levels higher than baseline, *i.e.*, rebound BHR (47).

Taylor and Sears reviewed studies on the relationship between bronchodilators and BHR (48). The changes noted were often small and not always statistically significant. Nevertheless, there was considerable evidence for a negative effect of β-agonists on airway hyperresponsiveness. Of 15 studies, 10 demonstrated increased BHR, lower $PC_{20}$ (provocative concentration causing a 20% fall in $FEV_1$) or lower $PD_{20}$ (provocative dose causing a 20% fall in $FEV_1$) during regular $\beta_2$-adrenergic agonist therapy, and in 5 of these the change was statistically significant. Decreased responsiveness (higher $PC_{20}$ or $PD_{20}$) was found in only 2 studies, in 1 of which it was statistically significant (23, 25, 32, 47-59). Although more studies are needed to conclude that these drugs heighten BHR of asthmatics, this may be a mechanism for diminished asthma control and increased mortality rate detected by several authors in recent years.

In an attempt to explain the reported increase in deaths caused by asthma in some countries (60, 61), attention has turned toward the possibility that

$\beta_2$-agonists were contributing to the process. Spitzer *et al.* examined the prescription of asthma medication and deaths and near deaths in Saskatchewan, Canada. The results revealed that deaths increased among patients using more than 1.4 canister of $\beta_2$-adrenergic agonists per month, and the greatest risk was associated with a pattern of increasing use. The investigators concluded that the greater use of β-agonists was principally a marker of a greater severity of asthma, which itself was associated with an increased risk of fatal or near fatal asthma (62-64).

In the 1970s there was an epidemic of deaths from asthma in New Zealand, possibly caused by fenoterol, a relatively nonselective $\beta_2$-adrenergic bronchodilator, delivered at a higher dose than the other commonly used drugs. Three case-control studies of patients with asthma who died during this period indicated an increased risk of death among patients treated with fenoterol, and the risk increased further in subgroups selected for increased severity of asthma. Finally, a dramatic reduction in the use of fenoterol in New Zealand was associated with a return of mortality due to asthma to low levels despite continued increases in total sales of $\beta_2$-adrenergic agonists (65). Other authors argued that the association between fenoterol and deaths from asthma did not coincide in time (66) and that countries such as Germany and Belgium have used fenoterol extensively but have been spared an epidemic of asthma fatalities (67).

The use of $\beta_2$-adrenergic agonists on an as-needed (for symptoms relief) basis is accepted and frequently recommended, but is still a matter of considerable controversy. Sears *et al.* showed that asthma was better controlled when patients used the β-agonist of their choice only as needed, compared with regular use (q.i.d.) of fenoterol (50). However, other trials compared albuterol or terbutaline on a regular basis with an as-needed basis and failed to find differences (6, 68-70). The Asthma Clinical Research Network demonstrated that, in patients with mild asthma, the regular use of albuterol is not associated with a deleterious effect on asthma control. On the other hand, in this study the authors were unable to demonstrate any additional beneficial effect of regularly scheduled treatment beyond that achieved with an as-needed basis despite a more than 5-fold difference in the amount of drug administered (9.3 puffs *vs.* 1.6 puffs per day). This indicated that patients with mild asthma should receive inhaled albuterol on an as-needed basis only; this approach also reduces the cost of medication (71).

$\beta_2$-Adrenergic agonists are the treatment of choice for exercise-induced bronchospasm (EIB). Two inhalations of these agents will typically prevent EIB (72). For instance, albuterol prevents EIB in more than 80% of subjects (73), but the protection lasts less than 3 hours in most patients (74, 75). The use of salmeterol before exercise protects against EIB over a 12-hour period, thus enabling most adults and adolescents with EIB to inhale a single dose in the morning before leaving home and then be protected throughout their work or school hours (76, 77). However, the role of tolerance to protection against EIB has not been assessed in long-term clinical studies on the treatment of EIB.

The long-acting $\beta_2$-adrenergic agonists are properly administered as inhalation twice daily to prevent symptoms of asthma. They are particularly effective for patients who awaken at night with asthma. For some patients who have only nocturnal awakening, the long-acting $\beta_2$-adrenergic agonists may be given once daily. A study carried out over 3 months confirmed the efficacy of salmeterol for nocturnal worsening of asthma. In addition, no increased adverse effects or decreased asthma control was seen with the salmeterol group (6). Fitzpatrick *et al.* showed that a dose of 50 μg of salmeterol inhaled twice daily objectively improved sleep quality and nocturnal asthma lung function (78). To investigate whether these benefits in nocturnal asthma are due to postulated antiinflammatory actions of salmeterol, Kraft *et al.* treated moderate to severe asthmatics not taking steroids with 100 μg salmeterol twice daily or placebo for 6 weeks in a double-blind, crossover study. There were no significant changes in BHR, lung function or indices of airway inflammation, although clinical parameters improved as measured by percentage of nights with awakening and rescue $\beta_2$-agonist use. These data indicate that the improvement caused by salmeterol in nocturnal symptoms of asthma is not associated with changes in airway inflammation, BHR or lung physiology in moderately severe asthma (79).

In acute asthma, a $\beta_2$-adrenergic agonist is the medication of choice. Commonly, initial treatment consists of inhaling a short-acting $\beta_2$-adrenergic agonist up to 3 times an hour for the first hour, then once an hour. Inhaled treatment can also be given continuously until an adequate clinical response is achieved or adverse side effects limit further

administration (*e.g.*, excessive tachycardia, arrhythmias or tremor). Long-acting $\beta_2$-adrenergic agonists play no role in the treatment of acute exacerbations (80).

*Theophylline*

Theophylline has been shown to have so many different antiasthma actions that it is still undetermined which ones are important in the treatment of chronic or acute asthma. Although it is generally considered to be a bronchodilator, evidence indicates that it may also have important immunologic, antiinflammatory and muscular effects. Bronchodilation is associated with increased concentrations of cAMP within airway smooth muscle. The finding that theophylline inhibits phosphodiesterase (PDE) isoenzymes, thus preventing the breakdown of cAMP, supports the hypothesis that its ability as a bronchodilator is derived from this mechanism (81-83). Inhibition of PDE isoenzymes probably has other beneficial consequences than bronchodilation. For instance, inhibition of PDE-IV, considered important in inflammatory cells (84-87), can explain some of the antiinflammatory and immunomodulatory properties of theophylline observed in asthmatics.

Theophylline at therapeutic serum concentrations has been shown to influence IgE-mediated immediate reactions in the upper airways of allergic patients (88). Pauwels *et al.* demonstrated that both theophylline and enprofylline (a methylxanthine similar in structure to theophylline, lacking adenosine antagonist activity) were effective at attenuating the late-phase response in patients with asthma who were subjected to a bronchial allergen challenge (89). Also studying asthmatics after allergen challenge, Sullivan *et al.* demonstrated, on biopsy specimens, that both total eosinophil number and activation were significantly decreased after treatment with theophylline when compared with placebo (90). Ward *et al.* observed that theophylline, at a low serum concentration, inhibited the late asthmatic reaction and the allergen-induced increase in $CD4^+$ and $CD8^+$ lymphocytes observed in peripheral blood 48 hours after allergen challenge (91). More recently, other antiinflammatory and immunomodulatory effects of theophylline in asthma were shown by withdrawal of therapy (92) and in nocturnal asthma studies. In a study by Kraft *et al.*, theophylline caused an improvement in overnight lung function in asthma associated with a suppression of alveolar macrophage leukotriene (LT) $B_4$ production, a decrement in bronchoalveolar lavage (BAL) neutrophils and a correlation between the theophylline-induced decrease in $LTB_4$ and decrement in BAL granulocytes (93).

An effect of theophylline which remains controversial is its action on respiratory muscles. Aminophylline increases diaphragmatic contractility and reverses diaphragm fatigue (94, 95). This effect has not been observed by all investigators, and there are now doubts about the relevance of these observations to the clinical benefit provided by theophylline (96, 97).

Theophylline has the greatest potential for serious toxicity of any medication for asthma. Toxicity is not idiosyncratic, it relates to concentration. Serious toxicity increases in likelihood and degree as serum concentrations exceed 20 μg/ml. This made theophylline use more complicated by requiring serum concentration measurements and special attention to variables that influence blood levels. In addition, the emphasis on the antiinflammatory treatment of asthma contributed to positioning theophylline as a third-line medication by some expert panels. The decline in theophylline use is illustrated in Figure 2. Nevertheless, the development of sensitive and rapid assays, the advent of slow-release products and the knowledge about antiinflammatory actions have greatly changed the future place of theophylline in the management of asthma.

Excessive serum theophylline concentrations can be the result of error by medical personnel or the patient or they can occur as a consequence of drug interactions, fever or physiologic abnormalities such as liver disease or heart failure. Sessler surveyed 5557 consecutive serum theophylline concentrations measured in the emergency departments of two hospitals over 2 years. Ten percent of the theophylline concentrations were > 20 μg/ml and 2.8% (116 cases) were > 30 μg/ml. Factors contributing to high serum concentrations are listed in Table II. The most common side effects were gastrointestinal, neurologic (tremor and nervousness) and cardiovascular manifestations, as well as metabolic disturbances. Seizures were present in 6% of the cases (98).

Many studies have now shown that dosing theophylline on a time-related basis is superior to the standard homeostatic dosing (99-102). That is, looking for the serum theophylline concentration over a 24-hour period to be relatively constant is not as beneficial to the asthmatic individual

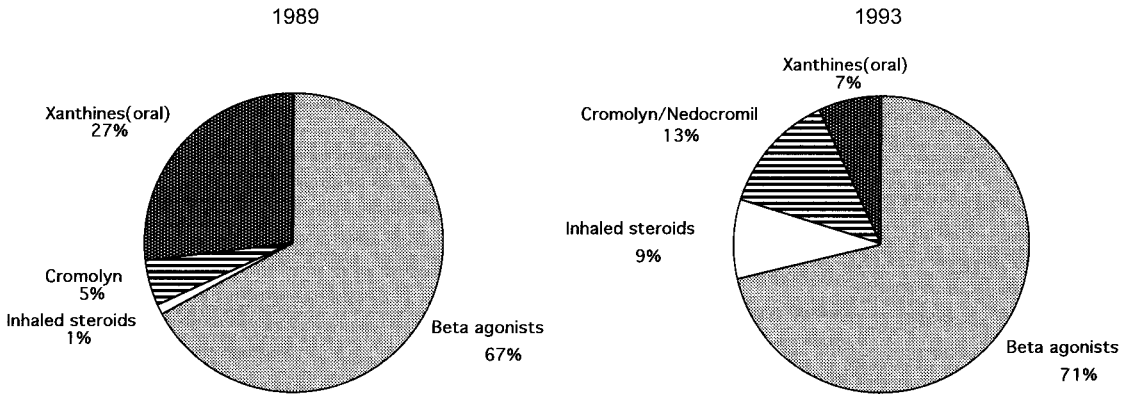


Fig. 2. Asthma medication use by U.S. pediatricians. The individual segments of each circle represent the proportion of total asthma prescription accounted for by the respective drug categories. Data from the National Drug Therapeutic Index, IMS America, Ltd., 1994.

*Table II: Factors contributing to theophylline toxicity in 116 cases.*

| Contributing factors | % of cases |
|---|---|
| Patient error | 29 |
| Took extra doses for symptoms relief | 17 |
| Given extra by parent or caretaker | 8 |
| Took incorrect dosage or medication | 3 |
| Accidental ingestion by an infant | 1 |
| Physician or pharmacy error | 21 |
| Excessive dosage prescribed | 16 |
| Duplicate theophylline prescriptions | 4 |
| Mislabeled medication container | 1 |
| Impaired theophylline metabolism | 21 |
| Congestive heart failure | 14 |
| Liver disease | 6 |
| Medications: erythromycin, cimetidine | 5 |
| Viral infection | 3 |
| Intentional self-poisoning | 10 |
| None or unknown | 26 |

Adapted from Sessler (98). In some case more than one factor was present.

as having peaks and troughs of the serum theophylline concentration at the appropriate times of day. Martin *et al.* (99) have shown that giving a twice-daily theophylline preparation which produced relatively constant therapeutic serum theophylline concentrations in the 11-14 μg/ml range was not as effective in treating patients as a single daily preparation giving peaks of approximately 16-18 μg/ml during sleep-related hours and falling to as low as 7-8 μg/ml during the daytime hours. Comparing the $FEV_1$ measured every 2 hours during the daytime showed no difference because during the daytime, lung function independent of medication is at its best. Thus, high drug levels are not required to produce a given amount of bronchodilation during the daytime. The improvement in the overnight decrement in lung function indeed depended on a higher serum theophylline concentration. Although the traditional way of administering theophylline produced a nocturnal therapeutic theophylline level, there still was an approximately 28% decrease in overnight $FEV_1$. With the higher serum theophylline concentration, the overnight decrement in $FEV_1$ was only approximately 9%.

D'Alonzo *et al.* also demonstrated the concept of time-related drug levels in improvements of lung function. These investigators looked at the effects over a 4-hour period of time from 2-6 p.m. compared with 2-6 a.m. In the afternoon they did not find a significant correlation of increasing serum theophylline concentrations with improvement in $FEV_1$, which was similar to many other daytime studies. Looking at the 4-hour time period of 2-6 a.m., however, they did find a progressive and significant increase in the $FEV_1$ as the serum theophylline concentration was increasing (103).

Another myth about theophylline needs to be addressed, which is that theophylline will grossly disturb sleep. In the study by Martin *et al.,* no significant difference was found between the higher and lower serum theophylline concentrations in regard to polysomnographic evaluation. The sleep latency (how long it takes an individual to go to sleep), the sleep efficiency (how well the patient sleeps) and the different sleep stages were not different between the two concentrations of

theophylline. Interestingly, there was a marked reduction in the amount of oxygen desaturation that occurred overnight with the higher serum theophylline concentration (99).

For acute severe asthma that is refractory to initial conventional treatment and that may lead to death, aminophylline should be used as a slow intravenous infusion with careful monitoring and a plasma theophylline concentration should be measured prior to infusion.

*Anticholinergics*

Being specific antagonists of acetylcholine at the muscarinic receptor, atropine-like drugs relieve cholinergically mediated airway obstruction. Also called antimuscarinics, anticholinergic drugs were accepted as possibly useful in asthma treatment only after the introduction of the atropine derivative ipratropium bromide. This drug is insoluble in lipids and, unlike atropine, it does not cross biologic membranes easily and has only minimal systemic absorption. Only inhaled forms of anticholinergics are safe for clinical use because systemic availability of these drugs is related to major adverse reactions. Side effects include dryness of the oropharynx, bad taste after inhaling, cough, nervousness and irritation from the aerosol (104, 105).

Anticholinergic drugs may be of some use in asthma, particularly in acute severe asthma and nocturnal asthma. In chronic asthma, ipratropium may also be useful as an alternative means of therapy when the side effects of $\beta_2$-adrenergic agonists become an issue or when adverse reactions to other agents arise, for example, an intolerance to theophylline. Although acute asthma exacerbations are associated with increased vagal tone, suggesting a rationale for the use of anticholinergics, the results of clinical trials have been contradictory. While some studies have found inhaled anticholinergics to be effective bronchodilators in acute asthma, others have reported no additional benefit when they are combined with $\beta_2$-adrenergic agonists.

Studies comparing ipratropium to a $\beta_2$-adrenergic agonist concluded that anticholinergics should not be used alone to treat acute asthma exacerbations (106-109). In addition, these studies found clinical benefits of ipratropium in association with a $\beta_2$-adrenergic agonist as compared to a $\beta_2$-adrenergic agonist alone. However, trials with a similar design, comparing single-dose albuterol with single-dose albuterol and ipratropium, failed to show that combined therapy was better (110, 111).

Two separate meta-analyses have suggested that if a difference does exist between the ipratropium/β-agonist combination and a β-agonist alone, it is quite small. Higgins *et al.* found an approximately 12.5% improvement in pulmonary function with the ipratropium/β-agonist combination compared to a β-agonist alone (112). Ward suggested that the ipratropium/albuterol combination conferred an additional 0.55 SD units (peak expiratory flow rate or FEV1) compared with a β-agonist alone. This represents an additional mean increase in peak expiratory flow rate (PEFR) of 44 l/min (113). The applicability of such a conclusion is limited by the fact that most regimens employed featured only single doses of albuterol rather than the multiple sequences recommended in current consensus reports.

To obtain data on this issue, McFadden *et al.* combined ipratropium bromide with a therapeutic regimen anchored by the sequential administration of albuterol. One hundred and thirty-one patients received ipratropium and 123 who did not served as controls. The presence of ipratropium in the regimen did not influence discharge/admission patterns, length of stay in the emergency department, rate of improvement of the patients or the level of PEFR achieved. The authors concluded that anticholinergic agents such as ipratropium are not first- or even second-line treatment for acute asthma in emergency situations (114). Future studies are necessary to evaluate the role of combination therapy for those patients not initially responding to inhaled $\beta_2$-adrenergic agonists. In the meantime, anticholinergics should be used in patients who do not respond adequately to initial therapy (corticosteroids and β-agonists) and who progressively develop more severe bronchoconstriction.

The increased vagal tone at night is one possible mechanism of circadian alteration in lung function. Many studies have not demonstrated a benefit of vagolytics such as atropine or ipratropium bromide, but these studies were all carried out during the daytime. Morrison *et al.* have shown that marked bronchodilation depends on the time of day the anticholinergic medication is administered. That is, during the daytime hours they found only slight bronchodilatory effects from atropine. Alternately, at 4 a.m. there was a marked improvement in PEFR to approximately the daytime levels (115, 116). The problem with any vagolytic medication is that the duration of effect is not particularly long. Thus, even if given only at bedtime,

within 2-3 hours the potency of the medication will have been eliminated.

**Corticosteroids**

Corticosteroids are considered the mainstay of asthma therapy. The introduction of inhaled preparations and the revelation of asthma as an inflammatory disease made this class of drugs the most suitable for treatment of asthmatic patients. Corticosteroids alleviate major symptoms of asthma by reducing airway reactivity while restoring the integrity of the airways. However, the mechanism(s) of action used to achieve these effects are not fully understood. Clinical efficacy of steroid therapy is, to a great extent, the result of their inhibitory effect on leukocyte recruitment into the airways.

Corticosteroids enter the cell via passive diffusion through the plasma membrane (117). In the cytoplasm, the hormone binds to the glucocorticoid receptor. Translocation to the nucleus and DNA binding are the next steps necessary for exertion of the biologic effects of corticosteroids. Almost all cells implicated as contributing to the inflammatory process, including lymphocytes, eosinophils, neutrophils, macrophages, monocytes, mast cells and basophils, are susceptible to inhibition by corticosteroids (118) (Table III).

Probably due to their actions on cells and mediators involved in the inflammatory mechanisms of asthma, corticosteroids have measurable clinical benefits regarding airway inflammation. They reduce BAL, sputum and tissue parameters of inflammation concomitantly with a reduction in BHR. Laitinen *et al.* compared the effect of budesonide, an inhaled steroid, and inhaled terbutaline on symptoms, lung function and airway inflammation assessed by electron microscopy of bronchial biopsy specimens. Treatment with budesonide was accompanied by increased numbers of ciliated cells and intraepithelial nerves and fewer inflammatory cells, including eosinophils, especially in the epithelium. Budesonide also improved bronchial responsiveness to inhaled histamine (119).

A variety of patterns of pulmonary allergic reactions can develop following antigen challenge in sensitized individuals (120, 121). Immediate reactions generally occur within minutes following antigen exposure or challenge, resolve 30-60 minutes later and are characterized by airway obstruction. The late-phase reactions (LPR) begin approximately 3-4 hours following exposure and reach maximal intensity within 4-8 hours, and the airway

*Table III: Cellular effects of corticosteroids.*

| Cells affected | Effects of corticosteroids |
|---|---|
| Lymphocytes | Reduction of circulating cell counts, apoptosis<br>Inhibition of IL-2 produciton<br>Inhibition of IL-2 receptor generation<br>Inhibition of antigen-driven proliferation<br>Inhibition of IL-4 production |
| Eosinophils | Reduction of circulating cell counts<br>Reduction of epithelial and mucosal cell counts<br>Reduction of cell influx into cutaneous late-phase reaction<br>Inhibition of IL-4 and IL-5-mediated cell survival |
| Neutrophils | Reduction of cell influx into cutaneous late-phase reaction<br>Reduction of cell influx after nasal challenge |
| Macrophages | Inhibition of IL-1 release<br>Inhibition of interferon-$\gamma$ release<br>Inhibition of tumor necrosis factor release<br>Inhibition of granulocyte-monocyte colony-stimulating factor release<br>Inhibition of enzyme release |
| Monocytes | Reduction of circulating cell counts |
| Mast cells | Reduction of mast cell-derived mediators after nasal challenge<br>Possible reduction of histamine content and releasibility |
| Basophils | Reduction of circulating cell counts<br>Reduction of cell influx into cutaneous late-phase reaction |

obstruction resolves in 12-24 hours. The latter is associated with tissue inflammatory response (122). A number of factors, such as circadian rhythms and viral upper respiratory tract infections, have been noted to enhance the likelihood of developing an LPR following allergen challenge (123, 124). The pulmonary LPR has provided a more comprehensive understanding of asthma pathophysiology and treatment as a human model of asthma and airway inflammation.

In contrast to the immediate reaction, corticosteroids significantly affect the LPR in the lungs. Booij-Noord *et al.* were the first to observe the protective effects of a 9-16 day treatment with prednisolone on the late response to house dust inhalation challenge (125). Using toluene diisocyanate (TDI) for challenge, Fabbri *et al.* demonstrated that 3 days of daily single-dose prednisone could block both the late reaction and the resultant increase in airway responsiveness following TDI challenge (126). Pepys *et al.* found that inhaled steroids (200 mcg of beclomethasone dipropionate) given 30 minutes prior to challenge blocked the late, but had no effect on the immediate, response (127). Finally, Cockroft and Murdock also found that inhaled beclomethasone had no effect on the immediate reaction, but it did block the LPR and the subsequent development of BHR (128).

Beneficial effects on BHR have been observed within as little as 3 weeks of inhaled steroid therapy for chronic asthma, and with long-term treatment no tolerance has been observed up to 3 years of follow-up (Fig. 3). Unfortunately, discontinuation of the inhaled steroid has often been shown to result in a disappearance of the beneficial effects within weeks to months of stopping therapy (25, 129-134). Haahtela *et al.* investigated whether inhaled steroids can be discontinued after a 2-year treatment. Thirty-seven patients taking 1200 μg of budesonide were assigned either to a reduced dose (400 μg) or to placebo treatment. Treatment with the lower dose did not appear to be a problem. In contrast, discontinuation of budesonide led to deterioration of bronchial responsiveness and lung function (Fig. 3) (134). Therefore, it

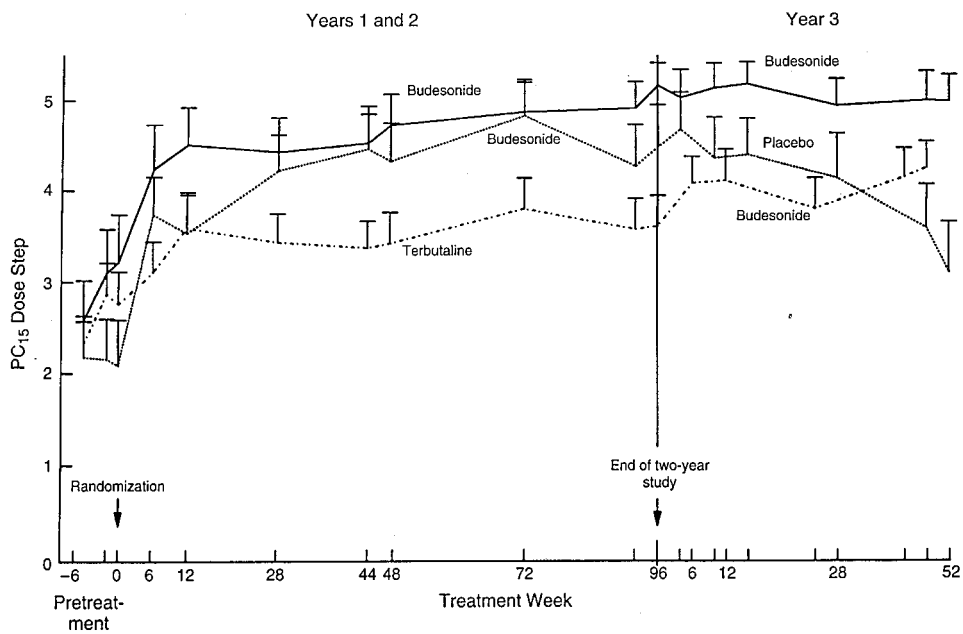


Fig. 3. The $PC_{15}$ dose steps 0, 1, 2, 3, 4 and 5 represent histamine concentrations of 1, 2, 4, 8, 16 and 32 mg/ml, respectively. The three groups of patients were treated as follows: double-blind budesonide for 3 years (solid line), double-blind budesonide for 2 years followed by double-blind placebo for 1 year (dotted line), and double-blind terbutaline for 2 years followed by open-label budesonide for 1 year (dotted and dashed line). The first two groups were treated as one until the beginning of the third year. (Reproduced from T. Haahtela et al. *Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma*. New Engl J Med 1994, 331: 700-705. With permission of the Massachusetts Medical Society, Waltham, Massachusetts.)

seems that for the majority of patients treatment with inhaled steroids suppresses the underlying mechanisms of asthma and causes remission of the condition but does not cure the disease (135).

Beclomethasone, triamcinolone, flunisolide, budesonide and fluticasone are the steroid compounds already in clinical use as inhaled medication for asthma treatment. The advantage of these drugs is given by the proportion of the inhaled drug that reaches the target cells in the airways as well as the fraction of the dose that enters the systemic circulation to produce side effects. Comparable ratios of topical to systemic potency for beclomethasone dipropionate (0.10), flunisolide (0.05) and triamcinolone acetonide (0.05) and a substantially higher ratio for budesonide (1.00) were reported. Similar measurements were subsequently performed for fluticasone propionate and an even higher ratio of topical to systemic potency (25.00) was observed (136-137).

Another desirable property in an inhaled steroid is a rapid metabolic clearance of any corticosteroid that reaches the systemic circulation. After inhalation a large proportion of the dose, 80-90% is deposited on the oropharynx and swallowed. It is then available for absorption into the systemic circulation through the liver. Fluticasone and budesonide are subject to extensive first-pass metabolism in the liver so that less of these drugs reaches the systemic circulation. Complete data are not available for comparison of all agents. Available information indicates that the newer corticosteroids possess lower oral bioavailability, as in the case of fluticasone (138-141). The systemic availability is also a consequence of the method used for administration. For instance, pressurized metered-dose inhaler and dry powder inhaler lead to different proportions between lung deposition and systemic availability of budesonide (142).

The purported side effects of inhaled steroids are adrenal suppression, bone demineralization, carbohydrate metabolism alteration and reduction of linear growth in children. The incidence of hypothalamic-pituitary-adrenal suppression is dose-dependent. The available data indicate that doses of 400 μg/day or less in children and 800 μg/day or less in adults can be considered safe (143). Although some bone remodeling indices suggest alterations caused by chronic use of inhaled steroids, the clinical utility of these markers remains unclear, making prospective studies on bone density and risk for fractures necessary (144). Also, for changes in carbohydrate metabolism, particularly decreased insulin sensitivity, clinical relevance is improbable except perhaps in patients with subclinical diabetes mellitus (145). The possible effects of inhaled steroids on linear growth in asthmatic children have been extensively studied and general agreement indicates that poor control of asthma is the major determinant of poor growth, although the immediate peripubertal growth velocity may be more vulnerable to high doses of inhaled steroids. Therefore, the lowest effective dose should be used (146, 147).

Garbe *et al.* recently showed that prolonged administration of high doses of inhaled steroids increased the risk of ocular hypertension or open angle glaucoma. Neither doses smaller than 1600 μg of beclomethasone nor nasal steroids were associated with increased risks. The authors suggested that inhaled steroids should be routinely questioned in newly diagnosed cases of ocular hypertension or glaucoma, and ocular pressure should be monitored in patients receiving high doses of inhaled steroids over several months (148).

Local side effects of inhaled steroids depend on the delivery system, dose and frequency of administration. The most common side effect is dysphonia, which affects one-third of patients and is reversible after discontinuation of treatment. The incidence of oral candidiasis can be decreased by using a volume spacer or by rinsing the mouth after administration (149, 150). In contrast to adverse effects of inhaled steroids, adverse effects of systemic steroids are a well-recognized clinical problem in the treatment of asthmatic patients. The side effects of systemic corticosteroids include osteoporotic fractures, cataract development, weight gain, hypertension, myopathy, glucose intolerance, easy bruising, adrenal insufficiency, immune dysfunction and a range of mood and behavioral changes.

Inhaled steroids are now the appropriate first treatment for patients who need almost daily inhalation therapy with $\beta_2$-adrenergic agonists, as recommended by the International Consensus on Asthma (151). Recently, some investigators proposed inhaled steroids for patients with milder asthma and stressed the importance of early start to avoid possible irreversible airway obstruction, mainly in children (152). However, there is a need to balance the potential for adverse systemic effects with the expected benefits. The dose of inhaled steroid to start the treatment is not known. As this form of administration has a slow onset of

action, some authors argue that patients who are not controlled lose confidence in the treatment and this is likely to decrease compliance. In addition, a higher dose would be more effective and eventually could be reduced (153). However, therapy with inhaled steroids has been shown to be effective in low doses. Jeffery *et al.* showed that 4 weeks of treatment with 400 μg/day of budesonide decreased the numbers of mast cells, eosinophils and foci of eosinophil degranulation in the bronchial mucosa (154). While future trials comparing the two approaches (high-to-low *vs.* low-to-high doses) are necessary, high doses should be reserved for patients with moderate and severe asthma.

In terms of frequency of inhaled steroid administration, although a schedule of 4 doses per day may be chosen for patients with more severe asthma, twice-daily administration has been shown to be equally effective (155). Recent studies on chronotherapy have provided more insight on timing of corticosteroid administration. For those patients with marked nocturnal worsening of disease, pharmacotherapy must be altered to specifically tailor treatment for sleep hours. Even in the treatment of asthma which does not worsen at night there may be optimal timing of medication use to provide maximal efficacy and minimal toxicity.

Although numerous investigators have demonstrated that corticosteroid side effects, such as adrenal suppression, are influenced by the dosing schedule as well as the dosage, the alternative approach of evaluating differences in corticosteroid efficacy by varying dose schedules has received less attention. Endogenous corticosteroid secretion is at its circadian peak level at the beginning of the activity span, and if dosing of corticosteroids is timed to this natural peak, the risk and magnitude of adrenal suppression are thought to be minimized. Recognition that corticosteroid administration should be adjusted to achieve the most favorable balance between time-dependent variations in both efficacy and adversity is central to therapeutic success.

An initial study by Reinberg *et al.* in 1974 evaluated the spirometric response of 12 asthmatic boys to a single variably timed dose of methylprednisolone (40 mg) or placebo. The 24-hour mean PEFR improved more over the placebo baseline when the steroid injection was administered at 3 p.m. or 7 a.m. The 7 p.m. and 3 a.m. dosing times were less effective (156). In a follow-up study, 9 adult asthmatics were treated with a combination corticosteroid preparation dosed at 8 a.m. and 3 p.m. daily for 5 weeks. In addition to subjective improvement in dyspnea, the 24-hour mean PEFRs increased significantly over the 5 weeks without the development of significant adrenal suppression as determined by urinary corticosteroid metabolite production (157). Furthermore, in a similar study involving 8 asthmatic adults, Reinberg *et al.* evaluated the response over 8 days to corticosteroids dosed at 8 a.m. and 3 p.m. compared with 3 p.m. and 8 p.m. In agreement with their prior studies, the 8 a.m. and 3 p.m. dosing schedule was more effective in producing an improvement in the 24-hour mean PEFRs than the alternative 3 p.m. and 8 p.m. dosing schedule (158). Based on these studies, the authors conclude that in the treatment of chronic asthma with nocturnal worsening, administration of corticosteroids should be restricted to the morning and early afternoon hours for a diurnally active patient.

To better clarify the contribution of timing of corticosteroids on their ability to block circadian recruitment of inflammatory cells into the lung and attenuate the nocturnal worsening of asthma, Beam *et al.* evaluated the response of blood eosinophil counts, bronchoalveolar lavage cytology and overnight pulmonary function to a single variably timed dose of prednisone. Seven asthmatic males with stable, well-controlled daytime asthma but persistent nocturnal worsening of spirometry were treated in a double-blind, placebo-controlled design with a single 50 mg dose of prednisone at dose times of 8 a.m. or 3 p.m. or 8 p.m. Compared with placebo, a single prednisone dose at 3 p.m. resulted in a reduction in the overnight percent fall in $FEV_1$ (Fig. 4). In contrast, neither the 8 a.m. nor the 8 p.m. prednisone dose when compared with placebo resulted in overnight spirometric improvement (159). These dose times represent the common components of once-daily and twice-daily dose schedules. Because a single 50-mg dose of prednisone was used in all three phases, these data suggest that timing of corticosteroid may be more pertinent than dosage in altering the pathogenesis of nocturnal asthma. Although the study was not a therapeutic trial, it is in agreement with the studies of Reinberg *et al.*

In addition to effects on overnight spirometry, the 3 p.m. dose phase of the study of Beam *et al.* resulted in a significant pancellular reduction in 4 a.m. BAL cytology not demonstrated with either

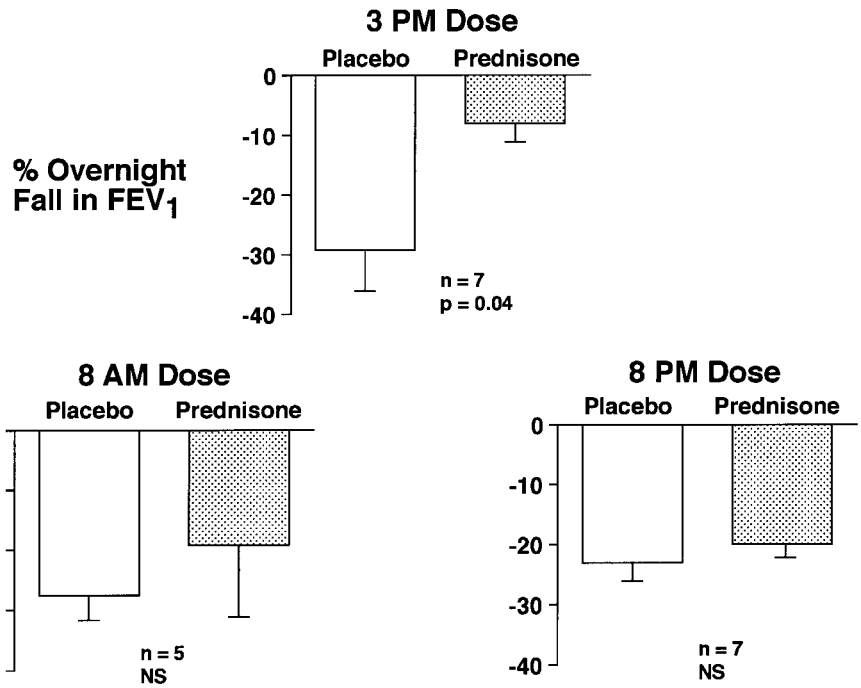


Fig. 4. The overnight $FEV_1$ response, expressed as a percentage of the bedtime $FEV_1$, to a single dose of prednisone and placebo. All vertical axes are the percentage overnight fall in $FEV_1$ measured from bedtime to 4 AM awakening (before bronchodilator treatment). Only the 3 PM dose of prednisone significantly reduced the percentage overnight fall in $FEV_1$. (Reproduced from W.R. Beam et al. *Timing of prednisone and alterations of airways inflammation in nocturnal asthma.* Am Rev Respir Dis 1992, 146: 1524-30. With permission of the American Journal of Respiratory and Critical Care Medicine.)

alternative dose phase. Indeed, the 8 p.m. and 8 a.m. dose phases produced no significant change in any BAL cellular profile. This observation suggests that the 3 p.m. dose of prednisone interrupted the inflammatory cascade at one or more critical steps in its genesis. It is noteworthy that Martin *et al.* demonstrated elevations in total white cell number, neutrophil, eosinophil and lymphocyte counts in the BAL fluid of the nocturnal asthma cohort when compared with asthmatics without nocturnal worsening (160). These observations support a collaborative cellular mechanism of inflammation which is corticosteroid-sensitive yet dependent on timing in addition to dosage.

In a study by Pincus *et al.* using inhaled steroids for asthma therapy, the 3 p.m. dose timing effect was again evaluated. In this study, a single dose of 800 μg of triamcinolone acetonide at 3 p.m. was compared with the same total dose divided into 200 μg administered al 7 a.m., 12 p.m., 7 p.m. and 10 p.m. The group receiving the 3 p.m. inhaled steroid had improvement equivalent to that seen in the q.i.d. dosing group as measured by $FEV_1$, morning and evening PEFR and the use of β-agonists. The finding that 3 p.m. dosing for inhaled steroids was as effective as q.i.d. dosing again provided evidence for the value of the 3 p.m. dosage time in asthma therapy. In addition, the group receiving treatment at 3 p.m. had no greater evidence of adrenal suppression or drug toxicity than the four times daily treatment group (161). At this time there is no evidence to support an evening dose schedule because it poses the greatest risk of adrenal impairment without documented efficacy in improving nocturnal asthma.

An ongoing study by Pincus *et al.* was designed to assess whether a single administration at 8 a.m. or 5:30 p.m. would be equally beneficial when compared to conventional q.i.d. dosing. Subjects were given 4 weeks of triamcinolone acetonide as 200 μg q.i.d. or 800 μg at 5:30 p.m. or 800 μg at 8 a.m. Preliminary data shows that the three treatment groups are comparable at baseline. For PEFR in the morning, the 8 a.m. group had statistically less improvement than the other two groups. For PEFR in the evening, there was a

trend toward least improvement in the 8 a.m. group. There are no significant differences between groups for changes in $FEV_1$, $PC_{20}$ or β-agonist use. The data suggests that once-daily dosing at 5:30 p.m. may be as effective as q.i.d. dosing, whereas 8 a.m. is not as effective as either of the other time points. Thus, the optimal window of time for dosing of inhaled steroids may be between 3 and 5:30 p.m. (162).

All patients admitted to the hospital for acute asthma require systemic corticosteroids for several days. However, patients with acute asthma in the emergency department still pose a question about who should receive corticosteroid early as a first-line drug therapy. Most available data support a corticosteroid benefit in this setting, and there is evidence that failure to treat with corticosteroids contributes to asthma deaths (163). A meta-analysis reviewed more than 700 articles to identify 30 randomized, controlled trials suitable for analysis. The investigators conclude that steroids given in the emergency department significantly reduced the rates of admission and the number of future relapses in the first 7-10 days. It did not matter whether steroids were given orally or intravenously, as long as a minimum of 30 mg of prednisone (or its equivalent) was given every 6 hours (164). Higher doses had no obvious advantage, but further studies are needed to establish the best dose and frequency.

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