Reassessment Of The Role Of Theophylline In The Current Therapy For Nocturnal Asthma

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Abstract: ***Background:*** **Symptoms of asthma commonly increase at night for a variety of reasons. While different options are available for the management of nocturnal asthma, theophylline has maintained a prominent role in treating this problem, and it is widely promoted as a first-line agent. Very recent reports stress the use of anti-inflammatory agents as the drugs of choice for the long-term treatment of asthma.**

Methods: **Using the key words "asthma," "theophylline," "bronchodilators," "adrenal cortex hormones," "beclomethasone," "triamcinolone acetonide," and "disodium cromoglycate," the MEDLINE files were searched from 1982 to the present. Articles dating before 1982 were accessed from cross-reference of the more recent articles.**

Results: **Sustained-release theophylline preparations are effective in decreasing the rate of exacerbations of nocturnal asthma symptoms, but theophylline has risks of major toxicity and serum concentrations must be monitored. Inhaled corticosteroids are also useful in controlling nocturnal asthma, and they reduce inflammation, which is the basic problem in asthmatics. Inhaled anticholinergics and oral controlled-release albuterol are also helpful in reducing symptoms of nocturnal asthma.**

Conclusions: **A suggested approach to managing nocturnal asthma includes corticosteroids inhaled through a spacer device at optimum doses, adding inhaled albuterol or oral sustained-release albuterol and then ipratropium with a spacer. If control is not maintained with this regimen, sustained-release theophylline may add benefit to inhaled steroid therapy in reducing nighttime asthma symptoms. Long-acting inhaled β_2 agonists show promise and could be the adjunctive treatment of choice when they become available in the United States. (J Am Board Fam Pract 1992; 5:281-8.)**

Theophylline is an effective agent for managing nocturnal asthma. Many authors have reported the efficacy of sustained-release forms of theophylline for reducing symptoms associated with the "morning dip" or nighttime asthma.[1-7] The purpose of this article is to examine the role of theophylline in managing this aspect of asthma. Specifically, we look at alternatives to theophylline and offer guidelines for determining when theophylline is indicated. The issue presented in this article is not whether theophylline is effective in nocturnal asthma, because clearly it is helpful. The issue is whether safer alternatives are also efficacious. In light of the recently launched National Asthma Education Program[8] by the National Institutes of Health emphasizing anti-inflammatory therapy for asthma and in light of continued reports of devastating theophylline toxicity,[9-12] this issue is quite timely.

Using the key words "asthma," "theophylline," "bronchodilators," "adrenal cortex hormones," "beclomethasone," "triamcinolone acetonide," and "disodium cromoglycate," the MEDLINE files were searched from 1982 to the present. Articles dating before 1982 were accessed from cross-reference of the more recent articles.

Pathogenesis of Nocturnal Asthma

As many as 85 percent of patients with asthma who are seen in general practice admit to waking up at night with wheezing or other symptoms.[13] Fifty percent of these patients will wake up at least once during a week's time, in spite of their symptoms being well-controlled during the day. Other patients may not awaken at night but may have some chest tightness or wheezing when they wake

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up in the morning. Those with asthma experience this increase in symptoms independent of the time they go to sleep. Objective measurements, such as the peak expiratory flow rate (PEFR), may reflect this "early morning dip," and this morning dip also correlates with asthmatic deaths, most of which tend to occur in the early morning.[14]

The theories accounting for nocturnal asthma are many, including recumbent posture, impaired mucociliary clearance, airway cooling, allergens in the bedroom, gastroesophageal reflux, and the time when bronchodilator therapy has been taken. These factors, however, are probably only contributory and do not explain why asthmatic patients deteriorate at night. This disease is difficult to study, as there is no easy way to monitor pulmonary function at night without disturbing sleep. Rapid eye movement might be important.[15]

Circadian rhythms are generally regulated in the hypothalamus and in humans exhibit a 24-hour schedule.[16] Even persons without asthma will have a diurnal variation in lung function, with the widest airway caliber at 4 PM and the narrowest at 4 AM (Figure 1).[17] The normal change is only about 10 percent and therefore is generally not noticed by the healthy person. In asthmatic patients there appears to be a greater increase in the diurnal variation of airway width. This change in airway caliber is directly related to the degree of bronchial hyperresponsiveness. Generally, by

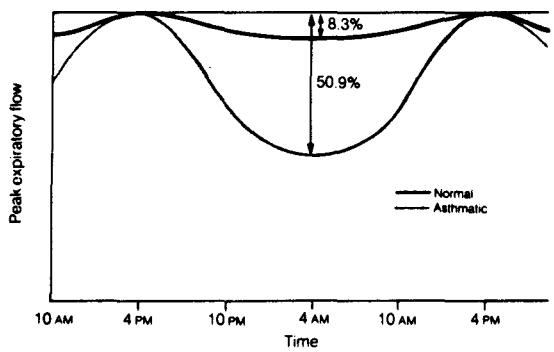

Figure 1. Diurnal variation in peak expiratory flow is exaggerated in patients with asthma. The difference between maximal airflow at 4 PM and minimal airflow at 4 AM normally averages 8.3 percent; in patients with asthma, however, the average variation can be as high as 50.9 percent.

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4 AM asthmatic patients are in the late phase of an acute asthmatic attack, and their airways will respond to nonspecific stimuli, for example, histamine or cigarette smoke.[19]

Possible abnormalities in nocturnal asthma include the following:

1. The parasympathetic nervous system is the major control of airway caliber, and increased cholinergic activity at night results from an increase in vagal tone.[15,18,19] At night, acetylcholine release from the nerve endings, facilitated by the increased cholinergic activity, in both healthy and asthmatic persons[15] corresponds to the increase in airway narrowing.[20] Asthmatic patients have an abnormal inhibitory mechanism in the cholinergic nerves (the M_2 muscarinic receptor), and acetylcholine release may be enhanced by inflammatory mediators.[18,20] Asthmatic airways are more responsive to acetylcholine release from cholinergic nerves, which causes the airways to be hyperresponsive to any type of stimulus, resulting in bronchospasm. Intravenous atropine is very effective in reversing nocturnal bronchoconstriction. Cholinergic mechanisms, therefore, are extremely important in nocturnal asthma.[21]
2. There is a paucity of adrenergic nerves in the lung.[18] To bronchodilate, the airways must rely on circulating serum epinephrine to stimulate the β_2-adrenergic receptors.[21] At night, especially in those with asthma, the level of epinephrine circulating in the blood is extremely low. In addition, a significant change in β-adrenergic receptor density and function occurs in patients with nocturnal asthma.[22] Consequently, persons with asthma have a tendency to experience bronchoconstriction. Release of inflammatory mediators at night may result from a low level of endogenous circulating serum epinephrine. Epinephrine levels may be even lower during an acute attack. This low level of epinephrine reduces the time of stimulation of the β-adrenergic receptors in the mast cells and smooth muscle of the airways. An increase in the plasma histamine is found at night. Similarly, at 4 AM microvascular leakage and plasma exudation occur. Epinephrine is very effective in counteracting microvascular leak-

age through stimulation of the α-adrenergic receptors in the bronchial arterioles.[21]

3. During normal circadian rhythm, serum cortisol reaches its lowest concentration around midnight, about 4 hours before the maximum fall in the PEFR. Cortisol levels fall even lower in asthmatic patients. A lack of cortisol will allow release of mediators from the steroid-sensitive cells, such as eosinophils and macrophages. Correspondingly, bronchoalveolar lavage shows a marked increase in the amount of inflammatory cells at 4 AM compared with the amount found at 4 PM, especially in asthmatic patients who have acute nocturnal exacerbations. Low endogenous cortisol levels are also important in regulating microvascular leakage.[23] Circadian changes in both epinephrine and cortisol have little effect on normal airways, but because of this inflammatory response in asthmatic patients, even small changes are exaggerated.[23]
4. The role of the products of the noncholinergic nonadrenergic system, such as substance P, could be important in the inflammatory response; however, the lack of substances, such as epinephrine, which counteracts the inflammatory response in asthmatic patients, is more important than the mediators of the response itself.[19]
5. The greatest increase in release of mediators of the inflammatory response occurs at 4 AM. The major mediators are platelet-activating factor and leukotrienes. Inflammation is augmented by the drop in plasma cortisol and epinephrine levels and helps in the production of submucosal edema of the airways. Mucosal edema is worsened by the supine position because of the associated increase in bronchial venous pressure. Similarly, the increased mucosal thickness will exaggerate any constrictor influences in the airways.[23] Recent research has defined further the role of inflammation in nocturnal asthma.[24]
6. Gastroesophageal reflux is worse at night and has been shown to stimulate vagal responses. In most cases, reflux is not a factor, but in some asthmatic patients who are deteriorating and in whom there is an already marked increase in cholinergic tone, inflammation, and edema, any additional insult can be of consequence.[15-21,23]

Efficacy of Theophylline in Nocturnal Asthma

Several studies in the past decade clearly have shown the efficacy of theophylline both in reducing nighttime and morning symptoms and in improving pulmonary function tests.[1-7,25] Symposia on the specific subject of nocturnal asthma and theophylline have been published recently.[26,27] Different sustained-release dosage formulations with varying serum concentration-time profiles have shown efficacy.[1-3] Both single daily dose preparations given in the evening and products given every 12 hours have proved effective.[1-3]

When choosing a theophylline product, clinicians should be aware not only of its absorption characteristics, including any effect of food on absorption, but also of when to expect peak serum theophylline concentrations, so they can know the appropriate time in the evening to prescribe the medication. Products designed to have peak serum concentrations from midnight to 6 AM (after a dose between 5 and 8 PM) have been quite effective.[1,2] Once a product is chosen, switching to another product is not recommended without again establishing serum concentrations and patient response. All sustained-release theophylline products are definitely not the same. Detailed analyses of various products are available in the literature[26-28] and are beyond the scope of this article. Although theophylline is helpful for nocturnal asthma, it is not an anti-inflammatory agent, and concomitant therapy that reduces inflammation is also needed.

Efficacy of Inhaled Corticosteroids

Because asthma is primarily an inflammatory disease, steroids inhaled with a spacer device are now recommended as routine maintenance therapy for all but those with the mildest of adult asthma.[8,29] Because of the high efficacy of inhaled steroids that are properly delivered and have optimal dosages and because of the long duration of action of these agents, many patients will experience the elimination of nocturnal asthma with their use. Inhaled steroids available in the United States, including beclomethasone, triamcinolone, and flunisolide, are indicated for use every 12 hours. If a patient's asthma is not well controlled, an inhaled steroid schedule of every 6 to 8 hours will likely be needed, but most patients do well on a 12-hour schedule.

Horn, et al.[30] studied 14 patients with asthma who had nocturnal symptoms and morning dips in PEFR. Morning dips in PEFR were substantially reduced in 8 of 14 patients who were treated with beclomethasone plus inhaled albuterol therapy. Joad, et al.[3] reported a very low rate (9 percent) of "bothersome" asthma between 4 AM and 8 AM in 8 patients who were receiving maintenance-inhaled beclomethasone therapy and inhaled albuterol (every 6 hours) and in 1 patient receiving alternate-day prednisone plus albuterol. Harper, et al.[31] found that patients with asthma who were not fully controlled with theophylline therapy or inhaled β_2-agonists had their symptoms and morning PEFR improved with the addition of inhaled beclomethasone. Tan, et al.[32] reported that even in asthmatic patients who were dependent on oral steroids, the addition of the inhaled steroid budesonide resulted in a reduction in nocturnal symptoms and a smaller drop in morning PEFR. Tan, et al. also found that oral prednisone dosage could be reduced. Other investigators have found budesonide to be effective in nocturnal asthma.[33,34]

When prescribing inhaled steroids, it is important to include a spacer device (a holding chamber such as Aerochamber™ or InspirEase™) for three reasons. First, oropharyngeal candidiasis will be virtually eliminated,[35] and second, efficacy will be increased.[35,36] Finally, most patients do not use plain metered-dose inhalers optimally. Even when they demonstrate use correctly to a health professional, proper technique will not be routinely used at home. Spacer devices enhance aerosol deposition, especially in patients who have poor inhaler technique. Use of a spacer is certainly not always correct either, and the patient's technique should be checked frequently.

Efficacy of Controlled-Release Albuterol

Although inhaled β_2-adrenergic agonists are preferred to oral products during the day for "rescue" therapy and for prevention of exercise-induced asthma, inhaled agents currently available in the United States are relatively short acting. As a result, the efficacy of agents, such as albuterol aerosol, is not of sufficient duration to cover the typical 8 hours of sleep required by many individuals. Controlled-release albuterol tablets have been shown by at least four groups of investigators to have an efficacy similar to that of sustained-release theophylline.[37-40]

Pierson, et al.[37] conducted a double-blind placebo-controlled study in adolescents and adults comparing sustained-release theophylline with controlled-release albuterol (Volmax™) for 12 weeks, with both drugs being given every 12 hours. No differences in efficacy between the two treatments were found including increase in 1-second forced expiratory volume (FEV_1) and symptoms.

Higenbottam, et al.[38] also compared sustained-release theophylline with controlled-release albuterol in adults with asthma in a randomized crossover trial and found no difference in efficacy between the two treatments, including sleep interference. More side effects were observed in the theophylline group, and patients and physicians favored controlled-release albuterol. To our knowledge, there are no reports comparing a dose used every 12 hours with use of controlled-release albuterol at bedtime only. A regimen of daily use of aerosol albuterol and controlled-release albuterol given at bedtime would be appealing, because there is higher efficacy and fewer side effects with the inhaled drug. While study is needed on this question, a therapeutic trial in an individual patient is reasonable. In the United States currently a twice-daily form of albuterol tablets is available (Proventil Repetabs™), which is formulated to provide two stages of drug release. Controlled-release albuterol (Volmax™) is not currently available in the United States. It has less serum-concentration fluctuation because of its osmotic pump delivery, but the clinical significance of this design has not been reported. As with theophylline, these products do not address inflammation and thus are adjunctive to anti-inflammatory agents.

Efficacy of Salmeterol and Formoterol

Long-acting inhaled β_2-agonists have been released outside the United States and provide an effective means of managing nocturnal asthma. The duration of action for salmeterol and formoterol extends for 12 hours. Fitzpatrick, et al.[41] conducted a double-blind, randomized, placebo-controlled, crossover study in adults with asthma and found that salmeterol inhaled twice daily was effective in improving nocturnal peak expiratory flow rates and the quality of sleep.

Formoterol has been shown to be superior to albuterol aerosol in the treatment of nocturnal asthma, including improvement in FEV_1 and a diminished need for "rescue" medication.[42]

Further studies are needed regarding regular use of 12-hour inhaled β_2-agonists because of a recent study by Sears, et al.,[43] which has raised concerns over the scheduled use of fenoterol. Although worsening asthma in some patients with regular use of fenoterol does not necessarily implicate other β_2-agonists, this area is controversial.[44] In our opinion, studies of bedtime-only use of salmeterol or formoterol are definitely warranted. Bedtime-only use would remove some of the concerns raised when full doses of inhaled β_2-agonists are taken around the clock. As with other bronchodilators, these agents are adjunctive to anti-inflammatory therapy. While one report suggests an anti-inflammatory component to the action of salmeterol, much more research is needed.[45]

Efficacy of Anticholinergics

As discussed earlier, vagal mechanisms are important in nocturnal asthma, and this point has been recently emphasized by Morrison, et al.,[46] who almost totally reversed bronchoconstriction at 4 AM by giving intravenous atropine. Cox, et al.[47] found that a large dose (160 μg) of inhaled ipratropium given in the evening was effective in reducing the dip in PEFR in the early morning. Coe and Barnes[48] reported that 9 of 18 patients responded to oxitropium in a double-blind, placebo-controlled study. The mean dip in PEFR with 400 μg of oxitropium was 5 percent versus a 19 percent drop in PEFR with a placebo. Further study is needed to define the role of anticholinergic bronchodilators in nocturnal asthma.

Concerns about Theophylline Toxicity

Despite hundreds of articles in the last 20 years regarding theophylline pharmacokinetics and factors that alter theophylline clearance, adverse effects, including serious toxicity, continue.[9-12] Considering the incentive most clinicians have not to report toxicity, the true rate could be much higher than realized. In addition, although the rate of toxicity in carefully controlled studies is often low, this rate does not reflect the reality of routine practice. Relatively common adverse effects include anorexia, nausea, and vomiting, as well as nervousness and insomnia. Life-threatening toxicity, which may occur without the warning of "minor" side effects, includes seizures and cardiac arrhythmias.

If theophylline is to be prescribed for nocturnal asthma, a thorough knowledge of the numerous factors that modify dosage requirements is as essential as is appropriate monitoring of serum concentrations.[9-12]

When using theophylline, such factors as concurrent diseases and drugs, as well as the patient's age, diet, and smoking history, must be evaluated. Although a discussion of these factors is beyond the scope of this article, several reviews are available.[49-51]

A Rational Approach to Managing Nocturnal Asthma

Because of the concern over theophylline toxicity and because of the efficacy of inhaled steroids and other therapies, we believe that other therapies should be tried before theophylline. If theophylline is then indicated to control nocturnal asthma, it is a useful agent. A trial of rela-

Table 1. Suggested Approach to Managing Nocturnal Asthma.

1. Initiate inhaled corticosteroid therapy delivered with a spacer device. Start with a low dose, e.g., beclomethasone 4 puffs every 12 hours with spacer; if the patient is poorly controlled during the day as well, use every 6 hours until the patient is well controlled.[54,55] Carefully observe inhalation technique in both children and adults. Routine asthma therapy in children should include cromolyn for all but the mildest cases. If beginning inhaled steroids, consider dropping cromolyn.
2. If inhaled corticosteroid therapy is insufficient at current dose, gradually increase the dose up to the maximum recommended daily doses for adults and children. Periodically recheck inhalation technique.
3. If morning dip persists after optimizing doses of inhaled steroids, try adding 2 puffs of inhaled albuterol at bedtime; if response is inadequate, drop inhaled albuterol at bedtime and begin a trial of sustained-release albuterol at bedtime.*
4. If response is still insufficient, begin a trial of ipratropium using a spacer, e.g., at least 4 puffs (80 μg) at bedtime.
5. If all above measures are inadequate, maintain the anti-inflammatory therapy, drop sustained-released albuterol and ipratropium and add a low dose of sustained-release theophylline (e.g., target serum concentrations ≤10 μg/mL using a single daily-dose product that when taken at 5 to 8 PM is designed to achieve peak serum concentrations between 12 midnight and 8 AM). Slightly increase dose if response is inadequate.
6. If all above measures are insufficient, reassess environmental controls and consider other options as appropriate, such as specific immunotherapy and oral steroids.

Note: Establish presence of nocturnal asthma through symptoms and peak expiratory flow rate upon awakening.

*When approved, salmeterol or formoterol will be the agents of choice to add to inhaled steroids.

tively low-dose theophylline (target serum concentration 5 to 10 μg/mL) is appropriate when accompanied by careful monitoring of serum concentrations and watching for factors that modify theophylline clearance. Serum concentrations of 5 to 10 μg/mL are adequate for many patients.[53] If the initial low dose of theophylline is not sufficient, a small increase in dosage can be tried, while keeping the serum concentrations less than 15 μg/mL in most patients. Very few patients need a steady state serum theophylline concentration of 15 to 20μg/mL at home.

Table 1 summarizes a rational approach to managing nocturnal asthma. This summary is consistent with the NIH National Asthma Education Program and other current literature on the management of asthma.[8,29] Most patients with asthma can be controlled very well on long-term aerosol-only therapy, including inhaled steroids and inhaled β_2-agonists for "rescue" treatment and prevention of exercise-induced asthma.[29,52] Children should receive cromolyn as their basic therapy; if control on cromolyn is not adequate, then a regimen using inhaled steroids with a spacer device should be initiated.[8,29]

Conclusion

Because of the efficacy of the basic and safer therapy of inhaled steroids (or cromolyn initially in children) and inhaled β_2-agonists, theophylline should not be used initially for nocturnal asthma. We agree with other authors[29,52] that most patients who have asthma can be managed extremely well with aerosol-only therapy. For patients who still have nocturnal asthma after optimizing inhaled steroid therapy, a trial of sustained-release albuterol tablets or ipratropium or both is warranted. If that therapy is insufficient, a careful trial of relatively low-dose theophylline is warranted. When the inhaled β_2-agonists, such as salmeterol, which have greater than 12-hour durations of action, are released in the United States, they should become the agents of choice to supplement inhaled steroid therapy for patients with nocturnal asthma.

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Editor's Comment

The use of β-agonists in the treatment of asthma continues to be controversial, and their therapeutic role continues to receive close scrutiny. As the above paper goes to press, the reader is referred to two additional references recently published on the subject, which were not available to the authors of the preceding paper:

1. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habrick B, Cockcroft D, et al. The use of β-agonists and the risk of death and near death from asthma. N Engl J Med 1992; 326:501-6.
2. Burrows B, Lebowitz MD. The β-agonist dilemma. N Engl J Med 1992; 326:560-1.

The "Guidelines for the Diagnosis and Management of Asthma," released last year as an Expert Panel Report by the National Heart, Lung, and Blood Institute (reference 8 in the above paper), will be further discussed in a forthcoming issue of *JABFP*.