

Update

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Theophylline's place in today's asthma therapy

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Theophylline was once hailed as an efficient bronchodilator in managing bronchial asthma, but in recent years has fallen from favor as a treatment of choice because of its narrow margin of safety and various adverse effects.

However, when properly monitored and employed, this drug can play a highly useful and appropriate role in the treatment of patients with asthma.

History

Recognition of theophylline's bronchodilating properties in the 1920s led gradually from intravenous use for status asthmaticus to oral preparations for acute episodes of asthma. After a period of clinical use, however, reports indicated that adverse effects were potentiated when theophylline was combined with ephedrine, the usual oral preparation. The major side effect was seizures.

Knowledge about the pharmacokinetics of theophylline and the consequent development of assays for serum levels of the drug enabled correlation of serum level with clinical efficacy and side effects. The ability to measure serum levels greatly reduced the risk of seizures, as did individualizing the dosage. Sustained-release delivery sys-

tems have further altered the way the drug is used.

Over the years, theophylline's approval rating among clinicians has gone through several cycles, but today many do not consider this medication first-line therapy for the management of chronic asthma.

Current asthma pharmacotherapy

Beta-adrenergic agonists and corticosteroids. One current approach to asthma treatment is to first use an aerosolized B-adrenergic agonist.¹ If that fails, we add cromolyn sodium or aerosolized corticosteroids. If baseline pulmonary function is low, inhaled corticosteroids may be augmented by a short course of systemic corticosteroids and/or theophylline.

The emphasis in the mid-1980s on inflammation as a major factor in the treatment of asthma has led to a more liberal use of aerosolized corticosteroids — medications with the anti-inflammatory activity of oral steroids, but far fewer side effects.

Each drug considered as first-line therapy for chronic asthma has both benefits and limitations. The most potent bronchodilators are the B-agonists, making them most effective in coping with

exercise-induced asthma (EIA) and other causes of acute attacks.

Both B-agonists and theophylline have a very rapid onset of effect compared with cromolyn. However, for long-term therapy for patients with chronic asthma, cromolyn has some advantages, due to its anti-inflammatory properties. When duration of effect is desired, theophylline has unique advantages.

Despite the widespread popularity of corticosteroid therapy, we may be focusing too intently on what initiates an inflammatory response. It's also important to become aware of what stops an inflammatory response and especially on what reverses it. What are the relationships among the various drugs, not only in stopping the inflammatory process, but also in promoting healing?

Theophylline. Although theophylline has been relegated to a relatively lower position, it still has important roles to play in the management of asthma. Benefits of theophylline therapy include:

- rapid onset of action,
- long duration of action,
- ease of administration,
- individualization of dosage, and
- reduction of corticosteroid requirements.

Moreover, theophylline's use has

This report is based on an article that originally appeared in a supplement to the June 1989 issue of *The Journal of Respiratory Diseases*, entitled, "Asthma: Concepts and Controversies."

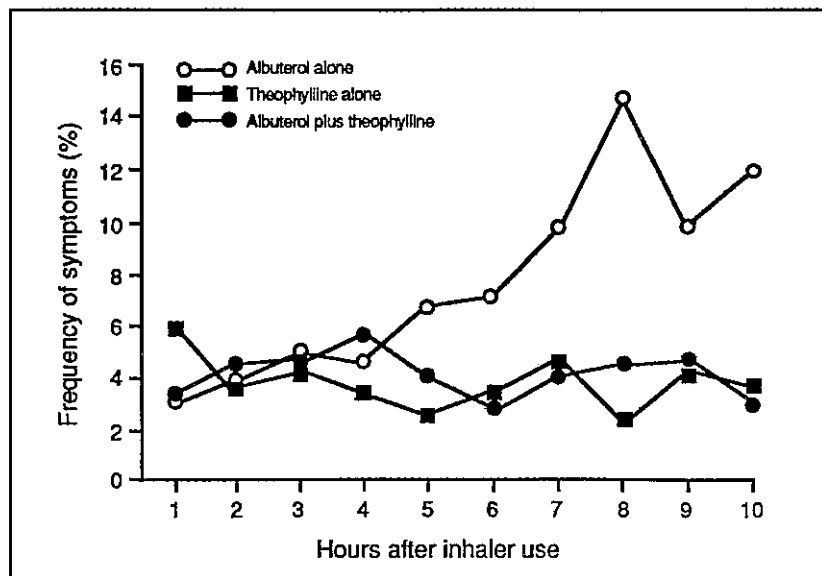


Figure 1

Mean frequency of symptoms among asthma patients using three types of bronchodilator therapy for asthma: Note that breakthrough symptoms with albuterol are related primarily to treatment during the night. (From Joad JP, Ahrens RC, Lindgren SD, et al: "Relative efficacy of maintenance therapy with theophylline, inhaled albuterol and the combination for chronic asthma." *J Allergy Clin Immunol* 1987; 79:78-85.)

taught us a great deal about asthma, such as:

- increasing sophistication in application of clinical pharmacology,
- the importance of individualizing drug dosage,
- a unique perception of the potential for drug interactions,
- limitation of sustained-release delivery systems, including potential effects of food intake and other variables on delivery and absorption of the drug,
- appreciation of the chronopharmacology of asthma — the differences between daytime and nighttime control, and
- the concepts of circadian variation of pulmonary function and the importance of controlling symptoms of nocturnal asthma.

Theophylline in nocturnal asthma

The favorable properties of theophylline for nighttime coverage are demonstrated by a recent study comparing it with inhaled albuterol and the combination of albuterol plus theophylline.² When the mean frequency of symptoms was measured, the limitation of the B-agonist became apparent four

hours after dosing (Figure 1). It is far more convenient for patients to sleep through the night after taking a sustained-release drug than to wake up after four hours to inhale a dose of short-duration B-agonist. Theophylline's pre-eminence in this area, however, could be

reduced by the recent introduction of oral controlled-release B-agonists and longer-acting inhaled B-agonists.

Use in EIA

The effect of theophylline in preventing exercise-induced asthma has been the subject of numerous studies. EIA is markedly reduced when theophylline serum concentrations are at least 6 micrograms/ml,³ and the drug is perhaps more effective at 15 micrograms/ml.⁴ There appears to be a significant correlation between serum theophylline concentration and degree of inhibition of exercise-induced bronchoconstriction.

Effects on airway reactivity

Somewhat surprisingly, although theophylline does not completely block the late-phase pulmonary response to an antigen challenge, it does attenuate it.⁵ Researchers have therefore studied its

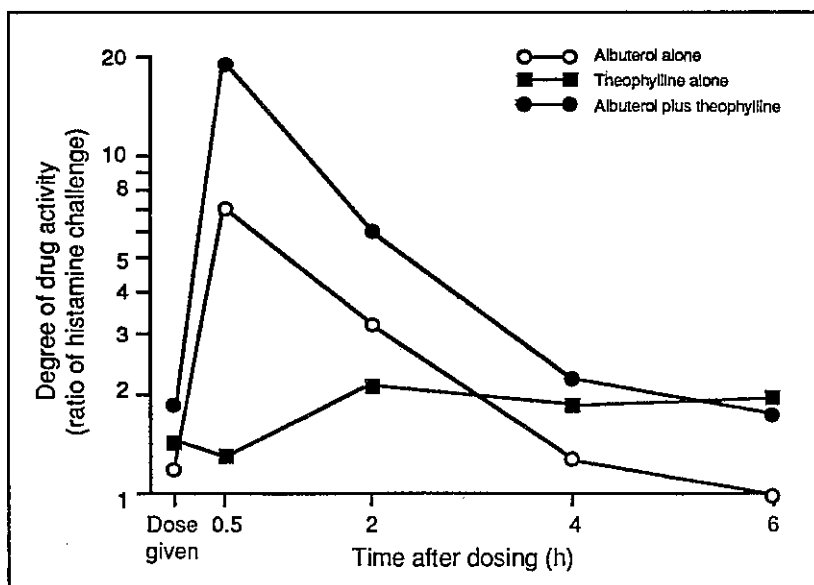


Figure 2

Comparison of the duration of protection afforded by three antiasthma regimens against serial bronchial challenges with histamine. (From Joad JP, Ahrens RC, Lindgren SD, et al: "Relative efficacy of maintenance therapy with theophylline, inhaled albuterol and the combination for chronic asthma." *J Allergy Clin Immunol* 1987; 79:78-85.)

value in reducing airway reactivity.

A study mentioned earlier (Joad et al),² considered the protective effects of three regimens — theophylline, a B-agonist and a B-agonist/theophylline combination — against a histamine challenge. As Figure 2 shows, the B-agonist's protective margin lasts no more than four hours, whereas the protective effect of theophylline alone, although initially not as great as that of the other drug, lasts considerably longer. After about three hours, the B-agonist's effect drops below that of theophylline. Note also that with the two drugs combined, the protective effect is additive.

Effects on mediators. Following an allergen challenge, many mediators of inflammation are released from mast cells and basophils.⁶ A number of these mediators may contribute to the pathogenesis of asthma. It has been proposed that the beneficial effects of theophylline may lie in its ability to inhibit the release of mediators into the airways.⁷ Thus, theophylline may play a role in the reduction of mediator-induced vasodilation and vascular permeability.

This concept is extremely relevant to asthma therapy. It shifts emphasis away from airway reactivity, in which a provocative agent, such as histamine or methacholine, is administered to airways already inflamed by exposure to mediators. Instead, it suggests that theophylline may be important in preventing mediators from reaching the airways.

Theophylline's effects on reducing such postchallenge mediator release include:

- reduction in plasma histamine after grass or ragweed pollen challenge,⁸
- reduction in number of sneezes and quantity of mediators after a pollen challenge in patients with allergic rhinitis,⁹
- effective inhibition of histamine and leukotriene (LT) C₄ release by isobutyl methylxanthine (a congener of theophylline).¹⁰ In the same study, isoproterenol, a B-agonist, only weakly inhibited release.

Effect on macrophages

In a 1986 study by O'Neill and associates, alveolar macrophage function

was impaired in patients treated with theophylline, raising the question of the drug's potential adverse effects on resistance to infection.¹¹ A decrease in bactericidal activity and oxidative metabolite release led the investigators to conclude that theophylline's use in patients with chronic obstructive pulmonary disease could predispose them to infections.

On the other hand, we might interpret this finding as a beneficial anti-inflammatory effect on the progression of a disease such as asthma, because it inhibits the release of harmful mediators from such inflammatory cells as alveolar macrophages.

Effect on learning and behavior

Several well-described undesirable effects have been attributed to theophylline, but of recent concern are potential effects on learning and behavior in children. One study identified adverse effects on behavior as assessed by teachers.¹² However, the abnormalities were not reported by parents, nor did psychological testing detect differences attributable to the use of theophylline. The clinical significance of the changes noted by the teachers was not apparent from this report. Nevertheless, these observations require careful consideration and emphasize the need for further studies.¹³

Role in corticosteroid-dependent patients

Relatively little information exists on the importance of theophylline in patients receiving optimal therapy, including systemic corticosteroids. However, Brenner, et al, evaluated this question in a National Jewish double-blind, placebo-controlled trial.¹⁴ During the placebo period, all five patients required increased corticosteroid dosage because of deterioration in symptom control and a decline in pulmonary function.

These observations emphasize the importance of trying theophylline therapy, even in patients with severe asthma, if symptoms cannot be controlled with available bronchodilators, cromolyn or inhaled systemic corticosteroids.¹⁴

Alternative agents with similar benefits

Because inhaled corticosteroids have anti-inflammatory properties which reduce or prevent airway hyperreactivity, they now are being considered not only for treating patients with severe asthma, but also for managing milder degrees of chronic asthma.¹⁵

Another advantage of corticosteroids is that they can be administered by inhalation, which avoids undue systemic effects. Other favorable aspects include their wide margin of safety, long-term safety and apparent absence of drug interactions.

Pitfalls

Despite theophylline's recognized benefits, several clinical concerns have limited its usefulness as a first-line drug in the treatment of asthma.

Narrow margin of safety. Theophylline has a very narrow margin of safety compared with B-agonists, cromolyn and inhaled corticosteroids in conventional doses. However, theophylline has the important advantage of allowing individualized oral administration, which may be more convenient for the patient and more effective in controlling asthma symptoms.

Allergists and pulmonologists have greatly increased our awareness of the myriad factors that can alter the disposition of theophylline.¹⁶ These include: the patient's age, diet, smoking habits, concomitant medications, nonlinear drug kinetics, other diseases and genetic predisposition.

Serum theophylline concentration. In an individual patient, serum theophylline concentration only reflects theophylline disposition at a particular instant in time. Thus, serum theophylline concentration is a single measurement that reflects the influence of theophylline absorption, distribution and elimination.

While elimination factors can increase or decrease metabolism, absorption properties also play a large role in drug concentration. This variable is affected by such factors as patient compliance, dosage and specific

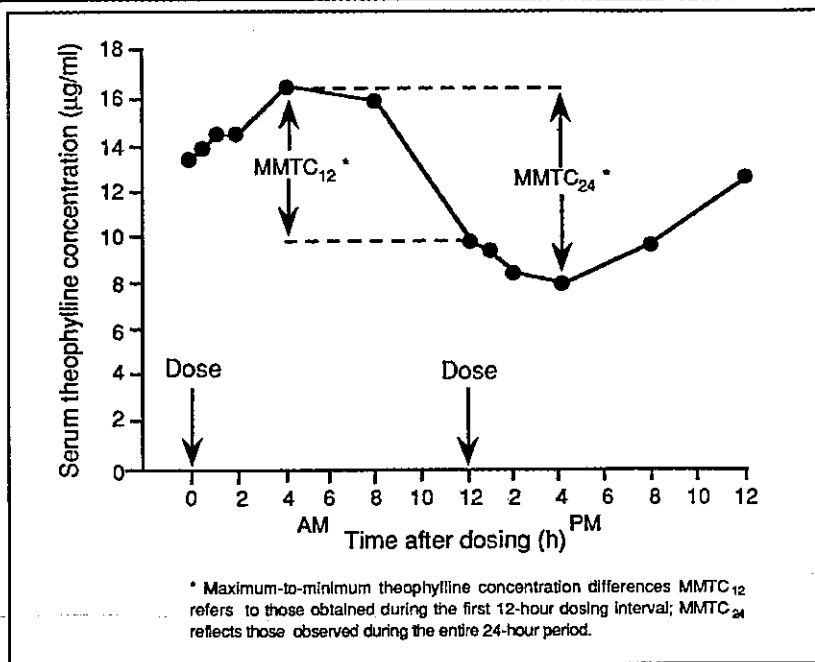


Figure 3

*Variation between daytime and nighttime serum theophylline levels in adolescent patients with asthma who were given sustained-release theophylline twice a day. (From Scott PH, Tabachnik E, MacLeod S, et al: "Sustained-release theophylline for childhood asthma: Evidence for circadian variation of theophylline pharmacokinetics." *J Pediatr* 1981; 106:496-501.)*

shows that significant differences may appear in absorption properties and serum concentration time profile when a patient is switched from one theophylline preparation to another.¹⁷

Circadian variation. A particular problem in children with asthma is the variation in serum theophylline concentrations throughout the day. In one study, serum theophylline concentrations were measured for 24 hours in a group of adolescent patients with asthma.¹⁸ The variation between nighttime and daytime levels was considerable (Figure 3). This finding is related to the reduced absorption of the drug at night.¹⁹

Thus, serum levels measured four hours after the dose do not necessarily represent peak concentration (except in the morning). In fact, when this value is measured at night, it may represent the lowest concentration of the day. This may help explain why many nighttime emergency room patients with asthma exacerbations have unusually low serum theophylline concentrations.

formulation. Moreover, in individual patients, variables of gastrointestinal physiology, such as gastric emptying and intestinal motility, may exert a significant influence on the rate and extent of theophylline absorption.

Any features that can alter drug absorption and metabolism may be crucially important in determining drug concentration level throughout the day. It's imperative to carefully monitor other medications the patient may be using, e.g., macrolide antibiotics, cimetidine and oral contraceptives, and alert patients to conditions that may influence theophylline pharmacokinetics.

Variations among formulations.

Another complicating factor is the availability of more than 25 sustained-release theophylline formulations, each with its own idiosyncratic absorption properties. These preparations differ in dose strength, dosage form and degree to which their absorption properties are influenced by gastric pH and food ingestion.

Once a patient has become adjusted to one formulation, indiscriminately switching to another preparation may introduce problems. A recent study

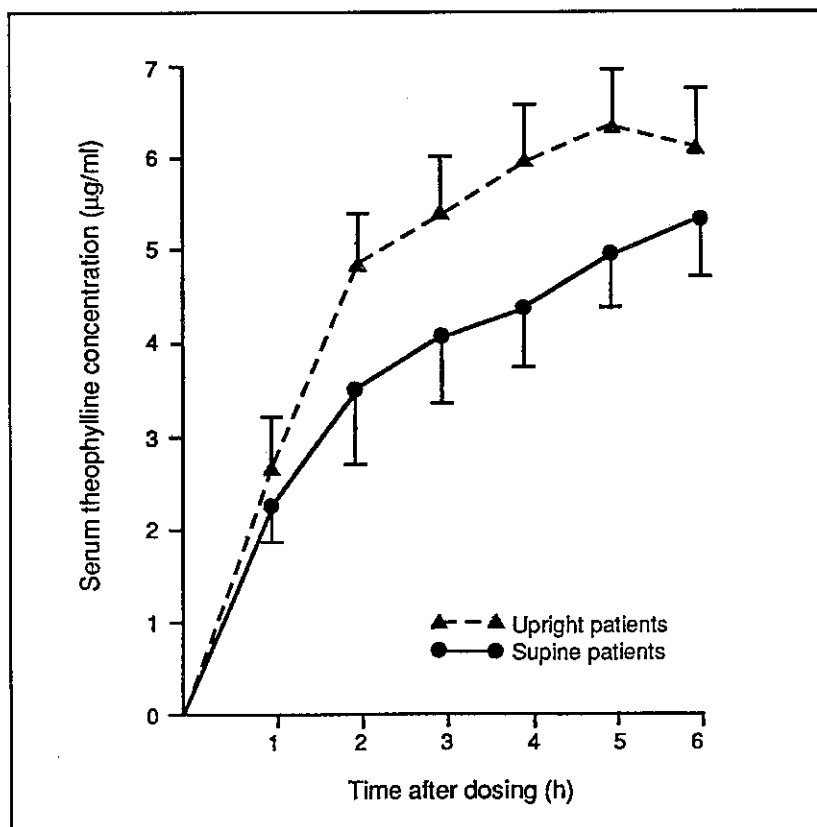


Figure 4

*Serum theophylline levels recorded after a dose of sustained-release theophylline in subjects who remained upright, compared with those of subjects (from a similar study) who were asked to remain supine. (From Warren JB, Cuss F, Barnes PJ: "Posture and theophylline kinetics." *Br J Clin Pharmacol* 1985; 19:707-709.)*

Such patients are often thought to be noncompliant, and the decision may be made to institute bolus dosing or to increase the maintenance theophylline dose. Remember that serum drug concentrations can vary throughout the day when considering important dosage alterations.

Various theories have been proposed to explain the nocturnal decrease in serum theophylline concentration, including the effects of food in the gut and release properties of the drug. I believe, however, the most likely factor is posture.

Figure 4 shows markedly different drug concentrations in patients who remained standing compared with those who were supine after taking their sustained-release theophylline dose.²⁰ Such widely differing absorption rates probably would be found with all formulations. Patients most susceptible to such nighttime falls in theophylline concentration are fast metabolizers, i.e., children and patients on medications that promote theophylline metabolism.

Another important lesson is that to derive maximum benefit from theophylline, we should try to compensate for known drops in serum concentration. In some of our patients, with primarily nocturnal asthma exacerbations, we have been using once-a-day preparations given in the evening.²¹ The object is to make maximum use of B-agonists during the day, and then obtain maximum levels with the sustained-release theophylline at night. This regimen may be particularly effective in patients with nighttime attacks.

To monitor serum theophylline concentrations effectively, pick specific times and look for specific information. With most twice-daily drug preparations, a good time to measure peak concentration level is four hours after the morning dose. The lowest concentration of the day is most likely to be just before the evening dose, although it sometimes occurs in the middle of the night.

With once-daily preparation, the

rules are different. Here, the peak concentration level tends to occur eight to 12 hours after the dose; the lowest is observed just before dosing.

Summary

Despite its limitations, theophylline therapy for asthma patients offers unique properties that we should consider in future evaluations of the drug. By viewing the patient as an individual and making adjustments in both formulations and dosage regimen, we can do much to maximize the benefits of this useful drug. □

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A study on theophylline side effects will be reviewed in the next Update.

CME Calendar

The following weekly conferences are conducted at National Jewish. Unless otherwise noted, each is held in Heitler Hall in the Goodman Building. All physicians in the community, as well as those traveling through Denver, are welcome to attend.

Immunology

Course/Immunocorrelates—

Monday, 8 a.m.

Research in Progress—

Tuesday, noon

Denver Allergy Rounds—

Wednesday, 8 a.m.

Pulmonary Medicine Grand Rounds—

Thursday, 7:30 a.m.

(Location varies; call for details.)

Pediatric Grand Rounds—

Thursday, 8 a.m.;

8:30 a.m. on second Thursday

Medicine and Pediatrics, Immunology Research in Progress—

Thursday, 4 p.m.

Topics in Pulmonary Biology, Physiology and Pathology—

Friday, 7 a.m.

Pulmonary Research Conference—

Friday, 8 a.m.

Medicine Second Opinion Conference—

Friday, 11:30 a.m.

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