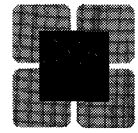

DONALD G. VIDT, MD, AND ALAN BAKST, PHARMD, EDITORS

Theophylline in the ambulatory treatment of chronic obstructive lung disease: resolving a controversy

GORDON L. SNIDER, MD

■ **BACKGROUND** Recent reports of a high frequency of theophylline toxicity, which usually occurs at theophylline blood levels >20 μg/mL, coupled with the recent addition of metered-dose, inhaled anticholinergics to the beta-2 agonist inhalers already available for treatment of chronic obstructive pulmonary disease, has led some authors to suggest that theophylline should no longer be used in the ambulatory management of this disease.

■ **OBJECTIVE** The author suggests an alternate approach to theophylline dosing as a means of resolving the current controversy.

■ **SUMMARY** Because of the log-linear relationship between bronchodilation and blood level, little bronchodilator efficacy is lost by using a target therapeutic theophylline blood level of 10 ± 2 μg/mL. This target provides a greater range between therapeutic and toxic blood levels than the 17 ± 2 μg/mL therapeutic target blood level that has also been recommended.

■ **CONCLUSIONS** Because theophylline has a different mode of action than the sympathomimetic or anticholinergic drugs, it continues to have a useful place in the ambulatory management of chronic obstructive pulmonary disease.

■ INDEX TERMS: THEOPHYLLINE; LUNG DISEASES, OBSTRUCTIVE
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From the Boston Veterans Administration Medical Center, Boston.
Address reprint requests to G.L.S., Chief, Medical Service, Boston VA Medical Center, 150 South Huntington Avenue, Boston, MA 01230.

PHYSICIANS IN THE US have used theophylline to treat airflow limitation for about 70 years.[1] The frequency with which theophylline has been prescribed for ambulatory patients with chronic obstructive pulmonary disease (COPD) has risen sharply over the past two decades. However, some authors have recently advocated that the use of theophylline in COPD should be decreased or stopped.

The disillusionment with theophylline stems in part from a high frequency of toxicity,[2] and in part from several double-blind crossover studies[3–5] that showed little or no improvement in dyspnea, wheezing, and cough, even though increases of 10% to 15% were noted in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). There was also no improvement in patients' exercise tolerance as assessed by progressive cycle ergometry and the 12-minute walk test.[5]

This assault on theophylline has been countered by reports that document improved maximal ex-

ercise performance in patients taking theophylline,[6] a 16% decrease in pulmonary work during walking, and patient preference for theophylline over placebo.[7] A significant reduction in dyspnea employing an elaborate three-component dyspnea rating system has also been reported, even though there was no significant difference between placebo and theophylline treatment with respect to spirometry, arterial blood gases, or exercise performance.[8] The earlier, unfavorable reports have also been criticized on theoretical grounds by Sharp,[9] who gave greater weight to the objective evidence that theophylline was an effective bronchodilator and less to its failure to improve subjective symptoms. He also proposed that the known relative inability of COPD subjects to detect changes in resistive loads could partially account for their failure to note improvement in dyspnea while taking theophylline.

The position I take in this review is that discarding theophylline from the therapeutic armamentarium for COPD is an overreaction to the problems associated with use of the drug. There is an alternative strategy, which will be presented following a discussion of the toxicity, metabolism, and physiologic effects of theophylline.

THEOPHYLLINE TOXICITY

The toxic effects of theophylline may be minor or major.[10] Minor effects consist of insomnia, irritability, upper gastrointestinal upset (nausea, heartburn), and lower intestinal upset (flatulence, bloating). These symptoms may occur at blood levels below 20 μg/mL and generally subside after 1 to 2 weeks of treatment. Major effects include vomiting, sinus tachycardia, supraventricular and ventricular arrhythmias, hypotension, and seizures. The last may be fatal or may result in serious impairment of cerebral function. Major toxicity generally does not occur unless blood levels are above 30 to 35 μg\mL; however, especially in those over age 60, it can occur at blood levels close to 20 μg/mL. It should be emphasized that major toxicity can occur without the prior warning of minor toxicity.

THEOPHYLLINE METABOLISM

Approximately 85% to 90% of orally administered theophylline is metabolized into relatively inactive compounds in the liver, probably by the cytochrome P-450 system. Less than 15% of a theophylline dose is excreted unchanged in the urine.[10,11] Many factors can influence theophylline metabolism[12] (*Table*). Factors such as hyperthyroidism, cystic fibrosis, smoking tobacco or marijuana, and ingesting drugs such as phenytoin all increase theophylline metabolism and decrease the theophylline blood level. Metabolism of theophylline is higher in children and adolescents than in adults and decreases as adults grow older.

Theophylline metabolism is decreased and blood levels are increased in patients with hepatic dysfunction due to hepatitis, cirrhosis, or congestive heart failure. In fact, the daily theophylline dose required to maintain a particular blood level may fall by 25% to 50%. Metabolism of the drug is decreased by a high carbohydrate diet, and severe acute illnesses. Cimetidine, ciprofloxacin, oral contraceptives, and propranolol are among the drugs that may slow theophylline excretion.

PHYSIOLOGIC EFFECTS OF THEOPHYLLINE

The bronchodilating action of theophylline has long been ascribed to its ability to promote the intracellular accumulation of cyclic adenosine monophosphate (cAMP) through its inhibitory effect on smooth-muscle phosphodiesterase, the enzyme responsible for the break-down of cAMP. However, a number of studies recently reviewed[12] indicate that concentrations of theophylline in the range of 10 to 20 μg/mL are well below those required to effectively inhibit phosphodiesterase activity in human airway smooth muscle. In addition, other drugs that are potent inhibitors of cAMP phosphodiesterase, are ineffectual as bronchodilators. Alternative proposals that attempt to explain theophylline bronchodilation include its stimulation of adrenal catecholamine release, its action as a prostaglandin antagonist, and its action to reduce the cytosol free calcium concentration, thereby reducing excitation-contraction coupling in bronchial smooth muscle. Theophylline has been reported to have an anti-inflammatory effect mediated by inhibition of the release of inflammatory mediators like leukotriene B_4 and oxygen metabolites from polymorphonuclear leukocytes.

Whatever its mechanisms, theophylline can dilate both large and small airways, and tolerance to its bronchodilating activity does not appear to develop, even after long-term use. It also seems quite clear

that theophylline has a different mode of action than sympathomimetic or anticholinergic drugs.

Theophylline has been shown to have many physiologic effects other than bronchodilation which might benefit COPD patients. These include enhancement of mucociliary clearance,[13] increased hypoxic ventilatory drive,[14] and reduced pulmonary vascular resistance along with improved cardiac output and right and left ventricular ejection fractions.[15] It has been reported that theophylline augments diaphragmatic contractility and reverses low-frequency fatigue, as well as increasing strength and endurance.[16] Other authors have failed to demonstrate a beneficial effect of theophylline on ventilatory endurance.[17] That is, the extent to which physiologic effects translate into an overall improvement in patients remains controversial.

THEOPHYLLINE DOSING

A major advance in ambulatory theophylline therapy has been the development of slow-release anhydrous theophylline preparations. These are well absorbed following oral ingestion and improve patient compliance. A variety of tablet sizes simplifies dose adjustments. More than 15 formulations of long-acting theophylline are presently available in the United States under more than 25 brand names. These products may significantly differ with respect to the completeness, rate, and consistency of absorption,[18] and physicians should become familiar with and prescribe only one or two of these slow-release theophylline formulations.

An ideal slowly absorbed theophylline preparation would have stable plateau blood levels and minimal blood level fluctuation in patients on a fixed dosing schedule. Preparations are available for once-daily (q24h) or twice-daily (q12h) dosing. However, in patients who metabolize theophylline rapidly, it may be necessary to give the q12h preparations every 8 hours and the q24h preparations twice daily to avoid wide fluctuations in blood concentration.

Diet and time of dosing can also influence the theophylline blood level and the rate of drug bioavailability. The ingestion of some slow-release formulations immediately following a meal can slow intestinal absorption, reduce peak serum levels, and cause fluctuations in the serum theophylline concentration. On the other hand, the ingestion of a large morning dose (>900 mg) of some q24h preparations with a large fat-laden breakfast can markedly enhance the absorption of this drug and produce potentially toxic theophylline serum levels. This "dose dumping" phenomenon can be prevented by smaller morning doses and by delaying breakfast for about 2 hours after taking the drug.[19]

Given the problems associated with once-daily theophylline preparations—ie, dose dumping and the danger posed by long absorption and excretion times of once-daily preparations in the event of a toxic drug level—I find they have little advantage over the twice-daily preparations and do not use them. However, slow-release theophylline formulations are clearly superior to the rapidly absorbed formulations of this drug.

When the ability to rapidly monitor theophylline blood levels became available in the early 1970s, it was reported[20] that in young asthmatic patients there was a linear relationship between normalized improvement in FEV_1 and the logarithm of theophylline blood level over a concentration range of 5 to 20 μg/mL. These authors cautioned against blood levels above 20 μg/mL because of the risk of toxicity. They recommended a dosing schedule for

TABLE
FACTORS THAT AFFECT THEOPHYLLINE METABOLISM*

Increase metabolism	Decrease metabolism
Cigarette smoking	Hepatic dysfunction
Marijuana smoking	Congestive heart failure
Phenytoin	Cimetidine
Barbiturates	Erythromycin
Carbamazepine	Troleandomycin
Rifampin	Ciprofloxacin
Hyperthyroidism	Thiabendazole
Cystic fibrosis	Oral contraceptives
High-protein diet	Propranolol
Young age (children, adolescents)	Severe acute illness
	Viral infections (influenza)
	Chronic obstructive pulmonary disease with severe hypoxemia (PaO_2† <45 mm Hg)
	High-carbohydrate diet
	Older age

*Reprinted from reference 12 (Faling LJ, Snider GL. Treatment of chronic obstructive pulmonary disease. Curr Pulmonol 1989;10:209–264), with permission
†Partial pressure of arterial oxygen

intravenous theophylline that would result in a theophylline blood level of 10 ± 5 mg/L. Nevertheless, many authors subsequently recommended that theophylline blood levels of 17 to 20 μg/mL were the proper target for assuring therapeutic efficacy of this drug.

Since the relation between bronchodilating effect and theophylline blood level is log-linear, there is much less bronchodilating effect for the 5 μg/mL change between 15 and 20 μg/mL than between 5 and 10 μg/mL. A target level of 10 ± 2 μg/mL provides a wider therapeutic range with little loss of efficacy.

A STRATEGY FOR THEOPHYLLINE DOSING IN AMBULATORY PRACTICE

In the light of the variable metabolism of theophylline and the relations between blood level and toxicity and bronchodilation, a reasonable dosing schedule for an average-sized adult without heart failure or liver disease is 200 mg of a slowly absorbed theophylline preparation every 12 hours. If the therapeutic response is not satisfactory, the dose may be increased by 100 or 200 mg daily at 4- to 7-day intervals to a dose of 800 to 1000 mg/day. If the response is still not satisfactory, a blood level should be ascertained before further increasing the drug dose.

Theophylline in combination with other bronchodilators

Several studies in COPD patients have convincingly shown that combination therapy with oral theophylline and an inhaled beta agonist produce more bronchodilation than when either agent is used alone.[21–23] Such an additive effect has been shown even following a high (800-μg) dose of inhaled albuterol.[21] An additive benefit following combination therapy has been noted with respect to improvement in spirometric indices (FVC, FEV_1), reduced breathlessness following exercise or during the usual activities of daily living, and a decreased likelihood of treatment failure requiring additional therapy.[22] Although combination therapy of theophylline with ipratropium aerosol has not been as intensively studied as combination therapy with the beta-2 agonists, additional improvement in lung function was observed when the anticholinergic aerosol was given to patients who had therapeutic blood levels of theophylline.[24]

Theophylline blood level monitoring in ambulatory practice

Theophylline blood levels are mainly useful to determine whether a therapeutic blood level has been reached before increasing theophylline dose above 800 to 1000 mg/day, and to determine whether symptoms are due to theophylline toxicity. To determine if a therapeutic level has been reached or if a patient is a "rapid metabolizer" of theophylline, the blood level should be measured after a steady state has been reached—ie, no doses missed during the preceding 48 hours, and no extra doses taken. The peak serum concentration should be used; this is generally reached 4 to 7 hours after a dose of a slow-release preparation.

If patients are on low-dose theophylline, are having an adequate therapeutic response, and show no evidence of toxicity, I do not measure theophylline blood levels, either initially or at any regular interval. However, if this approach is to be followed, patients must be questioned at each visit as to how much theophylline they are actually taking, because some patients adjust their dosage upward. If patients are seeing more than one physician, it is important to make sure that another theophylline preparation or a drug that may delay theophylline excretion has not been prescribed.

CONCLUSION

Theophylline is an old drug that has gained prominence during the last two decades in the ambulatory treatment of COPD in the United States. The availability of rapid methods of measuring theophylline blood levels led to expanded knowledge and understanding of its pharmacodynamics, toxicity, and bronchodilating and other physiologic properties, and contributed to its increased use. The formulation of a large number of slow-release preparations of theophylline and their promotion by the pharmaceutical industry also played a major role in the popularity that this drug attained. The choice of a high upper limit for the target therapeutic blood level for theophylline results in a small range between toxic and therapeutic blood levels. Since the relation between bronchodilating effect and blood level is log-linear, little therapeutic efficacy is lost by targeting a lower blood level, and the therapeutic range of the drug is thereby widened—although it is still low compared with other bronchodilators such as beta-2 agonist and anticholinergic aerosols.

Nevertheless, because the mode of action of theophylline is different than the two bronchodilator aerosols, and because there is relatively little potential reversibility of airflow obstruction in COPD, theophylline continues to play a role in the management of this disabling chronic disease.

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