Theophylline has emerged as a major prophylactic agent for controlling the symptoms of chronic asthma, but it provides little if any relief of pulmonary symptoms caused by irreversible chronic airways obstruction. Although in vitro it inhibits phosphodiesterase and antagonizes adenosine receptors, theophylline’s mechanism of action in asthma is unknown. Often, 10 to 20 μg/ml is used as the range of serum concentrations where there is the greatest likelihood of obtaining maximal benefit safely. Slow-release products have the potential to provide more stable serum concentrations with longer dosing intervals. However, clinically important differences in rate and sometimes extent of absorption exist between the 15 formulations sold under 29 brand names in this country. In patients with more rapid elimination, few products have sufficiently slow absorption to allow twice-daily use. Often these formulations must be administered every eight hours to prevent breakthrough in asthmatic symptoms despite promotional claims to the contrary. In patients with slower elimination, differences among products are unlikely to be clinically important with 12-hour dosing intervals. Current products approved for “once-a-day” dosing are clinically inadequate because of erratic absorption or excessive serum concentration fluctuations. Moreover, food induces dose dumping of potentially toxic amounts of theophylline from Theo-24, greatly increases the extent of absorption of theophylline from Uniphyll, decreases extent of absorption from Theo-dur-Sprinkle capsules, but has no clinically important effect on Theo-Dur tablets, Theobid, Slo-Bid, or Somophyllin-CRT. The effects of food or other factors that alter gastrointestinal physiology on theophylline absorption are unknown for most other products.

Theophylline has emerged as a major prophylactic agent for controlling the symptoms of chronic asthma during the past 10 to 15 years in the United States. This has been a result of definition of its pharmacokinetics and pharmacodynamics, the availability of rapid specific methods of measuring serum concentrations, and the development of reliably absorbed slow-release formulations.

Since there have been a great many of articles, book chapters, and proceedings from symposia published on theophylline, this review will focus on only the most recent advances in knowledge about this drug. While we recognize that many adult patients may have varying degrees of airway hyperreactivity combined with an irreversible component of airways obstruction, well-controlled studies have demonstrated little or no benefit from theophylline in relieving pulmonary symptoms caused by irreversible airway obstruction. Therefore, to avoid confusion, “asthma” in this article refers to reversible airways obstruction and COPD to chronic irreversible airways obstruction.

**Pharmacology**

The mechanism of theophylline’s action as a bronchial smooth muscle relaxant remains elusive. Inhibition of phosphodiesterase has been a popular proposed mechanism, but this theory is based on in vitro studies that used concentrations that would be toxic in vivo. Furthermore, other phosphodiesterase inhibitors such as dipyridamole and papaverine are not bronchodilators. Thus, phosphodiesterase inhibition can no longer be accepted as the mechanism of theophylline’s action.

It has been suggested that theophylline may act as a prostaglandin antagonist, but effects on intracellular calcium and increased binding of cyclic AMP (cAMP) to cAMP-binding protein also have been described. Recently, theophylline has been shown to antagonize adenosine receptors and to block bronchoconstriction induced by adenosine bronchial provocation. However, in vitro, adenosine receptors are not antagonized by enprofylline, a xanthine derivative that has greater potency as a bronchodilator than theophylline. Enprofylline does not stimulate gastric acid secretion or diuresis and has less CNS and cardiac toxicity than theophylline, suggesting that adenosine antagonism may be responsible for some of the side effects of methylxanthines but not their bronchodilator effects.

As with other methylxanthines such as caffeine, theophylline can produce cerebral vasoconstriction, transiently increase plasma glucose, and inhibit...
uterine contractions. It also exerts a complex set of actions on the cardiopulmonary system. Serum concentrations >10 μg/ml increase contractility and reduce experimentally induced fatigue of diaphragmatic muscles, decrease the work of breathing, increase biventricular performance, stimulate hypoxic ventilatory drive, reduce pulmonary artery hypertension, and enhance mucociliary clearance. However, it is unclear if these pharmacologic effects are of any clinical importance or result in the relief of symptoms from COPD.

**Pharmacodynamics**

**Asthma**

The various studies published on the efficacy and toxicity of theophylline have led to a carefully defined range of serum concentrations, between 10 and 20 μg/ml, where there is an optimal likelihood of maximal safe effect. It is this optimal range for maximal safe effect that has been commonly termed the “therapeutic range.” The connotations of this term have sometimes been misinterpreted to suggest that there is no effect from theophylline at serum concentrations under 10 μg/ml and no further potential for antiasthmatic effect at serum concentrations over 20 μg/ml. Even a cursory examination of the literature, however, would argue that this is not so. A measurable effect of theophylline is apparent at lower serum concentrations, and higher serum concentrations almost certainly would provide more effect for some patients.

However, the studies that have argued for a downward extension of the therapeutic range to 5 μg/ml generally have been limited to demonstration of a bronchodilator effect or some decrease in symptoms at lower serum concentrations and have not demonstrated that the measurable effects were indeed maximal or, alternatively, associated with a lower frequency of side effects than serum concentrations within the 10 to 20 μg/ml range. Moreover, no studies examining the efficacy of serum concentrations less than 10 μg/ml have demonstrated the remarkably high degree of efficacy of theophylline in preventing symptoms that interfere with sleep, reduction in need for emergency medications, including corticosteroids, and blocking of exercise-induced bronchospasm documented at concentrations above 10 μg/ml. As to the argument that more effects might be attained for some patients at serum concentrations over 20 μg/ml, it is acknowledged that this may be so, but not with adequate safety. The 10 to 20 μg/ml range for serum concentrations most likely to obtain maximal safe clinical effect is well supported by multiple clinical studies and by considerable clinical experience by many clinicians over the past ten years. It appears that to some extent efforts to promote a wider therapeutic range, 5 to 20 μg/ml, have been motivated by drug companies whose products and/or dosing interval recommendations cannot maintain concentrations within the 10 to 20 μg/ml range around the clock.

Similarly, arguments for using “low-dose” theophylline in combination with an oral β₂ agonist have been based on single-dose studies demonstrating additive bronchodilator effects. There are no studies comparing the relative efficacy and safety of the combination with carefully titrated doses of theophylline alone in suppressing the frequency and severity of asthmatic symptoms. This would be particularly important, since the intensity and duration of bronchodilatation decreases with continued use of oral β₂ agonists, and exercise-induced bronchospasm is not inhibited when these drugs are given orally. Last, on an annual basis, the combination therapy is more expensive and less convenient than a slow-release theophylline product used alone in individualized doses, even when the cost of serum level measurements is included.

Thus, the issue then is no longer whether or not to target 10 to 20 μg/ml range when optimal likelihood of safe maximal effect is desired, but how to attain, maintain, and sustain these serum concentrations given the interpatient variability, the range of available products, and the realities of patients’ lifestyles.

**COPD**

Although a definite relationship exists between serum concentration and effect in patients with asthma, serum concentrations correlate poorly with pulmonary function in patients with COPD. Moreover, several double-blind, placebo-controlled studies have demonstrated little or no difference in symptom control between placebo and theophylline at serum concentrations >10 μg/ml (Fig 1). Jenne et al., for example, investigated the effect of theophylline in patients with emphysema during rest (standing) and exercise (walking). Theoretically, any potential benefit would be most noticeable during walking, since patients with COPD experience a large increase in the

![Figure 1. Mean symptom scores from patients with COPD who received placebo and individualized oral doses of theophylline, each for one month, in a double-blind, cross-over manner. (Reproduced with permission of Journal of American Medical Association.)*](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21484/ on 04/06/2017)
work of breathing, particularly during exercise. They found a modest increase in FEV₁, a small decrease in lung work, and slight subjective improvement during theophylline at a mean concentration of 12 μg/ml, but neither spirometric nor subjective improvement correlated with the decrease in lung work. Patients preferred theophylline over placebo in this double-blind study, but the possibility that theophylline altered the perception of dyspnea was not excluded. In another study of COPD patients, where reversible airways obstruction was carefully excluded, theophylline decreased dyspnea to a small and significant degree but did not alter exercise performance. Thus, effects of theophylline can be demonstrated in COPD patients, but there is no evidence that these effects are clinically important in the overall management of this disease. Effects on diaphragmatic contractility, work of breathing, biventricular performance, and stimulation of hypoxic drive might offer some benefit in treating or preventing respiratory failure associated with COPD, but there are no controlled studies to support this conjecture.

Since theophylline is a potentially toxic drug, particularly in COPD patients, who are more sensitive to its arrhythmogenic effects and at risk of accumulating excessive serum concentrations as a result of impaired metabolism from cor pulmonale, the small potential benefit must be weighed against the potential risk of toxicity. If it is used in COPD, greater caution must be exercised to prevent accumulation of toxic serum concentrations. In such patients, it might be prudent to maintain serum concentrations at the lower end of the therapeutic range.

Pharmacokinetics

Absorption

Theophylline is rapidly, consistently, and completely absorbed from oral liquids and plain, uncoated tablets, while enteric coating (e.g., Choledyl) delays dissolution, which can result in incomplete absorption and/or unpredictable absorption rates. Rectal solutions are nearly completely absorbed, but rectal suppositories are erratically and incompletely absorbed. Because rapid-release formulations can result in large fluctuations in serum concentrations between doses, particularly in rapid metabolizers, slow-release products have become popular. They are formulated in various ways to decrease the rate of disintegration and dissolution of the drug. However, extent and, particularly, rate of absorption differ among the 29 brands of the 15 slow-release formulations available in this country. Even among completely absorbed products, differences in rates of absorption may result in clinically important differences in serum concentration fluctuations (Fig 2).

However, if the dosing interval is appropriate for the absorption rate of the product and elimination rate of the patient, serum concentrations generally can be maintained within the therapeutic range around the clock. Absorption of theophylline from the so-called once-daily formulations is either incomplete, erratic, or too rapid to achieve relatively constant serum levels over a 24-hour dosing interval in most patients.

Influence of Food on Absorption: The influence of age, GI physiology, and pathology on the bioavailability of slow release theophylline formulations has not been adequately evaluated. Food markedly impairs theophylline absorption from Theo-Dur Sprinkle (a bead-filled capsule with pH-independent dissolution) given to children 8 to 12 years old, but has no clinically important effect on Theo-Dur tablets, Theo-Bid, Somophyllin-CRT, or Slo-Bid (unpublished data). In contrast, food results in dumping of potentially toxic amounts of theophylline from Theo-24, a product that, on average, is 71 percent absorbed when taken fasting. During a recent bioavailability study, four of eight volunteers developed excessive serum concentrations and clinical toxicity when Theo-24 was taken with food but had no adverse effects when the dose was taken fasting. In the subject with the most severe symptoms of toxicity, the peak concentration after a single dose taken with a bacon and eggs breakfast was 31.4 compared with a peak of 12.5 μg/ml when the same 1,500-mg dose was previously taken fasting (Fig 3). Apparently, dissolution of the coating on the Theo-24 beads is pH-dependent; the coating dissolves slowly at pH 6.8 but rapidly at 7.4 to 8.0, the pH range of the small intestine after a meal. Food also appears to increase the extent of absorption without much effect on rate from Uniphyl, another 24-hour product that, like Theo-24, appears to be incompletely absorbed when taken fasting.
Food decreases the rate, but not extent, of absorption from Theolair-SR, a product with pH dependent dissolution, in children and adults. Antacids also significantly increase the rate of theophylline absorption from Theolair-SR but not from Theo-Dur tablets or Slo-Phyllin Gyrocaps. Theoretically, absorption from products with pH-dependent dissolution may be more rapid in patients with less acid gastric contents, such as the elderly, or during concurrent administration of H₂-receptor antagonists.

Thus, the effect of food and pH may alter the absorption characteristics of slow-release products differently, since product formulation design and rates of absorption vary. Studies are needed to define these effects on most slow-release products. Clearly, only products unaffected by food and other factors such as pH should be considered for routine clinical use.

Distribution

Once theophylline enters the systemic circulation, on average 40 percent becomes bound to plasma protein and the remaining free drug distributes throughout body water. The 60 percent protein binding reported in previous studies was artificially elevated due to the lower temperature and increased pH that occurred during in vitro testing. The apparent volume of distribution, the space into which theophylline distributes, averages 0.5 L/kg among both children and adults. Since the peak concentration after a single loading dose is equal to the dose divided by the volume of distribution, 1 mg/kg will increase the serum concentration, on average, by 2 μg/ml. The mean volume of distribution during uncorrected acidemia and hepatic cirrhosis, is slightly larger, since protein binding is reduced in these patients.

Elimination

Theophylline is eliminated from the body at variable rates through multiple parallel pathways, some of which are saturable or capacity-limited. Approximately 10 percent is eliminated by the kidneys unchanged, while the remainder is metabolized to relatively inactive metabolites by the cytochrome P-450 enzyme system in the liver. Variability of dosage requirements among individuals occurs as a result of the variable rates of elimination. Total body clearance, the product of volume of distribution and elimination rate constant, most accurately reflects theophylline removal from the body. Interpatient variability in clearance is large and appears to be due to differences in the rate of hepatic biotransformation that change with age, concurrent illness, thyroid function, smoking, aberrations in diet, and other drugs.

Effects of Disease and Altered Physiology: Conflicting reports have been published on the influence of obesity, old age, and gender on theophylline clearance. Available evidence suggests that there is no clinically important difference between obese and normal-weight subjects or between men and women. In contrast, the decrease in theophylline clearance associated with hepatic cirrhosis, acute hepatitis, cardiac decompensation, and cor pulmonale can be quite large and require a major dosage decrease to prevent toxic reaction. However, the clearance in patients with cholestasis or stable COPD without cor pulmonale is not reduced.

Theophylline clearance is reduced during febrile viral respiratory tract infections, but it is unclear if the cause is the fever or the viral infection. In either event, the magnitude of the effect can be sufficient to warrant a temporary dosage reduction. Influenza vaccine was also thought to reduce theophylline clearance, but several subsequent well-controlled studies have failed to demonstrate any clinically important interaction.

Cigarette and marijuana smokers have rapid clearance on the average and require larger doses to achieve therapeutic serum concentrations than nonsmokers. Even among the elderly, clearance is more rapid in smokers than in nonsmokers. More rapid than average clearance has also been found in adolescents with cystic fibrosis. Hyperthyroidism increases the clearance of theophylline, presumably from increased hepatic metabolism during thyrotoxicosis, but even in euthyroid asthmatic patients, there is a correlation between T₄ and theophylline clearance, suggesting that interpatient differences in thyroid function contribute in part to the variability in theophylline clearance. Changes in the amount of dietary carbohydrate and protein can alter clearance, but the magnitude of change is not large and is unlikely to require changes in dose requirements for individuals except when radical and persistent alterations in diet occur, e.g., a heavy meat eater becoming a high-carbohydrate vegetarian.
Table 1—Clinically Important Drug Interactions with Theophylline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nature of interaction</th>
<th>Suggested circumvention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that increase theophylline concentrations&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol (Zyloprim)</td>
<td>On average, a 600 mg/day dose of allopurinol reduces theophylline clearance by 25% but a 300 mg/day dose has no effect.</td>
<td>Reduce theophylline dose by 25%, when high doses of allopurinol are required, eg, tophacious gout.</td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
<td>Average clearance reduction is 40%; serum levels may double. The interaction begins within 24 hours after initiation of cimetidine and is gone 3 days after discontinuing it.</td>
<td>Use ranitidine (Zantac) in place of cimetidine. It does not inhibit theophylline metabolism at standard doses.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Theophylline clearance decreases by 25%, on average, after 5 days of concurrent therapy with erythromycin. The higher the erythromycin serum concentration, the greater the effect on theophylline clearance.</td>
<td>Reduce theophylline dose by 25% or measure serum concentration if erythromycin therapy is continued for more than 5 days and previous theophylline serum concentration was ≥13 μg/ml.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Theophylline clearance reduced 30%, on average, with an oral contraceptive containing a moderate amount of estrogen (Ovral).</td>
<td>Reduce theophylline dose by 30% and measure serum level 5 days later to make final dose adjustment.</td>
</tr>
<tr>
<td>Troleandomycin (TAO)</td>
<td>Theophylline clearance decreased by 50%, on average.</td>
<td>Reduce theophylline dose by 50% and measure serum level 5 days later.</td>
</tr>
<tr>
<td>Drugs that decrease theophylline concentrations&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Theophylline clearance may double and serum concentrations may drop 50%</td>
<td>Measure theophylline concentration to guide final dosage during concurrent therapy.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>May increase theophylline clearance by 25% after 3-4 weeks of phenobarbital therapy at doses producing therapeutic phenobarbital concentrations</td>
<td>Measure theophylline concentration after 1 month of concurrent therapy and adjust dose if indicated.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>May increase theophylline clearance 50-75% after 10 days of phenytoin at doses producing therapeutic phenytoin concentrations. Theophylline may also inhibit phenytoin absorption.</td>
<td>Use cromolyn or inhaled β&lt;sub&gt;2&lt;/sub&gt; agonist in place of theophylline. If theophylline can not be avoided, both phenytoin and theophylline serum concentration measurements will have to be obtained on several occasions to adjust the dose of each drug.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>May increase theophylline clearance 50-75%</td>
<td>If rifampin is used for more than a few days, measure theophylline concentration to adjust final dose.</td>
</tr>
<tr>
<td>Interactions that do not alter theophylline serum levels&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Ephedrine</td>
<td>Additon of ephedrine to therapeutic serum concentrations of theophylline increases the frequency of headache, insomnia, nervousness, and nausea disproportionate to that seen with either drug alone, ie, synergistic toxicity.</td>
<td>Use β&lt;sub&gt;2&lt;/sub&gt; selective agonist by the inhaled route.</td>
</tr>
<tr>
<td>Oral β&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>The frequency of tremors is increased when oral β&lt;sub&gt;2&lt;/sub&gt; agonists are added to therapeutic serum concentrations of theophylline</td>
<td>Use β&lt;sub&gt;2&lt;/sub&gt; selective agonist by the inhaled route.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Theophylline may increase lithium clearance and decrease its effectiveness</td>
<td>Measure serum levels to readjust lithium dose after 3 days of concurrent therapy or use an alternative to theophylline for chronic prophylaxis of asthma, eg, cromolyn or inhaled β&lt;sub&gt;2&lt;/sub&gt; agonists.</td>
</tr>
</tbody>
</table>

**Drug Interactions:** The peak serum concentration at steady state is a function of dose, total body clearance, the absorption rate of the product, and the dosing interval. If a second drug is added that increases or decreases theophylline clearance, the steady-state peak serum concentration will change unless the dose is altered. The magnitude of the change in clearance differs between patients and between drugs.<sup>34</sup> Consequently, the clinical relevance of an interaction may vary (Table 1). If the theophylline serum concentration is within the 10 to 20 μg/ml range at steady state and a second drug such as cimetidine is added, serum concentrations may increase twofold or more, and result in potentially serious toxicity, unless the theophylline dose is decreased when the cimetidine therapy is started. Conversely, if the patient has been taking cimetidine when theophylline dosage is first titrated, and then the cimetidine treatment is discontinued, theophylline serum concentrations may precipitously fall. Erythromycin has a much smaller effect on theophylline clearance, and its addition to an existing theophylline regimen only becomes clinically relevant when the theophylline concentration is in the upper end of the therapeutic range and the erythromycin is continued for more than five days.<sup>34</sup> Thus, the clinical circumstances must be evaluated to assess the importance of a potential interaction.

Well-controlled studies have demonstrated that amoxicillin, ampicillin, cefaclor, metronidazole, and tetracycline have no effect on theophylline clearance.<sup>34</sup> In contrast, ascorbic acid, furosemide, thiamethazol, verapamil, and vidarabine have been cited in case...
reports as drugs that potentially interact with theophylline; but well-controlled studies on these alleged interactions have not been reported in the literature.

**PRODUCT SELECTION**

Selection of a theophylline product, dose, and dosing interval must be based on the specific clinical indication, *ie*, treatment of acute asthmatic symptoms or maintenance prophylactic therapy for chronic asthma, the absorption characteristics of the formulation, and the rate of elimination of the drug in the individual patient. For the treatment of acute symptoms in the patient with intermittent asthma, an inhaled β₄ agonist such as terbutaline or albuterol provides greater bronchodilation with fewer side effects than theophylline. However, when the addition of theophylline is required, an intravenous (IV) formulation provides the most rapid and ensured delivery of medication, but plain, uncoated or chewable tablets, liquids or liquid-filled capsules, and rectal solutions (but not suppositories) may also be satisfactory. There are no clinically important differences in rates of absorption between the various rapid release oral formulations, and generally these products can be used interchangeably.

To achieve the greatest likelihood of maximum benefit from theophylline for chronic asthma, serum concentrations should be maintained within the 10 to 20 μg/ml therapeutic range around the clock. Since the width of the therapeutic range is only 10 μg/ml, serum concentration fluctuations must be less than 100 percent (% Fluctuation = Peak–Trough × 100) to maintain concentrations within this range, even if the peak is as high as 20 μg/ml. Fluctuations are a function of the absorption rate of the product, the elimination rate of theophylline from the patient, and the length of the dosing interval selected by the physician. In patients with slow elimination, differences in rates of absorption between products do not result in clinically important differences in serum concentration fluctuations when given at 12-hour intervals (Table 2). However, among patients with rapid elimination, such as most children, the average cigarette or marijuana smoker, and about 25 percent of nonsmoking adults, most products are absorbed too rapidly to be given routinely twice daily without excessive serum concentration fluctuations (Table 2). All but two of these products must be given every eight hours to avoid excessive fluctuations, despite promotional claims to the contrary.

Recently, the FDA approved Theo-24, Uniphyll, and Theo-Dur tablets for once-a-day administration. However, none of these products is capable of reliably maintaining serum concentrations within the 10 to 20 μg/ml therapeutic range around the clock in most patients, and absorption from Theo-24 and Uniphyll is markedly affected by food. Absorption of theophylline from Theo-Dur, a 100 percent absorbed product with or without food, is too rapid for once-a-day dosing, unless the half-life of elimination, a patient variable, is greater than ten hours. In the multiple-dose study on which the FDA based approval of the once-a-day labeling, serum concentration fluctuations averaged 196 percent in volunteers with a mean half-life of about seven hours, but only 46

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Brand Name</th>
<th>% Fluctuation†</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>t½ = 3.7 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t½ = 7.7 hr</td>
</tr>
<tr>
<td>Plain tablets</td>
<td>Slo-Phyllin, Theophylline</td>
<td></td>
</tr>
<tr>
<td>Rorer, Johnson &amp; Johnon, Riker</td>
<td>Theolair</td>
<td>465</td>
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<tr>
<td>Bead-filled capsules</td>
<td>Bronkodyl S-R</td>
<td>230</td>
</tr>
<tr>
<td>Cord Laboratories</td>
<td>Slo-Phyllin Gyrocaps</td>
<td>73</td>
</tr>
<tr>
<td>Graham Laboratories</td>
<td>Aerolate</td>
<td>130</td>
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<tr>
<td>K-V Laboratories</td>
<td>Somophyllin-CRT</td>
<td>47</td>
</tr>
<tr>
<td>Theobid</td>
<td>Eliophyllin SR</td>
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<tr>
<td>Theovent-LA</td>
<td>167</td>
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<tr>
<td>Rorer</td>
<td>Slo-bid Gyrocaps</td>
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<td>Slow-release tablets</td>
<td>Constant-T</td>
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<tr>
<td>Cord Laboratories</td>
<td>Theo-Dur 200, 300</td>
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<td>Key Pharmaceuticals</td>
<td>Theo-Dur 100</td>
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<tr>
<td>Mead Johnson</td>
<td>Quibron T/SR</td>
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<tr>
<td>Mundipharma</td>
<td>Phyllocontin</td>
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<tr>
<td>Norwich-Eaton</td>
<td>LaBID</td>
<td>252</td>
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<tr>
<td>Parke-Davis</td>
<td>Choledyl SA</td>
<td>154</td>
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<tr>
<td>Riker</td>
<td>Theolair SR</td>
<td>122†</td>
</tr>
<tr>
<td></td>
<td>Resbid</td>
<td>47†</td>
</tr>
</tbody>
</table>

*For a comprehensive review of slow-release theophylline, see reference 34.
†Percent fluctuation = peak–trough serum concentration ÷ trough serum concentration × 100; actual fluctuations may somewhat exceed predictions because of circadian variation in absorption. Half-lives of elimination (t½) are the medians for the average adult (3.7 hr) and the average nonsmoking adult (7.7 hr), respectively. Predicted fluctuations for the average cigarette smoking adult are similar to those for the average child. Fluctuations in excess of 100 percent indicate that peak serum concentrations will be more than twice the trough and therefore not compatible with maintaining serum concentrations within the therapeutic range, even if peak levels as high as 20 μg/ml are attained; 8-hour intervals are then advisable, regardless of advertising claims for b.i.d., or 12-hour intervals. The methodology and validation of the derivation of these values has been described previously.‡‡
†Prediction for dose taken fasting. Fluctuations may be smaller if taken with food, since dissolution of this product is pH dependent, and when taken with food, rate of absorption is slowed.
percent when the same dose was divided into 12-hr doses. In contrast, Theo-24 (Pulmo-Timelets outside the United States), an ultraslowly absorbed product when taken fasting, will result in acceptable fluctuations with once-daily dosing in the average nonsmoking adult, but higher doses will be needed because of incomplete absorption (on average, 71 percent of the dose) and, if taken with food, theophylline toxicity may result from dose dumping. In one study, Uniphyl was only 55 percent absorbed when taken fasting, but substantially larger amounts were absorbed when the dose was taken with food. It appears from these and other data on experimental 24-hour products with ultra-slow absorption that attempts to slow absorption sufficiently to minimize fluctuations during 24-hour dosing generally result in incomplete absorption proportional to the degree of slowing. Thus, innovative technology will be needed before a product with relatively constant and complete absorption will be available for once daily dosing. With the current technical limitations of the products and the absence of data documenting that decreasing the frequency of dosing from twice-a-day to once-a-day improves compliance, once-a-day dosing appears to be more of a marketing gimmick than an advance in formulation technology.

**Dosage**

Variations in the clearance of theophylline among individuals result in large differences in dosage requirements to maintain serum concentrations within the 10 to 20 μg/ml therapeutic range. Initial dosage must be low to circumvent transient caffeine-like side-effects (eg, 400 mg for otherwise healthy adults) and slowly titrated over a period of nine days to average requirements according to age and the presence of concurrent physiologic abnormalities (Fig 4). Subsequently, serum concentrations should be obtained to guide the final dosage adjustments (bottom of Fig 4). Unless this slow titration process is followed, the frequency of adverse effects will be unacceptably high. In patients with cardiac failure, liver dysfunction or cor pulmonale, where theophylline clearance may fluctuate, alternative therapy with other safer drugs, eg, inhaled β agonists, should be selected for maintenance therapy. If theophylline use cannot be avoided in such
patients, the total dose should not exceed 400 mg/day before serum level measurements are obtained to guide final dosage, and the final target serum concentration should be at the lower end of the therapeutic range, e.g., 10 μg/ml.

**Methods of Measuring Theophylline Concentration**

As a result of increased physician demand and improved methodology, facilities for measuring theophylline in serum are now readily available in most communities in the United States. In addition, inexpensive office methods of measuring theophylline that are rapid, specific, and require very small amounts of serum or blood have recently become available. An immunoassay by Ames utilizes a dry reagent contained on a plastic strip with a colorimetric indicator that is measured in a reflectance photometer (Seralyzer). Another method by Syntex Medical Diagnostics requires no instrument and can be performed on only a 12 μl-drop of whole blood from a finger stick.

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**DISCUSSION**

**Audience:** Has anybody compared the tablet form of a beta adrenergic agonist such as albuterol vs oral theophylline?

**Dr. Hendeles:** There has been a comparison study with Theo-Dur given every eight hours and Alupent tablets given every eight hours. There were significant differences between the two groups favoring the theophylline regimen, particularly when a standardized exercise stress test was used as an endpoint. The oral beta adrenergic agonists were not efficacious in blocking exercise-induced bronchospasm, whereas the inhaled beta agonists had a potent effect even though the same degree of bronchodilatation was obtained through both formulations. In other words, if you raise the FEV1, to the same point, the inhaled adrenergic agonist will block exercise-induced asthma and the oral form will not, suggesting that the topical effect of the beta adrenergic agonist is important. Theophylline, with a therapeutic serum level, has a reasonably good effect on exercise-induced bronchospasm, but not as good as inhaled beta adrenergic agonists.

**Audience:** There have been a number of studies comparing the cardiovascular effects of theophylline and beta adrenergic agonists. Usually beta adrenergic agonists appear to have a bit more potential for causing cardiac ectopy. In your discussion on this point, could you clarify the experimental design?

**Dr. Hendeles:** In the study which I cited, there were some patients receiving Digoxin whose levels were measured and were in the therapeutic range. Arterial blood gas abnormalities were not associated with arrhythmias. The most important factor was stopping or adding theophylline to the therapeutic regimen. So theophylline itself or through synergy with other agents may cause cardiac arrhythmia. In patients with normal hearts without pre-existing cardiac arrhythmia, the combination of inhaled beta adrenergic agonists with theophylline in usual clinical doses does not produce arrhythmia. It's only when excessive doses are employed that cardiac arrhythmia occurs.

**Audience:** But my question was specifically addressed as to whether or not the threshold for causing cardiac arrhythmia was lowered because of other drugs they were using.

**Dr. Hendeles:** It's entirely possible that some of them were on oral terbutaline or fenoterol and it is possible that the effects were additive.