SLOW-RELEASE THEOPHYLLINE FOR THE MANAGEMENT OF CHRONIC ASTHMA

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RATIONALE FOR SLOW-RELEASE THEOPHYLLINE

In 1974 a report of a placebo-controlled double-blind crossover study indicated that treatment with theophylline was associated with a dramatic decrease in symptoms and signs of chronic asthma without adverse effects when used in individualized doses that maintained serum theophylline concentrations between 10 and 20 mcg/ml; doses of theophylline that approximated previous customary usage produced lower serum concentrations and were not effective in reducing symptoms (1). Although some bronchodilatory effect occurs at lower serum concentrations of theophylline (2), these and other data (3) suggest that stabilization of the hyperreactive airways that characterize asthma becomes most prominent at levels above 10 mcg/ml, and that adverse effects are uncommon at serum concentrations below 20 mcg/ml (4, 5). Subsequent studies and much clinical experience have substantiated a high degree of efficacy and a relative freedom from adverse effects when serum concentrations of the drug are maintained in this "therapeutic range" (6-10).

Theophylline is so rapidly absorbed, however, that liquid and plain uncoated tablet formulations that undergo rapid dissolution are frequently associated with excessive fluctuations in serum concentrations, even when intervals between doses are as short as six hours (11). Formulations that decrease the rate of absorption potentially result in more stable serum concentrations, and a recent crossover designed study in 35 children with chronic asthma suggested greater efficacy and improved compliance when doses of a slow-release theophylline product were given every 12 hours, as compared with the same total daily dosage of plain tablets administered every 6 hours (12).

EVALUATION AND SELECTION OF PRODUCTS

At last count, 29 brands of slow-release theophylline products were available in the United States, and some of these are available in other countries. Some pharmaceutical companies have persisted in using so-called salts of theophylline — e.g., aminophylline (Phyllocontin, theophylline with ethylenediamine) and oxtriphylline (Choledyl, theophylline with choline). These formulations, however, have no additional therapeutic benefit (13). The various bases merely serve to increase solubility which is irrational for a slow-release formulation where the goal is to slow the rate of dissolution in order to slow the rate of absorption.

Xanthine derivatives other than theophylline have also been marketed as bronchodilators. Dyphylline (dihydroxypropyl theophylline), availabe in both plain and slow-release formulations, has about 1/10 the bronchodilator potency of theophylline (13, 14) and a clinical advantage over theophylline has not been established for this drug or other xanthines.

Slow-release theophylline products are formulated in various ways that decrease the rate of disintegration and dissolution of the drug. The resulting products, however, may differ to clinically important degrees in completeness, rate, and consistency of absorption (15), and these products have been marketed in some countries without drug regulatory agency approval. Furthermore, current criteria for government approval does not ensure the general applicability of advertising claims for twice-daily dosage administration. Consequently, data used to support claims for product performance must be examined critically.

When the product in question and a reference product known to be completely absorbed are given in a crossover manner to the same subjects on different days, completeness of absorption can be measured after single or multiple doses. The ratio of the total areas under the concentration-time curves provides a measure of the total fraction absorbed. Complete absorption could only be demonstrated by this method for three of six slow-release formulations available in the USA before 1978 (Theo-dur, Slophyllin Gyrocaps and Theophyl-SR) (15). Subsequent studies have demonstrated that Theograd (16), Theo-24 (Pulmo-Timelets) (17) and Euphyllin Retard (18) are incompletely absorbed, while additional studies are needed to determine the extent of absorption of Uniphyllin (Theocontin) because of conflicting data.

Assuming that absorption is reasonably and consistently complete, fluctuations in serum concentration during regular daily use of theophylline are a function of the rate of absorption (a product variable), the rate of elimination (a patient variable), and the prescribed interval between doses. Rates of absorption for theophylline products have been determined from the calculation of cumulative fractions of single doses absorbed over time (Fig. 1) (15). Rates of elimination are defined as the half-life of the disappearance of drug from the plasma after absorption and distribution are complete (Fig. 2).

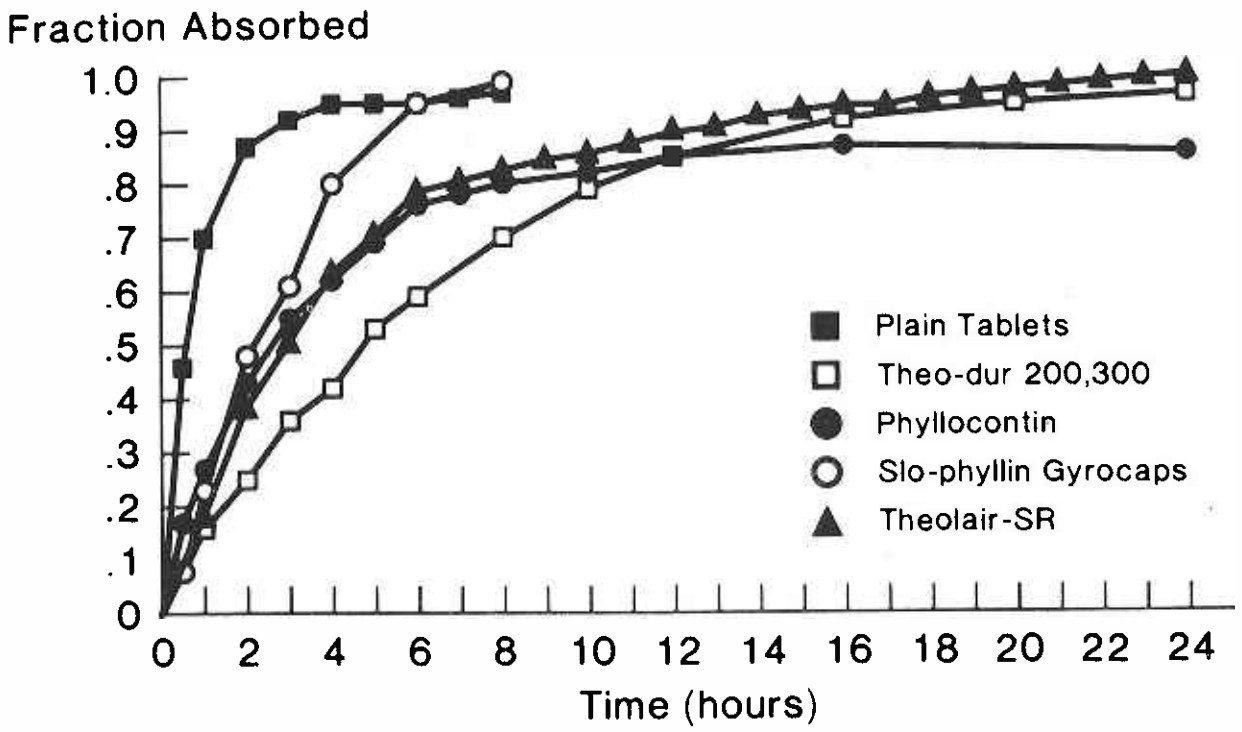

Fig. 1. Rate and completeness of absorption of four internationally distributed slow-release theophylline preparations and plain uncoated tablets. Each determination of the cumulative fraction absorbed represents the mean of values calculated as previously described from sequentially measured serum concentrations after adminiistration to adult volunteers of single doses of the slow-release product and a rapidly absorbed reference product (15).

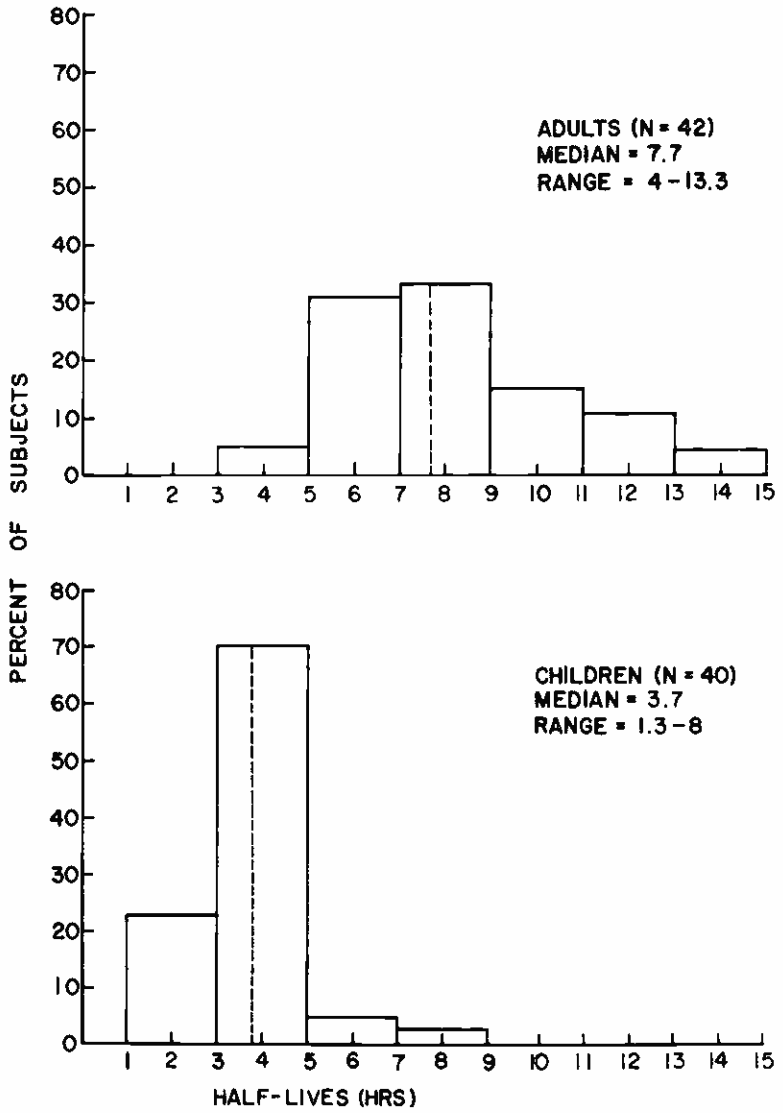

Fig. 2. Distribution of elimination half-lives among 42 nonsmoking healthy adults (upper) and 40 children with asthma (lower). These subjects were pooled from several studies (31). Values for adult smokers (not illustrated) more closely approximated the values for children. Infants have very slow rates of elimination that increase wtih age, approaching the above values for children by one year of age (47).

Once the rates of absorption and elimination have been defined and the dose interval has been chosen, steady-state serum concentrations after multiple doses can be predicted with reasonable accuracy (19), and expected fluctuations in serum concentration can be examined (Table 1). Most slow-release theophylline preparations will be associated with relatively small fluctuations in serum concentration if administered q12h to non-smoking adults in whom the mean half-life of elimination is about eight hours. Comparative studies in such subjects given multiple doses therefore indicate little difference among products, even when rates of absorption actually differ sufficiently to be associated with clinically important fluctuations in serum concentration in patients with more rapid elimination (Fig. 3).

Although serum concentrations have appeared to be relatively consistent during maintenance therapy with the slow-release formulations most commonly used in the USA — i.e., Slo-Phyllin Gyrocaps and Theo-Dur, a recent study has reported intrapatient dose-to-dose variability in absorption of these products (20). However, the clinical importance of the degree of variability that was reported after single doses has not been established during clinical use and some of the observed differences could have resulted from estimates of serum concentration from salivary measurements and the normal variability in gastrointestinal motility. In a more sophisticated study designed to isolate the formulation as a dependent variable, Fagerstrom and Heintz performed a crossover trial among 12 subjects to examine the

Table 1. Predicted Per cent Fluctuations in Serum Concentrations of Various Completely Absorbed Theophylline Preparations Available in Southeast Asia during a 12-Hour Dose Interval.

Distributor	Product	Per Cent Fluctuation* $t_{1/2}$ = 3.7 hr	Per Cent Fluctuation* $t_{1/2}$ = 7.7 hr
Plain tablets			
Riker	Nuelin	465	125
Bead-filled capsules			
Rorer	Slo-Phyllin Gyrocaps	230	73
Schering	Theovent-LA	167	60
Slow-release tablets			
Astra	Theo-Dur 200,300	39	17
	Theo-Dur 100	88	35
Mead Johnson	Quibron T/SR	128	46
Riker	Nuelin SR**	122	47

* Per cent fluctuation = $\frac{\text{peak - trough serum concentration}}{\text{trough serum concentration}} \times 100$; actual fluctuations may somewhat exceed predictions because of diurnal fluctuation in absorption (49). Half-lives of elimination ($t_{1/2}$) are the median indicated in Figure 2.

Fluctuations in excess of 100 per cent 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 mcg/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 (17).

**pH-dependent dissolution may alter the rate of absorption depending on gastric pH and emptying.

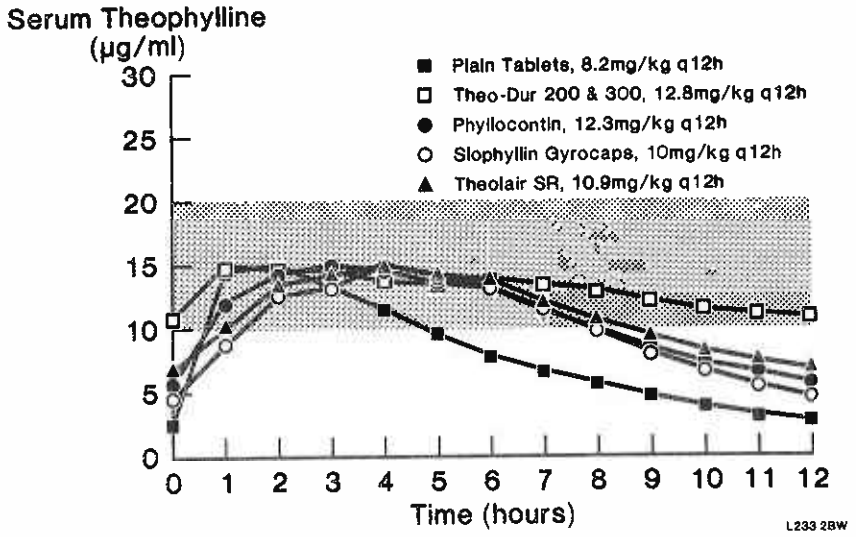

Fig 3. Predicted steady-state serum concentrations for an average child ($t_{1/2}$ = 3.7 hours, Vd = 0.5 L/kg) receiving plain uncoated tablets and 4 slow release products at 12-hour dosing intervals. Doses were calculated to achieve a 15 mcg/ml peak concentration. The more rapid the rate of absorption, the greater the fluctuations, and the longer the serum concentration remains in the subtherapeutic range (< 10 mcg/ml). Predicted fluctuations in serum concentrations are 459%, 225%, 165%, 149% and 38% for the plain tablets, 'Slo-Phyllin Gyrocaps', 'Phyllocontin', 'Theolair-SR' and 'Theo-Dur 300 mg', respectively. Predicted serum concentrations for 'Slo-Bid Gyrocaps' (not shown) are similar to ' Theo-Dur' tablets with a 43% predicted fluctuation. These predictions slightly underestimate actual fluctuations since the method does not reflect the circadian variation in absorption observed for both rapid and slow release formulations (49). Adjusting the dose rather than the dosing interval will not alter the percentage fluctuation. Therefore, children, smoking adults and about 25% of otherwise healthy non-smoking adults will generally require 8-hour dosing intervals for most slow release products, i.e. those with predicted fluctuations of 100% at a $t_{1/2}$ of 3.7 hours (17).

variance of the "mean residence time" — a measure of the time required for a drug to be absorbed and eliminated — for an elixir and three slow-release theophylline preparations (18). Although the slow-release theophylline preparations, to varying degrees, had longer mean residence times as a result of slower absorption than the elixir, Euphyllin Retard and Phyllocontin but not Theo-Dur were associated with significantly greater intersubject variance in mean residence time than the elixir (Table 2). This suggests that variability in absorption for these first two products but not the last differed significantly from that of a rapidly absorbed formulation.

Food affects the absorption characteristics of slow release products in different ways. It decreases the extent of theophylline absorption from Theo-dur Sprinkle capsules (21) but has no clinically important effect on Theo-dur tablets (22-24) or Theobid capsules (23). In contrast, food increases extent while decreasing the rate of absorption from Theograd (25). With Theo-24 (Pulmo-Timelets), a product that is incompletely absorbed when taken fasting (17), food causes both an increase in extent and such a precipitous increase in rate of absorption (e.g. dose-dumping) that several volunteers in a bioavailability study developed excessive serum levels and clinical toxicity (26).

In vitro dissolution of Nuelin-SR (Theolair SR) is pH dependent (27). Therefore, food results in a decreased rate of absorption (28) while antacids increase the rate of absorption from this product (29). In contrast, antacids have no effect on the rate or extent of theophylline absorption from Theo-dur (29) or Slophyllin Gyrocaps (30).

INDICATIONS AND CLINICAL USE

Slow-release theophylline is indicated for patients with relatively continuous or frequently recurring symptoms of asthma and should not be used indiscriminately for other obstructive pulmonary diseases. Inhaled beta-2 selective agonists such as terbutaline or salbutamol are preferable for acute symptoms of asthma even when maintenance theophylline is used, and corticosteroids are essential for the treatment of airway obstruction from asthma that is unresponsive to bronchodilators. Theophylline should be used with caution in patients who have a seizure disorder or peptic ulcer; it should be avoided, if possible, in patients with fluctuating degrees of cor pulmonale or left heart failure where large changes in theophylline elimination may occur and consequently increase the risk of toxicity.

Although rapid attainment of therapeutic serum concentrations may be indicated in the acutely ill hospitalized patient, the dosage of theophylline in the ambulatory patient is best determined by slow clinical titration using a product with unit sizes that allow adequately small increases (Fig. 4). Initial doses should be sufficiently low to minimize the risk of adverse effects. Subsequent increments in dosage can then be made, if tolerated, until average doses for age are reached. Half the daily dose given at 12-hour intervals can be used when fluctuations in serum concentration are expected to be less than 100 per cent (Table 1); otherwise, one third of the daily dose should be given at 8-hour intervals to minimize fluctuations. When dose requirements exceed the second incremental increase, the rate of elimination is likely to be more rapid than average, and doses may be required every eight hours, even when predicted fluctuations for an "average" patient are not excessive. A dose should be temporarily withhled in the presence of any suspected adverse effect, and subsequent doses should be reduced until the serum theophylline concentration is measured; the concentration should then be used to determine the final dosage. This procedure generally avoids the transient caffeine-like side effects that commonly occur when therapy is initiated at higher doses, and also allows optimal doses to be determined with a minimum number of blood samples. The result is an exceedingly low incidence of adverse effects (Table 3). Thus, only an occasional patient will report uncomfortable side effects when this dosage scheme is followed, whereas over 50 per cent experience discomfort when serum concentrations reach the therapeutic range more rapidly (31).

Table 2. Comparison of mean residence times for 3 slow release theophylline products with conventional bioavailability parameters among 12 subjects (18)

Product	Extent of absorption (mean %)[a]	Time required for absorption of 50% of the dose (h)[b]	Mean residence time (h)	Variance of mean residence time[c]	Statistical significance of Variance[d]
Reference solution	100	0.3	7.8	0.8	—
'Euphyllin Retard'	84	11	15.6	11.8	$p<0.001$
'Phyllocontin'	88	2.5	11.1	3.1	$p<0.05$
'Theo-Dur tablets'	93	4.5	11.4	1.0	NS

[a] samples collected for 33 hours after a single dose.

[b] A measure of rate of absorption.

[c] The square of the standard deviation of the mean residence time.

[d] Statistical significance of differences in the variance of the mean residence time for each slow release product compared with the reference solution.

NS = not significant

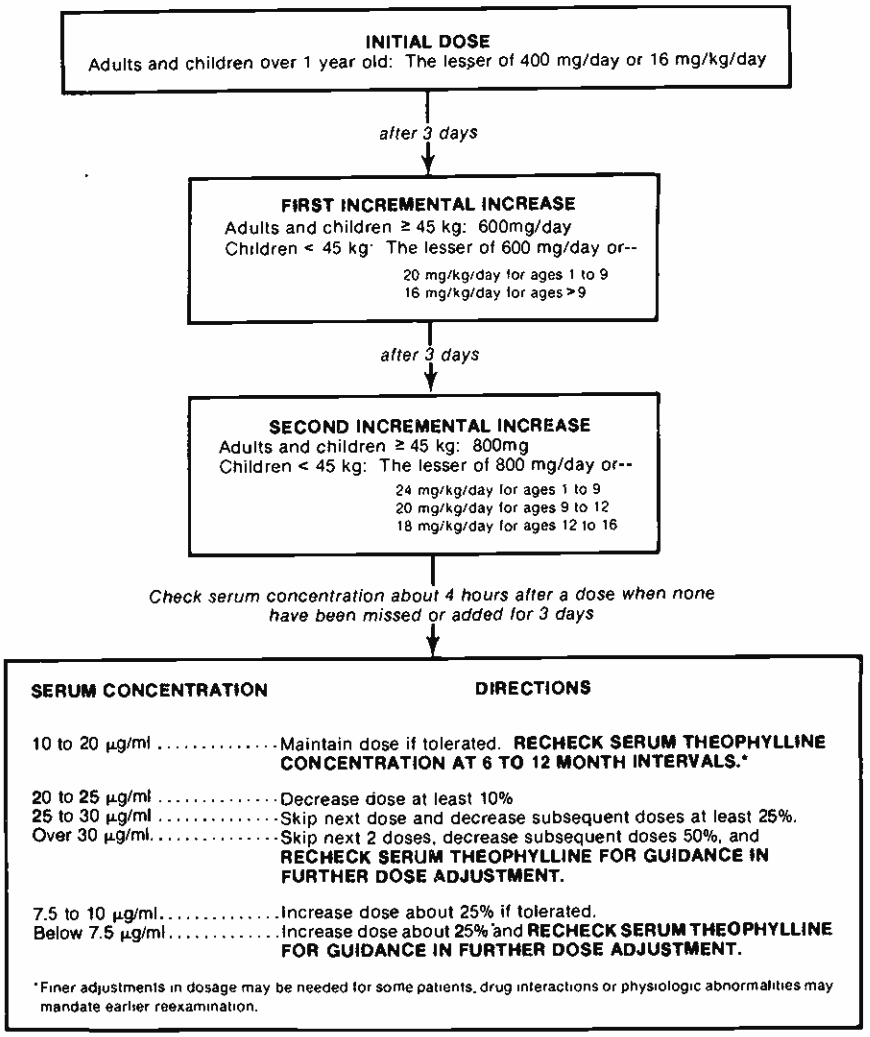

Fig 4. Scheme for establishing optimal oral theophylline dosage in ambulatory patients (47). This is a conservative application of the recommendations incorporated into the US Food and Drug Administration-approved package insert. Ideal body weight should be used for obese patients. Dose recommendations are unique for infants under one year of age; the clinician should review the recommendations of Nassif et al (47). before treating patients in this age group.

Table 3. Frequency of Adverse Effects of Theophylline, According to Serum Drug Level.*

Serum Level	No. affected/no. studied (percent) Children	Adults
<10 mcg/ml	0/29	0/12
10-19.9 mcg/ml	5/258 (2)	3/38 (8)
< 20 mcg/ml	17/61 (28)	4/6 (67)

*Data obtained through history taking at initial blood sampling in sequentially selected ambulatory patients whose dose had been titrated over nine days, according to the schedule in Figure (34).

None of the products currently promoted for "once-a-day" administration will provide relatively constant serum levels over a 24-hour dosing interval in a majority of patients. In average non-smoking adults fluctuations in serum concentrations are much larger with Uniphyllin given once-a-day compared to the same dose of Theo-dur divided q12h (32). In contrast, Theo-24 (Pulmo-Timelets) is absorbed slowly enough in the fasting state for once daily dosing in the average non-smoking adult but absorption of theophylline from this product is incomplete and erratic when taken on an empty stomach and food causes dose dumping of potentially toxic amounts of theophylline (17, 26).

For children too young to swallow tablets whole, the slow-release formulations available as bead-filled capsules in appropriate unit sizes for incremental doses can be sprinkled on a spoonful of food and washed down (without chewing) with a beverage as long as food does not affect the absorption characteristics of the product.

Once the dosage is established, serum concentrations generally remain relatively stable over time (4, 33). Re-examination of the serum concentration, therefore, need be performed only annually if the patient is clinically stable, except during rapid growth periods in children, in whom examination every six

months is appropriate. Exogenous factors and some physiologic abnormalities alter theophylline elimination, however, requiring more careful drug monitoring in selected patients (34). Cigarette or marijuana smoking, for example, increases the rate of theophylline elimination and consequent dosage requirements; discontinuation of smoking may result in a gradual decrease of theophylline elimination, with the potential for toxicity from drug accumulation if serum concentrations are not monitored and dosage is not appropriately adjusted. Heart failure and liver disease slow theophylline elimination, which decreases dosage requirements. Sustained fever – e.g., fever lasting longer than 24 hours — from various causes slows theophylline elimination sufficiently to justify a temporary 50 per cent reduction in dosage. Slowing of theophylline elimination by influenza vaccine has been reported (35) but was not confirmed in a more recent study (36). Cimetidine (but not the newer H_2 antagonist ranitidine) is a potent inhibitor of hepatic microsomal enzymes and decreases theophylline metabolism and elimination by about 40 per cent (37-40). Macrolide antibiotics also decrease the rate of theophylline elimination and thus dose requirements: troleandomycin by half (41) and erythromycin more variably but by an average of about 25 per cent (42-46). Drugs commonly used for asthma have not been shown to affect theophylline dosage, but the potential for drug interactions with other added medications should always be considered.

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