Selection of a slow-release theophylline product

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Slow-release formulations of theophylline, if absorbed completely, consistently, and at a sufficiently slow rate, provide more stable serum concentrations at longer dosing intervals than plain uncoated tablets or liquids and thus have the potential to improve efficacy, safety, and compliance. However, clinically important differences in extent and rate of absorption exist among the 15 slow-release formations available under 29 different brand names or as generic products in the United States. Moreover, food has different effects on the various formulations. Whereas some formulations are little affected by food with only a slight delay in absorption, others undergo malabsorption in either the presence or absence of food, depending on as yet unidentified but specific formulation factors. Because fluctuations in serum concentrations at any selected dosing interval are a function of the rate of elimination of theophylline from the patient and the rate of absorption of theophylline from the formulation, selection of a product and dosing interval needs to be an individualized clinical decision independent of marketing or regulatory influences. Most formulations with claims for twice-daily dosing cannot reliably maintain fluctuations in serum concentration whereby the peak will not exceed twice the trough. Moreover, of the three products approved for once-a-day dosing, fluctuations in serum concentration are more likely to be larger than are clinically optimal, and malabsorption occurs with two of the three approved formulations unless taken after food; one, in fact, has such a large increase in rate and extent of absorption when taken with food that its postprandial absorption characteristics are aptly described as "dose-dumping." (J ALLERGY CLIN IMMUNOL 1986;78:743-51.)

Until the late 1970s, Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, the American Medical Association's *Drug Evaluations*, and other authoritative references stated that "theophylline was erratically and incompletely absorbed." They quoted a study published in 1950 that demonstrated incomplete absorption from enteric-coated tablets and suppositories, but this study actually indicated no evidence of a bioavailability problem with plain uncoated tablets.[1] Subsequently absolute bioavailability studies have demonstrated that theophylline is rapidly, completely, and consistently absorbed from formulations that rapidly release the drug.[2, 3]

Rapid-release formulations, however, can result in excessive serum concentration fluctuations, particularly in patients with rapid elimination.[4, 5] There are three possible solutions to this problem. First, the dosing interval can be shortened to 4 to 6 hours, but this is incompatible with a normal life-style. Second, a drug such as cimetidine could be given to inhibit theophylline metabolism, but this is an inappropriate method of dealing with the problem because it places the patient at risk of toxicity from the second drug. The third and only practical method of reducing fluctuations is to decrease the rate of absorption of the formulation.[5, 6]

Abbreviations used
$t_{1/2}$: Elimination half-life
V_d: Volume of distribution

At least one clinical study[7] has demonstrated that slow-release formulations offer the potential for greater efficacy and improved compliance. Among 35 children with chronic asthma randomly assigned in a crossover manner to receive a rapid-release product

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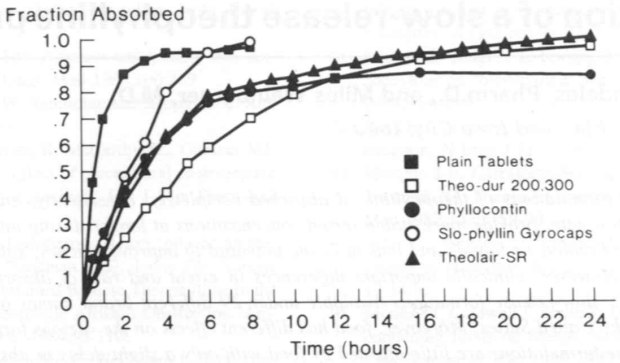

FIG. 1. Rate and completeness of absorption of four slow-release theophylline formulations and plain uncoated tablets. Each determination of cumulative fraction absorbed represents mean of values calculated from sequentially measured serum concentrations after administration of single doses of slow-release product and a rapidly absorbed reference product to adult volunteers, as previously described.[6] (From Hendeles L, Weinberger M. Theophylline: a "state of the art" review. Pharmacotherapy 1983;3:2-44.)

over, compliance was significantly higher during the slow-release treatment regimen.

METHODS OF EVALUATING PRODUCTS

Slow-release products are formulated in various ways to decrease rate of dissolution, the rate-limiting step in the absorption process. There are at least 15 formulations available in the United States as 29 different brands, and some also are sold as generic products without a brand name. Because manufacturers use various methods to formulate their products, many of these formulations differ in extent or rate of absorption.[6, 8, 9]

Two slow-release theophylline products are bioequivalent, and thus can be expected to produce the same therapeutic response, when they have the same rate and extent of absorption. Extent of absorption can be measured 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. The serum concentration-time curve after each product is divided into trapezoids, the area of each trapezoid calculated, and the results summed. This provides the area under the serum concentration-time curve, which is directly proportional to the amount of drug absorbed into the systemic circulation. The actual amount of drug absorbed from the product in question, relative to the reference product, is then calculated from the ratio of areas under the curves. Theo-Dur Sprinkle (Key Pharmaceuticals, Miami, Fla.) (after food),[13, 14] Uniphyl (Purdue Frederick, Norwalk, Conn.) (fasting),[14] and two products available outside the United States, Euphyllin Retard (Byk-Guiden, Konstanz, West Germany),[15] and Theograd (Abbott Laboratories, North Chicago, Ill.) (fasting).[16]

Rate of absorption is determined from the cumulative fraction of a single dose absorbed over time.[8] When the various slow-release products are compared in this manner, marked differences in rates of absorption become readily apparent (Fig. 1). Slo-Phyllin Gyrocaps (William H. Rorer, Fort Washington, Pa.), for example, is one of the most rapidly absorbed slow-release formulations,[6] whereas Theo-24 (taken fasting) is so slowly absorbed that its absorption is incomplete.[11, 12] Once the rate of absorption of a product is known, steady-state serum concentrations after multiple doses can be predicted, with reasonable accuracy, for different dosing intervals, in patients with different rates of elimination.[5, 8] From these data, expected fluctuations in steady-state serum concentrations can be calculated:

$$\% \text{ Fluctuation} = \frac{\text{Peak} - \text{trough}}{\text{Trough}} \times 100$$

Because the width of the 10 to 20 μg/ml therapeutic range is only 10 μg/ml, fluctuations must be <100% (i.e., the peak less than twice the trough) to maintain serum concentrations within the therapeutic range,

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TABLE I. Extent of absorption and predicted fluctuations in serum concentrations during a 12-hour dose interval of various slow-release theophylline products

Manufacturer	Brand name	Extent of absorption (%)	% Fluctuation*	
			$t_{1/2}$ = 3.7 hr	$t_{1/2}$ = 7.7 hr
Plain tablets				
Rorer, Johnson & Johnson, Riker	Slo-Phyllin, Theophyl, Theolair	100	465	125
Bead-filled capsules				
Central Pharmacal	Physpan			
	Quibron-BID			
	Theoclear LA	95	240	73
	Theon-300			
	Theospan-SR			
Cord Laboratories	Bronkodyl S-R			
	Slo-Phyllin Gyrocaps	99	230	73
	Theophyl-SR			
Graham Laboratories	Aerolate			
	Somophyllin-CRT	101	130	47
Key Pharmaceuticals	Theo-Dur Sprinkle	91/44†	‡	‡
K-V Laboratories	Elixophyllin SR			
	Theobid	94	140	54
	Theovent-LA	94	167	60
Rorer	Slo-bid	101	43	18
Searle	Theo-24	71/100†	‡	‡
Slow-release tablets				
Cord Laboratories	Constant-T	76	155	57
Key Pharmaceuticals	Theo-Dur 200,300	97	39	17
	Theo-Dur 100	103	88	35
Mead Johnson	Quibron T/SR	99	128	48
Mundipharma	Phyllocontin	95	165	58
Norwich-Eaton	LaBID	87	252	77
Parke-Davis	Choledyl SA	93	154	57
	Teovent-SR			
Purdue Frederick	Uniphyl	61/83†	§	§
Riker	Theolair-SR	99	‖	‖
	Respbid			

From Hendeles L, Weinberger M. J ALLERGY CLIN IMMUNOL 1985;76:285-91.

*Percent fluctuation = (Peak − trough serum concentration)/Trough serum concentration × 100; actual fluctuations may somewhat exceed predictions because of circadian variation in absorption.[28] The $t_{1/2}$ values are the median value for the average child (3.7 hours) and the average nonsmoking adult (7.7 hours), respectively. Predicted fluctuations for the average cigarette smoking adult are similar to those for the average child. Fluctuations >100% indicate that peak serum concentrations will be more than double the trough level and thus 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 twice-daily or 12-hour dosing. Methodology and validation of the derivation of these values have been described.[5, 8]

†Extent of absorption when taken fasting and with food, respectively.

‡Because rate and completeness of absorption change with food, meaningful predictions of fluctuations cannot be made.

§Measured fluctuations at steady state with once-daily dosing in subjects with mean $t_{1/2}$ = 8.3 hours were 232% fasting and 109% (range 22% to 240%) after food.[24]

‖pH-Dependent dissolution may alter the rate of absorption depending on gastric pH and emptying.[25] Therefore, meaningful predictions of fluctuations cannot be made.

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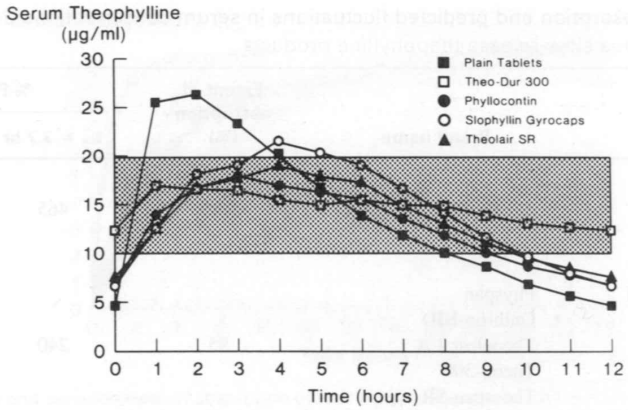

FIG. 2. Predicted steady-state serum concentrations for an average child ($t_{1/2}$ = 3.7 hours, V_d = 0.5 L/kg) receiving plain uncoated tablets and four slow-release products in Fig. 1 at 12-hour dosing intervals. The more rapid the rate of absorption, the greater the fluctuations outside the therapeutic range. Predicted serum concentration fluctuations are 459% for plain tablets, 225% for Slo-Phyllin Gyrocaps, 165% for Phyllocontin, (Mundipharma, Limberg/Lahn, West Germany), 149% for Theolair-SR, and 38% for Theo-Dur 300 mg tablets. Predicted fluctuation for Slo-bid Gyrocaps (not shown) is 59%. These predictions slightly underestimate actual fluctuations because method does not reflect circadian variation in absorption observed for both rapid- and slow-release formulations.[28] Adjusting dose rather than dosing interval will not alter percentage fluctuation. Therefore, children, smoking adults, and about 25% of otherwise healthy nonsmoking adults will generally require 8-hour dosing intervals for most slow-release products, for example, those with predicted fluctuations of >100% at $t_{1/2}$ of 3.7 hours.[5] (From Weinberger M, Hendeles L, Wong L, Vaughan L. Relationship of formation and dosing interval to fluctuation of serum theophylline concentration in children with chronic asthma. J Pediatr 1981;99:145.)

venous formulation, serum concentrations will increase, possibly to toxic concentrations. Conversely, if the dose initially is adjusted to achieve serum concentrations in the 10 to 20 μg/ml range with a 100% absorbed product and the patient subsequently is given an incompletely absorbed product, serum concentrations could decrease to subtherapeutic concentrations that might result in exacerbation of asthmatic symptoms. Because of the potential for nonlinear pharmacokinetics, a small change in extent of absorption is, in effect, a change in dose and could result in a disproportionate change in serum concentrations. These problems could occur without the physician's awareness if the dispensing pharmacist refills the prescription with a generic substitute that is absorbed to a different extent than the prescribed formulation.

Different rates of absorption. Fluctuations in steady-state serum concentrations after multiple doses are a function of the rate of absorption of the product, the rate of elimination of theophylline from the patient, and the dosing interval. In fact, in these patients elimination is slow enough, on average, that serum concentration fluctuations generally will be <100% with an inexpensive rapid-release plain uncoated tablet administered every 8 hours.[8] However, clinically important differences in absorption rates between slow-release theophylline products become apparent when steady-state serum concentrations are predicted for 12-hour dosing intervals in patients who metabolize the drug as rapidly as does the average child or cigarette-smoking adult (Fig. 2).

Because of differences in rates of absorption, most slow-release theophylline products are not interchangeable (Fig. 2). Recently, a change in the product stocked by the Walter Reed Army Hospital Pharmacy to a less expensive generic slow-release theophylline resulted in the clinical impression of increased asthmatic symptoms or increased side effects among some patients.[17] This prompted a controlled study comparing the same dose of four slow-release formulations

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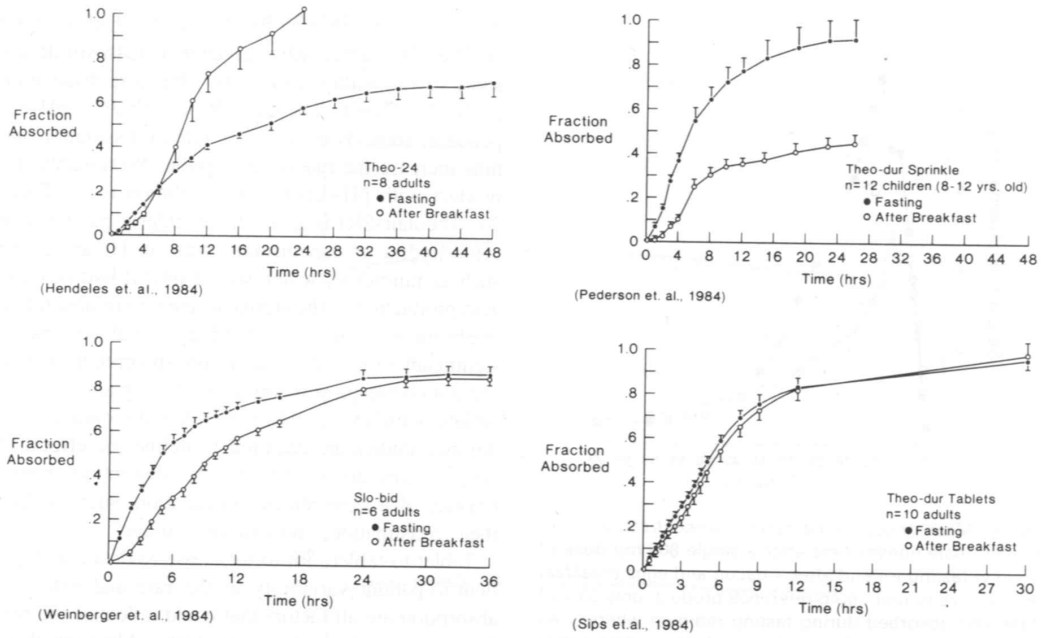

FIG. 3. Effect of food on rate and completeness of absorption of four slow-release theophylline products. Each determination of cumulative fraction absorbed represents mean of values calculated as previously described[6] from sequentially measured serum concentrations after administration of a single dose. ○, Fraction absorbed–time profile after food; ●, fraction absorbed fasting. Data for Theo-24,[12] Theo-Dur Sprinkle,[13] and Theo-Dur tablets[20] have been published previously whereas data for Slo-bid are unpublished (Weinberger et al., 1984). (From Weinberger M. Clinical and pharmacokinetic concerns of 24-hour dosing with theophylline. Ann Allergy 1986;56:2-8.)

23% of intervals when serum concentrations were measured twice in the same subjects given the same product. Moreover, in five of the 10 patients serum concentrations increased above 25 μg/ml with one product even though they were <20 μg/ml with one of the other products. Three of these five had symptoms of theophylline toxicity at the higher serum concentrations but not when given the same dose of a different product that resulted in concentrations <20 μg/ml. Thus, the substitution of one brand for another by the pharmacist could result in a change in asthmatic control or increased frequency of toxic serum concentrations.

With the current emphasis on generic drug substitution, physicians may not be aware which formulation has been dispensed for their patient. Because they

of acquisition cost, it is possible for a patient to get a different formulation with each refill. At the least, any money saved by changing to a less expensive generic product will be offset by the cost of measuring an additional theophylline serum concentration, usually about $40. We therefore recommend that all prescriptions for slow-release theophylline products be written for a specific brand name product and that the physician direct the pharmacist not to substitute another formulation.

FACTORS AFFECTING THE ABSORPTION OF SLOW-RELEASE PRODUCTS

Food. Food affects the absorption characteristics of slow-release products in different ways depending on the formulation (Fig. 3). In addition, the composition

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