The absorption characteristics of six sustained-release theophylline preparations

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Summary

Dosing intervals for sustained-release theophylline preparations depend on the rate of formulation absorption, the rate of elimination by the patient, and clinically acceptable fluctuations in serum concentration. A comparative study of intersubject variation in fraction absorbed-time profiles, a process-independent method of comparing rates of absorption, was performed with 6 sustained-release preparations in 6 healthy male volunteers. The sulphasalazine/sulphapyridine method of assessing oro-caecal transit time was implemented so that upper gastrointestinal and colonic absorption could be estimated. Time until 90% absorption varied from 4.43 hours to 7.46 hours and the mean percentages of theophylline remaining to be absorbed from the colon were limited to between 7.5% and 29.7% with the various formulations. There was a great intersubject variability in the rate of theophylline absorption and also considerable differences among the volunteers in their formulation-to-formulation absorption profiles. Promotional literature depicting mean or group data masks this variability in absorption profiles. Because host factors related to gastrointestinal physiology impose highly variable theophylline absorption profiles on sustained-release formulations, it is technically impossible to formulate a suitable once-a-day product for the majority of patients.

Materials, subjects and methods

Six healthy non-smoking ambulatory white male student volunteers, mean age 20.6 years and mean weight 73.5 kg, were the subjects. None had cardiac, hepatic, endocrine or renal disease. The volunteers were requested to abstain from strenuous exercise, alcohol and caffeine-containing beverages for at least 24 hours before a trial session. Written informed consent was obtained after the protocol had been approved by the Ethics Committee of the University of Pretoria.

During each study session, after an overnight fast, the subjects remained supine for the first 6 hours after drug administration. Sulphasalazine and one of the theophylline-containing preparations was taken at zero time with 250 ml of water. Nothing else was ingested before breakfast was provided 3 hours later. A cannula with heparin lock was placed in an antecubital vein for blood sampling. Baseline samples were taken and, thereafter, blood samples were obtained for determination of serum theophylline and sulphapyridine levels at 1, 2, 3, 5, 7, 9, 12, 24 hours. A cross-over randomised sequence design was followed, allowing at least 2 weeks' interval between the following 6 regimens, each taken simultaneously with 2 g sulphasalazine (Salazopyrin (Pharmacia), non-enteric coated tablets): (i) 2 × 350 mg Euphyllin Retard (Byk Gulden); (ii) 2 × 250 mg Nuelin SA 250 (Riker); (iii) 2 × 250 mg Micro-Phyllin 250 (Restan); (iv) 2 × 375 mg Chronophyllin (Byk Gulden); (v) 2 × 250 mg Somophyllin CRT (Fisons); and (vi) 1 × 200 mg plus 1 × 300 mg Theo-Dur (Astra; Rio Ethicals).

The criterion for oro-caecal transit time was the appearance of at least 1 µg/ml of sulphapyridine in the plasma.

Drug assay

Assay of serum theophylline concentrations was performed by homogeneous enzyme immunoassay (EMIT; Syva), which uses an antibody inhibition technique to quantify the concentration of theophylline. Plasma was assayed for sulphapyridine by a spectrophotometric method.
### Pharmacokinetic analysis

The cumulative fraction of a dose absorbed ($f_a$) at each serum concentration following a single dose was calculated by the following equation:

$$ f_a = \frac{\text{AUC}(0 \to t) + (C_r \cdot \beta^{-1})}{\text{AUC}} $$

where $C_r$ = serum concentration of the slow-release product at time $t$; $\beta$ = the elimination rate constant determined from theophylline given as reference product; AUC($0 \to t$) = the area under the serum concentration time curve for the slow-release product from zero to time ($t$) calculated by the trapezoidal method; and AUC = the total area under the serum concentration-time curve for the reference product.

### Statistical analysis

For statistical analysis the average concentration of theophylline and the fraction of drug absorbed after administration of the various sustained-release formulations was compared at specific time intervals by means of Student's paired $t$-test, $P < 0.05$ being regarded as significant throughout.

### Results

Theophylline bio-availability from all 6 formulations was essentially complete. Fig. 1 illustrates the mean fraction absorbed-time profile, i.e. the time required for a mean cumulative fraction of the dose to be absorbed from the 6 different brands of sustained-release formulations of theophylline, while the last data point represents the extent of absorption. The mean rate of absorption of Somophyllin CRT was significantly faster than Nuelin SA 250 during the 2 - 6-hour interval after administration, but differed from Micro-Phyllin 250 and Chronophyllin 375 only at 4 hours. Mean theophylline absorption from it was 90% complete at 4.43 hours, which was significantly faster than the rate from all the other formulations (Table I). However, time until 90% absorption with
the most slowly absorbed formulation, i.e. Micro-Phyllin 250, still was only 7.46 hours.

Figs 2 and 3 show the fraction absorbed-time profiles of, respectively, Euphyllin Retard and Nuasil SA 250 in the 6 individuals, demonstrating the great intersubject variability in the rate of theophylline absorption and at the same time also the considerable differences among the volunteers in their formulation-to-formulation absorption profiles.

The mean orocaecal transit times ranged from 4.09 hours to 5.23 hours, as judged by the appearance of sulphapyridine in the plasma, and this would suggest that the mean percentages of theophylline remaining to be absorbed from the colon were limited to between 7.5% and 29.7% with the various formulations (Table I).

Discussion

Theophylline is an important anti-asthmatic preparation but the many factors which affect its use must be appreciated. It is subject to a relatively rapid rate of elimination and its metabolism is not only susceptible to drug interactions, but is also impaired in patients with liver disease and with passive hepatic congestion due to heart failure. Further, metabolism can become saturated, resulting in dose-dependent or zero-order elimination in some patients. Fluctuations in serum concentration are paralleled by fluctuations in effect and levels of 10 μg/ml (56 μmol/l) and greater usually provide therapeutic control in most patients, while levels between 5 μg/ml and 10 μg/ml (28 μmol/l and 56 μmol/l) provide symptom control in some patients and therapeutic improvement in others. In addition, serum levels that exceed 20 μg/ml (111 μmol/l) are associated with a greater incidence of untoward reactions. 15

The present single-dose bio-availability studies on sustained-release formulations, some with claims for 24-hour dosing intervals, confirm that it is technically impossible to slow the rate of formulation absorption sufficiently to provide clinically acceptable fluctuations in the theophylline serum concentration in individuals where the elimination half-life is less than 5 - 6 hours and/or the serum clearance rate is more than 1.0 ml/min/kg.17 These patients include most children, smoking adults and about 25% of otherwise healthy non-smoking adults. 6 Once-daily dosing should, therefore, definitely be limited to a population subset, clinically identifiable as those whose dose requirements are below average and in whom 'breakthrough' wheezing does not occur at the end of a dosage interval, i.e. those with the ability to tolerate wider peak/trough fluctuations. Alternatively, the formulation may be administered once daily in the evening, thus providing the highest serum theophylline concentrations during the night for patients with nocturnal worsening of asthma, the only absolute indication for theophylline anyway. Therapy should probably be initiated at dosing intervals no longer than 12 hours. The bronchodilator effect of theophylline is transient and with 24-hour dosing there is more fluctuation. Moreover, there are no data documenting that decreasing the frequency of dosing from twice a day to once a day improves compliance. 8

In conclusion, host factors impose highly variable theophylline absorption profiles on sustained-release formulations between subjects, and intersubject variation in elimination kinetics is large. Therefore, promotional literature depicting mean serum concentration-time curves for non-smoking adults tends to mask the excessive fluctuations observed for a large portion of patients during long-term dosing with theophylline.

REFERENCES