Food induced changes in theophylline absorption from a once-a-day theophylline product

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1 Bioavailability and the absorption pattern of theophylline from the sustained release theophylline (SRT) product, Uniphyllin, were studied in eight adults and eight children under fasting conditions in the morning, after a standardised breakfast in the morning, and under fasting conditions in the evening (adults only). Theophylline given intravenously was used as a reference.

2 The extent of absorption of theophylline was complete for all administrations of SRT both in adults and children.

3 In adults the absorption profiles after the three administrations of SRT were very similar and at no time point was there any difference in serum theophylline concentration or fraction absorbed between the three regimens. In addition, inter and intra individual variations in absorption were small.

4 In children food caused a substantial change in the absorption pattern of theophylline so that the profiles became rather unpredictable with delays in absorption and periods of rapidly increasing serum drug concentrations. In three of the patients the dose dumping phenomenon resulted in toxic serum drug concentrations. Dumping of the dose could take place at any time interval between 3 and 15 h post dosing. $C_{\max}$ was about 50% higher after fed than after fasting medication ($P < 0.01$).

5 It is concluded that children should not take SRT in large doses in combination with food.

Keywords food sustained release theophylline dose dumping

Introduction

During recent years it has been realized that the many advantages of sustained release theophylline (SRT) preparations may sometimes be outweighed by the fact that the absorption characteristics of these preparations are more vulnerable to the influence of gastrointestinal factors such as intake of food. This is unfortunate because the preconditions for safe and optimally effective therapy with these products, which are often given in rather large doses once or twice daily, are that they demonstrate complete and reproducible bioavailability and reliable sustained release profiles with small intra- and intersubject variations in absorption. If this is not the case

then accurate therapeutic monitoring using a single blood sample is not possible.

At present the influence of food upon the absorption of theophylline from a SRT product cannot be predicted on the basis of fasting absorption curves or *in vitro* dissolution tests. Therefore, the absorption profiles of all SRT preparations should be investigated in combination with food.

This study was performed to assess the effect of a solid meal on the absorption characteristics of the SRT preparation, Uniphyllin, a preparation which is often recommended to be taken in rather large doses once daily.

Methods

Three women and five men aged 21 to 42 years (mean = 34 years) and four girls and four boys with ages ranging from 9 to 14 years (mean = 10.7 years) were included in the study. Apart from asthma in the children all participants were in good health. The mean weight of the adults was 65 kg (range 51 to 78 kg) and two were smokers. The mean weight of the children was 38 kg (range 30 to 53 kg). The study was approved by the ethics committee of Northern Jutland, and informed consent was obtained from all of the participants and the parents of the children.

The children participated on three and the adults on 4 separate study days with a wash out period of 1 week between each study day. The following treatments were administered in an open randomised cross-over fashion:

- A. An intravenous injection of 4.0 mg anhydrous theophylline kg^{-1} bodyweight administered over a 5 min period.
- B. SRT tablets (Uniphyllin) administered under fasting conditions at 08.00 h.
- C. SRT tablets (Uniphyllin) administered after a standardised meal at 08.00 h.
- D. SRT tablets (Uniphyllin) administered under fasting conditions at 20.00 h (adults only).

Serum theophylline concentrations were determined by high-pressure liquid chromatography. On the day of intravenous injection blood was drawn before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 h after dosing. On the days of SRT administration the blood sampling times were: before dosing and 1, 2, 3, 4, 6, 8, 10, 12, 15, 19, 22, 26 and 30 h after. In all cases blood samples were collected through an indwelling catheter in a forearm vein and the sera were stored at -20°C until assayed. The laboratory staff were blind to the experimental dose regimen design.

The adults received a mean dose of SRT of 11.2 mg kg^{-1} (range $10.3\text{--}11.8 \text{ mg kg}^{-1}$) and the children took $10.5\text{--}12.0 \text{ mg kg}^{-1}$ (mean 11.8 mg kg^{-1}). The dose of SRT was the same on all study days.

On the fasting days the participants did not eat for 8 h prior to dosing and 4 h after dosing. On the non-fasting day they did not eat for 8 h prior to the standardised breakfast. Medication was taken immediately after the breakfast and no other drinks or food were allowed for 4 h after dosing. The tablets were always swallowed with 200 ml of water.

The standardised breakfast consisted of a weighed quantity of cornflakes, rye bread, butter, salami and low fat milk. Calorically it was composed of 19–20% fat, 68–70% carbohydrates and 12–13% protein.

The participants were asked to refrain from using xanthine-containing preparations, foods and drinks for 72 h prior to and during the test periods. Apart from inhaled β_2 -adrenoceptor stimulants and inhaled corticosteroids no other medications were taken during the study period.

Pharmacokinetic analysis

The individual elimination rate constant (k) for theophylline was calculated by determining the slope of the least-squares regression line from the log concentration-time curve after i.v. administration of theophylline. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule and the area under the curve from the last data point to infinity was extrapolated by dividing the last serum theophylline concentration by k .

The fraction absorbed at the time of each measurement of serum concentration was calculated from the following equation:

$$F(t) = \frac{C(t)/k + \text{AUC}(t)}{\text{AUC}}$$

where $F(t)$ is the fraction absorbed at each measurement of serum drug concentration, $C(t)$ is the measurement of serum drug concentration at that point in time, k is the elimination rate constant, $\text{AUC}(t)$ is the area under the concentration-time curve up to each point in time, and AUC is the area under the concentration-time curve that would occur if the total dose was absorbed. For statistical comparisons of absolute bioavailability AUC was corrected for dose differences between the intravenous and oral doses assuming linear kinetics.

Statistics

Analysis of variance and paired t -tests were used to compare the results from the various administrations of SRT $P < 0.05$ was considered statistically significant.

Definition

In the present paper 'dose dumping' refers to a period of unexpected, rapid increase in serum theophylline concentration during which more than 50% of the total dose is absorbed in less than 2 h.

Results

Owing to blood sampling difficulties one boy did not receive SRT under fasting conditions.

The remaining 15 patients completed the study. Owing to differences in food effects between children and adults the results from these two groups are presented separately.

Adults

The serum concentrations of theophylline and the fraction absorbed at time of each measurement of serum concentration after the various administrations of SRT are shown in Figure 1. Some individual data are shown in Table 1.

The bioavailability of theophylline was complete for all three administrations of SRT and there was no significant difference between dosing with food (100%) and dosing under fasting conditions in the morning (103%) or in the evening (99%).

The mean absorption profiles after the three administrations of SRT were very similar and at no time point was there any difference in serum theophylline concentration or fraction absorbed between the three regimes (Figure 1 and Table 1). Only the mean maximum serum theophylline level measured (C_{max}) differed significantly—this parameter being slightly higher after administration with food (Table 1).

A short period of accelerated increase in serum theophylline concentration was observed in one subject when the drug was taken after food; otherwise satisfactory sustained absorption characteristics with minimal inter and intra-subject variations were found in all cases.

Two subjects experienced nausea and abdominal discomfort 3–12 h after medication on all three days of SRT treatment. In addition they

Figure 1 Mean serum theophylline concentrations and fraction absorbed at each time point of measurement in eight adults taking a single dose of Uniphyllin under fasting conditions in the morning (+), under fasting conditions in the evening (◆) and after a standardized breakfast (■).

Table 1 Absorption characteristics of theophylline from Uniphyllin when taken under fasting conditions in the morning, fasting conditions in the evening and after a solid meal in the morning by eight adults

Patient	$t_{1/2}$ (h)	C_{max} ($\mu\text{mol l}^{-1}$)			t_{max} (h)			Bioavailability (%)		
		Fasting	Food	Night	Fasting	Food	Night	Fasting	Food	Night
1	5.6	76.6	77.1	85.4	6	10	8	106	103	111
2	10.4	102.3	105.5	89.5	6	8	10	119	111	102
3	5.6	69.2	79.5	60.7	6	6	6	107	105	99
4	11.5	81.2	94.3	84.2	10	8	8	87	90	88
5	6.6	60.8	88.1	87.9	12	8	4	92	96	84
6	5.2	66.3	74.8	75.2	10	6	6	115	83	106
7	3.4	52.4	68.6	73.3	6	3	6	91	100	102
8	4.3	53.1	51.1	54.4	8	8	6	108	115	103
Mean	6.6	70.2*	79.9*	76.3	8.0	7.1	6.8	103	100	99

 $P < 0.05$

complained of insomnia after dosing in the evening.

Children

In contrast to the findings in adults food delayed the absorption of theophylline so that the serum concentrations of theophylline and the fraction absorbed at the time of each measurement of serum drug concentrations were significantly lower during the first 4 h after administration with food as compared with dosing under fasting conditions ($P < 0.01$) (Figure 2). Furthermore C_{max} was about 50% higher after food than after fasting medication (Table 2). This was due to the fact that the initial delay in absorption was followed by a short period of rapidly increasing serum theophylline concentration in all children. In three children this period of rapid absorption fulfilled the criteria of dose dumping (Figure 3). It was quite unpredictable when this rapid absorption would take place. It could occur at any time interval between 3 and 15 h after dosing.

The mean bioavailability was high for both doses of Uniphyllin and there was no significant difference between fed (114%) and fasted (101%) intake of the product (Table 2). The very high bioavailability, which was observed in some children after food, seemed to be due to dose-dependent kinetics, with the higher serum drug concentrations after this regime resulting in a decreased rate of elimination.

t_{max} results were rather similar for the two doses of SRT but in one patient a difference of 11 h was observed (Table 2).

Two children complained of abdominal pains and headache and one of dizziness when SRT was taken under fasting conditions. When the preparation was taken with food only the children

in whom dose dumping was observed experienced adverse effects which could be ascribed to theophylline: nausea (three children), abdominal pains (one child) and headache (one child).

Discussion

The present study confirmed that it is important to examine the absorption characteristics of SRT preparations after dosing with food—both in children and adults, otherwise clinically important information may be missed. After fasted intake satisfactory sustained absorption profiles were found in all children and adults. In the latter group this was also the case when the preparation was taken with food. In contrast, the profiles in the children showed substantial variability with delays in absorption and unexpected periods of rapid absorption, which often resulted in toxic serum drug concentrations and side effects, when the preparation was taken with the breakfast.

Differences between children and adults in food effect on absorption of theophylline have also been reported with other SRT products (Pedersen & Møller-Petersen, 1982; Pedersen & Steffensen, 1986; Pedersen, 1986). The cause of this remains unclear. Since the size of the meal in g kg^{-1} bodyweight and the calorie composition of the meal were identical in children and adults in the present study the difference in food effect could not be ascribed to differences in these parameters. Therefore, the present finding points to the recommendation that all SRT products should be thoroughly tested in the age groups in which they are going to be used. Results from adult studies cannot merely be extrapolated to children.

Figure 2 Mean serum theophylline concentrations and fraction absorbed at each time point of measurement in eight children taking a single dose of Uniphyllin under fasting conditions in the morning (+), and after a standardised breakfast (■).

Table 2 Absorption characteristics of theophylline from Uniphyllin in eight asthmatic children who took the preparation under fasting conditions and after a solid meal

Patient	$t_{1/2}$ (h)	C_{max} ($\mu\text{mol l}^{-1}$)		t_{max} (h)		Bioavailability (%)	
		Fasting	Food	Fasting	Food	Fasting	Food
1	3.5	51.9	60.4	6	8	107	95
2	4.1	62.4	85.0	8	6	91	104
3	4.6	72.5	126.0	4	15	115	171
4	3.7	61.9	79.6	10	10	106	108
5	8.2	66.0	115.0	4	8	84	104
6	2.7	49.6	74.3	10	8	111	106
7	5.0	66.5	91.4	10	8	91	109
8	4.0	—	115.7	—	6	—	114
Mean	4.5	61.5*	90.2*	7.4	9.0	100	113

* $P < 0.01$

Figure 3 Serum theophylline profiles in three children in whom dose-dumping was observed when Uniphyllin was taken after a standardised breakfast.

The results illustrated that it is not sufficient to present mean data in studies evaluating absorption characteristics of SRT products. Actually the mean curves of the children were directly misleading since they gave the impression of a rather smooth curve from which an appropriate time of serum theophylline control could be easily and safely depicted. This was in marked contrast to the fact that one of the important findings of our study was that adjustment of dosage or planning of intravenous theophylline in emergency situations on the basis of a single serum theophylline determination should be made with caution if the child had taken the preparation with food.

To our knowledge the absorption profiles of SRT (Uniphyllin) with food have not previously been studied in children. However, the substantial variations in profiles, which were found after food were in accordance with the steady state serum theophylline profiles in children treated with SRT (Uniphyllin) once a day in a recent clinical trial in which food intake in relation to dosing was not controlled (Nerminathan & McKenzie, 1984).

Dose dumping is potentially dangerous, especially when large doses are taken once a day. Even if the children's doses were not very high in our study three out of eight children achieved serum theophylline concentrations within the toxic range. More severe toxic effects might reasonably be anticipated to occur during multiple dosing and therefore we think that the present finding should lead to the recommendation that SRT (Uniphyllin) should not be used in

children in doses exceeding $8\text{--}9\text{ mg kg}^{-1}$ body-weight per dose if the product is taken with food.

Dose dumping has recently been reported to occur with the SRT product Theo-24 and pH-dependent dissolution has been suggested as a possible explanation for this phenomenon (Hendeles *et al.*, 1984, 1985). Uniphyllin, however, shows pH-independent *in vitro* dissolution and yet pronounced dose dumping. So the exact mechanism of dose dumping remains unclear.

Karim *et al.* (1985) recently examined the influence of food upon the absorption of SRT (Uniphyll) in adults. In contrast to our findings Karim *et al.* (1985) found a significant reduction in bioavailability when Uniphyll was taken under fasting conditions. In addition, dose dumping was not observed in his study. This discrepancy between Karim *et al.* (1985) and the present results indicates that Uniphyll and Uniphyllin are probably formulated in different ways and therefore not identical preparations. The difference in food effect, however, may also have been due to differences between the meals used in the two studies since various meals may influence absorption in different ways (Pedersen, 1984).

Circadian fluctuation in absorption has been reported to occur with various SRT preparations (Birkett *et al.*, 1984; Isles *et al.*, 1984; Taylor *et al.*, 1984; Kelly & Murphy, 1980; Lesko *et al.*, 1980). However, differences may exist among products (Birkett *et al.*, 1984) and sometimes different results have been obtained with the same formulation (Busse & Bush, 1985; Rivington *et al.*, 1985). The reason for these discrepancies remains unclear, but often other factors which

may influence the absorption of the theophylline (food, body position, physical activity) have not been controlled in studies investigating the diurnal variation in absorption of SRT. In the present study there was no important circadian variation in the absorption of theophylline from Uniphyllin when the preparation was taken under identical conditions in the morning and in the evening. This is in accordance with the findings of Thompson *et al.* (1984).

Conclusion

Unpredictable absorption profiles with periods

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