

Food and Fasting Absorption of a Single Dose of a Sustained Release Theophylline Sprinkle Formulation in Children

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The bioavailability and absorption pattern of theophylline from a single dose of a slow release theophylline sprinkle product (Somophyllin®) were investigated in 10 asthmatic children both in fasting conditions and after a standardized breakfast. Theophylline given intravenously was used as a reference. The fasting absorption of Somophyllin was rather fast with peak serum theophylline levels 3-5 h (mean 3.7 h) after dosing. Food produced a small but statistically significant reduction in the rate of absorption of theophylline, so that the mean time to peak serum theophylline level was 5.6 h (range 4-8 h) after food. In no case was there any important difference between the absorption profiles on the test days, and the bioavailability was complete after both fasted and fed intake of the product (92.5 % and 105 %, respectively). It is suggested that to obtain the optimum absorption profile children should take Somophyllin with food rather than between meals.

Key words: food; absorption; sustained release theophylline; children.

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Many asthmatic children have difficulty in swallowing whole tablets and therefore cannot receive continuous prophylactic treatment with sustained release theophylline (SRT) tablets. This is unfortunate because children, due to long sleep intervals and rapid clearance of theophylline, comprise a group of asthmatics in which SRT preparations are of most value.

Recently, SRT formulations with coated granules dispensed in capsules have been developed. These preparations can be given by sprinkling the beads inside the capsule upon easily ingested food. This is a great advantage in some children, but only on condition that the food does not have an unfavourable influence on the absorption characteristics of the preparation. Earlier studies have shown that the absorption profiles and bioavailability of various SRT formulations may be influenced by the intake of food in many, often unpredictable, ways, which may sometimes complicate a safe effective therapy (1, 2, 5, 6, 7, 9, 10, 11, 13).

We performed the present study in children to investigate the influence of food on bioavailability and absorption characteristics of theophylline from a single dose of Somophyllin, a SRT product which may be taken after sprinkling the beaded contents onto soft food.

PATIENTS AND METHODS

Nine boys and one girl, with ages ranging from 4 to 12 years (mean 9 years) were included in the study. Apart from asthma all were in good health. Their mean weight was 36 kg (range 18-58 kg). The study was approved by the Ethical Committee of Northern Jutland and informed consent was obtained from all parents.

All children participated on 3 separate days with a wash-out period of 24 h between days 1 and 2 and of 6 days between days 2 and 3.

On the first day, theophylline (4 mg anhydrous/kg) was given intravenously as a bolus over a 5-min period.

On study days 2 and 3 the children took Somophyllin at a mean dose of 9.4 mg/kg (range 8.3–11.1 mg/kg) either in a fasted state or with a standardized meal. The two treatments were allocated in an open randomized crossover fashion.

The contents of the SRT capsules were always sprinkled onto a spoonful of water and swallowed, taking care not to chew the beads. Immediately after medication the children drank 100 ml of water. On all occasions the children fasted from midnight. On the fasting day they continued their fast for 4 h after medication. On the non-fasting day medication was taken immediately after the breakfast and no other drinks or food were allowed for 4 h after dosing.

Serum theophylline concentrations were determined by high pressure liquid chromatography at our department of clinical chemistry. The blood samples were collected through an indwelling catheter in a forearm vein before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, and 16 h after the bolus, and before, and 1, 2, 3, 4, 6, 8, 11, 17, 23, and 30 h after Somophyllin. The sera were stored at -18°C until assayed. The laboratory staff were blind to the experimental design.

The children were asked not to take products containing xanthines for 72 h before and during the test periods. No other oral medications were taken, but inhaled therapy with corticosteroids and β_2 -stimulants continued unchanged throughout the study period.

The standardized breakfast consisted of a weighed quantity of corn flakes, rye bread, butter, salami and 180 ml of low fat milk. In all cases the composition was such that 19–20 % of the calories were made up by fats, 68–70 % by carbohydrates and 12–13 % by proteins. The children received 10.8 to 13.0 kcal/kg (mean 12.3 kcal/kg).

Pharmacokinetic analysis

The individual elimination rate constant (K) for theophylline was calculated by determining the slope of the least-square regression line from the log concentration-time curve after i.v. administration of theophylline. The area under the

concentration-time curve (AUC) was calculated by 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:

$$FA_t = \frac{C_t/K + AUC_t}{AUC_{\infty}} \text{ where}$$

FA_t is the fraction absorbed at each measurement of serum concentration, C_t is the measurement of serum concentration at that point in time, K is the elimination rate constant, 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.

The absorption rate constant, K_a (hour^{-1}) was estimated using linear regression on the log (amount unabsorbed) versus time curve (0–6 h only).

Statistics

Paired t -tests and Wilcoxon Matched-Pairs Signed-Ranks Tests were used to compare the results of the two modes of administration of Somophyllin. $P < 0.05$ was considered statistically significant.

RESULTS

All children completed the study. The serum levels of theophylline after ingestion of Somophyllin in the fasted and the fed state are shown in Fig. 1. The individual data for fraction absorbed at various time points and bioavailability are given in Table 1.

Food produced a small but statistically significant reduction in the rate of absorption of theophylline so that in all patients a shift to the right in the absorption curve was seen. The slower absorption was reflected in a signifi-

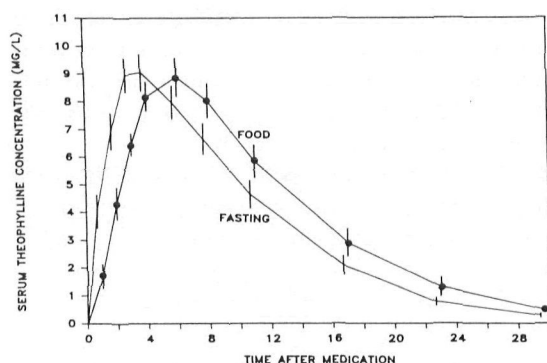


Fig. 1. Serum levels of theophylline (mean $\pm$ SEM) in 10 asthmatic children taking a single dose of Somophyllin under fasting conditions and after breakfast.

cantly lower absorption rate constant with food ($0.21 \text{ h}^{-1} \pm 0.01$) than without food ($0.29 \text{ h}^{-1} \pm 0.03$) ($P < 0.01$), and in a significant difference between the two treatments in time to measured peak concentration - $5.6 \pm 0.40 \text{ h}$ on the day of food and $3.7 \pm 0.30 \text{ h}$ on the day of fast ($P < 0.05$) respectively.

No major difference was observed between the absorption profiles on the 2 test days in any patient. This is illustrated in Fig. 2, which shows the absorption curves in the two patients who exhibited the greatest difference between the two modes of ingestion. The difference between the 2 days in serum theophylline levels

measured at 4 or 6 h post medication was less than 2 mg/ml in eight patients at 4 h, and nine patients at 6 h, respectively. In no case did the serum concentration on the 2 days vary by more than 4.0 mg/l at these times of measurement.

The maximal serum theophylline level ($C_{\max}$) was not significantly different after the fed ($9.2 \pm 0.61 \text{ mg/l}$) and fasting ($9.7 \pm 0.61 \text{ mg/l}$) dosing of Somophyllin (mean $\pm$ SEM).

The bioavailability was high for both modes of ingestion of Somophyllin and was unaffected by whether or not the dose had been taken with food (105 %) or under fasting conditions (95 %) (Table 1).

On the day of intravenous theophylline two children complained of side effects (dizziness and nausea) during the first hour after administration. After fasting medication, three children complained of headache and abdominal discomfort 2-4 h post ingestion. No adverse effects were reported after dosing with food.

DISCUSSION

The study showed, that in children, the bioavailability of Somophyllin was complete both with and without food and that the absorption characteristics of the preparation were not influenced to any clinically important degree by the

Table 1

Fraction absorbed at various time points, and bioavailability of Somophyllin taken by 10 asthmatic children under fasting conditions and after a solid meal

Subject No.	Fraction absorbed at 2 h (%)		Fraction absorbed at 4 h (%)		Fraction absorbed at 6 h (%)		Bioavailability (%)	
	Fasting	Food	Fasting	Food	Fasting	Food	Fasting	Food
1	44.4	36.3	72.6	53.6	78.2	75.5	112.8	114.6
2	40.5	33.0	64.1	62.8	74.3	75.8	119.6	105.2
3	53.6	22.7	71.1	43.4	80.1	62.2	90.9	86.4
4	35.9	16.0	54.7	39.0	65.1	63.9	95.5	113.5
5	45.6	26.3	82.1	66.1	89.1	77.0	82.4	99.6
6	53.9	14.6	69.7	48.2	79.7	68.5	108.1	116.4
7	36.0	21.9	73.0	49.5	86.5	69.0	80.6	108.1
8	37.8	18.4	80.2	51.9	94.0	70.9	84.7	98.1
9	31.6	22.8	69.8	65.7	79.5	77.0	81.8	79.7
10	26.6	11.8	47.2	35.2	70.2	50.8	95.9	127.9
Mean	40.6	22.4	68.4	51.5	79.7	69.1	95.2	105.0
	$P < 0.001$		$P < 0.001$		$P < 0.01$		NS	

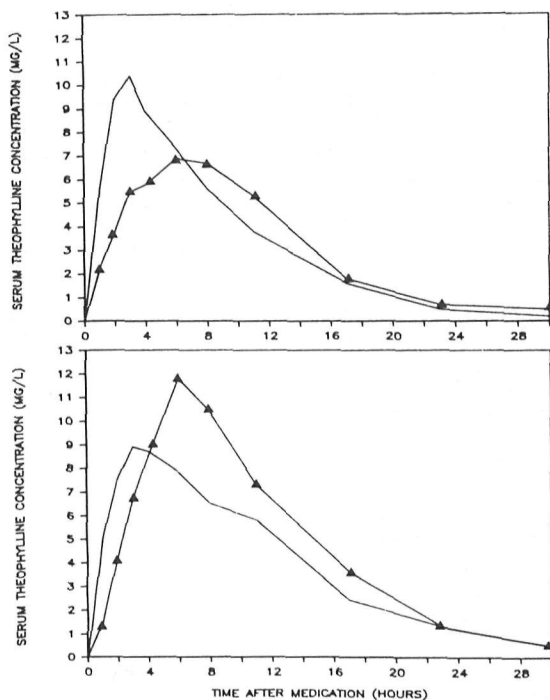


Fig. 2. Absorption curves of theophylline in the two children who exhibited the greatest difference between fed (▲) and fasting dosing of Somophyllin.

concomitant consumption of a substantial breakfast. The results after fasting medication are in accordance with the findings in other studies (3, 4, 12). To our knowledge the absorption profiles of Somophyllin after food have not previously been investigated in children.

We used a rather substantial meal because children often take their medicine with heavy meals, and because we have previously found that a light meal had only little influence upon the absorption of SRT in patients in whom a more substantial meal had a pronounced effect (8). By choosing a heavy meal we thus ensured that a lack of influence of food was not due to an unrealistic light test meal.

Dose dumping (a short period of very rapid increase in serum theophylline level after an initial delay in absorption), which has been reported with certain other SRT preparations when taken with food (4, 6, 8, 9), was not observed in any patient, and the differences between the Somophyllin treatment days were

caused by small but consistent differences in all patients rather than by very large differences in some patients. This means that a serum theophylline level taken before dosing will always be the trough and a serum level 4 h post dosing will be close to the peak in most patients during continuous treatment with Somophyllin. This makes therapeutic monitoring based upon a single blood sample easier and facilitates individualisation of dosage.

Newth found that six of 16 children receiving continuous therapy with Somophyllin under fasting conditions needed 8-h dosing to maintain serum theophylline concentrations within the therapeutic range (10). We also found a rather rapid absorption of theophylline when Somophyllin was taken under fasting conditions. However, food seemed to improve the sustained release properties of the preparation (Table 1) so that the mean peak level occurred about 2 h later after medication with food than under fasting conditions. On the basis of our results we therefore believe that Somophyllin can be safely sprinkled upon food easily ingested, as recommended by the manufacturers, provided that care is taken not to chew the beads. Furthermore, the results indicate that children receiving continuous therapy with Somophyllin will probably have smaller fluctuations in serum theophylline levels if they take their medicine with meals rather than between meals. This may also reduce side effects (3).

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