PHARMACOKINETICS OF SUSTAINED RELEASE THEOPHYLLINE IN LOW AND HIGH MULTIDOSE REGIMENS

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- 1 The *in vitro* characteristics (dissolution rate) of a sustained release theophylline preparation (Theo-Dur®) were first measured in acid medium (pH = 1) for 2 h and after that in a phosphate buffer (pH = 6.8) for 6 h.
- 2 The tablets released more than 95% of the active ingredient within 6 h at a rate of approximately 11% of the dose per hour at pH = 1 and about 18% at pH = 6.8.
- 3 Dose dependency of the pharmacokinetics of theophylline was tested in seven healthy volunteers by giving them either 300 mg Theo-Dur® or 900 mg Theo-Dur® in two doses a day for 5 days in a cross over design. After the last tablet on day 6 the fall-off curve was followed in order to calculate the pharmacokinetic parameters.
- 4 Theophylline (300 mg) resulted on day 6 in a mean serum concentration of $4.4 \pm 0.8 \mu\text{g ml}^{-1}$. The dose of 900 mg resulted in a proportional increase in the serum concentration. The result was $13.3 \pm 2.2 \mu\text{g ml}^{-1}$.
- 5 The $T_{1/2}$ (300 mg) was 9.3 ± 1.4 h and the $T_{1/2}$ (900 mg) was 8.5 ± 2.0 h. These values do not significantly differ ($0.10 < P < 0.20$).
- 6 It was concluded that theophylline exhibits the rules of linear pharmacokinetics when serum concentrations are in the therapeutic range.

Introduction

Theophylline preparations are bronchodilators that are frequently used in maintenance therapy. Dosage titration is recommended because several authors have described a considerable intersubject variation in theophylline elimination. Now that more sophisticated analytical methods for measuring serum levels have become available drug monitoring can more easily be done. The development of sustained release theophylline preparations has made dosage titration more precise. Clearance was found to be influenced by factors like age, weight, diet, habits (e.g. smoking), drugs, disease, etc. (see review by Ogilvie, 1978). It has been suggested recently (Weinberger & Ginchansky, 1977; Kadlec *et al.*, 1978) that the clearance of theophylline in children is also influenced by the drug itself. Data obtained by Weinberger & Ginchansky (1977) support the view that the kinetics of theophylline elimination are dose dependent. While first-order elimination appears to exist at lower serum concentrations, some patients (children) appear to have clinical important decreases in clearance at the upper end of the therapeutic serum concentration range. It was proposed by Kadlec *et al.* (1978), that the elimination process of theophylline

was comparatively slow ($T_{1/2} = 12.6$ h) at high plasma levels and comparatively rapid ($T_{1/2} = 5.4$ h) at low plasma levels.

Occurrence of such a biphasic elimination can be indicative of saturation of hepatic biotransformation processes, since it has been reported that theophylline is mainly excreted as metabolites (Brodie, Axelrod & Reichenthal, 1952; Cornish & Christman, 1957; Jenne, Nagasawa & Thompson, 1976; Grygiel *et al.*, 1979).

In order to investigate whether the reported non-linear pharmacokinetics of theophylline might be of any importance when dealing with therapeutic doses in adults, we have studied theophylline clearance in healthy volunteers administering two doses (300 mg and 900 mg/day) for 5 days, using a sustained release theophylline preparation.

Methods

Seven healthy volunteers weighing 67 ± 6 (s.d.) kg, aged 31 ± 5 (s.d.) years (Table 1), were selected and informed consent was obtained. Routine laboratory

determinations were carried out before drug administration and the tests showed no abnormalities. Smokers were excluded from the study. Diet was not controlled during the study. A sustained release theophylline preparation (Theo-Dur[®], Draco, Lund, Sweden) was administered at 08.00 h and 20.00 h for 5 days. The last tablet was taken on day 6 at 08.00 h. Two dosage regimens were used in each volunteer, namely an intake of 150 mg (= 0.5 Theo-Dur[®] tablet) and 450 mg (= 1.5 Theo-Dur[®] tablet) on each occasion. For each person there was an interval of at least 1 week between the two studies. The dissolution behaviour of this dosage form was tested by an adapted USP XX method using Apparatus 3. The procedure was changed into a 'half-change method' starting with an acid medium (hydrochloric acid pH = 1.0) that was replaced after 2 h by a phosphate buffer of pH = 6.8. Sampling was done every 15 min over a period of 8 h. As required the experiments were done in sixfold. Blood samples were drawn (with Vacutainers[®]) at day 1 at 09.00 h, 11.00 h, 14.00 h, 16.00 h. On day 6 blood was sampled at 08.00 h, 11.00 h, 14.00 h, 17.00 h, 20.00 h and on day 7 at 08.00 h, 10.00 h, 12.00 h, 14.00 h and 16.00 h. Serum samples were stored at -20° C until analysis.

The theophylline concentrations in serum were determined by using a HPLC method (Jonkman, Schoenmaker *et al.*, 1980). The area under the serum theophylline concentration time curve was calculated from day 6 at 8.00 h to day 7 at 16.00 h. The serum clearance was calculated by dividing the dose per time interval by the steady state serum concentrations, and was expressed per kg body weight.

Results

In vitro studies

Dissolution test With the unbroken tablets in acid medium we saw a release of about 13% of the dose

Figure 1 Dissolution characteristics of 150 mg (= 0.5 tablet, ○), 300 mg (= one tablet, □) and 450 mg (= 1.5 tablet, ●) of sustained release theophylline (Theo-Dur[®]), *n* = 6.

during the first 30 min. It was followed by a zero order release process with a release rate of approximately 11% of the dose per hour during the next 90 min. For the broken tablets these figures were 23% and 14% respectively. In the phosphate buffer a zero order release process was observed until approximately 80% of the dose was dissolved; the rate of release was found to be approximately 18% of the dose per hour

Table 2 Serum theophylline concentrations on day 1 as obtained from administration of 150 and 450 mg at 08.00 h

Time	Dose (mg)			
	150		450	
	Mean ($\mu\text{g ml}^{-1}$)	s.d.	Mean ($\mu\text{g ml}^{-1}$)	s.d.
0.900 h	1.1	0.6	1.9	0.8
11.00 h	1.9	1.1	4.3	0.7
14.00 h	2.3	1.0	6.5	1.4
16.00 h	2.5	0.9	6.7	1.1

Table 1 Subject characteristics and pharmacokinetic parameters as obtained after administration of a 300 mg/day dose and a 900 mg/day dose in the same seven subjects.

Subject	1	2	3	4	5	6	7	Mean $\pm$ s.d.
Sex	F	F	M	M	F	M	M	—
Age (years)	27	36	28	32	41	26	29	31 $\pm$ 5
Weight (kg)	58	64	74	76	62	67	65	67 $\pm$ 6
Height (m)	1.63	1.64	1.78	1.76	1.71	1.80	1.84	1.74 $\pm$ 0.08
$T_{1/2}$ 300 (h)	7.2	9.4	9.4	9.1	10.1	8.4	11.3	9.3 $\pm$ 1.3
$T_{1/2}$ 900 (h)	6.6	8.8	8.3	8.2	6.9	8.2	12.7	8.5 $\pm$ 2.0
Clearance 300 ($\text{lh}^{-1} \text{kg}^{-1}$)	0.038	0.041	0.037	0.051	0.038	0.041	0.051	0.042 $\pm$ 0.006
Clearance 900 ($\text{lh}^{-1} \text{kg}^{-1}$)	0.049	0.039	0.044	0.043	0.033	0.038	0.044	0.041 $\pm$ 0.005
AUC ₃₀₀ ($\mu\text{g ml}^{-1} \text{h}$)	106.3	101.1	93.9	64.9	102.0	89.3	80.8	91.2 $\pm$ 14.5
AUC ₉₀₀ ($\mu\text{g ml}^{-1} \text{h}$)	260.8	309.3	231.7	223.4	332.9	307.4	299.9	108.8 $\pm$ 42.2
(AUC ₃₀₀) _{d.c.}	0.354	0.337	0.313	0.216	0.340	0.298	0.269	0.304 $\pm$ 0.048
(ACU ₉₀₀) _{d.c.}	0.290	0.344	0.257	0.248	0.370	0.342	0.333	0.312 $\pm$ 0.047

AUC = area under the serum theophylline concentration-time curve from day 6 08.00 h to day 7 at 16.00 h ($\mu\text{g ml}^{-1} \text{h}$)
(AUC)_{d.c.} = area under the curve, corrected for the dose (AUC per mg of dose).

Figure 2 Individual serum theophylline concentration-time curve, (○ 300 mg/day, ● 900 mg/day).

Table 3 Serum theophylline concentrations on day 6 as obtained after administration of a 300 and 900 mg/day dose.

Time	<i>2 × 150 mg theophylline</i>		<i>Dose</i>		<i>2 × 450 mg theophylline</i>	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
	(μg ml ⁻¹)				(μg ml ⁻¹)	
08.00 h	4.0	0.9	12.7	2.3		
11.00 h	4.7	1.2	14.3	3.8		
14.00 h	4.8	1.1	14.2	2.4		
17.00 h	4.3	0.8	13.7	2.1		
20.00 h	3.8	0.6	11.7	2.2		

for the unbroken tablets, and about 26% for the broken ones (Figure 1).

Although the manufacturer claims that their sustained release properties do not change when the tablets are broken, our findings show that there is a slight difference between the dissolution characteristics of unbroken and of broken tablets. However, we agree that it is not likely that this difference will result in important differences in blood levels, because both tablet forms release almost all the drug before the next dose is given. We therefore decided that broken tablets could be used in our experiments.

In vivo studies

(a) *The 300 mg/day dose* The slow release process resulted in slowly increasing serum theophylline concentrations on day 1 (Table 2, Figure 2), cumulating to a steady state level on day 6 (Table 3).

The average serum concentration on day 6 was $4.4 \mu\text{g ml}^{-1} \pm 0.8$ (s.d.) while the mean trough levels by 08.00 h and 20.00 h were about the same, namely 4.0 and $3.8 \mu\text{g ml}^{-1}$ respectively (Table 3).

In most subjects the highest serum level was found in the sample of 14.00 h, but in some of them it was observed at 11.00 h. The pharmacokinetic parameters are given in Table 1. No side effects were observed.

(b) *The 900 mg/day dose* Again slowly increasing serum levels were observed on day 1 (Table 2, Figure 2). The average serum concentration on day 6 was $13.3 \mu\text{g ml}^{-1} \pm 2.2$ (s.d.), which is about three times the value found for the 300 mg/day dose. Minimum concentrations were observed at 08.00 h and 20.00 h namely 12.7 and $11.7 \mu\text{g ml}^{-1}$ (Table 3). All steady state serum concentrations were in the therapeutic range ($10\text{--}20 \mu\text{g ml}^{-1}$). The maximum serum level was found at 17.00 h. The pharmacokinetic parameters are shown in Table 1.

Half-life and clearance do not differ significantly on the low and the high dose. The values of the areas under the curve corrected for the dose (so the area under the curve per mg of dose) showed no significant

difference either. On the 900 mg dose five of the seven subjects complained about headaches, nausea and sometimes coffee intolerance.

Discussion

Small differences only were established between the *in vitro* dissolution rate of theophylline of broken and of unbroken tablets. Since after breaking the tablets the sustained action is maintained, divided tablets can be used to obtain the optimum individual dose. The tablets were absorbed slowly but completely (Weinberger, Hendeles & Bighley, 1978), and showed that plateau serum concentrations could be reached.

There is only a slight difference between minimum and maximum serum concentrations. An explanation could be that there is an equilibrium between the dissolution rate of theophylline from this tablet and the half-life of elimination. The mean level at 08.00 h was higher than at 20.00 h, but this was not a difference that was significant. So our observations do not support the findings of Lesko *et al.* (1980), who, using a sustained release preparation, reported a significantly higher level in the morning. It must be stated that when comparing the 300 mg/day dose with the 900 mg/day dose, the maximum serum concentration appeared somewhat later. This is in agreement with the slow release of unbroken Theo-Dur® tablets (1.5 tablet). From the results of both regimens obtained in volunteers we may conclude that there is no significant difference in the pharmacokinetic processes. There is indeed a threefold increase in serum level when the dose is trebled. It suggests that the phenomenon of non-linear pharmacokinetics, which is still the subject of further research, is of relatively small importance when dealing with serum concentrations in the lower and middle therapeutic range.

Because of the steady serum concentration it seems sufficient to measure one serum concentration 2 to 5 h after the last tablet intake. It would be more accurate to measure the minimum concentrations, but taking blood samples at the required point of time would be inconvenient for out-patients.

To avoid side effects, which however need not always be caused by toxic theophylline serum concentrations, it is recommended to begin with a low dose of 300 mg/day and to increase this dose every 3 days till a dose of 900 mg/day is reached. After 1 week, one can then measure the patient's serum concentration to decide on the best individual dose.

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