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INVESTIGATION OF DIURNAL CHANGES IN THE DISPOSITION OF THEOPHYLLINE

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1 The mechanism of observed temporal variations in plasma theophylline concentrations has been investigated.

2 Eight healthy volunteers were given both oral and intravenous doses of theophylline (5 mg/kg) at 09.00 h and 21.00 h under controlled conditions. Regular plasma concentration measurements were made following each dose in order to determine the diurnal and nocturnal disposition of the drug.

3 Plasma theophylline concentrations at 0.5 h following each oral dose were 6.9 ± 0.8 μg/ml, a.m., and 3.9 ± 0.6 μg/ml, p.m. ($P < 0.05$). Time to peak concentration was 1.69 ± 0.28 h, a.m.; 2.13 ± 0.23 h, p.m. ($P < 0.05$). Values for k_a were not significantly different, however. Overall bioavailability, volume of distribution and systemic clearances, calculated for the 12 h period after each dose, did not differ significantly between day and night.

4 Diurnal variations in theophylline disposition do not appear to be the result of changes in metabolism or excretion, but may reflect minor differences in absorption.

Keywords theophylline diurnal changes pharmacokinetics

Introduction

For several reasons attention has been directed at whether there may be differences between the diurnal and nocturnal disposition of theophylline in man. Firstly, nocturnal symptoms may be troublesome in certain asthmatics (Turner–Warwick, 1977). Secondly, since it has been shown that the control of such symptoms may be enhanced by maintaining 'therapeutic' concentrations of theophylline throughout the night (Barnes *et al.*, 1982), diurnal changes in theophylline kinetics may be particularly important. Temporal variations in plasma theophylline levels after oral drug administration have been reported (Kyle *et al.*, 1980; Lesko *et al.*, 1980; Scott *et al.*, 1981). The mechanism is unclear but a temporal change in the half-life of phenacetin was associated with variations in hepatic metabolism (Shiveley & Vessell, 1975).

The purpose of this study was to investigate the influence of time of administration on the drug disposition of theophylline in normal subjects following single doses.

Methods

The study was approved by the University Ethical Committee.

Eight healthy, non-smoking subjects (four male, four female), aged 19–23 years, volunteered after full explanation of the procedures involved. Their mean weight was 62.6 ± 3.5 kg. None had evidence of hepatic dysfunction on biochemical testing. Four doses of theophylline (5 mg/kg) were administered to each subject in random order, separated on each occasion by a 7-day interval. On two occasions, one at 09.00 h and the other at 21.00 h, the dose was given as aminophylline injection B.P., by constant rate intravenous infusion over 30 min. On two other occasions, again at 09.00 h and 21.00 h, equivalent doses of theophylline sodium glycinate elixir were administered orally, followed by 100 ml of water. Prior to each study, a 12 h fast was observed and food was not permitted for a further 2.5 h following drug administration. Subjects slept between 01.00 h and 08.00 h following each evening dose, and were disturbed on only one occasion during that period. Venous blood samples were obtained via a heparinised indwelling cannula at 0, 0.5, 1, 2, 3, 4, 6, 12 and 24 h following each dose. After centrifugation, plasma was stored at −20°C until assayed. Theophylline concentrations were measured by a high performance liquid chromatography technique (Kelly & Leahey, 1976). The coefficient of variation at 4.8 μg/ml was 8.8%, and at 16.8 μg/ml was 3.3%. The results were used to cal-

culate k_a, the apparent absorption rate constant following each of the oral doses, by the method of residuals. k_{el}, the elimination rate constant, was calculated by the method of least squares from the elimination phase of each individual plasma concentration-time curve up to and including 12 h after each dose. The area under the plasma concentration-time curve was calculated using the trapezoidal rule. The apparent volume of distribution was established by the formula

$$V = \frac{\text{Dose}}{\overline{\text{AUC}} k_{el}} \text{ l}$$

and body clearance calculated using the formula

$$\text{Clearance} = \frac{\text{Dose}}{\overline{\text{AUC}}} \text{ l/h}$$

Results are presented as the mean ± s.e. mean. Values for V and clearance are expressed with respect to body weight. Statistical analysis was performed by Student's paired t-test.

Results

In presenting data on temporal effects on pharmacokinetic parameters, consideration was given as to whether analysing the results over the 24 h sampling period following drug administration might bias the conclusions. Thus calculations based on 24 h periods would include both nocturnal and diurnal influences and consequently diminish any possible differences between the two. It was, therefore, decided to present evidence based only on data derived for the first 12 h after each drug administration. However, there were no significant differences between the diurnal and nocturnal elimination half-lives calculated for either oral or intravenous administration when the 12 h and 24 h periods were compared. Similarly the overall conclusions for differences in diurnal and nocturnal drug disposition were not affected by using the 12 h period for assessment instead of the 24 h period.

The results are shown in Table 1 and in Figures 1 and 2. Following oral administration, although plasma concentrations at 0.5 h differed significantly (6.9 ± 0.8 μg/ml, a.m.; 3.9 ± 0.6 μg/ml, p.m.; $P < 0.05$), and the time to peak concentration was significantly shorter in the morning (1.69 ± 0.28 h, a.m.; 2.13 ± 0.23 h, p.m. $P < 0.05$), there was no significant difference between the values for k_a, the absorption rate constant. However, these values may be confounded by drug distribution and do not necessarily reflect the absolute rate of drug absorption. Peak concentrations achieved (9.7 ± 0.6 μg/ml, a.m.; 8.9

Table 1 Results following both intravenous and oral administration of theophylline (5 mg/kg) at 09.00 h and 21.00 h to eight normal subjects

Subject	$\hat{k}_a$[1] (h^{-1})	C_{max}[1] ($\mu g\,ml^{-1}$)	*AUC*[1] ($\mu g\,ml^{-1}\,h$)	*AUC*[2] ($\mu g\,ml^{-1}\,h$)	F (%)	$t_{1/2}$[2] (h)	V[2] (l/kg)	*Clearance*[2] ($l\,kg^{-1}\,h^{-1}$)
1	1.31	10.7	78.2	110.6	70.7	6.63	0.45	0.048
2	3.35	9.2	63.4	109.4	57.9	5.19	0.36	0.048
3	1.20	8.5	83.3	78.5	106.1	6.11	0.59	0.067
4	NA	10.9	98.4	73.1	134.6	5.56	0.56	0.070
Day 5	6.12	12.1	114.5	119.5	95.8	6.78	0.41	0.042
6	2.75	11.3	104.1	131.1	79.4	6.96	0.40	0.040
7	4.45	6.5	82.7	72.1	114.7	6.44	0.63	0.068
8	1.46	8.5	122.3	143.8	85.0	9.43	0.50	0.037
Mean	2.95	9.7	93.4	104.8	93.0	6.64	0.49	0.053
s.e. mean	0.70	0.6	7.0	9.7	8.8	0.45	0.10	0.014
1	1.54	9.9	94.9	86.1	110.2	8.58	0.72	0.058
2	2.40	9.9	106.7	78.0	136.7	5.19	0.50	0.067
3	1.25	7.3	60.9	87.4	69.7	6.81	0.57	0.058
4	3.82	8.1	93.9	88.6	106.0	7.28	0.57	0.054
Night 5	1.47	10.7	95.5	97.2	98.3	5.87	0.42	0.050
6	1.69	9.5	166.9	135.4	123.3	8.27	0.39	0.033
7	0.90	6.5	57.4	92.7	61.9	7.23	0.57	0.055
8	1.01	8.9	133.8	137.8	97.1	10.84	0.59	0.038
Mean	1.76	8.9	104.8	100.4	100.4	7.51	0.54	0.052
s.e. mean	0.36	0.5	9.7	8.1	8.9	0.62	0.10	0.011

1 Data following oral dose
2 Data following intravenous dose
k_a Absorption rate constant
C_{max}: Maximum observed plasma concentration
AUC Area under curve calculated by trapezoidal rule
F $\frac{AUC_o}{AUC_{iv}} \times 100\%$
$t_{1/2}$ Elimination half-life
V Volume of distribution

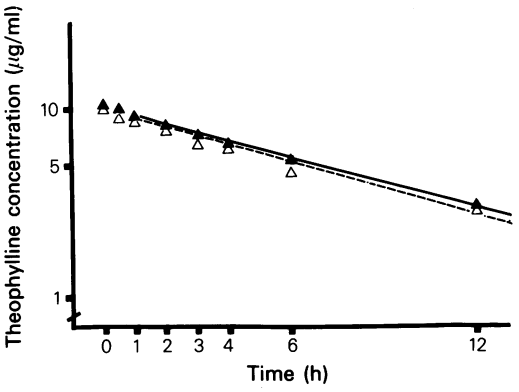

Figure 1 Mean plasma theophylline concentrations in eight subjects following intravenous dose (5 mg/kg) at 09.00 h (▲) and 21.00 h (△).
Solid line: linear regression using a.m. data
Dashed line: linear regression using p.m. data
The s.e. mean ranged from ± 0.1 to ± 1.1 μg/ml for both.

± 0.5 μg/ml, p.m.) and bioavailability of the oral preparation (93.0 ± 8.8%, a.m.; 100.4 ± 8.9%, p.m.) were similar for both times of administration.

No significant differences were noted in the elimination half-life, volume of distribution, and systemic clearance between diurnal and nocturnal values.

Discussion

The results from the present study demonstrate only minor differences in the disposition of theophylline after single doses are given in the morning and evening. The concentration at 0.5 h after oral administration was significantly higher and the time to peak concentration significantly shorter in the morning compared to the evening. This might suggest more rapid absorption but, although the absorption rate constant showed a trend in this direction, it did not reach significance. Despite these early changes, the maximum concentrations achieved and the overall bioavailability were similar for the morning and evening doses, suggesting that temporal variations were not substantial. This was confirmed when the drug was given intravenously: the plasma concentration-time profiles, the elimination half-lives, the volumes of distribution and the systemic clearances after morning and evening administration did not differ significantly.

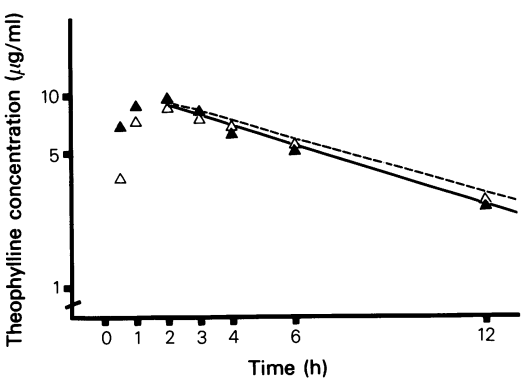

Figure 2 Mean plasma theophylline concentrations in eight subjects following oral dose (5 mg/kg) at 09.00 h (▲) and 21.00 h (△).
Solid line: linear regression using a.m. data
Dashed line: linear regression using p.m. data
The s.e. mean ranged from ± 0.1 to ± 1.1 μg/ml for both.

Several previous studies have examined temporal variations in theophylline disposition after single oral doses, although the effects after intravenous drug administration do not appear to have been reported. In summary, time to peak concentration has been found to be shorter after morning administration (Kyle *et al.*, 1980; Decourt *et al.*, 1982; Nakano *et al.*, 1982) and early plasma concentrations have been found to be higher with the morning dose (Nakano *et al.*, 1982). Peak plasma concentrations have been found to be higher in the morning by some (Nakano *et al.*, 1982) but not by others (Decourt *et al.*, 1982). The absorption rate constant was shown to be significantly greater in the morning in one study (Decourt *et al.*, 1982) but it was not clear how food intake was controlled with evening administration: the plasma elimination half-life was significantly shorter after evening administration in this study, in contrast to another study (Kyle *et al.*, 1980) where the shortest half-life occurred with the morning dose.

These findings, in general, tend to supplement our own conclusion that temporal variations in theophylline disposition probably reflect differences in absorption more than alterations in metabolism or excretion. In clinical practice, differences of this type might be re-enforced by the influence of diet since the rate of absorption of theophylline is delayed by the presence of food (Welling *et al.*, 1975; Pedersen & Moeller-Petersen, 1982).

This may explain the observed differences in trough plasma theophylline concentrations between 08.00 h and 20.00 h in two groups of subjects—one normal volunteer (Lesko *et al.*, 1980), the other asthmatic children (Scott *et al.*, 1981—receiving twice-daily theophylline on a regular basis in a sustained release form. Drug concentrations were approximately 25% higher just prior to the morning dose, perhaps reflecting delayed absorption during the night-time dosing interval. In another study in asthmatic children (Kelly & Murphy, 1980), the differences in plasma theophylline concentrations prior to morning and evening dose administration were not so large.

In conclusion, temporal variations in the disposition of theophylline may reflect faster absorption in the morning but do not seem to be of large magnitude under controlled conditions. However, more rapid absorption of the morning dose, combined with higher morning trough concentrations observed during chronic oral dosing with sustained-release preparations, could be to the benefit of asthmatic patients whose symptoms are at their worst in the early morning.

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