Circadian variation in theophylline absorption during chronic dosing with a slow release theophylline preparation and the effect of clock time of dosing

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1 Eight volunteers were given seven doses of 200 mg of slow release theophylline at either 11.00 h and 23.00 h (regimen 1) or 17.00 h and 05.00 h (regimen 2). At the time of the sixth dose (60 h) hourly blood sampling was started and continued for 24 h. After at least 1 week volunteers crossed over to the other regimen.

2 Volunteers retired to bed at 23.00 h and arose after the 07.00 h sample during both regimens.

3 During regimen 1 there was a marked rise in mean $t_{\max}$ from 3.3 h after dosing at 11.00 h to 9.3 h after dosing at 23.00 h ($P < 0.001$). There was also a fall in AUC(0,12) from 89.9 mg l^{-1} h after dosing at 11.00 h to 79.0 mg l^{-1} h after dosing at 23.00 h. There was no difference in mean $C_{\max}$ values.

4 During regimen 2 these circadian changes were abolished with mean values after both dosing times lying between those observed during regimen 1.

5 A marked delay in absorption occurs at night and cannot be explained by food intake.

Keywords theophylline chronopharmacology circadian variation

Introduction

We and others (Jackson *et al.*, 1984; Lesko *et al.*, 1980) have established the presence of circadian variation in predose theophylline concentrations with both slow release and conventional preparations during repeated oral dosing regimens. Our previous study suggested such circadian changes could be abolished by changing the clock times of dosing (Jackson *et al.*, 1984). The aim of this study was to identify the circadian effect on full concentration-time profiles and to examine the effect on these profiles of changes in the clock times of dosing. The same preparation was used as in our first study (Jackson *et al.*, 1984) and, unlike some previous studies (Scott *et al.*, 1984) we performed hourly sampling in order to improve the precision of the pharmacokinetic parameters.

Methods

Eight healthy volunteers (four male and four female) were studied. Each was given 200 mg of slow release theophylline (Uniphyllin) 12 hourly with 20 ml of water. All the volunteers were day workers. Prior to the sixth dose (60 h) an intravenous cannula was inserted and blood samples taken at the time of dosing and subsequently at hourly intervals. At 12 h another dose was taken and a further 12 samples were drawn at identical times in relation to dosing making a total of 25 samples over 24 h.

Four volunteers (subjects 1–4) started dosing at 11.00 and 23.00 h (regimen 1) and the other four (subjects 5–8) started dosing at 17.00 and 05.00 h (regimen 2). Subjects then crossed over to the other regimen for the second 24 h profile. The sampling periods were separated by at least

1 week. During both dosing regimens volunteers retired to bed immediately after the 23.00 h blood sample and arose after the 07.00 h sample. The timing of doses during the two 24 h profiles was supervised by the investigators. Doses prior to these periods were administered by the subjects themselves, each being provided with a wristwatch with a preset alarm.

The maximum serum concentration ($C_{\max}$), the time to reach $C_{\max}$ ($t_{\max}$) AUC(0,12) and percentage fluctuation in serum concentration were derived from each dosing interval and AUC(0,24) was derived for each regimen. Percentage fluctuation was calculated from $C_{\max}$ and the minimum serum concentration ($C_{\min}$) using the equation (Jackson & Wright, 1983):

$$\text{percentage fluctuation} = \frac{C_{\max} - C_{\min}}{C_{\max}} \cdot 100$$

These derived parameters were compared using Student's paired *t*-test. Serum theophylline concentrations were assayed using an enzyme mediated immunoassay technique (Chang *et al.*, 1982) with a coefficient of variation at a concentration of 5.4 mg l⁻¹ of 3.1%.

Results

The most striking difference in the mean pharmacokinetic parameters derived from the four dosing periods was the prolongation of $t_{\max}$ from 3.3 h after dosing at 11.00 h to 9.3 h after dosing at 23.00 h ($t = 7.7$, $P < 0.001$) (Table 1, Figures 1

Figure 1 Mean theophylline concentration-time profile (with s.d. bars) after dosing at 11.00 h and 23.00 h (Regimen 1) and at 17.00 h and 05.00 h (Regimen 2).

and 2). There was also a statistically significant fall in AUC(0,12) values from 89.9 mg l⁻¹ h after dosing at 11.00 h to 79.0 mg l⁻¹ h after dosing at 23.00 h ($t = 4.2$, $P < 0.005$) (Table 1).

Table 1a Mean ($\pm$ s.d.) values of $t_{\max}$, AUC(0,12) and $C_{\max}$ following each of the four dosing times: 11.00, 23.00, 17.00 and 05.00 h together with the AUC(0,24) value for each regimen

	Regimen 1		Regimen 2	
	11.00 h	23.00 h	17.00 h	05.00 h
$t_{\max}$ (h)	3.3 $\pm$ 1.7	9.3 $\pm$ 1.8	6.4 $\pm$ 3.4	5.3 $\pm$ 1.7
$C_{\max}$ (mg l ⁻¹)	8.7 $\pm$ 2.6	7.8 $\pm$ 2.5	8.2 $\pm$ 2.4	8.2 $\pm$ 2.7
AUC(0,12) (mg l ⁻¹ h)	89.9 $\pm$ 29.0	79.0 $\pm$ 25.0	85.4 $\pm$ 27.4	84.8 $\pm$ 29.0
AUC(0,24) (mg l ⁻¹ h)	168.9 $\pm$ 53.7		170.2 $\pm$ 55.7	
% fluctuation	29.5 $\pm$ 4.5	31.5 $\pm$ 11.2	28.8 $\pm$ 10.6	30.6 $\pm$ 5.8

Table 1b Statistical analysis using Student's *t*-tests of the parameters $t_{\max}$, $C_{\max}$, AUC(0,12) and percentage fluctuation within dosing regimens and AUC(0,24) between dosing regimens

	Regimen 1		Regimen 2	
	11.00 h	23.00 h	17.00 h	05.00 h
$t_{\max}$ (h)	$t = 7.7$, $P < 0.001$		NS	
$C_{\max}$ (mg l ⁻¹)	NS		NS	
AUC(0,12) (mg l ⁻¹ h)	$t = 4.2$, $P < 0.005$		NS	
AUC(0,24) (mg l ⁻¹ h)			NS	
% fluctuation	NS		NS

Figure 2 Mean values of $t_{\max}$ (with s.d. bars) for both dosing intervals during each dosing regimen in eight volunteers.

In contrast, during regimen 2, no significant differences for any pharmacokinetic parameters were seen between dosing at 17.00 h vs 05.00 h (Table 1). $AUC(0,12)$ and $t_{\max}$ values were similar and lay between those seen during the two dosing intervals of regimen 1 (Table 1).

$C_{\max}$ concentrations for all four dosing periods were very similar with mean values between 7.8 and 8.7 mg l⁻¹ (Table 1). No differences reached statistical significance.

Despite the differences in $AUC(0,12)$ values between the dosing periods, mean $AUC(0,24)$ values for the two regimens were very similar—regimen 1: 168.9 mg l⁻¹ h and regimen 2: 170.2 mg l⁻¹ ($t = 0.3$, $P = 0.8$) (Table 1).

Mean percentage fluctuations in serum theophylline concentrations were very similar for the four dosing periods: all were between 28.8% and 31.5% (Table 1).

Discussion

This study has demonstrated a nearly threefold increase in $t_{\max}$ after dosing at 23.00 h vs 11.00 h and this was associated with a highly significant

reduction in $AUC(0,12)$. When dosing times were delayed by 6 h this circadian variation was abolished. $AUC(0,24)$ values during the two 24 h profiles were almost identical suggesting that clearance and the extent of absorption did not differ during the two 24 h study periods. The similar $AUC(0,12)$ and $t_{\max}$ values during the two dosing intervals of regimen 2 suggest that the rate of absorption was similar. The inequality of these parameters during the two dosing intervals of regimen 1 suggest that there was a change in the rate of absorption such that there was unequal spillover of unabsorbed drug into the next dosing interval producing unequal $AUC(0,12)$ values. These findings, therefore, suggest that higher morning predose concentrations are a result of a relative delay in absorption of the evening dose. These observations have not been described previously.

The value of $t_{\max}$ was greater after 05.00 h dosing (mean 6.4 h) when a further 2 h in bed followed dosing than after dosing at 11.00 h (mean 3.3 h) when subjects were performing their normal days work. Thus the delay in absorption starts within 2 h of dosing yet can still be seen if subjects retire to bed 6 h after dosing (mean $t_{\max}$ 5.3 h after dosing at 17.00 h).

Rommel *et al.* (1978) demonstrated delayed absorption of single doses of cephadrine in the supine and left recumbent positions compared with standing and the right recumbent position. Whilst the effect of recumbency is an attractive hypothesis it cannot explain the circadian variation in the absorption of some other drugs (Smith *et al.*, 1986; Nakano & Hollister, 1983). The recumbent posture has been suggested as an explanation for lower theophylline concentrations at night due to a 10% increase in volume of distribution on lying (Warren, 1983). Such an effect cannot explain the observed circadian variation in predose concentrations nor changes in the rate of absorption. This view is supported by the findings of i.v. studies showing no change in volume of distribution in the supine position at night vs the upright position during the day (Coulthard *et al.*, 1983; Taylor *et al.*, 1983; St-Pierre *et al.*, 1984). Most authors have found no differences in i.v. pharmacokinetic parameters after single doses of aminophylline in the morning and evening (Taylor *et al.*, 1983; St-Pierre *et al.*, 1984; Coulthard *et al.*, 1983; Uematsu *et al.*, 1986).

More recently, an attempt has been made at investigating the effect of posture on single dose pharmacokinetics of a slow release aminophylline preparation, Phyllocontin (Warren *et al.*, 1985). Whilst not proven, this effect might be capable of explaining the circadian variation in both

predose concentrations and $t_{\max}$ seen during chronic dosing.

In their single dose studies, Taylor *et al.* (1983) found a significant prolongation of $t_{\max}$ after evening vs morning dosing with a conventional theophylline preparation. St-Pierre *et al.* (1984) demonstrated a doubling in $t_{\max}$ after evening dosing. Apart from the findings in children of Scott *et al.* (1984) where a prolongation of $t_{\max}$ of 5.5 h was seen, the prolongation of $t_{\max}$ in other studies after evening dosing has been of the order of 2–3 h (Primrose, 1983; St-Pierre *et al.*, 1984). The results of the present study show that prolongation of $t_{\max}$ by as much as 6 h is not confined to children and probably reflects both formulation differences and the interval between dosing and retiring to bed.

The effect of food on the absorption of slow release theophylline preparations is formulation dependent, the usual effect being to reduce the rate of absorption with no effect on the extent of absorption (Leeds *et al.*, 1982; Sips *et al.*, 1984). In children taking Uniphyllin, although food produced higher $C_{\max}$ values, $t_{\max}$ values did not differ significantly (Steffenson & Pedersen, 1986). In adult volunteers after a 10 h overnight fast, a high fat breakfast was associated with a statistically significant increase in $C_{\max}$, $t_{\max}$ and AUC(0,72) compared with the same breakfast given 4 h after the dose of Uniphyllin (Karim *et al.*, 1985). These data, however, are not comparable with the data reported here as the only dose not taken within approximately 2 h of a meal was the 23.00 h dose and that dose did not follow an overnight fast. Even ignoring this difference in methodology and the fact that the study of Karim *et al.* (1985) was a single dose study, the lack of difference in $C_{\max}$ values in the presence of a marked difference in $t_{\max}$ values is further evidence that food ingestion cannot account for these circadian changes.

A number of possible mechanisms for circadian changes in a variety of pharmacokinetic parameters have been postulated (Table 2). In addition, a number of underlying physiological factors

Table 2 Possible mechanisms underlying the circadian variation in theophylline pharmacokinetic parameters described in the literature together with possible physiological changes that might trigger them

Possible mechanisms

Change in gastric emptying
Change in renal clearance
Change in hepatic clearance
Change in volume of distribution
Change in gastrointestinal blood flow

Underlying physiological changes

Posture
Sleep
Physical activity
Circadian 'rhythm'
Food ingestion

have been proposed to account for these changes (Table 2). As far as the prolongation of $t_{\max}$ is concerned, the most attractive hypothesis concerning the mechanism is a reduction in gastric emptying at night producing a delay in the delivery of drug to the small bowel.

In conclusion, 24 h concentration-time profiles showed an almost threefold increase in $t_{\max}$ after dosing at 23.00 h compared with 11.00 h which was abolished during regimen 2. This must be due to delayed gastrointestinal absorption during the night and thus a likely explanation is a delay in gastric emptying. Although the staging of circadian rhythms under normal circumstances is affected primarily by temporal patterns of rest and activity (Halberg & Simpson, 1967), it is not clear whether the underlying physiological change responsible for the delay in absorption, however that delay is mediated, is due to the supine posture, sleep itself, a reduction in physical activity, an underlying endogenous circadian rhythm or a combination.

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