Is circadian variation in theophylline trough serum concentrations determined by time of dosing?

S. H. D. JACKSON, J. K. WIFFEN, M. M. SMYTHE & A. JOHNSTON

Department of Clinical Pharmacology, St Bartholomew's Hospital, London, EC1A 7BE

Ten healthy volunteers were each given two separate courses of eight doses of theophylline 200 mg as a slow release preparation at 12 hourly intervals. In the first course (regimen 1) the dose was given at 11.00 h and 23.00 h and in the second (regimen 2) at 05.00 h and 17.00 h. Sixty hours after the start of each course, four consecutive trough serum theophylline concentrations were measured. On regimen 1 the trough concentration of theophylline was 6.2 ± 2.2 mg/l (mean $\pm$ s.d.) at 11.00 h compared with 5.4 ± 1.9 mg/l at 23.00 h ($P < 0.01$). This circadian variation was abolished during regimen 2 when the mean theophylline concentrations were identical at 5.2 mg/l. The higher trough concentrations after the evening dose on regimen 1 and the loss of circadian variation on regimen 2 may be due to the change in sleep period in relation to the time of dosing.

Keywords theophylline circadian rhythm

Introduction

Trough serum concentrations of theophylline were consistently higher in the morning than at other times during both 6-hourly dosing with oral aminophylline solution and 12-hourly dosing with slow release theophylline (Lesko *et al.*, 1980). Taylor *et al.* (1983) found no differences in i.v. pharmacokinetic profiles after single doses of aminophylline at 09.00 h and 21.00 h. In night workers the absorption of theophylline was slower yet clearance was higher in the evening compared with the morning (Decourt *et al.*, 1982). These differences could produce trough serum concentrations higher in the evening in contrast to day workers. We therefore decided to test the hypothesis that changing the time of dosing, whilst keeping sleeping habits unchanged, would influence the circadian variation in trough serum concentrations. In order to avoid the effect of prolonged multiple blood sampling on sleeping habits, we studied trough serum concentrations only, rather than a full pharmacokinetic profile.

Methods

Ten healthy volunteers (four males) were given 200 mg of slow release theophylline (Uniphyllin Unicontin) at either 11.00 h and 23.00 h (regimen 1) or 05.00 h and 17.00 h (regimen 2) in a cross-over design, each regimen lasting for 4 days. All volunteers were day workers. The order of treatments was not randomized, three subjects received regimen 2 first, and the remainder received it last. Steady state was assumed after 60 h following which blood was taken for four consecutive trough serum concentrations. Subjects then crossed over to the other treatment regimen and after a further 60 h a second series of four consecutive trough serum concentrations were taken. During regimen 1 samples were taken immediately before dosing at 11.00 h and 23.00 h and during regimen 2 immediately before the 05.00 h and 17.00 h doses.

During the study period, subjects were asked to retire to bed at 23.00 h and to keep constant their morning rising and meal times. Serum theo-

phylline concentrations were determined using the EMIT assay with an intra assay coefficient of variation (CV) at 5.7 mg/l of < 4% and an inter assay CV of < 7%.

Statistical analysis was performed using two-way analysis of variance looking for the component of variance due to both subjects and time of sampling simultaneously using a repeated measures technique to include both trough serum concentrations at each time of day.

Results

During regimen 2, the mean trough serum concentration (of 20 samples) at 05.00 h and 17.00 h were identical at 5.2 mg/l, whilst during regimen 1 the mean 11.00 h trough serum concentration was 6.2 mg/l compared with 5.4 mg/l at 23.00 h (subjects: $F(9,30) = 17.6$, $P < 0.001$; sampling time: $F(1,38) = 7.6$, $P < 0.01$) (Table 1 and Figure 1). In order to confirm that steady state had been achieved before the blood sampling began at 60 h, mean trough serum concentrations were calculated for the first, second, third

and fourth sample actually taken from each subject regardless of treatment regimen. These were 6.0 mg/l, 5.4 mg/l, 5.2 mg/l and 5.8 mg/l respectively.

Discussion

The expected circadian variation in trough serum concentrations was present during regimen 1, but was completely abolished during regimen 2. This has not previously been demonstrated.

The assumption that all subjects were in steady state by 60 h is crucial to the interpretation of this study. If this were not the case the imbalance between the number of subjects receiving each of the two regimens first would introduce a biased error to our results. It has been convincingly demonstrated during 12 hourly dosing with slow release theophylline that steady state is reached in 24 h (Taylor *et al.*, 1982). There was no trend towards rising levels when mean trough concentrations were analysed by order rather than regimen with the concen-

Table 1 Theophylline trough serum concentrations (mg/l) for each subject at each sampling time during chronic dosing with 200 mg slow release theophylline 12-hourly.

Subject	Regimen 1		Regimen 2	
	11.00 h	23.00 h	05.00 h	17.00 h
1	3.6	4.5	1.4	2.7
	3.8	3.9	2.8	3.0
2	7.6	5.6	6.8	5.3
	6.6	7.2	5.0	7.0
3	5.5	5.0	4.3	3.4
	5.2	3.8	4.8	5.5
4	9.0	7.1	5.5	6.5
	7.3	6.3	7.2	6.5
5	6.0	5.5	5.5	6.4
	5.5	5.7	5.5	6.9
6	3.1	3.2	4.5	3.6
	3.8	3.4	3.6	3.3
7	11.0	8.5	5.8	7.5
	10.2	7.8	6.6	6.5
8	3.4	3.3	5.2	4.5
	4.8	4.8	2.7	4.6
9	7.0	4.5	9.5	4.5
	7.0	3.8	3.5	5.5
10	7.5	9.4	6.0	5.0
	6.5	5.5	7.5	5.4
Mean ± s.d.	6.2 ± 2.2	5.4 ± 1.9	5.2 ± 1.9	5.2 ± 1.5

Figure 1 Individual (●) and mean (—) trough theophylline concentrations at each sampling time.

tration at 60 h (6.0 mg/l) being higher than subsequent concentrations.

If the number of hours sleep during the previous 12 h is an important determinant of trough serum concentration, the 05.00 h serum concentration would be higher than the 17.00 h serum concentration. The lack of difference between these two means suggests this is not so. If sleep or a supine posture is important it would seem that the first 8 h after dosing is the most important period that determines the circadian variation in trough serum concentrations. During regimen 2 there was no prolonged period of sleep following

dosing and trough serum concentrations were identical. This is an attractive hypothesis and has been suggested as an explanation for circadian variation in the pharmacokinetics of other drugs. In a preliminary report Rommel *et al.* (1978) demonstrated delayed absorption of cephadrine in the supine position. The supine posture as opposed to sleep itself is also associated with a short-lived increase in liver blood flow (Daneshmend *et al.*, 1981) therefore this is unlikely to explain our findings. A reduction in gastro-intestinal motility or blood flow or some other mechanism might delay absorption after a late evening dose. Taylor *et al.* (1983) demonstrated no change in i.v. kinetics suggesting absorption changes are responsible for circadian variation. They were, however, unable to demonstrate a significant difference in absorption of oral doses in the morning and evening but their study was confined to single doses.

Higher peak concentrations and bioavailability of theophylline after oral dosing have been observed when the drug is taken after a meal (Lagas & Jonkman, 1983) or with 500 ml of water (Welling *et al.*, 1975). These studies were both performed using single doses of theophylline preparations. In our study the only dose not followed by a meal within the next 3 h was the 23.00 h dose. Food ingestion cannot therefore explain our results.

A final possibility is that greater absorption of theophylline from the bladder during the night could explain the observed circadian variation in serum concentrations.

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