Circadian variation in plasma theophylline concentrations during maintenance therapy with a sustained-release preparation in patients with obstructive airways disease

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- 1 Circadian variation in plasma theophylline concentrations was studied in eight patients with obstructive airways disease during regular 12-hourly dosing at 09.00 and 21.00 h with a sustained-release theophylline formulation.
- 2 After regular dosing for a minimum period of 3 days, plasma concentration measurements were made at 09.00, 13.00, 21.00 and 01.00 h on 3 consecutive days and at more regular intervals during a complete 24 h period on day 4.
- 3 On each day, theophylline concentrations for the first 4 h of the dosing interval were consistently higher during the day than at night. However, the differences were significant only at 13.00/01.00 h on day 2, and for each of the first 4 h on day 4.
- 4 On day 4, following the dose at 21.00 h the mean peak plasma theophylline concentration occurred 6.9 ± 0.8 h after dosing; in contrast, after the morning dose the mean peak concentration occurred at 4.5 ± 0.8 h. However, the mean 'steady-state' concentrations during the two dose intervals were not significantly different.
- 5 Thus circadian variations in plasma drug concentrations do occur in patients taking maintenance theophylline therapy: differing rates of absorption may account for the observed pattern.

Keywords theophylline circadian rhythm

Introduction

It has been reported that maintenance of plasma theophylline concentrations within the range 10-20 µg/ml controls many of the symptoms of bronchial asthma (Weinberger & Bronsky, 1974). More recently Barnes *et al.* (1982) have claimed that sustained-release theophylline preparations are effective in the management of nocturnal asthma, provided adequate plasma theophylline concentrations are sustained. Hence observations of diurnal variations in plasma theophylline concentrations during regular dosing (Bell & Bigley, 1978; Lesko *et al.*, 1980) may be of clinical relevance. In a previous study we have failed to show significant diurnal changes in either the distribution or metabolism

of theophylline during single dose administration to normal subjects (Taylor *et al.*, 1983). We now report an investigation of circadian variation in plasma theophylline concentrations in patients with chronic airways obstruction receiving maintenance treatment with a sustained-release preparation.

Methods

The study was approved by the University Ethical Committee.

Eight patients, admitted for control of

obstructive airways disease, and for whom theophylline was being regularly prescribed, agreed to participate after a full explanation. None had clinical or biochemical evidence of cardiac or hepatic disease. Using a sustained-release theophylline preparation (Theodur, Fisons PLC), given in equally divided 12-hourly doses, adjustments in dose were made until trough plasma theophylline concentrations prior to the morning dose, lay in the range 8–15 µg/ml. This dose was administered for a minimum period of 72 h, following which plasma samples were obtained on 3 consecutive days immediately prior to drug administration at 09.00 and 21.00 h and also 4 h after theophylline was given (13.00 and 01.00 h). On day 4, plasma samples were again taken at 09.00 and 21.00 h, and thereafter at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after each drug administration. For the purposes of the study each 'day' commenced at 09.00 h. Plasma samples were stored at -20°C until assayed for theophylline using a high performance liquid chromatography technique (Kelly & Leahey, 1976). The coefficient of variation for the assay was 7.1% at 4.8 µg/ml and 4.3% at 16.8 µg/ml. Statistical comparisons were made using analyses of variance and Student's paired *t*-test. The results are shown as the mean ± s.e. mean.

Results

Of the eight patients studied, six had chronic obstructive airways disease and two had bronchial asthma. There were seven male and one female; mean age 61.6 ± 3.8 years; mean weight 69.9 ± 6.5 kg. Seven were non-smokers and one a cigarette smoker. Doses ranging from 700–

1200 mg/day were required to establish trough plasma theophylline concentrations of 8–15 µg/ml in the group prior to commencement of the formal 4-day study. However, despite fulfilling these pre-admission criteria, in two patients (nos. 6 and 8, Table 1) the 'mean' concentration was lower than expected during the study.

The results are shown in Figures 1 and 2. The mean plasma theophylline concentrations at 09.00, 13.00, 21.00 and 01.00 h on a particular day did not differ significantly from that at the corresponding time on any of the other 3 days except for the concentrations at 01.00 h on days 2 and 3 (Figure 1). Thus, effectively the patients appeared to have reached the equilibrium state with their theophylline therapy. In general, the plasma concentrations measured at 09.00 and 13.00 h on days 1–4 appeared to be higher than those found at 21.00 and 01.00 h although only the differences between 13.00 and 01.00 h on days 2 and 4 were significant (Figure 1). On day 4 the plasma concentration was higher for the first 5 h after administration at 09.00 h compared to when the drug was given at 21.00 h (*P* < 0.01) (Figure 2).

Following administration of the 21.00 h dose on day 4, the mean plasma concentration continued to decline slightly for 2 h and a significant rise was not recorded until 03.00 h (Figure 2): by contrast, a significant rise occurred during the first hour after administration at 09.00 h. Thus, on day 4, whereas the time to peak concentration was 6.8 ± 0.8 h following the evening dose, it was only 4.5 ± 0.8 h after the morning dose (Table 1): the difference, however, was not significant. In addition, the areas under the drug concentration/time curves and the 'mean' plasma theophylline concentrations for the intervals 09.00–21.00 h and 21.00–09.00 h on day

Table 1

Patient	Dose (mg)	Time to peak concentration (h)		Mean concentration (µg/ml)†	
		Day	Night	Day	Night
1*	1200	3	8	13.9	12.3
2	800	1	8	16.5	11.4
3	800	6	6	10.0	10.8
4	700	3	3	9.5	10.3
5	1200	5	8	13.2	10.8
6	800	4	10	6.2	5.3
7	800	8	4	12.2	13.2
8	700	6	8	7.7	6.8
Mean		4.5	6.9	11.2	10.1
s.e. mean		± 0.8	± 0.8	± 1.2	± 1.0

* Denotes smoker

† Calculated using the formula AUC/dosing interval

Figure 1 Results (mean $\pm$ s.e. mean) in eight patients of plasma theophylline concentration measurements made immediately before, and 4 h after dosing on 4 consecutive days.

● plasma levels following morning dose (09.00 h), ▲ plasma levels following evening dose (21.00 h), * $P < 0.05$ compared to mean concentration at 01.00 h on Day 2, † $P < 0.01$ compared to mean concentration at 01.00 on same day.

4 were not significantly different (Table 1), indicating that, although absorption was delayed following the dose at 21.00 h, its extent was not impaired. The mean difference between maximum and minimum plasma theophylline concentrations at steady state on day 4 was 5.7 ± 1.0 $\mu\text{g/ml}$ (range 2.2–9.6 $\mu\text{g/ml}$) following the morning dose and 4.7 ± 0.4 $\mu\text{g/ml}$ (range 3.3–6.9 $\mu\text{g/ml}$) after the evening dose.

Discussion

The present study confirms that circadian variations in plasma theophylline concentrations can

be observed in patients who are receiving regular therapy with a sustained-release theophylline preparation. The mean plasma theophylline concentrations measured before and 4 h after the morning dose were consistently higher than those after the evening dose, although these changes achieved statistical significance only post-drug on days 2 and 4. In addition, more detailed observations on day 4 revealed that plasma concentrations were significantly higher for the first 5 h after the morning dose compared to the evening dose, with a significant rise occurring within 1 h of administration in the morning but only after 6 h during the night. These findings might suggest that the rate of absorption is

Figure 2 Results (mean $\pm$ s.e. mean) in eight patients of plasma theophylline concentration measurements during each of two consecutive dosing intervals on day 4.

● plasma levels following morning dose (09.00 h), ▲ plasma levels following evening dose (21.00 h), † $P < 0.01$ compared to concentration at equivalent time following evening dose.

delayed in the evening, although the extent of absorption is not eventually impaired.

Our findings are consistent with those of other investigators who reported that plasma theophylline concentrations were higher immediately prior to the morning dose compared to the evening dose by factors of 24 (Lesko *et al.*, 1980) and 23% (Scott *et al.*, 1980): in this study, the mean difference was 18%, although it failed to reach significance. The plasma concentration-time profile on the final 24 h was also remarkably similar to that observed by Scott *et al.* (1980) in 13 asthmatic children, using the same sustained-release preparation. Thus, in general it would appear that the peak concentration during the night-time dosing interval occurs after 6 and 8 h: in one study with another sustained-release preparation, it was as long as 10 h (Thompson *et al.*, 1981). In contrast, Kelly & Murphy (1980) whilst noting that the pre-dose concentration was higher at 08.00 than 20.00 h in 20 asthmatic children, found no other significant diurnal differences and concluded that substantial circadian variation did not occur during chronic administration.

Possible explanations for the present observations have been considered. In a single dose study in normal volunteers, no significant circadian changes in the distribution or elimination of theophylline were detected (Taylor *et al.*, 1983), although a trend for more rapid diurnal absorption was observed. In that study, theophylline was administered under carefully controlled

fasting conditions, whereas in this study no attempt was made to control either the timing or the constituents of dietary intake so that 'normal' clinical conditions would obtain. It has been demonstrated that the peak concentration in asthmatic children may be delayed from 3.6 to 10.2 h if sustained-release theophylline is given with food instead of fasting (Pedersen, 1981). In our patients, whose meal-times were at 08.00, 12.00, 17.00 and 22.00 h, a close relationship between rates of rise in plasma theophylline concentration and the presence of food is difficult to establish. Although food intake preceded each theophylline dose by 1 h in the morning and by 4 h in the evening, in general, quantities of food would be greater later in the day. It would appear possible that differences in absorption, in part related to these environmental influences, may account for circadian variations in plasma theophylline concentrations.

Evidence from this study would suggest that in many patients, the pattern of absorption from a sustained release preparation will help to maintain plasma concentrations during the hours of sleep. However, the times of peak and trough concentrations for each dosing interval are erratic and unpredictable. Thus, as was found in two of our eight patients, dose adjustments based on single day-time 'steady state' concentration measurement may yield incongruous results and require caution.

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