Posture and theophylline kinetics

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The effect of posture on theophylline kinetics was examined in six healthy men who took 450 mg slow-release aminophylline orally at the same time of day on two separate occasions. On one day they remained standing and on the other supine throughout. Plasma theophylline was measured hourly for 6 h from ingestion. Mean theophylline levels were significantly higher in the standing position at all times ($P < 0.01$). We conclude that diurnal variation in theophylline kinetics can be explained, at least in part, by differences in posture.

Keywords theophylline posture circadian rhythms

Introduction

Although a valuable drug, the usefulness of theophylline has been limited by a high incidence of side effects. It has recently been suggested that a higher dose of theophylline given at night is not only effective in treating nocturnal asthma but also causes few side effects (Barnes *et al.*, 1982). A possible reason for increased patient tolerance could be the slower rise in theophylline plasma levels when the drug is given at night rather than in the morning (Kyle *et al.*, 1980; Lesko *et al.*, 1980; Scott *et al.*, 1981; Isles *et al.*, 1981; Primrose, 1983; Taylor *et al.*, 1984). Since there is no significant diurnal variation in theophylline metabolism or excretion, it has been suggested that this diurnal difference arises from altered absorption (Taylor *et al.*, 1983).

The short term kinetics of intravenous theophylline are affected by posture, with a substantially higher peak occurring in the upright position (Warren *et al.*, 1983). Therefore, a change in posture could be a simple explanation of the circadian variation in theophylline pharmacokinetics. For this reason we studied the effects of posture on the pharmacokinetics of a commonly prescribed oral slow-release preparation in normal subjects.

Methods

Six healthy men, who gave informed consent, were studied on two separate occasions. They were hospital personnel aged 25–33 years with a mean height of 1.82 m (range 1.72–1.96) and a mean weight of 75 kg (range 69–79). All were non-smokers and on no regular medication. The study was approved by the hospital ethical committee.

On one occasion they lay supine throughout the experiment and after a 15 min rest, heart rate and blood pressure were measured. A catheter was inserted in a forearm vein for blood sampling and they then took 450 mg of slow release aminophylline (two tablets of Phyllocontin, Napp Laboratories, Cambridge). Venous blood was sampled at 60 min intervals after tablet ingestion for a total of 6 h. Heart rate and blood pressure were recorded before each sample.

On another occasion the same experiment was repeated with the subject standing throughout. They were allowed to walk around the laboratory but stood stationary for 5 min before each set of readings. Each subject started both experiments at the same time of day and all studies started between 07.00 h and 09.30 h. The lying and standing experiments were performed in random order at least 5 days apart. The subjects

fasted from the previous evening and were allowed breakfast and lunch after the 1 h and 4 h sample respectively. The food and drink taken on the two separate days were identical for each subject.

After sampling, blood was placed in a heparinized tube and plasma separated by centrifugation. Samples were stored at -70°C until assayed by a fluorescent polarization immuno-assay (Abbott TDX) method, which has a coefficient of variation of $< 3\%$. Blood pressure was measured by sphygmomanometer.

Results

No subject experienced any side effects although all measured theophylline levels were below 8 mg/l.

The peak concentration of theophylline with the subjects standing occurred at 5 h and was 6.4 mg/l (Figure 1). The peak level measured during the lying experiment occurred at 6 h and was 5.4 mg/l, although this may have risen further after the end of the experiment. Theophylline concentrations were significantly higher in the standing experiment ($P < 0.01$, analysis of variance).

Table 1 shows that theophylline had little effect on blood pressure or heart rate.

Discussion

Following the initial description of a circadian variation in theophylline toxicity in animals (Kyle *et al.*, 1979), several studies have confirmed a diurnal variation in theophylline pharmacokinetics in humans (Kyle *et al.*, 1980; Lesko *et al.*, 1980; Scott *et al.*, 1980; Isles *et al.*, 1981; Primrose, 1983; Taylor *et al.*, 1980). When the drug is given at night, plasma concentrations of theophylline are characteristically lower over the first 6 h when compared with daytime dosing, although after this time the curves cross over. However, total absorption as measured by the area under the whole curve, is similar. The most

Figure 1 Effect of posture on theophylline pharmacokinetics. Each point is the mean ($\pm$ s.e. mean) for six subjects. Δ — Δ standing, $\bullet$ — $\bullet$ supine.

tenable explanation is that absorption is delayed at night, particularly since theophylline metabolism and excretion show no diurnal variation (Taylor *et al.*, 1983).

When theophylline is given intravenously the effect is far greater if the recipient is standing rather than lying (Warren *et al.*, 1983). In part this is caused by higher peak plasma levels in the upright position. One reason for the difference is a 12–15% reduction in plasma volume on standing (Thompson *et al.*, 1928), the smaller initial volume of distribution in the standing position causing a higher plasma theophylline concentration. This initial difference disappears as the drug diffuses into the extravascular space. It is possible that these differences in plasma volume may also affect the kinetics of theophylline as it is absorbed from a slow release preparation in the gut. An alternative explanation of the current findings is that the upright posture delays gastric

Table 1 Effect of theophylline on mean ($\pm$ s.e. mean) heart rate and blood pressure

		Base	1 h	2 h	3 h	4 h	5 h	6 h
Heart rate (beats/min)	Lying	63 $\pm$ 4	57 $\pm$ 4	62 $\pm$ 4	61 $\pm$ 5	59 $\pm$ 4	63 $\pm$ 4	62 $\pm$ 4
	Standing	74 $\pm$ 3	70 $\pm$ 4	76 $\pm$ 4	78 $\pm$ 6	82 $\pm$ 6	81 $\pm$ 5	83 $\pm$ 8
Systolic BP (mm Hg)	Lying	112 $\pm$ 3	110 $\pm$ 5	107 $\pm$ 3	110 $\pm$ 5	117 $\pm$ 4	111 $\pm$ 3	110 $\pm$ 4
	Standing	110 $\pm$ 6	103 $\pm$ 2	106 $\pm$ 4	108 $\pm$ 3	110 $\pm$ 4	105 $\pm$ 4	103 $\pm$ 3
Diastolic BP (mm Hg)	Lying	81 $\pm$ 4	78 $\pm$ 4	78 $\pm$ 3	81 $\pm$ 2	82 $\pm$ 2	76 $\pm$ 2	77 $\pm$ 4
	Standing	81 $\pm$ 5	80 $\pm$ 2	76 $\pm$ 4	78 $\pm$ 4	79 $\pm$ 4	78 $\pm$ 2	76 $\pm$ 3

emptying and therefore the rate of theophylline absorption from the small bowel. It would have been interesting to extend the experiment beyond 6 h but the volunteers found standing beyond this time too tiring.

None of the subjects studied reached therapeutic theophylline levels within 6 h of ingestion despite taking the normally recommended dose of slow-release aminophylline. This highlights the need for adequate dosing in clinical practice.

In the present experiment oral slow release aminophylline produced a more rapid rise in

theophylline levels in the upright position. The difference between the absorption curves is very similar to the difference seen between day and night-time dosing. Therefore, it seems that the supine position during sleep may be an adequate explanation for this diurnal variation.

We thank the Chemical Pathology Department, Ealing Hospital, for assaying the theophylline samples, the volunteers who took part, and Napp Laboratories for financial support.

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(Received October 31, 1984,
accepted January 14, 1985)