Acute and chronic pharmacokinetics of assymetrical doses of slow release choline theophyllinate in asthma

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1 The day and night pharmacokinetics of assymetrical doses of slow release choline theophyllinate (Sabidal SR 270) were compared at day 1 and at day 4 of treatment when steady state had been achieved.

2 Ten patients with chronic asthma were given oral choline theophyllinate 424 mg at 09.00 h and 848 mg at 21.00 h for 4 days. At regular intervals during day 1 and day 4 of treatment theophylline concentrations were measured in plasma and dried blood spots by fluorimmunoassay.

3 Theophylline concentrations measured from dried blood spots were slightly lower than those in plasma, the difference remaining constant at all time points during day 1 and day 4 of treatment.

4 On day 1 the mean peak plasma theophylline concentration was 5.4 ± 1.0 ($\pm$ s.e. mean) $\mu\text{g ml}^{-1}$ 4 h after the morning dose and 11.2 ± 1.6 $\mu\text{g ml}^{-1}$ 4 h after the evening dose which were significantly ($P < 0.01$) different. Similarly the areas under the plasma theophylline concentration–time curves at night were significantly ($P < 0.001$) greater than those observed during the day.

5 During day 4 mean peak plasma concentrations of theophylline after the morning and larger evening dose were 13.2 ± 1.3 and 12.1 ± 1.4 $\mu\text{g ml}^{-1}$ respectively, which were not significantly different. No significant difference was observed between the areas under the plasma theophylline concentration–time curves during the day and at night. However the post-dose time to peak was significantly delayed at night (6 h) compared to the morning (2 h, $P < 0.001$).

6 Asymmetrical doses of slow release choline theophyllinate administered twice daily are suitable for maintenance therapy in patients with chronic airflow obstruction for the treatment of nocturnal and early morning symptoms.

Keywords theophylline slow release asthma pharmacokinetics

Introduction

It is now widely accepted that slow-release preparations of methylxanthines offer patients with asthma some protection against nocturnal and early morning symptoms. For optimal effects it is frequently stated that plasma concentrations of the drug should be maintained between 10 and 20 $\mu\text{g ml}^{-1}$ throughout the night (Weinberger & Hendeles, 1983). It has recently been shown that theophylline pharmacokinetics are altered

at night (Taylor *et al.*, 1984; Lesko *et al.*, 1980; Scott *et al.*, 1981; Thompson *et al.*, 1981). Thus, in patients taking a conventional regime of two equal doses of a slow release theophylline preparation in the morning and evening, lower nocturnal plasma theophylline concentrations occur which may be 'subtherapeutic' at the time when symptoms may be severe (Taylor *et al.*, 1985; Scott *et al.*, 1981).

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Choline theophyllinate is a well established methylxanthine preparation which for many years has been used to treat patients with chronic airflow limitation. A slow-release preparation of this drug is now available in the form of Sabidal SR270 which contains 424 mg choline theophyllinate (equivalent to 270 mg anhydrous theophylline) in a non-toxic, plastic membrane containing microholes to allow slow diffusion of the active drug into the gastrointestinal tract along a concentration gradient (Dahlqvist & Billing, 1983; Jonkman *et al.*, 1984; Berg *et al.*, 1985). The present study investigates the day and night pharmacokinetics of choline theophyllinate with asymmetrical doses of 424 mg in the morning and 848 mg at night in a group of patients with severe chronic reversible airflow obstruction. The study was designed to compare theophylline pharmacokinetics during the first and last 24 h of a 4 day treatment regime. Circulating blood theophylline concentrations were measured by substrate label-fluoroimmunoassay applied to plasma and dry blood spots, the latter being applicable to domiciliary theophylline monitoring.

Methods

The study was approved by the Southampton University and Hospitals Ethics Sub-committee. Ten patients (eight male, two female) with severe chronic obstructive airways disease in whom a 15% increase in FEV₁ had been demonstrated 15 min after inhaling 200 µg salbutamol agreed to participate in the study. All were non-smokers and their mean $\pm$ s.e. mean FEV₁ was 1.52 ± 0.24 l (40% predicted). Patients were aged between 54 and 72 years (mean 62 ± 7 years) and had had a weight range of 56–78 kg. None of the patients had any clinical or biochemical evidence of hepatic disease and all were non-smokers. Three of the subjects were taking preparations of theophylline prior to the study and were therefore asked to stop these 4 days before starting the investigation. None of the patients was taking any drugs known to interfere with theophylline pharmacokinetics.

Patients were admitted to hospital at 09.00 h after a normal breakfast. A Teflon® cannula was inserted into an antecubital vein and patency maintained with small injections of heparinised saline solution. Blood (10 ml) was removed for assay of theophylline (baseline). Patients were then given one capsule of slow-release choline theophyllinate 424 mg (Sabidal SR270, Zyma) followed by blood sampling at 2, 4, 6, 11 and 12 h. After the last sample taken at 21.00 h, two further capsules of choline theophyllinate were given (848 mg) followed by further blood sampling at 2, 4, 6, 11 and 12 h post-dose.

After completing the first 24 h of the study patients were asked to continue on the asymmetrical dose regime for a further 2 days prior to their readmission to hospital on the morning of the fourth day for a further pharmacokinetic study. Patients were readmitted to the hospital at 09.00 h and the same procedure of drug administration and blood sampling undertaken as described for day 1. No restriction was placed on the activity or diet of the patients during the 2 days when patients were not in hospital.

Immediately the blood samples were obtained they were centrifuged at 2000 g and the plasma separated and stored at -20°C until assay. Before centrifugation several drops of whole blood were transferred on to a single 1 cm marked circle on absorbent paper which was subsequently dried and used for assay of dried blood spot theophylline concentrations as described for blood obtained by finger prick (Coombes *et al.*, 1984). Substrate label fluoroimmunoassay was used to estimate the theophylline concentration in both plasma and eluted blood spots (Li *et al.*, 1981). The intra assay coefficient of variation of the assay in plasma was 3.4% at $7.5 \mu\text{g ml}^{-1}$ and 3.9% at $15 \mu\text{g ml}^{-1}$. The coefficient of variation for the assay applied to blood spots was 6.1–6.9% at $7.9 \mu\text{g ml}^{-1}$ (Coombes *et al.*, 1984).

Theophylline concentrations were expressed as mean $\pm$ s.e. mean and statistical comparisons performed using the Student's paired *t*-test. On days 1 and 4 the areas under the plasma concentration–time response curves from 0–11 h after each of the morning and evening doses of choline theophyllinate were calculated by trapezoidal integration and compared using Student's *t*-test for paired data. The relationship between theophylline concentrations measured in plasma and in dried blood spots was analysed by least squares linear regression and by plotting the difference between measurements against the mean (Altman, 1980).

Results

From all the patients and at all the time points throughout the study (179 measurements) theophylline measured from extracted dry blood spots showed a close correlation with plasma concentrations, the regression line passing through a point which was not significantly different from zero ($y = 0.785x + 0.056$, $r = 0.989$) (Figure 1a). Theophylline concentrations measured in blood spots were consistently lower than those measured in plasma (Figure 1a) but exhibited the same pharmacokinetic profile as measured in plasma (Figure 2). On day 1 the mean plasma concentration of theophylline was $0.8 \pm 0.5 \mu\text{g ml}^{-1}$ (mean $\pm$ s.e. mean) which could largely be

Figure 1 Relationship between plasma and blood spot theophylline concentrations measured by fluorimmunoassay: a) least squares linear regression, b) mean vs difference where x = plasma theophylline and y = blood spot theophylline (Altman, 1980).

accounted for by a single subject who had a value of $4.4 \mu\text{g ml}^{-1}$. The remaining subjects had a range of starting plasma theophylline concentrations of $0\text{--}0.3 \mu\text{g ml}^{-1}$ which was within the error of the assay.

After the first dose of choline theophyllinate 424 mg, the mean plasma theophylline concentration rapidly increased to reach a maximum of 5.4 ± 1.0 (range $0.7\text{--}10.3$) $\mu\text{g ml}^{-1}$ 4 h after

dosing which was followed by a trough of 3.1 ± 0.4 (range $1.0\text{--}4.9$) $\mu\text{g ml}^{-1}$ at 12 h (Figure 2a). After the second dose of choline theophyllinate, 848 mg, administered at 21.00 h mean plasma concentration of theophylline rapidly increased to a peak of 11.2 ± 1.6 (range $5.6\text{--}19.0$) $\mu\text{g ml}^{-1}$ 4 h after dosing which was followed by a slow decline to 8.5 ± 1.2 (range $4.2\text{--}10.4$) $\mu\text{g ml}^{-1}$ at 08.00 h, 11 h after the evening dose. Both the trough and peak theophylline values were significantly ($P < 0.05$) elevated above baseline at all time points following the drug administration, and values at night were significantly ($P < 0.01$) higher than the corresponding values measured at the same post-dose time points during the day. The areas under the plasma theophylline concentration-time curve (AUC) were significantly greater after the evening dose of 848 mg choline theophyllinate ($101.6 \pm 13.0 \mu\text{g ml}^{-1} \text{ h}$) than after the smaller morning dose ($44.1 \pm 8.0 \mu\text{g ml}^{-1} \text{ h}$, $P < 0.001$).

After continuous treatment with choline theophyllinate a completely different pharmacokinetic profile was observed. The resting morning plasma theophylline concentration of 9.8 ± 0.7 (range $5.9\text{--}12.9$) $\mu\text{g ml}^{-1}$ at 09.00 h (Figure 2b) was not significantly different from that observed at 08.00 h following the first day's treatment (Figure 2a), suggesting that steady state had been achieved within 24 h. Following choline theophyllinate, 424 mg on the morning of day 4, plasma theophylline concentrations rapidly increased to a peak of 13.2 ± 1.3 (range $6.4\text{--}17.7$) $\mu\text{g ml}^{-1}$ 2 h after dosing. Theophylline concentrations then decayed to a mean trough value of 6.2 ± 0.7 (range $2.7\text{--}9.4$) $\mu\text{g ml}^{-1}$ 12 h after dosing which was almost twice as high as that achieved on day 1 of the study. Despite the

Figure 2 Time-related changes in plasma (●) and dried blood spot (○) theophylline concentrations during the first (a, upper panel) and fourth (b, lower panel) 24 h of treatment with choline theophyllinate.

higher theophylline trough value, further nocturnal dosing with choline theophyllinate, 848 mg, only increased mean plasma concentrations to a peak of 12.0 ± 1.4 (range 8.2–17.4) $\mu\text{g ml}^{-1}$ which was not significantly different from the peak observed earlier during the day or the nocturnal peak observed on day 1. However, the nocturnal peak concentration was not achieved until 6 h after the evening dose which was significantly ($P < 0.01$) later than the time to peak observed during the day (2 h) (Figure 2b). With 3 days of choline theophyllinate treatment the AUC after the morning dose on the fourth day ($113.8 \pm 11.2 \mu\text{g ml}^{-1} \text{ h}$) was not significantly different from that achieved at night following the large dose ($117.2 \pm 11.1 \mu\text{g ml}^{-1} \text{ h}$). At no time point during the study were any side effects noted by the subjects.

Discussion

The present study demonstrates that with regular asymmetrical doses of choline theophyllinate 424 mg in the morning and 848 mg at night, plasma concentrations of theophylline are greater than $9.5 \mu\text{g ml}^{-1}$ between 23.00 h and 09.00 h and maintained during the day for at least 6 h. This would indicate that for patients with chronic airflow obstruction who develop their major symptoms at night and in the early hours of the morning, plasma concentrations of theophylline fall within the accepted therapeutic range. On this regime none of the 10 patients achieved a plasma theophylline level of $> 20 \mu\text{g ml}^{-1}$, though in one subject a nocturnal peak of $6.4 \mu\text{g ml}^{-1}$ might be considered subtherapeutic (Weinberger & Hendeles, 1983). Several studies have previously shown that with a conventional twice-daily equal dose regime of a slow release theophylline preparation, the concentrations of theophylline in the morning are consistently higher than those in the evening and at night. This observation may be explained either by an alteration in nocturnal elimination of theophylline (Jonkman *et al.*, 1984) or by delayed nocturnal absorption of the drug (Kyle *et al.*, 1980; Decourt *et al.*, 1982; Nakano *et al.*, 1982). In the present study the time between dosing and peak plasma concentrations after regular treatment with this slow-release preparation was three times as long after the evening than after the morning dose, a difference which was not apparent during the first day of the study (Figure 2a). Other authors have demonstrated a similar phenomenon in subjects who had not previously been fasted prior to receiving the evening dose (Scott *et al.*, 1981; Thompson *et al.*, 1981; Taylor *et al.*, 1984). Pederson & Moeller-Peterson

(1982) have observed that after a large meal at night a slow-release preparation of theophylline undergoes delayed absorption. With chronic dosing reduced drug absorption may be overridden by reduced hepatic metabolism (Trembath *et al.*, 1979) and reduced drug elimination (Leung *et al.*, 1978; Dahlqvist & Billing, 1983).

Theoretically, with slower nocturnal elimination and equally divided morning and evening dosing, the peak plasma concentrations achieved at night would be significantly higher than those achieved during the day. In the present study we have demonstrated that by doubling the nocturnal dose of choline theophyllinate, a similar peak plasma theophylline concentration is achieved at night as during the day (Figure 2b). The comparable areas under the plasma concentration-time curves during the two halves of the day indicate that the asymmetrical dose schedule provides a relatively constant plasma concentration of theophylline throughout the day. At no time were toxic plasma concentrations recorded and none of the patients reported any side effects. After regular dosing the morning trough values of theophylline were significantly higher than the corresponding evening level as might be expected from the increased nocturnal dose and its delayed pharmacokinetics.

Our study has further demonstrated that measurement of theophylline in dried blood spots, while giving values slightly lower than those recorded in plasma (Figure 1b), is a highly reproducible technique applicable for monitoring drug concentrations in domiciliary practice. We were unable to demonstrate any differences in the relationship between plasma and whole blood theophylline concentrations at any time point during the acute or chronic dosage study. It is therefore unlikely that any diurnal variation occurs in the distribution of theophylline between the circulating plasma and cellular compartments.

In conclusion, this study has shown that a twice daily asymmetrical dose schedule of choline theophyllinate produces plasma concentrations of theophylline at night and during the first half of the day which would produce maximal effects on the airways at a time when patients with chronic airflow obstruction frequently experience their most severe symptoms. Since no side effects were reported by the patients, this regimen would be appropriate for maintenance therapy when this slow-release theophylline preparation is used.

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