The effect of dosing time on the pharmacokinetics and pharmacodynamics of a 'once-a-day' sustained release theophylline preparation

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- 1 The pharmacokinetics and the bronchodilating effect of theophylline were studied during 1 week of morning dosing and 1 week of evening dosing in a randomized cross-over design in thirteen patients with reversible airways obstruction, treated with a new 'once-a-day' theophylline capsule formulation.
- 2 There were no differences between the mean pre-dose trough plasma concentration, maximal plasma concentration, trough-to-peak variation, $t_{\max}$, area under the plasma drug concentration time-curve after morning or evening dosage. There was only a slightly but significantly higher plasma theophylline concentration between 16 and 20 h after evening dosing.
- 3 The mean plasma drug concentration time-curves were relatively flat with a mean trough to peak variation of 73.9% after morning dosing and 66.7% after evening dosing. Both sets of mean data were within the 10–20 mg l⁻¹ therapeutic range.
- 4 The variations in FEV₁ and PEFR throughout the 24 h after either morning or evening dosing were similar and followed the normal pattern of diurnal variation.
- 5 Adverse effects were mild and occurred in three patients without causing discontinuation of the study.
- 6 The theophylline preparation used appears suitable for once a day administration either in the morning or in the evening.

Keywords theophylline chronopharmacology pharmacokinetics

Introduction

Theophylline is widely used in the treatment of bronchial asthma. The oral route is mainly used in the chronic treatment of reversible airways obstruction. The therapeutic effect of theophylline is correlated with its plasma concentration over a rather narrow range of 10–20 mg l⁻¹. In addition, since side-effects occurring during theophylline treatment are usually related to high plasma drug concentrations (Ogilvie, 1978), adequate control of the plasma theophylline concentration is essential.

For this purpose sustained release oral theophylline preparations have been developed and shown to provide adequate plasma theophylline concentrations in most adult patients when administered twice daily (Weinberger *et al.*, 1978). The reduction in dosing frequency has also been shown to increase patient compliance (Tinkelman *et al.*, 1980). Several theophylline preparations have recently been recommended for once-a-day administration (Cohen, 1984; Busse & Bush, 1985). However, none of the

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presently available preparations have sufficiently reliable pharmacokinetics for routine use as once-a-day preparations (Weinberger, 1986). In the present study we investigated the pharmacokinetics and pharmacodynamics of theophylline administered as a new slow-release preparation consisting of spheronised beads of coated theophylline monohydrate in a hard gelatine capsule. We compared 1 week of morning dosing with 1 week of evening dosing in thirteen patients with reversible airways obstruction using a randomized cross-over design.

Methods

Patients

Patients regularly attending the outpatient department were enrolled according to the following criteria: reversible airways obstruction (an FEV₁-increase of at least 20% after the inhalation of 400 µg salbutamol or fenoterol), current treatment with an oral sustained release theophylline preparation; non-smoking male and female patients without clinically significant endocrine, haematological, gastro-intestinal, hepatic, cardiac or renal abnormalities. Pregnant women were excluded together with patients receiving cimetidine/ranitidine, erythromycin or macrolide antibiotics or antacids.

Established oral or inhaled steroid treatment was maintained at a constant dose throughout the study. Similarly, treatment with sodium cromoglycate was maintained at a constant dosage. In order to avoid patients having to depend entirely on the test-theophylline capsules, a 'rescue aerosol' of a β -adrenoceptor stimulant bronchodilator was given to all the patients. Patients were instructed to use their rescue aerosol only when necessary and to record, in their diary cards, the number of puffs taken and the time at which they were taken. Patients at home were asked to record their peak expiratory flow rate (PEFR) before using the rescue aerosol.

Materials

Theophylline in controlled release (CR) capsules (Riker) is a new divided-dose, slow-release theophylline preparation which consists of spheronised beads of coated theophylline monohydrate in a hard gelatine capsule. The preparation has been designed to give sustained-release over a sufficiently long time period to permit once daily dosing in patients with an 'average' theophylline half-life of 6–8 h. Capsules containing 300 mg of theophylline (batch no 28/12) were supplied by Riker Laboratories.

Study design

The patients, already established on chronic treatment with oral sustained release theophylline twice daily, were each entered into a dose titration phase to establish the dose of theophylline CR capsules required to produce a trough plasma concentration greater than 10 mg l⁻¹. The trough concentration was measured by sampling at 08.00 h with a further sample taken at 14.00 h to check that excessively high 'near-peak' levels were not occurring. Since patients entering the study were already being treated with theophylline, 'titration' of their required dose of theophylline capsule preparation was facilitated by taking their previous theophylline dosage into account. From a previous single-dose study, the absolute bioavailability of the novel CR formulation had been shown to be 81% (Data on file, Riker Laboratories). The initial dose of the capsule preparation was therefore selected by increasing the pre-study dose by approximately 20%. Thus, patients who were previously adequately controlled on 700 mg day⁻¹ were given 900 mg day⁻¹ of the capsule; patients previously on 1000 mg day⁻¹ were transferred to 1200 mg day⁻¹ of the capsules. These doses were sufficient to produce plasma drug concentrations in the range 10–20 mg l⁻¹ in all patients. Five patients required 900 mg, six required 1200 mg and two patients needed 1500 mg of the capsule preparation.

Following the dose titration phase patients were randomly allocated to receive their individually titrated dose of theophylline capsules administered, as a single dose, either in the morning at 08.00 h or at night at 20.00 h for 6 consecutive days. On days 1–4 patients took the assigned dose at home after breakfast for the morning dosing phase and after a small 'snack meal' in the evening dosing phase. Pulmonary function was measured at home as PEFR using a Wright Mini-meter at the following times: 08.00 h, 12.00 h, 16.00 h, 20.00 h and at bedtime.

On day 5 patients attended hospital for a pre-dose, trough blood sample taken at either 07.30 or 19.30 h for day-time/night-time dosing regimes, respectively. Drug concentrations were measured by high pressure liquid chromatography (h.p.l.c.) (Jonkman *et al.*, 1984) to check that steady-state had been established by day 5.

On day 6 patients were admitted to the hospital by 07.30 h or 19.30 h having fasted from midnight for the morning dose group or midday for the evening dosing phase. After withdrawal of the pre-dose blood samples, the capsules were taken with 200 ml of water. Blood samples were taken pre-dose and at 2, 4, 8, 10, 12, 14, 16, 18, 20, 22,

24 and 36 h after dosing. Using a Hewlett-Packard flow-volume system generating a flow-volume loop, pulmonary function was measured from which forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), PEFR, mid expiratory flow rate at 50% and 75% of vital capacity (MEF₅₀ and MEF₇₅), forced expiratory flow rate at between 25% and 75% of vital capacity (FEF₂₅₋₇₅) were obtained at pre-dose and 4, 8, 12, 16, 20 and 24 h after dosing. Patients allocated to morning dosing were crossed over to receive their next dose at 20.00 h on Day 7, that is, 36 h after the previous dose. The same procedure was followed for patients allocated to the evening dosing first. The patients were monitored again on day 5 and studied on day 6 of the second treatment period as outlined above.

Meals on the test days

Following morning dosing patients fasted for 4 h, only water being allowed. A standard lunch was then taken at midday after the 4 h blood sample. An unrestricted evening meal was allowed at 18.00 h. After evening dosing patients were allowed a standardised 'lunch' at midnight after the 4 h blood sample (this meal was given to correspond to the normal lunch in the daytime dosing regime). Breakfast was allowed at or after 06.00 h during this phase. Xanthine containing food or drinks were not allowed during the 24 h of the steady-state day.

Results

Thirteen patients completed the cross-over study.

Of these seven were men and six were women. Their mean age was 53 years (range 20–67) and their mean body weight was 71 kg (see Table 1). All patients had previously been receiving a twice daily theophylline preparation before entry into this study.

Serum theophylline concentrations

The mean concentrations of theophylline during daytime and night-time dosing are shown in Figure 1. There was no statistically significant difference between plasma concentrations obtained after morning or evening dosing with the exception of the 16, 18 and 20 h sampling time. At these times the mean night-time values were greater by 2.0, 2.4 and 2.1 mg l⁻¹, respectively ($P < 0.05$). There was no difference between the mean pre-dose, 'trough' plasma drug concentrations for either daytime or night-time dosing (08.00 or 20.00 h). Both of the mean curves were within the 10–20 mg l⁻¹ therapeutic range.

After daytime dosing the mean $\pm$ s.d., maximum plasma drug concentration ($C_{\max}$) was 15.3 ± 2.9 mg l⁻¹ which was reached ($t_{\max}$) at 9.5 ± 4.5 h after dosing (Table 2). The mean trough-to-peak difference was 6.4 ± 1.7 mg l⁻¹ (73.9%). Only in one patient did the plasma drug concentration exceed 20 mg l⁻¹ by 1.7 and 0.6 mg l⁻¹ at 6 and 10 h after dosing, respectively.

Following night-time dosing the mean $C_{\max}$ was 16.8 ± 3.1 mg l⁻¹, reached at 10.8 ± 3.9 h after dosing. The mean night-time trough-to-peak difference was 6.5 ± 1.3 mg l⁻¹ (66.7%). Again, plasma drug concentrations greater than

Table 1 Patients demographic data

Patient	Sex M/F	Age (years)	Weight (kg)	Height (m)	Dose (mg)	Dose (mg kg ⁻¹)
1	M	52	104	180	1500	14.42
2	F	20	57	167	1200	21.05
3	F	68	54	150	900	16.67
4	F	55	92	168	1200	13.04
5	F	55	44	160	1200	27.27
6	M	52	80	167	1500	18.75
7	M	61	78	178	1200	15.38
8	M	50	70	169	1200	17.14
9	M	67	76	180	900	11.84
10	M	50	82	171	1200	14.63
11	F	45	60	156	900	15.00
12	F	63	64	153	900	14.06
13	M	51	63	172	900	14.29
Mean		53	71.08	167	1131	16.43
s.d.		12.14	16.47	9.83	217.5	4.06
Range		20	44	150	900	11.84
		68	104	180	1500	27.27

Figure 1 Mean ($\pm$ s.e. mean) serum theophylline concentrations at steady state after morning (●) or evening (■) dosing with the theophylline CR preparation.

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d.)

	Morning dose	Evening dose
$C_{\min}$ (mg l ⁻¹)	8.9 (1.9)	10.4 (2.6)
$C_{\max}$ (mg l ⁻¹)	15.3 (2.9)	16.8 (3.1)
$C_{\max}-C_{\min}$ (mg l ⁻¹)	6.4 (1.7)	6.5 (1.3)
$\frac{C_{\max}-C_{\min}}{C_{\min}}$ (%)	73.9 (22.1)	66.7 (24.8)
$t_{\max}$	9.5 (4.5)	10.8 (3.9)
Mean time within the therapeutic range	16.6 (6.5)	20.3 (5.1)
AUC(0-24 h) (mg l ⁻¹ h)	296 (55)	328 (65)

20 mg l⁻¹ occurred in only one patient, in whom values of 21.8 and 23.6 mg l⁻¹ were measured at 12 and 14 h respectively. Four other values for the same patient exceeded 20 mg l⁻¹ by less than 1.0 mg l⁻¹.

The mean plasma drug concentration curves were both relatively flat over each of the 24 h periods following daytime or night-time admin-

istration. The daytime curve was within 75% of $C_{\max}$ for the whole 24 h and the evening curve for 22 h.

All patients had their doses individually titrated to ensure a steady-state trough concentration of more than 10 mg l⁻¹. Clearly this was achieved and when individual plasma drug concentration curves were evaluated the time for which plasma

drug concentration was greater than 10 mg l^{-1} was 16.6 h for daytime and 20.3 h for the night-time dosing phases. The areas under the daytime ($296 \pm 55 \text{ mg l}^{-1}$) and night-time ($328 \pm 65 \text{ mg l}^{-1} \pm \text{h}$) plasma drug concentration curves were not significantly different.

Pulmonary function measurements

Since all the patients had previously been receiving routine treatment with a twice daily theophylline preparation and this was discontinued without a wash-out period, untreated, baseline values for pulmonary function were not available.

Home measurement of pulmonary function

From the routine measurement of PEFR recorded by the patients in their diary cards, it appeared that pulmonary function was equally well maintained during both dosing regimes. There were no statistically significant differences between the morning and evening dosing regimes for any of the time-points at which PEFR was measured.

Serial pulmonary function on the steady-state day

The pattern of change in all of the measured pulmonary function parameters was the same and, therefore, only the data for FEV_1 and PEFR are discussed and illustrated (Figure 2). After morning administration of the capsules there were increases in PEFR and FEV_1 which reached maximum values at approximately 12 h after dosing. These values were statistically significantly greater than the pre-dose measurements. The changes in FEV_1 and PEFR appeared to reflect the increase in plasma theophylline concentration. The increase in PEFR which occurred during the daytime was followed by a fall from 20.00 h with a minimum value at approximately 04.00 h i.e. 20 h after dosing. A similar pattern was seen in the FEV_1 measurements. The increase in PEFR compared with pre-dose values was statistically significant ($P < 0.05$) at 12 h after dosing. The corresponding changes in FEV_1 , however, were significant at 4, 8, 12 and 16 h after dosing. Although not statistically significantly different from the baseline

Figure 2 Mean ($\pm$ s.e. mean) FEV_1 at steady state following either morning (●) or evening (■) dosing with the theophylline CR preparation.

measurements, the fall in both FEV₁ and PEF_R during the night was significant compared with the peak values. A similar pattern of pulmonary function was seen for the evening dosing regime, again with statistically significant differences between the maximum and minimum values recorded. As for morning dose, the minimum values occurred at approximately 04.00 h, that is only 8 h after dosing. The peak values were recorded between midday and 16.00 h in the afternoon some 16 and 20 h after dosing. Variation in pulmonary function after evening capsule administration did not therefore reflect the corresponding plasma theophylline concentrations. The variations in FEV₁ and PEF_R throughout the 24 h after either morning or evening dose were similar and closely followed the normal pattern of diurnal change. The changes were apparently unrelated to the plasma theophylline concentrations. Patients were, however, equally well maintained by both daytime and night-time dosing regimes.

Additional use of bronchodilator aerosols

Seven of the patients did not need the use of their rescue bronchodilator aerosols during either the daytime or night-time phases of the trial. The total requirement for extra aerosols, counted as the number of times they were used rather than the number of doses, was 121 for the daytime and 172 for the night-time dosing phases. One patient, number 12, who started with the night-time dosing regime first, used her aerosol 44 times in the night phase and not at all during the daytime. If this patient's usage is discounted, the requirements for extra treatment at 121 for daytime and 128 for the night-time periods were virtually identical.

Adverse effects

Ten of the 13 patients were free of adverse-effects throughout the whole study. The symptoms reported by the remaining three patients were, five incidences of palpitation, two of 'diarrhoea and weakness', two of tremor and one each of headache and dizziness. None of these adverse-effects inconvenienced the patients sufficiently for them to discontinue the study. On the contrary, all three of the patients reporting side-effects in the formal cross-over have voluntarily continued long-term treatment with the theophylline capsule preparation, during which regular clinical assessment and plasma drug concentration measurements have been made at monthly intervals. A total of eleven patients agreed to continue treatment with the capsule

and attend for monthly reassessment. During the follow up period of 3 months no significant changes in mean plasma theophylline concentrations were observed and all individual values remained within the therapeutic range.

Discussion

The bronchodilating and therapeutic effect of theophylline has been amply documented (Ogilvie, 1978). Consequently, great efforts have been made to develop reliable sustained release preparations that provided adequate therapeutic serum theophylline concentrations in most patients with asthma. Several twice-a-day oral sustained release preparations have been developed and shown to fulfill the above criteria and give minimal trough-to-peak variability at steady-state (Weinberger *et al.*, 1978). More recently efforts have been made to develop once-a-day sustained release preparations, but the currently available preparations do not fulfill the same stringent criterion of minimal peak-trough variability. In addition, some of these preparations have been shown to give erratic absorption (Weinberger, 1986). Our study in asthmatic patients has shown that the theophylline CR capsules produce minimal trough-to-peak variability and appear to be suitable for once-a-day administration in patients with asthma. The sustained release mechanism maintained serum drug concentrations in the therapeutic range over the whole 24 h dosing interval. The mean plasma drug concentration profiles after either morning or evening administration exhibited trough-to-peak variations of 73.9% and 66.7%, respectively. These values compare with those observed with twice daily administration of preparations considered suitable for dosing every 12 h (Weinberger *et al.*, 1978).

The development of this new once a day-sustained release oral theophylline preparation with low trough-to-peak variability allowed us to study the effect of the time of dosing on both the diurnal variation in pharmacokinetics and the diurnal variation in the pharmacodynamics of theophylline. Several investigators have studied the circadian variation in pharmacokinetics of theophylline administered in different dosage forms (Lemmer, 1984). In healthy volunteers Jonkman *et al.* (1984) observed an increased half-life of theophylline during the night after intravenous administration. Similarly St. Pierre *et al.* (1985) found in healthy volunteers a 12% increase in elimination rate after morning dosing in comparison with evening administration of intravenous theophylline. This difference in

elimination rate failed to reach statistical significance. Taylor *et al.* (1983) and Watanabe *et al.* (1984) did not find any significant difference in the elimination of theophylline in healthy volunteers. Most investigators therefore agree that the diurnal variation in theophylline pharmacokinetics after oral administration is due to a slower absorption of theophylline during the night (Kyle *et al.*, 1980; Lemmer, 1984; Lesko *et al.*, 1980; Ogilvie, 1978; Pradelier *et al.*, 1982; Scott *et al.*, 1981; St. Pierre *et al.*, 1985; Taylor *et al.*, 1983, 1984). The diurnal variation in absorption differs depending on the theophylline preparation and its sustained release mechanism.

The therapeutic effect of theophylline on nocturnal asthma has been documented in placebo-controlled studies (Barnes *et al.*, 1982; Davies *et al.*, 1984). The results of the present study show that despite the presence of therapeutic serum theophylline concentrations a significant decrease of the FEV₁ and PEFR occurs at night. The absence of a placebo control day does not permit

any conclusion about the possible effect of theophylline on the magnitude of the morning dip. However, we may conclude that small differences in serum theophylline concentration within the therapeutic range, such as we observed between the night following the morning dosing and the night following the evening dosing, do not influence significantly the airway calibre at night. This observation also illustrates the diurnal variation in the pharmacodynamics of theophylline as is most clearly demonstrated by the parallel course of the serum theophylline concentration curve with the FEV₁ or PEFR curve after the morning dosing, but an absence of parallelism after the evening dosing (Lemmer, 1984).

This study has shown that the theophylline CR capsule preparation is suitable for once-a-day administration, and may be given in the morning or evening. All the subjects involved in the study were non smokers. Additional investigations are necessary before the conclusions of our study can be applied in smokers.

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