

A Pharmacokinetic Study of the Recommended Dosing Schedules of Theo-Dur and Uniphylline

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Theo-Dur, 300 mg twice daily, and Uniphylline, 600 mg once daily taken with food were compared in an open cross-over study in healthy volunteers. Uniphylline had significantly ($P < 0.001$) higher peaks, lower troughs and wider variation in theophylline concentrations than Theo-Dur. Peak plasma concentrations were reached earlier for Theo-Dur but the difference failed to reach statistical significance ($0.05 < P < 0.1$). There was no significant difference between the two drugs in area under the plasma concentration time curve. Therapeutic occupancy lasted significantly longer ($P < 0.05$) with Theo-Dur; eight volunteers attained 24 h therapeutic occupancy after administration of Theo-Dur compared to 4 h with Uniphylline.

Key words: pharmacokinetics; Theo-Dur; theophylline levels; Uniphylline.

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Twice daily administration of slow-release theophylline preparations has become an effective and convenient means of controlling bronchodilation, over a 24 h period, in patients with airway obstruction (9). In 1981 Thompson et al. (8) demonstrated that a single dose of slow-release tablets taken at night achieved therapeutic levels of theophylline over a 24 h period. Subsequently, in mid 1982, Napp Laboratories introduced into the U.K. a controlled release theophylline tablet, Uniphylline, designed to be taken once daily. The recommended dosage regimen for patients under 70 kg is 600 mg daily after an initial week of 400 mg once daily. The comparative recommended dosage schedule for Theo-Dur is the same amount of theophylline but given at 12 h intervals. The object of this study was to investigate the pharmacokinetic parameters of the two dosing schedules, peak to trough variation, therapeutic occupancy and the area under the plasma concentration time curve over 24 h.

METHODS

Twelve healthy, non-smoking volunteers (7 female, 5 male) aged 19-34 years (mean 25.2 years), all weighing < 70 kg (mean 61.6 kg, range 53-69 kg), participated in the study. Using a randomised open cross-over study design each volunteer received either Uniphyllin 400 mg as a single daily morning dose for 3 days, followed by 600 mg (1½ tablets) as a single daily morning dose for 4 days, or Theo-Dur 200 mg, twice daily (morning and evening 12 h apart) for 3 days, followed by 300 mg twice daily (morning and evening 12 h apart) for 4 days. On the eighth day, the day of sampling when steady-state kinetics would have been attained, a 600 mg dose of Uniphylline or the first 300 mg dose of Theo-Dur was administered directly after a standard breakfast. The second dose of Theo-Dur 300 mg was given 12 h later directly after a standard evening meal. Since the Uniphylline dosing schedule doses not

state whether administration should be morning or evening, Uniphylline was taken in the morning. Nolte & Neumann (5) have shown that there were no differences in absorption and elimination kinetics between morning or evening administration of Uniphylline.

Blood samples were taken via an indwelling cannula immediately before the morning dose and at 2 hourly intervals thereafter for 24 h.

Plasma was assayed immediately for theophylline by enzyme immunoassay (EMIT, Syva, U.K.). The between batch coefficient of variation was 6.4%, the lower limit of measurement was $1.0 \mu\text{g ml}^{-1}$. The pharmacokinetic parameters; maximum and minimum plasma concentrations peak to trough differences over 24 h; time to reach maximum concentrations, the therapeutic occupancy and plasma half-lives were measured. The area under the plasma concentration curve ($\text{AUC}_{(0-24)}$) was calculated by the trapezoidal rule. Area under the curve, maximum and minimum theophylline levels and peak to trough difference were analysed using analysis of variance. A paired t-test was

used to determine the statistical significance of any differences in therapeutic occupancy.

Since two cycles of Theo-Dur were available, the means of the two peaks, two troughs and two peak trough differences in serum theophylline concentrations were used in the analyses.

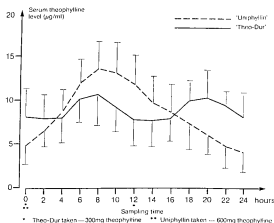


Fig. 1. Steady-state serum theophylline levels (mean $\pm$ SD) over 24 h in 12 volunteers.

Table 1
Summary of plasma theophylline concentrations for Uniphylline

	Volunteer												Mean ($\pm$ SEM)
	1	2	3	4	5	6	7	8	9	10	11	12	
$\text{AUC}_{(0-24 \text{ h})}$	245.2	161.5	221.3	206.7	254.5	214.9	138.9	236.0	183.4	115.0	242.4	343.4	213.6 ($\pm$ 13.27)
Peak plasma concentrations ($\mu\text{g ml}^{-1}$)	14.3	9.7	12.6	13.6	16.8	18.8	10.5	14.1	12.4	10.6	13.6	20.0	13.9 ($\pm$ 0.93)
Trough plasma concentrations ($\mu\text{g ml}^{-1}$)	5.4	2.8	4.7	3.9	4.3	1.8	0.7	5.1	2.2	0.7	5.8	5.8	3.6 ($\pm$ 0.55)
Peak to trough variation ($\mu\text{g ml}^{-1}$)	8.9	6.9	7.9	9.7	12.5	17.0	9.8	9.0	10.2	9.9	7.8	14.2	10.3 ($\pm$ 0.84)
Time to maximum concentration (h)	10	10	7	8	8	10	8	10	6	8	8	8	8.4 ($\pm$ 0.38)
Therapeutic occupancy (h)	24	17.6	23	21.8	23.3	18	13.6	24	18.3	13.2	24	24	20.4 ($\pm$ 1.18)

RESULTS

The theophylline half-lives for these subjects ranged between 3.6 to 11.2 h (mean 8.2 h) and the elimination rate constants between 0.062 and 0.191 h⁻¹ (mean 0.096 h⁻¹). The pharmacokinetic parameters measured are summarised in Tables 1 and 2 and Fig. 1. The mean AUC₀₋₂₄ was 211.3 (± 19.43 SEM) and 213.6 (± 13.27 SEM) µg ml⁻¹ for Theo-Dur and Uniphylline respectively. There were no statistically significant differences.

There were highly significant differences ($P < 0.001$) in peak theophylline and trough theophylline concentration with Uniphylline having a

higher peak and lower trough than Theo-Dur. Similarly, there was a highly significant difference ($P < 0.001$) in the peak to trough variations with Uniphylline having a much wider spread than Theo-Dur.

The mean time to maximum serum theophylline concentrations was approximately 1 h earlier with Theo-Dur than with Uniphylline. In individual subjects, t_{max} was earlier in seven, later in one and the same in four, using the mean of two peaks. This difference failed to reach significance ($0.05 < P < 0.10$).

The therapeutic occupancy (time in which theophylline levels lie between 5.0 and 20 µg ml⁻¹) was determined. By a paired t-test it was

Table 2
Summary of plasma theophylline concentrations for Theo-Dur

	Volunteer												Mean (± SEM)
	1	2	3	4	5	6	7	8	9	10	11	12	
AUC _{0-24 h}	238.9	183.2	213.8	185.3	190.6	208.8	138.1	224.1	162.3	134.6	272.6	383.0	211.3 (± 19.43)
1st peak plasma concs. (µg ml ⁻¹)	11.4	9.4	10.5	9.6	10.0	9.8	8.7	9.7	9.8	6.5	14.0	19.4	10.7 (± 0.93)
1st trough plasma concs. (µg ml ⁻¹)	8.4	7.0	7.8	5.6	4.0	6.8	3.6	7.2	5.2	3.9	10.3	15.0	7.1 (± 0.92)
1st peak to trough variation (µg ml ⁻¹)	3.0	2.4	2.7	4.0	6.0	3.0	5.1	2.5	4.6	2.6	3.7	4.4	3.6 (± 0.33)
2nd peak plasma concs. (µg ml ⁻¹)	11.7	8.3	10.0	10.5	10.4	11.9	7.5	13.2	7.3	7.6	11.8	18.0	10.7 (± 0.88)
2nd trough plasma concs. (µg ml ⁻¹)	8.7	5.5	7.5	5.7	6.3	7.3	3.2	7.5	4.2	3.9	9.1	14.0	6.9 (± 0.04)
2nd peak to trough variation (µg ml ⁻¹)	3.0	2.8	2.5	4.8	4.1	4.6	4.3	5.7	3.1	3.7	2.7	4.0	3.8 (± 0.28)
Time to reach maximum concentration (h)													
peak 1	6	8	8	8	6	8	6	10	6	6	8	8	7.33 (± 0.38)
peak 2	6	9	6	8	8	8	6	6	10	8	8	8	7.58 (± 0.38)
Therapeutic occupancy (h)	24	24	24	24	23.2	24	19.9	24	20	13.7	24	24	22.4 (± 0.90)

found that the mean therapeutic occupancy of Theo-Dur of 22.4 h was significantly greater ($P < 0.05$) than that of Uniphylline (20.4 h). Eight subjects achieved 24-h therapeutic occupancy compared to four with Uniphylline.

Ten subjects had noted symptoms of either headache or gastro-intestinal upset when questioned. Four reported symptoms on Theo-Dur alone, two on Uniphylline alone and four on both Uniphylline and Theo-Dur.

DISCUSSION

One of the benefits of twice daily administration of a slow-release theophylline tablet is a reduction in the peak to trough variation of serum concentrations compared with the administration of plain theophylline tablets (9). If a slow-release theophylline tablet, designed to release theophylline at a controlled rate over 12 h, was administered as a single daily dose, greater peak levels and greater peak to trough variation would be expected.

This study shows once daily administration of Uniphylline to have a significantly greater mean peak to trough variation of $10.3 \mu\text{g ml}^{-1}$, compared to $3.7 \mu\text{g ml}^{-1}$ for twice daily administered Theo-Dur. This concurs with the work by Nolte & Neumann (5), who found that patients receiving a mean of 9.7 mg/kg per day of theophylline had a peak to trough variation of $11.33 \mu\text{g ml}^{-1}$ when given once daily Uniphylline. This conflicts with the work of Cohen (2) who found a peak to trough variation of $5.2 \mu\text{g ml}^{-1}$ in six patients with obstructive airway disease, and $4.9 \mu\text{g ml}^{-1}$ in normal subjects when administered a larger dose of 800 mg Uniphylline daily.

These differences could be explained by diurnal variation and the disregard in these studies of the effects of food. Taylor et al. (7) found no significant differences in elimination half-life, volume of distribution and systemic clearance between diurnal and nocturnal values in theophylline administered orally as sodium glycinate elixir or by the intravenous route. But the time to reach peak concentration was significantly shorter in the morning compared to the evening. These results are in agreement with

Birkett et al. (1), who suggested that there is a period of faster absorption in the morning and slower absorption in the afternoon and early evening. As discussed elsewhere, this disagrees with the work by Nolte & Neumann (5) who found no difference, and MacLeod (4) who suggested that there could be as much as 40% increase in nocturnal elimination compared to diurnal elimination.

Neither Cohen or Nolte & Neumann accounted for the effect of food on the absorption of slow-release theophylline tablets. Leeds et al. (3) found 300 mg Theo-Dur tablets taken immediately after a standard breakfast has a peak concentration of 8 h after administration. This is similar to our own study where the mean peak concentrations were 7.58 and 7.33 h after the administration of 300 mg Theo-Dur immediately after a standard breakfast and evening meal respectively. The time to peak levels of 8.4 h for Uniphylline is longer than that reported by Cohen or Nolte & Neumann but can be explained by the delayed absorption due to food (6).

The significant difference in therapeutic occupancy demonstrates one of the problems of once daily dosing: higher peaks and lower troughs. Eight volunteers on Theo-Dur, compared to four on Uniphylline, achieved levels between $5\text{--}20 \mu\text{g ml}^{-1}$ for the whole of the 24 h period. In volunteer 6, if therapeutic occupancy whilst taking Uniphylline was to be improved from 18.00 h by increasing the dose, the associated increase in peak levels would have taken these levels above $20.0 \mu\text{g ml}^{-1}$, and increased the possibility of toxic side effects. Due to the higher peak levels with Uniphylline, an increase of a further 200 mg would have achieved peak levels close to or over $20 \mu\text{g ml}^{-1}$ in five volunteers. Assuming first-order kinetics, this would only have occurred in two volunteers due to the lower peak levels and flatter plasma profile curve of 12 h Theo-Dur.

Clinically, there could be advantages to patients in a once a day administration of a sustained release theophylline; the preparation must be formulated to ensure that adequate levels of theophylline are maintained over 24 h. The only advantage in the present once daily

formulation of Uniphylline would be for those patients who are slow metabolisers of theophylline, and the so-called "morning dippers" where higher peak levels in the morning would result if the drug was taken before retiring at night.

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