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# PHARMACOKINETIC ANALYSIS OF SUSTAINED-RELEASE DOSAGE FORMS OF THEOPHYLLINE IN HUMANS: COMPARISON OF SINGLE AND MULTIPLE DOSE STUDIES

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## ABSTRACT

A pharmacokinetic analysis of two sustained-release dosage forms of theophylline (Theo-Dur® and Theotrim®) was carried out following single and multiple dose administrations of the two formulations in five healthy subjects. Despite the prolonged absorption after administration of the two sustained-release formulations, theoretical predictions of theophylline steady-state levels following multiple dosages based upon data obtained from the single dose study, correlated with the data of the multiple dose study. This study shows that the recommended dose and dosage regimen of new sustained-release formulations of theophylline can be based upon single dose studies. In the population studied, repetitive doses of 450 mg b.i.d. of Theo-Dur® and Theotrim® maintain steady-state concentrations of theophylline within the drug's therapeutic window.

KEY WORDS Theophylline Pharmacokinetics Sustained-release dosage forms

## INTRODUCTION

Several methods exist by which drugs can be formulated into slow-release dosage forms. Common to each design is the aim of controlling the release rate from the solid dosage form so that dissolution, the rate limiting step in the absorption process, is slower than the inherent rate of the drug's absorption. Oral theophylline has been shown to be effective in the treatment of lung diseases. In order to achieve maximum therapeutic benefits with a relatively low risk of severe side-effects, the serum concentration should be maintained within the narrow range of 8 to 20 mg $l^{-1}$.[1–5] Because of the average short half-life of theophylline in most of the population, in order to

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avoid large fluctuations in plasma concentration,[5,6] a theophylline pharmaceutical formulation with rapid absorption should be administered on a 6–8 h dosing interval. With such a regimen, lack of patient compliance is a serious problem. Therefore, low trough levels can be expected in the morning, with a possible risk of breakthrough of symptoms. Accordingly, sustained-release dosage forms of theophylline are useful for maintenance therapy of chronic obstructive lung diseases.[7] The bioavailability of certain sustained- release dosage forms of theophylline has been shown to vary well below 100 per cent, while other brands have been documented to be completely bioavailable.[2,3,8,9]

This study investigates the absorption kinetics and pharmacokinetic profile of a new sustained-release formulation of theophylline (Theotrim®)[9] in comparison with the standard sustained-release formulation of Theo-Dur®. Evaluation of the effect of the sustained-release formulation on the pharmacokinetics of theophylline was carried out by comparing the pharmacokinetic profile of the drug following single and multiple dose administrations. The steady-state predictions from the single dose administrations were compared with the multiple dose data.

## METHODS

### *Subjects*

Five healthy male subjects, ranging in age from 24 to 29 years and weighing 65–82 kg, were selected for this study after a medical history, physical examination, normal routine blood chemical analysis and morphology, and urinalysis. Written informed consent was obtained from each volunteer. The entire clinical experiment was approved by the Helsinki Committee of the Hadassah Medical Center and the Israel Ministry of Health.

### *Procedure*

In the single dose study, each volunteer received, at separate times (in a randomized cross-over design) 300 mg of the two sustained release dosage forms of theophylline (Theo-Dur® and Theotrim®). A wash-out period of 2 weeks was allowed between any two consecutive studies in each subject. Each formulation was administered at 8 am following an overnight fast. Food was withheld for 6 h after the administration of the various theophylline formulations. Tea, coffee, coke, and other caffeinated beverages and food were not permitted 2 days prior to the beginning of and until the end of each study. Venous blood samples (6 ml) were collected via an indwelling catheter from the forearm vein at 0, 0·5, 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 30, 38, and 48 h following oral administration. Plasma was immediately separated by centrifugation at 7000 rev $min^{-1}$ for 15 min and stored at $-20°$. Before assaying, the plasma was allowed to reach room temperature, vortexed,

centrifuged, and the residual clot removed. Plasma theophylline levels were determined by HPLC at a UV wavelength of 275 nm. The assay procedure was a modification of a previously reported method.[10] Previous studies have already outlined the stability of theophylline in plasma at room temperature.[11]

During the first 4 days of the multiple dose study, each subject received in random design, 450 mg of Theotrim® or Theo-Dur® twice a day (b.i.d.) at 8 am and 8 pm. On the 5th day, each subject received 450 mg of Theotrim® or Theo-Dur® at 8 am only. A washout period of 3 weeks was allowed between any two multiple dose administrations of Theotrim® and Theo-Dur®. Venous blood samples (6 ml) were collected from the forearm vein at time 0 and 12 h after the first daily dosing on day 3; on day 4 at time 0 and at 2, 4, 6, 8, 10, and 12 h after the first daily dosing; on days 5 and 6 at time 0 and at 2, 4, 6, 8, 10, 12, 24, 28, and 36 h after the 8 am dosing of day 5. The plasma was treated and assayed according to the procedure outlined for the single dose study.

The linear terminal slope ($\beta$) of log $C$ (theophylline plasma concentrations) versus $t$ (time) plot was calculated by the method of least squares (using at least 8 points in the descending portion of the log $C$ versus $t$ plot). The half-life of theophylline ($t_{1/2}\beta$) was calculated from the quotient of 0·69/$\beta$. The AUC (area under the $C$ versus $t$ curve) was calculated using the trapezoidal rule, with extrapolation to infinity by dividing the last experimental point by the linear terminal slope.[12] Peak plasma concentration of theophylline ($C_{max}$) and the time to reach $C_{max}$, $t_{max}$ have also been recorded. In the single dose study, the relative bioavailability ($F$) of theophylline was calculated from the ratio of AUC obtained after the administration of Theotrim® to that of Theo-Dur®. In the multiple dose study, the relative bioavailability of theophylline was calculated from the ratio of AUC at steady-state during a single dosing interval ($\tau$) obtained after the oral administration of Theotrim® to that of Theo-Dur®. The per cent fluctuation and the fluctuation index (FI) were calculated by using equations (1) and (2).[13,14]

$$\text{per cent fluctuation} = 100 \cdot \frac{(\text{peak plasma concentration} - \text{trough plasma concentration})}{(\text{trough plasma concentration})} \quad (1)$$

$$\text{FI} = \frac{(\text{peak plasma concentration} - \text{trough plasma concentration})}{(\text{average plasma concentration})} \quad (2)$$

The merits of estimating fluctuations in drug plasma concentrations according to equation (1) are called into question when trough plasma concentrations are low. In this case, the percentage of fluctuations may vary considerably between subjects. An alternative approach has been proposed by Caldwell *et al.* who used the fluctuation index (FI—equation (2)) for evaluating the

performance of sustained-release tablets of lithium at steady-state.[14] The average plasma concentration was calculated from the quotient of the area under the drug plasma concentrations vs time curve ($AUC_{ss}$) during a steady-state dosage interval and the dosage interval ($\tau$). Peak and trough experimental plasma concentration at steady-state ($C_{ss,max}$ and $C_{ss,min}$) were also recorded.

Theoretical predictions from single to multiple doses were carried out by using equations (3) and (4),[12]

$$C^*_{ss,max} = \frac{C_{max}}{1 - e^{-K\tau}} \tag{3}$$

$$C^*_{ss,min} = \frac{C_{min}}{1 - e^{-K\tau}} \tag{4}$$

where $K$ (which is equal to $\beta$ in the one compartment open body which was found to be the best model in this study) is the elimination rate constant. $C_{max}$, $C_{min}$, $C^*_{ss,max}$ and $C^*_{ss,min}$ are the peak and trough plasma concentrations obtained after single and multiple administrations (theoretical values at steady-state), respectively.

## RESULTS AND DISCUSSION

Mean plasma concentrations obtained after the single and multiple dose administrations of the two theophylline formulations are presented in Figures 1 and 2. Table 1 summarizes the individual and mean pharmacokinetic parameters obtained after the single and multiple dose administrations.

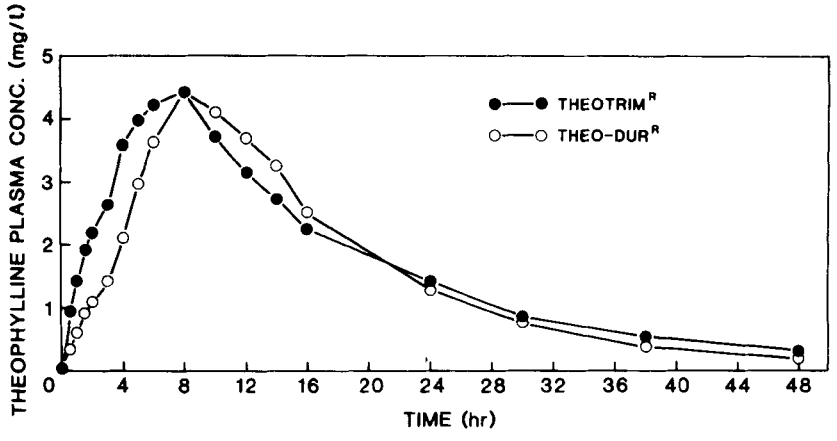


Figure 1. Mean plasma concentrations of theophylline obtained after oral administration of Theotrim® (300 mg) and Theo-Dur® (300 mg) to five healthy subjects

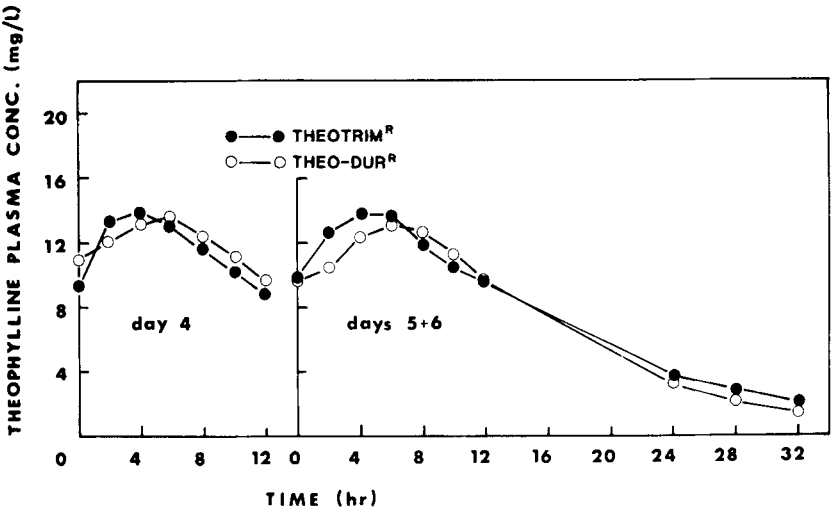


Figure 2. Mean plasma concentrations of theophylline obtained during repetitive oral dosing of Theotrim® and Theo-Dur® (450 mg b.i.d) in five healthy subjects

There were no significant differences in the half-life of theophylline in the two studies. The theophylline half-life found in this study is within the average range of $9{\cdot}0 \pm 2{\cdot}1$ h reported in the literature[15] for non-smoking adults. The various pharmacokinetic parameters such as $C_{max}$, $t_{max}$, and AUC which are related to the extent and rate of absorption were not significantly different for Theotrim® and Theo-Dur®. The mean bioavailability of Theotrim® relative to Theo-Dur® after the single and multiple doses was $1{\cdot}08 \pm 0{\cdot}19$ and $1{\cdot}05 \pm 0{\cdot}05$, respectively. It therefore can be concluded that Theotrim® is bioequivalent to Theo-Dur®.

Table 2 summarizes predicted and experimental pharmacokinetic parameters obtained at steady-state after the administration of Theo-Dur® and Theotrim®. There was a considerable similarity between the experimental and the theoretical (predicted) parameters presented for both formulations. As there was no significant difference between the predicted and experimental parameters, it can be concluded that despite the prolonged absorption of theophylline observed after administering Theo-Dur® and Theotrim®, multiple dose steady-state parameters of theophylline can be predicted from experimental parameters, it can be concluded that despite the prolonged absorption of theophylline observed after administering Theo-Dur® and Theotrim®, multiple dose steady-state parameters of theophylline can be predicted from experimental single dose data. In this study, Theotrim® as well as Theo-Dur®, could maintain steady-state plasma levels of theophylline within the therapeutic window of the drug after a daily dosage of 450 mg b.i.d. It should be emphasized that this dosage schedule is good for

Table 1. Summary of various pharmacokinetic parameters obtained after single (300 mg) and multiple dose (at steady-state −450 mg b.i.d.) administration of Theo-Dur® (Formulation A) and Theotrim® (Formulation B) to five healthy subjects

| Subject | H.D. | | R.A. | | K.I. | | H.Z. | | S.D. | | Mean ± SD | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| dosage form | A | B | A | B | A | B | A | B | A | B | A | B |
| Pharmacok. parameters | | | | | | | | | | | | |
| $^{a}\beta$ ($h^{-1}$) | 0·09 | 0·05 | 0·14 | 0·10 | 0·10 | 0·07 | 0·08 | 0·05 | 0·07 | 0·08 | 0·10 ± 0·03 | 0·07 ± 0·02 |
| $^{a*}\beta$ ($h^{-1}$) | 0·08 | 0·08 | 0·10 | 0·08 | 0·10 | 0·09 | 0·10 | 0·06 | 0·07 | 0·06 | 0·09 ± 0·01 | 0·07 ± 0·01 |
| $t_{½}\beta$ (h) | 7·7 | 13·6 | 5·0 | 6·8 | 6·8 | 9·4 | 8·7 | 13·0 | 9·5 | 8·4 | 7·5 ± 1·8 | 10·2 ± 3·0 |
| $^{a*}t_{½}\beta$ (h) | 8·5 | 9·2 | 6·9 | 8·7 | 7·0 | 7·6 | 6·9 | 11·2 | 10·3 | 11·0 | 7·9 ± 1·5 | 9·5 ± 1·5 |
| $C_{max}$ (mg $l^{-1}$) | 6·8 | 4·4 | 6·2 | 6·8 | 3·6 | 5·0 | 4·0 | 3·6 | 3·0 | 2·9 | 4·7 ± 1·7 | 4·5 ± 1·5 |
| $^{a*}C_{ss,max}$ (mg $l^{-1}$) | 14·3 | 13·9 | 15·1 | 14·6 | 13·4 | 15·4 | 14·2 | 14·6 | 10·0 | 10·8 | 13·4 ± 2·0 | 13·9 ± 1·8 |
| $t_{max}$ (h) | 8 | 8 | 8 | 8 | 12 | 10 | 6 | 8 | 6 | 6 | 8·0 ± 2·4 | 8·0 ± 1·4 |
| $^{a*}t_{max}$ (h) | 6 | 6 | 6 | 4 | 4 | 4 | 6 | 6 | 4 | 6 | 5·2 ± 1·1 | 5·2 ± 1·1 |
| AUC (mg h $l^{-1}$) | 99 | 93 | 83 | 95 | 59 | 78 | 74 | 86 | 58 | 48 | 75 ± 17 | 80 ± 19 |
| $^{a*}$AUC (mg h $l^{-1}$) | 149 | 149 | 149 | 153 | 137 | 155 | 148 | 152 | 102 | 106 | 137 ± 20 | 143 ± 21 |
| $F$ relative | – | 0·94 | – | 1·14 | – | 1·32 | – | 1·16 | – | 0·83 | – | 1·08 ± 0·19 |
| $^{a*}F$ relative | – | 1·00 | – | 1·03 | – | 1·13 | – | 1·03 | – | 1·04 | – | 1·05 ± 0·05 |

KEY

| | |
|---|---|
| $^{a}$ | The pharmacokinetic parameters marked with * are the ones obtained after the multiple dose study. |
| $\beta$ | Linear terminal slope |
| $t_{½}\beta$ | Terminal half-life |
| AUC | Area under $C$ vs $t$ plot from zero to infinity after the single dose study. |
| *AUC | Area under $C$ vs $t$ plot as steady-state during the 0 to 12 h dosing interval of day 5. |
| $C_{max}$ | Peak plasma concentration after the single dose study. |
| $^{*}C_{ss,max}$ | Peak plasma concentration at day 5 within the 12 hour dosing interval. |
| $^{*}t_{max}$ or $t_{max}$ | Time to reach $C_{max}$ or $C_{ss,max}$ respectively. |
| $F$ | Bioavailability of Theotrim® (formulation B) relative to Theo-Dur® (formulation A). |

Table 2. Summary of predicted and experimental pharmacokinetic parameters obtained at steady-state after oral administration of Theo-Dur® (formulation A) and Theotrim® (formulation B) (450 mg b.i.d.) to five healthy subjects

| Subject | H.D. | | R.A. | | K.I. | | H.Z. | | S.D. | | Mean ± S.D. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| dosage form | A | B | A | B | A | B | A | B | A | B | A | B |
| Pharmacok. parameters | | | | | | | | | | | | |
| $^{a*}C_{ss,min}$ (mg $l^{-1}$) | 10·6 | 9·8 | 9·9 | 8·5 | 5·6 | 7·0 | 8·0 | 8·2 | 6·2 | 4·2 | 8·1 ± 2·2 | 7·5 ± 2·1 |
| $C_{ss,min}$ (mg $l^{-1}$) | 10·6 | 10·4 | 9·3 | 10·6 | 9·5 | 9·1 | 10·6 | 10·6 | 6·8 | 6·6 | 9·4 ± 1·6 | 9·5 ± 1·7 |
| $^{a*}C_{ss,max}$ (mg $l^{-1}$) | 15·4 | 14·4 | 13·8 | 14·4 | 7·7 | 12·7 | 9·8 | 11·4 | 8·1 | 6·7 | 11·0 ± 3·5 | 11·9 ± 3·2 |
| $C_{ss,max}$ (mg $l^{-1}$) | 14·3 | 13·9 | 15·1 | 14·6 | 13·4 | 15·4 | 14·2 | 14·6 | 10·0 | 10·8 | 13·4 ± 2·0 | 13·9 ± 1·8 |
| $^{a*}\overline{C_{ss}}$ (mg $l^{-1}$) | 12·4 | 11·6 | 10·4 | 11·9 | 7·4 | 9·8 | 9·3 | 10·8 | 7·3 | 6·0 | 9·4 ± 2·2 | 10·0 ± 2·4 |
| $\overline{C_{ss}}$ (mg $l^{-1}$) | 12·4 | 12·4 | 12·4 | 12·8 | 11·4 | 12·9 | 12·3 | 12·7 | 8·5 | 8·8 | 11·4 ± 1·7 | 11·9 ± 1·8 |
| $^{a*}F$(relative) | – | 0·94 | – | 0·94 | – | 1·32 | – | 1·16 | – | 0·87 | – | 1·09 ± 0·18 |
| $F$ (relative) | – | 1·00 | – | 1·03 | – | 1·13 | – | 1·03 | – | 1·04 | – | 1·05 ± 0·05 |
| $^{a*}$% Fluctuation | 45 | 47 | 39 | 69 | 38 | 81 | 23 | 39 | 31 | 60 | 35 ± 8 | 59 ± 17 |
| % Fluctuation | 35 | 34 | 62 | 38 | 41 | 69 | 34 | 38 | 47 | 64 | 44 ± 11 | 49 ± 17 |
| $^{a*}$FI (%) | 39 | 40 | 38 | 50 | 38 | 58 | 19 | 29 | 26 | 42 | 30 ± 8·5 | 44 ± 11 |
| FI (%) | 30 | 28 | 47 | 31 | 34 | 49 | 29 | 32 | 38 | 48 | 36 ± 7 | 37 ± 10 |

KEY

| | |
|---|---|
| $^a$ | The pharmacokinetic parameters marked with * are the predicted (theoretical) ones. |
| $C_{ss,max}$, $C_{ss,min}$ | Peak and trough plasma concentrations within the 12 h dosing interval of day 5, respectively. |
| $\overline{C_{ss}}$ | Average plasma concentration at steady-state ($\overline{C_{ss}}$ = AUC/$\tau$) |
| $F$ | Bioavailability of Theotrim® (formulation B) relative to Theo-Dur® (formulation A). |
| % Fluctuation | See equation (1) in the text. |
| FI | See equation (2) in the text. |

patients with individual theophylline half-lives of 7 to 10 h. Smokers or patients in whom the half-life is shorter (about 4 h) may require more frequent dosages. The two pharmacokinetics parameters for measuring fluctuations at steady-state, per cent fluctuations and FI were similar for both fluctuations. Measuring the fluctuations at steady-state, in addition to the extent and rate of absorption, is an important criterion for evaluating the performance of an oral sustained-release dosage form.[16,17]

Theoretical calculations with 300 mg b.i.d. of Theo-Dur® or Theotrim® produced subtherapeutic concentrations during some of the 12 h dosage intervals and therefore this dose was found insufficient. It seems that young healthy subjects in whom theophylline has a mean half-life of 8 to 10 h need a repetitive dose of 450 mg b.i.d. in order to maintain steady-state concentrations within the drug's therapeutic window.

The objective of treating with sustained-release dosage forms is to achieve a state in which the duration of drug effect is determined by the duration of drug release from the dosage forms rather than by the pharmacokinetics of the drug.[18] Since, in certain cases, absorption may last through most of the dosage interval and the (apparent) half-life of the drug will thus be longer than the (real) half-life obtained after i.v. administration or a rapid release formulation, problems may arise in extrapolating single- to multiple-dose administrations. The situation may be complicated in the case of a drug released for absorption at a zero or first order rate with an instantaneous release component. Thus, classical equations such as (3) and (4) can not be applied for predicting steady state plasma levels after administration of sustained-release dosage forms.

This paper shows that in the case of sustained-release dosage forms of theophylline such as Theo-Dur® or Theotrim®, experimental single dose data can serve as a good prediction for steady-state date obtained after repetitive administrations.

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