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Sustained release properties of the once daily theophylline capsule Euphylong as compared with Theo-Dur tablets

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Summary

In a multiple dose cross-over experiment in 18 healthy male volunteers the sustained release properties and relative bioavailability of new once daily Euphylong 375 mg capsules (= A) were studied using twice daily Theo-Dur (= B) as reference. Theophylline was given over a period of 8 days: A once daily as a 750 mg dose at 20.00 h (with placebo at 08.00 h) and B twice daily as a 400 mg dose at 08.00 and 20.00 h. Plasma concentration–time profiles were evaluated on days 5/6 and 8/9. Theophylline in plasma was measured by high-performance liquid chromatography (HPLC). Considerable sustained release properties for A were indicated by an extended shape of the plateau phase on days 5/6 and 8/9, resulting in high $T_{75\%}$ values (11.0 h and 10.6 h). As to be expected, peak-to-trough fluctuations (defined as $\%PTF = 100\ (C_{max} - C_{min})/C_{av}$)) on the two steady-state days with once daily A ($\%PTF$: 104% and 108%) were significantly larger than fluctuations with twice daily B (52% and 53%). The two products were found to be bioequivalent although bioavailability of A was slightly lower on both days (85% and 90%). In conclusion, A was found to be of good sustained release quality. In once daily dosing it may occasionally (e.g. in fast metabolizers) be difficult to keep theophylline plasma concentrations within the therapeutic range during the 24-h dosing interval, although in asthmatic patients, who generally have slower elimination than healthy young adults, smaller peak–trough fluctuations can be anticipated.

Introduction

The antiasthmatic drug theophylline has a great variability in clearance (elimination half-lives in children 3–4 h, adults 6–12 h) and a narrow therapeutic range (7.5–20 mg · l^{-1}). Once or twice daily administration of sustained release preparations in patients with chronic obstructive airway diseases is recommended for better control of plasma concentrations and for improving patient compliance. Additionally, a high evening dose of sustained release theophylline may prevent the morning dip in peak expiratory flow (PEF).

Sustained release properties especially in once daily dosing should be such that peak–trough

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fluctuations are minimized and plasma concentrations can be kept within the therapeutic range.

Sustained release characteristics of most theophylline preparations until 1984 allowed 12-h dosing intervals. Since then, however, once daily dosing in slow or average metabolizers was introduced with FDA approval of some 24-hour preparations (Theo-24, Uniphyl).

The once-a-day preparation A was recently developed by Byk Gulden Research Laboratories (F.R.G.), using a new pharmaceutical bead technology.

This paper presents the results of a cross-over comparison of the sustained release quality and multiple dose bioavailability of once daily given Euphylong (A) relative to twice daily administered Theo-Dur (B).

Materials and Methods

The study was designed as a two-way cross-over multiple dose trial with a one-week interval between the treatments. The study protocol and written informed consent form were approved by the regional Medical Ethical Committee.

In treatment A a 750 mg theophylline dose was taken once daily over 8 days at 20.00 h as two Euphylong (BY 158) 375 mg capsules (Byk Gulden Research Laboratories, Konstanz, F.R.G., lot no. BJ676, actual content 376.2 mg). Two Euphylong placebo capsules (lot no. BJ677) were taken at 08.00 h on days 2–9. In treatment B a total 800 mg daily theophylline dose was taken over 8 days as two Theo-Dur 200 mg tablets (Key Pharmaceuticals, Miami, FL, U.S.A., lot no. 550731, actual content 199.3 mg) at 08.00 and 20.00 h. Each dose was ingested with 200 ml of water, 0.5 h after a standardized breakfast/dinner.

Standardized meals on days 5/6 and 8/9 were taken at 19.30 h (dinner), at 07.30 h (breakfast) and at 13.00 h (lunch).

Subjects were hospitalized on days 5/6 and 8/9 and serial blood samples were taken 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 h after intake of the evening dose on days 5 and 8. Pre-dose samples were taken prior to each drug intake.

Theophylline plasma concentrations were measured in duplicate by means of a highly sensitive and specific high-performance liquid chromatography method, a slightly modified version of the assay developed by Jonkman et al. (1980). The assay is free from interference by other xanthines and allows detection of concentrations down to 0.05 $mg \cdot l^{-1}$.

Eighteen adult male volunteers, with ages ranging from 19 to 31 years (mean $\pm$ S.D.: 23.2 ± 3.0 years) and weights between 64.5 and 82 kg (74.6 ± 5.5 kg), participated in the trial. All were non-smokers and were in good health, as assessed by extensive pre-trial and post-trial medical examinations, including hematology, biochemical tests of blood and urine and ECG-recording. Pre-trial urine screening tests on street drugs were negative. Signed informed consent was obtained from all volunteers. No alcohol or other drugs were taken for 3 days and one week, respectively prior to and during each study phase. No xanthine containing foods or drinks were allowed 24 h prior to each study period.

*AUC*s (adjusted to an actual reference dose of 800 mg) and peak–trough differences with A and B were compared by non-parametric ratio analysis and according to Westlake (1976) and Steinijans and Diletti (1983).

Results and Discussion

Individual pre-dose plasma concentrations indicated steady-state conditions in all subjects after 4 days of dosing. Absorption of theophylline from both A and B was slow in all subjects; a more extended shape of the plateau was observed with A (Fig. 1). In several subjects the plasma concentration continued to decrease for some time (1–2 h) after ingestion of the drug. This phenomenon was more pronounced with A. Retardation of gastrointestinal absorption may occur as a result of delayed gastric emptying after food intake and theopylline, as a weak acid, is poorly soluble in gastric fluid at low pH. It may, in part, also be explained by the food mass creating a physical barrier between the gastrointestinal epithelium and the dissolved drug (Welling et al., 1975; Jonkman

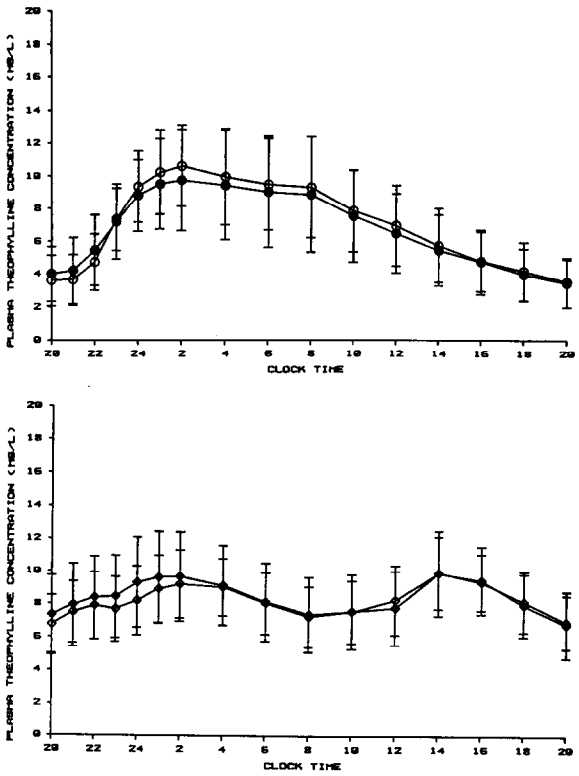

Fig. 1. The mean (±S.D.) theophylline plasma concentration–time curves after once daily administration of A (= Euphylong, 750 mg theophylline) on days 5/6 (●) and 8/9 (○) and after twice daily administration of B (= Theo-Dur, 2×400 mg theophylline) on days 5/6 (◆) and 8/9 (◇).

et al., 1985; Jonkman, 1987). Also a chronopharmacokinetic phenomenon was observed. The individual plasma concentration–time curves indicated that the rate of absorption of theophylline from B in many cases was lower at night, resulting in flatter curves. The amount absorbed at night, however, was not significantly smaller.

Maximum plasma concentrations (C_{max}) with A reached 10.2 ± 3.4 mg $\cdot l^{-1}$ (mean ± S.D.; range: 5.3–14.7 mg $\cdot l^{-1}$) and 10.6 ± 2.7 mg $\cdot l^{-1}$ (range: 6.2–15.4 mg $\cdot l^{-1}$), respectively on day 5/6 and day 8/9. Values for B reached 10.2 ± 2.7 mg $\cdot l^{-1}$ (range: 5.8–15.2 mg $\cdot l^{-1}$) during the first 12-h interval and 10.1 ± 2.4 mg $\cdot l^{-1}$ (range: 6.4–15.8 mg $\cdot l^{-1}$) during the second 12-h interval on day 5/6. During the total 24-h interval these numbers were 10.7 ± 2.6 mg $\cdot l^{-1}$ (range: 6.4–15.8 mg $\cdot l^{-1}$). On day 8/9 values for B were the following: 9.8 ± 1.8 mg $\cdot l^{-1}$ (range: 7.0–12.3 mg $\cdot l^{-1}$) at day-time, 10.3 ± 2.2 mg $\cdot l^{-1}$ (range: 6.7–15.4 mg $\cdot l^{-1}$) at night-time and 10.7 ± 2.1 mg $\cdot l^{-1}$ (range: 7.2–15.4 mg $\cdot l^{-1}$) during the total 24-h interval.

The actually measured value of time to peak T_{max}) with A was 6.2 ± 2.6 h (range: 4–12 h) and 6.8 ± 2.4 h (range: 5–12 h) on the 2 days, but due to an extended plateau shape of the plasma concentration–time curve in many cases it was difficult to determine T_{max}. Values for B were 5.7 ± 1.6 h (range: 2–8 h) and 6.7 ± 1.0 h (range; 6–8 h) on day 5/6 and 6.7 ± 1.1 h (range: 5–8 h) and 6.6 ± 1.3 h (range: 4–10 h) on day 8/9. Although not significantly, there seems to be a tendency towards slower absorption of B during night-time (see Fig. 1).

Rather than by values of T_{max}, the plateau shape of the plasma concentration–time curve and the sustained release properties of A are best characterized by the plateau time ($T_{75\%}$, i.e. the time period during which the plasma concentration during a dosing interval exceeds 75% of the maximum concentration) and by the percentage peak–trough fluctuation ($\%PTF = 100\ (C_{max} - C_{min})/C_{av}$, where C_{min} is the minimum (trough, which need not be the same as pre-dose) concentration and C_{av} is the average steady-state concentration during a dosing interval: $C_{av} = AUC/$ dosing interval).

Values of $T_{75\%}$ for A were 11.0 ± 1.7 h (range: 8.5–15.4 h) and 10.6 ± 2.1 h (range: 6.8–13.8 h) on days 5/6 and 8/9, respectively, indicating considerable sustained release properties. Values for B on day 5/6 were at day-time 9.7 ± 2.5 h (range: 5.0–12.0 h), at night-time 8.8 ± 3.1 h (range: 4.2–12.0 h) and 15.4 ± 5.9 h (range: 8.1 ± 24.0 h). On day 8/9 these numbers for preparation B were: 8.9 ± 2.5 h (range: 4.5–12.0 h), 8.6 ± 2.9 h (range: 4.5–12.0 h) and 14.5 ± 6.3 h (range: 4.9–24.0 h), respectively. Significantly higher values over the two 24-h intervals were not surprising since B was given as a divided dose.

Values for $\%PTF$, which is the method recommended by the FDA to express peak to trough variations, for A were $104 \pm 13\%$ (range: 85–136%) on day 5/6 and $108 \pm 26\%$ (range: 73–144%) on day 8/9. Although fluctuations were considerable in the majority of the healthy volunteers, it is

anticipated that individual dose titration would keep theophylline plasma concentrations within the therapeutic range in most subjects. In addition, smaller fluctuations can be anticipated in asthmatic patients, who on average have 20–25% slower elimination (clearance = 0.05–0.06 $l \cdot h^{-1} \cdot kg^{-1}$ in 24 healthy male volunteers (Steinijans et al., 1987a) and clearance = 0.044 $l \cdot h^{-1} \cdot kg^{-1}$ in 50 patients with chronic obstructive lung diseases (Steinijans et al., 1982). However, in certain patients (fast metabolizers) it may still be difficult to keep plasma concentrations of theophylline within the therapeutic range for the entire 24-h dosing interval. As might be expected in twice daily dosing, values for B over the two 24-h intervals were significantly smaller: $52 \pm 16\%$ (range: 24–82%) and $53 \pm 17\%$ (range: 18–77%). Peak–trough fluctuations over the 12-h intervals for B were on day 5/6 $38 \pm 16\%$ (range: 12–62%) and $44 \pm 16\%$ (range: 24–70%) and on day 8/9 they accounted for $41 \pm 13\%$ (range: 17–58%) and $43 \pm 19\%$ (range: 16–74%), which all can be considered to be small figures.

Slightly smaller C_{av} values (average steady-state plasma concentration) for A reflect slightly smaller areas under the curve $AUC_{96\text{-}120\ h}$ and $AUC_{168\text{-}192\,h}$). The bioavailability of A relative to B was calculated from the ratios of the dose adjusted 24-h AUC values and accounted for 85% (80–91%) on day 5/6 and 90 (81–100%) on day 8/9, results given as geometric mean and distribution free 95%-confidence limits. As the 95%-confidence limits according to Westlake were within the bioequivalence range from 80% to 120% on both steady-state days, A and B were considered to be bioequivalent.

Since the morning dip in peak expiratory flow (PEF) can be prevented by high plasma theophylline concentrations in early morning hours (between 02.00 and 06.00 h), it is of interest to reference nocturnal plasma concentrations to average plasma concentrations for any dose regimen. The chronotherapeutic characteristic % Nocturnal Excess relates time-average plasma concentrations at 02.00, 04.00 and 06.00 h ($C_{av(2\text{-}6)} = (C_2 + 2C_4 + C_6)/4$) to the average steady-state plasma concentration within a 24-h dosing interval (% Nocturnal Excess = $100\ (C_{av(2\text{-}6)} - C_{av})/C_{av}$ (Steinijans et al., 1987b). Nocturnal Excess with A on days 5/6 and 8/9 was $36 \pm 10\%$ (range: 19–56%) and $40 \pm 13\%$ (range: 18–59%), respectively, while nocturnal excess with B was only $7 \pm 5\%$ (range: -2 to $+15\%$) and $7 \pm 6\%$ (range: -3 to $+25\%$). In general, once daily evening administration of sustained release theophylline will produce the highest nocturnal excess. In fast metabolizers, for example, once daily dosing of A in the evening could be replaced by unequally divided twice daily dosing with a higher evening dose. Such a dosing scheme would produce a significant nocturnal excess (Steinijans et al., 1987b). However, maximizing the nocturnal excess must be balanced by acceptable peak-to-trough fluctuations.

Results for A showed that the determination of theophylline in plasma between 06.00 and 08.00 h might well serve to predict nocturnal peak concentrations.

Both A and B were well tolerated by the majority of the volunteers. Few side-effects, generally of mild character, were reported in treatments A and B. Among them diuresis, nervousness and insomnia were reported most frequently.

There were no large differences between the two preparations with regard to intensity and/or frequency of the reported adverse events, although insomnia was reported 7 times with preparation A as compared 3 times with preparation B.

Conclusions

Considerable sustained release quality with extended plateau shape of the plasma concentration–time profile was observed with A.

A and B were found to be bioequivalent, but the extent of absorption of theophylline from A was slightly smaller, probably as a result of slower release of the drug.

Despite good sustained release characteristics for A, once daily intake of the product caused considerable peak-trough fluctuations in the majority of the healthy volunteers. Smaller peak–trough fluctuations, however, can be anticipated in asthmatic patients.

Fluctuations with B can all be considered as being small.

Individual dose titration is of course necessary to keep plasma concentrations of theophylline within the therapeutic range.

Nocturnal excess with A taken once daily in the evening was considerably larger than with twice daily B. Day-to-day reproducibility was good for both products.

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