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Multiple-dose bioavailability study of a sustained-release theophylline product: Choledyl S.A. tablets

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Summary

The bioavailabilities of two sustained release preparations containing choline theophyllinate (Choledyl S.A. 400 mg and 600 mg tablets) have been studied in 12 healthy volunteers using multiple doses. The extent of bioavailability estimated for each tablet was not significantly different to that of Choledyl elixir. When data were adjusted to give a mean steady-state theophylline concentration of 12.5 mg/litre, no significant differences in peak–trough swings were observed between the elixir taken over a 5-h dosage interval and the tablets taken over a 12-h dosage interval. The tablets would therefore appear adequate for use on a twice-daily basis in the majority of patients but in those with short half-lives, e.g. children and smokers, 8 hourly dosing would be more appropriate.

Introduction

Theophylline has been used for many years in both the chronic and acute treatment of asthma (Touriaf and Bourel, 1947; Herman and Aynesworth, 1937). Problems which limited its usefulness initially included toxic symptoms such as nausea, vomitting, headaches and in some rare instances epileptic-like seizures, while

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other patients failed to demonstrate any response to the drug. With a better understanding of the pharmacokinetics of theophylline came an explanation of the wide ranging responses to therapy that were observed.

Whereas the apparent volume of distribution of the drug varies little between individuals from a mean value of 0.48 l/kg (Powell et al., 1978; Piafsky et al., 1977), clearance values and therefore half-lives exhibit considerable intersubject variation. In previous studies within this laboratory involving over 100 subjects, clearances have been observed which range from 1.8 to 7.8 l/h. Therefore the use of a single dosage regimen for all patients would result in patients with low clearance developing toxic symptoms, while therapeutic levels might never be achieved in patients with high clearance.

Several authors (Buelow et al., 1975; Jenne et al., 1972, Weinberger and Bronsky, 1974) have reported that to achieve an adequate therapeutic effect, plasma concentrations of theophylline should be in the range of 10–20 μg/ml. Above 20 μg/ml the risks of developing toxic symptoms increase markedly. To achieve and maintain levels in the appropriate therapeutic range for patients with a short half-life it is necessary to administer theophylline every 6 h, a dosage regimen that is inconvenient during chronic therapy. A well designed sustained release preparation would be advantageous to such patients in that not only would it reduce the frequency of dosage administration necessary but it would also reduce the fluctuation in plasma levels between consecutive doses.

One product recently introduced in an attempt to reduce the need for frequent dosing, is Choledyl S.A., which contains the choline salt of theophylline (oxtriphylline). On the basis of a single dose study in adult volunteers, Hendeles et al. (1984) have reported it to be 93% bioavailable. In a study involving 50 asthmatic patients dosed to steady-state, Fox et al. (1983) compared a theophylline sustained release product with Choledyl S.A. and noted an increase in the mean plasma concentration of theophylline when patients were dosed with the latter product. However, a possible reason for the increased levels was given as improved compliance. Food has been shown to affect the absorption pattern and the extent of bioavailability of some sustained release theophylline products (Pedersen and Moller-Petersen, 1984; Vaughan et al., 1984) while Fox et al. (1984) have suggested that overnight fasting might explain differences they observed between diurnal and nocturnal theophylline disposition.

The present study was undertaken to investigate the bioavailability of Choledyl S.A. 400 and 600 mg tablets in healthy adult volunteers dosed to steady-state, and to observe whether this was affected in any way by food.

Materials and methods

Products studied

Two sustained release products were compared to an elixir in the following regimens (all three products were manufactured by Warner-Lambert, U.S.A.).

(A) Choledyl Elixir (100 mg oxtriphylline in 5 mls ≡ 64 mg theophylline) 15 ml 4 times a day.

TABLE I

DOSAGE REGIMENS AND BLOOD SAMPLING TIMES FOR THE TEST DOSE OF OXTRIPHYLLINE AND EACH OF PRODUCTS A, B AND C

Test dose Blood sampling times 0, 0.5, 1, 2, 3, 4, 5, 7, 9, 12 and 24 hours						
PRODUCT A Choledyl elixir (dose 15 ml)						
Dosing Schedule: Day	*I*	*II*	*III*	*IV*	*V*	*VI*
Dosing Schedule: Times	8*am*, 1, 6, 11*pm*	8*am*, 1, 6, 11*pm*	8*am*, 1, 6, 11*pm*	8*am*, 1, 6, 11*pm*	8*am*	
Blood sampling times			8, 1, 6	8, 9, 10, 11, 12, 1, 6	8, 9, 10, 11, 12, 1, 2, 4, 6, 8	8, 12
PRODUCT B Choledyl S.A. (dose 400 mg tablet)						
Dosing Schedule: Day	*I*	*II*	*III*	*IV*	*V*	*VI*
Dosing Schedule: Times	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	
Blood sampling times			8 8	8, 10, 12, 2, 4, 6, 8	8, 10, 12, 2, 4, 6, 8	8, 10, 12, 2, 4
PRODUCT C Choledyl S.A. (dose 600 mg tablet)						
Dosing Schedule: Day	*I*	*II*	*III*	*IV*	*V*	*VI*
Dosing Schedule: Times	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	8*am* 8*pm*	
Blood sampling times			8 8	8, 10, 12, 2, 4, 6, 8	8, 10, 12, 2, 4, 6, 8	8, 10, 12, 2, 4

(B) One Choledyl SA tablet (400 mg oxtriphylline ≡ 265 mg theophylline) twice a day.
(C) One Choledyl SA tablet (600 mg oxtriphylline ≡ 384 mg theophylline) twice a day.

Subject selection

Volunteers found to be normal upon detailed physical examination, blood screen and urinanalysis were administered a test dose of either 190 mg or 380 mg of theophylline to determine their clearance. Only those with a theophylline clearance of 2.7 l/h or greater (assuming 100% extent of bioavailability) or a half-life of 9 h or less (mean $T_{1/2} = 7.17$ h, range 9.11–4.7 h), proceeded to the multiple dosing phase of the study. These participants were each assigned randomly to receive the above multiple dosing regimens in one of six sequences deriving from two 3×3 latin squares, there being two subjects per sequence. Twelve males aged 22–47 years and weighing 63.5-93.0 kg completed the study. One smoked tobacco.

Clinical procedures

As the timing of doses and blood samples varied according to the product taken (Table 1), volunteers were provided with a diary containing a schedule on which they were asked to record accurately the times at which doses were actually taken. All doses were taken with 200 ml of water. Blood samples (6 ml) were collected from an arm vein either by repetitive venipuncture or through an indwelling catheter. Plasma samples were stored at −20°C prior to assay.

Subjects abstained from caffeine-containing foods and beverages for the 24 h prior to the test dose and prior to commencing multiple dosing with each of products A, B and C. Caffeine was also excluded from the diet for the duration of the study period for each product and the test dose. Subjects were also required to abstain from all food: (a) for 12 h prior to and 2 h following the test dose; and (b) from 20.00 h on day 4 to 10.00 h on day 5 of the dosing regimen with each product.

Assay

The theophylline content of plasma was determined by a specific high-pressure liquid chromatography (HPLC) assay able to distinguish theophylline, caffeine and their metabolites. Acetonitrile (2 ml) containing β-hydroxyethyl-theophylline (2.5 μg/ml) was added to 0.5 ml of plasma to precipitate proteins. After centrifugation, the supernatant was decanted and subjected to vortex-evaporation under vacuum at 45°C for 30 min when less than 0.5 ml of liquid remained. Glass-distilled water (0.6 ml) was added to increase the small volume to 1.0 ml. A 20-μl aliquot was injected onto an Ultrasphere ODS column (Altex, 15 cm × 2.0 mm) via a precolumn (Lichrosorb RP2, 4.5 cm × 2.0 mm). With a flow rate of 90 ml/h the sample was eluted with 12.5% methanol containing 0.01 M sodium acetate and 0.005 M tetrabutylammonium sulphate, adjusted to pH 4.5, and monitored by a UV-detector at 274 nm. Calibration was achieved using a daily standard curve based on spiked plasma from caffeine-abstaining donors. Samples containing less than 1 μg/ml theophylline were reanalyzed using a suitably diluted internal standard solution and an injection volume of 150 μl.

The interday coefficient of variation was 2.5% (3 μg/ml) and 2.2% (12 μg/ml), respectively.

Pharmacokinetic analysis

(i) Test dose

To determine theophylline clearance following administration of the test dose the area under the plasma concentration–time curve from zero time to infinity ($AUC_{0-\infty}$) was calculated. The $AUC_{0-\infty}$ was calculated in three segments: (a) linear trapezoidal estimation of the area from time of dosing to establishment of log-linearity; (b) log-linear trapezoidal estimation of the area from establishment of log-linearity to the time of the last blood sample; and (c) extrapolation of the area from the time of the last blood sample (t_n) to infinity according to Eqn. 1.

$$[AUC]_{t_n}^{\infty} = \frac{\hat{C}_p \cdot t_n}{k_d} = \frac{C_p^{0\leftarrow} e^{-kd \cdot t_n}}{k_d} \tag{1}$$

where k_d and $C_p^{0\leftarrow}$, respectively, are the least-squares fitted terminal log-linear slope and the plasma concentration at time of dosage extrapolated from that slope.

For the purpose of estimating both AUC and k_d, the commencement of log-linearity was taken as the time of the second blood sample after the peak in the plasma concentration–time curve (Upton et al., 1980). Assuming 100% bioavailability of the test dose:

$$CL = \frac{\text{Dose}}{AUC_{0-\infty}} \tag{2}$$

(ii) Product A

For Product A it is not possible to relate simply the bioavailability to the AUC in an interdose interval, because of the unequal dosing intervals used (Table 1). The following approach was therefore employed. Plasma levels ($C_{p_i}^*$) attributable solely to the final dose were calculated according to the expression:

$$C_{p_i}^* = C_{p_i} - C_{p_1} e^{-k_d \cdot t_i^*} \tag{3}$$

where C_{p_1} = plasma level observed at t_1 immediately prior to the last dose and $t_i^* = t_i - t_1$. The AUC for the final dose was then calculated using the values $C_{p_i}^*$ and t_i^* and the method described for the test dose. This approach assumes that the value of k_d used, that calculated from the terminal portion of the curve following the last dose, is identical to that which would have been observed if the final dose had not been administered. This method is particularly dependent on an accurate measurement of C_{p_1}. For this reason the sample obtained at this time was analyzed on two separate occasions to estimate the reliability of this data point. Since the second determination always deviated from the first by less than 7%, the result of the first analysis was the one always used in the calculation of AUC.

(iii) Products B and C

Because Products B and C were taken at regular intervals (viz. every 12 h), bioavailability of these products can be related simply to the AUC in an interdose interval. AUC between the first two doses on each of days 4 and 5 was calculated by means of the trapezoidal rule but an adjustment was made for discrepancies in the volunteer presentation times so that interdose intervals would correspond exactly to scheduled dosage intervals. For volunteers presenting themselves early for withdrawal of the blood sample closest to 12 h after the dose, the concentration in that sample was multiplied by the discrepancy between the actual interdose interval and the scheduled interdose interval, and this adjustment area added to the AUC between the first two doses. For volunteers who presented themselves late for their "12-h" blood sample, the adjustment area was calculated similarly, but subtracted from the AUC between the first two doses. Both the early and late cases lead to slight overestimates of the AUC-interdose. Since the overestimation is only a small fraction of the adjustment area which itself is almost less than about 5% of the total AUC, this overestimation is negligible.

(iv) Projected data

In order to compare plasma concentration swings in an interdose interval, plasma concentrations, were "normalized" (Eqn. 4) to give a mean steady-state level of 12.5 mg/l for each individual during each regimen, i.e. using principles of linear pharmacokinetics, a projection was made of concentrations which would have been observed if the dose had been calculated perfectly to give a mean steady-state concentration of 12.5 mg/l.

$$C_{p_{predicted}} = C_{p_{observed}} \cdot \frac{12.5}{AUC/\tau} \tag{4}$$

where τ is the dosing interval.

Statistical analysis

Analyses of variance were performed using repeated measures analysis of variance (Bostrom, 1979). The between-subject factor investigated was dosing sequence. Products, days within a dosing sequence and dosing periods were analyzed as within-subject factors. The Newman-Keuls range test (Keuls, 1952) was applied to those data showing significant differences. Unless otherwise stated, values quoted represent the mean $\pm$ S.D., (n = 12).

Results

The highest peak plasma concentration observed throughout the study was 14.3 μg/ml since the selection of subjects for the multiple dosing regimen on the basis of clearance or half-life measurements, was to ensure that peak plasma theophylline levels did not exceed 15 μg/ml, thereby minimizing the risk of toxic symptoms.

The plasma concentration data obtained from a typical volunteer are shown in Fig. 1. Theophylline levels in plasma samples drawn just prior to the 08.00 h dose on

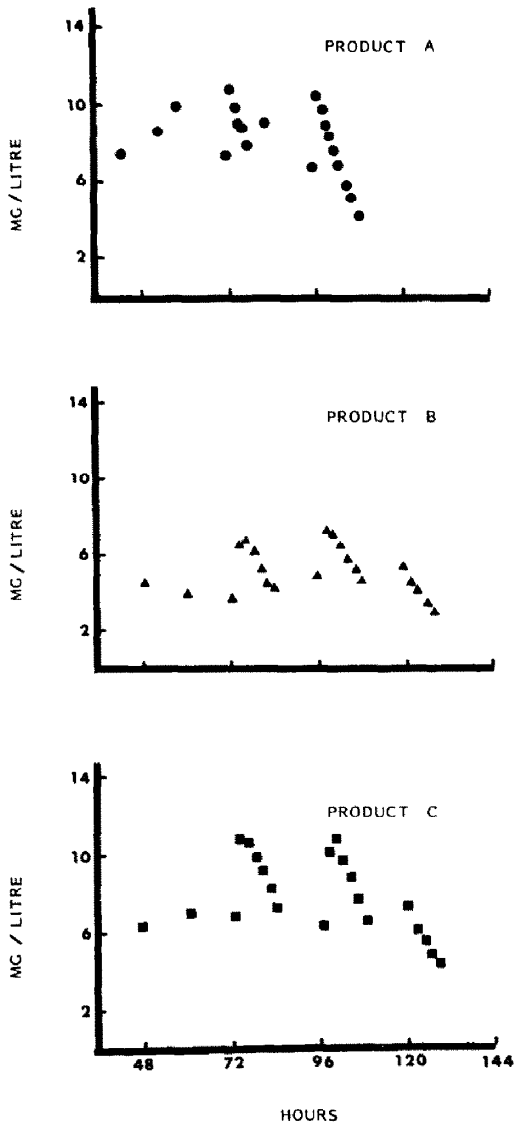

Fig. 1. Typical concentration profiles of theophylline observed in one volunteer during the multiple dosage regimen described in Table 1. Time is measured from the administration of the first dose. (Elimination half-life for test dose was 7.6 h.)

days 3 through 6 were compared for each individual during each product dosage regimen. The 08.00 h concentration of theophylline was not found to increase from day 3 onwards indicating that steady-state had been achieved by this time. However, there was a significant decrease in the 08.00 h theophylline levels ($P < 0.05$) between days 3 and 5 of dosing with the elixir (6.33 ± 1.83 μg/ml → 5.83 ± 1.73 μg/ml) and days 3 and 6 of dosing with Product C (8.04 ± 2.69 μg/ml → 6.84 ± 1.80 μg/ml).

TABLE 2

MEAN AND COEFFICIENT OF VARIATION (%) OF BIOAVAILABILITY ESTIMATES

	PRODUCT A		PRODUCT B		PRODUCT C	
	Day 4	Day 5	Day 4	Day 5	Day 4	Day 5
Bioavailability (AUC) relative to test dose	–	1.00 (14.90%)	1.07 (7.02%)	1.07 (10.58%)	1.11 (15.73%)	1.06 (14.41%)
Bioavailability (AUC) relative to product A (final dose)	–	–	1.10 (18.13%)	1.08 (14.33%)	1.13 (18.24%)	1.09 (23.17%)
Bioavailability ($AUC \cdot k_d$) relative to test dose	–	1.05 (13.87%)	–	–	–	–
$AUC_{DAY\,5}$ relative to $AUC_{DAY\,4}$ for each product	–	1.01 (8.78%)	–	1.00 (10.01%)	–	0.97 (9.78%)

No significant differences ($P > 0.05$) were detected in bioavailability estimates.

The relative extent of bioavailability of each of the products was investigated by comparing AUC for the test dose, AUC for the final dose of elixir and AUC-interdose for each of days 4 and 5 of dosing with the sustained release products. (In each case the AUC was corrected for dose.) Table 2 lists the bioavailabilities of Products A, B and C relative to the test dose and of Products B and C relative to Product A. No significant differences were observed between products nor between successive days of dosing (i.e. between days 4 and 5 with either of the sustained release preparations). No significant difference was found either, between days 4 and 5 of the elixir regimen, if an AUC-interdose was compared after similar calculation to AUC-interdose for the two sustained release regimens. Bioavailability of the final dose of elixir taken on a multiple dosing regimen was also estimated relative to the test dose of elixir by comparing $AUC \times k_d$ values, the latter term having been suggested as a more precise index of bioavailability than AUC alone in those cases where clearance may vary between successive doses during a bioavailability study (Upton et al., 1980; Wagner, 1967). Again no significant differences were detected. Therefore not only were no significant differences in the extent of bioavailability observed between products, but also no significant differences were detected in the bioavailability of individual products between day 4 when breakfast was permitted prior to the 08.00 h dose and day 5 when food was not consumed for 12 h prior to and 2 h following the 08.00 h dose.

To assess whether drug was still being absorbed 12 or more hours after taking the final tablet, the terminal log-linear slopes (k_d values) were determined for Products B and C (Choledyl S.A. 400 mg and 600 mg) using the data obtained from day 6 plasma samples. Comparison with k_d values obtained from the test dose and following the final dose of Product A (Choledyl elixir) failed to detect any significant differences.

Peak plasma levels were observed 69 ± 20, 189 ± 58 and 137 ± 47 min following the final 08.00 h dose for Products A, B and C, respectively. From the projected data the maximum fluctuations in plasma levels for each of the Products A, B and C following the 08.00 h dose on day 5, and assuming the appropriate dosing interval, were 6.7 ± 1.5, 6.7 ± 1.3 and $6.6 \pm 1.7\,\mu g/ml$ with peak levels of 15.3 ± 0.7, 15.5 ± 0.7 and 15.5 ± 1.0, respectively. No significant difference in peak–trough swings between Choledyl elixir taken over a 5-h dosage interval and Choledyl SA tablets taken over a 12-h dosage interval, was found.

Discussion

Oxtriphylline was originally developed because of its increased solubility compared to theophylline, and it is therefore unclear why it was chosen for incorporation into a product where the aim is to control the rate at which the drug enters solution. The fact that 600 mg of oxtriphylline contains the equivalent of only 384 mg of anhydrous theophylline might cause problems when patients change between Choledyl and other theophylline containing products. However, this is not a new problem for clinicians as other theophylline salts are already in use, not the least of which is aminophylline.

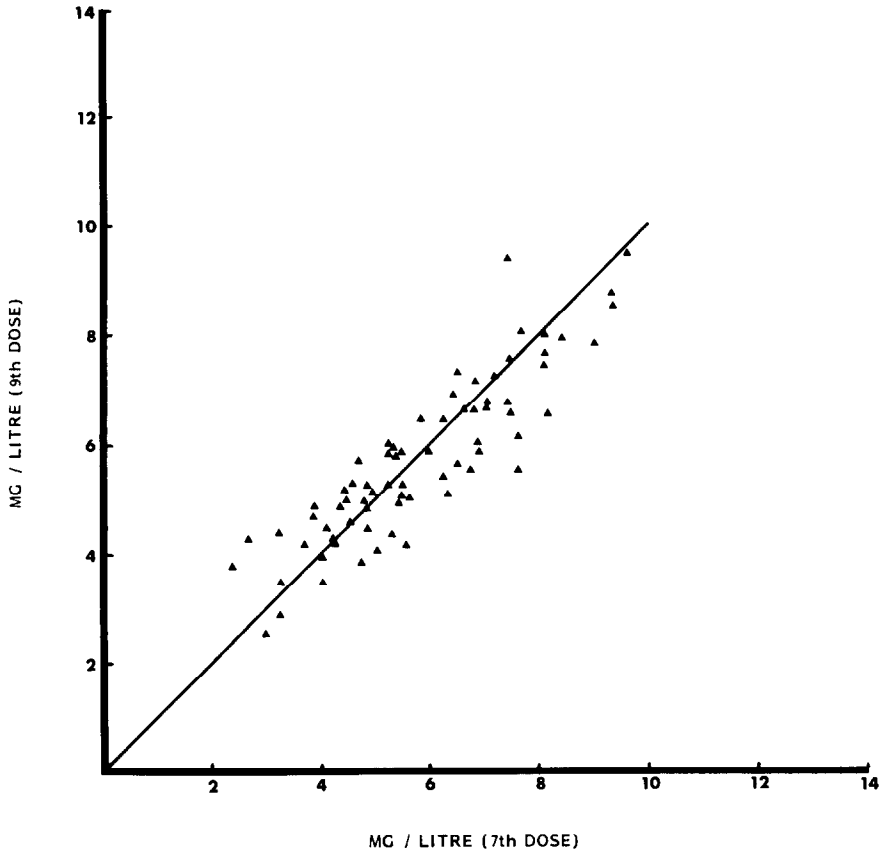

Fig. 2. Each point represents a measured theophylline concentration on day 5 (9th dose) of the dosage regimen with Product B, plotted against the corresponding measured level on day 4 (7th dose). The solid line is the line of identity.

Assuming drug dissolution and absorption to be equivalent to an intravenous infusion, (the ideal situation for a sustained release preparation), 97% of the steady-state level is achieved after 5 half-lives. The longest half-life observed in the volunteers was 9 h so that when the first blood sample was withdrawn 48 h after commencing each dosage regimen, the plasma level should have reached a discernable plateau and, indeed, the 08.00 h plasma level was not found to increase significantly over the 3 or 4 days of sampling. The reason for the decrease seen in certain instances is not clear. There was no evidence to suggest that any of the volunteers had omitted to take a dose of theophylline. However, when data resulting from the 7th and 9th doses are compared (see Figs. 2 and 3) it can be seen that with product B, 71 of 72 observations (98.6%) differed by less than 2 mg/l and 61 (84.7%) by less than 1 mg/l. With product C which gave higher levels, 67 and 72 observations (93.1%) differed by less than 2 mg/l and 48 (66.6%) by less than 1 mg/l. This suggests not only that steady-state had been achieved but also that the release

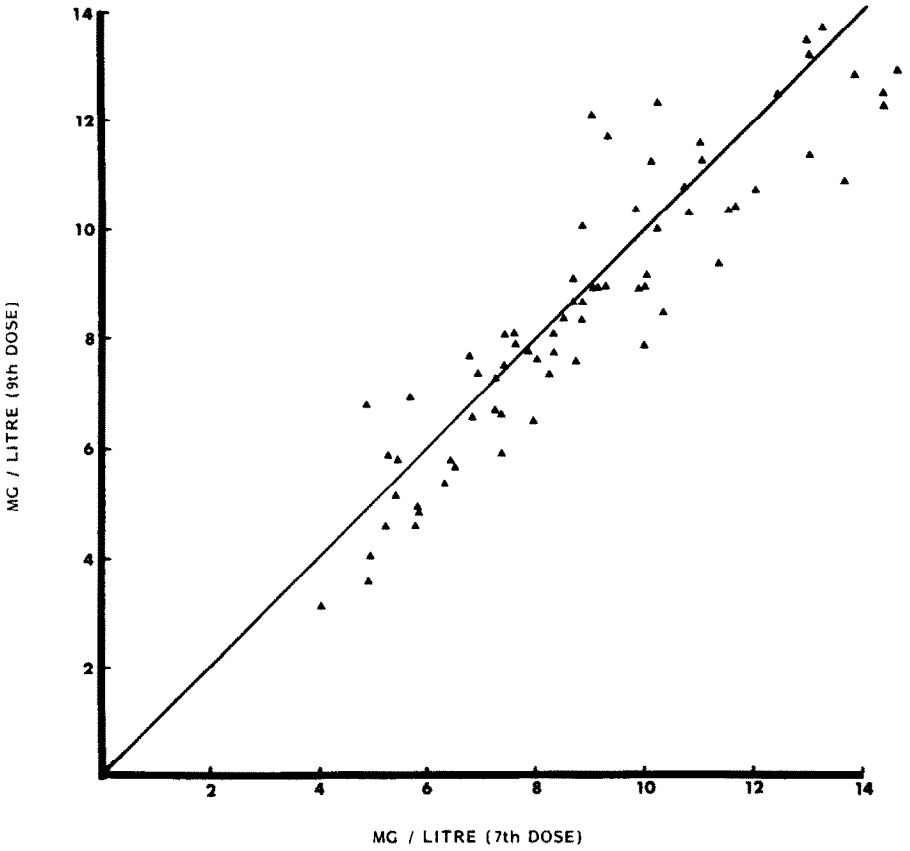

Fig. 3. Each point represents a measured theophylline concentration on day 5 (9th dose) of the dosage regimen with Product C, plotted against the corresponding measured level on day 4 (7th dose). The solid line is the line of identity.

characteristics of the products were consistent within individuals between days 4 and 5. Also, in contrast to the observations with other sustained release theophylline preparations reported by Pedersen and Moller-Petersen (1984) and Vaughan et al. (1984), there was no evidence to suggest that food interfered with the absorption of drug from the Choledyl preparations examined.

Although non-linearity of theophylline metabolism has been demonstrated within the therapeutic range (Tang-Lui et al., 1982) the increased urinary excretion of theophylline observed at higher plasma levels results in apparent linear kinetics (Tang-Lui et al., 1982). Milavetz et al. (1984) have demonstrated dose dependency for elimination half-lives when comparing doses of theophylline differing by a factor of 3. However, in the present study where differences between doses were much smaller, no significant differences were observed between the terminal rate constants obtained with each product. No significant difference was observed when the results from multiple dosing with either 400 mg or 600 mg oxtriphylline were used for the

calculation of predicted data having a mean $\bar{C}_{p_{ss}}$ of 12.5 mg/l. Also there was no significant difference between the bioavailability estimates of the sustained release preparations obtained using as reference either the single test dose of elixir or the final dose of the multiple dosing regimen with the elixir. Therefore the assumption of linear kinetics in calculating both projected data and bioavailability would appear to be appropriate in this instance.

When considering the projected data, the fact that peak–trough fluctuations resulting form 12 hourly administration of the tablets were not greater than those resulting from the elixir during the first 5-h dosing interval of the day, indicates that the tablets qualify as sustained release preparations. Moreover, since the dosage regimen adopted with the elixir gave an overnight dosage interval of 9 h compared to 5 h during the daytime, the overnight peak–trough fluctuation with the elixir would be much greater than was observed during the first dosage interval of the morning. This schedule rather than a regular 6-hourly one, is, however, the more likely "four times daily" dosage regimen to be adopted by the patient on chronic treatment. For patients with a short half-life this could result in either a sub-therapeutic level prior to taking the first dose of the morning or dosing to levels in the late evening that are close to or in the toxic range, so as to prevent too low a level on waking. The appropriate dose of Choledyl S.A. tablets taken at 12-hourly intervals could therefore result in significantly less overnight fluctuation in plasma levels than would Choledyl elixir because of the night-time schedule of dosing normally maintained by the asthmatic patient. For the average patient Choledyl S.A. tablets would appear to be a satisfactory sustained release preparation. It is, however, the patient with a short half-life for whom a sustained release preparation is more of a necessity. With a zero-order release product, the plasma level achieved will not fluctuate over a dosing interval once steady-state has been achieved. However, few sustained release products deliver drug at a constant rate. Therefore any fluctuations in plasma level seen over a dosing interval at steady-state are determined both by the release characteristics of the formulation and the elimination rate constant of the drug, the largest fluctuations being seen in the patient with the shortest elimination half-life. The subject with the shortest elimination half-life in this study (4.7 h) would have experienced fluctuations in plasma levels of 9.0, 9.4 and 10.5 μg/ml and peak concentrations of 16.0, 16.4 and 17.9 μg/ml with doses of Products A, B and C achieving a mean steady-state plasma concentration ($\bar{C}_{p_{ss}}$) of 12.5 μg/ml. With the elixir the plasma level would have fallen below 10 μg/ml during the last hour of the 5-h dosage interval. With both of the sustained release preparations the plasma level would have fallen below 10 μg/ml 8–10 hours after taking the previous dose, i.e. 2–4 hours before the next dose. With the restriction of adjusting dosage with multiples of 400 mg and/or 600 mg, Choledyl S.A. tablets would, in practice, lead to peak levels in this subject higher than those projected or alternatively trough levels lower than those projected with the level below 10 μg/ml for an even longer period of time than that discussed above. It might therefore be necessary to consider using an 8-h dosing interval when using Choledyl S.A. in patients with short half-lives.

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