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Bioavailability study of a theophylline oral controlled release capsule containing film coated mini-tablets in beagle dogs

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Summary

Multiple-unit oral controlled release capsules of theophylline containing film-coated mini-tablets exhibited the desired in vitro release characteristics. Certain of these were subjected to single-dose in vivo studies in beagle dogs in a cross-over manner. Hard gelatin capsules each contained a specific number of uncoated and/or film-coated mini-tablets. Individual mini-tablets weighed 15 ± 0.5 mg and were 0.3 cm in diameter. Two experimental formulations (A and B) as well as parallel studies using a 300 mg oral dose of anhydrous theophylline and a commercial controlled release product (Theo-Dur 300 mg) were tested. Formulations A and B each contained 10 uncoated tablets and 10 film coated with Eudragit RS 2% or Eudragit RL 2%, respectively. After oral administration various pharmacokinetic parameters such as AUC, t_{max} and C_{max} were calculated and compared. Formulation B had certain advantages over Theo-Dur in that it had a greater extent of bioavailability, faster onset of action, more constant serum concentrations and serum levels remained above 7 μg/ml for 9.3 h as compared to Theo-Dur (7.9 h).

Introduction

Sustained release oral dosage forms of theophylline should provide release properties such that peak-trough fluctuations are minimised. The bronchodilating effect is closely related to the plasma concentration (Mitenko and Ogilvie, 1973) and concentrations between 10 and 20 μg/ml are considered best for both therapeutic efficacy and freedom from toxicity (Jacobs et al., 1976). However, its pharmacokinetic characteristics are such that plasma levels within the desired range are difficult to maintain. There is great inter-individual and age-dependent variability in elimination rates (Jenne et al., 1972; Paifsky and Ogilvie, 1975; Ellis et al., 1976) depending upon factors such as age, smoking history, diet, disease and concurrent use of other drugs (Ogilvie, 1978; Lefebvre et al., 1988). Numerous single-unit and multiple-unit oral controlled release dosage forms have been developed (Lippold and Förster, 1984; De Haan and Lerck, 1986; Gangadharan et al., 1987).

The production and in vitro release of theophylline from mini-tablets film coated with polymers were described in earlier work (Munday and

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Fassihi, 1989). Hard gelatin capsules containing a certain number of mini-tablets film coated with Eudragit RL and RS 2% w/w were subjected to in vivo evaluation in beagle dogs using a single-dose cross-over design study. The various pharmacokinetic parameters were calculated such as area under the curve (AUC), extent of bioavailability (EBA), peak concentrations (C_{max}), time to peak (t_{max}) and the constancy of serum concentrations. A comparison was made with parallel studies using a commercial oral controlled release preparation (Theo-Dur) as well as administration of theophylline anhydrous powder enclosed in a hard gelatin capsule.

Materials and Methods

Products tested

Hard gelatine capsules containing a certain number of film-coated mini-tablets (3 mm diameter, 15 ± 0.5 mg each) of theophylline manufactured by a process previously described (Munday and Fassihi, 1989) were used.

Test Unit A: capsules (size 1) each containing 20 mini-tablets (300 mg theophylline) of which 10 were uncoated (immediate release 150 mg) and 10 were coated with Eudragit RS 2% (sustained release 150 mg).

Test unit B: capsules similar to test unit A but the sustained release component was film coated with Eudragit RL 2% w/w.

Parallel studies

Test unit C: capsule (size 1) containing 300 mg theophylline anhydrous powder BP.

Tablets of a standard marketed controlled release theophylline product (Theo-Dur 300 mg).

Dosing and blood sampling

Four Beagle dogs (one male and three females) weighing 12–15 kg (13.78 ± 1.72 kg) were used in this cross-over design single-dose study on each test unit after a suitable wash-out period (14 days). The dogs were fasted for 24 h before administration of the first test dose with water ad libitum. A test unit was administered between 06:00 and 07:00 h on the day of study.

Oral administration of the unit was achieved by opening the mouth of the dog, depressing the tongue, placing the unit in the throat region with subsequent administration of about 100 ml water, and firmly closing the mouth and blowing air through the dog's nose in order to facilitate swallowing (Gangadharan et al, 1987). The dogs received their normal food on the day of study.

Blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. About 3–5 ml of blood were drawn each time from the jugular vein via a teflon 16 G cannula. The projecting end of the cannula was sutured to the skin to prevent it from being pulled out. The neck of the animal was bandaged to prevent interference. During sampling the bandage was removed to facilitate blood withdrawal after which the cannula was flushed with heparinised normal saline. The blood samples were allowed to stand for 1 h, centrifuged and the serum kept frozen ($-20\,^{\circ}$C) until analysis.

Assay of the theophylline in serum

Theophylline concentrations in serum were determined using a fluorescence immunoassay system (TDX Analyser, Abbott).

Pharmacokinetic analysis

The pharmacokinetic parameters relevant to this single dose study include area under the curve ($AUC_{0\rightarrow\infty}$), peak concentration, time to peak and time for which blood levels remain above 7 μg/ml. The $AUC_{0\rightarrow\infty}$ was calculated in each case using the linear trapezoidal rule.

Dissolution studies

The in vitro dissolution of theophylline from the encapsulated mini-tablets and the Theo-Dur 300 tablets was determined by the USP XX1 paddle method. The dissolution medium was distilled water (1 l) at $37\,^{\circ}$C at a paddle speed of 50 rpm [pH did not influence the release profiles significantly (Fassihi and Munday, 1989)]. The concentrations of theophylline were assayed by UV spectrophotometry at 275 nm.

Results

In vitro dissolution studies

The dissolution profiles of theophylline from test units A and B and also from Theo-Dur 300 mg tablets are shown in Figs 1 and 2. The mini-tablets from test units A and B released the drug in excess of 90% over periods of 4 and 2 h, respectively. The maximum amount of theophylline released in vitro from the Theo-Dur 300 tablets was about 70% of the amount stated on the label over 12 h.

Bioavailability studies

The mean serum theophylline concentrations (μg/ml) as a function of time in hours for each test unit is shown in Figs 3 and 4. Table 1 shows the relevant pharmacokinetic parameters after single dosing with each test unit.

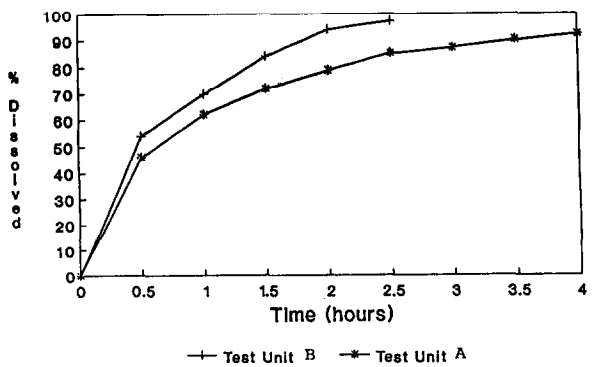

Fig. 1. Percent theophylline dissolved in vitro from test units A and B.

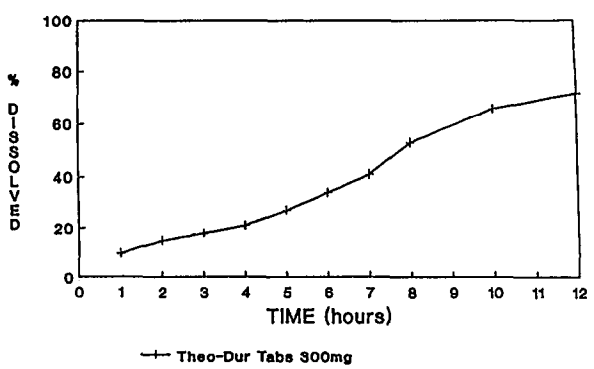

Fig. 2. Percent theophylline dissolved in vitro from Theo-Dur 300 mg tablets.

Discussion

The pharmacokinetic parameters and serum concentration profile show that test unit B compares favourably with that of the commercially available controlled release product (Theo-Dur 300 mg). The AUC of the test unit B (175.2 μg/ml per h) was significantly greater than that of Theo-Dur (118.9 μg/ml per h). The time to peak (t_{max}) was

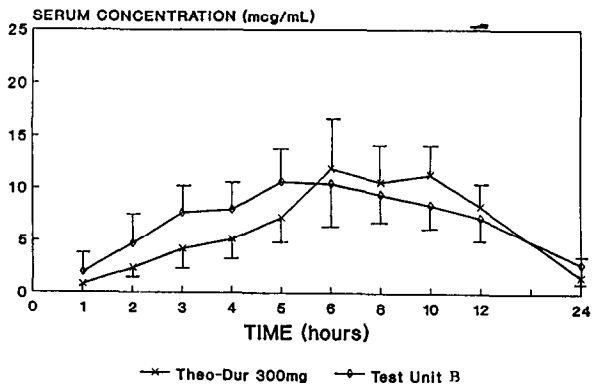

Fig. 3. Mean theophylline concentrations as a function of time in serum following peroral administration of 1 unit of each of the test unit B and Theo-Dur 300 ($n = 4$). The composition of the test unit is described in the text.

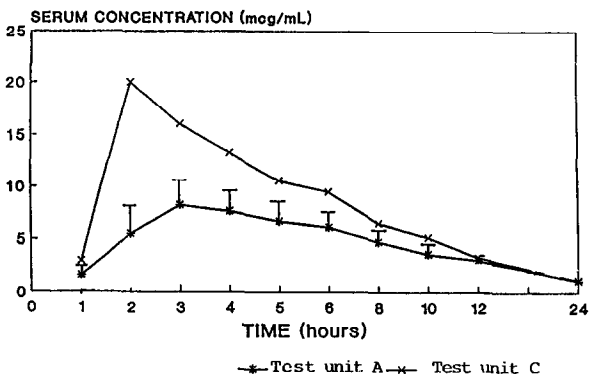

Fig. 4. Mean theophylline concentrations as a function of time in serum following peroral administration of 1 unit of test units A ($n = 4$) and C ($n = 2$). Compositions of test units are described in the text.

TABLE 1

Pharmacokinetic parameters calculated (± S.D.) from the data from four dogs after a single oral dose of each of the test products

Parameter	Product			
	Test unit A	Test unit B	Test unit C	Theo-Dur 300
$AUC_{0\rightarrow\infty}$ (μg/ml per h)	88.2 (±19.3)	175.2 (±26.3)	166.4	118.9 (±22.4)
EBA (test unit D as standard)	0.53	1.05	1.0	0.71
C_{max} (μg/ml)	8.2 (±2.6)	10.7 (±3.8)	20.0	11.9 (±3.6)
t_{max} (h)	3.0 (±0.6)	5.0 (±0.6)	2.0	6.0 (±1.4)
Duration > 7 μg/ml (h)	2.2 (±1.2)	9.3 (±1.7)	6.2	7.9 (±1.1)

Test unit A: mini-tablets uncoated and coated with Eudragit RS 2%; Test unit B: mini-tablets uncoated and coated with Eudragit RL 2%; Test unit C: anhydrous theophylline (300 mg).

smaller for test unit B (5 h) than Theo-Dur (6 h) which means that the onset of action for the test unit was faster. Although the C_{max} value for Theo-Dur was greater than that for test unit B (11.9 and 10.7 μg/ml, respectively), the test unit over the time period 2–10 h produced more constant serum concentrations with a range of 4.7–10.7 μg/ml while the range for Theo-Dur was 2.4–11.9 μg/ml. In addition, the time period over which the serum levels remained above 7 μg/ml (assumed level above which the drug will produce a therapeutic effect) was longer for test unit B compared to Theo-Dur (9.3 and 7.9 h, respectively).

The faster onset of action by test unit B was probably achieved by the uncoated mini-tablets in the capsule which provided the immediate release component. This immediate rise in blood levels occurred over the first 3 h after dosing and it is worthy of note that a similar rise occurred with test unit A in which the immediate release component was identical.

Test unit A contained mini-tablets coated with Eudragit RS 2% combined with an immediate release component of uncoated mini-tablets. The immediate release portion caused serum level to rise to 8 μg/ml within 3 h but thereafter levels dropped steadily to just above 3 μg/ml after 12 h. The $AUC_{0\rightarrow\infty}$ for this test unit was 88.2 μg/ml per h which was lower than that for Theo-Dur which in turn was significantly lower than the AUC for test unit B.

By virtue of their content of quaternary ammonium groups, Eudragit RL films are, in contrast to Eudragit RS, freely permeable to water and dissolved drugs so that theophylline release is relatively modestly retarded. The in vitro dissolution profile for mini-tablets coated with Eudragit RL 2% w/w confirms this fact (Fig. 1). Although test unit B (mini-tablets coated with Eudragit RL 2%) released theophylline in vitro to the extent that over 90% was released in 2 h the release profile in vivo was much slower and test unit B produced serum concentrations within the therapeutic range over a period of about 9 h.

The parallel study using theophylline anhydrous powder 300 mg (test unit C) produced a C_{max} of 20 μg/ml and a t_{max} of 2 h. After peak concentration serum levels dropped rapidly to 3.4 μg/ml after 12 h. The $AUC_{0\rightarrow\infty}$ was 166.4 μg/ml per h and by comparison with the AUC for test unit B (175.2 μg/ml per h) there is no significant difference between test units B and C (EBA is close to 1). Therefore, the degree of theophylline absorption from test unit B is similar to that from capsules containing 300 mg of anhydrous theophylline powder. However, the extent of bioavailability (EBA) of test unit B (1.47) is significantly higher compared to the commercial marketed product (Theo-Dur). This indicates that test unit B liberates the total amount of its theophylline content and is more bioavailable compared with Theo-Dur 300 (which only releases 70% of its theophylline content in 12 h).

In summary, this study has shown that the test unit B, a capsule containing uncoated min-tablets and mini-tablets film coated with Eudragit RL 2% w/w (each providing 150 mg theophylline as immediate release and controlled release, respectively), can offer advantages over the commercially available product.

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