International Journal of Pharmaceutics, 73 (1991) 89–93

ADONIS 037851739100247S

IJP 02438

Note

Multiple dose in vivo evaluation of an oral controlled release capsule of theophylline containing film coated mini-tablets in beagle dogs

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(Received 30 November 1990)
(Modified version received 21 January 1991)
(Accepted 11 February 1991)

Key words: Theophylline; Controlled release; Mini-tablet; Film coating; Bioavailability; Pharmacokinetics

Summary

Controlled release capsules containing mini-tablets of theophylline 200 mg, film coated with Eudragit RL 2% w/w were administered orally every 12 h to beagle dogs over a period of 4 days. Parallel single-dose studies were also carried out using the test capsule, a standard marketed product (Theo-Dur 200 mg) and a capsule containing 200 mg of theophylline anhydrous powder. The pharmacokinetic parameters such as area under the curve (AUC), extent of bioavailability (EBA) and dosage form index (DI) were calculated and compared. Results show that the absorption from the test capsule was maximal and when compared to Theo-Dur the test capsule had a greater EBA (1.09 for the test capsule and 0.74 for Theo-Dur). Dosage titration can be made more precise with this multiple unit sustained release theophylline preparation for the particular needs of the patient.

Oral controlled release theophylline preparations are well established in the treatment of chronic asthma in both children and adults. The bronchodilating effect of theophylline is closely related to the plasma concentration of the drug (Mitenko and Ogilvie, 1973) and concentrations between 10 and 20 μg/ml are considered best for both therapeutic efficacy and freedom from toxicity. This therapeutic range is small and it is known that the same dose causes considerable variation in plasma concentration in different patients, some patients may have subtherapeutic concentrations while others may show plasma levels above the recommended values. This interpatient variability depends on a number of factors including age, smoking history, diet, diseases, weight, concurrent use of other drugs (Ogilvie, 1978; Lefebvre et al., 1988) as well as differences in absorption and elimination.

The introduction of modern sophisticated methods of drug monitoring has made precise dosage titration possible to suit individual patient needs. Current commercial slow release oral theophylline preparations make precise dosage difficult in both single-unit and multiple-unit dosage

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forms. The need exists for a simple homogeneous, inexpensive, yet effective dosage form which may be used for dosage titration.

A controlled release multiple-unit oral dosage form for theophylline exhibiting the desired in vitro characteristics has been developed (Munday and Fassihi, 1989). Single-dose bioavailability studies in beagle dogs were performed and results were comparable with a marketed product with certain advantages (Munday et al., 1991). The aim of this study was to characterise the in vivo profiles under steady-state conditions after multiple dosing. The areas under the curve (AUC), extent of bioavailability (EBA) and the dosage form index (DI) were compared with parallel studies in which theophylline was administered orally in the form of a commercial standard controlled release product (Theo-Dur) and theophylline anhydrous powder in a hard gelatine capsule. Multiple-dose study was conducted over 4 days (96 h) on four beagle dogs which had not been used in any other test over the previous 14 days. The dogs (one male and three females) weighed 12–15 kg (13.78 ± 1.72 kg). The dogs were fasted for 24 h prior to administration of the first dose with water ad libitum. The dosage units consisted of capsules each containing 14 film-coated mini-tablets providing a dose of 200 mg of theophylline. Each capsule (size 1) contained seven uncoated mini-tablets providing 100 mg of drug as an immediate release component. The other seven mini-tablets of identical dimensions were film coated with an amount of Eudragit RL 2% w/w; the method of manufacture and coating is described previously (Munday and Fassihi, 1989). The film coated mini-tablets comprised the 100 mg of controlled release drug.

The first dose unit was administered between 06:00 and 06:45 on the first day of the study. Dosing of each dog was staggered at 15-min intervals so as to facilitate subsequent blood sampling. Oral administration of the unit was achieved by opening the mouth of the dog, depressing the tongue, placing the capsule in the throat region with subsequent administration of about 100 ml of water. The mouth was firmly closed and air was blown through the dog's nose in order to facilitate swallowing (Gangadharan et al., 1987). The second, third, fourth, fifth, sixth and seventh doses were administered in the same manner every 12 h after administering of the first, corresponding to 12, 24, 36, 48, 60 and 72 h. Normal feeding was resumed after the first dose until 72 h when food was again discontinued for a period of 24 h. Blood samples were drawn at 0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 74, 76, 78, 80, 82, 84, 87 and 96 h. About 3–5 ml of blood were drawn each time from the cephalic veins in the forelegs of the dogs. The blood samples were allowed to stand for 1 h, centrifuged and the serum kept frozen until analysis.

Parallel studies were carried out using the same four dogs and a further two dogs. These were single-dose studies involving the oral administration of theophylline anhydrous powder (200 mg) enclosed in a hard, gelatine capsule, to two dogs, another two received orally a commercially controlled release theophylline tablet (Theo-Dur 200 mg), while the third pair received the test capsule (200 mg). In these parallel studies blood was sampled every hour until 12 h and then at 24 h. In this case, blood was drawn each time from the jugular vein via a teflon 16 G cannula and flushed with heparinised normal saline. The parallel studies were performed so that the extent of bioavailability (EBA) of the test unit may be calculated. The concentrations of theophylline in serum were determined using a fluorescence immunoassay system (TDX Analyser, Abbott). The pharmacokinetic parameters relevant to this multiple-dose study include area under the curve (AUC), extent of bioavailability (EBA) and dosage form index (DI). These were calculated in each case using the linear trapezoidal rule.

Serum levels of theophylline (μg/ml) following the first and seventh doses of the dose unit are shown individually for the four dogs in Fig. 1. The area under the curve ($AUC^{0\rightarrow\infty}$) for each dog after single-dose treatment, the $AUC_{\tau_n \rightarrow \tau_n+1}$ (the AUC during one dosing interval at steady state) after multiple dosing, the dosage form index (DI), and EBA values are shown in Table 1. The DI is defined as the ratio of the maximum to minimum concentrations of the drug in serum within each inter-dose interval (in h), τ, during repetitive administration of the dosage form in the quasi-steady state (Theeuwes and Bayne, 1977). Fig. 2 shows

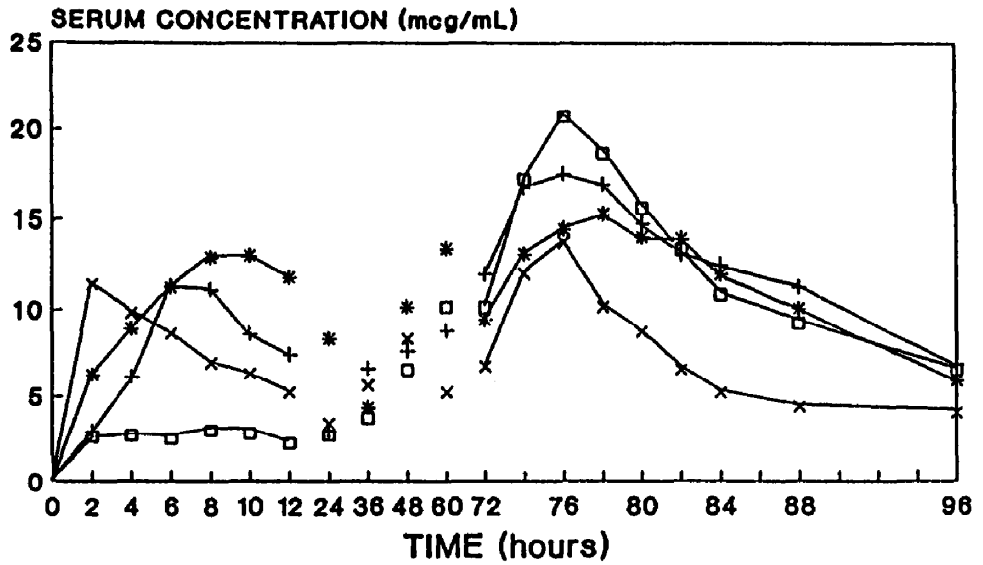

Fig. 1. Theophylline concentration as a function of time in serum following peroral administration of 1 unit (200 mg) of experimental controlled release dosage form every 12 h in beagle dogs. The serum concentrations of four dogs are shown. (×) Dog A, (+) dog B, (*) dog C, (□) dog D.

the mean serum theophylline concentration ± S.D. vs time following the first and seventh doses to the dogs ($n = 4$).

The theophylline serum concentration as a function of time for each dog following oral administration of seven dose units of the experimen-

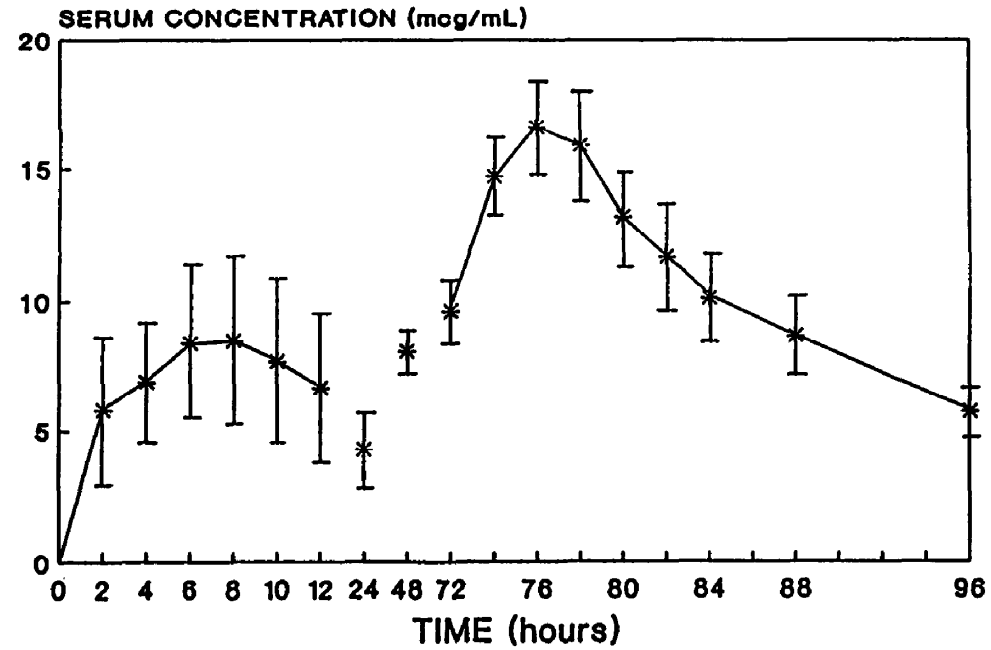

Fig. 2. Mean theophylline concentration ± S.D. as a function of time in serum following peroral administration of 1 unit (200 mg) of experimental controlled release dosage form every 12 h in beagle dogs ($n = 4$).

TABLE 1

Areas under the serum concentration-time curves (AUC) for theophylline after oral administration of single and multiple doses of capsules containing 200 mg of drug in controlled release form to four dogs (the dosage form index (DI) and the terminal disposition rate constant (β) are shown)

Dog	Single dose		Multiple dose		DI
	β	$AUC_{0\to\infty}$ (μg/ml per h)	$AUC_{\tau_n\to\tau_{n+1}}$	$\frac{AUC_{0\to\infty}}{AUC_{\tau_n\to\tau_{n+1}}}$	
A	0.041	154.30	181.7	0.85	1.45
B	0.037	236.52	162.6	1.45	1.62
C	0.047	51.52	191.3	0.27	2.04
D	0.040	141.21	113.9	1.24	2.63
Mean	0.041	145.89	162.38	0.95	1.73
S.D.	0.00419	75.75	34.45	0.52	0.53
S.E.	0.00296	53.56	24.36	0.37	0.37

Note: Mean $AUC_{0\to\infty}$ from parallel study (single dose) was 98.55 and 133.14 for Theo-Dur and theophylline powder, respectively. The EBA using theophylline powder as standard was 1.09 for test unit and 0.74 for Theo-Dur.

tal product over 96 h (Fig. 1) shows that there is considerable variation in serum levels from dog to dog, particularly in the case of dog C, where in the first 12 h the serum level never exceeded 3.0 μg/ml, compared to dog B where the concentration reached as high as 13.0 μg/ml after 10 h. However, under steady-state conditions (after 72 h and seventh dose) this variability was reduced significantly.

With two dogs (B and D) there was a relatively small difference between peak concentrations (C_{max}) during the first 12 h compared with that during the last dosage interval, whereas with the other two (dogs A and C in particular) the higher C_{max} during the last dosage intervals was significant. It is also noteworthy that the time to peak (t_{max}) during the first 12 h varied considerably (2 to 10 h). On the other hand, the serum concentration curves from 72 to 96 h show that the t_{max} was reasonably consistent (at 76 h) although the C_{max} value itself was variable. In one case (dog C) the C_{max} at 76 h exceeded 20 μg/ml but no noticeable signs of theophylline toxicity occurred.

Higher peak concentrations after the seventh dose were expected, since upon multiple dosing with equal dose sizes in equal dosing intervals, steady-state level is achieved.

However, it is apparent that dose dependency is absent (i.e., no enzyme induction or inhibition occurs), as shown in Table 1. The mean AUC during any dosing interval on multiple dosing ($AUC_{\tau_n\to\tau_{n+1}}$) at steady-state is almost the same as the mean AUC after single-dose administration ($AUC_{0\to\infty}$). The ratio in individual dogs does vary, however. For dogs A and D this ratio is close to 1 (0.85 and 1.24, respectively), whereas dogs B and C are significantly different (see Table 1). Although the beagle dogs may be a good model for controlled release formulations of theophylline, this work has shown that considerable inter-individual variation in the pharmacokinetic parameters does exist. The mean DI for the experimental dosage unit was calculated to be 1.73 $\pm$ 0.53 (obtained from the '$C^{SS}_{max}/C^{SS}_{min}$' values) which is small enough to ensure that maintenance of blood concentrations in the therapeutic range over a 12 h dosage interval is possible.

It is well known that considerable intersubject variation in theophylline elimination exists (Hendeles et al., 1978; Ogilvie, 1978). It is not surprising, therefore, that dosage titration is recommended, especially now that some sophisticated analytical methods for measuring serum levels have become available and drug monitoring can be more easily done. Dosage titration can be made more precise with multiple-unit sustained release theophylline preparations. A multiple-unit sustained release preparation like encapsulated film-coated mini-tablets described in this article makes precise adjustment of the dose for particular needs of the patient easily possible by adjustment and placement of the exact number of identical mini-tablets in the capsule.

Acknowledgement

The authors wish to thank Mrs D. Herbert, Technician at the Department of Pharmacology, University of Cape Town for assistance with the analysis of serum samples using the TDX Analyser.

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