Pharmaceutical Research, Vol. 6, No. 12, 1989

Report

The Beagle Dog as an Animal Model for a Bioavailability Study of Controlled-Release Theophylline Under the Influence of Food

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Received March 13, 1988; accepted June 4, 1989

Beagle dogs were evaluated as an animal model to study the effect of food on the bioavailability of two commercially available oral controlled-release theophylline products. The products were administered with and without food in single doses, and the bioavailability parameters were compared with those following an i.v. aminophylline dose. The total plasma theophylline clearance in dogs following an i.v. dose was 0.128 liter/hr/kg and the volume of distribution was 0.8 liter/kg using a one-compartment model. The absolute bioavailabilities of these two products under fasting conditions were 31 and 48%, respectively. The food increased the bioavailability of one product and decreased the bioavailability of the other. The overall trends in relative bioavailability of these two products with and without food appeared to be similar to those reported in humans.

KEY WORDS: theophylline; controlled release; food effects; beagle dogs.

INTRODUCTION

The administration of some controlled-release (C.R.) theophylline products with food in humans may have unexpected effects on the bioavailability of the products (1–6). Changes in rate and extent of absorption of the C.R. products due to food effects could greatly increase the risks to the patients because of the higher single dose that is usually given. In the recent food effect studies on two C.R. theophylline capsule products (both contain beads in the capsules), one has shown that the absorption rate and extent were increased substantially when the drug was given immediately after a high-fat breakfast (5), while another product has shown the opposite effects on bioavailability (6). These differences not only illustrate the complexity of the food–drug interactions among C.R. formulations, but also demonstrate the necessity for studying the food effect on absorption of all C.R. formulation products.

To reduce the risks to human subjects and to minimize the cost of human study, a suitable animal model for testing is generally a good choice. Our previous study in miniswine (7) as an animal model for C.R. theophylline products has turned out to be less than desirable because of the noticeable differences in pharmacokinetics of theophylline between miniswine and human. In this study beagle dogs were used to examine two brands of C.R. theophylline formulations which have exhibited opposite food effects in humans under fasted and fed with high-fat meal conditions. The objective is to assess the suitability of the beagle dog as an animal model for a food effect study on the rate and extent of absorption of the C.R. theophylline products.

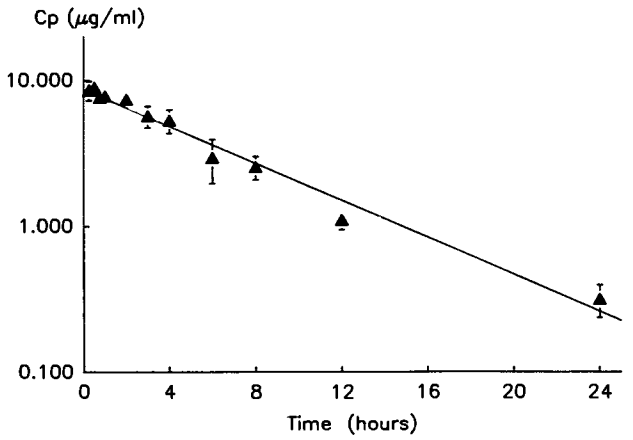

Fig. 1. Mean plasma level (±SE) of theophylline following an intravenous dose of 100 mg aminophylline in four beagle dogs.

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0724-8741/89/1200-1039$06.00/0

Table I. Pharmacokinetic Parameters of Theophylline Following Intravenous Administration of 100 mg of Aminophylline (Equivalent to 78.8 mg Theophylline Base) to Four Beagle Dogs

Pharmacokinetic parameter[a]	Arithmetic mean (range)	C.V. (%)
A (μg/ml)	8.79 (8.25–9.68)	7.5
K_e (hr^{-1})	0.153 (0.144–0.160)	4.8
V_d (liters/kg)	0.834 (0.802–0.901)	5.5
Cl (liters/hr/kg)	0.128 (0.116–0.136)	6.6
$t_{1/2}$ (hr)	4.54 (4.34–4.81)	4.8
AUC (μg/hr/ml)	59.2 (52.4–69.9)	12.7

[a] Calculated using a one-compartment open model.

MATERIALS AND METHODS

Study Design

Four male beagle dogs (about 1 year of age, weighing 10–12 kg) were administered a single 100-mg intravenous dose of theophylline ethylene diamine salt (Aminophylline injectable, G. D. Searle & Co., equivalent to 78.8 mg theophylline base) in the first week of study. Theo-24 capsules (G. D. Searle and Co., 200 mg, Lot 983-715, product A) and Theo-Dur sprinkles (Key Pharmaceuticals, 200 mg, Lot 416-101, product B) were administered to these dogs under fasted and fed conditions in a four-way crossover design with 1-week dosing intervals. All dogs were fed once a day with fatty food which consisted of approximately 20% crude fat 1 week before (training period) and throughout the experimental periods. The fatty food (25% protein, 20% fat, 45% carbohydrates, and 10% moisture) was prepared as described in our previous study (7). Under the fasted condition, drugs were administered orally at least 16 hr after the last meal and 6 hr before the next meal. While under the fed condition, drugs were given within 30 min immediately after the animals were fed. Blood samples were collected through venopuncture of the jugular vein into heparinized tubes at various time intervals up to 48 hr after dose administration. Plasma samples were immediately separated and frozen at −30°C until assayed.

Analytical Method

The reverse-phase high-performance liquid chromatographic (HPLC) method used to determine the plasma theophylline concentration has been described in our previous paper (7).

Data Analysis

Plasma theophylline levels after i.v. administration were fit to a one-compartment pharmacokinetic model using the PROPHET computer program as described previously (7). Other model-independent parameters including maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were determined by a standard procedure. The area under the concentration time curve (AUC) was calculated by a linear trapezoid method and the AUC beyond the last sampling time point for individual animals after oral administration was estimated using K_e values obtained from i.v. administration in the same animal. The absolute bioavailability (F) was calculated by dividing the normalized AUC values of the oral dose by that of the intravenous dose. Times to 50% (T-50) and 80% (T-80) theophylline absorption after oral administration were obtained using the Wagner-Nelson equation (8) in which K_e values from i.v. administration in the same animal were utilized.

RESULTS AND DISCUSSION

Pharmacokinetics of Theophylline Following an i.v. Dose

The plasma theophylline levels in dogs following a single 100-mg aminophylline i.v. dose declined monoexponentially (Fig. 1). The pharmacokinetic parameters calculated from the plasma theophylline levels following an aminophylline injection are shown in Table I. The volume of distribution, plasma clearance, and terminal plasma half-lives calculated in this experiment are very similar to those previously reported for beagle dogs in the literature (9). The total plasma clearance for the i.v. dose in dogs (0.128 liter/hr/kg) appears to be three times higher than the 0.043 liter/hr/kg reported in humans (10). The volume of distribution (V_d) in

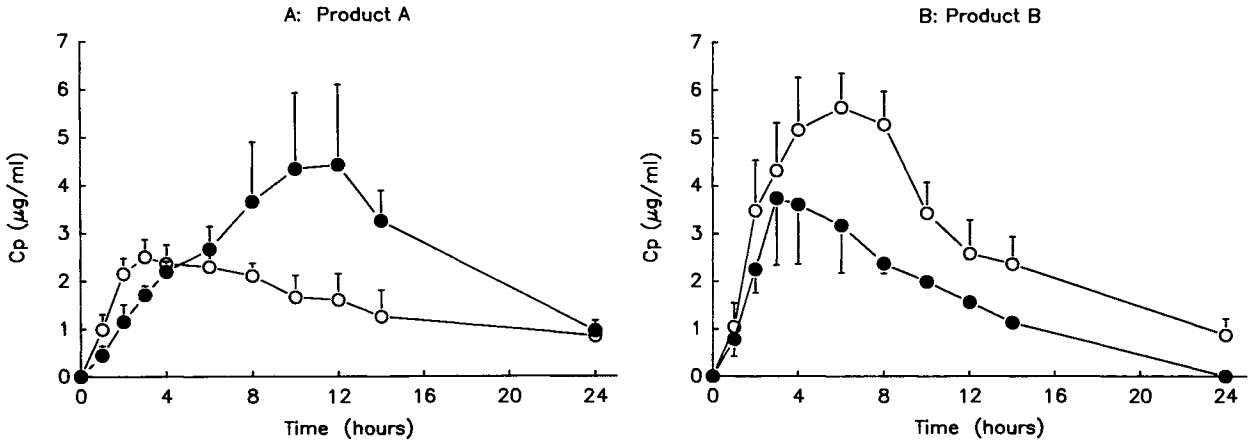

Fig. 2. The mean (±SE) plasma theophylline concentration (Cp; μg/ml) versus time (hr) profiles after oral administration of the C.R. theophylline of (A) product A, and (B) product B. The open circles (○) represent mean values of four dogs under the fasted condition, while the filled circles (●) represent mean values of four and three dogs under the fed condition for products A and B, respectively.

Table II. Summary of Theophylline Pharmacokinetic Parameters Following Oral Administration of Two C.R. Theophylline Products to Four Beagle Dogs Under Fasted and Fed Conditions

Pharmacokinetic parameter	Mean parameter value (SD)			
	Product A		Product B	
	Fasted	Fed	Fasted	Fed[a]
AUC (μg/hr/ml)	47.0 (24.1)	65.4 (20.9)	74.5 (22.9)	37.80 (8.54)
C_{max} (μg/ml)	3.00 (0.40)	4.67 (3.16)	6.20 (1.92)	4.24 (2.01)
T_{max} (hr)	5.50 (4.36)	9.00 (4.76)	7.00 (1.16)	6.00 (2.00)
F^b (%)	31.2 (17.6)	42.5 (14.3)	47.8 (10.4)	24.4 (7.04)
T-50 (hr)	4.40 (3.24)	7.7 (0.77)	3.47 (1.72)	3.37 (1.72)
T-80 (hr)	9.3 (6.48)	12.6 (3.48)	7.70 (4.3)	6.42 (1.86)

[a] Mean values of three dogs. Data for one dog were not available due to the mishandling of the samples during analysis.
[b] Absolute bioavailability.

dogs found in this study (0.8 liter/kg) was higher than that (0.4 liter/kg) reported in humans. The terminal half-life in dogs found in this experiment was 4.5 hr, which appears to be similar to the 4.3 hr observed in children (4) and somewhat lower than the 6- to 8-hr half-life observed in adult human subjects (10). From these results, it is apparent that the physiological pharmacokinetic parameters V_d and Cl are higher in dogs than in adult humans.

Effect of Food on the Absorption of Product A and Product B

The average plasma theophylline levels following product A and product B are shown in Fig. 2. The plasma peak drug levels following Product B without food (Fig. 2B) were approximately similar to those of product A with food (Fig. 2A) in dogs. The same trend was also reported in humans with these two products (12). The estimated absolute bioavailability of product A increased by 36% with food compared to that under the fasting condition. This trend was also consistent with findings in human studies (13). The rate of absorption of product A was initially lower followed by a rapid increase after 6 hr compared to that administered under fasting conditions in dogs (Fig. 2A). The shape of these average plasma theophylline vs time curves are very similar to those observed in adult humans following a single 900-mg Theo-24 dose (12). The average T_{max} under fed conditions in dogs was 9 hr, versus the 5.5 hr that was observed under fasting conditions. There appears to be no clear trend for an increase or decrease in T_{max} associated with food in humans for product A. The average C_{max} increased with food by 55% in dogs compared to that under fasting conditions and these findings were similar to those observed in humans.

The calculated absolute bioavailability for product B declined by 49% and the C_{max} by 32% under fed conditions compared to fasting conditions in dogs. A similar trend was observed with this product in human adults (6,12) and in children (14). The average T_{max} values were fed and fasting conditions were approximately similar in dogs (Table II) as well as in humans (12,14) following a single dose of product B. The T-50 and T-80 values increased under fed conditions with product A and decreased slightly with product B compared to those under fasting conditions.

The extents of absorption of product A (F = 31.2%) and product B (F = 47.8%) under fasting conditions in dogs were lower compared to the 70 to 80 and 80 to 100%, respectively, reported for these products in humans following single doses (15). However, our findings were consistent with literature reports which indicated that the bioavailability of product A in beagle dogs was 32% compared to an i.v. dose of aminophylline (16) and was only 38% compared to an immediate-release (I.R.) oral liquid theophylline dose (17). Even though there were no published reports to describe the absorption of product B in beagle dogs, the absorption (F) of similar formulations developed by the same firm ranged from 28 to 53% (18) depending on the density and diameter of the beads in these formulations. Absorption of the product B was reported to be decreased further when it was given with dry food compared to wet food in humans (19). A trend of a decrease in absorption due to intake of a low fluid volume following an I.R. theophylline product was also reported (20). Some of the differences in absorption between beagle dog and human studies could be the hydration level of these species because the GI fluid volume may be important for the absorption of the controlled-release products. The overall poor absorption of the C.R. theophylline products in dogs could be due to a combination effect of short GI transit as well as low GI fluid volumes in dogs compared to humans.

In conclusion, the beagle dog, although not a perfect animal model for accurately predicting absolute bioavailability, appears to be a good model for predicting the potential food effect for these C.R. theophylline products. Furthermore, the beagle dog may also be a good *in vivo* model for bioequivalent study of the C.R. theophylline dosage forms while administered with and without food.

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