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Report

The Effect of Food on the Absorption of Controlled-Release Theophylline in Mini-Swine

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The effect of differing fat contents of food on the bioavailability of theophylline following a 400-mg single dose of Theo-24 was studied in mini-swine. The pharmacokinetics of theophylline, following the intravenous administration of aminophylline equivalent to 5 mg/kg as a single dose, were also studied in the same animals. The terminal plasma half-life of theophylline following an i.v. dose was found to be approximately 24 hr. The volume of distribution, $V_{d_{ext}}$, and clearance following the i.v. dose were approximately 0.7 liter/kg and 0.023 liter/hr/kg, respectively. The terminal half-life of theophylline following the administration of theophylline capsules under fasting conditions was 21 hr. The average bioavailability under fasting conditions was approximately 80% compared to the i.v. dose. Food appeared to have decreased the rate of absorption but no significant effect on the extent of absorption.

KEY WORDS: theophylline; controlled release; food effects; mini-swine.

INTRODUCTION

The effect of food on the absorption of several theophylline controlled-release (CR) products in humans has been studied recently by several investigators (1–7). The reported food-induced changes varied quite differently among products, with some exhibiting an increase (1–4) and others a decrease (4–7) in the rate and/or extent of absorption of theophylline. In addition, the absorption from one product was not affected by the administration of food (7). These differences as reported in the literature indicate a necessity to investigate the food effect not only on the absorption of CR theophylline formulations, but also on other marketed controlled-release products, e.g., procainamide CR, quinidine CR, phenytoin extended, etc.

This investigation was undertaken with the idea of developing a suitable animal model, capable of simulating food effects similar to those seen in humans, so as to reduce both the risks to human subjects and the cost of human studies. Since 1983, immediately after the adverse effect of food on certain controlled-release dosage forms was discovered, the Food and Drug Administration (FDA) has required a single-dose, high-fat, food effect study for approval of all newly submitted new drug applications (NDA) for controlled-release dosage forms.

Domestic swine (Yorkshire-cross gilt) have been previously evaluated as a potential human model for use in drug bioavailability studies (8). In the present study, the use of the Hormel-Hanford mini-swine was investigated to determine its suitability as a model capable of predicting fasted bioavailability as well as the effects of food on drug absorption from a once-a-day theophylline product known to have a different bioavailability when given with food than when administered in fasting humans.

MATERIALS AND METHODS

Study Design. Five Hormel-Hanford mini-swine weighing between 25 and 40 kg were given a single dose of Theo-24 capsules (G. D. Searle & Co.), 400 mg orally, after an overnight fast or 15 min after one of the following meals: (i) regular chow (Purina high-octane lactation chow that contains approximately 4% crude fat), 25 g/kg body weight; (ii) chow mixed with additional 15% fat; and (iii) chow mixed with additional 30% fat. The additional fat was made up by substituting a portion of the chow with pure lard, e.g., substituting 3.75 and 7.5 g of chow/kg body weight with lard. Five mini-swine (two or three animals at any one time) were given the drug orally on each experiment day. The dietary conditions were randomized and at least a 1-week washout period was allowed for each animal between dosings. At the end of the study, all five swine were given an intravenous dose of aminophylline injectable solution equivalent to 5 mg of theophylline base/kg of body weight. Blood samples were collected through an intravenous catheter (or venopuncture of the anterior vena cava) into heparinized tubes at various intervals of time up to 82 hr after dose administration. Plasma samples were separated immediately and frozen at −30°C until assayed.

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Analytical Techniques. Plasma theophylline concentrations were quantified by modified high-performance liquid chromatographic (HPLC) method (8). Briefly, 0.5 ml of plasma was spiked with an internal standard, β-hydroxyethyl theophylline, and was deproteinated with 0.2 ml of 20% trichloroacetic acid (TCA). After centrifugation, an aliquot of clear supernatant was injected into a reverse-phase HPLC system which utilized a solvent of 0.005 *M* acetate buffer (pH 4.8) and acetonitrile (92:8) and a UV detector monitored at 272 nm. The method is sensitive to detect 0.05 μg of theophylline under these chromatographic conditions.

Data Analysis. The data were fit to a pharmacokinetic model using PROPHET (PROPHET computer programs for pharmacokinetics study, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services).

Fractions of the amount absorbed plots for CR theophylline (administered under different dietary conditions) were obtained using the Wagner–Nelson equation (9) (utilizing the terminal K_e value from the plasma drug profiles of the fasted animals). The absolute bioavailabilities of the CR theophylline, both corrected (F_c) and uncorrected (F_u) for the terminal K_e values (10), were calculated by dividing dose-normalized $AUC_{0-\infty}$ (AUC) values of the oral dose with that of the intravenous dose. The relative bioavailability (F') of the test product following the administration of food was calculated for each animal as the ratio of the $AUC_{0-\infty}$ of the food treatment to that of the fasted treatment. The area under the concentration–time curve beyond the last sampling time point for individual animals following food treatment was estimated using K_e values obtained under fasted conditions in the same animal. In order to compare the volume of distribution of theophylline in different species, the $V_{d_{ext}}$ (dose/*B*) calculated from the present study using a two-compartment analysis was compared with the V_d (dose/C_0) that was reported in the literature using a one-compartment model. The total plasma clearance (Cl) was calculated as dose/AUC.

RESULTS

Plasma theophylline levels were best fit to a two-compartment model after i.v. administration, whereas a one-compartment model with first-order absorption and elimination was found to be suitable to fit data obtained from oral dosage (Fig. 1). The pharmacokinetic parameters obtained after an intravenous dose of aminophylline and an oral dose of the test product under fasting conditions are shown in Tables I and II, respectively. Theophylline distributed very rapidly in mini-swine after i.v. administration but was eliminated at a much slower rate (Table I). The mean terminal elimination half-life following the i.v. dose was approximately 23.7 hr, which was similar to the 20.8 hr found after an oral dose in the same animals. The absorption half-life calculated from the mean K_a values following oral doses under fasting conditions was 4.8 hr. The absolute bioavailabilities, corrected (F_c) and uncorrected (F_u) for terminal K_e values, were found to be 88 and 81%, respectively, after a single 400-mg oral dose of the drug to five swine under fasting conditions.

The dose-normalized mean plasma concentrations versus time profile following oral doses is shown in Fig. 2.

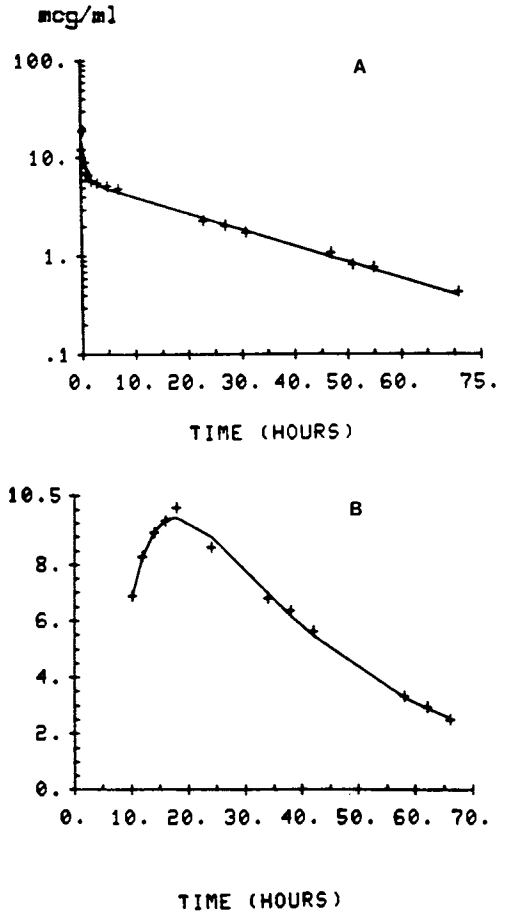

Fig. 1. Plasma levels of theophylline following an intravenous dose of aminophylline (A) and an oral dose of the CR theophylline product (B) in a mini-swine.

The error bars represent the calculated standard errors of the means (SE) of dose-normalized peak concentrations (C_{max}) and also point out the times to attain them (T_{max}). Under the four described dietary conditions, namely, fasting, normal chow, extra 15% fat, and extra 30% fat, the

Table I. Pharmacokinetic Parameters of Theophylline Following Intravenous Administration of 5 mg/kg of Aminophylline to Five Hormel-Hanford Mini-Swine

Pharmacokinetic parameters[a]	Arithmetic Mean (range)		CV (%)
A (μg/ml)	14.16	(6.67–23.61)	43.4
B (μg/ml)	6.95	(5.90–7.53)	8.6
α (hr^{-1})	4.19	(1.53–11.54)	40.3
β (hr^{-1})	0.0325	(0.0176–0.0414)	31.8
K_e (hr^{-1})	0.097	(0.0524–0.174)	49.2
$V_{d_{ext}}$ (liters/kg)[b]	0.724	(0.680–0.847)	9.6
Cl (liters/hr/kg)	0.023	(0.012–0.030)	34.8
$t_{1/2(\beta)}$ (hr)	23.7	(16.8–39.3)	40.5
AUC (μg · hr/ml)	247.3	(169.3–417.3)	43.3

[a] Calculated using a two-compartment open model.
[b] Calculated using dose/*B*.

Table II. Summary of Theophylline Pharmacokinetic Parameters Following Oral Administration of 400 mg Theo-24 to Five Fasted Hormel-Hanford Mini-Swine

Pharmacokinetic parameter[a]	Arithmetic mean (range)	CV (%)
K_a (hr^{-1})	0.144 (0.073–0.214)	34.5
K_e (hr^{-1})	0.0342 (0.0272–0.0415)	18.4
V_d (liters/kg)	0.839 (0.653–1.007)	20.1
Cl (liters/hr/kg)[b]	0.029 (0.018–0.042)	30.2
$t_{1/2}$ (hr)	20.8 (16.7–25.5)	18.1
AUC (μg · hr/ml)	424.8 (306.2–503.6)	17.5
Lag t (hr)	4.1 (0–6.8)	74.4
F_u (%)[c]	81.0 (64–105)	21.5
F_c (%)[d]	88.0 (72–103)	15.2

[a] Calculated using a one-compartment open model with lag time.
[b] Uncorrected for bioavailability, F.
[c] F_u, bioavailability that was uncorrected for K_e.
[d] F_c, bioavailability that was corrected for K_e.

mean T_{max} increased significantly with food compared to that under fasting conditions. The T_{max} values were 50 to 100% longer following the administration of the drug when it was given with meals containing 15 and 30% fat contents, respectively, compared to those found under fasting conditions. On the contrary, the mean dose-normalized C_{max} values under the three different fed conditions (irrespective of fat content in meals) were similar but significantly lower than those under the fasted condition ($P < 0.05$). The mean test product absorption profiles for five animals under the four dietary conditions are shown in Fig. 3. Data were available only for two animals on the 30% fat diet because three of five swine vomited after an intake of food with 30% fat. The influence of food on the rate of absorption of CR theophylline varied among these animals. However, most of these animals showed a decrease in the absorption rate when food, especially food with a higher fat content, was given before dosing.

The relative bioavailability (F') of the test product under various dietary conditions is shown in Table III. With a normal diet or a diet with 15% extra fat, the average F' value was approximately the same (88%). However, with 30% extra fat in the diet, the average F' value was approximately 111%.

DISCUSSION

A two-compartment open model was found to be suitable to describe theophylline disposition in the mini-swine following intravenous administration of aminophylline. Frequent early sampling (0.25, 0.5, 0.75 hr) yielded an initial distribution phase in this study. The distribution phase was found to be very short and the distribution half-life was less than 30 min for the five animals studied. Therefore, it may be difficult to characterize the early distribution phase following an i.v. dose without sampling prior to 0.5 hr postdose. The pharmacokinetics of theophylline have been reported (8) in domestic swine following an i.v. dose using a one-compartment model without any blood sampling prior to 0.5 hr. By taking these differences into consideration, the calculated volume of distribution ($V_{d_{ext}}$ using a two-compartment model) in mini-swine was 0.7 liter/kg, compared to 0.6 liter/kg (V_d using a one-compartment model) in domestic swine (8). The volume of distribution in humans using the one-compartment model was determined as 0.51 liter/kg (11,12). On the other hand, the mean terminal elimination half-life of theophylline in mini-swine (23.7 hr) is much longer than the 11 hr observed in domestic swine (8) or the 6 to 8 hr in humans (12,13). These differences in half-life probably reflect inter- as well as intraspecies disposition differences.

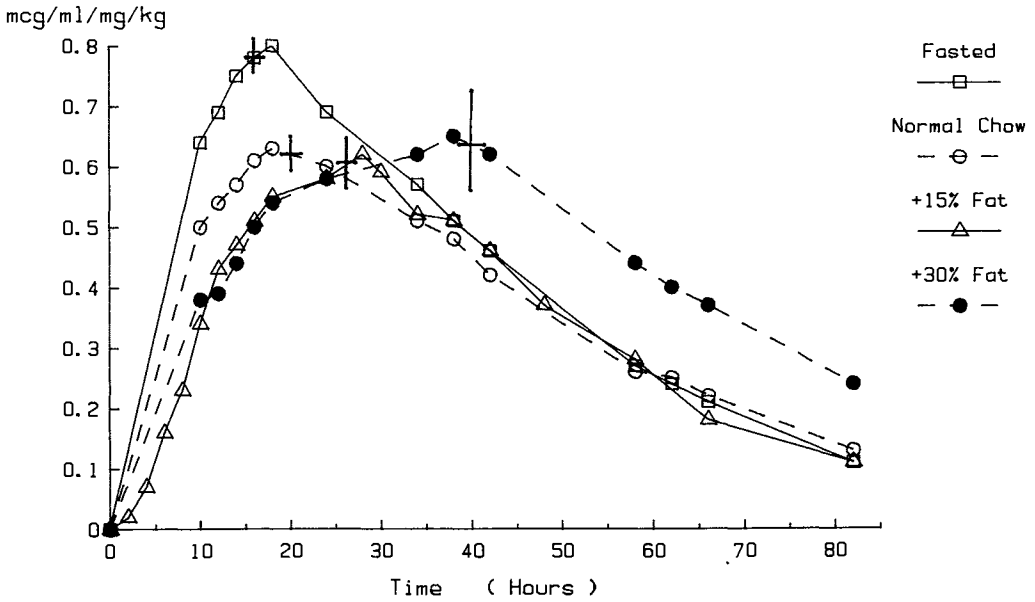

Fig. 2. The dose-normalized mean plasma concentrations versus time profiles after oral doses of the CR theophylline product following fasted (□), normal chow (○), +15% fat (△), and +30% fat (●) as described in the text.

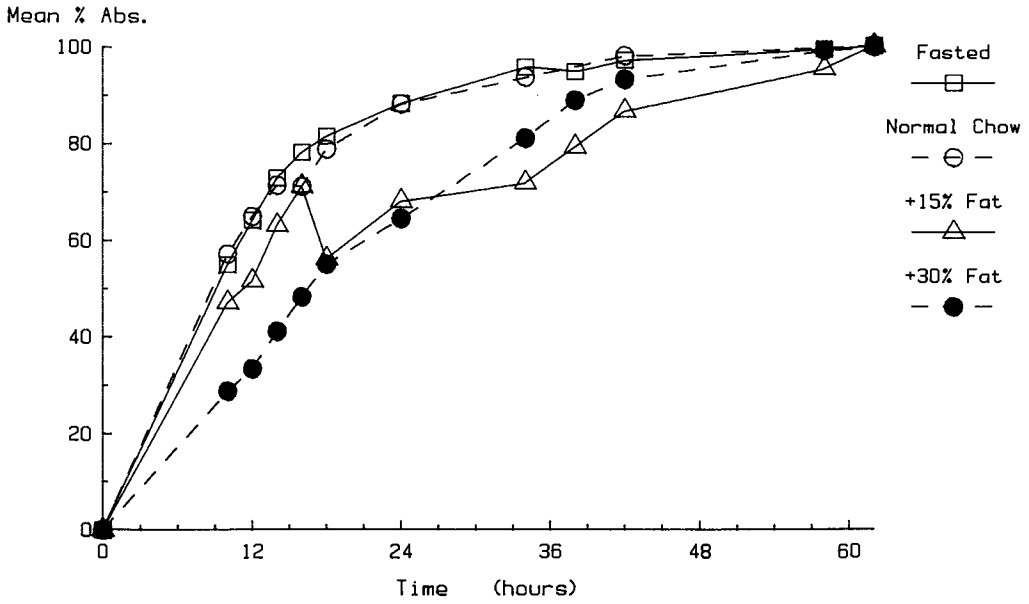

Fig. 3. The mean Theo-24 absorption profiles under fasted (□), normal chow (○), +15% fat (△), and +30% fat (●) as described in the text. Percentage absorbed calculated by Wagner–Nelson equation is shown on the vertical axis, and time in hours on the horizontal axis.

Plasma theophylline profiles following oral administration of the drug to fasted animals was reasonably described by a one-compartment open model with first-order absorption and elimination with lag time. The absorption plots (Wagner–Nelson) also indicated that absortion did not follow zero-order kinetics. From these results, the absorption of Theo-24 in mini-swine appears to be pseudo-first order, similar to the absorption from a bioavailability study in humans (14). The average absolute bioavailability of the test product following a single 400-mg dose to mini-swine was found to be approximately 81% (range, 64% to 105%) compared to an aminophylline i.v. dose under fasting conditions. The bioavailability of the CR theophylline in humans after fasted single oral doses was reported (14,15) to be 71% (range, 57 to 100%) compared to a solution which was assumed to be 100% bioavailable.

Similar terminal half-lives observed following CR theophylline oral and aminophylline i.v. dosage indicate that the first-order absorption process is not contributing (to any noticeable extent) to the terminal elimination rate constant. The mean absorption rate is about four times the elimination rate in five swine that were given 400 mg of the drug. Therefore, a flip-flop model, generally observed with ultraslow controlled-release products in humans, cannot be seen with plasma drug levels following oral doses in swine. In this aspect, the mini-swine model differs substantially from humans.

Food appears to delay the absorption of the test product compared to fasting conditions in this study. Although this is similar to what was reported with many other CR theophylline products in humans (6,16), the increase in C_{max} that was observed with the test product in humans (3,17) was not seen in this study.

The largest relative bioavailability values (138 and 144%) were observed with 15 and 30% fat food compared to fasting. However, due to the animal's intolerance to a high-lard diet and the large variability observed, it is difficult to determine accurately the food effect in the mini-swine.

The pharmacokinetics (terminal half-life, volume of distribution, absorption rates) of theophylline following an oral dose of theophylline capsules are noticeably different from those seen in humans. Only the nature (first order) and the extent of absorption are to some extent similar to those found in humans. Therefore, mini-swine may not be an ideal model to study the bioavailability of CR theophylline products.

Table III. Food Effects on Bioavailability of Theo-24 in Hormel-Hanford Mini-Swine

Food	Relative bioavailability, F' (%)[a]		
	Mean (range)	N	CV (%)
Normal chow	88.5 (60.5–109.4)	5	20.1
+15% fat	87.5 (66.6–137.9)	5	33.1
+30% fat	111.0 (78.0–143.5)	2	41.8

[a] Compared to the fasted condition.

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