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Bioavailability study of Theo-dur tablets in the fasted cannulated dog

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Summary

The present study uses the cannulated dog to verify the major elements of gastrointestinal (GI) motility affecting the performance of oral sustained release dosage forms. It appears that the residence time of a Theo-dur tablet in the fasted canine stomach and small intestine is dictated by the phasic activity of the motility pattern at the time of ingestion. The tablet does not disintegrate in vivo but undergoes surface erosion. Onset of tablet discharge corresponded with late phase II and phase III activity. The discharged eroded tablet was entrapped within mucus plugs. Mucus may play a significant role in the dissolution of administered tablets. There is little variability in the duodenal and ileal effluent pH, observed after onset of Theo-dur tablet discharge.

Introduction

In the past two decades there has been considerable interest in understanding how the GI tract processes sustained release dosage forms. Development of oral controlled release dosage forms is usually determined by the interplay of biological factors, physico-chemical properties of the drug, and composition and characteristics of the dosage form. Until relatively recently, the field of biopharmaceutics as a discipline has largely neglected direct experimental examination of those GI factors influencing performance of sustained release products, e.g. chemical and enzymatic degradation in the stomach and intestine, gastric emptying, small intestinal transit time, dispersion in the enteral canal, mucosal barriers and pH gradient.

With the recent increased interest in sustained release oral products there has been a renewed interest in the study of GI barriers to drug delivery. The interaction of the gastrointestinal tract with sustained release dosage forms is highly complex and dynamic and controlled, in part, by transit of the product through the stomach and intestine. It is now well documented that there are two modes of GI motility patterns, namely, digestive (fed) and interdigestive (fasted) in man and other animals that consume food on a discrete basis (Weisbrodt, 1981; Meyer, 1987). The motility pattern in the fasted state is commonly called

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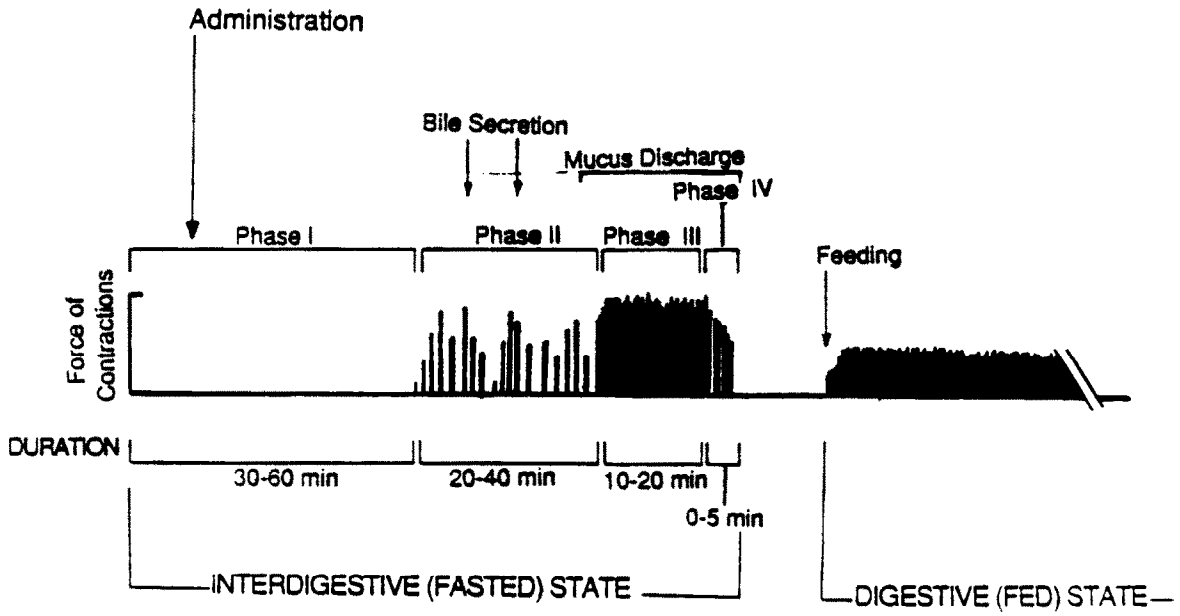

Fig. 1. A pictorial representation of typical motility patterns in the interdigestive (fasted) and digestive (fed) states.

the migrating myoelectric cycle (MMC). The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into three phases, namely, phase I–III (Fig. 1) (Code and Marlett, 1975). However, phase IV has been found only occasionally (Amidon and Oberle, 1987). In general, the cycle takes about 2 h for the wave to migrate from the stomach to the ileocecal junction. Since the primary function of phase III appears to be to clean the residual content of the stomach and intestine in the fasted state, it is also called the housekeeper wave.

In a previous study, it was shown that in the fasted dog, gastric emptying of large non-digestible solids (0.7–6.4 mm in diameter) appeared to be highly variable (10–120 min) and occurred primarily during phase III of the MMC (Gruber et al., 1987). When the test dosage form was administered immediately prior to phase II, variability of discharge decreased substantially. Thus, entry of large, single-unit drug delivery systems into the small intestine can be expected to be highly variable (Park et al., 1984; Li, 1987). Therefore, variability in stomach emptying rates over the course of the entire absorption process, following a single dose, would likely result in variable absorption rates, and thus, a somewhat complex plasma concentration-time profile (Kelly and Sarr, 1980; Amidon and Oberle, 1987).

Although there have been many reports of non-invasive radioisotope studies in humans to measure transit of dosage forms (Daly et al., 1982; Digenis, 1982), there are no direct experimental studies on processing of digestible solid dosage forms in the entire gastrointestinal tract. Using the cannulated dog model, one can not only measure the rate of movement of the dosage form as well as pH changes in the GI tract, but also simultaneously visualize and measure drug released in that segment together with the associated blood levels. The present study uses the fasted cannulated dog to obtain elements of the dissolution/absorption profiles of Theo-dur® tablet, a known zero-order release dosage form of theophylline, in the stomach and small intestine.

Materials and Methods

In vivo dissolution of Theo-dur was studied in four adult, female dogs of mixed breed, weighing 15–20 kg, prepared with permanent indwelling

duodenal and ileal cannulas (Li, 1987). The dogs were housed in a room with air and humidity control and a 12 h light/dark cycle.

Materials

Theo-dur® tablets (lot no. 623351) and anhydrous theophylline (lot no. 5B-186) were received as gifts (Schering Pharmaceuticals). Acetonitrile (UV grade, EM Science), methanol (UV grade, EM Science), and 8-chlorotheophylline (Sigma) were all purchased commercially. All chemicals were used as received.

Dog preparation

The surgical procedure employed was adapted from Reinke and Rosenbarum (1967). Two different modified Thomas cannulas (Rubinstein et al., 1988), were implanted in the duodenum and the ileum. The first cannula (with an oval flat surface) was inserted through a longitudinal cut approx. 15 cm from the pylorus on the side free of the mesenteric blood supply. The second cannula (with a cylindrical tubular T shape) was implanted around 10 cm proximal to the ileocecal junction by a 2 cm longitudinal cut. The animals were allowed 2 weeks to recover before initiating studies. Four dogs were trained to stand quietly, supported by a sling and to accept oral administration of solids. There was one dog with only an ileal cannula which allowed comparison of the transit time through the small intestine with that in the four dogs with two cannulae.

In vivo studies

Administration of Theo-dur tablet

Prior to each experiment, the dog was deprived of food, but not water, for 16 h. In the first study, each animal was injected intravenously (cephalic vein) over a 10–15 s period with 118 mg of aminophylline dihydrate (Aminophyllin injectable®, Searle Laboratories, Chicago, IL) equivalent to 93.1 mg of theophylline. Blood samples were collected at 0, 10, 15 and 30 min, then at 1, 2, 3, 4, 5, 6, 10, 12 and 18 h from a jugular catheter which had been placed into the cranial vena cava.

In the subsequent oral studies, at time zero of the experiment, which was approx. 10–20 min after cessation of mucus discharge (phase III) as judged by visual inspection of the discharge from the duodenal cannula, a Theo-dur tablet was orally administered by placing it on the back of the dog's tongue followed by normal swallowing. All tablets were given with 50 ml of normal saline. Either the duodenal or ileal cannula was then opened, depending on the purpose of the experiment; i.e., to study the region between the mouth and duodenum (M-D), the duodenal cannula was opened or to study the region between the duodenum and ileum (D-I) or the mouth and ileum (M-I), the ileal cannula was opened. To study in vivo dissolution of the Theo-dur tablet in the region between the duodenum and ileum (D-I), the tablet was inserted through the duodenal cannula 10 min after appearance of bile (phase II).

Blood samples (3–4 ml) from the cephalic or femoral vein were collected at 10, 15, 30 and 45 min post-dosing and then at 1, 2, 3, 4, 5, 6, 10 and 12 h following a single oral administration of a Theo-dur tablet. Clotting of blood samples was prevented by use of a Vacutainer tube which contained 143 USP units of sodium heparin. Blood samples were refrigerated immediately after collection, centrifuged within 30 min to separate the plasma, and theophylline was quantified using a high-performance liquid chromatography method.

Analysis of theophylline

The HPLC assay of theophylline was modified from Wenk and Eggs (1983) and 8-chlorotheophylline was used as an internal standard. Separation of theophylline was achieved with a C-18 reverse-phase column (Lichrosorb RP-18, Merck, F.R.G.). The plasma was extracted with 2 ml ethyl acetate and centrifuged for 15 min. The upper organic layer was evaporated to dryness in a water bath at 40 °C under a gentle stream of dry nitrogen. The residue was reconstituted in 250 μl of the mobile phase and vortexed for 1 min. The mobile phase was acetonitrile and methanol in 0.01 M sodium acetate buffer solution (1:1:8, by vol.). The pH of the mobile phase was adjusted to 4.0 with glacial acetic acid.

A flow rate of 1.5 ml/min was used to elute the sample. Theophylline and 8-chlorotheophylline

were detected at 274 nm with retention times of 3.5 and 6.0 min, respectively. Quantitation of theophylline can be performed in plasma by this method for as long as 24 h post-dosing with a single 200 mg tablet of theophylline (Wenk and Eggs, 1983).

Duodenum and ileum effluent collection

Effluent from the stomach and oral portion of the duodenum was collected through the duodenal cannula after administration of a tablet in the mouth to duodenum (M-D) study. In addition, effluent was obtained through the ileal cannula after administration of a tablet via the mouth (M-I) or the duodenum (D-I). Typically, effluent was collected for at least two MMC cycles and the pH and volume of each effluent sample were measured. Each study (M-D, D-I, M-I) was conducted on the four dogs with five experiments. Before administration of the test tablet, the pH values of the effluent at the duodenal and ileal cannulae were measured and mean values were found to be pH 6.7 (range 2.4–8.3), and 7.2 (range 6.5–8.0), respectively.

Methods

Intravenous study

Assuming a linear, one-compartment model (Wagner, 1986), the following pharmacokinetic parameters were calculated: (1) elimination rate constant, which represents the slope of the terminal serum concentration-time plot from the 1 h time point as determined by linear regression analysis; (2) area under the concentration time curve as calculated using the trapezoidal rule; (3) elimination half-life, $t_{1/2} = 0.693/K_e$.

Oral study

The input functions from each tablet were computed by means of a numerical deconvolution method (Langenbucher, 1982; Moller and Langenbucher, 1982; Malagelada et al., 1984; Iga et al., 1986) as represented by the expression:

$$I(t) = R(t)//W(t) \qquad (1)$$

where $R(t)$ denotes the response (plasma concentration) after tablet administration. $W(t)$ the unit response, or weighting function of the body system, as observed after intravenous dosing, and $I(t)$ the combined release/absorption-time input function. The deconvolution input function according to Eqn. 1 was computed by the point-area method (Vaughan and Dennis, 1978). A common time step of 0.5 h was chosen for analysing the plasma concentration data. The cumulative input function, i.e. the cumulative amount absorbed, was calculated by summation of $\Sigma I(t_n - t_{n-1})$. Instability in the calculation due to the generation of negative input values was minimized by replacing the calculated negative input value with zero (Iga et al., 1986).

Statistical analysis

Data are presented as mean ± S.E. Differences between the parameters were evaluated using Student's t-test for paired observations.

Results and Discussion

Mean plasma concentrations obtained after administration of an intravenous injection of theophylline are presented in Fig. 2. The intravenous study data ($K_e = 0.08 \pm 0.01$) are consistent with those of Wagner (1986) demonstrating the validity of a one-compartment model assumption for this study.

Gastric emptying and intestinal transit time

The onset of Theo-dur discharge from the stomach and intestine depends on the time of administration relative to phasic activity. When a test tablet was orally administered approx. 10 min after cessation of mucus discharge (phase III) or inserted approx. 10 min after the appearance of bile (phase II), the emptying and transit pattern of the tablet could be deduced. The results are shown in Table 1. Transit time ranges of the M-D, D-I, M-I, were 1.08–1.60, 1.41–2.50 and 2.50–3.60 h, respectively. Davis and Hardy (1986) found that the mean intestinal transit time of adult young men was 3 h with a 1 h standard deviation. In these studies, the small intestinal transit time was found to be between 1.41–2.5 h in the fasted dog.

TABLE 1

The onset of tablet discharge for mouth-duodenum (M-D), duodenum-ileum (D-I), and mouth-ileum (M-I) transit

Route	Onset of tablet discharge (h after administration)						
	1	2	3	4	5	Mean	SE
Mouth-duodenum (M-D)	1.60	1.50	1.08	1.41	1.20	1.36	0.09
Duodenum-ileum (D-I)	2.00	2.00	2.50	1.41	1.73	1.92	0.18
Mouth-ileum (M-I)	3.00	3.00	2.50	3.00	3.60	3.02	0.17
M-D + D-I	3.60	3.50	3.58	2.82	2.93	3.28	0.16
M-I without duodenal cannula [a]	3.10	4.00	2.48	–	3.50	3.27	0.32

[a] One dog without duodenal cannula as a test animal.

There was no significant difference in the transit time between M-I and M-D + D-I (t-test: $0.05 < P < 0.1$). The transit times in the dog without the duodenal cannula, i.e. only one cannula, compared with the dogs with two cannulae were similar (t-test: $P < 0.375$). These comparable results indicate that the transit times to the ileocecal junction are similar for the dog and man.

The implication of these studies is that whatever the formulation, once past the pylorus, a sustained release preparation has little time to release its active principle and be absorbed. It follows, therefore, that controlled drug release over 24 h can only be achieved in the fasted state if the dosage form containing the drug can remain in the stomach for an extended period of time or if significant absorption occurs around the ileocecal junction or in the colon.

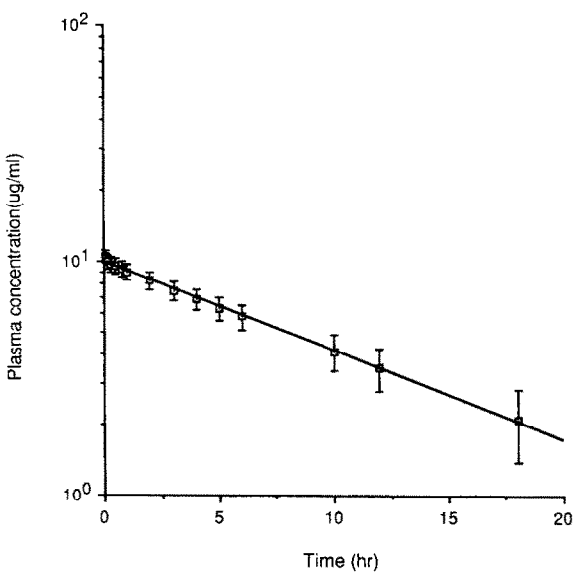

Fig. 2. Semi-logarithmic plot of averaged (mean ± S.E.) plasma concentrations of theophylline in four dogs for 18 h following intravenous injection.

Disintegration / dissolution of a Theo-dur tablet

Theo-dur tablets consist of sustained release pellets compressed within a matrix containing immediately available theophylline. In in vivo studies, the tablet surface was observed to erode slowly in the stomach and the pellets closest to the eroding surface were the first to become wet and be eroded (Fig. 3). As erosion continues, pellets deeper in the tablet matrix are exposed and come into play sequentially until tablet dissolution is completed. The residual tablet was collected from either the duodenal or ileal cannula. The discharged tablets were entrapped in gastric or intestinal mucin plugs (Fig. 4). Kearney and Marriott (1986) reported that mucus glycoprotein reduced the dissolution rate of tetracycline as compared to that in a simple medium. Due to the high viscosity of the mucin, which creates an additional diffusion layer, they suggested that mucus could be a potential absorption rate-limiting barrier.

Previous studies from this laboratory (Gruber et al., 1987), have demonstrated a strong interaction between administered particles and mucus. Indeed, the particles are emptied as a bolus during phase III because they are entrapped in mucus. While mucus may affect the hydrodynamics around a non-disintegrating tablet, it can have a significant influence on the dissolution rate as well as the distribution of pellets.

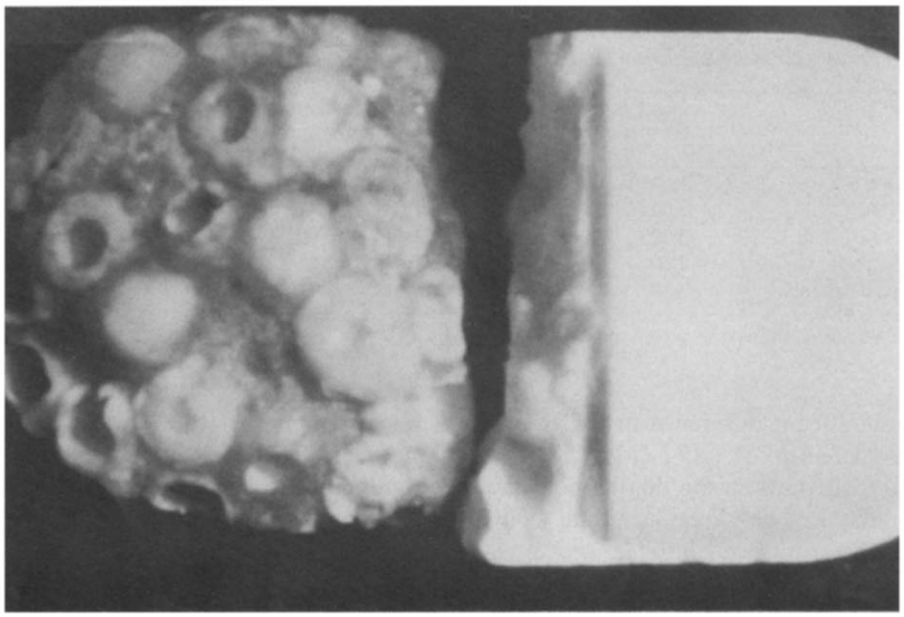

Fig. 3. Theo-dur tablet before duodenal administration (right) and after duodenal administration and ileal discharge (left) in the fasted dog.

Table 2 shows the percent recovery of the eroded tablet and the percent of dissolved tablet in the effluent which was collected from either the duodenal or ileal cannula. The mean recovery of eroded Theo-dur tablet was as follows: 63.6 ± 2.0, 58.8 ± 2, 45.7 ± 5.07% for the three different forms

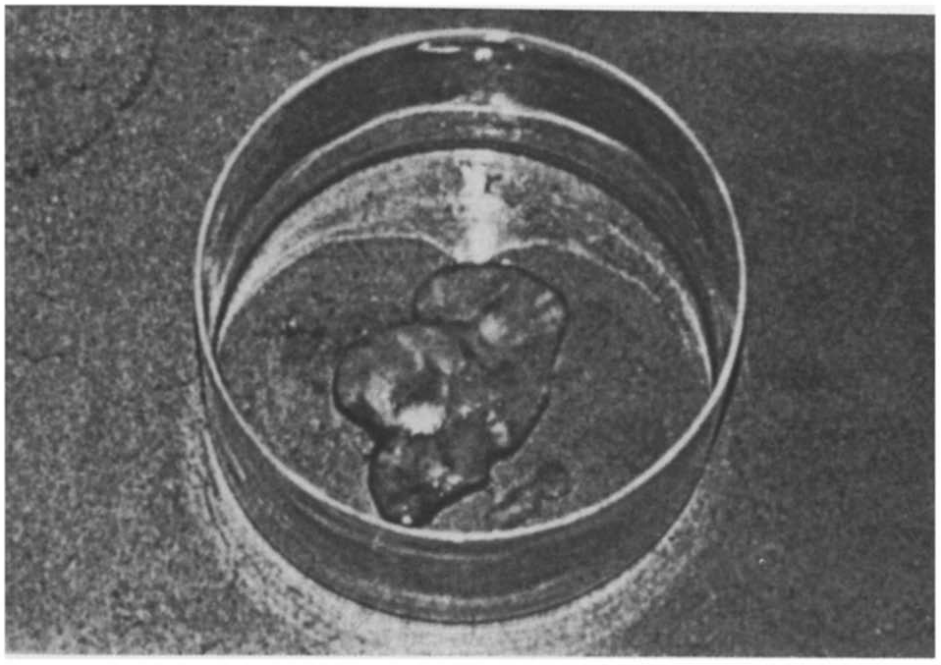

Fig. 4. Typical mucus plug, containing discharged particles collected from the duodenal cannula in the fasted dog.

TABLE 2

Recovery (mean ± S.E.) of theophylline from the eroded tablet, effluent and pH of effluent

	Mouth-duodenum (M-D)	Duodenum-ileum (D-I)	Mouth-ileum (M-I)
(1) % recovery of tablet	63.6 ± 2.0	58.8 ± 2.9	45.7 ± 5.0
(2) % recovered from effluent	2.0 ± 0.1	1.0 ± 0.1	1.2 ± 0.2
(3) pH of the effluent before administration of tablet	6.7 ± 0.5 (2.4–8.3) [a]	7.2 ± 0.4 (6.5–8.0)	7.2 ± 0.4 (6.5–8.0)
(4) pH of the effluent after administration of tablet	6.8 ± 0.4 (5.3–7.6) [a]	7.7 ± 0.2 (7.4 ± 8.2)	7.8 ± 0.2 (7.4–8.0)

[a] Ranges of the pH of effluent before and after administration of tablet.

of transit (M-D, D-I, M-I). There was no difference in the percent of dissolved drug in the effluent among the M-D, D-I, M-I studies (range 0.7–2.1%).

The effluent was collected before and after administration of the test tablet. Table 2 shows the mean pH of the effluent before and after tablet discharge in the case of dosing with 50 ml of normal saline. The pH of the effluent before administration was highly variable in the duodenal cannula (2.4–8.3) as compared with the ileal cannula (6.5–8.0). After tablet administration, the pH of the effluent was less variable in both the duodenal (5.3–7.6) and ileal cannula (7.4–8.2). There was no significant difference between the pH of the duodenal effluent (6.8 ± 0.4) and ileal effluent (7.7–7.8 ± 0.2) after tablet administration. The pH of the duodenal effluent was a little lower than the ileal effluent, probably due to gastric acid

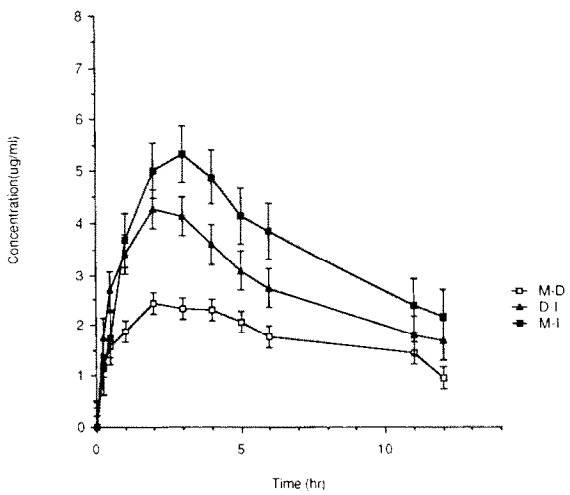

Fig. 5. Mean (±S.E.) plasma concentration of theophylline from a Theo-dur tablet obtained after recovery from the mouth-duodenum (M-D), duodenum-ileum (D-I) and mouth-ileum (M-I) in beagle dogs.

TABLE 3

Pharmacokinetic parameters (mean ± SE) of a Theo-dur tablet in the fasted dog following recovery from mouth-duodenum (M-D), duodenum-ileum (D-I) and mouth-ileum (M-I)

Parameters	Mouth-duodenum	Duodenum-ileum	Mouth-ileum
C_{max} ($\mu g\ ml^{-1}$) [a]	2.44 ± 0.41	4.64 ± 0.69	5.53 ± 0.49
T_{max} (h) [b]	2.20 ± 0.20	2.20 ± 0.37	2.80 ± 0.20
AUC ($\mu g\ h\ ml^{-1}$) [c]	35.73 ± 7.72	57.96 ± 8.10	68.16 ± 4.09
K_e (h^{-1}) [d]	0.07 ± 0.01	0.08 ± 0.01	0.09 ± 0.01

[a] Peak plasma concentration of theophylline (C_{max}) and the time to reach C_{max}. [b] T_{max} values (times to reach C_{max}) were determined by visual inspection. [c] AUC (area under the concentration vs time curve) was calculated using the trapezoidal rule, with extrapolation to infinity, by dividing the last experimental point by the linear terminal slope. [d] K_e (elimination rate constant) was calculated from the linear terminal slope.

TABLE 4

The mean fraction (SE) of cumulative Theo-dur tablet absorbed and the dissolution / absorption rate after recovery by mouth-duodenum (M-D), duodenum-ileum (D-I) and mouth-ileum (M-I): determined by a model-independent numerical deconvolution method

Time (h)	Mouth-duodenum (M-D)		Duodenum-ileum (D-I)		Mouth-ileum (M-I)	
	Input rate [a]	Cumulative [b]	Input rate	Cumulative	Input rate	Cumulative
0.5	0.32 ± 0.03	0.16 ± 0.02	0.49 ± 0.07	0.24 ± 0.03	0.35 ± 0.05	0.18 ± 0.03
1.0	0.07 ± 0.02	0.20 ± 0.03	0.21 ± 0.04	0.35 ± 0.05	0.41 ± 0.05	0.38 ± 0.01
1.5	0.07 ± 0.03	0.23 ± 0.04	0.15 ± 0.05	0.43 ± 0.07	0.24 ± 0.08	0.50 ± 0.03
2.0	0.06 ± 0.02	0.26 ± 0.04	0.09 ± 0.03	0.48 ± 0.08	0.24 ± 0.08	0.50 ± 0.03
2.5	0.01 ± 0.01	0.27 ± 0.04	0.04 ± 0.02	0.50 ± 0.09	0.11 ± 0.06	0.56 ± 0.08
3.0	0	0.27 ± 0.04	0.03 ± 0.02	0.52 ± 0.09	0.08 ± 0.02	0.60 ± 0.06
3.5	0	0.27 ± 0.04	0	0.52 ± 0.09	0.09 ± 0.03	0.65 ± 0.06
4.0	0	0.27 ± 0.04	0	0.52 ± 0.09	0.02 ± 0.01	0.65 ± 0.05
4.5	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05
5.0	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05
5.5	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05
6.0	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05
11	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05
12	0	0.27 ± 0.04	0	0.52 ± 0.09	0	0.65 ± 0.05

[a] Input rate denotes the rate of dissolution/absorption into the body determined by a deconvolution method. [b] Cumulative indicates the total amout of theophylline absorbed into the body as determined by a deconvolution method.

emptying from the stomach. There was no significant influence by the Theo-dur tablet on pH. However, whether other acidic or basic drugs will influence effluent pH is not known. Also, there is a difference between ingestion of small and large volumes due to a change from the fasted to the fed state. Gupta and Robinson (1986) showed that there is a difference in the pH of the duodenal effluent between ingestion of small (50 ml) and large volumes (500 ml) due to a change from the fasted (pH 6.4) to the fed state (pH 2.12). Therefore, the duration of residence of the tablet in the GI tract, the dissolution rate, and the properties of the drug will all influence the absorption profile.

In vivo release of theophylline from a Theo-dur tablet

Mean plasma concentration time profiles and the associated pharmacokinetic characteristics from the three different recovery routes are shown in Fig. 5 and Table 3. As shown in Fig. 5, considerable differences in serum concentration-time levels were observed between M-D and M-I or D-I studies. There was no significant difference between M-I and D-I mean plasma concentration-time profiles. The C_{max} values showed no difference between D-I (4.64 ± 0.69 μg/ml) and M-I (5.53 ± 0.49 μg/ml) (*t*-test: $P < 0.375$). The elimination rate constant (K_e) ranged from 0.07 to 0.09 (h^{-1}) with no difference between the three recovery routes. T_{max} was not significantly different between M-D and D-I ($P > 0.4$). Similar re-

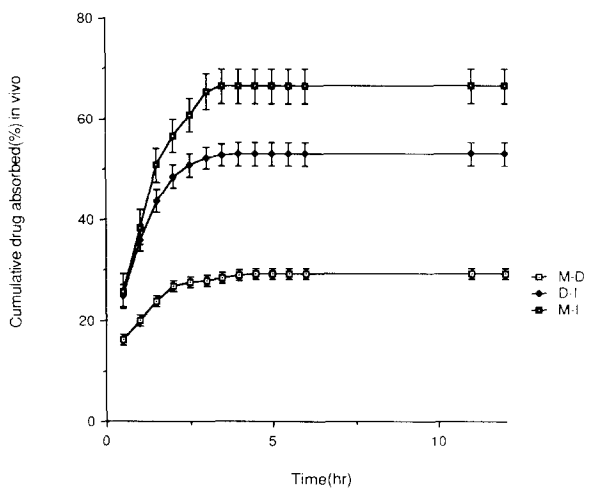

Fig. 6. Mean (± S.E.) cumulative percent drug absorbed in vivo after recovery from the mouth-duodenum (M-D), duodenum-ileum (D-I) and mouth-ileum (M-I) routes in beagle dogs.

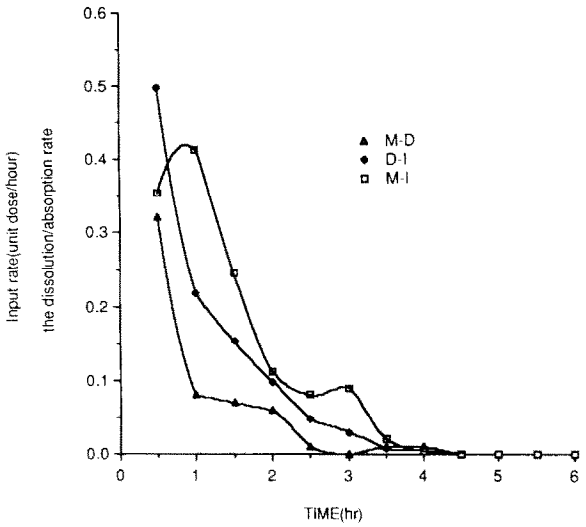

Fig. 7. Profile of the mean (±S.E.) input rate (dissolution/absorption rate) after recovery of Theo-dur tablets from the mouth-duodenum (M-D), duodenum-ileum (D-I) and mouth-ileum (M-I) routes.

sults were observed between M-I and M-D + D-I in the three parameters ($P < 0.375$).

Estimation of dissolution / absorption kinetics

A deconvolution method was used in estimating the in vivo dissolution/absorption rate of the Theo-dur tablet. In spite of its complexity in formulation and manufacture, Theo-dur has established a record of constant drug delivery (Shangraw, 1988), and the product is not substantially affected by food (Leeds et al., 1982; Pederson and Moeller-Petersen, 1984). This is attested to in the dog studies as shown in Table 4. The means of the cumulative percent absorbed after M-D, D-I and M-I administration are shown in Fig. 6. Most drug absorption ceased after 3 h. Cumulative drug absorptions from the M-I, D-I and M-D studies were 66.9 ± 6.54, 52.1 ± 9.01 and 28.5 ± 4.48%, respectively. Fig. 7 shows the dissolution/absorption rates in different regions of the GI tract for the three recovery routes. The dissolution/absorption rates for the M-D and D-I studies were high at 30 min and decreased sharply at first, then slowly declined between the first and second hour. During the first 30 min, the duodenum-ileal region showed a higher absorption rate compared with the mouth-duodenum. For the mouth-ileum study, during the first 1 h, the dissolution/absorption rate of the tablet increased and then decreased. During the next 2 and 3 h period, the rate of dissolution/absorption did not change appreciably for this study.

The intervals between drug administration and appearance of phase II and III motility patterns were about 20–40 and 30–60 min, respectively. After dissolution, the drug must diffuse to the luminal wall for absorption. In phase I, while dissolution takes place, diffusion of the drug is rather slow. In phase II, increased motility helps in rapid diffusion and subsequent absorption of the drug. It is possible that after mucus discharge during the end of phase II, the tablet or drug particle is entrapped in or coated with mucus. This may impede diffusion and dissolution of the drug which is manifested by a sharp decrease in input rate after this period.

The observed differences between the dissolution/absorption profiles for M-I and M-D are to be expected (Fig. 7). This is because for the M-D, the drug does not have a chance to dissolve and be absorbed from the small intestine. On the other hand, for the M-I study, the dosage form continues to move along the small intestine, resulting

TABLE 5

Total recovery (mean ± SE) of theophylline after recovery by M-D, D-I and M-I routes

	Mouth-duodenum	Duodenum-ileum	Mouth-ileum
% dissolved in the effluent	2.0±0.1	1.0±0.1	1.2±0.2
% recovered from eroded tablet (not dissolved) [a]	63.6±2.0	58.8±2.9	45.7±5.0
% absorbed into the body (in vivo absorption) [b]	28.5±4.4	52.1±9.0	66.9±6.5
% total recovery [c]	94.1±4.3	110.8±7.1	112.9±4.9

[a] The eroded tablet was collected via the cannula. [b] % absorbed into the body was calculated by the deconvolution method. [c] % total recovery represents the sum of the above 3 recoveries.

in further absorption. Since most of the absorption is expected to take place from the small intestine, it is not surprising to see that the peak arises after the dosage form has emptied from the stomach and travelled beyond the proximal duodenum. Since no gastric emptying process is involved in the D-I study, the resulting plasma levels are higher and peak at an earlier time.

Total recovery was calculated by summing the percent dissolved in the effluent, the percent recovery of the eroded tablet and the percent absorbed into the body (Table 5). Total recovery for M-D (94.1 ± 4.3) was a little lower than the D-I (110.8 ± 7.17) or M-I (112.9 ± 4.93). In conclusion the residence time of a Theo-dur tablet in the fasted canine stomach is dictated by the phasic activity of the motility pattern at the time of ingestion. Mucus may play a significant role in the dissolution of an administered tablet or, more significantly, pellets.

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