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GASTROINTESTINAL SITES OF FUROSEMIDE ABSORPTION IN RATS

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SUMMARY

The rate of absorption of [^{35}S]furosemide from the lumen of the gastrointestinal tract of rats, in situ, was studied by following the disappearance of radioactivity from the lumen and its appearance in plasma, urine, and bile. Absorption appeared to be most rapid and efficient in the stomach at pH 3.5 and least rapid and efficient in the jejunum at pH 5.4. To confirm these preliminary results, a fluorimetric assay was utilized to study furosemide disappearance from various segments of the rat gastrointestinal tract, in situ, at various pHs. The most rapid absorption was found to occur from the stomach at pH 3.0 ($t_{1/2}$ = 2.5 ± 0.3 h). Absorption was slower from the duodenum at pH 5.0 ($t_{1/2}$ = 3.1 ± 0.4 h); even slower from the duodenum + 30 cm of jejunum at pH 5.0 ($t_{1/2}$ = 11.7 ± 2.2 h). In intact rats the absorption process following gastric gavage in fasted animals was found to be biexponential, and the results were consistent with an absorption model in which rapid absorption occurs from the stomach and slower absorption occurs from the small intestine. Preliminary experiments in non-fasted intact rats suggested that oral absorption of furosemide with food in the stomach was slower but more complete than in the absence of food.

INTRODUCTION

Furosemide is a potent diuretic which is most often administered orally. It is a derivative of anthranilic acid, and contains a functional carboxyl group, with a pKa of 3.6 (Hajdu and Haussler, 1964). As a result, furosemide is highly ionized in the pH range of the duodenum and small intestine.

The oral absorption of furosemide has been studied in humans (Kelly et al., 1974; Preston et al., 1974; Beermann et al., 1975), and the results showed that the oral bio-

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availability of furosemide from solutions of sodium salts ranged from 20 to 60%. On the other hand, the absorption appeared to be very rapid, with peaks occurring in the blood level curves at or before 1 h, post-dose. These results suggest that oral absorption of furosemide in humans might be site limited.

The purposes of this study were (1) to determine the rates of absorption of furosemide at various pHs from various segments of the rat gastrointestinal tract, in situ, and (2) to study the influence of delayed stomach emptying, i.e. the presence of food in the stomach, on the oral absorption rate and total availability of furosemide in intact unanesthetized rats.

MATERIALS AND METHODS

Analytical procedures

The disappearance of [^{35}S]furosemide [1] from the gut lumen was followed by removing and counting 0.1 ml of samples of the lumen solution at appropriate time intervals. The total radioactivity in urine and bile samples was determined by weighing the entire sample and counting an aliquot. Plasma was separated from the blood samples and a 0.1 ml aliquot was counted.

All samples were counted after diluting them in 15 ml of a scintillation cocktail (2,5-diphenyloxazole [2], 4 g; 1,4-bis-2-(5-phenyloxazolyl)-benzene [2], 0.1 g; octyl phenoxy-polyethoxyethanol [2], 360 g; and toluene [2] to make 1000 ml).

Unlabeled furosemide was analyzed fluorometrically (Forrey et al., 1974) using an Amico–Bowman spectrophotofluorometer [3]. A separate standard curve was prepared for each experiment by extracting samples of buffer or plasma containing known concentrations of drug. Care was taken to expose all samples containing furosemide to a minimum amount of light.

Animals

Male Sprague-Dawley rats [4] weighing 200–250 g were kept under observation for 7–10 days. Food was withdrawn 16–20 h prior to the experiments, but water was allowed ad libitum.

In situ procedures

[^{35}S]Furosemide solutions were prepared either in citrate–phosphate buffer [5] at pH 3.5 (furosemide concentration 10 μg/ml; 0.01 μCi/ml) or Sorensen's buffer [5] at pH 5.4 (furosemide concentration 20 μg/ml; 0.01 μCi/ml). The solutions were made isotonic (300 mOsm/kg) with sodium chloride, and the osmolarity verified with an osmometer [6].

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[1] Farbwerke Hoechst Ag., 623 Frankfurt, G.F.R.

[2] Scintillation Grade, Research Products International Corp., 2692 Delta Lane, Elk Grove Village, Ill. 60007, U.S.A.

[3] American Instrument Company, Inc., Silver Spring, Md., U.S.A.

[4] Charles Rivers, 251 Ballardville St., Wilmington, Mass. 01887, U.S.A.

[5] Scientific Tables, Published by Ciba-Geigy, Ltd., Basle, Switzerland, 1971.

[6] Wescor, Inc., Model 5210, 459 South Main St., Logan, Utah 84321, U.S.A.

Furosemide [7] solutions analyzed fluorometrically, were prepared either in citrate–phosphate buffer [5] at pH 3.0 (initial concentration 9.92 μg/ml) or Sorensen's buffer [5] at pH 5.0 (initial concentration 400 μg/ml). The solutions were made isotonic (300 mOsm/kg) with sodium chloride, and the osmolarity was verified with an osmometer [6].

The rats were anesthetized with ketamine HCl [8] and pentobarbital [9], as described previously (Chungi et al., 1978). The various segments of the rat intestinal tract as well as the stomach were isolated and cannulated as reported previously (Doluisio et al., 1969). During all the in situ experiments the bile duct was cannulated, and bile was collected. The drug solution was instilled into the lumen of the gastrointestinal segment, and 0.1 ml samples of the lumen solution were taken for analysis at appropriate time intervals. Blood samples (approximately 0.2 ml) were collected through a jugular cannula into small heparinized centrifuge tubes. At the end of the experiments the animals were sacrificed and urine was collected from the urinary bladder with a hyperdermic syringe. All samples were protected from light during collection and preparation for analysis.

Studies in intact rats

Intravenous administration. Rats were fasted for 12–16 h prior to the experiment, but water was allowed ad libitum. The rats were anesthetized with ketamine and pentobarbital, and the jugular vein was exposed and cannulated using silastic tubing [10]. The exposed area was closed using a surgical suture [11]. Intravenous doses of 5mg/kg of furosemide dissolved in 0.5 ml of normal saline were administered through the cannula and washed in with 0.5 ml of saline. Blood specimens (0.2 ml) were taken from the cannula at specified time intervals and transferred to small heparinized centrifuge tubes. The samples were centrifuged, and the plasma was separated and stored in the dark in a freezer until analyzed.

Oral administration. Rats were surgically prepared 24 h before drug administration by cannulating the jugular vein as described above and bringing the tubing out on the dorsal side of the neck where it terminated in a standard hypodermic hub. This procedure permitted blood samples (0.2 ml each) to be drawn while the rat was awake and moving about. Following surgical preparation, the rats were fasted overnight, and 15 mg/kg doses of furosemide dissolved in 1 ml of 0.1 M phosphate buffer at pH 7.0 were administered orally. The rats were allowed to eat 4 h following drug administration. The plasma samples were analyzed as described above.

To study the effect of food on the oral absorption of furosemide, the rats were surgically prepared as described above, and food was withdrawn 8–12 h prior to the experiment. Just before oral dosing, a weighed amount (1–1.5 g) of food pellets was given to the rats, which they consumed in about 15 min. Blood was drawn at specified time intervals, and plasma was analyzed as described above.

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[7] Hoechst-Roussel Pharmaceuticals, Inc., Rt 202–206 North, Somerville, N.J. 08876, U.S.A.
[8] Ketaject, Bristol Labs., Syracuse, N.Y. 13201, U.S.A.
[9] Nembutal Sodium Solution, Abbott Labs., North Chicago, Ill. 60064, U.S.A.
[10] Dow Corning Corporation, Medical Products Division, Midland, Mich. 48640, U.S.A.
[11] Ethicon, Inc., Sommerville, N.J. 08876, U.S.A.

RESULTS AND DISCUSSION

Fig. 1 shows semi-logarithmic plots of percent of the initial amount of [^{35}S]furosemide remaining unabsorbed versus time in two segments of the rat gastrointestinal tract at two pHs. The rate of absorption of furosemide from the stomach at pH 3.5 and pH 5.4 and the jejunum at pH 5.4 showed significant statistical differences, $F = 139.37$ following an analysis of variance procedure (Barr et al., 1976). A Duncan's multiple range test ($\alpha = 0.05$) (Barr et al., 1976) showed that the rate of absorption was fastest from the stomach at pH 3.5 ($t_{1/2} = 2.0 \pm 0.15$ h); slower from the stomach at pH 5.4 ($t_{1/2} = 3.6 \pm 0.44$ h); and slowest from the jejunum at pH 5.4 ($t_{1/2} = 12.6 \pm 3$ h). These results suggest that the gastrointestinal absorption of furosemide is highly pH dependent, and in the intact animal, a significant amount of furosemide may be absorbed from the stomach.

The appearance of total radioactivity in the plasma, urine, and bile of rats following instillation of [^{35}S]furosemide solutions into various segments of the gastrointestinal lumen is shown in Fig. 2. The results confirm that disappearance of [^{35}S]furosemide from the gastrointestinal lumen reflects appearance in the systemic circulation and that absorption is highly pH dependent, since higher plasma concentrations were produced and a greater amount of total radioactivity was recovered in urine and bile at pH 3.5 than at pH 5.4 in the stomach.

Fig. 2 also shows plasma, urine, and bile data following instillation of a [^{35}S]-furosemide solution (pH 5.4) into the duodenum (from the pyloric sphincter to the ligament of Trietz) and into the jejunum (30 cm beginning at the ligament of Trietz). The results show that the rate of absorption of [^{35}S]furosemide is less from the duodenum than from the stomach and less from the jejunum than from the duodenum at a comparable pH.

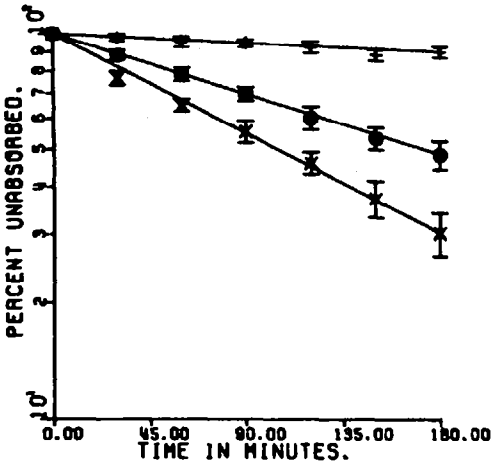


Fig. 1. Disappearance of radioactivity, expressed as percent of initial amount of [^{35}S]furosemide, from the lumen of the GI tract of rats in situ. x, stomach at pH 3.5, initial concentration 10 μg/ml; •, stomach at pH 5.4; and +, 30 cm segment of jejunum at pH 5.4, initial concentration 20 μg/ml, (n = 3).

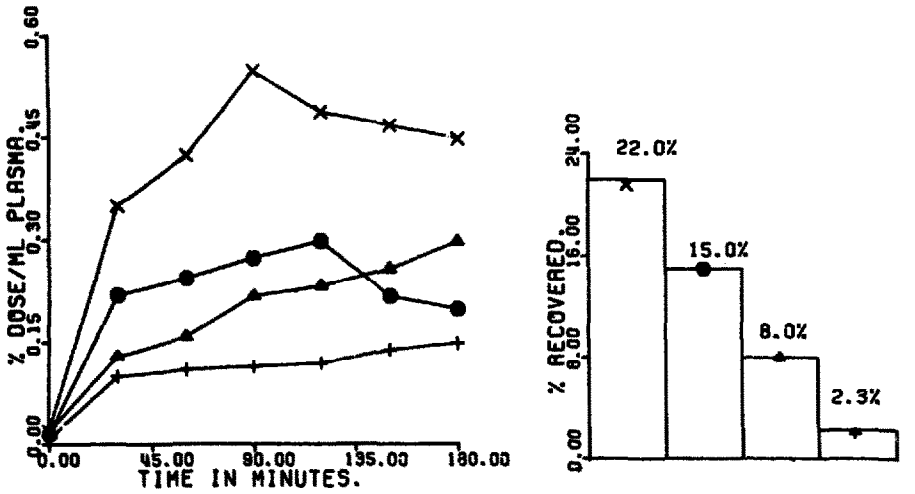


Fig. 2. Appearance of radioactivity expressed as percent of dose per ml of plasma (lines) or percent of dose recovered in urine + bile (bar graphs) following instillation of [^{35}S]furosemide into the lumen of the GI tract of rats in situ. X, stomach at pH 3.5 (n = 2); •, stomach at pH 5.2 (n = 2); ▲, duodenum at pH 5.4 (n = 2); and +, 30 cm segment of jejunum at pH 5.4 (n = 1).

These preliminary observations suggest that the efficiency of gastrointestinal absorption of furosemide in the rat is greatest in the stomach at low pHs and decreases rapidly at sites beyond the stomach, as the pH rises. These results are consistent with the observation that oral absorption of furosemide in humans appears to be site-limited. Limitations on the supply of [^{35}S]furosemide did not allow further radioactive experiments to be carried out, and a fluorimetric assay (Forrey et al., 1974) was used for the following studies.

Fig. 3 shows semi-logarithmic plots of percent of the initial amount of furosemide remaining unabsorbed versus time in four segments of the gastrointestinal tract of rats in situ. The rate constant for the loss from the lumen of the four segments were submitted to analysis of variance and were found to be significantly different, $F = 70.29$. Using Duncan's multiple range test ($\alpha = 0.05$) absorption of furosemide is fastest from the stomach ($t_{1/2} = 2.5 \pm 0.3$ h), slower from the duodenal segment ($t_{1/2} = 3.1 \pm 0.4$ h), even slower from the duodenum plus 30 cm of the jejunum ($t_{1/2} = 4.7 \pm 0.7$ h), and slowest from the initial 30 cm segment of the jejunum ($t_{1/2} = 11.7 \pm 2.2$ h).

These results are identical to the preliminary observations made with [^{35}S]furosemide and are consistent with selective absorption of unionized furosemide. A similar observation was made by Deetjen (1966) with regard to diffusion of unionized [^{35}S]furosemide across the kidney tubular epithelium of rats. On the other hand, it is somewhat surprising to find that furosemide is more rapidly absorbed from the rat stomach than from the small intestine even at favorably low pHs because of the vast difference in the membrane surface area of these two regions.

If it is indeed true that absorption of furosemide from the stomach is more efficient than from the small intestine, experimental factors which alter gastric pH and stomach emptying time should affect the oral absorption of furosemide. The presence of food in

the stomach increases gastric pH and can delay stomach emptying (Bates and Gibaldi, 1970). Therefore, the effect of food on the oral absorption of furosemide was investigated in intact rats.

To calculate the rate and extent of oral absorption of furosemide in intact rats, it was first necessary to study the pharmacokinetics of the drug following intravenous administration. Fig. 4 shows a semi-logarithmic plot of four-animal average plasma concentrations of furosemide following intravenous administration. The data was fitted to the following bi-exponential equation using the SAAM 23 program of Berman and Weiss (1966) and an IBM 370/65 computer:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C_p = plasma concentration in μg/ml; A = 133.2 ± 7.64 μg/ml; B = 47.1 ± 3.14 μg/ml; α = 0.111 ± 0.0076 min^{-1}; β = 0.0198 ± 0.0025 min^{-1}; and t = time in minutes. Values for each individual animal's coefficients and exponents are shown in Table 1 along with values for the total areas under the plasma concentration–time curves. The half-life corresponding to overall elimination of furosemide calculated from the four-animal average β value was 35.7 min, which is in close agreement with the value previously reported by Wallin et al. (1976).

Plasma concentrations vs time following oral administration of furosemide solution, pH 7.0, to fasted rats are shown in Table 2. The kinetics of the oral absorption process were determined by the method of Loo and Riegelman (1968) for extravascular administration of a drug showing two-compartment pharmacokinetics. The following intercompartmental rate constants, calculated from the coefficients and exponents from the averaged

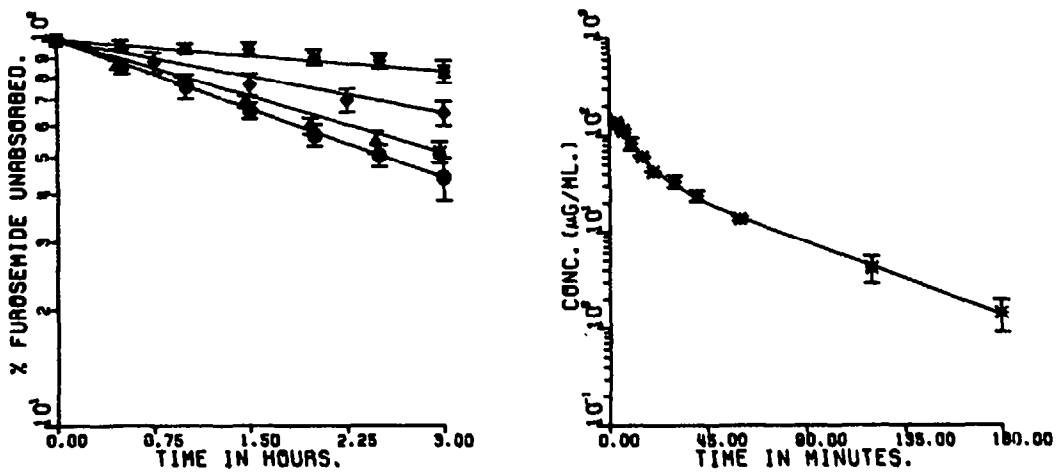


Fig. 3. Disappearance of furosemide (fluorimetric assay) from the lumen of the GI tract of rats in situ. ●, stomach, pH 3.0; ▲, duodenum, pH 5.0; ◆, duodenum + 30 cm of jejunum, pH 5.0; and ■, 30 cm segment of jejunum, pH 5.0 (n = 4).

Fig. 4. Semi-logarithmic plot of plasma concentrations (±S.D.) versus time following an intravenous dose 5 mg/kg of furosemide (n = 4).

TABLE 1

PHARMACOKINETIC PARAMETERS FOR FUROSEMIDE IN RATS

(Dose 5 mg/kg i.v.)

Rat no.	A (μg/ml)	B (μg/ml)	α (min^{-1})	β (min^{-1})	AUC [c] (μg/ml h)	AUC [d] (μg/ml h)
1	139.1	44.4	0.103	0.0175	55.3	64.78
2	140.5	45.7	0.108	0.0181	56.9	63.76
3	126.5	46.7	0.111	0.0214	58.2	55.36
4	126.7	51.6	0.121	0.0225	57.5	55.61
Mean [a]	133.2 ± 7.64	47.1 ± 3.14	0.111 ± 0.0076	0.0198 ± 0.0025	57.0 ± 1.24	59.8 ± 4.4
Average [b]	129.3	45.2	0.105	0.0194	59.35	62.13

[a] Mean ± S.D. of individual rat parameters.

[b] Parameters calculated from four-animal averaged plasma concentrations vs time.

[c] AUC calculated using trapizoidal rule.

[d] Using equation $AUC = A/\alpha + B/\beta$.

TABLE 2

PLASMA CONCENTRATIONS AND AUC AFTER ORAL ADMINISTRATION OF FUROSEMIDE IN FASTED AND UNFASTED INTACT RATS

(Dose 15 mg/kg)

Fasted rats				Unfasted rats			
Time (h)	Plasma concentration (μg/ml)			Time (h)	Plasma concentration (μg/ml)		
	Rat 7	Rat 8	Rat 9		Rat 10	Rat 11	Rat 12
0.25	5.45	3.4	4.1	0.5	1.8	1.5	1.02
0.33	–	6.6	6.05	0.75	3.0	1.83	2.46
0.50	7.45	7.7	10.65	1.0	4.12	2.32	3.12
0.67	–	8.65	12.8	1.5	4.87	2.78	3.56
1.0	8.2	11.4	14.1	2.0	6.44	3.01	4.85
1.25	–	8.0	16.2	4.0	7.36	4.5	4.41
1.5	6.1	6.0	11.1	8.0	3.8	2.28	2.67
2.0	4.3	3.25	9.0	12.0	2.72	1.44	1.02
3.5	2.85	–	–				
4.0	–	4.0	4.42	Area under the curve (μg/ml × h)			
6.0	2.05	–	–				
8.0	0.98	0.67	1.85		61.93	39.75	38.33
12.0	0.465	0.445	0.73	Average = 46 ± 13			
Area under the curve (μg/ml × h)							
	29.95	26.36	56.54				
Average = 38 ± 16							

parameters following intravenous administration (Table 1), were used in the calculation: $k_{12} = 0.0338\ min^{-1}$; $k_{21} = 0.0416\ min^{-1}$, $k_{e1} = 0.049\ min^{-1}$; $V_p = 0.036$ liters/kg.

Fig. 5 shows the results of the Loo–Riegelman calculations for rat in terms of a semilogarithmic plot of the percent remaining to be absorbed versus time. This plot appears to be biexponential, suggesting that oral absorption of furosemide in intact rats takes place by at least two processes with significantly different rates. The absorption process can be described in terms of the following biexponential equation:

$$\text{fraction remaining to be absorbed} = A'e^{-\alpha' t} + B'e^{-\beta' t} \quad (2)$$

where A' = percent absorbed by the rapid process; B' = percent absorbed by the slower process; α' = rate constant for the rapid process; and β' = rate constant for the slower process.

The data shown in Table 2 were fitted to a pharmacokinetic model in which the intercompartmental rate constants were fixed at the values calculated from the averaged intravenous parameters (see above) and the absorption process was described by Eqn. 2. The fitting was accomplished using the SAAM-23 program (Berman and Weiss, 1966) and an IBM 370-65 computer. The best estimates of the parameters describing the absorption

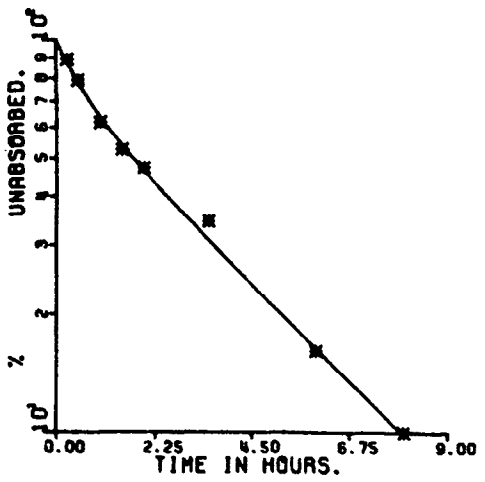


Fig. 5. Semi-logarithmic plot of percent remaining to be absorbed versus time following oral administration of furosemide (15 mg/kg) in solution (pH 7.0) to fasted intact unanesthetized rats. Experimental data points (*) are observed values for a single rat. The solid line is a computer generated curve based on Eqn. 2 (n = 1).

process for individual rats are shown in Table 3. Fig. 6 is a typical plot showing the data for the fasted rat 7. The solid line in Fig. 6 is a computer generated curve representing theoretical plasma concentrations given by the pharmacokinetic model in which the absorption process is described by Eqn. 2.

Although the solid line in Fig. 6 fits the data points rather well, a model in which oral absorption occurs by two completely independent processes (as suggested by Eqn. 2) is not easily explained physiologically. Alternative models are: (1) absorption occurs at distinctly different rates from two or more sites in the GI tract; (2) absorption begins at a rapid rate but slows down considerably as it proceeds, perhaps because the drug changes the permeability of the GI membrane barrier; or (3) rapid absorption occurs with the drug solution, but the drug subsequently precipitates and absorption becomes dissolution rate limited.

Since the preliminary experiments in the in situ rat gut suggested that there was a great difference between the stomach and the small intestine with regard to rate of absorption

TABLE 3

VALUES OF THE PARAMETERS IN EQUATION 2

Rat no.	A' %	B' %	α' min^{-1}	β' min^{-1}
7	24.54	75.45	0.0248	0.00351
8	58.21	41.79	0.0163	0.00252
9	36.30	63.7	0.0152	0.00266

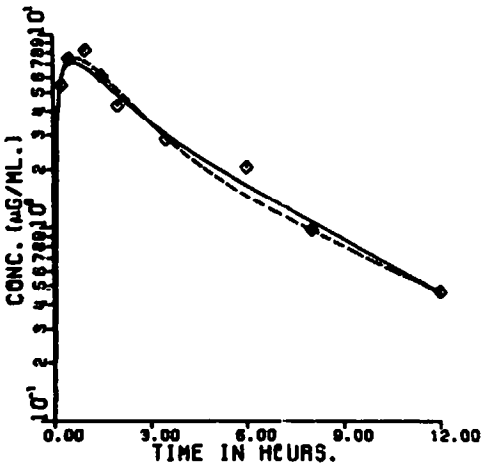
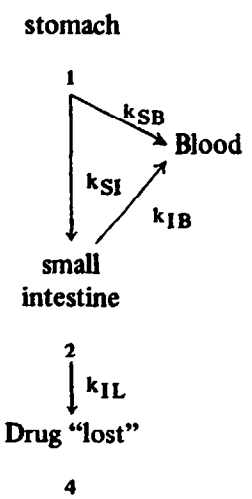


Fig. 6. Semi-logarithmic plot of plasma concentration versus time following oral administration of furosemide (15 mg/kg) in solution (pH 7.0) to a single fasted rat. The data points (◇) are experimentally observed values. The solid line is a computer generated curve with the absorption process described by Eqn. 2. The dashed line is a computer generated curve with the absorption process described by Scheme 1 (n = 1).

of furosemide, the following absorption model was investigated:



Scheme 1.

In this model, furosemide introduced into the stomach is partially absorbed by a rapid process (k_{SB}) and partially emptied into the small intestine (k_{SI}). Furosemide absorption also occurs from the small intestine, but at a slower rate (k_{IB}) than from the stomach. Finally, some furosemide is 'lost' by passage down the GI tract (k_{IL}) to sites where little or no absorption occurs.

Explicit values for the rate constants of Scheme I can be calculated from the coefficients and exponents of Eqn. 2 using a set of integrated equations describing the amount in each compartment of Scheme 1 derived by LaPlace transformation (Wagner, 1975).

The following values were calculated for the data shown in Fig. 6; $k_{SI} = 0.010\ min^{-1}$; $k_{SB} = 0.00812\ min^{-1}$; $k_{IB} = 0.00275\ min^{-1}$; $k_{IL} = 0.00030\ min^{-1}$. These values, plus the intercompartmental rate constants previously calculated from the averaged i.v. data, were used to generate the dashed line shown in Fig. 6. In this simulation, all rate constants were fixed at the values indicated above, and Fig. 6 shows that the theoretical line fits the experimental data points rather well. Similar agreement was obtained with the data from two additional rats.

As indicated above, Scheme 1 is not the only model that describes furosemide oral absorption in intact rats, but it does represent a plausible explanation for the apparent biexponential nature of the absorption process.

Scheme 1 suggests the efficiency of oral absorption of furosemide would increase if the drug were retained in the stomach for a longer period of time. The presence of food in the stomach delays stomach emptying which would favor furosemide absorption. However, it also increases the stomach pH which would decrease the rate of furosemide absorption. Therefore it would be expected that absorption of furosemide would be slower but with a greater extent of absorption when administered after a meal. The influence of food was studied in intact rats which were fasted overnight then given a fixed amount of food prior to oral administration of furosemide solution. The results shown in Fig. 7 suggest that the oral absorption process is slower than in fasted rats, evident from the increase in time required to attain maximum plasma concentration. But a greater fraction of the dose is absorbed when food is present as indicated by AUC calculations (Table 2). The difference in fraction of the dose absorbed in fasted and non-fasted rats is not statistically significant, but a trend towards more efficient absorption in the presence of food is evident.

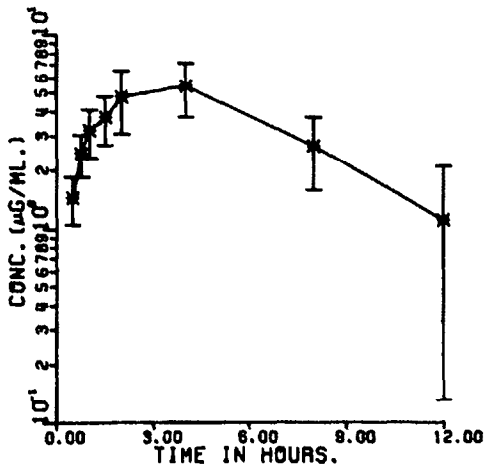


Fig. 7. Semi-logarithmic plot of plasma concentrations (±S.D.) versus time following oral administration of furosemide (15 mg/kg) in solution (pH 7.0) to unfasted rats (n = 3).

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