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Gastrointestinal First-pass Effect of Furosemide in Rats

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Abstract

The first-pass effect of furosemide was investigated in rats. Furosemide intravenous solution (20 mg kg^{-1} Lasix), was administered via the jugular vein and the portal vein, orally, and instilled directly into the duodenum of rats. The first-pass effects of furosemide by lung, heart, and liver seemed to be negligible in rats. The absolute bioavailability of furosemide was 28·9 and 48·3% after oral and intraduodenal administration, respectively. Based on the gastrointestinal (GI) recovery study, 68·3 and 69·5% of furosemide were found to have disappeared mainly due to absorption and/or metabolism from rat GI tract after oral and intraduodenal administration, respectively.

The results indicate that gastrointestinal and intestinal first-pass effects of furosemide were approximately 40% (68·3–28·9%) and 20% (69·5–48·3%) of the dose, respectively.

Furosemide, a loop diuretic, was reported to have a low and variable extent of absolute oral bioavailability (F) in man; the F values in healthy subjects (Smith et al 1980) and patients with various diseases (Brater et al 1982; Fredrick et al 1991; Martin et al 1995), ranged from 11 to 84% with a mean value of approximately 40%. Potential causes for the incomplete and highly variable F values of furosemide in man have previously been studied using rats as a model (Lee & Chiou 1983); the F value was approximately 30%, the maximum hepatic first-pass effect was estimated to be approximately 10%, and approximately 39% of the oral dose was not absorbed from gastrointestinal (GI) tract (approx. 61% of the oral dose was absorbed and/or metabolized) after a 120-fold (0·05–6 mg) dose range after oral administration. These data suggested that approximately 20–30% of an oral dose could be metabolized in the rat GI wall during absorption (Lee & Chiou 1983). But the exact first-pass organs and extent of first-pass effect of furosemide has not reported to the best of our knowledge in rats.

The aim of this study was to report the first-pass organs and the extent of the first-pass effect of furosemide after intravenous, intraportal, oral, and intraduodenal administration of 20 mg kg^{-1} furosemide (Lasix) to rats.

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Materials and Methods

Chemicals

Furosemide intravenous solution (Lasix), as a sodium salt (10 mg mL^{-1}; 2 mL ampule) was kindly donated by Han Dok Pharmaceutical Company (Seoul, Korea), and one of its metabolites, 4-chloro-5-sulphamoyl anthranilic acid (CSA) was purchased from U.S. Pharmacopoeia (Rockville, MD). β-Glucuronidase was obtained from Sigma Chemical Co. (St Louis, MO). Other chemicals were of reagent grade or HPLC grade and were used without further purification.

Animals

Male Sprague–Dawley rats, 255–325 g, were purchased from Charles River Company (Atsugi, Japan). The rats were housed in a clean room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University) and had free access to food (Samyang Company, Seoul, Korea) and water. The protocol for this animal study was approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University.

Measurement of hepatic first-pass effect of furosemide

In the morning, the jugular vein and the carotid artery of each rat were catheterized with poly-

ethylene tubing (Clay Adams, Parsippany, NJ) under light ether anesthesia. Both cannulae were exteriorized to the dorsal side of the neck and terminated with a long Silastic tube (Dow Corning, Midland, MI). At the same time, the portal vein was also cannulated (Kim et al 1997) by the modified Suzuki method (Xu et al 1992). After a midline abdominal incision, the middle portion of the portal vein was isolated, and the tapered end of a 23-gauge needle, bent at angle of 60°, was inserted into the pyloric vein, the tributary flowing directly into the portal vein (to minimize the impairment of blood flow
in the portal vein). Bleeding was prevented by applying epoxy glue (Krazy Glue; Krazy Glue Inc., Itasca, IL). A 5-cm piece of the Silastic tube was attached to the other end of the needle which linked with the dorsal side cannula of the neck. All three Silastic tubes were covered with a wire coil to allow free movement of the rats. The exposed areas, the neck and abdomen, were closed using surgical suture. Each rat was housed individually in a rat metabolic cage (Daejong Scientific Company, Seoul, Korea) and allowed 2–3 h to recover from anaesthesia.

Lasix (20 mg kg^{-1}) was infused over 1 min via the jugular vein for the intravenous study (n = 4), and via the portal vein for the intraportal study (n = 5). The total injection volume was approximately 0·6 mL. At the same time, the same volume (0·6 mL) of 0·9% NaCl injectable solution was also infused over 1 min via the portal vein for the intravenous study and via the jugular vein for the intraportal study. Blood samples (0·12 mL) were collected via the carotid artery at 0 (control), 1 (at the end of the infusion), 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min after administration of Lasix. Blood samples were centrifuged immediately to minimize the blood storage effect of furosemide (the change in plasma concentration of furosemide due to time elapsed between collection and centrifugation of the blood sample) (Lee et al 1981). A 0·05-mL sample of plasma sample was kept at −20°C freezer until HPLC analysis of furosemide (Lee & Chiou 1983). Heparinized 0·9% NaCl injectable solution (20 units mL^{-1}; 0·3 mL), was used to flush each cannula immediately after each blood sampling to prevent blood clotting. It has been reported (Li et al 1986) that the pharmacokinetic and pharmacodynamic parameters of furosemide were dependent on the rate and composition of fluid replacement. Therefore, the loss of fluids and electrolytes in urine induced by furosemide was immediately replaced v/v by intravenous infusion of lactated Ringers solution (Dai-Han Pharmaceutical Company, Seoul, Korea) via the carotid artery for up to 8 h after dosing. Urine was collected between 0–8 and 8–24 h after administration of Lasix. Each metabolic cage was rinsed with 15 mL distilled water at the end of 8 and 24 h, and the rinsings were combined with the 0–8 and 8–24 h urine samples. After measuring the exact volume of each combined urine sample, 0·05 mL of the each combined urine sample was stored in the freezer until HPLC analysis of furosemide (Lee & Chiou 1983) and CSA (Smith et al 1980). A 0·5 mL fraction of the combined 8-h urine sample was also added to 1 mL Sørensens phosphate buffer (pH 7·4) containing 10 000 units of β-glucuronidase, and the mixture was incubated for 24 h in a water-bath shaker (37°C, 50 oscillations min^{-1}). At the end of 24 h, the entire GI tract (including contents and faeces) was removed, transferred into a beaker containing 0·01 M NaOH (to facilitate the extraction of furosemide), and cut into small pieces with scissors. After shaking manually and stirring with a glass rod for 10 min, 0·05 mL of the supernatant was collected from each beaker and stored in the freezer until HPLC analysis of furosemide (Lee & Chiou 1983) and CSA (Smith et al 1980). All biological samples were protected from light (Kerremans et al 1982; Moore & Sithipitaks 1982).

Measurement of gastric and intestinal first-pass effects

Rats were fasted overnight with free access to water. The carotid artery was catheterized with polyethylene tube (Clay Adams) under light ether anesthesia. The cannula was exteriorized to the dorsal side of the neck and terminated with a long Silastic tube. At the same time, the portal vein was similarly cannulated (Kim et al 1997) by the modified Suzuki method (Xu et al 1992). For intraportal administration (n = 5), 0·9% NaCl injectable solution (0·6 mL) was administered orally using a feeding tube and the same volume of solution was also instilled into the duodenum using a 23-gauge needle. Thereafter, 20 mg kg^{-1} (0·6 mL) Lasix, was infused over 1 min via the portal vein. For intraduodenal instillation (n = 5), the same dose of Lasix (0·6 mL) was instilled into the duodenum, followed by oral administration of 0·9% NaCl injectable solution (0·6 mL) using a feeding tube. At the same time, 0·9% NaCl injectable solution (0·6 mL) was infused over 1 min via the portal vein. For oral administration (n = 5), after instillation of 0·9% NaCl injectable solution (0·6 mL) into the duodenum, the same dose of Lasix (0·6 mL) was administered orally using a feeding tube. At the same time, the same volume of

0·9% NaCl injectable solution was infused over 1 min via the portal vein. Blood samples (0·12 mL) were collected at 0 (control), 1 (at the end of the infusion for intraportal infusion study only), 5 (for intraportal infusion study only), 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720, and 1440 min. Other procedures were similar to those described for the measurement of hepatic first-pass effect.

Analytical procedures

The concentrations of furosemide (Lee & Chiou 1983) and CSA (Smith et al 1980) in the biological samples were measured by HPLC. The sample preparation for CSA was modified; the sample was deproteinized with 1 volume of saturated $Ba(OH)_2$ and $ZnSO_4$. Therefore, the detection of CSA in rat urine samples was not due to artifacts by photolytic degradation (Kerremans et al 1982; Moore & Sithipitaks 1982) or the process of acid extraction for the sample preparation (Smith et al 1980).

Pharmacokinetic analysis

The total area under the plasma concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) for intravenous and intraportal studies, or for up to the last measured time, 24 h, in plasma (AUC_{0-24}) for other studies was calculated by the trapezoidal rule extrapolation method using the logarithmic trapezoidal rule (Chiou 1978) for the calculation of area during the declining plasma concentration phase and the linear trapezoidal rule for the rising plasma concentration phase. The area from the last data point to time infinity (AUC for intravenous and intraportal studies) was estimated by dividing the last measured plasma concentration by the terminal rate constant.

Standard methods (Gibaldi & Perrier 1982) were used to calculate the time-averaged total body clearance (CL; Eqn 1), the area under the first moment of the plasma concentration–time curve (AUMC; Eqn 2), the mean residence time (MRT; Eqn 3), the apparent volume of distribution at steady state (Vd_{SS}; Eqn 4), and the time-averaged renal (CL_R; Eqn 5) and nonrenal (CL_{NR}; Eqn 6) clearances (Kim et al 1993).

$$CL = Dose/AUC \quad (1)$$

$$AUMC = \int_0^\infty tC_P dt \quad (2)$$

$$MRT = AUMC/AUC - T/2 \quad (3)$$

$$Vd_{ss} = CL \times MRT \quad (4)$$

$$CL_R = X_{u(\infty)}/AUC \quad (5)$$

$$CL_{NR} = CL - CL_R \quad (6)$$

where C_P is the plasma concentration of furosemide at time t, and $X_{u(\infty)}$ is the total amount of unchanged furosemide excreted in 24-h urine.

The F value of furosemide after oral or intraduodenal administration of the drug to rats was calculated (Eqn 7) for comparison (Lee et al 1997):

$$F = \frac{CL_{o/d} \times X_{u\,fur,0-24,o/d}}{CL_{i.v.} \times X_{u\,fur,0-24,i.v.}} \quad (7)$$

where $CL_{o/d}$, the CL of furosemide after oral or intraduodenal administration, was calculated by the summation of CL_R of furosemide obtained from oral or intraduodenal administration and CL_{NR} of furosemide obtained from the intravenous study. Since the total amount of urinary excretion of unchanged furosemide was collected only for up to 24 h ($X_{u\ fur,0-24}$) after oral and intraduodenal administration, the F values could be somewhat underestimated.

The mean values of each CL (Chiou 1980), Vd_{SS} (Chiou 1979), and terminal half-life (Eatman et al 1977) were calculated by the harmonic mean method.

Statistical analysis

All results are expressed as mean ± s.d. $P < 0.05$ was considered to be statistically significant using the unpaired *t*-test.

Results and Discussion

Measurement of hepatic first-pass effect of furosemide

The mean arterial plasma concentration–time curves of furosemide after intravenous and intraportal administration of 20 mg kg^{-1} Lasix, to rats are shown in Figure 1 and some relevant pharmacokinetic parameters are listed in Table 1. The plasma concentrations of furosemide declined similarly in both groups of rats (Figure 1) and this resulted in a similar (not significantly different) AUC for both groups of rats (Table 1). The mean CL values of furosemide based on plasma data after intravenous and intraportal administration of the drug (5·70 and 6·39 mL min^{-1} kg^{-1}) were sig-

nificantly smaller than the reported (Davies & Morris 1993) cardiac output of rats based on blood data (296 mL min^{-1} kg^{-1}), suggesting that first-pass effects, if any, of furosemide by the lung and heart seemed to be negligible in rats. Although, the AUC after intraportal administration was 89·2% of that after intravenous administration (Table 1), they were not significantly different, suggesting that the hepatic first-pass effect of furosemide is not considerable in rats. This could be supported by comparable (not significantly different) percentages of intravenous dose of furosemide excreted in 0–8 and 8–24 h urine as unchanged furosemide, CSA, and CSA-glucuronide between the two groups of rats (Table 1). An insignificant role of liver for the metabolism of furosemide has also been reported in man (Fuller et al 1981), dogs (Verbeeck et al 1981), and rats (Lee & Chiou 1983). The furosemide-glucuronide in the rat urine in this study was not measured because this has been found to be almost negligible in rats (Lee et al 1997); this could be due to inhibition of uridinediphosphate glucuronyltransferase activity by furosemide in rats (Sörgel et al 1980).

Measurement of gastric and intestinal first-pass effects of furosemide

The mean arterial plasma concentration–time curves of furosemide after intraportal, intraduodenal, and oral administration of 20 mg kg^{-1} Lasix to rats are shown in Figure 2 and some relevant pharmacokinetic parameters are listed in Table 2. After intraportal administration, the plasma concentrations of furosemide declined in a poly-exponential fashion with a mean terminal half-life of 72·2 min (Table 2). After both oral and intraduodenal administration, however, the plasma concentrations of furosemide were almost constant

Table 1. Pharmacokinetic parameters of furosemide after intravenous and intraportal administration of 20 mg kg^{-1} Lasix to rats.

Parameter	Intravenous	Intraportal
Bodyweight (g)	311 ± 10·3	304 ± 14·8
$AUC_{0-\infty}$ (μg min mL^{-1})	3510 ± 734	3130 ± 880
Terminal half-life (min)	74·6 ± 5·15	63·5 ± 11·9
MRT (min)	23·4 ± 7·17*	35·2 ± 6·62
Vd_{SS} (mL kg^{-1})	127 ± 37·8*	222 ± 84·0
CL (mL min^{-1} kg^{-1})	5·70 ± 1·06	6·39 ± 1·92
CL_R (mL min^{-1} kg^{-1})	3·34 ± 0·76	3·45 ± 1·32
CL_{NR} (mL min^{-1} kg^{-1})	2·33 ± 0·39	2·84 ± 0·89
Furosemide excreted in 24-h urine as unchanged furosemide (% i.v. dose)	59·0 ± 3·77	55·0 ± 7·32
Furosemide excreted in 8-h urine as unchanged CSA (% i.v. dose)[a]	4·20 ± 0·71	5·81 ± 2·73
Furosemide excreted in 8-h urine as CSA-glucuronide (% i.v. dose)[a]	1·69 ± 0·88	2·42 ± 0·61
Furosemide recovered from gastrointestinal tract at 24 h as unchanged furosemide (% i.v. dose)	0·407 ± 0·23	0·411 ± 0·29

[a]Expressed in terms of furosemide. Data are mean ± s.d., n = 4 and 5 for intravenous and intraportal administration, respectively. *$P < 0·05$ significant difference between intravenous and intraportal administration.

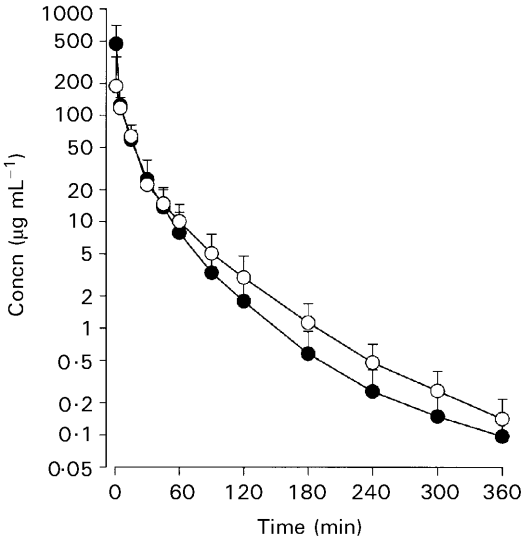

Figure 1. Arterial plasma concentration–time curves of furosemide after intravenous (●; n = 4) and intraportal (○; n = 5) administration of 20 mg kg^{-1} Lasix to rats. Data are mean ± s.d.

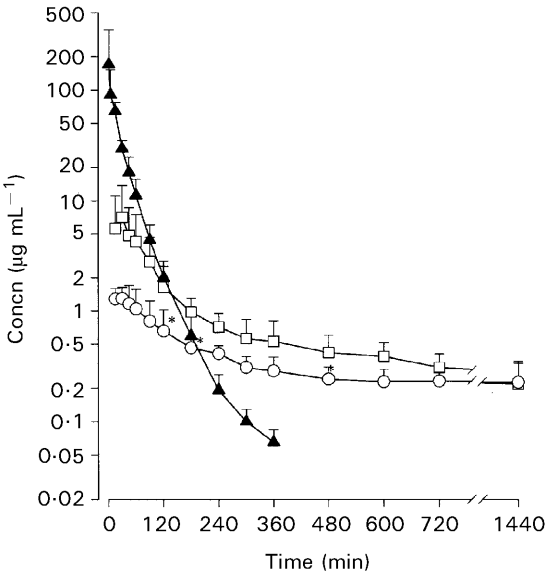

Figure 2. Arterial plasma concentration–time curves of furosemide after intraportal (▲; n = 5), intraduodenal (□; n = 5), and oral (○; n = 5) administration of 20 mg kg^{-1} Lasix to rats. Data are mean ± s.d. *$P < 0·05$ significant difference between oral and intraduodenal administration.

Table 2. Pharmacokinetic parameters of furosemide after intraportal, oral, and intraduodenal administration of 20 mg kg^{-1} Lasix to rats.

Parameter	Intraportal	Oral	Intraduodenal
Bodyweight (g)	287 ± 16·8	286 ± 10·8	277 ± 19·2
AUC[a] ($\mu g\,min\,mL^{-1}$)	2990 ± 758	460 ± 53·2*	989 ± 360
Terminal half-life (min)	72·2 ± 10·8		
CL ($mL\,min^{-1}\,kg^{-1}$)	6·70 ± 2·13		
CL_R ($mL\,min^{-1}\,kg^{-1}$)	3·35 ± 0·99	5·70 ± 0·49	5·04 ± 0·79
CL_{NR} ($mL\,min^{-1}\,kg^{-1}$)	3·17 ± 1·37		
Furosemide excreted in 24-h urine as unchanged furosemide (% i.v. dose)	50·9 ± 8·21	13·2 ± 1·65*	24·7 ± 7·27
Furosemide excreted in 8-h urine as unchanged CSA (% i.v. dose)[b]	2·98 ± 0·11	1·91 ± 1·97*	3·69 ± 1·51
Furosemide excreted in 8-h urine as CSA-glucuronide (% i.v. dose)[b]	3·41 ± 1·05	2·47 ± 0·76*	3·75 ± 1·68
Furosemide recovered from gastrointestinal tract at 24 h as unchanged furosemide (% i.v. dose)	2·14 ± 0·74	31·8 ± 14·4	30·7 ± 15·0
F (%)		28·9	48·3

[a]AUC for intraportal administration and AUC_{0-24} for oral and intraduodenal administration. [b]Expressed in terms of furosemide. Data are mean ± s.d., n = 5. *$P < 0·05$ significant difference between oral and intraduodenal administration.

from 4 to 24 h due to continuous absorption of the drug from the various rat GI segments. Considerable absorption of furosemide from various rat GI segments using closed-loops has also been reported (Lee et al 1997). The absorption of furosemide from the rat GI tract after oral and intraduodenal administration was fast; furosemide was detected in plasma from the first blood sampling time (15 min) and reached a peak at 30 min for both routes of administration (Figure 2).

After oral administration, the plasma concentrations of furosemide were lower (Figure 2) and the resultant AUC_{0-24} was significantly smaller (460 vs 989 $\mu g\,min^{-1}\,mL^{-1}$) than those after intraduodenal administration (Table 2). This was due to an increase in furosemide metabolism in the stomach after oral administration and this was supported by a significant decrease in the percentages (13·2 vs 24·7%) of administered furosemide excreted unchanged in 24-h urine, a significant increase in the percentages (expressed in terms of furosemide) of administered furosemide excreted in 8-h urine as CSA (3·69 vs 1·91%) and CSA-glucuronide (3·75 vs 2·47%), and considerable decrease in F (28·9 vs 48·3%) after oral administration (Table 2). Similar results were also reported in rats and man (Lee et al 1997). It has also been reported (Lee & Chiou 1983) that the in-vitro metabolic activity (9000 g supernatant fraction of each tissue homogenate) for furosemide in rat stomach was much greater than that in rat liver and small intestine based on gram tissue.

The F values were 28·9 and 48·3% for oral and intraduodenal administration, respectively. The percentages of administered furosemide recovered from the entire GI tract at 24 h as unchanged drug were 31·8 and 30·7% after oral and intraduodenal administration, respectively (Table 2). It is possible that the unchanged furosemide recovered from GI tract at 24 h might be partly attributed to the GI excretion (including biliary excretion) from the absorbed drug. Based on linear pharmacokinetics, the mean true fraction of unabsorbed dose (F_{unabs}) after oral (Eqn 8) and intraduodenal (Eqn 9) administration can be estimated by the following equations (Lee & Chiou 1983);

$$0·318 = F_{unabs} + (0·289 \times 0·00407) \quad (8)$$

$$0·307 = F_{unabs} + (0·483 \times 0·00407) \quad (9)$$

where 0·00407 is the mean fraction of the intravenous dose of furosemide recovered intact from the GI tract at 24 h (Table 1) and 0·289 and 0·483 were F values after oral and intraduodenal administration, respectively. The calculated F_{unabs} values were 31·7 and 30·5% for oral and intraduodenal administration, respectively. Therefore, the contribution of GI excretion (including biliary excretion) of the absorbed furosemide to the total drug recovered from GI tract at 24 h after oral and intraduodenal administration appears to be not significant. Approximately 68·3% (100–31·7%)

and 69·5% (100−30·5%) of the administered furosemide was absorbed and/or metabolized after oral and intraduodenal administration, respectively. Since the hepatic first-pass effect was almost negligible, the major site for first-pass metabolism of furosemide in rats is probably the GI tract. In this study, the F values were 28·9 and 48·3% after oral and intraduodenal administration, respectively. In the GI recovery study after oral and intraduodenal administration, 68·3 and 69·5% were found to be absorbed and/or metabolized, respectively. Therefore, approximately 40% (68·3−28·9%) and 20% (69·5−48·3%) of the dose could be lost through metabolism after oral and intraduodenal administration, respectively. Based on these data, it could be concluded that approximately 20% (40−20%) of the oral dose disappeared by gastric first-pass effect and this value was comparable to intestinal first-pass effect (approx. 20%). This was surprising given the considerably smaller surface area of the stomach compared with the intestine. The AUC_{0-24} values after oral and intraduodenal administration were 15·4 and 33·1% of the AUC, respectively, after intraportal administration, supporting a considerable gastrointestinal and intestinal first-pass effect of furosemide in rats. The AUC_{0-24} after oral administration was 46·5% (Table 2) of the value after intraduodenal administration, supporting a considerable gastric first-pass effect of furosemide in rats. The gastrointestinal first-pass effect of furosemide seemed to be biological, not chemical, although furosemide is known to be unstable in acidic conditions with degradation half-lives of approximately 3 and 20 h at 37°C (pH 1 and 2, respectively) (Cruz et al 1979), negligible degradation of furosemide was found after incubation with human gastric and/or duodenal fluids (Beerman et al 1975; Andreasen et al 1982; Lee & Chiou 1983). The considerable gastric first-pass effects of 2-AP, a new chemoprotective agent (Han & Lee 1999) in rats, and intestinal first-pass effect of azosemide (Kim et al 1997), YH 439, a new hepatoprotective agent (Kim et al 1998), YJA-20379-8, a new reversible proton pump inhibitor (Kim et al 1999), and ipriflavone (unpublished data) in rats, and midazolam (Paine et al 1996) and saquinavir (Fitzsimmons & Collins 1997) in man have been reported.

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