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Intestinal first-pass effect of bumetanide in rats

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Abstract

The intestinal first-pass effect of bumetanide was investigated after intravenous and intraportal infusion, and intragastric and intraduodenal instillation of the drug to rats. The $AUC_{0\rightarrow 8\ h}$ values of bumetanide after intragastric and intraduodenal instillation of the drug, 10 and 20 mg/kg, were significantly smaller than AUC values after intraportal administration, suggesting that the gastrointestinal first-pass effect of bumetanide was considerable in rats. However, the $AUC_{0\rightarrow 8\ h}$ values of bumetanide between intragastric and intraduodenal instillation were comparable, suggesting that the gastric first-pass effect of bumetanide was almost negligible in rats. The $AUC_{0\rightarrow 8\ h}$ values of bumetanide after intraduodenal instillation were significantly smaller than AUC values after intraportal infusion at 10 (89.8 vs 569 μg min per ml) and 20 (304 vs 1230 μg min per ml) mg/kg, indicating that the first-pass organ(s) of bumetanide was intestine. The *F* values were 15.8 and 24.7% after intraduodenal instillation of bumetanide, 10 and 20 mg/kg, respectively. Approximately 76.1 and 76.5% of intraduodenally instilled bumetanide disappeared (as a result of absorption and first-pass effect) after 10 and 20 mg/kg, respectively. Therefore, it could be concluded that approximately 60.3 and 51.8% of the oral dose of bumetanide disappeared by intestinal first-pass effect at 10 and 20 mg/kg, respectively.

Keywords: Bumetanide; Intestinal first-pass effect; Rats

1. Introduction

Bumetanide (3-butylamino-4-phenoxy-5-sulfamoyl benzoic acid) is a loop diuretic that closely resembles furosemide in its diuretic action (Imai, 1977). On the molecular weight basis, its natriuretic potency is reportedly 40–60 times that of furosemide after intravenous administration in humans (Branch et al., 1976). The effective oral dose of bumetanide in humans is 1–2 mg and it induces a rapid diuretic response which subsides rapidly (Olesen et al., 1973). The diuretic activity of bumetanide is the most potent in both man and dog (Halladay et al., 1978), but relatively ineffective in rat (Magnussen and Eilertsen, 1974; Halladay et al., 1978; Lee et al., 1994). This species difference is probably the result of rapid and extensive metabolism of bumetanide in rat (Magnussen and Eilertsen, 1974; Lee et al., 1994). For

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example, the percentages of intravenous dose of bumetanide, 0.5 mg/kg, excreted in urine as unchanged bumetanide were 36–49% in humans (Pentikäinen et al., 1977, 1980; Brater et al., 1983), and 39.4% in dogs (Kolis et al., 1976). The values in rats were 1.78–6.62% after intravenous administration of bumetanide, 2–20 mg/kg (Lee et al., 1994). The liver (Marcantonio et al., 1983; Ward and Heel, 1984; Choi et al., 1991) and kidney (Bekersky and Popick, 1983; Choi et al., 1991) were suggested metabolizing organs for bumetanide in humans and rats.

The area under the plasma concentration-time curve from time 0 to time infinity (AUC) values of bumetanide after intravenous administration of the drug, 2, 8, and 20 mg/kg, to rats were 55.9, 419, and 1490 μg min per ml, respectively, and the corresponding values after oral administration were not calculable, 140, and 652 μg min per ml (Lee et al., 1994). The percentages of oral dose of bumetanide recovered from entire gastrointestinal tract at 24 h after oral administration of the drug, 2, 8, and 20 mg/kg were 3.80, 4.56, and 1.85%, respectively (Lee et al., 1994). Bumetanide was stable in acidic human gastric juices (Lee et al., 1994). The above data indicated that there was a considerable first-pass effect of bumetanide after oral administration of the drug to rats. However, the exact first-pass organ(s) for bumetanide after oral administration was not thoroughly studied.

The purpose of this study is to report intestinal first-pass effect of bumetanide after intravenous and intraportal infusion, and intragastric and intraduodenal instillation of the drug, 10 and/or 20 mg/kg, to rats.

2. Materials and methods

2.1. Chemicals

Bumetanide was donated from Dong Hwa Pharmaceutical (Seoul, South Korea). β-Glucuronidase was a product of Sigma (St Louis, MO). Other chemicals were of reagent grade or HPLC grade and used without further purification.

2.2. Animals

Male Sprague-Dawley rats, weighing 255–310 g, were purchased from Charles River (Atsugi, Japan). The animals were housed in a clean room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University, Seoul, South Korea) and had free access to food (Samyang, Seoul, South Korea) and water.

2.3. Measurement of hepatic first-pass effect of bumetanide

The jugular vein and the carotid artery of each rat were catheterized with polyethylene tube (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 midline abdominal incision, the middle portion of the portal vein was isolated, and the tapered end of a 23-gauge needle, bent at 60° angle, was inserted into the pyloric vein, the tributary flow directly into the hepatic portal vein (to minimize the impairment of blood flow in the portal vein). Bleeding was prevented by applying epoxy glue (Krazy Glue, Krazy Glue, Itasca, IL). A long Silastic tube (Dow Corning) was attached to the other end of the needle which was exteriorized to the dorsal side of the neck. All of the three Silastic tubes were covered with a wire to allow free movement of the rat. The exposed areas, the neck and abdomen, were closed using surgical suture. Each animal was kept individually in a metabolic cage (Daejong Scientific, Seoul, South Korea) and allowed 2–3 h to recover from anesthesia.

Bumetanide powder (5.2 mg) was dissolved in NaOH solution (0.1 N; 1 ml), filtered through a 0.45-μm filter, and diluted with 0.9% NaCl injectable solution before use; the final pH was approximately 11 (Lee et al., 1994). By means of this solution, bumetanide was infused over 15 min with the assistance of an infusion pump (Harvard Instrument, Model 2400-006, Southnatick, MA) at a dose of 10 mg/kg for intravenous ($n = 6$) or

intraportal ($n = 6$) administration. The total infusion volume was approximately 1.0 ml. At the same time, the same volume (1.0 ml) of 0.9% NaCl injectable solution was also infused over 15 min via the portal vein for intravenous study and via the jugular vein for intraportal study. Blood samples (0.12 ml) were collected at 0 (to serve as a control), 7.5, 15 (at the end of infusion), 16, 20, 30, 45, 60, 75, 105, 135, 195, and 255 min. Blood samples were centrifuged immediately to minimize 'blood storage effect' (the change in plasma concentration of bumetanide as a result of time elapsed between collection and centrifugation of the blood sample) (Chang et al., 1988), and a 0.05-ml aliquot of plasma was stored at −20°C freezer until HPLC analysis of bumetanide (Choi et al., 1991). Heparinized 0.9% NaCl injectable solution (20 U/ml), 0.3 ml, was used to flush each cannula immediately after each blood sampling to prevent blood clotting. Any loss of fluids and electrolytes in urine induced by bumetanide was immediately replaced volume-for-volume by intravenous administration of lactated Ringer's solution (Dai-Han Pharmaceutical, Seoul, South Korea) via the carotid artery up to 8 h after dosing, because it was reported (Yoon et al., 1995) that the pharmacokinetic and pharmacodynamic parameters of bumetanide were dependent on the rate of fluid replacement. Urine was collected between 0–8 h after administration of the drug. The metabolic cage was rinsed with 15 ml of distilled water at the end of 8 h, and the rinsings were combined with the 0–8-h urine samples. After measuring the exact volume of combined urine sample, an aliquot (0.05 ml) of the combined urine sample was stored in the freezer until HPLC analysis of bumetanide (Choi et al., 1991). An aliquot (0.5 ml) of the combined 8-h urine sample was also added to 1 ml of pH 7.4 Sørensen phosphate buffer containing 10 000 units of β-glucuronidase, and the mixture was incubated for 24 h in a water-bath shaker kept at 37°C and at a rate of 50 oscillations per min. At the end of 8 h, the entire gastrointestinal tract (including its contents and faeces) was removed, transferred into a beaker containing 50 ml of 0.01 N NaOH (to facilitate the extraction of bumetanide), and cut into small pieces with scissors. After shaking manually and stirring with a glass rod for 10 min, an aliquot (0.05 ml) of the supernatant was collected from each beaker and stored in the freezer until HPLC analysis of bumetanide (Choi et al., 1991).

2.4. 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 anaesthesia. The cannula was exteriorized to the dorsal side of the neck and terminated with long Silastic tube (Dow Corning). At the same time, the portal vein was also cannulated (Kim et al., 1997) by the modified Suzuki method (Xu et al., 1992). For intraportal administration, 0.9% NaCl injectable solution (0.6 ml) was instilled into each stomach and duodenum using a 23-gauge needle, and bumetanide, 10 ($n = 5$) and 20 ($n = 5$) mg/kg, was infused over 15 min via the portal vein (total infusion volume was 1.0 ml). For intraduodenal instillation, 0.9% NaCl injectable solution was instilled into the stomach and the same solution (1.0 ml) was infused over 15 min via the portal vein, and bumetanide, 10 ($n = 5$) and 20 ($n = 5$) mg/kg, was instilled into the duodenum (total instilled volume was 0.6 ml). For intragastric instillation, 0.9% NaCl injectable solution was instilled into the duodenum, and the same solution (1.0 ml) was infused over 15 min via the portal vein, and bumetanide, 10 ($n = 7$) and 20 ($n = 5$) mg/kg was instilled into the stomach (total instilled volume was 0.6 ml). Blood samples (0.12 ml) were collected at 0 (to serve as a control), 7.5, 15 (at the end of infusion), 16, 20, 30, 45, 60, 75, 105, 135, 195, 255, 315 (for 20 mg/kg only), and 375 (for 20 mg/kg only) min after intraportal infusion and 0 (to serve as a control), 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, and 480 min after intragastric and intraduodenal instillation. Other procedures were similar to those described for the measurement of hepatic first-pass effect.

2.5. Pharmacokinetic analysis

Standard methods (Gibaldi and Perrier, 1982) were used to calculate the following pharmacokinetic parameters; AUC for intravenous and intraportal studies, or up to the last measured time in plasma ($AUC_{0\rightarrow 8\ h}$) for other studies, the time-averaged total body clearance (CL), the area under the first moment of the plasma concentration-time curve (AUMC), the mean residence time (MRT), the apparent volume of distribution at steady state (V_{ss}), and the time-averaged renal (CL_R) and nonrenal (CL_{NR}) clearances (Lee et al., 1994).

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

2.6. Statistical analysis

A P value of less than 0.05 was considered to be statistically significant using unpaired t-test. All results are expressed as mean $\pm$ S.D.

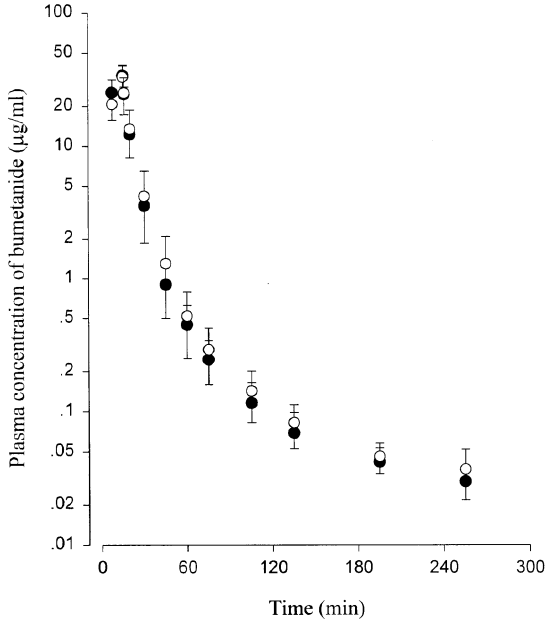

Fig. 1. Mean arterial plasma concentration-time curves after 15-min intravenous (●, $n=6$) and intraportal (○, $n=6$) infusion of bumetanide, 10 mg/kg, to rats. Vertical bars represent S.D.

Table 1
Pharmacokinetic parameters of bumetanide after intravenous and intraportal administration, 10 mg/kg, to rats[a]

	Intravenous ($n=6$)	Intraportal ($n=6$)
Body weight (g)	294 ± 7.36	293 ± 9.87
AUC (μg min per ml)	552 ± 95.8	540 ± 160
Terminal half-life (min)	107 ± 36.9	115 ± 17.5
MRT (min)	17.7 ± 7.18	19.0 ± 5.00
V_{ss} (ml/kg)	427 ± 94.2	551 ± 121
CL (ml/min per kg)	18.1 ± 1.37	20.4 ± 3.56
CL_R (ml/min per kg)	0.662 ± 0.243	1.33 ± 0.392*
CL_{NR} (ml/min per kg)	17.2 ± 1.28	19.1 ± 3.50
$X_{u,0\rightarrow 8\ h,Bum}$ (% of dose)[b,c]	4.87 ± 2.28	7.21 ± 5.61
$X_{u,0\rightarrow 8\ h,Bum\text{-}Glu}$ (% of dose)[d]	0.786 ± 0.507	1.32 ± 1.35
$GI_{8\ h,Bum}$ (% of dose)[e]	3.25 ± 1.30	2.73 ± 1.95
$GI_{8\ h,Bum\text{-}Glu}$ (% of dose)	0.403 ± 0.0895	0.313 ± 0.186

[a] Each value represents the mean ± S.D.
[b] Total amount excreted in 8 h urine.
[c] Bumetanide.
[d] Bumetanide glucuronide.
[e] Total amount recovered from gastrointestinal tract at 8 h after dosing.
* $P<0.05$.

3. Results and discussion

3.1. Measurement of hepatic first-pass effect of bumetanide

The mean arterial plasma concentration-time curves after intravenous ($n=6$) and intraportal ($n=6$) administration of bumetanide, 10 mg/kg, to rats are shown in Fig. 1; some relevant pharmacokinetic parameters are listed in Table 1. The plasma concentrations of bumetanide increased during infusion and declined in a polyexponential fashion post-infusion for both administration (Fig. 1) with mean terminal half-lives of 107 and 115 min (Table 1) after intravenous and intraportal administration, respectively. The mean CL values of bumetanide based on plasma data after intravenous (18.1 ml/min per kg) and intraportal (20.4 ml/min per kg) administration (Table 1) were considerably smaller than the reported (Davies and Morris, 1993) cardiac output value of

rats based on blood data (296 ml/min per kg), suggesting that first-pass effects of bumetanide by the lung and heart could be negligible in rats. The AUC values of bumetanide after intravenous and intraportal administration were very similar (not significantly different), only 2% difference (Table 1), suggesting that hepatic first-pass effect of bumetanide was also almost negligible in rats. The pharmacokinetic parameters of bumetanide (Table 1) were not significantly different between both administration except CL_R.

3.2. Measurement of gastric and intestinal first-pass effects of bumetanide

The mean arterial plasma concentration–time curves after intraportal administration, and intraduodenal and intragastric instillation of bumetanide, 10 and 20 mg/kg, to rats are shown in Fig. 2; some relevant pharmacokinetic parameters are listed in Table 2. The plasma concentrations of bumetanide increased during the infusion and declined in a polyexponential fashion post-infusion after intraportal administration of both doses (Fig. 2). After both intragastric and intraduodenal instillation, however, the plasma concentrations of bumetanide were almost constant from 4 to 8 h as a result of continuous absorption of the drug from various rat gastrointestinal segments. Considerable absorption of bumetanide from various rat gastrointestinal segments using closed-loops was also reported (Lee et al., 1994).

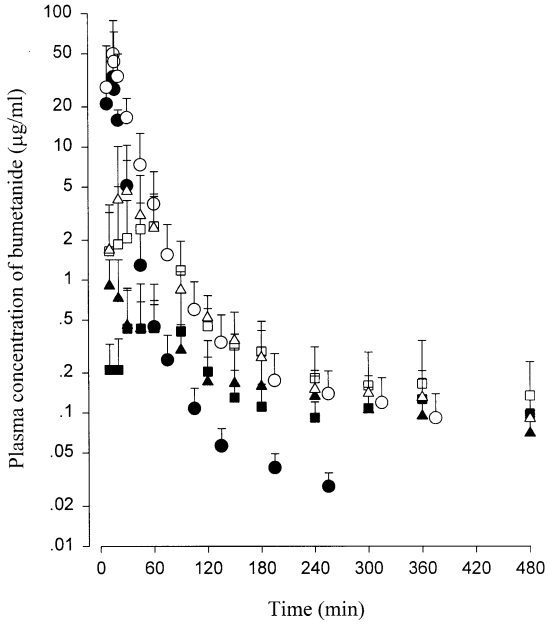

Fig. 2. Mean arterial plasma concentration-time curves after intraportal infusion, 10 (●, $n=5$) and 20 (○, $n=5$) mg/kg, intraduodenal, 10 (▲, $n=5$) and 20 (△, $n=5$) mg/kg, and intragastric, 10 (■, $n=7$) and 20 (□, $n=5$) mg/kg instillation of bumetanide to rats. Vertical bars represent S.D.

The $AUC_{0\rightarrow 8\ h}$ values of bumetanide after intragastric and intraduodenal instillation were significantly smaller than those after intraportal administration for both doses (Table 2), indicating that the gastrointestinal first-pass effect of bumetanide was considerable in rats. However, the $AUC_{0\rightarrow 8\ h}$ values of bumetanide between intragastric and intraduodenal instillation were very similar (not significantly different) for both doses (Table 2) suggesting that the gastric first-pass effect of bumetanide was almost negligible in rats. Therefore, it could be concluded that the intestinal first-pass effect of bumetanide was considerable in rats. The $AUC_{0\rightarrow 8\ h}$ values of bumetanide after intraduodenal instillation were significantly smaller than those after intraportal infusion of 10 (84% decrease) and 20 (75% decrease) mg/kg indicating that intestinal first-pass effects of bumetanide were approximately 84 and 75% of the absorbed bumetanide from intestine, respectively. It has been reported (Lee et al., 1994) that the pharmacokinetic parameters of bumetanide, especially CL_{NR}, were dose-dependent after intravenous administration of the drug, 2–20 mg/kg to rats. Therefore, the estimation of the extent of absolute oral bioavailability of bumetanide after intraduodenal instillation (F) could not be possible in rats. However, in the present study, F was estimated for comparison by comparing AUC values after intraportal administration, and $AUC_{0\rightarrow 8\ h}$ values after intraduodenal instillation; the F values after intraduodenal instillation were approximately 15.8 and 24.7% for 10 and 20 mg/kg, respectively (Table 2). The percentages of unchanged bumetanide recovered from the entire gastrointestinal tract at 8 h were 23.9 and 23.5% after intraduodenal instillation, 10 and 20 mg/kg, respectively (Table 2). Since hepatic and gastric

Table 2
Pharmacokinetic parameters of bumetanide after intraportal infusion, and intragastric and intraduodenal instillation, 10 and 20 mg/kg, to rats[a]

	10 mg/kg			20 mg/kg		
	Intraportal ($n=5$)	Intragastric ($n=7$)	Intraduodenal ($n=5$)	Intraportal ($n=5$)	Intragastric ($n=5$)	Intraduodenal ($n=5$)
Body weight (g)	284 ± 8.94	281 ± 15.7	277 ± 8.37	271 ± 12.9	279 ± 19.5	287 ± 13.0
AUC (μg min per ml)[b,c]	569 ± 86.8	81.2 ± 47.7	89.8 ± 27.0	1230 ± 397	254 ± 104	304 ± 192
Terminal half-life (min)	121 ± 28.3			184 ± 25.3		
MRT (min)	18.4 ± 6.02			46.2 ± 27.7		
V_{ss} (ml/kg)	429 ± 96.8			634 ± 574		
CL (ml/min per kg)	17.6 ± 1.47			16.3 ± 3.66		
CL_R (ml/min per kg)[b]	0.473 ± 0.168	0.0745 ± 0.0810	0.0618 ± 0.0213	0.451 ± 0.0825	0.0927 ± 0.0310	0.0646 ± 0.0975
CL_{NR} (ml/min per kg)	17.0 ± 1.42			15.7 ± 3.65		
$X_{u,0\rightarrow 8\ h,Bum}$ (% of dose)[b,d,e]	3.31 ± 1.70	0.108 ± 0.111	0.0613 ± 0.0231	2.99 ± 1.29	0.138 ± 0.0804	0.156 ± 0.121
$X_{u,0\rightarrow 8\ h,Bum\text{-}Glu}$ (% of dose)[f,g]	0.166 ± 0.221	0.0144 ± 0.0184	0.0281 ± 0.00434	0.431 ± 0.439	0.0118 ± 0.0115	0.0149 ± 0.0081
$GI_{8\ h,Bum}$ (% of dose)[b,h]	4.39 ± 1.02	39.5 ± 15.3	23.9 ± 9.75	3.60 ± 1.65	27.1 ± 19.1	23.5 ± 6.66
$GI_{8\ h,Bum\text{-}Glu}$ (% of dose)	0.123 ± 0.224	1.90 ± 2.69	1.55 ± 1.22	0.822 ± 0.604	1.32 ± 1.66	1.10 ± 1.07

[a] Each value represents the mean ± S.D.
[b] Intraportal infusion was significantly different from intragastric and intraduodenal instillation at each dose ($P<0.05$).
[c] AUC for intraportal administration, and $AUC_{0\rightarrow 8\ h}$ for intragastric and intraduodenal instillation.
[d] Total amount excreted in 8 h urine.
[e] Bumetanide.
[f] Bumetanide glucuronide.
[g] Intragastric instillation was significantly different from intraduodenal instillation at 10 mg kg dose ($P<0.05$).
[h] Total amount recovered from gastrointestinal tract at 8 h after dosing.

first-pass effects of bumetanide were almost negligible in rats, the major site for first-pass metabolism of bumetanide in rats may be expected to be intestine. In the present study, the F values were 15.8 and 24.7% after intraduodenal instillation of bumetanide, 10 and 20 mg/kg, respectively, and in the gastrointestinal recovery study after intraduodenal instillation, 76.1 (100 − 23.9%) and 76.5% (100 − 23.5%) were found to be disappeared (absorbed and first-pass effect) at 10 and 20 mg/kg, respectively. Therefore, approximately 60.3% (76.1 − 15.8%) and 51.8% (76.5 − 24.7%) of the oral dose, 10 and 20 mg/kg, respectively, should be lost through metabolism by the intestinal first-pass effect in rats. The dose normalized $AUC_{0\rightarrow 8\ h}$ values (based on 10 mg/kg) after both intragastric (81.2 ± 47.7 vs 127 ± 51.7 μg min per ml) and intraduodenal (89.8 ± 27.0 vs 152 ± 95.8 μg min per ml) instillation were not significantly different between 10 and 20 mg/kg, suggesting that the intestinal first-pass effect was not saturated at 20 mg/kg. Considerable intestinal first-pass effects of azosemide (Kim et al., 1997), furosemide, YH-439 (a new hepatoprotective agent, Kim et al., 1998), and YJ-20379-8 (a new reversible proton pump inhibitor) (Kim et al.,

1999) in rats and midazolam (Paine et al., 1996) and saquinavir (Fitzsimmons and Collins, 1997) in humans were reported.

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