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Pharmacokinetics and Pharmacodynamics of Azosemide after Intravenous and Oral Administration to Rats with Alloxan-induced Diabetes Mellitus

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Abstract

Because physiological changes occurring in diabetes mellitus patients could alter the pharmacokinetics and pharmacodynamics of the drugs used to treat the disease, the pharmacokinetics and pharmacodynamics of azosemide were investigated after intravenous and oral administration of the drug (10 mg kg^{-1}) to control and alloxan-induced diabetes mellitus rats (AIDRs).

After intravenous administration of azosemide to the AIDRs, the area under the plasma concentration–time curve (AUC) increased considerably (3120 compared with 2520 μg min mL^{-1}; $P < 0.135$) and the total body clearance decreased considerably (3.20 compared with 3.96 mL min^{-1} kg^{-1}; $P < 0.0593$). The considerable reduction in time-averaged total body clearance in the AIDRs was a result of the significant decrease in renal clearance (1.01 compared with 1.55 mL min^{-1} kg^{-1}) in the AIDRs, the non-renal clearance being comparable between the two groups of rats. After intravenous administration, the 8-h urinary excretion of azosemide (29.5 compared with 40% of intravenous dose; $P < 0.0883$) and one of its metabolites, M1 (2.15 compared with 2.60% of intravenous dose, expressed in terms of azosemide; $P < 0.05$) decreased in the AIDRs because of the impaired kidney function. The diuretic, natriuretic, kaliuretic and chloruretic efficiencies increased significantly in the AIDRs. After oral administration of azosemide, AUC decreased significantly in the AIDRs (115 compared with 215 μg min mL^{-1}) possibly because of the reduced gastrointestinal absorption of azosemide in the AIDRs. After oral administration of azosemide, the 8-h urine output decreased significantly in the AIDRs (9.32 compared with 16.1 mL per 100 g body weight) because of the significantly reduced 8-h urinary excretion of azosemide (3.00 compared with 9.14% of oral dose).

After both intravenous and oral administration some pharmacokinetic and pharmacodynamic parameters of azosemide were significantly different in AIDRs.

Many diabetic patients develop serious complications including cardiovascular disorders, nephropathy, neuropathy, and retinopathy (Gwilt et al 1991). Thiazide diuretics are generally effective for treatment of early hypertension in diabetic patients (Joseph & Schuna 1990), but when creatinine clearance is less than 30–35 mL min^{-1}, loop diuretics should be used (Houston 1986). Animal models of insulin-dependent diabetes mellitus, induced by administration of several chemicals, principally alloxan, streptozotocin, and zinc chelators, have been reported (Pickup & Williams 1991). Some physiological changes such as gastroparesis, decreased plasma albumin level, elevated plasma free fatty acid level, glycosylation of plasma proteins, and changes in cytochrome P-450 content were reported to occur as a result of diabetes mellitus (O'Connor & Feely 1987; Gwilt et al 1991); such physiological changes could alter the pharmacokinetics and hence the pharmacodynamics of the drugs used to treat diabetes mellitus patients. The effects of diabetes mellitus on the pharmacokinetics or pharmacodynamics, or both, of some drugs in patients or alloxan-induced diabetes mellitus rats (AIDRs) have been reported (O'Connor & Feely 1987; Gwilt et al 1991; Choi et al 1995; Lee et al 1995; Park 1995; Park et al 1995b). Although the pharmacokinetics and pharmacodynamics of azosemide (5-(4-chloro-5-sulphamoyl-2-thenylaminophenyl)-tetrazole), a loop diuretic, have been studied in man (Brater et al 1979a, b, 1983; Kuzuya 1983) and animals (Asano et al 1984; Inoue et al 1984; Lee et al 1994b), the effects of diabetes mellitus on the pharmacokinetics and pharmacodynamics of azosemide seem not to have been thoroughly studied. Urine output decreased significantly in AIDRs after both intravenous and oral administration of furosemide, a loop diuretic (Park 1995). The purpose of this study was to investigate the effect of alloxan-induced diabetes mellitus on the pharmacokinetics and pharmacodynamics of azosemide after its intravenous and oral administration to control rats and to AIDRs.

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Materials and Methods

Chemicals

Azosemide and one of its metabolites, M1 (5-(2-amino-4-chloro-5-sulphamoylphenyl)tetrazole), were kindly supplied by Sam Jin Pharmaceutical Company (Seoul, Korea) and Boeringer Mannheim (Mannheim, Germany), respectively. β-Glucuronidase and alloxan were from Sigma (St Louis, MO, USA). Other chemicals were of reagent grade or high-performance liquid chromatographic (HPLC) grade and used without further purification.

Induction of diabetics mellitus in rats by alloxan injection

Alloxan dissolved in 0·9% NaCl injectable solution, 40 mg kg^{-1}, was administered intravenously via the tail vein (total injection volume approximately 0·2 mL) for 2 consecutive days to overnight-fasted Sprague–Dawley rats (Central-Research Institute, Dong Shin Pharmaceutical Company, Pyungtak, Korea), 200–250 g. On the third day plasma glucose levels were measured and rats with plasma glucose levels higher than 200 mg dL^{-1} were chosen as AIDRs; the mean value was 414 ± 183 mg dL^{-1}. Induction of diabetes mellitus was evident by single administration of uranyl nitrate to rats; the mean plasma glucose levels in the AIDRs were 394 (Park 1995) and 404 (Choi et al 1995) mg dL^{-1}, and the value for the control rats was 161 mg dL^{-1} (Park 1995).

Intravenous study

In the early morning on the fourth day after the start of alloxan treatment, the carotid artery and the jugular vein were catheterized with polyethylene tubing (Clay Adams, Parsippany, NJ, USA) under light ether anaesthesia. Both cannulae were exteriorized to the dorsal side of the neck where each terminated with long silastic tubing (Dow Corning, Midland, MI, USA). Each piece of silastic tubing was covered with wire to allow free movement of the rat. Each rat was housed individually in a rat metabolic cage (Daejong Scientific, Seoul, Korea) and allowed to recover from anaesthesia for 4–5 h before drug administration. They were not restrained at any time during the study. Because it has been reported that the pharmacodynamic effects (such as urine output and urinary excretion of sodium) of intravenous furosamide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1995a) are dependent on the rate and composition of fluid replacement, azosemide-induced water losses (as urine) were replaced immediately volume-for-volume by intravenous infusion of Ringer's lactate solution (Dai Han Pharmaceutical, Seoul, Korea), via the jugular vein, for up to 8 h of the experiment. Access to food and water was prevented throughout the whole experimental period.

Azosemide powder (15 mg) was dissolved in NaOH solution (0·1 M; 1 mL), filtered through a 0·45-μm filter, and diluted with 0·9% NaCl injectable solution before use; the final pH was approximately 10. By means of this solution azosemide (10 mg kg^{-1}) was administered by intravenous infusion in 1 min via the jugular vein (total injection volume was approximately 1 mL) of the control rats ($n = 8$) and AIDRs ($n = 9$). Blood samples (0·12 mL) were collected via the carotid artery at 0 (to serve as a control), 1 (at the end of infusion), 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 min after administration. Heparinized 0·9% NaCl injectable solution (0·25 mL; 20 units mL^{-1}) was used to flush the cannula after each blood sampling to prevent the blood from clotting. Blood samples were centrifuged immediately and a sample (0·05 mL) of the plasma was stored at − 20°C until HPLC analysis of azosemide (Lee & Lee 1994). After 8 h intravenous administration of azosemide a large volume of blood was collected through the abdominal artery and each rat was killed. After measuring the exact volume of urine, the metabolic cage was rinsed with 10 mL of distilled water and the rinsings were combined with 8-h urine, and the urinary bladder was cut and washed into the combined urine. After measuring the exact volume of the 8-h combined urine, a sample was frozen before analysis for azosemide and M1 (Lee & Lee 1994), and sodium, potassium and chloride. At the same time a sample (0·5 mL) of the combined urine was incubated for 24 h with Sorensen phosphate buffer (pH 7·4; 1 mL) containing 10 000 units of β-glucuronidase in a water-bath shaker (50 oscillations min^{-1}) at 37°C for measurement of azosemide glucuronide formation.

Oral study

Azosemide (10 mg kg^{-1}) was also administered orally (total oral volume approximately 2 mL) by means of feeding tubing to control rats ($n = 9$) and AIDRs ($n = 9$) after overnight fasting with water freely available. Blood samples were collected via the carotid artery at 0 (to serve as a control), 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 min after oral administration of azosemide. Urine was collected 0–8 and 8–24 h after oral administration of azosemide. The other procedures were similar to those of the intravenous study.

Analytical procedure

The concentrations of azosemide and M1 were analyzed by a published sensitive HPLC method (Lee & Lee 1994). Concentrations of sodium, potassium and chloride in urine were determined using Lytening System 30 (Na/K/Cl Instant IZE Analyser, Baxter Lytening System, Danvers, MA, USA).

Pharmacokinetic analysis

The area under the plasma concentration–time curve from time zero to time infinity (AUC for intravenous study) or to the last measured time, 8 h, in plasma ($AUC_{0-8\ h}$ for oral study) was calculated by the trapezoidal rule-extrapolation method employing the logarithmic trapezoidal rule (Chiou 1978) for the calculation of area during the declining plasma level phase and the linear trapezoidal rule for the rising plasma level phase. The area from the last data point to time infinity (for intravenous study) was estimated by dividing the last measured plasma concentration by the terminal rate constant.

A standard method (Gibaldi & Perrier 1982) was used to calculate 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 (Vd_{SS}), and the time-averaged renal and non-renal clearances (CL_R and CL_{NR}, respectively; Kim et al 1993).

$$CL = Dose/AUC \tag{1}$$

$$AUMC = \int_0^\infty t \cdot C_p dt \tag{2}$$

$$MRT = AUMC/AUC \tag{3}$$

$$Vd_{SS} = CL \cdot MRT \tag{4}$$

$$\widehat{CLR} = Xu_{Azo}/AUC \tag{5}$$

$$CL_{NR} = CL - CL_R \tag{6}$$

where C_P is the plasma azosemide concentration at time t and Xu_{Azo} is the amount of azosemide excreted in the urine up to time infinity (assumed to equal the total amount excreted 8 h after intravenous administration, because a negligible amount of azosemide was found in the urine collected later). Only

$AUC_{0-8\,h}$ and CL_R (based on $Xu_{Azo,0-8\,h}$ and $AUC_{0-8\,h}$) of azosemide were estimated after oral administration.

The mean values of each clearance, Vd_{SS}, and terminal t½ were calculated by the harmonic mean method (Chiou 1979).

Pharmacodynamic analysis

The diuretic, natriuretic, kaluretic and chloruretic efficiencies, respectively, were calculated by dividing the total urine output (mL) and total amount (mmol) of sodium, potassium and chloride excreted in 8-h urine by the total amount (mg) of azosemide excreted in 8-h urine.

Statistical analysis

Levels of statistical significance were assessed using the *t*-test between two means for unpaired data. Significant differences were judged as $P < 0.05$. All results are expressed as mean ± standard deviation.

Results and Discussion

The mean arterial plasma concentration-time curves after intravenous administration of azosemide to the control rats (n = 8) and AIDRs (n = 9) are shown in Fig. 1; some relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration, the plasma levels of azosemide declined polyexponentially with significantly higher levels in the AIDRs than in the control rats (Fig. 1); this resulted in a higher AUC of azosemide in the AIDRs (3120 compared with 2520 μg min mL^{-1}, $P < 0.135$; Table 1). As expected, CL of azosemide was considerably lower in the AIDRs than in the control rats (3·20 compared with 3·96 mL min^{-1} kg^{-1}, $P < 0.0593$); this was because of a significant decrease in CL_R (1·01 compared with 1·55 mL min^{-1} kg^{-1}) in the AIDRs, because CL_{NR} was not significantly different between the two groups of rats (Table 1). Similar results were also obtained for furosemide administered to control rats and AIDRs (Park 1995). Because it has been reported that each type of clearance (CL, CL_R, and CL_{NR}) of azosemide was dose-dependent in rats (Lee 1995), and CL_R of azosemide was urine flow-dependent in rabbits (Lee et al 1994b), clearances of azosemide in the present rat studies were time-averaged values.

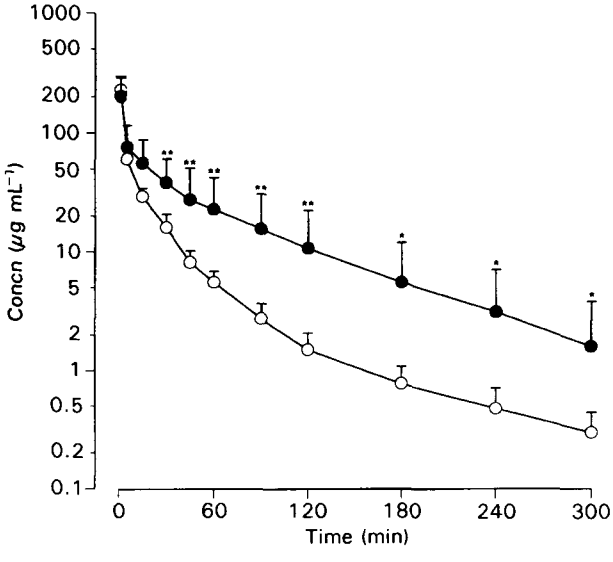

FIG. 1. Mean arterial plasma concentration–time profiles after 1 min intravenous infusion of azosemide, 10 mg kg^{-1}, to control rats (○, n = 8) and to AIDRs (●, n = 7). Bars represent standard deviation. $^*P < 0.05$, $^{**}P < 0.01$ compared with control.

The amount of unchanged azosemide excreted in 8-h urine was considerably lower in the AIDRs (29·5% of the intravenous dose, compared with 40·0%, $P < 0.0883$; Table 1). This could be because of the impaired kidney function brought about by alloxan treatment (Warren et al 1966): "kidney is perhaps next in importance to the pancreas as a site of lesions in alloxan diabetes and the severest damage occurs in the convoluted tubules and appears to be generally proportional to the size of the dose". Impaired kidney function in AIDRs was also shown (Park 1995) by a significant decrease in creatinine clearance (2·86 compared with 4·33 mL $min\ kg^{-1}$) and a significant increase in kidney weight (0·953% compared with 0·749% of body weight) in AIDRs when compared with those in the control rats. The percentages of the intravenous dose excreted as M1 in 8-h urine was also significantly lower in the AIDRs (2·15% compared with 2·60%, expressed in terms of azosemide; Table 1). The MRT increased significantly in the AIDRs (52·6 compared with 37·6), but the values of Vd_{SS} and terminal t½ were not significantly different between two groups of rats (Table 1). It is to be noted that the effect of intravenous injection of 1 mL of azosemide solution with a pH of approximately 10 on the pharmacokinetics and pharmacodynamics of azosemide in the present rats seemed to be minor, if any; 1 mL of bumetanide solution with a pH of 11 was injected to rats and the pH of blood was essentially constant up to 60 min after intravenous dosing and on the basis of tissue microscopy there was no significant histological changes in the liver, stomach and kidney 8 h after intravenous dosing (Lee et al 1994a).

The contribution of biliary or gastrointestinal excretion, or both, of azosemide to CL_{NR} of azosemide after intravenous administration seemed to be minor, because 4·78% and 3·50% of the intravenous dose were recovered as intact azosemide from the GI tract after 8 h intravenous administration to the control rats and AIDRs, respectively. Similar results were also reported by Lee (1995). The CL_{NR} of azosemide could, therefore, represent the non-renal metabolism of azosemide. The CL_{NR} was not significantly different between the two groups of rats (Table 1), indicating that metabolism of azosemide was not affected by alloxan-induced diabetes mellitus.

The mean arterial plasma concentration–time curves of azosemide after oral administration to control rats (n = 9) and to AIDRs (n = 9) are shown in Fig. 2; some relevant pharmacokinetic parameters are also listed in Table 1. The plasma concentrations of azosemide in the AIDRs tended to be lower than in the control rats (Fig. 2) and this resulted in a significant lower $AUC_{0-8\,h}$ in the AIDRs (115 compared with 215 μg min mL^{-1}; Table 1). This could be because of the reduced gastrointestinal absorption of azosemide in the AIDRs because the AUC of azosemide was considerably higher in the AIDRs after intravenous administration (Table 1 and Fig. 1). Because the CL_{NR} of azosemide after intravenous administration in rats was dose-dependent (Lee 1995), the estimation of the extent of bioavailability (F) after oral administration of azosemide in rats might not be possible. In the present study,

Table 1. Mean (± standard deviation) pharmacokinetic and pharmacodynamic parameters of azosemide (10 mg kg^{-1}) after administration by intravenous infusion for 1 min or orally, to control rats and alloxan-induced diabetes mellitus rats (AIDRs).

Parameter	Intravenous administration		Oral administration	
	Control rats (n = 8)	AIDRs (n = 9)	Control rats (n = 9)	AIDRs (n = 9)
Body weight (g)	280 ± 13·6***	245 ± 12·8	244 ± 21·9	250 ± 11·5
Area under the plasma concentration–time curve or Area under the plasma concentration–time curve from 0 to 8 h (μg min mL^{-1})[a]	2520 ± 378	3120 ± 989	215 ± 90·2*	115 ± 70·0
Terminal half-life (min)	44·3 ± 26·2	52·0 ± 15·0		
Mean residence time (min)	37·6 ± 15·2*	52·6 ± 13·7		
Apparent volume of distribution at steady state (mL kg^{-1})	140 ± 39·2	164 ± 53·1		
Amount of azosemide excreted in 8-h urine (% of dose)[b]	40·0 ± 6·79	29·5 ± 15·5	9·14 ± 3·60**	3·00 ± 3·36
Amount of metabolite M1 excreted in 8-h urine (% of dose)[b]	2·60 ± 0·380*	2·15 ± 0·372	3·30 ± 1·28**	1·70 ± 0·653
Amount of azosemide glucuronide excreted in 8-h urine (% of dose)[b]	3·87 ± 2·54	3·37 ± 2·04	2·31 ± 2·65	2·01 ± 0·654
Time-averaged total body clearance (mL min^{-1} kg^{-1})	3·96 ± 0·572	3·20 ± 0·891		
Time-averaged renal clearance (mL min^{-1} kg^{-1})	1·55 ± 0·343*	1·01 ± 0·559	1·93 ± 0·984	1·99 ± 1·04
Time-averaged non-renal clearance (mL min^{-1} kg^{-1})	2·35 ± 0·464	1·94 ± 0·865		
Bioavailability (%)[c]			8·53	3·69
Eight-hour urine output (mL per 100 g body weight)	38·5 ± 11·9	44·2 ± 20·8	16·1 ± 9·43*	9·32 ± 1·37
Eight-hour urinary excretion of sodium (mmol per 100 g body weight)	4·60 ± 1·41	5·36 ± 2·73	1·74 ± 0·874	1·09 ± 0·717
Eight-hour urinary excretion of potassium (mmol per 100 g body weight)	0·383 ± 0·0812	0·505 ± 0·172	0·246 ± 0·104*	0·132 ± 0·119
Eight-hour urinary excretion of chloride (mmol per 100 g body weight)	5·10 ± 1·62	5·29 ± 2·50	2·00 ± 0·968*	1·13 ± 0·737
Diuretic efficiency$_{0-8\,h}$ (mL mg^{-1})	96·1 ± 22·8**	158 ± 40·0	275 ± 109	423 ± 381
Natriuretic efficiency$_{0-8\,h}$ (mmol mg^{-1})	11·5 ± 2·85**	19·4 ± 6·33	40·1 ± 14·1	50·6 ± 48·2
Kaliuretic efficiency$_{0-8\,h}$ (mmol mg^{-1})	0·962 ± 0·153***	1·92 ± 0·608	5·82 ± 1·73	5·29 ± 4·17
Chloruretic efficiency$_{0-8\,h}$ (mmol mg^{-1})	12·8 ± 3·44*	19·3 ± 5·79	46·5 ± 16·1	53·9 ± 55·0

[a]AUC for intravenous studies; $AUC_{0-8\,h}$ for oral studies. [b]Expressed in terms of azosemide. [c]Extent of oral dose absorbed into the general circulation. *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

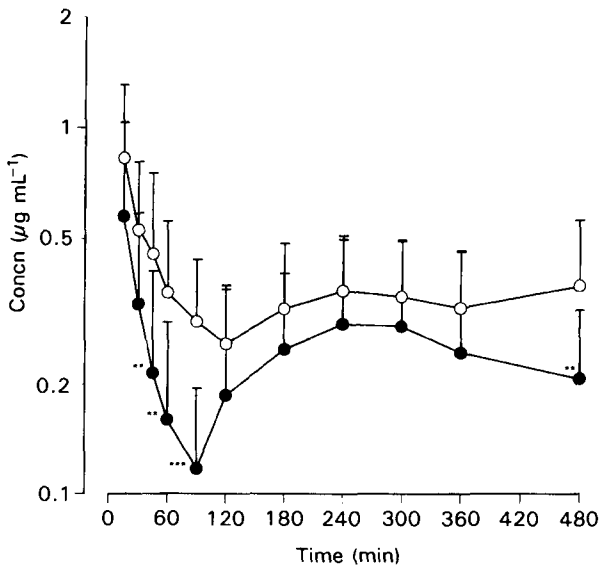

FIG. 2. Mean arterial plasma concentration–time profiles after oral administration of azosemide, 10 mg kg^{-1}, to the control rats (○, n = 9) and to AIDRs (●, n = 9). Bars represent standard deviation. **$P < 0·01$, ***$P < 0·001$ compared with control.

however, F was estimated for comparison on the basis of the AUC after intravenous administration of azosemide and $AUC_{0-8\,h}$ after oral administration; the F value was considerably reduced in the AIDRs, 3·69% compared with 8·53% for the AIDRs and control rats, respectively. It has also been reported (Gwilt et al 1991) that the rate and extent of absorption of drugs given orally could be expected to be altered in diabetes mellitus patients; disorders of the gastrointestinal tract, such as diarrhoea, constipation, and delayed gastric emptying, occurred as a result of the gastroparesis in as many as 20% of diabetic patients who have had the disease for several years. The percentages of the oral dose excreted in 8-h urine as unchanged azosemide (3·00 compared with 9·14%) and M1 (1·70% compared with 3·30%, expressed in terms of azosemide) was significantly lower in the AIDRs. It should be noted that the urinary excretion of azosemide glucuronide (being more hydrophilic than azosemide) was not significantly different between two groups of rats after both intravenous and oral administration of azosemide (Table 1).

The pharmacodynamic parameters of azosemide after both intravenous and oral administration to the control rats and AIDRs are also listed in Table 1. After intravenous administration of azosemide, the 8-h urine output, and 8 h urinary excretion of sodium, potassium and chloride per

100 g body weight were not significantly different between the two groups of rats (Table 1). The 8-h urinary excretion of azosemide was, however, considerably reduced in AIDRs (Table 1). This resulted in significantly increased diuretic (158 compared with 96·1 mL mg^{-1}), natriuretic (19·4 compared with 11·5 mmol mg^{-1}), kaliuretic (1·92 compared with 0·962 mmol mg^{-1}), and chloruretic (19·3 compared with 12·8 mmol mg^{-1}) efficiencies in the AIDRs (Table 1). Different results were obtained after oral administration of azosemide; the 8-h urine output (9·32 compared with 16·1 mL per 100 g body weight), and the 8-h urinary excretion of potassium (0·132 compared with 0·246 mmol per 100 g body weight) and chloride (1·13 compared with 2·00 mmol per 100 g body weight) decreased significantly in the AIDRs. However, the diuretic, natriuretic, kaliuretic and chloruretic efficiencies were not significantly different between the two groups of rats.

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