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EFFECT OF INTRAVENOUS INFUSION TIME ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THE SAME TOTAL DOSE OF FUROSEMIDE

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ABSTRACT

The pharmacokinetics and pharmacodynamics of furosemide were evaluated after intravenous administration of the same total dose of furosemide in different lengths of infusion time (10 s, 30 min, 2 h, and 8 h) to 6 dogs. The fluid loss in urine was immediately replaced volume for volume with intravenous infusion of Lactated Ringer's solution. The pharmacokinetic parameters such as per cent of the dose excreted in urine, total body and renal clearances, and terminal half-life were not significantly different with four different infusion times. The volume of distribution at steady state and mean residence time based on *venous* data, on the other hand, appeared to increase with increasing infusion time. The mean values for V_{ss} were 0·334, 0·478, 0·499, and 0·708 l kg^{-1} for 10 s, 30 min, 2 h, and 8 h of infusion, respectively, and the corresponding values for MRT were 17·5, 22·2, 24·8, and 38·1 min. The diuretic effects (urine output and urinary excretion of sodium) were generally found to increase with increasing infusion times; the total mean 24 h urine outputs were 1102, 1464, 2190, and 3470 ml for 10 s, 30 min, 2 h, and 8 h of infusion, respectively, and the corresponding values for sodium excretion were 170, 175, 272, and 440 mmol. Furosemide plasma concentrations and hourly urinary excretion rates of furosemide, sodium, and potassium during the apparent steady state (between 2 and 8 h) in the 8 h infusion study were fairly constant.

KEY WORDS Furosemide Pharmacokinetics Pharmacodynamics Intravenous infusion time

INTRODUCTION

Furosemide, a loop diuretic, is often administered as an intravenous bolus for treating ascites and oedema of cardiac, renal, and hepatic origin.[1,2] When

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administered in this way, furosemide usually produces a rapid and strong diuresis for 1–2 h, and the diuretic effect gradually reduces and subsides after 4 h.[1,2] This strong diuresis may cause side-effects such as fatigue, electrolyte imbalance, plasma volume depletion, decreased renal perfusion, oliguria, and azotemia.[3] For ascitic patients, such mode of administration may not be the most efficient since there is a limit to the amount of ascitic fluid that can be mobilized in a given period of time.[3,4]

Recently, Copeland *et al.*[5] reported that the total 12 h urine outputs from intravenous bolus administration (injected twice at 0 and 6 h) and 12 h of constant infusion of the same total dose (0·6 mg kg^{-1}) of furosemide were not significantly different in patients after cardiac surgery.[5] This is different from the report that the total diuretic activity of furosemide may be markedly affected by the rate of input or absorption.[6] Another interesting and unexplained finding from their study[5] is that after reaching the peak in the 3 h during the infusion, the hourly urine outputs gradually decreased and became approximately 50 per cent of the peak value at the end of 12 h of infusion.[5] Since no plasma concentrations or urinary excretion rates of furosemide were reported,[5] it appears difficult to rationalize the above seemingly unexpected results.

Although the pharmacokinetics and pharmacodynamics of furosemide after intravenous and oral administration to humans[1] and animals[7–9] have been extensively investigated, it appears that no detailed studies on the effect of intravenous infusion rate for the same total dose of furosemide on its kinetics and dynamics have ever been reported to date. This paper will report the results of such a study using dogs as a model.

EXPERIMENTAL

Animal preparation

Six conditioned, unanaesthetized male Beagle-Mongrel hybrid dogs (7·4–17·0 kg) were used. The dogs were fasted overnight with water ad libitum and restrained by means of a dog sling (Alice King Catham Medical Arts, Los Angeles, CA) during the experiment. An intravenous cannula (2 in., 22 ga., Sovereign, St. Louis, MO) with a 3-way stopcock (Pharmaseal K75, Pharmaseal Inc., Toa Alto, Puerto Rico) was placed into the cephalic vein of each foreleg for blood sampling or infusion of the drug and Lactated Ringer's solution, U.S.P. (Travenol Labs., Deerfield, IL). Urine collection was made from an indwelling polypropylene urinary catheter (5 Fr., 22 in., Sovereign). At the end of the experiment 1 ml of Flo-Cillin Suspension (Penicillin G, 300,000 units ml^{-1}, Veterinary Products, Bristol Labs, Division of Bristol-Myers, Syracuse, N.Y.) was administered intramuscularly for prophylactic purpose. A minimum washout period of 1 week elapsed between experiments.

Intravenous study

For intravenous bolus study (treatment I), 20 mg (15 mg was used for dog F) of furosemide (Lasix, 10 mg ml^{-1}, Hoechst-Roussel, Somerville, N.J.) was administered in 10 s and the midpoint of dosing was timed zero. For infusion studies, the same dose of furosemide was first diluted with normal saline solution, U.S.P. (Travenol Labs.) and then infused for 30 min (1·6 ml min^{-1}, treatment II), 2 h (0·3 ml min^{-1}, treatment III) or 8 h (0·11 ml min^{-1}, treatment IV) with the assistance of an infusion pump (Harvard Instruments, Model 975, Southnatick, MA). Treatment II was performed first and the other treatments were randomly chosen.

Approximately 0·5 ml of blood was collected at 0 (serving as control), 1, 5, 15, 30, 45, 60, 90, and 120 min for treatment I; 0, 15, 30, 35, 45, 60, 90, 120, 150, 180, and 240 min for treatment II; 0, 15, 30, 45, 60, 90, 120, 125, 135, 150, 180, 210, and 240 min for treatment III; and 0, 30, 60, 90, 120, 180, 240, 300, 360, 420, 480, 495, 510, and 540 min for treatment IV. Blood samples were centrifuged immediately to reduce or minimize the potential 'blood storage effect'.[10] Approximately 1 ml of heparinized normal saline (10 units ml^{-1}) was used to flush the cannula after each blood sampling in order to prevent blood clotting.

Urine collection times (the catheter being kept open during each collection period and urine was let to flow spontaneously into a collection beaker) were as follows: 0, 1, 2, 3, 4, 6, 8, and 24 h for treatment I; 0, 0·5, 1·5, 2·5, 3·5, 4·5, 8·5, and 24 h for treatment II; 0, 1, 2, 3, 4, 8, and 24 h for treatment III; and 0, 2, 3, 4, 5, 6, 7, 8, 10, and 24 h for treatment IV. Approximately 30 ml of air was used to flush the bladder to ensure completion of each urine collection. The dog was kept in a metabolic cage (Lab Products, Maywood, N.J.) with food and water *ad libitum* for the last (24 h) urine collection. Plasma and an aliquot of urine samples were stored in the freezer prior to analysis. The loss of fluid in urine during each collection period was immediately replaced with an infusion of equal volume of Lactated Ringer's solution.

Analysis of furosemide, sodium, and potassium

Furosemide in plasma and urine was assayed by a simple HPLC method[11] developed earlier in our laboratory. Sodium and potassium in urine were determined by Flame Photometry (Model IL 493, Instrumentation Lab., Lexington, MA).

Data analysis

The total area under the plasma concentration–time curve from time zero to infinity (AUC) was calculated using the trapezoidal rule-extrapolation method.[12] The logarithmic trapezoidal rule[13] was used during the declining phase and the linear trapezoidal rule during the rising phase or steady state. The area from the last point to infinity was estimated by dividing the last measured concentration by the terminal rate constant. The plasma

concentration of furosemide at time zero after bolus injection was assumed to be zero in order to reduce the potential significant overestimation of AUC when extrapolated based on the conventional instantaneous input principle or on the conventional central-compartment concept.[14]

The time-averaged[15] total body clearance (CL) and renal clearance (CL_r) were calculated by the following methods:

$$CL = \text{intravenous dose/AUC} \tag{1}$$

$$CL_r = U_{e(\infty)}/AUC \tag{2}$$

where $U_{e(\infty)}$ is the amount of furosemide excreted into the urine up to time infinity. (This was assumed to equal the total amount excreted in 24 h since no detectable furosemide could be found in urine collected later.)

The *venous*[12,16,17] mean residence time (MRT) was calculated using the conventional statistical moment method:

$$MRT = AUMC/AUC - T/2 \tag{3}$$

$$AUMC = \int_0^\infty t \times C_p dt \tag{4}$$

where T is the infusion time (zero for bolus study) and AUMC is the first moment of plasma concentration-time curve.

The volume of distribution at steady state (V_{ss}) based on *venous* data[16] was estimated by the following equation:

$$V_{ss} = MRT \times CL \tag{5}$$

The mean values of terminal half-life, V_{ss}, and clearances were determined by the harmonic mean method.[18]

The basal urine flow rates were 125, 456, 150, 200, 375, and 231 ml $24\,h^{-1}$ for dogs A–F, respectively; these were obtained based on the mean of a 4-day urine output. Therefore, in the calculation of the increase of urine output due to furosemide, the basal urine flow rate from each dog was subtracted from the total urine volume to obtain the 'net' diuretic effect.

Statistical analysis

The data were analysed for statistical significance ($p < 0{\cdot}05$) by analysis of variance with dogs as a block using the GLM procedure.[19]

RESULTS AND DISCUSSION

The mean furosemide plasma concentration–time curves after four treatments are shown in Figure 1, and the relevant pharmacokinetic and pharmacodynamic data are listed in Table 1. After intravenous bolus dose (treatment I), with the exception[14] of the initial period (0–1 min), the plasma

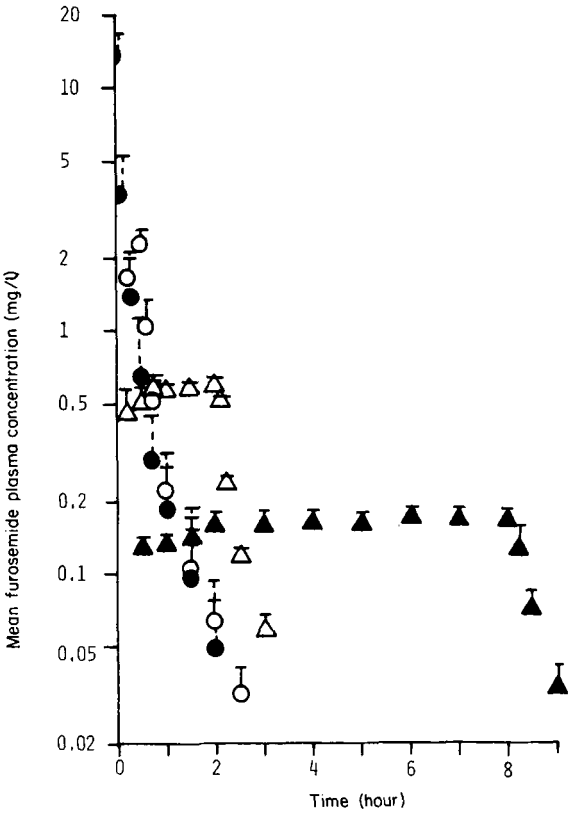

Figure 1. Mean furosemide plasma concentration-time profiles in 6 dogs following 10 s (●), 30 min (○), 2 h (△), and 8 h (▲) infusions of 20 mg of furosemide (15 mg was used for dog F). Each bar represents a standard deviation

levels decayed rapidly with a mean terminal half-life of 29·7 min (ranging from 25·6 to 33·6 min). After post-infusions (treatments II–IV), plasma concentrations also declined rapidly with a mean terminal half-life of 28·5 to 32·0 min. There was no significant difference in the mean time-averaged CL (19·1 to 22·0 ml min^{-1} kg^{-1}) and CL_r (10·5 to 13·7 ml min^{-1} kg^{-1}) among four different treatments. The mean contributions of renal clearance to total body clearance ranged from 54·1 to 67·5 per cent, which are consistent with early human,[1] dog,[7] and rat[11] studies. It took approximately 2 h of infusion to reach an apparent steady state plasma concentration of furosemide. This is also consistent with the prediction based on the plasma area method of Chiou,[20] since the 0–2 h plasma area after intravenous bolus could account for more than 97 per cent of the total area in all the 6 dogs studied.

The hourly urinary excretions of furosemide during the apparent steady state (between 2 and 8 h) in treatment IV were essentially constant in all the dogs studied (averaging about 1·3 mg h^{-1}) as shown on the top of Figure 2.

Table 1. Some pharmacokinetic and pharmacodynamic parameters of furosemide after 10-second, 30 min, 2 h, and 8 h of infusion of 20 mg (15 mg was used for dog F) of furosemide to 6 dogs

	Ten-second injection								Thirty-minute infusion							
Dog	A	B	C	D	E	F	Mean	(S.D.)	A	B	C	D	E	F*	Mean	(S.D.)
Body weight (kg)	15·0	12·8	13·1	13·0	17·0	8·0	13·2	(3·00)	14·0	11·6	12·3	16·0	11·4	7·4	12·1	(2·89)
% of the dose Excreted in urine	66·0	60·9	49·3	55·4	52·3	46·6	55·1	(7·30)	57·9	50·8	46·4	49·6	53·7	66·4	54·1	(7·16)
Terminal $t_{1/2}$ (min)	33·6	33·2	27·4	25·6	29·4	30·4	29·7	(3·17)	31·6	33·5	35·5	30·0	30·0		32·0	(2·39)
CL (ml min^{-1} kg^{-1})	17·6	16·7	16·6	25·8	22·7	19·3	19·3	(3·43)	19·2	26·1	19·8	24·1	22·3		22·0	(2·92)
CL_r (ml min^{-1} kg^{-1})	11·6	10·2	8·18	14·3	11·9	9·00	10·5	(2·25)	11·1	13·2	9·20	11·9	12·0		11·3	(3·22)
V_{ss} (1 kg^{-1})	0·281	0·303	0·395	0·347	0·337	0·366	0·334	(0·04)	0·355	0·608	0·406	0·557	0·573		0·478	(0·11)
MRT (min)	16·0	18·1	23·8	13·5	14·8	19·0	17·5	(3·68)	18·5	23·3	20·5	23·1	25·7		22·2	(2·78)
Urine output (ml)																
0–8 h	596	505	1006	873	614	1097	781	(222)	1659	1305	988	1284	1090	963	1215	(261)
0–24 h	862	711	1198	1433	1154	1252	1102	(298)	1974	1595	1204	1522	1304	1185	1464	(301)
Sodium excretion (mmol)																
0–8 h	118	108	130	151	122	130	126	(13·3)	197	158	118	172	143	97	148	(36·3)
0–24 h	168	151	152	220	191	138	170	(30·5)	230	191	136	210	177	107	175	(4·62)
Potassium excretion (mmol)																
0–8 h	34·9	23·2	21·3	40·3	32·0	15·1	27·8	(9·48)	31·1	20·3	19·3	29·4	25·9	20·2	24·4	(5·15)
0–24 h	72·0	57·4	26·7	82·7	80·5	20·1	56·6	(27·3)	37·6	37·6	28·9	34·3	44·5	27·1	35·0	(6·39)

* Blood sampling for dog F was not collected.

Table 1 Continued

	Two-hour infusion								Eight-hour infusion							
Dog	A	B	C	D	E	F	Mean	(S.D.)	A	B	C	D	E	F	Mean	(S.D.)
Body weight (kg)	13·3	12·3	13·0	13·0	16·0	8·0	12·7	(2·61)	14·0	12·3	13·5	13·1	17·0	8·0	13·0	((2·92)
% of the dose Excreted in urine	75·5	65·4	64·1	75·4	60·4	64·4	67·5	(6·36)	60·6	55·0	59·3	64·2	62·0	58·7	60·0	(3·14)
Terminal $t_{1/2}$ (min)	33·8	31·9	33·2	29·2	29·0	27·7	30·6	(2·51)	29·0	30·0	37·3	25·5	23·4	29·6	28·5	(4·82)
CL ($ml\,min^{-1}kg^{-1}$)	24·6	21·8	20·4	19·7	17·1	21·4	20·6	(2·50)	19·9	21·4	17·9	18·8	16·6	20·6	19·1	(1·41)
CL_r ($ml\,min^{-1}kg^{-1}$)	18·6	14·3	13·1	14·8	10·3	13·8	13·7	(2·74)	12·0	11·8	10·6	12·1	10·3	12·1	11·4	(0·82)
V_{ss} ($l\,kg^{-1}$)	0·686	0·592	0·485	0·522	0·422	0·396	0·499	(0·11)	0·723	0·832	0·885	0·643	0·509	0·807	0·708	(0·14)
MRT (min)	27·9	27·2	23·8	26·5	24·7	18·5	24·8	(3·43)	36·3	38·9	49·4	34·2	30·7	39·2	38·1	(6·37)
Urine output (ml)																
0–8 h	2477	1942	2005	2137	1841	1407	1968	(352)	3592	2429	3256	2527	2628	2623	2843	(468)
0–24 h	2813	2060	2091	2592	1996	1585	2190	(443)	4208	2877	3853	3554	3324	3004	3470	(508)
Sodium excretion (mmol)																
0–8 h	297	250	253	260	229	174	244	(40·8)	428	300	337	296	314	354	338	(49·3)
0–24 h	329	262	266	326	252	199	272	(49·0)	534	362	440	447	430	425	440	(55·3)
Potassium excretion (mmol)																
0–8 h	24·5	26·3	25·1	30·1	22·9	20·7	24·9	(3·19)	36·3	23·5	41·1	33·0	31·8	45·5	35·2	(7·69)
0–24 h	74·5	28·2	26·9	97·0	50·0	41·1	53·0	(27·7)	62·9	27·4	52·3	74·6	58·2	55·9	55·2	(15·7)

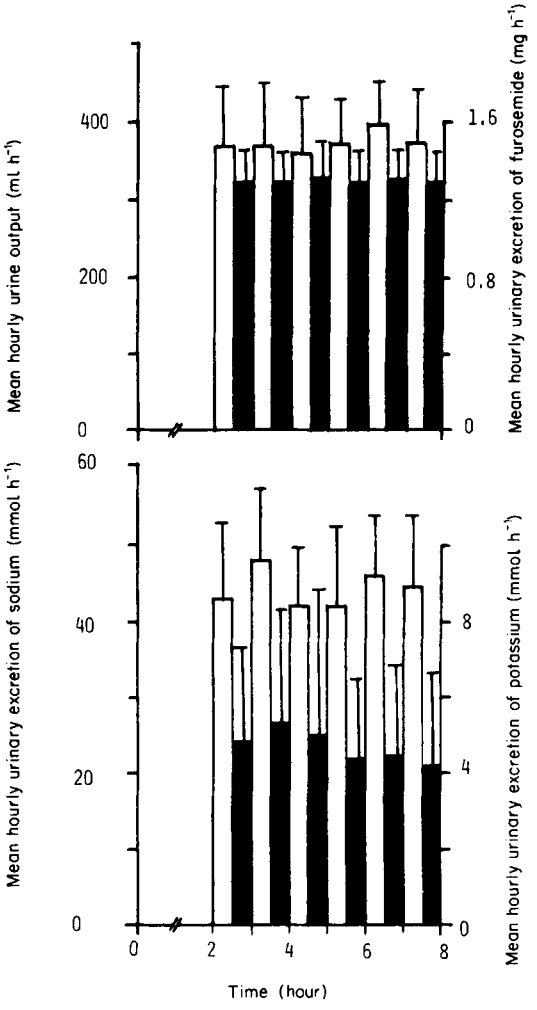

Figure 2. Mean hourly urine output (□) and urinary excretion (■) of furosemide (top), and mean hourly urinary excretion of sodium (□), and potassium (■) (bottom) in 6 dogs during steady state (between 2–8 h) following 8 h infusion of 20 mg of furosemide (15 mg was used for dog F). Each bar represents a standard deviation

The MRT and V_{ss} based on the *venous* data, on the other hand, showed a trend of infusion time dependency, being larger with a longer infusion time (Table 1). For example, both V_{ss} and MRT from treatment IV were approximately 2·0, 1·5, and 1·5 times larger than those from treatments I–III, respectively. The exact reason is unknown at this moment and remains to be fully explored. It is to be noted that although the systemic arterial plasma data should be more appropriate for estimating the 'true' MRT and V_{ss},[16,21] the

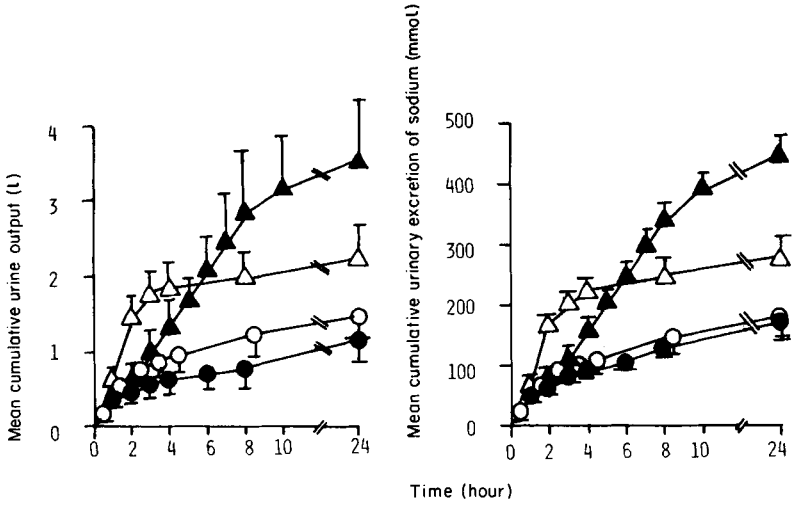

Figure 3. Mean cumulative urine output (left panel) and urinary excretion of sodium (right panel) as a function of time in 6 dogs following 10 seconds (●), 30 min (○), 2 h (△), and 8 h (▲) infusions of 20 mg of furosemide (15 mg was used for dog F). Each bar represents a standard deviation

results of the present findings based on venous data probably should also reflect the general trend if arterial data were employed.

The diuretic effects (urine output and urinary excretion of sodium) increased significantly with increasing infusion time (Figure 3 and Table 1) except for that between treatments I and II, although the total amounts of urinary excretion of furosemide among four treatments were not significantly different (Table 1). The mean 'net' total 24 h urine output for treatment IV was 4·31, 2·66, and 1·66 times higher than for treatments I–III, respectively, and the corresponding values for urinary excretion of sodium were 2·59, 2·51, and 1·62 (Table 1). The increase in diuretic effects with longer infusion time could be explained by relationship between the urinary excretion rate of furosemide and urinary excretion rate of sodium or urine flow rate as shown in Figure 4. It is clear that the higher diuretic effects from longer infusion times were due to their higher diuretic efficiencies (diuretic effect per unit of furosemide excreted) from more or most of the furosemide excreted into urine (lower graph in Figure 4). These results are consistent with the early study[22] showing similar diuretic effects from intravenous bolus and oral administrations of furosemide in humans even though the total urinary excretion of the drug after oral administration was only half of that obtained from intravenous administration. Our present dog data are, however, different from the early human study[5] showing the similar diuretic effect after the divided intravenous injection or intravenous infusion of the same total dose. The difference might mainly be due to the partial (as opposed to the full

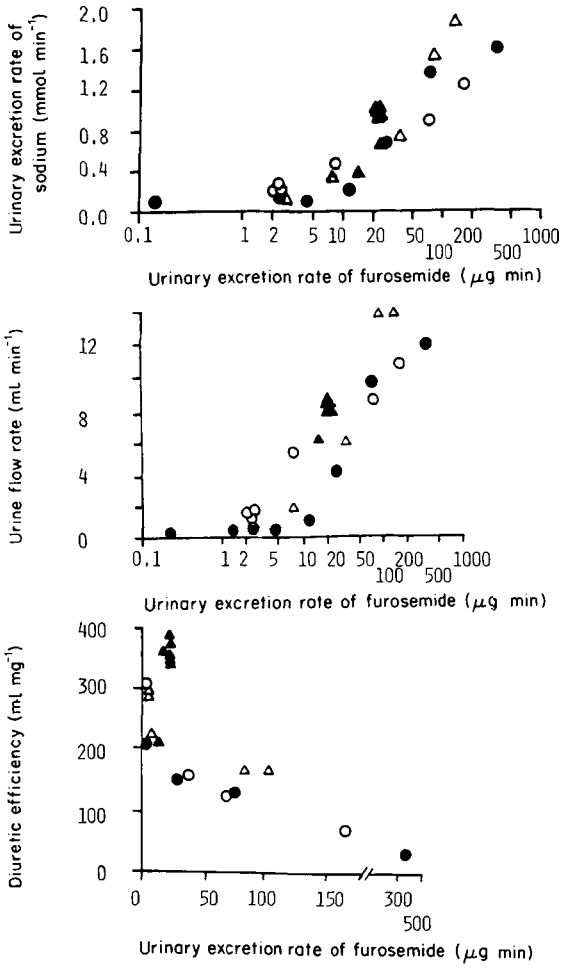

Figure 4. Relationship between urinary excretion rate of furosemide and urinary excretion rate of sodium (top) as well as urine flow rate (middle) and between diuretic efficiency ('net' urine flow rate/urinary excretion rate of furosemide) and urinary excretion rate of furosemide (bottom) in dog A following 10 s (●), 30 min (○), 2 h (△), and 8 h (▲) infusions of 20 mg of furosemide

replacement used in the present study) fluid replacement for urine loss used in their studies.[5] The importance of fluid replacement in the evaluation of kinetics and/or dynamics relationship of furosemide has been reported.[23,24]

The hourly urine outputs and hourly urinary excretions of sodium and potassium during steady state in treatment IV were fairly constant (Figure 2). The present urine output data are different from the trend of decreasing urine output in patients during the infusion reported by Copeland *et al.*[5] Again, this might be related to the incomplete replacement for urine loss used in their study[5] which might result in the development of acute tolerance.[23]

There was no significant difference in total urinary excretion of potassium with different infusion times although their urine outputs and urinary sodium excretions were significantly different (Table 1). Similar results were obtained after administration of furosemide to humans[25] and rats.[26] This might be due to the constant rate of potassium secretion in the distal tubule.[27]

Shear *et al.*[3] reported that there is a limit to the amount of ascitic fluid in patients that can be mobilized in a given period of time. Our present animal data (if it can be extrapolated to humans) might suggest that the intravenous infusion rather than bolus dosing could be preferred in treating ascitic patients.

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