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KINETIC DISPOSITION AND DIURETIC EFFECT OF FRUSEMIDE IN ACUTE PULMONARY OEDEMA

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1 The kinetic disposition and diuretic effect of frusemide was assessed in 16 patients with acute pulmonary oedema utilizing a specific gas-liquid chromatographic assay for the drug.

2 Serum frusemide concentrations decayed biexponentially with wide variation in both α half-life (range 15–79 min) and β half-life (range 127–1190 min). The β phase half-life was inversely related to creatinine clearance.

3 The apparent volume of distribution varied greatly among the patients (range 0.085–0.818 l/kg), and patients with an acute myocardial infarction had a larger peripheral kinetic compartment.

4 Patients with acute myocardial infarction excreted less unchanged drug and had a lesser urinary excretion of sodium and volume compared to patients without infarction.

5 The urinary excretion of sodium, chloride, calcium and volume was linearly related to the urinary excretion of unchanged frusemide.

Introduction

Frusemide is a potent diuretic agent recommended as treatment for several disease states such as renal failure, (Allison & Kennedy, 1971; Muth, 1968) ascites of hepatic cirrhosis (Fuller, Khambatta & Gobezie, 1977) as well as congestive heart failure or pulmonary oedema (Krupp & Chatton, 1978). Although widely used, there are a few studies available on its pharmacokinetic disposition in different disease states and its pharmacodynamic effect has been the subject of contradictory reports. Some authors have found no relationship between plasma frusemide concentrations and diuretic effect (Cutler, Forrey, Christopher & Kimpel, 1974; Huang, Atkinson, Levin, Levin & Quintalla, 1974), whereas others have observed a direct relationship between drug concentrations and the urinary excretion of sodium (Branch, Homeida & Levine, 1977). In contrast, some investigators have reported a direct relationship between urinary frusemide excretion and diuretic effect rather than with plasma frusemide concentrations (Lawrence, Ansari, Elliot, Dummer, Brunton, Whiting & Whitesmith, 1978; Rose, Pruitt, Dayton & McNay, 1976). The lack of data concerning the correlation of frusemide disposition and effect in patients with acute pulmonary oedema prompted the present study.

Methods

Patient selection and diagnosis

Sixteen patients with the diagnosis of acute, pulmonary oedema volunteered to participate in this study which was approved by the Ethics Committee of the Montreal General Hospital. Criteria for the diagnosis and admission into the study included:

1. Recent onset or acute exacerbation of severe dyspnea;
2. Acute respiratory distress with bilateral chest râles on auscultation;
3. Chest X-ray compatible with acute pulmonary oedema of cardiac origin.

The diagnosis was agreed upon by at least two physicians. The severity of the condition assessed on the basis of the chest X-ray (Aberman & Fulop, 1972) was classified as:

a) Mild: Hilar and pulmonary vascular congestion and either perivascular (hazy and undistinguished vessels) or septal (curly B lines) pattern of interstitial oedema.

b) Moderate: Alveolar oedema with small patchy nonconfluent densities, estimated to involve less than half the area of the lung fields.

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c) Severe: Alveolar oedema with large fluffy confluent densities estimated to involve more than half the area of the lung fields.

Some of the patients with acute pulmonary oedema had an acute myocardial infarction based on:

1. Increased serum enzymes, creatinine phosphate (CPK), glutamic oxaloacetic transaminase (SGOT), and lactic dehydrogenase (LDH) within 24–48 hours after onset of symptoms.
2. Electrocardiogram showing abnormal Q waves, changes in the ST segment and later, symmetrical inversion of T waves.

Clinical evaluation was completed within 20 min of the patient's arrival to the Emergency Unit. Frusemide (20 to 80 mg in 10 ml solution of 5% dextrose) was administered i.v. over 5 min by an infusion pump. The patient was asked to empty his bladder before the administration of frusemide. Patients were transferred to the Medical Intensive Care Unit (MICU) or Coronary Monitoring Unit (CMU). Other therapy was the responsibility of the attending staff in MICU or CMU. Administration of frusemide did not preclude other drug therapy. Routine treatment of acute pulmonary oedema instituted in the Emergency Unit may have included placing the patient in the semi-upright position, supplemental oxygen by mask, rotating tourniquets to the limbs as well as administration of morphine or theophylline.

Exclusions

Patients with pulmonary oedema secondary to inhalation, aspiration, or ingestion of toxins and patients with acute cardiac dysrhythmias or cardiovascular shock were excluded from this study. As patients received a drug which was accepted treatment of this disease, their consent was obtained only for blood and urine sampling in conjunction with this investigation.

Collection of biological samples

Blood samples were taken from the arm opposite to the one used for drug infusion via an indwelling venous catheter in an antecubital vein. The catheter was filled with a solution of heparin in saline (10 U/ml) between samples to prevent clotting. The catheter was withdrawn after the first 12 h. Thereafter, samples were taken by venepuncture.

Blood samples were taken at the following intervals: Predose, 10, 20, 30, 40, 50, 60, 70, 80, 100, 120 min and then 3, 4, 6, 8, 12, and 24 h after the dose and placed in glass tubes without anticoagulant. Serum was separated by centrifugation and frozen at −20°C until analyzed for drug and ionic content.

Urine samples

All urine excreted was collected during the following intervals for 24 h after drug administration: 0–20, 20–40, 40–60, 60–80, 80–100, 100–120 min and then 2–3, 3–4, 4–6, 6–8, 8–12, 12–24 h. The patient was asked to empty his bladder at the intervals described above. When that was not possible, urine was collected at the time the patient voided spontaneously. After measurement of volume, aliquots of urine samples were frozen at −20°C until subsequent analysis.

Sample analysis

Samples were analyzed over a period of 5 months and were checked during that time at least twice to assure that there were no differences in the measurements during that time. Serum samples were analyzed for frusemide and 2-amino-4-chloro-5-sulfamoylanthranilic acid, by gas liquid chromatography using an electron capture ^{63}Ni detector as described elsewhere (Perez, Sitar & Ogilvie, 1979). This method can distinguish frusemide from frusemide glucuronide and the anthranilic acid metabolite of frusemide.

Electrolyte assays

Sodium and potassium were determined by flame emission spectrophotometry. Calcium and magnesium were determined by atomic absorption spectrophotometry using an I.L. model 151 atomic absorption/emission spectrophotometer. Chloride was determined by titration with a Buchler-Catlove-chloridometer. Creatinine was determined by the Jaffe reaction and osmolality was determined by the freezing point depression with a Fiske osmometer.

Data analysis

Pharmacokinetic calculations were based on the assumption that the disappearance of frusemide from serum was consistent with a two compartment open kinetic model. Serum concentrations v time data were analyzed with an iterative least squares computer program, ASAAM-23 on an IBM 360/65 computer for derivation of pharmacokinetics constants (Berman & Weiss, 1966). This approach was possible for eleven of the sixteen patients. In the remaining five patients due to an additional dose of frusemide, it was not possible to estimate the α phase with precision but it was possible to calculate the late phase $T_{\frac{1}{2}}$ using a one compartment open model system after the last dose. Model independent kinetics were used to calculate Cl_S and Cl_R. Renal clearance of frusemide (Cl_R) was calculated for all the patients from the formula

$$Cl_R = \frac{(U).(V)}{AUC},$$

Where U = urinary concentration of frusemide (μg/ml), V = urine volume in ml, AUC = area under the serum concentrations *v* time curve for the time interval of urine collection. Urinary excretion rate (Exc) was calculated from the formula:

$$\text{Exc} = \frac{(U).(V)}{t},$$

where U = urinary concentration of frusemide (μg/ml), V = urine volume (ml), t = time of urine collection (min). A non-parametric method (Mann-Whitney U test) was used for the statistical analysis of data. Relationships between the kinetic disposition and dynamic effects of frusemide were assessed by correlation analysis using least squares linear regression followed by analysis of variance for goodness of fit. The minimum level for significance was accepted to be $P = 0.05$.

Results

a) *Patient population*

A majority of the 16 patients studied had a clinical diagnosis of acute myocardial infarction or coronary artery disease with severe or moderate acute pulmonary oedema by radiological classification (Table 1). Four patients had a creatinine clearance less than 60 ml/min. During the 24 h of this study, other drugs were administered in addition to frusemide. Twelve patients received digoxin, six received lignocaine, two morphine and two aminophylline.

b) *Kinetic disposition of frusemide*

Individual plots of serum frusemide concentrations over time revealed a biexponential decay in 11 patients. A representative plot of data from patient 1 is given in Figure 1. The α and β disposition phases can be readily distinguished and frusemide was detected 24 h after the single dose. Two compartment kinetic analysis of concentration over time data in the 11 patients revealed wide interpatient variability in the disposition rate constants and apparent volumes of distribution for frusemide (Table 2). One-compartment kinetic analysis applied to data from the five remaining patients because of additional doses of frusemide also revealed wide interpatient variability in these parameters. There was no difference in the $T_{\frac{1}{2}}\ \beta$ values of the 11 patients analyzed according to a two compartment model (median 306 min, range 127–1190 min) from half-life values of the five patients analyzed according to a one compartment model (median 192 min, range 138–293 min). The presence of an acute myocardial infarction or differences in the severity of pulmonary oedema did not correlate with variations in $T_{\frac{1}{2}}\ \alpha$ or $T_{\frac{1}{2}}\ \beta$. However, there was a negative correlation ($F_{1,14} = 12.2$; $P < 0.01$) between the frusemide $T_{\frac{1}{2}}\ \beta$ and urinary creatinine clearance measured during the 24 h period after frusemide administration (Figure 2). Patient 8 with the lowest creatinine clearance (25 ml/min) had the longest $T_{\frac{1}{2}}\ \beta$ (1190 min).

In the 11 patients for whom two compartment kinetic data are available (Table 2), the presence of an acute myocardial infarction was associated with a larger peripheral than central kinetic compartment for frusemide due to a larger rate constant k_{12} ($P < 0.02$). As a consequence, less frusemide would have been available in the central compartment for urinary elimination in these patients. During the first $T_{\frac{1}{2}}\ \alpha$, patients with an acute myocardial infarction excreted less of the administered dose as unchanged frusemide (3.4–10.2%) than patients without this diagnosis (11.7–19.5%) ($P < 0.01$). The larger proportion of the dose which was excreted unchanged in the urine during the first $T_{\frac{1}{2}}\ \alpha$ interval was associated with a larger urine volume and sodium excretion in the same interval in patients without an acute myocardial infarction as compared to those with acute infarction. Although the tendency for patients without an acute infarction to excrete a greater portion of the administered frusemide unchanged in the urine continued over the entire 24 h period after admission to the study (Table 3) differences in urine volume and sodium content did not maintain statistical significance. Patient 8 was omitted from this analysis because of his severe renal failure.

There was a wide interindividual variability in the apparent volume of distribution, $V_d$ss in the 11 patients analyzed by two compartment kinetic model and $V_d$area in the five patients analyzed by a one compartment model, with a median value of 0.353 l/kg and range 0.085–0.8181 l/kg. There was no apparent relationship between the $V_d$ss or $V_d$area and serum albumin, presence of an acute myocardial infarction or the severity of the pulmonary oedema.

As could be predicted from the relationship between the serum frusemide $T_{\frac{1}{2}}\ \beta$ and creatinine clearance (Figure 2) there was a positive but weak relationship between the serum frusemide clearance and the creatinine clearance ($F_{1,15} = 5.07$, $P < 0.05$, $r = 0.50$). Although the renal frusemide clearance was not related to the creatine clearance, non-renal clearance of frusemide and the creatinine clearance were weakly related ($F_{1,15} = 4.68$, $P < 0.05$, $r = 0.48$). The glucuronide metabolite of frusemide was the major biotransformation product in these patients. The excretion of both the glucuronide and anthranilic acid metabolites of frusemide was inversely related to the creatinine clearance in that as the creatinine clearance decreased, the amount of the two metabolites in the urine was increased.

Table 1 Description of the patient population

Patient	Age (years)	Sex	Weight (kg)	Acute pulmonary Oedema (cause*)	(classification)	Creatinine clearance (ml/min)
1	67	M	73	MI	severe	59
2	81	M	91	MI	moderate	89
3	75	M	90	hypertension	mild	145
4	74	M	66	MI	severe	115
5	69	F	52	MI	moderate	132
6	65	M	68	alcoholic cardiopathy	severe	161
7	51	M	73	CAD	mild	107
8	75	M	77	hypertension	severe	25
9	28	F	68	MI	moderate	142
10	65	M	77	MI	moderate	107
11	68	M	64	MI	moderate	55
12	88	F	50	CAD	moderate	134
13	70	M	82	MI	severe	114
14	75	M	100	CAD	moderate	123
15	88	F	56	MI	severe	70
16	64	F	47	CAD	severe	50
Mean	69.0		70.9			102
s.d.	14.3		15.3			40
Median	69		71			110

*MI acute myocardial infarction
CAD coronary artery disease

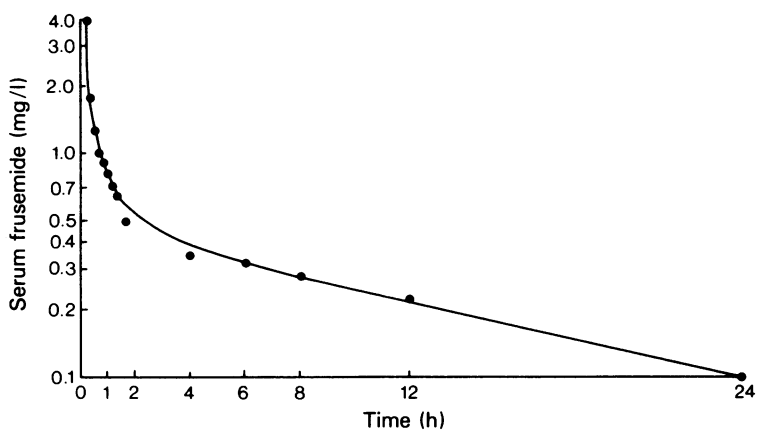

Figure 1 Semilogarithmic plot of serum frusemide concentrations over time in patient 1 (male, 67 years, 70 kg) after a single i.v 60 mg dose.

c) Diuretic effect of frusemide

Minimum urine osmolality values occurred during the α phase of serum frusemide disposition in all patients, coincident with the peak diuretic effect and always within 80 min of the dose. When the ratio of the renal clearance of sodium over the renal clearance of frusemide (Cl_{Na}/Cl_F) was examined, this ratio was always higher for the duration of the α phase of serum frusemide disposition (median 0.72, range 0.45–2.80) than it was during the β phase (median 0.35, range 0.02–1.31). Because of changing values of this ratio with time, correlation coefficients by linear regression analysis tested by ANOVA were weak for the relationship between Cl_{Na} and Cl_F in sequential urine samples of individual patients for the entire 24 h period (Table 4). Some improvement was obtained in the correlation between Cl_{Na} and the serum frusemide concentrations (CS_F) with significant r values observed in 9/16 patients. A significant r value

Table 2 Kinetic disposition and effect of frusemide in patients with acute pulmonary oedema with and without an acute myocardial infarction (MI)

Patients with acute MI (n=6)	*Dose (mg)*	$T_{\frac{1}{2}}\alpha$ *(min)*	$T_{\frac{1}{2}}\beta$ *(min)*	k_{12} (h^{-1})	k_{21} (h^{-1})	V_1 *(l/kg)*	V_2 *(l/kg)*	*Urine content in one $T_{\frac{1}{2}}\alpha$ interval: Frusemide (% of dose)*	*Volume (ml)*	*Sodium (mEq)*
1	60	18	816	1.720	0.435	0.164	0.647	10.1	157	17
2	20	35	306	0.413	0.246	0.031	0.054	9.1	253	21
9	20	29	554	0.811	0.253	0.058	0.210	9.7	147	10
10	80	28	290	0.550	0.240	0.248	0.570	8.2	187	18
11	80	25	414	0.903	0.300	0.156	0.461	11.3	272	28
13	40	15	145	1.140	0.610	0.073	0.137	3.4	250	20
Mean	50	25	420	0.922	0.347	0.122	0.346	8.6	211	19
s.d.	28	7	236	0.468	0.148	0.081	0.245	2.8	54	6
Median	50	27.5	360	0.856	0.276	0.113	0.335	9.4	218.5	19
Patients without acute MI (n=5)										
3	40	31	127	0.340	0.580	0.150	0.088	19.0	392	34
8	40	79	1190	0.257	0.090	0.082	0.235	—	—	—
12	40	26	203	0.600	0.760	0.205	0.163	19.5	361	34
14	40	46	265	0.260	0.270	0.144	0.148	12.2	926	56
16	40	35	344	0.351	0.188	0.124	0.231	11.7	460	36
Mean	40	43	426	0.361	0.377	0.141	0.173	15.6	535	40
s.d.	0	21	194	0.140	0.281	0.044	0.061	4.2	264	11
Median	40	35	265	0.340	0.270	0.144	0.163	15.6	426	35
Mann Whitney U test *P* value	NS	NS	NS	< 0.02	NS	NS	NS	< 0.01	< 0.01	< 0.01

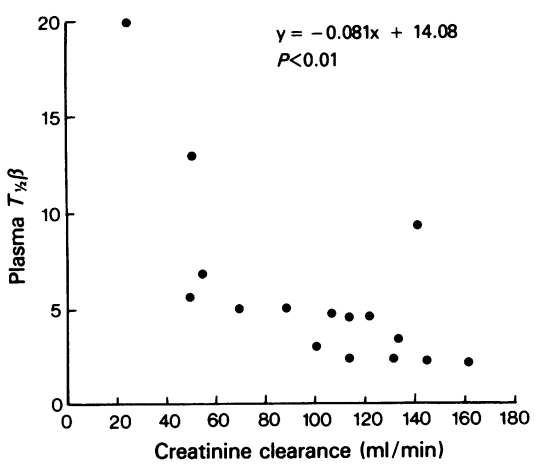

Figure 2 Relationship between the creatinine clearance and plasma frusemide $T_{\frac{1}{2}}$ β in patients with acute pulmonary oedema.

was obtained in all 16 patients for the correlation between the urinary excretion of sodium (Exc_{Na}) and the concomitant urinary excretion of unchanged frusemide (Exc_F). A similar relationship was obtained between urine volume and urinary frusemide excretion as well as for urinary chloride excretion or calcium excretion and concomitant urinary frusemide excretion (Table 4). Thus, the urinary excretion of sodium, chloride, calcium and volume increased linearly with the urinary excretion of frusemide. The urinary excretion of potassium or magnesium was unrelated to the urinary excretion of frusemide in these patients. Although there was considerable interindividual variation in the slopes of relationship Exc_{Na}/Exc_F (range 0.05 to 21.85) or urine volume/Exc_F (range 27.1 to 168.0), they were not correlated with the creatinine clearance values.

Discussion

Major observations in this study include the demonstration of altered frusemide disposition in patients with pulmonary oedema, the detrimental influence of an acute myocardial infarction on frusemide distribution and diuretic effect, and the direct relationships between the urinary excretion of unchanged frusemide and urine volume, sodium, chloride and calcium content.

The shortest $T_{\frac{1}{2}}$ α in our study was twice as long as mean values reported for normal volunteers or patients with uremia (Andreasen & Mikkelson, 1977;

Table 3 Twenty-four hour urine volume, sodium and content of unchanged furosemide expressed as a per cent of the dose administered

		24 h urine content		
Patients with acute MI ($n=9$)	*Dose* (*mg*)	*Frusemide* (% *of dose*)	*Volume* (*ml*)	*Sodium* (*mEq*)
1	60	55.8	1174	163
2	20	56.0	2411	236
4	160	55.6	3270	246
5	80	44.8	2860	325
9	20	48.7	1030	66
10	80	67.2	2490	205
11	80	31.2	1398	52
13	60	46.3	4290	166
15	80	67.5	2385	170
Mean	71	52.6	2348	181
s.d.	41	11.4	1047	86
Median	70	55.6	2411	170
Patients without acute MI ($n=6$)				
3	40	56.0	1878	167
6	80	57.6	6390	568
7	120	71.8	2340	217
12	60	73.4	2330	182
14	40	61.2	5070	248
16	40	62.5	1260	70
Mean	63	63.8	3211	242
s.d.	32	7.3	2034	171
Median	50	61.9	2335	200
Mann Whitney U Test *P* value	NS	< 0.05	NS	NS

Table 4 Correlation coefficient values for the relationship between the elimination of sodium, chloride, calcium and urine volume with the disposition of frusemide

Patients	Cl_{Na}/Cl_F	Cl_{Na}/Cs_F	Exc_{Na}/Exc_F	*Urine volume* $/Exc_F$	Exc_{Cl}/Exc_F	Exc_{Ca}/Exc_F
1	0.77	0.84	0.94†	0.97†	0.91†	0.90†
2	0.53	0.98†	0.91†	0.92†	0.96†	0.99†
3	0.47	0.78	0.99†	0.99†	0.99†	0.98†
4	0.53	0.72	0.94†	0.91†	0.97†	0.95†
5	0.80	0.97†	0.98†	0.99†	0.99†	0.99†
6	0.80	0.42	0.90†	0.90†	0.90†	0.80
7	0.82	0.48	0.99†	0.90†	0.97†	0.80
8	0.75	0.90†	0.96†	0.95†	0.99†	0.99†
9	0.87	0.99†	0.92*	0.92*	0.91*	0.94*
10	0.66	0.57	0.88*	0.90*	0.88*	0.92*
11	0.81	0.96*	0.99†	0.95†	0.99†	0.98†
12	0.49	0.95†	0.97†	0.96†	0.94†	0.88*
13	0.29	0.98†	0.93†	0.98†	0.98†	0.98†
14	0.50	0.84	0.98†	0.96†	0.94†	0.98†
15	0.70	0.11	0.90†	0.90†	0.88*	0.88*
16	0.72	0.99†	0.99†	0.93†	0.99†	0.97†

*P value (ANOVA) < 0.05
†P value (ANOVA) < 0.01

Calesnick, Christensen & Richter, 1966; Rane, Villeneuve, Stone, Neis, Wilkinson & Branch, 1978). The median $T_{\frac{1}{2}}\alpha$ of 29.4 min in this study was also twice as long as the mean value of 12.5 min previously observed in six patients with chronic congestive heart failure (Andreasen & Mikkelsen, 1977). Our patient population had acute pulmonary oedema with a high prevalence of acute myocardial infarction. It is likely that alterations in cardiovascular haemodynamics including a decreased cardiac output and changes in blood flow distribution could account for a considerable delay in drug distribution. However, longer $T_{\frac{1}{2}}\alpha$ values were not observed in patients classified as having severe pulmonary oedema compared with the rest of the patients. The rate constant k_{12} for transfer of drug from the central to the peripheral compartment (median 0.477 h^{-1}, range 0.257–1.580) was several fold smaller than values reported for normal subjects (Andreasen, Hansen, & Mikkelsen, 1978; Lesch, Carasos & Mulholland, 1962) but was similar to the mean of 0.39 h^{-1} reported for six patients with chronic congestive heart failure (Andreason & Mikkelsen, 1977).

The initial volume of distribution (V_1 median value 0.144 l/kg, range 0.031–0.248) was larger than values reported for normal subjects 0.083 ± 0.007 and 0.098 ± 0.026 (Andreasen *et al.*, 1978) 0.068 ± 0.007 (Rane *et al.*, 1978), patients with uremia 0.061 ± 0.009 (Rane *et al.*, 1978), 0.105 (Andreasen *et al.*, 1978) or patients with chronic congestive heart failure 0.080 ± 0.007 l/kg (Andreasen & Mikkelsen, 1977). We speculate that the initial volume of distribution for frusemide may include oedema fluid in the pulmonary bed. The final volume of distribution V_dss or V_darea (median 0.353l/kg, range 0.085–0.818 l/kg) was also larger than values reported for normal subjects 0.181 ± 0.105 (Andreasen & Mikkelsen, 1977); 0.197 ± 0.033 (Andreasen *et al.*, 1978); 0.110 ± 0.007 (Rane *et al.*, 1978) or for subjects with uremia 0.117 (Huang *et al.*, 1974); 0.124 ± 0.009 (Rane *et al.*, 1978) nephrotic syndrome 0.183 ± 0.027 (Rane *et al.*, 1978) or chronic heart failure 0.140 ± 0.083 (Andreasen & Mikkelsen, 1977). The larger V_dss in patients with acute pulmonary oedema was in part due to a larger V_1 in all patients and in part due to a larger V_2 in patients with an acute myocardial infarction (Table 2). In turn, the larger V_2 was due to the larger value for the rate constant k_{12} in these patients. A larger proportion of a given dose of frusemide would have been distributed to the peripheral compartment, and therefore would be unavailable for elimination in the urine as unchanged drug. This is supported by our observation that patients with an acute myocardial infarction excreted from 31.2–67.5% of the dose unchanged in 24 h whereas those without a myocardial infarction excreted from 56.0–73.4% of the dose as unchanged frusemide. It is likely that haemodynamic factors were responsible for the differences in drug distribution.

The proportion of the dose excreted in the urine as unchanged drug was less than average values reported for normal subjects 80% (Calesnick *et al.*, 1966), 92% (Cutler *et al.*, 1974), 82–84% (Beermann, Dalen, Lindstrom & Rosen, 1975) 63% (Andreasen & Mikkelsen 1977), 65% (Branch *et al.*, 1977), or patients with chronic congestive failure 63% (Andreasen & Mikkelsen, 1977). Non-renal clearance averaged 49.3% (range 23.6–84.2%) of total clearance which agrees with recent reports in normal subjects (Rane *et al.*, 1978). Although renal clearance values appeared normal and imply normal excretory process for frusemide by the kidneys, the reduced percentage of the dose eliminated by the renal route as unchanged frusemide is consistent with decreased delivery of drug to the site of elimination due to the larger than normal peripheral kinetic compartment.

The diuretic effect of frusemide was poorly correlated with its serum concentrations or renal clearance. This is in contrast to the report of Branch *et al.* (1977), who observed a linear relationship between plasma frusemide concentrations in the beta phase and the rate of sodium excretion. The excretion of sodium in the present study was best related to the excretion of unchanged frusemide in the urine. As the effects of most drugs are proportional to drug concentration at its site of action, the excretion of unchanged frusemide must have been closely related to the amount of drug at its receptor site. This is consistent with the conclusion *in vitro* that frusemide requires access to the luminal side of isolated nephron segments rather than the plasma membrane for a diuretic effect (Burg, Stoner, Cardinal & Green, 1973).

Although renal function as determined by creatinine clearance in these patients with acute pulmonary oedema was directly related to the serum frusemide clearance or $T_{\frac{1}{2}}\beta$, there was no apparent relationship between renal function, as indicated by creatinine clearance, and the renal response to frusemide. There was a linear relationship between the urinary excretion of frusemide and increase in urine volume and content of sodium, chloride, and calcium. The slopes of the frusemide excretion-sodium excretion curves were considerably more variable than those reported by Lawrence *et al.* (1978) in normal individuals. The slopes were independent of renal function, the presence of an acute myocardial infarction or the severity of pulmonary oedema. Other factors must have been responsible for the variability in the renal response to frusemide. Although several investigators have observed increased calcium excretion after the administration of frusemide (Gall, Raphael & Offenstade, 1971; Suki, Yium & Von Munder, 1970; Tolft & Rain,

1970; Walser, 1970; Walser & Robinson, 1963), this is the first report of a linear relationship between the rate of urinary calcium excretion and the rate of urinary frusemide excretion. Attention should be paid to the loss of calcium in older patients given high doses of frusemide chronically as the development of osteoporosis could be accelerated.

Acute pulmonary oedema was associated with a prolongation of the $T_{\frac{1}{2}}$ α and $T_{\frac{1}{2}}$ β values for frusemide, a larger initial and final volume of distribution and reduced elimination of the dose as unchanged drug in the urine as compared to values reported in the literature for normal subjects. Pharmacokinetic data from normal volunteers might be affected by aging. At this time, the effect of aging on alteration of the kinetic disposition of frusemide is not known. The presence of an acute myocardial infarction was associated with an increased distribution of frusemide out of the central kinetic compartment and a further reduction in the elimination of the dose as unchanged drug in the urine. Since the urinary excretion of unchanged drug was directly related to the urinary volume and sodium excretion, this altered kinetic disposition could acount in part for the variable diuretic effect of frusemide in patients with acute pulmonary oedema.

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