Europ. J. clin. Pharmacol. 12, 15–22 (1977)

European Journal of
Clinical Pharmacology

Distribution, Elimination and Effect of Furosemide in Normal Subjects and in Patients with Heart Failure

F. Andreasen and E. Mikkelsen

Institute of Pharmacology, University of Aarhus, and the Department of Cardiology, Aarhus Kommunehospital, Aarhus, Denmark

Summary. After furosemide 40 mg i. v. its plasma concentration was significantly higher during an 8-hour period in 6 patients with left sided heart failure than in 8 normal subjects. The plasma clearance was significantly lower in the patients than in the normal subjects – 1.23 and 2.34 ml/kg/min, respectively. The apparently smaller volume of distribution in the cardiac patients (0.140 l/kg and 0.181 l/kg, respectively) was not significantly different. In the group of normal subjects, whose ages ranged from 27 to 74 years, no correlation was found between age and either plasma clearance or volume of distribution. In all the patients, the renal clearance of furosemide rose from the first to the second hour after the injection (average ± SD) – 39 ± 17 and 77 ± 51 ml/min. In normal subjects, the average values did not change – 116 ± 79 and 117 ± 54 ml/min. The urinary excretion of furosemide and a metabolite (probably a glucuronide) was measured in 16 individuals. 24-hour urines from all the subjects investigated contained between 20 and 30 mg unchanged furosemide (average 25.2 mg). In addition, between 2.7 and 11.2 mg (average 6.7 mg) furosemide was excreted as the metabolite in five patients who had been treated with furosemide for at least the preceding 6 months. An average of 0.8 ± 0.8 mg of the metabolite was found in 11 subjects who had not previously been treated with furosemide.

Key words: Pharmacokinetics, furosemide, heart failure, anticoagulants, protein binding, drug metabolism.

Furosemide is given intravenously to patients suffering from acute left-sided heart failure. The relieving effect on the congestion of fluid in the capillary bed is described as dramatic (Peltola, 1965; Davidov et al., 1967; Dikshit et al., 1973). The drug is also used in long-term treatment of chronic congestive heart failure.

In the present investigation, furosemide was given to cardiac patients and to normal subjects in order to study:

1. Volume of distribution and plasma clearance of furosemide.
2. Renal excretion of furosemide.
3. The effect of long-term furosemide treatment on the excretion of possible metabolites.

Materials and Methods

The criteria for including patients in the study were:

1. Auscultatory and radiographic signs of pulmonary congestion and cardiac enlargement.
2. To study furosemide in untreated subjects, a selection of patients was made who had never previously been treated with diuretics or salt restriction.
3. For the study of effects of chronic treatment patients were chosen who had received furosemide daily for at least the preceding 6 months.

The following patients were excluded:

1. Patients with a diagnosis of hypertensive vascular disease and those with two or more blood pressure readings above 160 mm Hg systolic and/or 95 mm Hg diastolic.
2. Patients with symptoms or signs of renal disease.
3. Patients in "shock" and/or one blood pressure reading below 110 mm Hg systolic.

The attempt was made to select normal subjects with an age distribution similar to that anticipated in the patients.

The following subjects were studied: (1) Eight

volunteers (Group A) who at the time of the investigation showed no symptoms or signs of disease. Before the study they were informed of the procedures involved. The two women and six men were between 27 and 74 years of age (mean 52 years). Their chest-rays and electrocardiograms were normal and so were the blood concentrations of haemoglobin, erythrocytes and leucocytes. The erythrocyte sedimentation rate was normal and serum electrolyte concentrations and electrophoretic pattern were within normal limits. The serum creatinine concentration did not exceed 1.2 mg per 100 ml. The plasma concentrations of glucose, GPT and GOT and the prothrombin concentration were within normal limits; (2) Eighteen patients admitted to the hospital because of congestive heart failure. The four women and 14 men were between 40 and 90 years (mean 66 years). Six of the patients (Group B, mean age 69 ± 24) had just had their first attack with symptoms of cardiac decompensation; they are referred to as the acutely ill. The remaining 12 (Groups C and D) had been under daily treatment with furosemide for at least the preceding 6 months, and most of them were also on digoxin. Six of the 12 (Group D) were under anticoagulant therapy with phenprocoumon, warfarin or dicoumarol. At the time of the investigation, no drugs other than digoxin had been given for the preceding 12 h. No medication was given during the study.

Furosemide 40 mg was given intravenously through an armvein to all 26 subjects. Blood samples were collected from an indwelling cannula in a vein in the opposite arm. They were taken into a heparinized glass tube at short intervals during the first hour and then at longer intervals – at 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 300, 360, 420 and 480 min. The samples were centrifuged at once and the plasma kept at −20° for a few weeks until analyzed. The urine was collected in fractions as indicated in Table 6. When possible, the concentration of furosemide in blood and urine was followed for 24 h.

Plasma Assay

A fluorometric method was used for determination of the plasma concentration of furosemide (Andreasen and Jakobsen, 1974). The sensitivity of the method in in-vitro experiments is about 10 ng/ml, but the specificity is limited, and only values above 0.1 μg/ml can be regarded as reliable in individual patients. A plasma sample drawn from each subject before injection was used as an individual blank. In 11 subjects, duplicate determinations of the protein-bound fraction of the drug were carried out by the ultrafiltration method described by Andreasen (1973).

Urine Assay

Furosemide in urine was determined by the thin-layer chromatography (TLC) method of Kind and Schmid (1970). The procedure culminates in spectrofluorimetry of an extract of a spot scraped off the plate. The r_f value for furosemide was 0.50, for anthranilic acid it was 0.66, and for 4-chlor-5-sulphamoyl anthranilic acid 0.39. The latter two possible metabolites, which could increase the fluorescence in the final solution, were, therefore, easily separated from furosemide by this procedure. In the present study spots other than furosemide were removed for measurement of fluorescence only if it was possible to see a fluorescent area on the plate. Only concentrations above approx. 0.5 μg/ml of anthranilic acid and 1 μg/ml of 4-chlor-5-sulphamoyl anthranilic acid in the original urine sample gave visible fluorescence. The spot which followed the furosemide standard was not split in two-dimensional TLC with methanol for the second dimension. Furthermore, the fluorescence changed with the pH level, as described for furosemide by Forrey et al. (1974).

After extraction a linear relationship was found between the logarithm of the concentration and the relative fluorescence intensity in the range 0.1 to 32 μg/ml in the original sample. Fifteen separate determinations of a urine to which has been added furosemide 10 μg/ml gave 10.00 μg/ml ± 0.35 (S. D.). Fischermann's β-glucuronidase 400 μl (2000 units) was added to 1 ml of every urine sample, which was then incubated at 37 °C for 17 h. Simultaneously samples without β-glucuronidase were incubated. The difference in furosemide concentration between urine samples with and without β-glucuronidase was used as a measure of the concentration of a metabolite, which was then expressed in furosemide weight units.

Calculations

The calculations were based on the assumption that the disappearance of furosemide from the plasma could be described by an open two-compartment model, with elimination taking place only from the central compartment:

$$C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}, \quad (1)$$

where C_p is the plasma concentration of furosemide. A and B are the intercepts with the y-axis (value at time 0) derived from the two exponential curves

described by (1) and further characterized by the "hybrid" constants α and β. α is the slope of the distribution phase (residual value), and β is the slope of the elimination phase. The half life of each phase was calculated. The initial volume of distribution, V_c, (central volume) is:

$$V_c = \frac{D}{A+B} \tag{2}$$

where D is the dose. The volume of distribution at "steady state" $(V_D)_{ss}$, which compensates for the elimination of drug before the equilibrium state is reached, is:

$$(V_D)_{ss} = \frac{\frac{A'}{\alpha^2} + \frac{B'}{\beta^2}}{\left(\frac{A'}{\alpha} + \frac{B'}{\beta}\right)^2} \tag{3}$$

where $A' = \frac{A}{D}$ and $B' = \frac{B}{D}$.

The plasma clearance, Cl, of furosemide was calculated as:

$$Cl = \frac{1}{\frac{A'}{\alpha} \cdot \frac{B'}{\beta}}. \tag{4}$$

The equations (1)–(4) were used by Riggs (1963), Riegelmann et al. (1968) and Thompson et al. (1973) to characterize the distribution and elimination of drugs. Gibaldi et al. (1969) and Gibaldi and Perrier (1972) used a different proportionality constant, $(V_D)_\beta$ – equal to the $(V_D)_{area}$ discussed by Riegelmann et al. (1968) – to relate the drug concentration in plasma to the total amount of the drug in the body "at any time after the attainment of pseudodistribution equilibrium" such that:

$$(V_D)_\beta = \frac{V_c}{f_c}, \tag{5}$$

where f_c is the fraction of drug present in the central compartment. $(V_D)_\beta$ was calculated here as suggested by Gibaldi et al. (1969):

$$(V_D)_\beta = \frac{V_c \cdot \alpha}{K_{21}}, \tag{6}$$

where K_{21} is the rate constant for the transfer from the peripheral to the central compartment.

A Hewlett Packard computer (HP 30) was used to estimate these parameters (Tables 1 and 2). By a non-linear regression analysis programme the plasma concentrations for each subject or each group of subjects were used to obtain the best possible fit to (1). A weighting factor has to be used in the computer program, because the relative errors in the measured values of C_p increase as C_p decreases. A weighting factor was chosen which did not cause any obvious trend in the differences between the calculated, and observed values of C_p (cf. Boxenbaum, 1974), and (2) which for a given set of data resulted in the smallest spread (S. D.) of the estimated parameters. Accordingly, in this study each datum was weighted by the reciprocal of the plasma concentration. The procedure by which the volume of distribution and the clearance was calculated always gives very wide confidence intervals (cf. Westlake, 1971, and Table 2).

Table 1. Age and plasma clearance and volume of distribution of furosemide in the eight normal subjects

Age years	Plasma clearance ml/min · kg	Total volume of distribution 1/kg
27	2.19	0.266
40	2.71	0.205
42	3.54	0.139
53	2.71	0.138
60	1.53	0.136
60	1.86	0.187
62	2.20	0.240
74	2.00	0.210

The renal clearance of furosemide was calculated as

$$\text{clearance} = \frac{u \cdot v}{p},$$

where u is the average concentration (μg/ml) in the urine and, p, the average concentration in plasma (μg/ml) during a given period, where v ml urine is collected.

Results

The average concentration of furosemide in plasma as a function of time after intravenous administration of 40 mg to eight normal subjects and to six patients suffering from left-sided heart failure is shown in Figure 1. The 5-minute values were not significantly different in the two groups, but at all subsequent time intervals the heart failure group had significantly higher levels than the normals ($p < 0.05$, Mann Whitney test).

Average furosemide concentrations as a function of time in the 12 patients who had received long-term furosemide treatment prior to the study are shown in Figure 2. Six of the patients were not on anticoagulants, and the other six were. The average values for the former patients were higher at all

Table 2. Pharmacokinetic parameters calculated from the average plasma concentration during an 8-hour period after i. v. injection of furosemide 40 mg. (Mean ± S. D.) a) Indicates $p < 0.05$ compared to group A

	Half-life Distribution Phase	Half-life Elimination Phase	Initial Volume of Distribution		Total volume of Distribution $(V_d)_\beta$	$(V_d)_{ss}$		Plasma Clearance	
	min	min	1	1/kg	1	1	1/kg	ml/min	ml/min·kg
A Normal subjects (n = 8)	9.5	71.8	5.86 ±0.47	0.083 ±0.007	17.20 ±4.64	12.80 ±7.40	0.181 ±0.105	165.9 ±42.4	2.34 ±0.60
B Patients with cardiac decompensation not previously treated with furosemide (n = 6)	12.5	92.1	5.40 ±0.44	0.080 ±0.007	11.09 ±3.22	9.51 ±5.63	0.140 ±0.083	83.5[a] ±15.9	1.23[a] ±0.23
C Patients with cardiac decompensation under long-term furosemide treatment (n = 6)	9.4	134.1	5.07 ±0.52	0.076 ±0.008	13.27 ±5.53	11.77 ±10.04	0.176 ±0.150	68.6 ±21.6	1.02 ±0.32
D Patients with cardiac decompensation under long-term treatment with furosemide and a vitamin-K antagonist (n = 6)	18.9	115.9	6.14 ±1.02	0.091 ±0.015	21.16 ±13.87	12.73 ±19.06	0.188 ±0.281	126.5 ±82.2	1.86 ±1.21

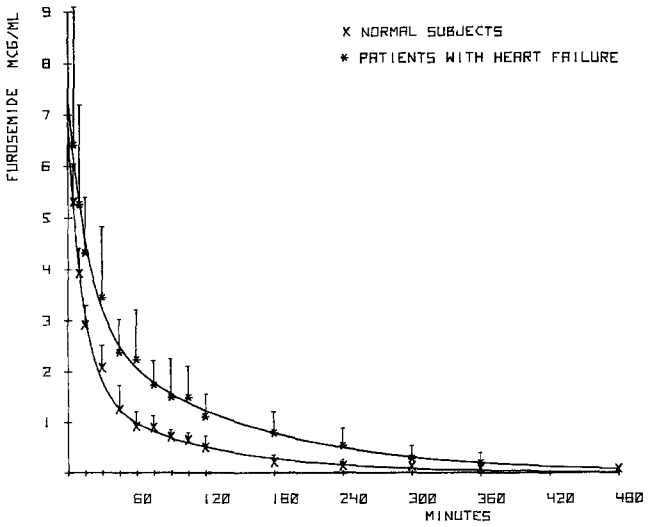

Fig. 1. Average plasma concentration of furosemide as a function of time after intravenous injection of 40 mg in eight normal subjects and in six previously untreated patients suffering from acute congestive heart failure. Standard deviations are shown

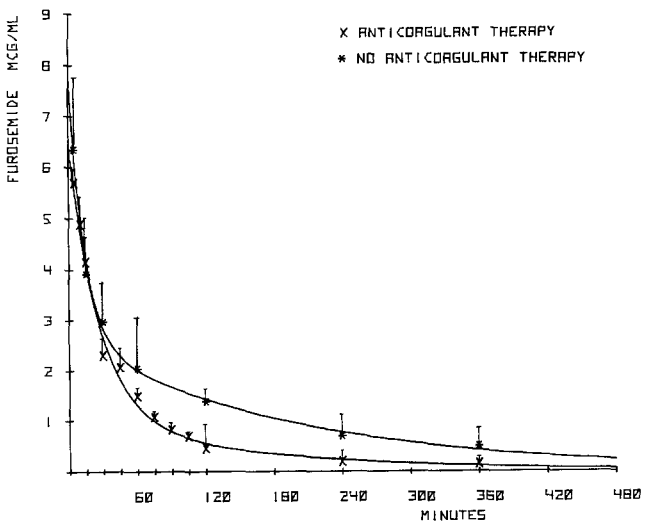

Fig. 2. Average plasma concentration of furosemide as a function of time after intravenous injection of 40 mg in six patients with congestive heart failure, who were on long-term treatment with furosemide and who were also receiving anticoagulant therapy with a vitamin-K antagonist, and in six furosemide-treated patients with congestive heart failure who were not on anticoagulants. Standard deviations are shown

times, but none of the differences were significant at the 0.05 level.

In Table 1 are listed individual values of the plasma-clearance of furosemide and its volume of distribution at steady state in the group of normal volunteers (Group A). There was no significant correlation between the age and either of these two parameters.

The pharmacokinetic parameters for the different groups are listed in Table 2. Using the individual values for the volume of distribution and for the plasma clearance, the significance of the differences between Groups B and A was tested by means of a Mann-Whitney test. The apparent difference in volumes of distribution were not significant, but the differences in the plasma clearances were ($p < 0.05$).

The chronically decompensated cardiac patients who had been under long-term treatment with furosemide as well as with a vitamin-K antagonist (Group D) had a plasma clearance between the values for the other cardiac patients (Groups B and C) and the normal group (Group A). It is noteworthy that the average volume of distribution in Group D was relatively high.

A major difference between the groups was found in the slower rate of transport from the central to the peripheral compartment in the patients (Table 3). The protein binding of furosemide in plasma from six patients treated with furosemide daily for at least 6 months is listed in Table 4. Three of them (AF, VP and KS) were under anticoagulant treatment, and they showed low protein binding compared to patients not on anticoagulants and normal subjects.

In the normal volunteers the average renal clearance of furosemide during the first hour after intravenous administration was higher than in acutely decompensated patients, but the values did not differ significantly (Table 5). The renal clearance in the second 1-hour period after injection was increased in all the five patients with acute heart failure, whereas in the normal group, the average value remained unchanged. In the group of patients previously treated with furosemide (cf. Table 4), PM and SS also showed increased renal clearance of furosemide. HS suffered from pronounced bilateral heart failure with ascites and showed the highest plasma concentration of any of the subjects studied. She had her highest furosemide excretion during the first hour. AF and VP, who were on anticoagulants, had the highest 0–1 h renal clearance of furosemide of all the cardiac patients. The urinary excretion of furosemide and of a furosemide metabolite in normal subjects, in previously untreated patients and in patients who had been under daily treatment with furosemide for at least 6 months is shown in Table 6. The 24-hour excretion of the metabolite was significantly higher in patients previously treated with furosemide. Their average excretion of unchanged furosemide was the same as in the normal subjects and in the group of acutely decompensated patients – 25.2 mg, but an additional amount of furosemide

Table 3. Rate constants of transport between the central and the peripheral compartments in the four groups of patients

Group	K_{12} min^{-1}	K_{21} min^{-1}
A	0.0154	0.0542
B	0.0065	0.0477
C	0.0072	0.0659
D	0.0107	0.0220

Table 4. Plasma protein binding of furosemide in six cardiac patients treated daily with furosemide for at least the preceding 6 months, and in six normal subjects. Blood samples were taken about 1 hour after i. v. injection of 40 mg (± SD). The apparent difference between the two groups is not significant

		Total furosemide µg/ml	Per cent bound	Other drugs
Patients	PM	5.5	95.6	digoxin
	SS	2.7	93.3	KCl tablets
	HS	7.3	96.3	digitalis
	AF	4.1	91.2	warfarin digoxin
	VP	1.6	88.5	phenprocoumon digoxin + KCl
	KS	1.9	90.2	phenprocoumon spirolactone digoxin
Normal subjects (n = 6)		3.7±0.6	96.3±1.2	none

Table 5. Average renal clearance (ml/min±SD) of furosemide during the first 2 h after administration of 40 mg i. v. The differences between the groups are not statistically significant

		Renal clearance ml/min	
		0–1 h	1–2 h
Normal volunteers (n = 5)		116±79	117±54
Patients with acute heart failure (n = 5)		39±17	77±51
Patients with heart failure previously treated with furosemide (cf. Table 4 and 6)	PM	33	55
	SS	30	74
	HS	52	34
	AF	98	99
	VP	89	65

Table 6. Urinary excretion of furosemide and a furosemide metabolite after furosemide 40 mg i. v. The drug was given at 8 a. m. to 6 normal volunteers, to 5 patients with heart failure not previously treated with furosemide, and to five patients who had been treated with furosemide daily for at least 6 months. Means ± SD are shown

Hours after furosemide	Urinary excretion		Normal volunteers (n = 6)	Patients (n = 5) with previously untreated acute congestive heart failure	Patients (n = 5) with chronic congestive heart failure treated with furosemide at least for 6 months
0–1	urine	ml/min	15.4±3.4	7.4±4	11.6±7.9
	furosemide	μg/min	245.0±156	141.4±40	182.4±84.0
	metabolite	"μg"/min	0.0	1.2±2.8	7.8±9.7
1–2	urine	ml/min	8.3±2.4	5.6±2.4	5.3±2.3
	furosemide	μg/min	83.0±38.0	116.6±53.4	77.0±14.8
	metabolite	"μg"/min	0.0	3.3±7.5	6.9±8.6
2–4	urine	ml/min	3.3±3.5	2.7±0.7	2.2±1.1
	furosemide	μg/min	26.6±9.3	41.8±13.2	29.5±14.5
	metabolite	"μg"/min	1.4±3.4	0.7±1.5	10.2±5.9
4–12	urine	ml/min	0.7±0.4	0.6±0.3	1.3±0.3
	furosemide	μg/min	4.3±4.4	9.2±2.4	9.2±4.0
	metabolite	"μg"/min	0.5±5.0	0.6±0.6	4.6±3.8
12–24	urine	ml/min	0.4±0.3	0.3±0.07	0.6±0.2
	furosemide	μg/min	0.6±0.5	0.9±0.7	2.6±1.3
	metabolite	"μg"/min	0.5±0.4	0.2±0.2	3.3±2.7
0–24	urine	ml	2470±885	1636±320	2347±1517
	furosemide	mg	25.2±9.5	25.8±4.6	25.2±3.7
	metabolite	"mg"	0.7±0.9	0.8±0.9	6.7±2.8
Age, years	Range		27–74	60–70	39–90
	Mean		58	67	68
Body weight, kg	Range	61–92	62–74	56–82	
	Mean		71	69	68

(averaging 6.7 mg) was found in the 24-hour urine after incubation with β-glucuronidase. No visible spot on any TLC plate, with an r_f value characteristic of 4-chlor-5-sulphamoyl anthranilic acid, was observed.

Discussion

The present groups of patients are small and heterogenous, and so the comparisons must be considered as for orientating and qualitative rather than definitive and quantitative. The normal group (A) had a wider age range and a lower average age than the other groups. However, no significant correlation was found between age and either plasma clearance or volume of distribution for furosemide in this group.

Pharmacokinetics

A plot of the logarithm of the plasma concentrations of furosemide observed in this study against time did not result in a straight line. By the method of residuals the curve could be resolved into two or, in some individuals, into three straight parts. The characteristics of the earliest of the three parts could not be accurately determined. A larger number of blood samples taken at very precise intervals in the early phase would have been necessary. Consequently, the computer was used to find the best possible fit of the data to a two-compartment open model. A good fit was obtained, which made it possible to compare the figures describing the distribution and elimination characteristics in the different groups. This approach was chosen for practical reasons. It is quite likely that the distribution and elimination of furosemide could be explained even more precisely by the use of a "multi-compartment" model. Rupp and Zapf (1973) used a three-compartment model and for the "middle segment" (½–4 h) they found a dilution volume of 17.4 litres in seven normal subjects given 40 mg furosemide i. v. Kelly et al. (1974) gave 80 mg furosemide i. v. to four normal subjects. They used a two-compartment mo-

del and found a total volume of distribution of only 5.05 l. However, their method for determining the furosemide concentration in serum was only sensitive down to 0.5 μg/ml. In normal subjects we found a $(V_D)_{ss}$ of 12.8 l (0.181 l/kg) and a $(V_D)\beta$ of 17.2 l. In patients with acute left-sided heart failure the $(V_D)_{ss}$ was 9.5 l (0.140 l/kg) and the $(V_D)\beta$ was 11.1 l.

The binding of a drug to plasma proteins influences its volume of distribution (Martin, 1965). The preliminary data from the patients on anticoagulants suggested that they might have had larger apparent volumes of distribution than the patients on long-term furosemide treatment. In agreement with theory (Martin, 1965), there was also evidence suggesting that a smaller fraction of furosemide was protein-bound in the patients on anticoagulants. It has previously been shown that the in vitro protein binding of phenprocoumon is decreased in the presence of furosemide (Foged et al., 1976). Further studies to elucidate the interaction between furosemide and phenprocoumon are in progress in the authors' laboratory. In normal individuals, the 8-hour plasma clearance of furosemide was 165.9 ml/min, and the renal clearance was 117 ml/min during the first 2 h after the injection. Kelly et al. (1974) found a plasma clearance of 138 ml/min. Calesnick et al. (1966) using ^{35}S-furosemide (40 mg i. v.) observed an average renal clearance of 108 ml/min during the first hour in one normal subject.

In the present patients with acute congestive heart failure the plasma clearance was 83.5 ml/min. The average renal clearance was doubled (from 39 to 77 ml/min) from the first to the second 1-hour period after the injection. This may be due to furosemide-induced improvement in renal circulation with increased tubular secretion (cf. Vorburger, 1964).

Two of the patients previously treated with furosemide (PM and SS; Table 5) followed the same pattern, but the other three (HS, AF and VP) behaved differently. In HS, who had impaired hepatic function, a very low initial volume of distribution (4.6 l) probably reflected poor blood perfusion of many tissues. Her renal clearance of furosemide did not increase from the first to the second hour; her average renal clearance of furosemide during the first 4 h was 32 ml/min and the 8-hour plasma clearance was only 35 ml/min. The small difference between the two clearances may be due to decreased ability to excrete the drug with the bile. AF and VP initially had a relatively high renal clearance of furosemide, which might in part have been caused by more extensive filtration of unbound drug (Tables 4 and 5).

A relatively high plasma concentration in patients with heart failure has been found for quinidine (Ditlefsen, 1957), procainamide (Koch-Weser and Klein, 1971) and for lidocaine (Thompson et al., 1973).

At the end of a 24-hour period about 63% of unchanged drug and about 2% of a metabolite (presumably a glucuronide) was found in urine from normal volunteers and in patients not previously treated with furosemide. During the first hour after i. v. administration of furosemide 40 mg the normal volunteers excreted on average 37%, and the cardiac patients 21% of the drug. In normal volunteers, Kindt and Schmid (1970) found that 7.5 mg of furosemide was excreted during the first hour after intravenous administration of furosemide 20 mg. Rupp and Zapf (1973) collected both urine and stools for five days after i. v. administration of ^{35}S-furosemide 40 mg to healthy subjects; 88% of the radioactivity was found in the urine and 12% in the stools. Calesnick et al. (1966) also gave ^{35}S-furosemide intravenously to healthy volunteers. They recovered about 80% of the radioactivity in urine excreted during the following 24 h.

Pharmacodynamics

The present study indicates that the diuretic effect of furosemide 40 mg i. v. may be more pronounced in individuals with normal heart, liver and kidney function than in patients with acute congestive heart failure. The resulting excretion of urine was lower in these patients. The results, however, are not conclusive, because the investigation was uncontrolled, and because the experimental conditions might have differed thus preventing statistical comparison between the relatively small groups.

Excretion of Metabolites

Incubation of urine with β-glucuronidase revealed a metabolite which is believed to be a glucuronide. It was excreted in amounts corresponding to furosemide 0.7–0.8 mg / 24 h in subjects who hat not previously been treated with furosemide. In patients who had been treated with furosemide daily for at least the preceding 6 months, an average amount of 6.7 mg/24 h was excreted. It appears therefore, as if the long-term use of furosemide is able to "induce" a glucuronidation process. The average 24-hour excretion of unchanged furosemide was not affected by its long-term use – 25.2 of the 40 mg was excreted unchanged.

Acknowledgement. The authors wish to thank Hanne Larsen and Lis Sommer Nielsen for their ex-

cellent technical assistance. Also, Lis Sommer Nielsen was of invaluable help in writing the computer program.

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Received: June 16, 1976, in revised form: January 2, 1977, accepted: February 28, 1977

Frederik Andreasen, M. D.
Farmakologisk Institut
Aarhus Universitet
DK-8000 Aarhus, Denmark