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Absorption and disposition of furosemide in congestive heart failure

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Absorption and disposition of furosemide in congestive heart failure. Changes in response to furosemide and other diuretics in patients with congestive heart failure (CHF) could occur because of disease-induced changes in absorption of the drug or changes in disposition which affect its access to its site of action. A difference was not found in the bioavailability of furosemide in patients with CHF compared to normal volunteers, 31 ± 12 vs. 38 ± 20% (mean ± SD), respectively. Both groups showed considerable interindividual variability, though serial analyses within individuals revealed consistency. Amounts of furosemide delivered into the urine after an intravenous dose correlated significantly to that after an oral dose implying that the interindividual variability is not caused primarily by variability in absorption in either group. Overall, disposition kinetics of furosemide did not differ between groups. Because of heterogeneity of renal and cardiac function among the patients, we were able to demonstrate correlations of plasma and renal clearance of furosemide with renal function; in turn, renal function correlated with left ventricular ejection fraction. Consequently, some patients had changes in furosemide disposition, but, for the most part, differences in response to furosemide were caused by abnormal responses to, rather than changed handling of the diuretic.

Absorption et disponibilité du furosémide au cours de l'insuffisance cardiaque congestive. Des modifications de la réponse au furosémide et à d'autres diurétiques chez des malades ayant une insuffisance cardiaque congestive (CHF) pouvaient se produire en raison de modifications de l'absorption du médicament induites par la maladie, ou de modifications de sa disponibilité, modifiant son accession à ses sites d'action. La différence n'été pas trouvé dans la biodisponibilité du furosémide chez des malades ayant une CHF par rapport à des volontaires normaux, 31 ± 12 contre 38 ± 20% (moyenne ± SD), respectivement. Dans les deux groupes, il existait une variabilité interindividuelle considérable, mais les analyses sériées par individu indiquaient une certaine constance. Les quantités de furosémide apparaissant dans l'urine après administration intraveineuse étaient significativement corrélées aux quantités apparaissant après prise orale, ce qui indique que la variation interindividuelle n'est pas primitivement due à des différences d'absorption dans l'un ou l'autre groupe. D'une façon générale, la pharmacocinétique du furosémide n'était pas différente entre les deux groupes. En raison de l'hétérogénéité des fonctions rénale et cardiaque des malades, nous avons pu mettre en évidence des corrélations entre le furosémide plasmatique et la clearance rénale du furosémide avec la fonction rénale; la fonction rénale était elle-même corrélée avec la fraction d'éjection ventriculaire gauche. En conséquence, si quelques malades avaient des modifications de la disponibilité du furosémide, mais chez la plupart d'entre eux, les différences de réponse au furosémide étaient dues à une réponse anormale au diurétique, plus qu'à une modification de sa pharmacocinétique.

The potent diuretic, furosemide, is used frequently to treat patients with congestive heart failure (CHF) and other edematous states. In these settings the diuretic response is variable, and subnormal responses commonly occur with occasional patients manifesting a refractory state. In patients with azotemia, decreased furosemide elimination correlates with the degree of renal dysfunction [1–3]. This decreased elimination is not only due to decreased nephron mass but also to the inhibition of furosemide secretion into the lumen of the proximal tubule by accumulated endogenous organic acids [4–6]. This altered disposition of furosemide in azotemia correlates with decreased diuretic response; which, in turn, correlates with decreased delivery of furosemide into the urine. In patients with CHF, the influence of myocardial dysfunction on the absorption and subsequent disposition of furosemide as a potential mechanism of diuretic resistance has been little explored. Previous investigators have suggested that CHF might affect the absorption of furosemide and observed a large variability in absorption in normal subjects and in patients with CHF [7]. Others have demonstrated increased serum concentrations and prolongation of the serum half-life in patients with CHF after intravenous administration of furosemide [8]. Relationships between indices of cardiac performance and furosemide disposition have not been reported. Understanding the changes in drug disposition caused by disease states might provide a more rational approach to the treatment of patients in whom resistance to the drug occurs. We performed this study to assess absorption and disposition of furosemide in patients with a broad spectrum of severity of congestive heart failure.

Methods

Subjects. The protocol for these studies was approved by the Committee on Human Experimentation at the University of Texas Health Science Center at Dallas. Each subject signed an informed consent for the study after explanation of the procedures. No adverse effects occurred.

Normal volunteers. For comparisons to patients with congestive heart failure, we studied 32 normal volunteers. In eight of these subjects, detailed pharmacokinetic analyses were performed and have been reported previously [9, 10]. Earlier

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studies of bioavailability of furosemide have showed great variability. Consequently, we wished to assess bioavailability in a greater number of subjects, and in an additional 17 volunteers paired studies of orally and intravenously administered furosemide were performed to provide bioavailability data in a total of 25 subjects. We also studied seven subjects after oral administration alone. In the first eight subjects, we sampled blood and urine serially; in the latter 24 subjects, total 24-hr urine samples were collected after the administration of furosemide. The subjects receiving both dosage forms were studied in random order, and at least 1 week elapsed between studies.

Patients with congestive heart failure. We studied 25 patients with CHF, hospitalized on the Internal Medicine Service of Parkland Memorial Hospital. Each patient was stable, a clinical assessment made by ourselves and housestaff. Six patients had peripheral edema at the time of the study. Two patients, 6 and 9, had regurgitation lesions in mitral and aortic valves. These patients had been hospitalized for varying periods of time. Each had been admitted for control of newly diagnosed or worsening CHF (usually secondary to poor compliance with diet or therapeutic regimen). They were receiving stable doses of digitalis and furosemide and were neither gaining or losing weight at the time of study. They were maintained on diets containing a sodium intake ranging from 50 to 150 mEq/day. In summary, these patients had been treated and stabilized and were studied during a state deemed suitable for their discharge from the hospital. Our data, therefore, may not be extrapolable to the acutely decompensated patient or the patient refractory to large parenteral doses of furosemide.

For complete pharmacokinetic studies in 16 patients, we administered 40 mg of furosemide via an indwelling intravenous catheter and collected serial blood and urine specimens. These patients were "resistant" to furosemide. Evaluation of "dose-response" curves relating urinary furosemide to sodium excretion (not shown) were shifted downward and to the right in patients with CHF. Similarly, 24-hr urinary sodium excretion (mean ± SD) in these patients administered furosemide was 158.4 ± 122.5 vs. 289.6 ± 52.0 mEq in normals ($P = 0.008$). In a 24-hr urine specimen collected the day prior to study while patients were receiving no diuretics, the sodium content was 74.9 ± 14.4 and 131.0 ± 51.8 mEq for patients and normal controls, respectively. Though sodium restriction per se can decrease response to diuretics, the moderate sodium restriction in these patients reflected by their basal sodium excretion rates is unlikely to have accounted for their subnormal response. In an additional nine patients, furosemide was administered either orally or intravenously with collection of a 24-hr urine sample. Patients remained recumbent except to void. Left ventricular ejection fraction was determined by gated blood pool scintigraphy [11]. Beginning the morning of the second day, seven of these patients were administered 40 mg of oral furosemide daily. We collected 24-hr urine samples in these patients for two to six consecutive days.

Laboratory determinations. Serum and urine samples were measured for furosemide, sodium, potassium, and creatinine. Furosemide was measured by HPLC as previously described [9, 10]. This assay has recently been confirmed to be highly specific [12]. Sodium and potassium were measured with an Instrumentation Laboratory Model 143 flame photometer and creatinine with a Technicon Autoanalyzer.

Data analysis. Pharmacokinetic analyses were performed in 16 patients in whom we completed serial collections of serum samples. Each set of data from individual patients was fit to an exponential equation of the form:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p equals serum concentration of furosemide at time t; A and B are hybrid constants; and α and β are hybrid rate constants of fast and slow components of disposition, respectively. We utilized the CSTRIP computer program to obtain initial parameter estimates, and the NONLIN computer program for final estimation of the parameters [13, 14]. The weighting function of the fit was $1/C_p$ or $1/C_p^2$ and the goodness of fit was assured by examining residuals, visual inspection of the fit, and R^2 [15]. The pharmacokinetic parameters for each patient were calculated from equations described by Wagner [16], that is, $Cl_p = \text{Dose}/AUC_{0\to\infty}$; Vd_{area} or $Vd_\beta = \text{Dose}/\beta (AUC_{0\to\infty})$; and $Vd_{ss} = \text{Dose} \times (A/\alpha^2 + B/\beta^2)/(AUC_{0\to\infty})^2$ where Cl_p = plasma clearance, Vd_{ss} = volume of distribution at steady state, Vd_{area} or Vd_β = apparent volume of distribution calculated by the area under the curve, and $AUC_{0\to\infty}$ = area under the curve calculated from the integral of the plasma concentration versus time from zero to infinity. The renal clearance, Cl_r, for each patient was determined usually by the linear regression slope of the urinary furosemide excretion rate against the serum concentration of furosemide at the midpoint of the urine collection. The intercepts of these regression lines did not differ from zero and were forced through zero. In a few patients renal clearance was calculated as the total amount of drug recovered in the urine divided by the serum AUC. The pharmacokinetic parameters of eight normal volunteers previously reported by us were used for comparison to this patient population [9, 10]. We also analyzed all the individual data using the noncompartmental method of Benet and Galeazzi [17]. Values using this method were virtually the same as those derived using compartmental analysis; we have elected to present the data generated by the latter approach.

Correlations within groups were tested parametrically by linear regression or nonparametrically using the Spearman Rho rank correlation. Significance of differences between groups was tested by Student's *t* test.

Results

The patients in whom complete pharmacokinetic evaluation was performed represented a spectrum of degrees of impaired left ventricular function with left ventricular ejection fractions (LVEF) ranging from 0.08 to 0.64 with a mean of 0.32. These patients showed varying degrees of moderate renal impairment with creatinine clearance ranging from 19 to 133 ml/min/1.73 m^2.

Effect of congestive heart failure on absorption or bioavailability of furosemide. Table 1 depicts total amounts of urinary furosemide after oral and after intravenous administration of a 40-mg dose plus the ratio of the two in the same individual. This ratio is a measure of bioavailability and did not differ between groups. However, patients with CHF delivered less drug into the urine after both dosing routes compared to normal subjects. This difference most likely occurred because of decreased renal function with concomitant lower renal clearance of furosemide in some of these patients (vide infra). There is large variability

Table 1. Twenty-four-hour urinary furosemide excretion relative to a 40-mg dose in patients with congestive heart failure (CHF) and normal subjects (mean ± SD)[a]

Subjects	*N*	Oral dose *mg/24 hr*	I.V. dose *mg/24 hr*	Ratio P.O./I.V.
Normal	25	9.17 ± 5.95 (1.8 – 23.6)	23.08 ± 6.37 (13.8 – 38.3)	0.38 ± 0.20 (0.11 – 0.79)
	7	5.94 ± 1.14 (4.3 – 7.2)		
CHF	13	5.38 ± 3.05 (1.5 – 10.4)	17.32 ± 7.99 (7.6 – 32.4)	0.31 ± 0.12 (0.13 – 0.57)
	7	5.91 ± 2.23 (2.9 – 10.0)		
	5		16.12 ± 8.79 (6.0 – 30.1)	
P value[b]		0.039	0.021	0.256

[a] Values in parentheses denote range.
[b] Statistical comparisons are made between groups only in patients receiving both oral and intravenous doses. Additional data are shown to demonstrate consistency of the findings.

Table 2. Sequential 24-hr urinary furosemide excretion after 40 mg dosing in patients with congestive heart failure

Patients	Oral administration, *mg* Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Mean ± SD	I.V. administration *mg*
1	13.36	7.29	3.56	4.17	5.66	5.11	6.53 ± 3.59	13.10
2	1.53	3.15	2.31	2.82	3.92	6.68	3.40 ± 1.79	13.62
3	2.93	4.40	4.83				4.05 ± 1.00	20.3
4	2.14	1.14	1.18				1.48 ± 0.57	11.3
5	8.62	13.22	9.36				10.40 ± 2.47	32.45
6	5.37	6.70	6.14				6.07 ± 0.67	21.29
7	2.24	3.11					2.67 ± 0.62	11.06

of urinary furosemide in both normal subjects and patients with CHF. However, the intraindividual variability is considerably smaller as indicated by a relatively smaller day-to-day variation in each patient with CHF when urinary furosemide was determined on serial daily urine collections for up to 6 days (Table 2).

The relationship in the same individual between urinary furosemide after intravenous and oral administration is depicted in Figure 1 for both normals and patients with CHF. Both groups demonstrated significant correlations: $r = 0.642$, $P = 0.008$, and $r = 0.791$, $P = 0.001$, respectively. In other words, individuals, either patients or normal volunteers, who excreted small amounts of furosemide after intravenous dosing also excreted small amounts after oral dosing, and the converse. The linear regression of the data from the two groups did not differ statistically.

In summary, patients with CHF differed from normal subjects in the total amount of drug delivered into the urine after both routes of administration. The ratio of drug delivered after oral and intravenous dosing, a measure of bioavailability, was no different. Each group showed considerable variability. The significant relationship between urinary furosemide after intravenous and oral dosing indicates that this variability is, at least in part, related to factors other than absorption (including first pass effect) and may imply a role of intrinsic interindividual differences in the contribution of nonrenal pathways of elimination to overall clearance of the drug.

Effect of CHF on disposition of furosemide. After intravenous administration of furosemide, the serum concentration versus time curve followed a two-compartment model for all patients and normal subjects. The urinary furosemide excretion rate and urinary sodium excretion rate declined parallel to the serum concentration. Figure 2 depicts examples of data of two patients (5 and 7) for serum concentration, furosemide excretion rate, and sodium excretion rate versus time. Table 3 presents pharmacokinetic parameters of the 16 patients. As a group, the patients with CHF did not differ from normal subjects. However, the group of patients with CHF consisted of patients with a range of renal and cardiac function. The serum and renal clearance and elimination rate constant correlated with creatinine clearance (Fig. 3). Serum half-life appeared to follow a curvilinear relationship with creatinine clearance as one would predict (Fig. 3). Also, as one might have predicted, the elimination rate constant correlated with both serum and renal clearances of furosemide ($P < 0.01$). Left ventricular ejection fraction correlated with creatinine clearance ($r = 0.590$) ($P < 0.05$) implying the renal dysfunction was at least, in part, a manifestation of the severity of cardiac disease. Decrements in renal function, in turn, resulted in decreased total and renal clearance of furosemide and diminished drug in the urine after either route of administration. Changes in handling of furosemide in patients with CHF, therefore, appear mainly to be dependent upon renal function.

Discussion

Theoretically, a reduced diuretic response in some patients with CHF could occur by decreased oral absorption with/or

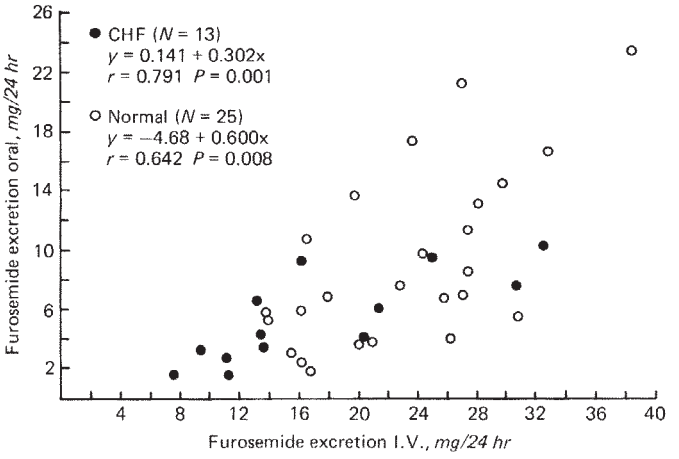

Fig. 1. *Relationship between total urinary furosemide after oral and after intravenous dosing of 40 mg.* The regression equations for the two groups are shown. *Open symbols* represent normal subjects. *Closed symbols* represent patients with congestive heart failure (CHF).

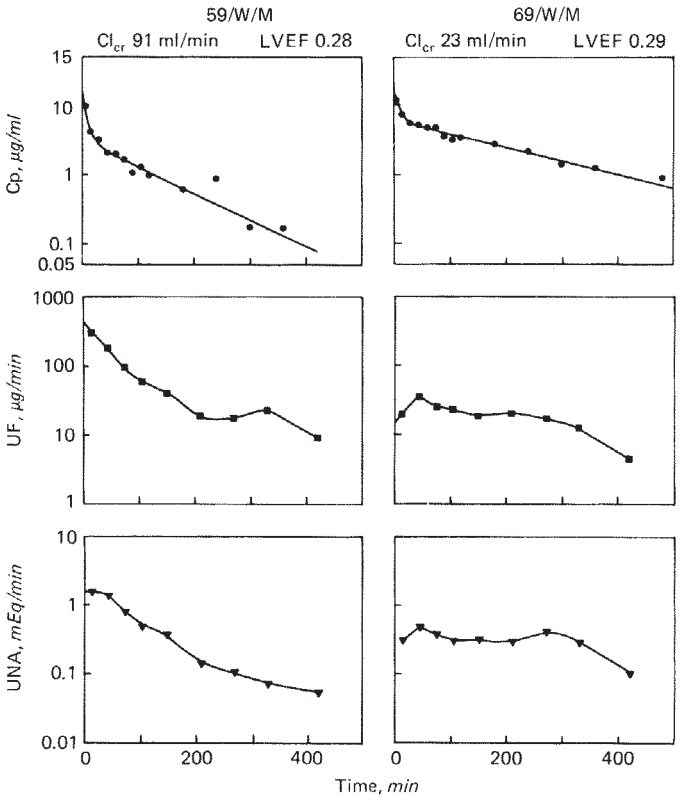

Fig. 2. *Representative data of two individual patients, no. 5* (left panel) *and no. 7* (right panel) *showing serum concentration of furosemide* (Cp), *urinary furosemide excretion rate* (UF), *and urinary sodium excretion* (UNA) *rate versus time* (top to bottom panels, *respectively*).

decreased urinary excretion of furosemide [18]. Overall, patients with CHF in this study did not differ from normal subjects in bioavailability of furosemide; however, delivery of drug to the urinary site of action after both oral and intravenous administration was decreased.

The ratio of urinary furosemide after oral to that after intravenous administration is a measure of bio-availability. In this study, therefore, bio-availability in patients with CHF did not differ from that of normal subjects, consistent with the data reviewed by Benet [19] and by Cutler and Blair [20]. In spite of theoretical postulates that patients with CHF may have edema, decreased perfusion, or changed motility of the gastrointestinal tract, all of which could affect absorption, this study provided no evidence for differences in extent of absorption of furosemide in patients compared to normal subjects. However, both groups demonstrated considerable interindividual variability of furosemide excretion into urine after both routes of administration while consistency within an individual was maintained. Interindividual variability in absorption, renal or nonrenal clearance could account for these findings. Our demonstration of the close correlation of furosemide delivery into the urine after oral compared to intravenous dosing implies that variability in absorption among individuals was not a major factor in the present study. Consequently, intrinsic differences in nonrenal and renal clearances were more likely causes of this interindividual variability. These data emphasize that nonrenal excretion of furosemide is also a major route of elimination and contributes importantly to its disposition.

Patients with CHF delivered less total drug into the urine than did normal subjects. This appears to have been a function of decreased renal and total clearance of furosemide, probably caused by decreased overall renal function which, in turn, appeared to be related to the severity of heart disease. It is likely that some of these patients also may have had a component of intrinsic renal disease. It is evident in patients with CHF comparable to those in this study that one would predict differences from normal subjects in handling of furosemide mainly when renal function is compromised, and even then, changes appear to be slight.

Andreason and Mikkelsen studied the distribution and elimination of furosemide in patients with CHF compared to normal subjects and demonstrated that the plasma clearance was significantly lower in patients than in normals, 1.23 vs. 2.34 ml/kg/min, respectively [8]. The volume of distribution at steady state (Vd_{ss}) did not differ significantly, 0.140 liter/kg and 0.181 liter/kg for the patients with CHF and the normal subjects, respectively. These pharmacokinetic parameters are similar to those of our study as well as more limited studies of other investigators. Tilstone and Lawson reported in abstract form that a lower volume of distribution of the central compartment and a lower plasma clearance of furosemide occurred in patients with CHF [21]. In the recent study by Perez, Sitar, and Ogilvie apparent volume of distribution varied greatly among patients with acute pulmonary edema ranging from 0.085 to 0.818 liter/kg with a median of 0.353 liter/kg [22]. Our findings of a correlation of plasma and renal clearance of furosemide with renal function which, in turn, correlated with cardiac function support the impression that the large variability reported in different studies is, in part, caused by studying patients with various degrees of cardiac and renal impairment. The correlation of plasma and renal clearance of furosemide with creatinine clearance is expected because furosemide is secreted by the proximal tubule, the capacity of which decreases with decreased renal mass and/or decreased perfusion to a normal nephron mass [23, 24]. Studies in patients with renal failure

Table 3. Pharmacokinetic parameters of furosemide (40 mg) in patients with congestive heart failure compared to eight normal volunteers

Patient	$t1/2_\alpha$	$t1/2_\beta$	Vd_β	Vd_{ss}	Cl_p	Cl_r	Cl_{nr}	LVEF	Cl_{Cr}
	min		*l/kg*		*ml/min/kg*			%	*ml/min/1.73 m²*
1	14	82	0.122	0.097	1.03	0.34	0.69	22	81
6	11	50	0.413	0.353	5.71	2.83	2.88	38	75
4	22	119	0.119	0.089	0.70	0.20	0.50	55	72
5	5	78	0.105	0.084	0.93	0.73	0.20	28	90
3	11	108	0.127	0.089	0.81	0.35	0.46	62	46
7	6	154	0.134	0.076	0.60	0.14	0.46	29	23
8	24	127	0.194	0.125	1.06	0.63	0.43	64	99
9	10	99	0.315	0.148	2.20	1.11	1.09	63	106
10	65	327	0.254	0.216	0.54	0.14	0.40	14	19
11	42	173	0.346	0.227	1.39	0.09	1.30	16	43
12	8	116	0.127	0.114	0.75	0.13	0.62	15	38
13	15	92	0.207	0.102	1.56	0.37	1.19	45	133
14	26	103	0.206	0.131	1.38	0.55	0.83	10	75
15	17	134	0.176	0.169	0.91	0.07	0.84	21	28
16	14	57	0.160	0.130	1.93	1.20	0.73	20	44
17	23	129	0.172	0.144	0.93	0.16	0.77	8	42
Mean	20	122	0.198	0.143	1.40	0.56	0.84		
± SD	±15	±64	±0.090	±0.071	±1.24	±0.70	±0.62		
Normal subjects (N = 8)									
Mean	17	91	0.351	0.161	1.84	1.05	0.80		
± SD	±3	±27	±0.344	±0.144	±1.02	±0.65	±0.48		
P value	0.585	0.206	0.103	0.682	0.396	0.112	0.875		

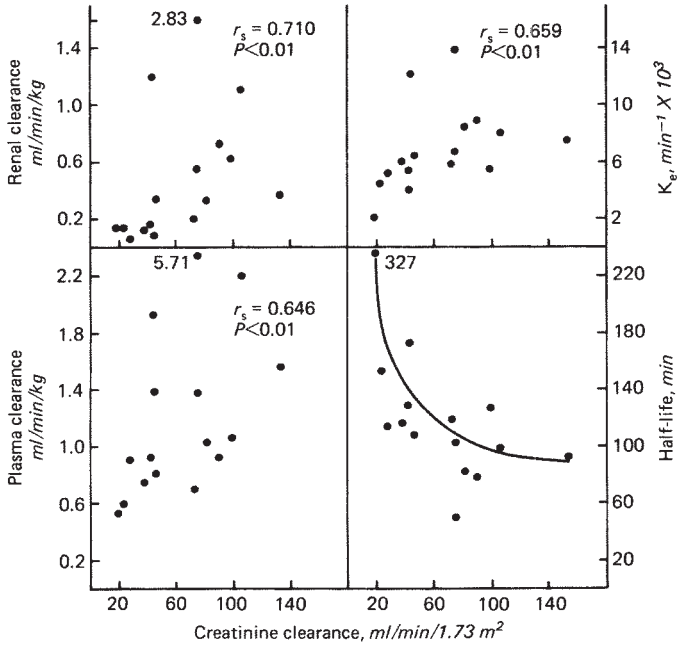

Fig. 3. *Relationship between renal function and furosemide pharmacokinetics in patients with congestive heart failure.* Spearman *r* values (r_s) and their significance are shown in the figure.

have demonstrated a similar relationship of renal and plasma clearance to renal function [1, 2].

It is important to point out limitations of our data. Because of the large interindividual variability among normal subjects and patients, detecting small differences between groups becomes difficult and would require a large number of subjects. Consequently, though our study groups were rather large for this type of study, the risk of a beta-type (false negative) error remains. Our goal was to assess patients with a broad spectrum of severity of cardiac disease. Though, in toto this group of patients did not differ from normal subjects in a number of variables measured, it is entirely possible that certain subgroups of patients may well have differed. Indeed, our demonstration of correlations of indices of disease severity with disposition of furosemide supports this possibility. Further studies are needed in subgroups of patients such as those "refractory" to furosemide or those "resistant" but at end-stage cardiac disease with uniformly very low LVEF's. Our data should be viewed most pertinent to the "average" patient with CHF.

Though, overall, only minor changes in handling of furosemide occurred in our patients with CHF, some individual patients may have sufficiently low absorption (either intrinsic or secondary to cardiac effects) and/or changed disposition such that their altered response is due to changed pharmacokinetics of furosemide [25]. However, for the most part, it appears that the resistance to furosemide in patients with CHF such as those in this study manifests as a change in the pharmacodynamics of response, the mechanisms of which are related undoubtedly to the pathophysiology of altered solute homeostasis in the disease [26]. The therapeutic implications of this study are unclear. For the unusual patient with abnormal handling of furosemide, a greater dose or administering the dose by vein might be appropriate. Patients with abnormal dynamics of response, however, would be more dependent on reversing pathophysiologic events in the kidney to manifest a response with incre-

ments in dose achieving little except subjecting the patient to potentially toxic amounts of drugs.

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