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ORIGINAL ARTICLES

Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with congestive heart failure

Four healthy subjects and six patients with congestive heart failure (CHF) were given 3 mg oral and intravenous doses of bumetanide in a random crossover fashion. Bumetanide was analyzed by HPLC, and sodium and potassium was analyzed by flame photometry. Aside from a modest reduction in renal clearance, the kinetics of bumetanide in CHF were similar to those in healthy subjects. The extent of bioavailability was 81%, with a variability of 20% to 25% about the mean for both groups. The cumulative dynamic responses to bumetanide, whether administered orally or intravenously, were essentially the same in each group. Pharmacodynamic modeling showed that there were no significant differences between healthy subjects and patients with CHF in either ER_{50} (bumetanide urinary excretion rate producing 50% of maximum drug effect) or S (slope), although the baseline effect was 15 times lower in CHF. The maximum effect attributable to bumetanide was twofold higher in healthy subjects and there was a significant correlation between this parameter and creatinine clearance ($r = 0.964$; $p < 0.001$). Overall, these results indicate that a predictable transition from 3 mg intravenous to oral doses of bumetanide is possible in CHF. (CLIN PHARMACOL THER 1988;44:487-500.)

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Bumetanide is a loop diuretic similar to furosemide with respect to its pharmacologic action and clinical indications. It differs from furosemide in that it is 40 times more potent on a milligram-per-milligram basis.[1,2] Bumetanide is highly protein bound[3-6] and relatively little drug undergoes glomerular filtration. However, bumetanide is actively secreted by the pars recta of the proximal tubule.[7-9] This is important because numerous investigators have shown that bumetanide exerts its primary natriuretic action on the thick ascending limb of Henle from the luminal side.[10] As a result, any pathophysiologic condition that affects the tubular secretion of bumetanide may attenuate the drug-induced pharmacologic effect.

The pharmacokinetics of drugs may be affected by cardiac disease.[11] Studies comparing healthy subjects with patients with congestive heart failure (CHF) have reported that changes in the bioavailability, volume of distribution, or clearance of drugs may occur in heart failure. Many investigators have focused on reduced drug clearance in CHF, which may be due to diminished blood flow to the kidney or liver or to compromised enzyme activity secondary to hepatic congestion.[11-13] However, very few studies have been completed that examine the effects of CHF on the bioavailability of compounds with low hepatic extraction, although alterations in absorption could result from changes in autonomic nervous activity, blood flow to the mesenteric area, or gut wall edema associated with cardiac congestion.

Both bumetanide and furosemide are used in the treatment of edema associated with CHF.[14-18] However, the pharmacodynamics of furosemide are variable, and suboptimal responses can occur, especially after oral dosing.[19-21] These problems may be due, in part, to the incomplete and unpredictable bioavailability of furosemide.[19,22-24] In contrast, bumetanide has consistently high bioavailability in healthy subjects[3,6,25-27] and in patients with hepatic or renal diseases.[6,28] Nevertheless, pharmacokinetic and pharmacodynamic data for bumetanide in CHF are very limited.[29] Therefore, we undertook a study to determine the pharmacokinetics, pharmacodynamics, and bioavailability of bumetanide in patients with severe CHF after both oral and intravenous dosing. Parallel studies were carried out in healthy subjects for the purpose of comparison.

METHODS

Materials. Bumetanide tablets (1 mg; lot 0303-1) and intravenous solution (0.25 mg/ml; lot 3003) were obtained from Hoffmann-La Roche, Inc., Nutley, N.J. All other chemicals and solvents were reagent grade or better, as previously reported.[30]

Study participants. This study was performed in the Clinical Research Center and the University of Michigan Hospitals. The control group consisted of four healthy subjects as judged by medical history, physical examination, and standard laboratory test results, including a creatinine clearance (CL_{CR}) determination (Table I). The group of patients with CHF consisted of six individuals with class III or IV heart failure, according to the New York Heart Association criteria for functional capacity.[31] CL_{CR} in these patients was stable at $\geq$35 ml/min (Table I). Patients must have been receiving a daily maintenance dose of 80 to 240 mg of furosemide as part of their prescribed drug therapy to be eligible for study. Patients were excluded from study if they had diabetes or signs and symptoms of hematologic, gastrointestinal, or hepatic diseases other than hepatic dysfunction associated with CHF. Patients receiving long-acting diuretics (i.e., metolazone, spironolactone) were also excluded from study. All diuretics were withheld for 24 hours before each study day, and drugs that have diuretic-like properties (i.e., theophylline) or that may inhibit the diuretic responses (i.e., nonsteroidal antiinflammatory drugs) were not allowed for a minimum of 3 days before bumetanide administration (except for patient 6, who was taking one aspirin tablet per day). Each volunteer was instructed to avoid caffeine-containing beverages throughout the study. All participants were fully informed of the nature of the study and signed an informed consent form approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan Medical Center.

Study design. After an overnight fast, each patient received a 3 mg dose of bumetanide, either orally (three tablets) or intravenously, at 8 AM in a random crossover design. There was a minimum of at least 2 days between the two treatments. Bumetanide tablets were taken with 8 oz of water; the solution was infused at a constant rate over 3 minutes. For the intravenous dose, serial blood samples (3 ml) were drawn from the contralateral arm through an indwelling heparinized (10 U/ml) scalp vein needle into tubes containing EDTA just before bumetanide dosing (blank) and at 3, 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 480, and 1440 minutes after the start of the infusion. For the oral dose, serial blood samples were drawn just before dosing (blank) and at 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, 480, and 1440 minutes after drug dos-

Table I. Clinical data of healthy subjects and patients with CHF

	Sex	*Age (yr)*	*Weight (kg)*	*LVEF (%)*	*CL_{CR}* (ml/min)*	*Concomitant drugs*
Healthy subjects						
1	M	34	68.1	—	125	—
2	M	25	73.1	—	117	—
3	M	38	68.1	—	108	—
4	M	23	66.1	—	121	—
Mean		30	68.9		118	
SD		7	3.0		7	
Patients with CHF						
1	M	70	62.7	14	35	Digoxin, captopril, potassium chloride
2	M	38	84.5	21	65	Digoxin, captopril, docusate sodium, quinidine, diphenhydramine
3	F	57	82.8	28	45	Captopril, ferrous sulfate, docusate sodium, potassium chloride
4	M	63	59.2	10	37	Digoxin, captopril, hydralazine, warfarin, allopurinol
5	M	61	53.2	15	55	Digoxin, captopril, potassium chloride, isosorbide dinitrate, imazodan
6	M	71	62.2	30	35	Amiodarone, enalapril, potassium chloride, isosorbide dinitrate, aspirin
Mean		60	67.4	20	45	
SD		12	13.0	8	12	

LVEF, left ventricular ejection fraction.
*Determined over 24 hours.

ing. Blood samples were centrifuged immediately and the plasma was harvested and frozen. Voided urine was collected just before bumetanide administration (blank), every half hour for the first 3 hours, hourly for the next 5 hours, and then pooled from 8 to 24 hours after drug dosing. Plasma and urine samples were stored at −20° C until subsequent analysis.

Healthy subjects were kept relatively euvolemic throughout the study by replacing urinary losses isovolumetrically; 75% was replaced with intravenous administration of lactated Ringer's solution and the remaining 25% was replaced orally with water. Patients were allowed water and fruit juices throughout the study according to their prescribed fluid and dietary restrictions (i.e., a no-added-salt diet before and during study). A low-sodium lunch (30 to 50 mEq) was provided for each participant 4 hours after dosing. All plasma samples in healthy subjects and patients showed normal sodium concentrations.

Analytic procedures. Plasma and urine samples containing bumetanide were analyzed by a sensitive and specific HPLC assay.[30] Plasma and urine samples were assayed for sodium and potassium with a flame photometer (Model 455, Corning Medical and Scientific, Medfield, Mass.).

Protein binding. The plasma protein binding of bumetanide was determined for each participant by spiking the pooled plasma samples with bumetanide over a concentration range of 5 to 50 μg/ml. The concentration of bumetanide in the original samples was <2% of the spiked concentrations. Plasma (0.5 ml) was dialyzed against an equal volume of isotonic phosphate buffer (0.067 mol/L at pH 7.4) at 37° C for 5 hours. Dialysis membranes with a molecular weight cutoff of 12,000 to 14,000 daltons and 1 ml dialysis cells were used throughout. Preliminary studies indicated that equilibrium was achieved within 2 hours and was maintained for 24 hours. Spiked plasma (0.2 ml) was prepared and analyzed as previously reported.[30] Dialyzed buffer (0.2 ml) was mixed with 50 μl acetophenone (0.25 mg/ml) and injected into the HPLC system, as reported previously.[30] A typical standard curve of bumetanide/acetophenone peak height ratio over the bumetanide buffer concentration range of 5.2

to 206 ng/ml resulted in the linear least-squares regression equation: $1.502X - 0.018$ ($r^2 = 0.999$). The volume-corrected bound concentration after dialysis (C_b'') was calculated as: $C_b'' = C_T - 2Cf'$, where C_T is the measured total concentration of drug in plasma before dialysis and Cf′ represents the measured unbound concentration of drug in the buffer after dialysis. This equation was developed by Tozer et al.[32] to correct for the osmotic water shift that occurs during equilibrium dialysis, resulting in lower protein and bound drug concentrations in the postdialysis plasma compartment. The appropriate bound and free concentrations were then fit with MKMODEL[33] to a nonlinear plasma protein binding model:

$$Cb'' = P1 \times Cf'/(P2 + Cf') \quad (1)$$

where P1 represents the maximum binding capacity of the plasma proteins and P2 is the Cf′ concentration that produces one half the maximum binding capacity. Other binding models were also tested (linear, one Langmuir plus a linear term, and two Langmuirs). However, the data were best described by Eq. 1, as judged by the Schwarz criterion[34] and by visual examination of the residuals.

Kinetics. Noninstantaneous mixing of drug in the sampling compartment was observed during the intravenous infusion of bumetanide. This resulted in peak plasma concentrations of bumetanide at times after the end of infusion. Therefore, plasma concentration-time curves of bumetanide after intravenous infusions were fit to the following general polyexponential equation:

$$C = R_o/V_c \sum_{i=1}^{n} (1 - e^{\lambda_i \cdot T})\, e^{-\lambda_i \cdot (t - tlag_{iv})} \cdot \frac{\prod_{k=2}^{n} (E_k - \lambda i)}{[-\lambda_i \prod_{\substack{k=1 \\ k \neq i}}^{n} (\lambda_k - \lambda_i)]} \quad (2)$$

where C is the plasma concentration of bumetanide at time t, R_o is the rate of bumetanide infusion, V_c is the volume of the central compartment, n is the number of exponents, λi is the exponent of the ith exponential term, T is the infusion time, $tlag_{iv}$ is the time lag between the beginning of the infusion and the appearance of bumetanide in the sampling compartment, and E_k is the sum of the exit rate constants from the kth compartment. Parameter estimates were obtained by the use of the nonlinear least-squares regression program MKMODEL.[33] The number of exponents needed for each data set was determined by the application of Schwarz criterion,[34] ensuring that the coefficients of the corresponding bolus dose equation were all positive, and by visual examination of the residuals. Once the regression parameters were obtained, the coefficients (Ci) of the corresponding bolus dose equation could be calculated as follows[35]:

$$C_i = D/V_c \prod_{k=2}^{n} (E_k - \lambda i)/ \prod_{\substack{k=1 \\ k \neq i}}^{n} (\lambda_k - \lambda_i) \quad (3)$$

where D is the total dose administered ($R_o \cdot T$).

The following pharmacokinetic parameters were then calculated from standard equations[35,36]

$$V_{ss} = D \sum_{i=1}^{n} C_i/\lambda_i^2 / [(\sum_{i=1}^{n} C_i/\lambda_i)^2] \quad (4)$$

$$V_{area} = D/(\lambda_z \sum_{i=1}^{n} C_i/\lambda_i) \quad (5)$$

$$CL = D/\sum_{i=1}^{n} C_i/\lambda_i \quad (6)$$

$$CL_R = Ae(0\text{-}\infty)/\sum_{i=1}^{n} C_i/\lambda_i \quad (7)$$

$$CL_{NR} = CL - CL_R \quad (8)$$

$$t_{1/2} = 0.693/\lambda_z \quad (9)$$

$$Fe = Ae(0 - \infty)/D \quad (10)$$

In Eqs. 4 to 10, V_{ss} is the volume of distribution steady state; V_{area} is that volume which, when multiplied by C in the log-linear phase, is equal to the amount of drug in the body; CL is the total plasma clearance; CL_R is the renal clearance; CL_{NR} is the nonrenal clearance; $Ae(0 - \infty)$ is the amount of unchanged drug recovered in the urine at time infinity; $t_{1/2}$ is the biologic half-life; λ_z is the smallest of the λ_i values; and F_e is the fraction of the dose excreted unchanged in the urine.

Plasma concentration-time profiles of oral bumetanide were not computer fit because of irregular absorption profiles in many of the participants. Pertinent kinetic parameters were therefore calculated by a noncompartmental approach. The biologic $t_{1/2}$ with oral dosing ($t_{1/2po}$) was graphically determined by linear regression of ln(C) vs. time with use of at least three data points from the log-linear terminal phase. CL_R was determined by division of $Ae(0 - \infty)$ by the plasma $AUC(0 - \infty)$, calculated by a combination of the trapezoidal and log-trapezoidal rules and extrapolated to infinity as $C_{last} \cdot t_{1/2po}/0.693$. The peak plasma concentration (C_{max}) and time to peak (t_{max}) after an oral dose were read directly from the plasma concentration-time curve.

Bioavailability. The extent of systemic availability

of bumetanide was calculated by the area ratios of oral (po) and intravenous (iv) dosing:

$$F_p = AUC(0 - \infty)_{po}/AUC(0 - \infty)_{iv} \quad (11)$$

by urinary excretion ratios:

$$F_u = Ae(0 - \infty)_{po}/Ae(0 - \infty)_{iv} \quad (12)$$

and by correction for differences in CL_R between oral and intravenous doses as suggested by Øie and Jung.[37]

$$F_{corr} = [(D_{iv} - Ae(0 - \infty)_{iv})AUC(0 - \infty)_{po}/ AUC(0 - \infty)_{iv} + Ae(0 - \infty)_{po}]/D_{po} \quad (13)$$

For the calculations of F_p and F_{corr}, $AUC(0 - \infty)_{iv}$ was determined by a combination of the trapezoidal and log-trapezoidal rules, extrapolated to infinity by $C_{last} \cdot t_{1/2iv}/0.693$. The $t_{1/2iv}$ was graphically determined by linear regression with use of at least four data points from the log-linear terminal phase. The computer-fitted and noncompartmental estimates of $AUC(0 - \infty)_{iv}$ differed from one another by <7%. These small deviations were probably due to differences between the computer fit and graphically determined estimates of $t_{1/2}$, and the overestimation of AUC by the noncompartmental method during the period of noninstantaneous mixing of drug in the sampling compartment.

The mean absorption time (MAT) was used as a measure of the absorption rate of oral bumetanide according to the noncompartmental method of statistical moments.[38,39] MAT was calculated as the difference of mean residence times (MRTs) between oral and intravenous dosing as:

$$MAT = MRT_{po} - MRT_{iv} \quad (14)$$

where MRT equals the area under the first moment curve (AUMC; extrapolated to infinity) divided by $AUC(0 - \infty)$. The AUMC was estimated by a combination of the trapezoidal and log-trapezoidal rules, extrapolated to infinity by $t_{last} \cdot C_{last} \cdot t_{1/2}/0.693 + C_{last}(t_{1/2}/0.693)^2$. An MAT value that corrects for the time lag ($tlag_{po}$) before drug absorption was also calculated:

$$MAT_{corr} = MAT - tlag_{po} \quad (15)$$

The $tlag_{po}$ was estimated from absorption profiles by use of the exact Loo-Riegelman equation of Wagner[40] and the second derivative criterion of Proost[41] for evaluation of the two integrals of that equation.

Dynamics. The relationship between the sodium excretion rate (E; in milliequivalents per minute) and the urinary excretion rate of bumetanide (ER; in micrograms per minute) was evaluated by use of the sigmoid E_{max} model:[42]

$$E = E_{max} \cdot ER^s/(ER_{50}^s + ER^s) + E_o \quad (16)$$

where E_{max} is the maximum effect attributable to the drug, ER_{50} is the urinary excretion rate of bumetanide that produces 50% of the E_{max}, E_o is the baseline effect, and S is the parameter influencing the slope of the dose-effect curve. The unknown parameters (E_{max}, ER_{50}, E_o, and S) were determined after intravenous dosing of bumetanide for each individual by use of the MKMODEL program.[33]

Pharmacodynamic data were also reported as the 8-hour cumulative excretion of sodium and the overall efficiency (Eff) of the response:

$$Eff = (\Delta E - \Delta E_o)/\Delta Ae \quad (17)$$

where ΔE and ΔAe are the amount of sodium and drug excreted in urine, respectively, over the same 8-hour period. ΔE_o was estimated by multiplying the computer-fitted value for baseline effect, E_o, by 240 minutes.

Statistics. Unless otherwise indicated, data are expressed as the mean ± SD. Statistical differences between the healthy subjects and the patients with CHF were determined by one-way ANOVA. Statistical differences between oral and intravenous dosing within each group were determined by a paired t test. Power

Table II. Binding parameters for bumetanide in healthy subjects and patients with CHF

	P1 (μg/ml)	*P2* (μg/ml)	f_u (%)
Healthy subjects			
1	343 ± 179	4.85 ± 2.87	1.40
2	428 ± 87	4.12 ± 0.96	0.95
3	112 ± 16	0.87 ± 0.20	0.77
4	421 ± 144	5.52 ± 2.11	1.30
Mean	326	3.84	1.11
SD	148	2.06	0.30
Patients with CHF			
1	235 ± 45	3.85 ± 0.88	1.60
2	234 ± 108	3.55 ± 1.91	1.49
3	240 ± 65	2.60 ± 0.88	1.07
4	244 ± 62	2.71 ± 0.84	1.10
5	381 ± 314	6.08 ± 5.65	1.57
6	132 ± 7	1.46 ± 0.11	1.10
Mean	244	3.38	1.32
SD	79	1.57	0.26
Significance	NS ($p > 0.20$)	NS ($p > 0.50$)	NS ($p > 0.20$)
$1 - \beta$ (%)	17.6	5.5	18.7

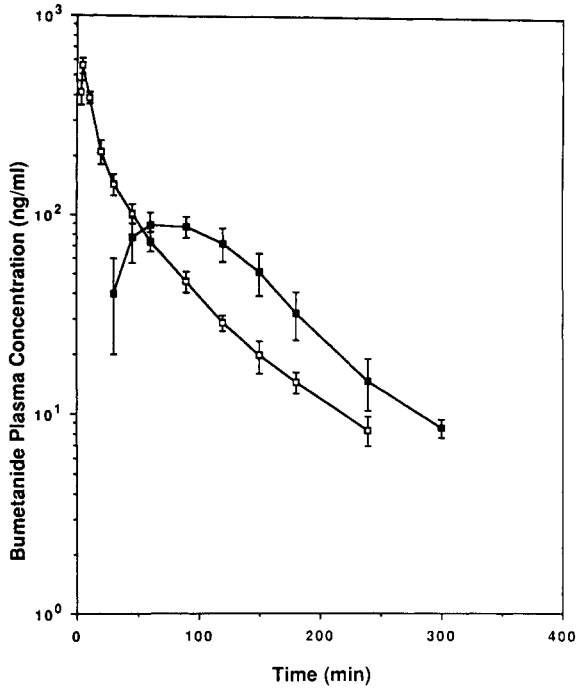

Fig. 1. Mean (± SE) plasma concentration-time profiles of bumetanide in healthy subjects after 3 mg oral (■) and intravenous (□) doses.

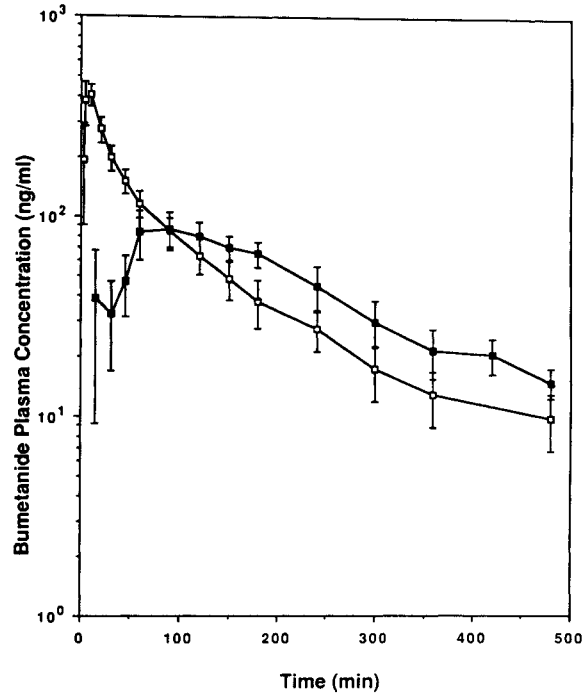

Fig. 2. Mean (± SE) plasma concentration-time profiles of bumetanide in patients with CHF after 3 mg oral (■) and intravenous (□) doses.

calculations ($1 - \beta$) were also performed at the $\alpha = 0.05$ level.[43] The linear relationship between two variables was assessed by the correlation coefficient r. A p value ≤ 0.05 was considered significant.

The nonlinear regression of the pharmacokinetic and pharmacodynamic modeling equations was estimated by MKMODEL.[33] This afforded the use of an extended least-squares objective function to make the selection of the weighting scheme less arbitrary.[44,45] The variance model used was:

$$\text{Var} = 1\text{E}-8 + \text{Y}^{\text{PWR}} \qquad (18)$$

where Var is the variance of the predicted Y and PWR is the power parameter. This model predicts VAR = 1E−8 when Y = 0. This was necessary when estimating lag times because predicted concentrations are equal to 0 for times less than tlag.

RESULTS

Results of the plasma protein binding fits are presented in Table II. Because the P2 values for all participants were >100 times those of unbound drug concentrations in plasma, it was concluded that the therapeutic concentrations were in the linear portion of the binding curve. The percent unbound (f_u) was thus calculated as:

$$f_u = 100/(\text{P1}/\text{P2} + 1) \qquad (19)$$

There was no statistically significant difference in f_u between the two groups.

Semilogarithmic plots of the plasma concentration-time curves for intravenous and oral bumetanide are shown in Fig. 1 for healthy subjects and in Fig. 2 for patients with CHF. In all cases the intravenous infusion data were best fit by a biexponential equation (Table III).

Pharmacokinetic parameters calculated from intravenous bumetanide data are listed in Table IV. No statistically significant differences were found among any of the reported parameters. There was, however, a trend for a longer $t_{1/2}$ (72.5 ± 29.3 minutes in patients with CHF vs. 46.1 ± 10.2 minutes in healthy subjects; $p = 0.13$) and longer $tlag_{iv}$ (2.93 ± 1.97 minutes in patients with CHF vs. 1.44 ± 0.35 minutes in healthy subjects; $p = 0.18$) in patients with CHF when compared with normal subjects. When data from the only participant (patient 3) who failed to show any $tlag_{iv}$

Table III. Coefficients and exponential terms of intravenous bumetanide in healthy subjects and patients with CHF

	C(1) ($\mu g/ml$)	λ_1 (min^{-1})	*C(2)* ($\mu g/ml$)	λ_2 (min^{-1})	*Schwarz criterion*[34]	*Power*	r^2*
Healthy subjects							
1	0.306	1.91E - 2	0.607	1.85E - 1	41.5	−1.08	0.999
2	0.132	1.30E - 2	0.421	1.09E - 1	50.5	+0.16	1.000
3	0.188	1.81E - 2	0.651	1.63E - 1	26.3	+1.25	0.997
4	0.222	1.23E - 2	0.368	7.56E - 2	47.9	+1.17	0.996
Mean	0.212	1.56E - 2	0.512	1.33E - 1			
SD	0.073	0.35E - 2	0.138	0.50E - 1			
Patients with CHF							
1	0.211	5.67E - 3	0.519	7.61E - 2	49.2	+0.45	0.999
2	0.211	1.20E - 2	0.288	4.71E - 2	34.9	+1.21	0.998
3	0.216	7.97E - 3	0.456	5.48E - 2	52.7	−0.16	1.000
4	0.180	1.86E - 2	1.049	4.11E - 1	33.0	−0.74	0.999
5	0.118	9.77E - 3	0.118	1.12E - 1	49.0	−0.07	0.999
6	0.258	1.16E - 2	0.414	1.12E - 1	47.6	−0.47	0.999
Mean	0.199	1.09E - 2	0.474	1.36E - 1			
SD	0.047	0.44E - 2	0.316	1.38E - 1			

*$r^2 = 1 - \Sigma (Y_{obs} - Y_{calc})^2 / \Sigma [Y_{obs} - (\Sigma Y_{obs}/N)]^2$.

Table IV. Pharmacokinetic parameters after intravenous bumetanide in healthy subjects and patients with CHF

Parameter	*Healthy subjects*	*Patients with CHF*	*Significance*	$1 - \beta$ (%)
CL (ml/min/kg)	2.55 ± 0.54	2.22 ± 1.36	NS ($p > 0.50$)	6.1
CL_R (ml/min/kg)	1.54 ± 0.40	1.23 ± 0.70	NS ($p > 0.40$)	10.6
CL_{NR} (ml/min/kg)	1.01 ± 0.56	0.99 ± 0.75	NS ($p > 0.50$)	2.7
$t_{1/2}$ (min)	46.1 ± 10.2	72.5 ± 29.3	NS ($p > 0.10$)	33.0
V_C (ml/kg)	63.3 ± 15.0	70.6 ± 26.4	NS ($p > 0.50$)	6.4
V_{ss} (ml/kg)	131 ± 32	164 ± 74	NS ($p > 0.40$)	11.1
V_{area} (ml/kg)	168 ± 46	201 ± 94	NS ($p > 0.50$)	8.2
F_e (%)	61.8 ± 19.7	58.2 ± 14.3	NS ($p > 0.50$)	4.8
$tlag_{iv}$ (min)	1.44 ± 0.35	2.93 ± 1.97	NS ($p > 0.10$)	26.1

were omitted, there was a significant difference in $tlag_{iv}$ between the two groups (3.51 ± 1.51 minutes in patients with CHF vs. 1.44 ± 0.35 minutes in healthy subjects; $p < 0.05$). Due to serial blood sampling difficulties, the first two postinfusion plasma samples from patient 3 were drawn at 4 and 8 minutes instead of 3 and 5 minutes, and may have rendered any $tlag_{iv}$ unobservable. It should be noted that although the number of subjects studied is small (n = 4), their kinetic parameters are remarkably similar to those reported by Lau et al.[6]

Kinetic data after oral bumetanide dosing are listed in Table V. CL_R was significantly reduced in patients (1.03 ± 0.46 ml/min/kg in patients with CHF vs. 1.83 ± 0.38 ml/min/kg in healthy subjects; $p < 0.025$). There were no significant differences among the other kinetic parameters after oral bumetanide despite the same trend of a longer $t_{1/2}$ in patients (98.7 ± 39.9 minutes in patients with CHF vs. 59.5 ± 25.0 minutes in healthy subjects; $p = 0.12$). In addition, there were no differences between groups in any of the values calculated for extent of systemic availability. Although no statistical difference was found in the biologic $t_{1/2}$ in either group as a function of the route of administration, CL_R was significantly different in healthy subjects ($p < 0.05$). Therefore, the F value corrected for changes in CL_R (81.3% ± 16.4% for patients with CHF vs. 81.3% ± 18.4% for healthy subjects) is probably the more accurate assessment of this parameter.

Table V. Absorption and disposition characteristics of oral bumetanide in healthy subjects and patients with CHF

Parameter	*Healthy subjects*	*Patients with CHF*	*Significance*	*1 − β (%)*
C_{max} (ng/ml)	106 ± 22	107 ± 42	NS ($p > 0.50$)	2.7
t_{max} (min)	74.4 ± 23.5	96.4 ± 48.0	NS ($p > 0.40$)	11.3
$tlag_{po}$ (min)	24.8 ± 7.4	20.5 ± 13.0	NS ($p > 0.50$)	6.9
MAT (min)	62.9 ± 20.0	103 ± 59	NS ($p > 0.20$)	20.9
MAT_{corr} (min)	35.9 ± 9.9	82.7 ± 47.5	NS ($p > 0.10$)	34.1
$t_{1/2}$ (min)	59.5 ± 25.0	98.7 ± 39.9	NS ($p > 0.10$)	34.1
CL_R (ml/min/kg)	1.83 ± 0.38	1.03 ± 0.46	S ($p < 0.025$)	72.2
F_p (%)	70.4 ± 17.4	85.1 ± 25.8	NS ($p > 0.30$)	14.2
F_u (%)	90.4 ± 21.0	77.4 ± 10.4	NS ($p > 0.20$)	21.8
F_{corr} (%)	81.3 ± 18.4	81.3 ± 16.4	NS ($p > 0.50$)	2.5

Table VI. Pharmacodynamic characteristics after intravenous and oral doses of bumetanide in healthy subjects and patients with CHF

Parameter	*Intravenous*	*Oral*	*Significance*	*1 − β (%)*
Healthy subjects				
Na (mEq/8 hr)	451 ± 55	542 ± 99	NS ($p > 0.10$)	24.2
Na (mEq/24 hr)	496 ± 82	624 ± 119	NS ($p > 0.10$)	25.8
K (mEq/8 hr)	68.0 ± 8.1	79.0 ± 7.8	NS ($p > 0.10$)	22.7
K (mEq/24 hr)	84.6 ± 19.7	105 ± 11	NS ($p > 0.05$)	58.3
Urine (ml/8 hr)	4230 ± 900	5180 ± 1060	NS ($p > 0.20$)	21.2
Urine (ml/24 hr)	4700 ± 1210	5780 ± 1130	NS ($p > 0.20$)	17.9
Eff(8 hr) (mEq/mg)	0.191 ± 0.052	0.267 ± 0.046	NS ($p > 0.05$)	46.8
Patients with CHF				
Na (mEq/8 hr)	188 ± 40	164 ± 63	NS ($p > 0.40$)	11.5
Na (mEq/24 hr)	204 ± 37	183 ± 73	NS ($p > 0.40$)	9.3
K (mEq/8 hr)	54.2 ± 20.6	60.9 ± 22.2	NS ($p > 0.20$)	21.2
K (mEq/24 hr)	86.2 ± 34.5	101 ± 43	NS ($p > 0.05$)	40.5
Urine (ml/8 hr)	2270 ± 850	2210 ± 570	NS ($p > 0.50$)	4.5
Urine (ml/24 hr)	2870 ± 970	3090 ± 1250	NS ($p > 0.20$)	15.6
Eff (8 hr) (mEq/mg)	0.112 ± 0.029	0.134 ± 0.053	NS ($p > 0.30$)	14.5

Eff(8 hr), efficiency of response over 8-hour collection period.

Natriuretic, kaliuretic, and diuretic responses after oral and intravenous dosing of bumetanide are listed in Table VI. Sodium excretion corrected for drug excretion (i.e., efficiency) is also shown in this table. As observed, bumetanide elicited equivalent pharmacologic responses in both healthy subjects and patients with CHF with oral or intravenous administration. Results from the dynamic modeling are prescribed in Table VII. There was a highly significant difference in E_{max} between groups (1.23 ± 0.22 mEq/min in patients with CHF vs. 2.65 ± 0.13 mEq/min in healthy subjects; $p < 0.001$). Baseline sodium excretion was also 15 times greater in healthy subjects (0.016 ± 0.015 mEq/min in patients with CHF vs. 0.252 ± 0.078 mEq/min in healthy subjects; $p < 0.001$). There were no significant differences in ER_{50} or S. In fitting the data to the sigmoid E_{max} model, the first collection period (value in parenthesis in Figs. 3 and 4) was omitted due to an observed counterclockwise hysteresis. This hysteresis, which has been reported for bumetanide in dogs[7,46,47] and in man,[6,48] results from a disequilibrium that occurs between the urine and effect compartments soon after dosing. Dynamic parameters were not evaluated during oral bumetanide dosing, because bumetanide excretion rates were not sufficient to describe all of the sigmoidal-shaped curve. Nevertheless, similar profiles were observed for the dose-response relationship of bumetanide when oral and intravenous data were superimposed on each other (Figs. 3 and 4).

DISCUSSION

Brater et al.[29] have studied the pharmacokinetics and pharmacodynamics of bumetanide in CHF after 1 and 2 mg oral doses. They observed a statistically signifi-

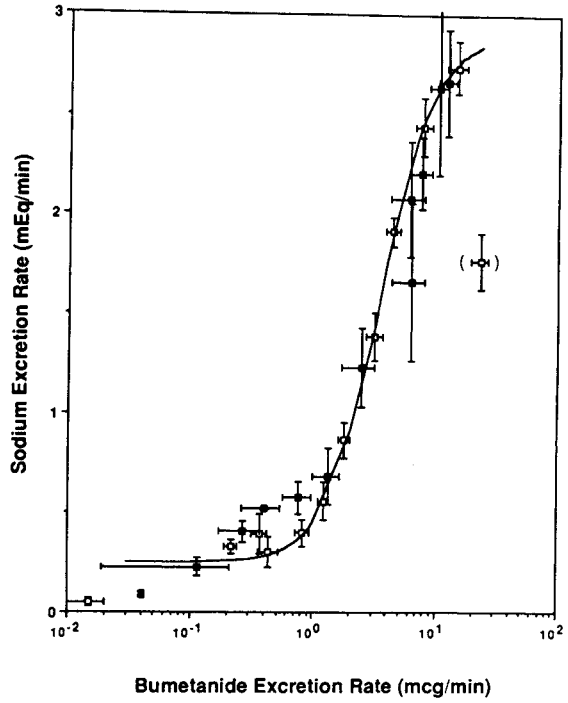

Fig. 3. Mean (± SE) sodium excretion vs. urinary excretion rates of bumetanide in healthy subjects after 3 mg oral (■) and intravenous (□) doses. *Solid line* represents the computer-generated regression line based on the fitted regression parameters in Table VII.

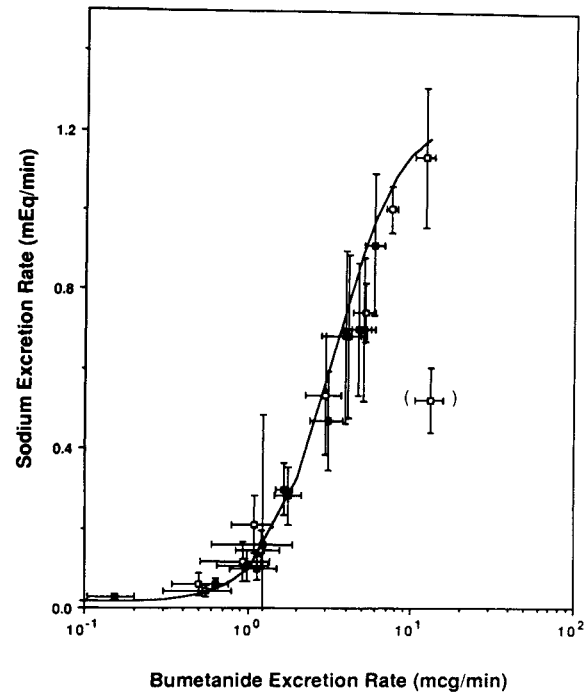

Fig. 4. Mean (± SE) sodium excretion vs. urinary excretion rates of bumetanide in patients with CHF after 3 mg oral (■) and intravenous (□) doses. *Solid line* represents the computer-generated regression line based on the fitted regression parameters in Table VII.

Table VII. Dose-response parameters in healthy subjects and patients with CHF after intravenous bumetanide

	E_{max} (mEq/min)	S	ER_{50} (μg/min)	E_o (mEq/min)	Schwarz criterion[34]	Power	r^2*
Healthy subjects							
1	2.35	1.49	2.69	0.273	8.13	−2.62	0.973
2	2.62	2.73	3.71	0.306	9.97	−3.02	0.988
3	2.70	2.17	2.77	0.137	6.57	−0.46	0.994
4	2.93	1.66	4.68	0.296	6.48	−1.07	0.992
Mean	2.65	2.01	3.46	0.252			
SD	0.24	0.56	0.93	0.078			
Patients with CHF							
1	1.03	1.28	4.25	1.78E-2	5.70	+1.86	0.884
2	1.47	1.76	2.97	7.02E-3	32.5	+9.24	0.862
3	1.42	3.66	3.32	9.75E-4	16.1	+2.11	0.960
4	1.06	2.03	3.72	2.70E-2	5.36	+1.75	0.970
5	1.39	1.60	4.04	6.45E-3	10.5	+1.16	0.979
6	1.00	2.71	1.58	3.91E-2	16.1	−0.04	0.996
Mean	1.23	2.17	3.31	1.64E-2			
SD	0.22	0.87	0.97	1.45E-2			
Significance	S ($p < 0.001$)	NS ($p > 0.50$)	NS ($p > 0.50$)	S ($p < 0.001$)			
1 − β (%)	>99.9	4.1	4.8	>99.9			

*$r^2 = 1 - \Sigma (Y_{obs} - Y_{calc})^2 / [Y_{obs} - (\Sigma Y_{obs}/N)]^2$.

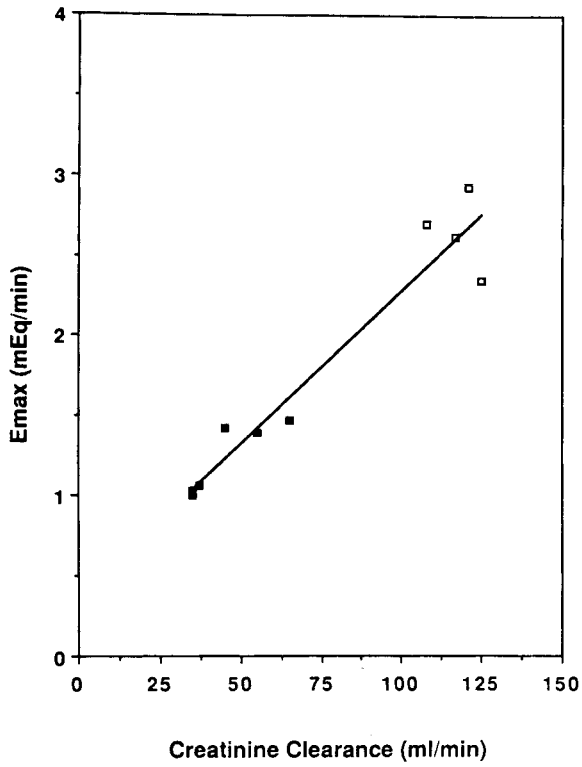

Fig. 5. Relationship between E_{max} and CL_{CR} in healthy subjects (□) and patients with CHF (■). *Solid line* represents linear correlation between these two parameters ($r = 0.964$; $p < 0.001$).

cant increase in $t_{1/2}$ between patients with CHF and normal subjects. This trend was also seen in our study (Tables IV and V), but the differences were not statistically significant. Brater et al. suggested that this twofold increase in $t_{1/2}$ observed for patients with CHF may be due to either a modest decrement in renal function or an increase in the volume of distribution, but they could not differentiate between the two because intravenous bumetanide was not administered in their study. In our study we saw no statistical difference in volumes of distribution. However, a substantial reduction (40%) in CL_R did occur after oral bumetanide administration when comparing healthy subjects and patients with CHF (1.83 ± 0.38 vs. 1.03 ± 0.46 ml/min/kg, respectively; $p < 0.025$). Additionally, a 20% reduction of renal clearance in patients with CHF (vs. healthy subjects) occurred when bumetanide was administered intravenously; this difference was not statistically significant.

As noted previously, there was a trend for the $tlag_{iv}$ in healthy subjects to be less than that in patients with CHF. This could be the result of a decreased cardiac output in patients with CHF, in whom the left ventricular ejection fraction (LVEF) averaged 20%. However, no significant correlation was found between LVEF and $tlag_{iv}$ in CHF. This may be a result of the limited number of patients studied and the narrow range of LVEF values observed (10% to 30%).

The absorption profile of bumetanide in both groups was found to be quite variable, with large coefficients of variation (35% in healthy subjects and 64% in patients) associated with the mean values for MAT_{corr}. In addition, a lag time of 20 to 25 minutes was observed for both groups. This value is in close agreement to values obtained by other authors.[6,26,27] When the extent of availability was calculated by correcting for differences in CL_R between oral and intravenous treatments of bumetanide, 81% bioavailability (F_{corr}) was obtained for both groups. This value was less than the 89% mean bioavailability reported by Marcantonio et al.[26] and greater than the 66% mean bioavailability reported by Lau et al.[6] in healthy subjects, even though similar sensitive and specific HPLC assays were used. It is conceivable that dose-dependent absorption may be occurring, as Marcantonio et al.[26] administered a 1 mg dose, the present study involved a 3 mg dose, and Lau et al. gave a 5 mg dose. Earlier studies by Pentikäinen et al.[3] and Halladay et al.[25] reported nearly complete absorption (>95%) of bumetanide, but these results are suspect because a nonspecific assay that measured drug with the total radioactivity in various biologic fluids was used. More recently, Holazo et al.[27] used an RIA to investigate the bioavailability of 1 mg doses of bumetanide in 12 healthy volunteers. These investigators reported bioavailabilities of 78% and 86%, depending on whether plasma data or urine data alone were used for calculation, respectively. In other disease states, Lau et al. reported a bioavailability of 69% in patients with chronic renal failure (5 mg doses) and Marcantonio et al.[28] reported a bioavailability of 83% in patients with chronic renal failure and 94% in patients with hepatic disease (1 mg doses).

As summarized in Table VI, bumetanide elicited an equivalent natriuresis, kaliuresis, and urine flow in healthy subjects and patients with CHF whether administered orally or intravenously. This occurred despite a 20% decrease in systemic availability when bumetanide was administered orally. Although not statistically significant, there was a trend for an increase in efficiency when both groups took bumetanide by mouth (0.267 ± 0.046 [oral] vs. 0.191 ± 0.052 mEq/μg/8 hr [intravenous] for the healthy subjects; 0.134 ± 0.053 [oral] vs. 0.112 ± 0.029 mEq/μg/8 hr [intravenous] for the CHF group); the lack of signifi-

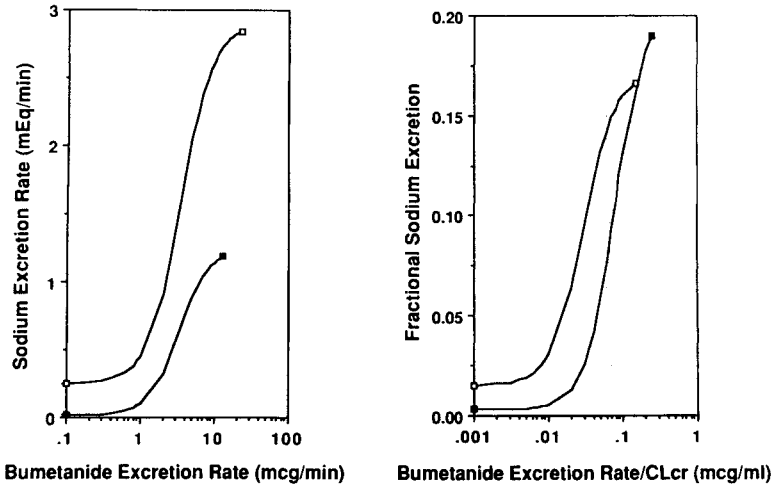

Fig. 6. Dose-response relationships of bumetanide in healthy subjects (□) and in patients with CHF (■). **Left,** dose is expressed as bumetanide excretion rate and response is shown as sodium excretion rate. **Right,** dose is expressed as bumetanide excretion rate corrected for CL_{CR} and response is expressed as fractional sodium excretion.

cance may reflect the limited number of study participants. Kaojarern et al.[49] calculated the existence of a single maximally efficient excretion rate in the pharmacodynamic (sigmoid E_{max}) model. As a result, if the drug can remain close to this maximally efficient excretion rate for prolonged periods during oral dosing, the same or greater cumulative response can occur with less total drug reaching the urine. This finding is in agreement with the data in our study and may explain the equivalency of response between oral and intravenous administration, despite 20% less drug reaching the urine after the oral dose.

As shown in Table VII, there were no significant differences between healthy subjects and patients with CHF in either ER_{50} or S. However, there was a 15-fold difference in the baseline sodium excretion rate (0.252 ± 0.078 mEq/min for healthy subjects vs. 0.016 ± 0.014 mEq/min for patients with CHF; $p < 0.01$). This difference may reflect, in part, the fact that patients were eating sodium-restricted diets, whereas the healthy subjects were not. In healthy subjects, urinary sodium losses were also replaced intravenously with lactated Ringer's solution, whereas in patients with CHF urine losses were not replaced. The E_{max} was 50% less in patients with CHF than in healthy subjects (2.65 ± 0.24 vs. 1.23 ± 0.22 mEq/min, respectively; $p < 0.001$). This may be due to diminished filtered sodium as reflected in the reduced CL_{CR} or an increased reabsorption of solute in the nephron.[50-53] Furthermore, there was a significant correlation between E_{max} and CL_{CR} (Fig. 5; $r = 0.964$; $p < 0.001$). It therefore seems logical to correct the pharmacodynamic parameters for changes in functional nephron mass between the two groups. This was accomplished by dividing E_{max} and E_o by CL_{CR} and by plasma sodium concentration; ER_{50} was divided by CL_{CR}. As shown in Fig. 6, a shift to the right is observed for the dose-response curve in patients with CHF as compared with healthy subjects (right panel of figure). A statistically significant difference in the corrected E_{max} was found ($1.57 \times 10^{-1} \pm 8.19 \times 10^{-3}$ for healthy subjects vs. $2.10 \times 10^{-1} \pm 7.78 \times 10^{-3}$ for patients with CHF; $p < 0.01$), but this difference was only 25% and may reflect the limited number of individuals studied. The corrected baseline response was statistically different between groups ($1.49 \times 10^{-2} \pm 2.19 \times 10^{-3}$ for healthy subjects vs. $3.10 \times 10^{-3} \pm 1.24 \times 10^{-3}$ for patients with CHF; $p < 0.001$) and, as explained previously, may be the result of differences in dietary intake of sodium and in replacement of urinary fluid losses between groups. Additionally, there was a two- to three-fold increase in the corrected value for ER_{50} ($2.94 \times 10^{-2} \pm 3.73 \times 10^{-3}$ μg/ml for healthy subjects vs. $7.67 \times 10^{-2} \pm 1.24 \times 10^{-3}$ μg/ml for patients with CHF; $p < 0.05$). These results may indicate that acute diuretic tolerance is occurring in CHF as urinary losses were not replaced, or that there may be diuretic resistance in CHF. If there is an enhancement of proximal tubular sodium reabsorption in CHF,[50-53] it would take higher urinary concentrations of bumetanide to elicit

the same response in a patient with CHF as compared with a healthy subject.

When the dose-response parameters of healthy subjects in our study were compared with healthy subjects in a study by Lau et al.,[6] there were no significant differences found between E_{max} (2.65 ± 0.24 vs. 3.82 ± 1.13 mEq/min, respectively) and the slope factor, S (2.01 ± 0.56 vs. 1.61 ± 0.24, respectively). However, there were significant differences in both ER_{50} (3.46 ± 0.93 vs. 14.0 ± 7.8 μg/min, respectively; $p < 0.05$) and E_o (0.252 ± 0.078 vs. 0.085 ± 0.065 mEq/min, respectively; $p < 0.001$). Previous studies in animals[54,55] and man[56] have shown that an acute tolerance can develop to furosemide when fluid and electrolyte replacement is inadequate. More recently, similar results have been confirmed for bumetanide in dogs[47] in which a statistically significant increase of ER_{50} occurred with increasing sodium and fluid deficits due to uncompensated urinary losses. These studies have demonstrated that when there is inadequate replacement of urinary losses, body mechanisms are rapidly brought into play within a single dose of diuretic to conserve body fluids. In the study by Lau et al., subjects were kept euvolemic by isovolumetric replacement of urinary losses, but this was done orally with fruit juices. In our study, urinary losses were replaced intravenously with lactated Ringer's solution. It may be that oral absorption of fluids cannot occur at a rate rapid enough to compensate for urinary losses. Consequently, acute tolerance to bumetanide was evident in the study by Lau et al. but not in the present one in healthy subjects.

Ideally, strict and consistent dietary control between the treatment groups is preferable. However, because we were ethically unable to replace intravenous fluids for urine losses in patients with CHF, and because patients' diets were adjusted as tolerated by the degree of heart failure, it was decided to study each participant while he or she was eating his or her normal, stabilized diet. Nonetheless, given this clinical necessity, the variability in dynamic parameters (E_{max}, ER_{50}, S) in healthy subjects and in patients with CHF was comparable (coefficient of variation, 10% to 40%) with those studies in which diet was strictly controlled.[57] Baseline values (E_o) tend to vary considerably between studies and may reflect the hydration status of the individual as well as the method of data analysis.

In conclusion, our results suggest that aside from a modest reduction in CL_R, the pharmacokinetics of bumetanide in patients with CHF are similar to those in healthy subjects. The extent of bioavailability of 3 mg oral doses of bumetanide is approximately 80%, with a variability about the mean of 20% to 25% in both patients with CHF and healthy volunteers. The cumulative pharmacodynamic responses to bumetanide, whether administered orally or intravenously, were not significantly different. As a result, it appears that with bumetanide the clinician can make a predictable transition from an intravenous 3 mg dose to a 3 mg oral maintenance dose in patients with CHF. Because the two modes of administration provide nearly identical respones, the intravenous route should be reserved for those patients who require a rapid onset of action or in whom oral therapy is not appropriate.

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