# Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure

**Six patients with chronic renal failure (CRF group) and four healthy subjects (HS group) were given 5 mg oral and intravenous doses of bumetanide in a random, crossover design. The CRF group had significantly lower plasma and renal clearances, resulting in a five- to sixfold reduction in the fractional urinary excretion of the drug. The percent free drug in plasma for the CRF group was more than double that for the HS group, and significant correlations were observed for volume of distribution at steady state vs. percent free ($r = 0.661$; $P < 0.05$), nonrenal clearance vs. percent free ($r = 0.796$; $P < 0.01$), and renal clearance vs. creatinine clearance ($r = 0.995$; $P < 0.001$). Although bioavailability was relatively consistent among the HS (0.664 ± 0.112) and CRF (0.689 ± 0.149) groups, the absorption-time profiles were more irregular for both groups. Cumulative sodium excretion and overall efficiency of response to bumetanide did not differ significantly between the two routes of administration in either group. (CLIN PHARMACOL THER 1986;39:635-45.)**

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Bumetanide (3-*n*-butylamino-4-phenoxy-5-sulfamoyl-benzoic acid) is a potent loop diuretic that is similar to furosemide with respect to its pharmacologic action and clinical indications.[1] Its principal site of action is the thick ascending limb of the loop of Henle,[2-4] where it has been shown to exert its natriuretic and diuretic effects from the luminal surface of the nephron.[4] Because bumetanide is highly protein bound,[5-7] glomerular filtration is a minor mechanism for drug excretion. Instead, bumetanide gains access to the kidney lumen through the nonspecific organic acid secretory pathway.[8-10] As a result, any pathophysiologic condition that affects the renal tubular secretion of bumetanide can thereby modify its dose-response relationship.

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Furosemide is typically used as therapy for patients with edematous states associated with a variety of diseases, including renal dysfunction.[11] However, the drug's pharmacodynamics are quite variable and suboptimal responses can occur, particularly after oral dosing.[11-13] The inability to predict a satisfactory clinical response for furosemide may be due, in part, to the extensive variability in its bioavailability.[11,14-16] In contrast, bumetanide has been reported to have a consistently high extent of systemic availability in healthy subjects[5,17-19] and in patients with hepatic or renal disease.[20] Nonetheless, pharmacokinetic and pharmacodynamic data for bumetanide in patients with chronic renal failure (CRF) are very limited,[7,20] and no such studies have been performed at therapeutic doses in these patients. Therefore, we proposed (1) to study the absorption and disposition of bumetanide in patients with CRF after 5 mg oral and intravenous doses, and (2) to determine if parenteral administration of bumetanide offers any advantage over oral dosing in eliciting sufficient natriuresis and diuresis. Parallel studies were performed in healthy subjects (HS group) for the purpose of comparison.

## METHODS

***Materials.*** Bumetanide tablets (1 mg; lot 0303-1) and intravenous solution (0.25 mg/ml; lot 0103) were ob-

**Table I.** Clinical data of healthy subjects and patients with CRF

| | Sex | Age (yr) | Weight (kg) | Serum albumin (gm/dl) | BUN (mg/dl) | $CL_{CR}$* (ml/min) | Diagnosis | Concomitant drugs |
|---|---|---|---|---|---|---|---|---|
| Subjects | | | | | | | | |
| 1 | F | 23 | 51.7 | 5.4 | 6 | 92.6 | Healthy | — |
| 2 | M | 32 | 67.8 | 4.8 | 17 | 107 | Healthy | — |
| 3 | F | 22 | 68.5 | 4.8 | 7 | 95.5 | Healthy | — |
| 4 | M | 27 | 62.4 | 4.9 | 19 | 130 | Healthy | — |
| $\bar{X}$ | | 26 | 62.6 | 5.0 | 12 | 106 | | |
| ±SD | | 5 | 7.8 | 0.3 | 7 | 17 | | |
| Patients | | | | | | | | |
| 5 | F | 48 | 69.2 | 4.8 | 81 | 17.4 | Chronic interstitial nephritis | Methyldopa, allopurinol, hydralazine, metoprolol tartrate |
| 6 | M | 59 | 73.0 | 4.3 | 43 | 20.5 | Hypertension | Propranolol HCl, isosorbide dinitrate, dipyridamole |
| 7 | F | 51 | 106 | 4.4 | 51 | 12.4 | Myeloma | Allopurinol |
| 8 | M | 68 | 69.0 | 4.2 | 74 | 7.3 | Hypertension | Multivitamin |
| 9 | F | 47 | 104 | 4.0 | 43 | 28.6 | Polycystic kidney disease | Metoprolol tartrate, multivitamin |
| 10 | M | 41 | 87.6 | 4.1 | 61 | 24.0 | Wegener's disease | Hydralazine, folic acid, cyclophosphamide, atenolol |
| $\bar{X}$ | | 52 | 84.8 | 4.3 | 59 | 18.4 | | |
| ±SD | | 10 | 17.1 | 0.3 | 16 | 7.7 | | |

*Determined over 24 hours.

tained from Hoffmann-La Roche, Inc. All other chemicals and solvents were reagent grade or better, as previously reported.[21]

***Study participants.*** This study was performed in the Clinical Research Center of the University of Michigan Hospitals. The control group consisted of four healthy subjects, as judged by medical history, physical examination, and standard laboratory tests, including a creatinine clearance determination (Table I). The patient group consisted of six individuals with moderate to severe CRF and a stable creatinine clearance ($CL_{CR}$) of <30 ml/min (Table I). Patients were excluded from the study if they had diabetes or signs or symptoms of hepatic, hematologic, or gastrointestinal diseases. 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 response (i.e., nonsteroidal anti-inflammatory drugs) were not allowed for a minimum of 3 days before bumetanide administration. Patients were instructed to adhere strictly to their prescribed dietary restrictions and each participant was asked 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 participant received a 5 mg dose of bumetanide, either orally (five tablets) or intravenously, at 8 AM in a randomized crossover design. A period of at least 1 week elapsed between the two dosing regimens. Bumetanide tablets were taken with 8 oz 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 and drawn into tubes containing EDTA at 0, 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 at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, 480, and 1440 minutes after drug dosing. Blood samples were centrifuged immediately and the plasma was harvested and frozen. Voided urine was collected from −24 to 0 (blank), 0 to 0.5, 0.5 to 1.0, 1.0 to 1.5, 1.5 to 2.0, 2.0 to 2.5, 2.5 to 3.0, 3 to 4, 4 to 5, 5 to 6, 6 to 7, 7 to 8, and 8 to 24 hours relative to drug dosing. Plasma and urine samples were stored at −20° C until subsequent

analysis. Participants were kept relatively euvolemic throughout the study by drinking fruit juices in a volume equal to the urine passed during the previous time period. Lunch was provided 4 hours after dosing and all plasma samples showed normal sodium concentrations.

***Analytic procedures.*** Plasma and urine samples containing bumetanide were assayed by a rapid, sensitive, and specific HPLC method, as described previously by Smith.[21] Sodium concentrations were measured with a flame photometer.

***Protein binding.*** The plasma protein binding of bumetanide was determined for each participant with the use of from three to seven data points from the intravenous drug profile. 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 6 hours. Dialysis membranes (molecular weight cutoff 12,000 to 14,000 daltons) and 1 ml equilibrium dialysis cells were used throughout, and preliminary studies indicated that equilibrium was achieved within 2 hours and remained constant for 24 hours. Dialyzed buffer (0.2 ml) was then mixed with 50 μl acetophenone (0.25 mg/ml) and injected into the HPLC system, as reported previously.[21] 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 following linear least-squares regression equation: $Y = 0.0213X + 0.0096$ ($r^2 = 0.9997$). The percent of unbound bumetanide in the original plasma sample ($f_u$) was calculated as: $f_u = 100/(C/C_f' - 1)$, where C represents the measured total concentration of drug in plasma before dialysis and $C_f'$ represents the measured unbound concentration of drug in buffer after dialysis. This equation was originally developed by Tozer et al.[22] to correct for the volume shift that can occur during equilibrium dialysis. It assumes that the initial plasma and buffer volumes are equal, that protein binding is linear, and that there is negligible binding of drug to the dialysis membrane (mean value of 1.24% for bumetanide).

***Kinetics.*** Plasma concentration-times curves of bumetanide were fit (weighting factor of $1/C^2$) to the general polyexponential equation for post–constant-rate infusion data[23]

$$C = \sum_{i=1}^{n} Y_i e^{-\lambda_i t} \quad (1)$$

where C is the plasma concentration at time t, n is the number of exponents, $Y_i$ is the coefficient of the ith exponential term for post–constant-rate intravenous infusion data, and $\lambda_i$ is the exponent of the ith exponential term. Initial estimates of the coefficients and exponential terms in Eq. 1 were obtained by use of the program RSTRIP (personal communication); their final estimates were obtained by use of the nonlinear least-squares regression program NONLIN.[24] The number of exponents needed for each data set was determined by the application of Akaike's information criterion.[25] Because

$$C = \sum_{i=1}^{n} (1 - e^{\lambda_i T}) C_i e^{-\lambda_i t} / (-\lambda_i T) \quad (2)$$

where T is the constant-rate infusion time and $C_i$ is the coefficient of the ith exponential term for bolus intravenous data, Eq. 1 can be rearranged to the corresponding equation[23]:

$$Y_i = \sum_{i=1}^{n} (1 - e^{\lambda_i T}) C_i / (-\lambda_i T) \quad (3)$$

Once the values of the coefficients and exponential terms in Eq. 1 are determined by computer fitting, the values of $C_i$ in Eq. 3 can be calculated.

The following pharmacokinetic parameters were calculated from standard equations[23,26]:

$$V_c = D/\sum_{i=1}^{n} C_i \quad (4)$$

$$V_{ss} = D \sum_{i=1}^{n} C_i/\lambda_i^2 / (\sum_{i=1}^{n} C_i/\lambda_i)^2 \quad (5)$$

$$V_{area} = D/(\lambda_1 \sum_{i=1}^{n} C_i/\lambda_i) \quad (6)$$

$$CL = D/\sum_{i=1}^{n} C_i/\lambda_i \quad (7)$$

$$CL_R = Ae(0\text{-}\infty)/\sum_{i=1}^{n} C_i/\lambda_i \quad (8)$$

$$CL_{NR} = CL - CL_R \quad (9)$$

$$t_{1/2} = 0.693/\lambda_1 \quad (10)$$

$$k_{10} = CL/V_c \quad (11)$$

$$f_e = Ae(0\text{-}\infty)/D \quad (12)$$

in which $V_c$ is the volume of the central compartment; D is the intravenous dose (equal to the product of the zero-order infusion rate and the length of infusion); $C_1$ and $\lambda_1$ are the coefficient and exponent, respectively, such that $\lambda_1$ is the smallest of the $\lambda_i$ values of the polyexponential equation; $V_{ss}$ is the volume of distribution at steady state; $V_{area}$ is the volume that, 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; Ae(0-∞) is the

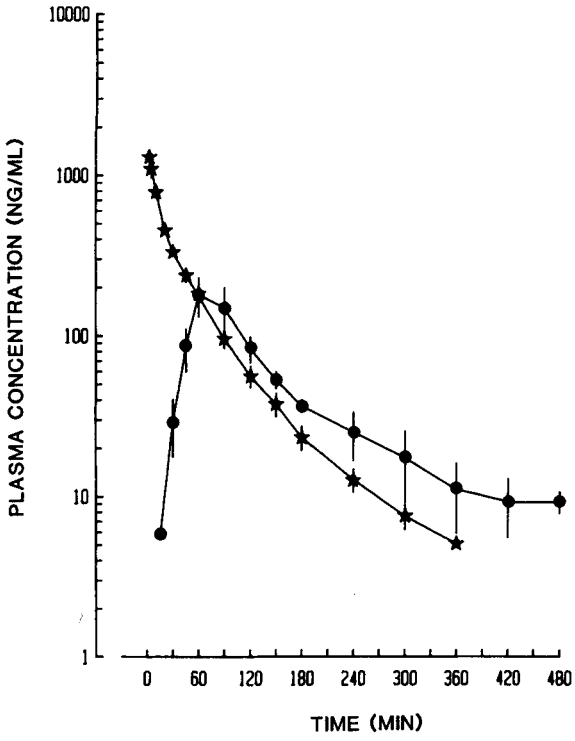


**Fig. 1.** Mean (±SE) plasma concentration-time profiles of bumetanide in healthy subjects after 5 mg oral (●) and intravenous (★) doses.

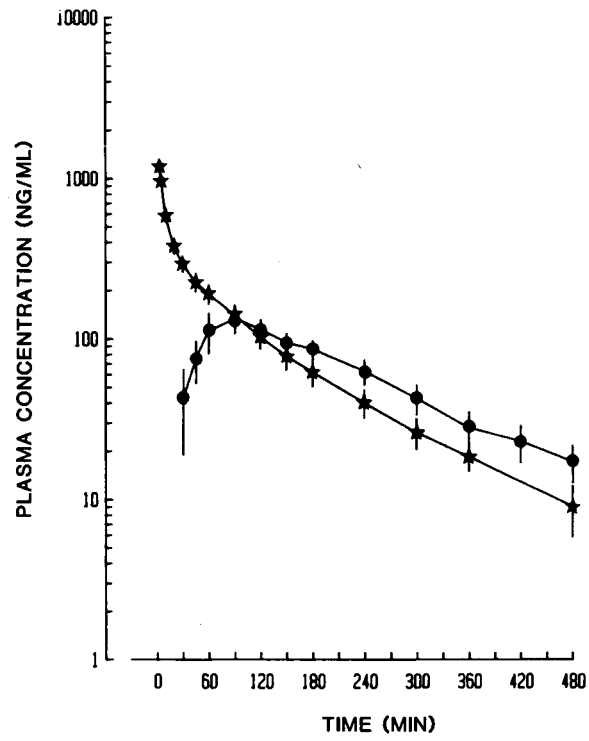


**Fig. 2.** Mean (±SE) plasma concentration-time profiles of bumetanide in patients with CRF after 5 mg oral (●) and intravenous (★) doses.

amount of unchanged drug recovered in the urine at time infinity; $CL_{NR}$ is the nonrenal clearance; $k_{10}$ is the first-order elimination rate constant from the central compartment; and $f_e$ is the fraction of the available 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 $t_{1/2}$ was graphically determined by linear regression with use of at least four data points from the log-linear terminal phase, and $CL_R$ was determined by division of Ae(0-∞) by the plasma AUC(0-∞), calculated by a combination of the trapezoidal and log-trapezoidal rules and extrapolated to infinity by $C_{last}/\lambda_1$. 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 area ratios of oral (subscript po) and intravenous (subscript iv) dosing ($F_p = AUC(0\text{-}\infty)_{po}/AUC(0\text{-}\infty)_{iv}$), by urinary excretion ratios ($F_u = Ae(0\text{-}\infty)_{po}/Ae(0\text{-}\infty)_{iv}$), and by correction for differences in $CL_R$ between oral and intravenous doses (extrapolated to infinity) as suggested by Øie and Jung[27]:

$$F_{corr} = \frac{(D_{iv} - Ae_{iv})AUC_{po}/AUC_{iv} + Ae_{po}}{D_{po}} \quad (13)$$

For the calculations of $F_p$ and $F_{corr}$, $AUC_{iv}$ was determined by a combination of the trapezoidal and log-trapezoidal rules, extrapolated to infinity by $C_{last}/\lambda_1$. The computer-fitted and noncompartmental estimates of $AUC_{iv}$ differed from one another by <2%.

The mean absorption time (MAT) was used as a measure of the absorption rate of oral bumetanide by use of the noncompartmental method of statistical moments.[28,29] MAT was calculated as the difference of mean residence times (MRT) between oral and intravenous dosing: $MAT = MRT_{po} - MRT_{iv}$, where MRT equals the area under the first moment curve (AUMC; extrapolated to infinity) divided by AUC(0-∞). The AUMC was estimated by a combination of the trapezoidal and log-trapezoidal rules, extrapolated to infinity by $t_{last} \cdot C_{last}/\lambda_1 + C_{last}/\lambda_1^2$. An MAT value that corrects for the time lag ($t_{lag}$) before drug absorption was also reported ($MAT_{corr} = MAT - t_{lag}$). The $t_{lag}$ was estimated from absorption profiles using the exact

**Table II.** Coefficients and exponential terms of intravenous bumetanide in healthy subjects and patients with CRF determined by bi- and triexponential equations

| | *C(1)* *(ng/ml)* | *C(2)* *(ng/ml)* | *C(3)* *(ng/ml)* | $\lambda_1$ *($min^{-1}$)* | $\lambda_2$ *($min^{-1}$)* | $\lambda_3$ *($min^{-1}$)* | *$R^2$** | *CORR†* |
|---|---|---|---|---|---|---|---|---|
| Subjects | | | | | | | | |
| 1 | 24.7 | 623 | 1094 | 0.0041 | 0.0185 | 0.1333 | 0.991 | 0.992 |
| 2 | 281 | 1080 | | 0.0141 | 0.1329 | | 0.996 | 0.997 |
| 3 | 83.0 | 725 | 1094 | 0.0078 | 0.0321 | 0.1769 | 1.000 | 1.000 |
| 4 | 129 | 812 | | 0.0113 | 0.0394 | | 0.994 | 0.994 |
| Patients | | | | | | | | |
| 5 | 324 | 1265 | | 0.0096 | 0.1412 | | 0.999 | 1.000 |
| 6 | 189 | 384 | 1512 | 0.0053 | 0.0184 | 0.1799 | 0.998 | 0.998 |
| 7 | 161 | 446 | 1338 | 0.0077 | 0.0581 | 0.3040 | 1.000 | 1.000 |
| 8 | 403 | 735 | | 0.0077 | 0.1202 | | 0.998 | 0.998 |
| 9 | 58.9 | 322 | 984 | 0.0033 | 0.0162 | 0.1612 | 0.990 | 0.992 |
| 10 | 58.3 | 282 | 625 | 0.0053 | 0.0171 | 0.2056 | 1.000 | 1.000 |

*$R^2 = [\Sigma(Obs)^2 - \Sigma(Dev)^2]/\Sigma(Obs)^2$, where $\Sigma(Dev)^2$ is the residual sum of squares.
†CORR represents the correlation between the calculated and observed plasma concentrations.

**Table III.** Pharmacokinetic parameters after intravenous bumetanide in healthy subjects and patients with CRF

| | *Subjects* | *Patients* | *Significance (P value)* |
|---|---|---|---|
| CL (ml/min · kg) | 2.25 ± 0.37 | 1.40 ± 0.32 | <0.01 |
| $CL_R$ (ml/min · kg) | 1.46 ± 0.20 | 0.153 ± 0.079 | <0.001 |
| $CL_{NR}$ (ml/min · kg) | 0.790 ± 0.304 | 1.25 ± 0.33 | NS |
| $t_{1/2}$ (min) | 92.2 ± 53.9 | 121 ± 50 | NS |
| $k_{10}$ ($min^{-1}$) | 0.0407 ± 0.0094 | 0.0351 ± 0.0130 | NS |
| $V_c$ (L/kg) | 0.0584 ± 0.0194 | 0.0434 ± 0.0156 | NS |
| $V_{ss}$ (L/kg) | 0.122 ± 0.019 | 0.147 ± 0.024 | NS |
| $V_{area}$ (L/kg) | 0.285 ± 0.140 | 0.234 ± 0.084 | NS |
| Ae (%) | 65.4 ± 8.1 | 11.4 ± 6.8 | <0.001 |
| $f_u$ (%) | 0.588 ± 0.058 | 1.36 ± 0.37 | <0.005 |

NS = Not significant.

Loo-Riegelman equation of Wagner[30] and the second derivative criterion of Proost[31] for evaluation of the two integrals of that equation.

***Dynamics.*** Pharmacodynamic data were reported as the 8-hour cumulative excretion of sodium and the overall efficiency (Eff) of the response: $Eff = (\Delta E - \Delta E_0)/\Delta Ae$, where $\Delta E$ and $\Delta Ae$ are the amount of sodium and drug excreted in urine, respectively, and $\Delta E_0$ is the baseline effect over the same 8-hour period.

The relationship between the sodium excretion rate (E; in milliequivalents per minute) and urinary excretion rate of bumetanide (ER; in micrograms per minutes) was evaluated by the sigmoid $E_{max}$ model[32]: $E = E_{max} \cdot ER^S/(ER_{50}{}^S + ER^S) + E_0$, where $E_{max}$ is the maximum effect attributable to the drug, $ER_{50}$ is the urinary excretion rate of drug producing 50% of $E_{max}$, $E_0$ is the baseline effect, and S is the parameter influencing the slope of the dose-effect curve. The unknown parameters ($E_{max}$, $ER_{50}$, $E_0$, and S) were determined after intravenous dosing of bumetanide for each individual by use of the NONLIN[32] program and a weighting factor of unity.

***Statistics.*** Unless otherwise indicated, data are expressed as the $\bar{X}$ ± SD. Statistical differences between the HS and CRF groups were determined by a two-sample t test. Statistical differences between oral and intravenous dosing within each group were determined by a paired t test. The linear relationship between two variables was assessed by the correlation coefficient r. A P value $\leq 0.05$ was considered significant.

## RESULTS

Semilogarithmic plots of the plasma concentration-time curves of intravenous and oral bumetanide are shown in Figs. 1 and 2 for healthy subjects and patients with CRF, respectively. After intravenous infusion, plasma concentrations of bumetanide were fit to a biexponential equation for four data sets and to a triexpo-

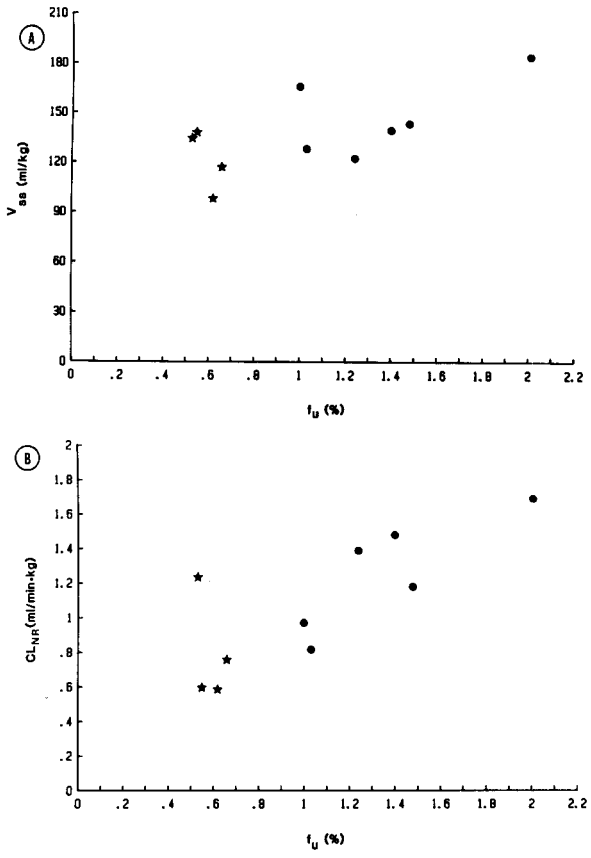


**Fig. 3. A,** Relationship between $V_{ss}$ and bumetanide $f_u$ in healthy subjects (★) and patients with CRF (●; r = 0.661; $P < 0.05$). **B,** Relationship between $CL_{NR}$ and bumetanide $f_u$ in healthy subjects (★) and patients with CRF (●; r = 0.796; $P < 0.01$).

nential equation for six data sets (Table II). The goodness of fit was evaluated by $R^2$ ($\geq$0.990) · CORR ($\geq$0.992) and by visual examination of the residuals.

Kinetic data after intravenous bumetanide are listed in Table III. In comparison with the HS group, the CRF group had a significantly lower $CL_R$ (1.46 ± 0.20 ml/min · kg for the HS group vs. 0.153 ± 0.079 ml/min · kg for the CRF group; $P < 0.001$) and CL (2.25 ± 0.37 ml/min · kg for the HS group vs. 1.40 ± 0.32 ml/min · kg for the CRF group; $P < 0.01$), resulting in a five- to sixfold reduction in the $f_e$ value of the diuretic (0.654 ± 0.081 for the HS group vs. 0.114 ± 0.068 for the CRF group; $P < 0.001$). Although the volume terms and $CL_{NR}$ did not differ statistically between the two groups, a significant correlation was observed between $V_{ss}$ and $f_u$ (Fig. 3, *A*; r = 0.661; $P < 0.05$) and $CL_{NR}$ and $f_u$ (Fig. 3, *B*; r = 0.796; $P < 0.01$), reflecting the greater than double increase in bumetanide $f_u$ in the CRF group. The biologic $t_{1/2}$ and $k_{10}$ values did not differ between the HS and CRF groups.

Kinetic data after oral bumetanide are listed in Table IV. No significant differences were observed between the two groups, except for $CL_R$ (1.71 ± 0.20 ml/min · kg in the HS group vs. 0.176 ± 0.096 ml/min · kg in the CRF group; $P < 0.001$), which is to be expected. The mean value for F ranged from 0.588 to 0.675 in the HS group and from 0.677 to 0.764 in the CRF group, depending on the method of calculation. Although no statistical differences were found in the biologic $t_{1/2}$ or $CL_R$ in the HS and CRF groups as a function of the route of administration, $CL_R$ was greater in seven of 10 participants after oral dosing. Therefore, the F value corrected for $CL_R$ (0.664 ± 0.112 for the HS group vs. 0.689 ± 0.149 for the CRF group) is probably the more accurate assessment of this parameter.

The Ae(0-8) and overall efficiency of bumetanide-induced natriuresis are listed in Tables V and VI, respectively. Bumetanide elicited an equivalent response in the HS and CRF groups whether taken by mouth or administered intravenously. Although the amount of sodium excreted per unit of bumetanide tended to be larger after oral dosing (Table VI), the difference was not statistically significant at the 95% confidence level, and may reflect the small number of participants studied.

The parameters for the dose-response relationships of intravenous bumetanide are listed in Table VII. The goodness of fit was evaluated by $R^2$ · CORR and by visual examination of the residuals. In comparison with healthy subjects, patients with CRF had a significantly lower $E_{max}$ (3.82 ± 1.13 mEq/min in the HS group vs. 1.09 ± 0.71 mEq/min in the CRF group; $P < 0.005$) and an eightfold reduction in $ER_{50}$ (14.0 ± 7.8 μg/min in the HS groups vs. 1.70 ± 0.87 μg/min in the CRF group; $P < 0.005$). In the fitting of the sigmoid $E_{max}$ model, the first data point (i.e., the highest value for ER) was omitted for five participants (two in the HS group and three in the CRF group) because of the presence of a counterclockwise hysteresis (Figs. 4 and 5). This phenomenon has been reported for bumetanide in dogs[8,33] and humans,[34] and reflects the disequilibrium that can occur between the urine and effect compartments during the early periods after dosing. Dynamic parameters were not evaluated after oral dosing because insufficient data were available to define the full extent of the sigmoid-shaped curve. Nonetheless, a similar profile was observed for the dose-response relationship of bumetanide when oral and intravenous administra-

**Table IV.** Absorption and disposition characteristics of oral bumetanide in healthy subjects and patients with CRF

| | *Subjects* | *Patients* | *Significance (P value)* |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 179 ± 98 | 140 ± 64 | NS |
| $t_{max}$ (min) | 60 ± 0 | 98 ± 44 | NS |
| $t_{lag}$ (min) | 23.4 ± 5.8 | 20.5 ± 6.4 | NS |
| MAT (min) | 128 ± 62 | 113 ± 49 | NS |
| $MAT_{corr}$ (min) | 105 ± 66 | 92.1 ± 46.9 | NS |
| $t_{1/2}$ (min) | 85.7 ± 9.2 | 108 ± 32 | NS |
| $CL_R$ (ml/min · kg) | 1.71 ± 0.20 | 0.176 ± 0.096 | <0.001 |
| $F_p$ | 0.588 ± 0.096 | 0.677 ± 0.154 | NS |
| $F_u$ | 0.675 ± 0.163 | 0.764 ± 0.156 | NS |
| $F_{corr}$ | 0.664 ± 0.112 | 0.689 ± 0.149 | NS |

NS = Not significant.

**Table V.** Natriuretic effect of bumetanide in healthy subjects and patients with CRF after oral and intravenous administration

| | *Oral (mEq/8 hr)* | *Intravenous (mEq/8 hr)* |
|---|---|---|
| Subjects | | |
| 1 | 465 | 281 |
| 2 | 266 | 501 |
| 3 | 407 | 279 |
| 4 | 292 | 365 |
| $\bar{X}$ | 358 | 357 |
| ± SD | 94 | 104 |
| P value | NS (>0.4) | |
| Patients | | |
| 5 | 103 | 53.5 |
| 6 | 227 | 203 |
| 7 | 158 | 167 |
| 8 | 180 | 146 |
| 9 | 194 | 210 |
| 10 | 212 | 225 |
| $\bar{X}$ | 179 | 167 |
| ± SD | 44 | 63 |
| P value | NS (>0.2) | |

NS = Not significant.

**Table VI.** Overall efficiency (sodium/bumetanide) in healthy subjects and patients with CRF after oral and intravenous administration

| | *Oral (mEq/μg · 8 hr)* | *Intravenous (mEq/μg · 8 hr)* |
|---|---|---|
| Subjects | | |
| 1 | 0.2116 | 0.0732 |
| 2 | 0.0973 | 0.1631 |
| 3 | 0.1297 | 0.0744 |
| 4 | 0.1348 | 0.0864 |
| $\bar{X}$ | 0.1434 | 0.0993 |
| ± SD | 0.0484 | 0.0430 |
| P value | NS (>0.1) | |
| Patients | | |
| 5 | 0.1520 | 0.0411 |
| 6 | 0.2393 | 0.1703 |
| 7 | 1.5288 | 0.9540 |
| 8 | 0.6684 | 0.4394 |
| 9 | 0.4832 | 0.2875 |
| 10 | 0.3972 | 0.3775 |
| $\bar{X}$ | 0.5782 | 0.3783 |
| ± SD | 0.5000 | 0.3163 |
| P value | NS (>0.05) | |

NS = Not significant.

tion curves were superimposed on one another in the HS and CRF groups (Figs. 4 and 5, respectively).

## DISCUSSION

The pharmacokinetics and pharmacodynamics of bumetanide after 1 mg oral and intravenous doses have been studied by Marcantonio et al.[20] in patients with hepatic and renal disease. In comparison with normal subjects (n = 8), these investigators observed that patients with CRF (n = 6) had higher serum concentrations of bumetanide and that the terminal $t_{1/2}$ values were significantly prolonged. They also state that the significant reduction in CL was attributable to the very low $CL_R$ in these patients because the $CL_{NR}$ was increased. Despite the fact that the F values were high for both groups (mean of 0.89 for the HS group vs. 0.83 for the CRF group), subtherapeutic doses of bumetanide were given to the patients with CRF, resulting in a poor pharmacodynamic response. Subsequently, Pentikäinen et al.[7] studied the pharmacokinetics of bumetanide after 1 mg iv doses in six healthy subjects and 22 patients with variable degrees of CRF (creatinine clearances range from 0 to 54 ml/min). These investigators reported that the most important changes in bumetanide kinetics for patients with CRF were the low $CL_R$ and the high $f_u$. As a result, significant increases were also

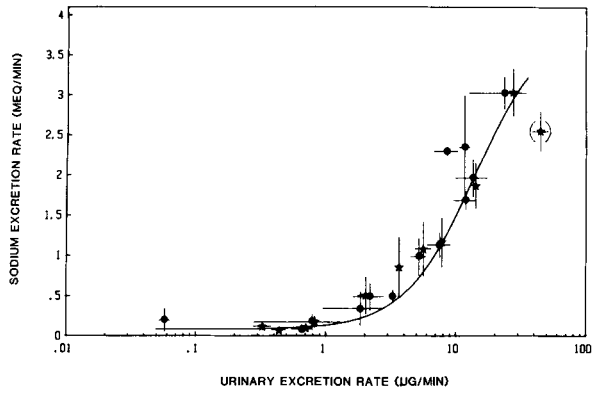


**Fig. 4.** Mean (±SE) sodium excretion rate vs. urinary excretion rate of bumetanide in healthy subjects after oral (●) and intravenous (★) doses. The *solid line* represents the computer-generated regression line based on the fitted parameters in Table VII.

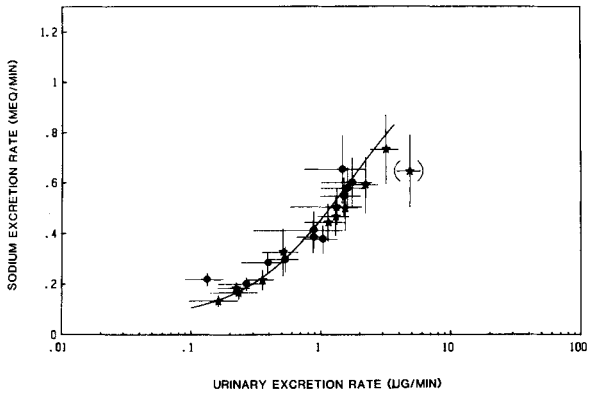


**Fig. 5.** Mean (±SE) sodium excretion rate vs. urinary excretion rate of bumetanide in patients with CRF after oral (●) and intravenous (★) doses. The *solid line* represents the computer-generated regression line based on the fitted parameters in Table VII.

observed for $CL_{NR}$, $V_{ss}$, and the elimination $t_{1/2}$. In our study, changes in the patients' pharmacokinetics were qualitatively similar to those in the studies above,[7,20] although these kinetic parameters were quantitatively in closer agreement to those of Marcantonio et al.[20] for both healthy subjects and patients. This finding may be because both studies (ref. 20 and ours) involved a specific HPLC assay in which the known metabolites of bumetanide were shown not to interfere with the analysis. Likewise, the large variability in the previously reported clearances of bumetanide for healthy subjects[6,7,19] probably reflects the use of different analytic methods in which drug was measured by RIA or by liquid scintillation counting after solvent extraction.

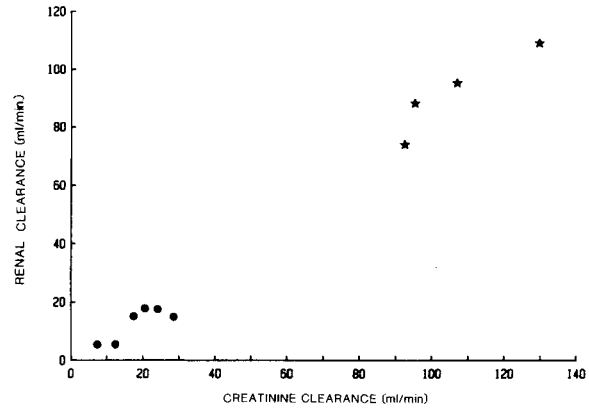


**Fig. 6.** Relationship between bumetanide $CL_R$ and $CL_{CR}$ in healthy subjects (★) and patients with CRF (●; $r = 0.995$; $P < 0.001$).

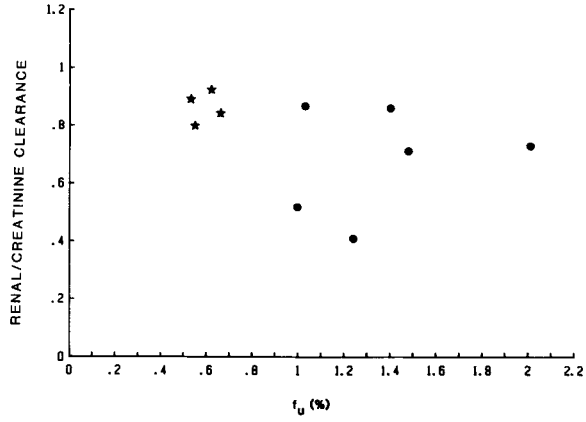


**Fig. 7.** Relationship between corrected $CL_R$ ($CL_R/CL_{CR}$) and bumetanide $f_u$ in healthy subjects (★) and patients with CRF (●; $r = -0.569$; $P > 0.05$).

In our study, the reduction in bumetanide $CL_R$ was paralleled by a concomitant reduction in nephron mass, as demonstrated by the significant positive correlation between $CL_R$ and $CL_{CR}$ (Fig. 6; $r = 0.995$; $P < 0.001$). However, no direct correlation could be made between the corrected $CL_R$ ($CL_R/CL_{CR}$) of bumetanide and $f_u$ (Fig. 7; $r = -0.569$; $P > 0.05$). As a result, the corrected $CL_R$ of unbound bumetanide ($CL_R/f_u \cdot CL_{CR}$) was significantly reduced in patients with CRF (143 ± 12 for subjects vs. 52.0 ± 19.6 for patients; $P < 0.001$). Although speculative, mechanisms consistent with this finding include the presence of capacity-limited transport, product inhibition, and competition for active secretion between bumetanide and endogenous substances in the patients with azotemia. This last hypothesis is particularly attractive because previous investigators have shown that endogenous organic acids can accu-

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

| | $E_{max}$ (mEq/min) | S | $ER_{50}$ (μg/min) | $E_0$ (mEq/min) | $R^2$* | CORR† |
|---|---|---|---|---|---|---|
| Subjects | | | | | | |
| 1 | 3.30 | 1.74 | 18.5 | 0.120 | 0.978 | 0.980 |
| 2 | 2.73 | 1.27 | 3.1 | 0.006 | 0.997 | 0.995 |
| 3‡ | 5.35 | 1.64 | 20.7 | 0.060 | 0.998 | 0.999 |
| 4‡ | 3.91 | 1.81 | 13.9 | 0.153 | 0.999 | 0.999 |
| $\bar{X}$ | 3.82 | 1.61 | 14.0 | 0.085 | 0.993 | 0.989 |
| ±SD | 1.13 | 0.24 | 7.8 | 0.065 | 0.010 | 0.008 |
| Patients | | | | | | |
| 5 | 0.30 | 0.62 | 1.81 | 0.007 | 0.998 | 0.992 |
| 6† | 0.70 | 1.86 | 1.66 | 0.122 | 0.980 | 0.934 |
| 7 | 2.30 | 0.67 | 2.96 | 0.012 | 0.996 | 0.993 |
| 8‡ | 0.72 | 1.02 | 0.59 | 0.031 | 0.988 | 0.965 |
| 9‡ | 1.48 | 1.14 | 2.25 | 0.087 | 0.978 | 0.965 |
| 10 | 1.08 | 1.32 | 0.92 | 0.110 | 0.994 | 0.990 |
| $\bar{X}$ | 1.09 | 1.10 | 1.70 | 0.061 | 0.989 | 0.973 |
| ±SD | 0.71 | 0.46 | 0.87 | 0.051 | 0.008 | 0.023 |
| Significance (P value) | $P < 0.005$ | NS | <0.005 | NS | | |

NS = Not significant.
*$R^2 = [\Sigma(Obs)^2 - \Sigma(Dev)^2]/\Sigma(Obs)^2$, where $\Sigma(Dev)^2$ is the residual sum of squares.
†CORR represents the correlation between the calculated and observed sodium excretion rates.
‡The sigmoid $E_{max}$ model was fit without the first data point.

mulate and block the active transport pathway of furosemide in azotemia in dogs[35] and humans.[36]

The absorption profile of bumetanide in healthy subjects and patients with CRF was found to be quite variable, as demonstrated by the large coefficients of variation (51% to 63%) surrounding the mean values for $MAT_{corr}$. In addition, a time lag of approximately 20 to 25 minutes was observed for both groups, a value in close agreement with those other studies in healthy subjects.[18,19] Although the F values did not differ between the subjects and patients, the mean values (65% to 70%) were smaller than those reported in previous studies.[5,17-20] Pentikäinen et al.[5] and Halladay et al.[17] stated that the absorption of bumetanide was nearly complete (>95%) in four healthy subjects. However, their results are suspect because a nonspecific assay was used in which the drug was measured by total radioactivity in the various biologic fluids. Subsequently, Holazo et al.[19] used an RIA to determine the bioavailability of bumetanide tablets in 12 normal subjects. They reported that 78% and 86% of the drug reached the systemic circulation when calculated by the area and urinary excretion methods, respectively. Using a specific HPLC assay with fluorescence detection, Marcantonio et al.[18,20] also reported high F values for bumetanide. In eight healthy subjects the F value was 90%[18] and in six patients with CRF the F value was 83%.[20] Unfortunately, the variability about the mean values was not reported by these investigators. The discrepancy in the F value between our study and those of Marcantonio et al. is difficult to reconcile because similar HPLC assays were used. Nevertheless, this discrepancy may reflect the different doses that were used. It is conceivable that a dose-dependent absorption may be occurring at the 5 mg doses in our study, but not at their 1 mg doses. Other investigators[5,17,19] studied the bioavailability of bumetanide at doses ranging from 0.5 to 2.0 mg.

As observed in Tables V and VI, bumetanide elicited an equivalent response in the HS and CRF groups whether administered orally or intravenously. This equivalency of response occurred despite the significantly smaller excretion of unchanged bumetanide after oral dosing in healthy subjects (2166 ± 529 μg/8 hr for oral vs. 3236 ± 394 μg/8 hr for intravenous; $P < 0.05$) and patients (399 ± 266 μg/8 hr for oral vs. 538 ± 315 μg/8 hr for intravenous; $P < 0.02$). Similar observations have been cited for bumetanide[18-20] and furosemide.[11] However, in the case of furosemide, on average only 50% of the oral drug reaches the systemic circulation. This phenomenon was explained by Kaojarern et al.,[37] who stressed the importance of the slope factor of the dose-response curve on the overall dynamics. They observed that when the slope factor is <2, the maximally efficient excretion rate is less than the $ER_{50}$. As a result, maximally efficient amounts of

drug can be maintained at the active site for prolonged periods after oral dosing because of the absorption profile. Thus the same or perhaps a greater cumulative effect can be obtained with less total drug in the urine. This finding is consistent with our results in subjects and patients, and may explain the equivalency of oral vs. intravenous bumetanide despite an F value of 65% to 70%.

The lower $E_{max}$ in patients with CRF (Table VII) was not surprising because their nephron mass is substantially reduced, as judged by the decrease in $CL_{CR}$. However, based on the $ER_{50}$ data alone, one might be misled to conclude that the HS group was more resistant to bumetanide therapy. Instead, a tolerance effect was probably developed to bumetanide because of an acute depletion of extracellular fluid volume and electrolytes. Although we replaced urinary losses with isovolumetric amounts of fluid by mouth, the body was apparently not replenishing the extracellular fluid volume at an equal rate. Furthermore, by the time the first fluid replacement was received (30 minutes after dosing), it may have already been too late. This hypothesis is supported by the occurrence of leg cramps in two of the healthy subjects. A similar phenomenon was also reported in a study by Hammarlund et al.,[38,39] in which acute tolerance developed to furosemide diuresis in rats and humans. In the study in the rat,[38] the $ER_{50}$ increased by a factor of 20 as single intravenous doses of furosemide were increased from 2.5 to 100 mg/kg. In the study in humans,[39] a clockwise hysteresis was noted when the oral doses were taken postprandially. In addition, the drug excretion-response curves showed parallel shifts to the right, depending on the mode of administration of furosemide. In both of these studies, the renal sensitivity to furosemide was attenuated within a very short period of time (i.e., minutes to hours) and in an unpredictable manner. An acute volume depletion may also explain the sharp contrast of our results in healthy subjects with those of Brater et al.[34,40] Despite the similar values for $E_{max}$, S, and $E_0$, the $ER_{50}$ was approximately 10 to 14 times greater in our study. This discrepancy may reflect the fact that urinary losses were replaced intravenously in their healthy subjects and that lower doses were used (1 mg as compared with the 5 mg doses in our study), thereby reducing the potential for volume and electrolyte depletion.

In conclusion, the bioavailability of 5 mg doses of bumetanide was approximately 65% to 70% with a variability about the mean of 15% to 20% in healthy subjects and patients with CRF. The cumulative pharmacodynamic effects of oral and intravenous doses were essentially equivalent despite the fact that a smaller amount of drug was delivered to the site of action after oral dosing. As a result, it appears that a predictable transition from 5 mg intravenous to oral maintenance regimens of bumetanide is possible in patients with CRF. Intravenous administration should be reserved for those conditions in which a more rapid onset of action is required.

### *References*

1. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. Drugs 1984;28:426-64.
2. Bourke E, Asbury MJA, O'Sullivan S, Gatenby PBB. The sites of action of bumetanide in man. Eur J Pharmacol 1973;23:283-9.
3. Jayakumar S, Puschett JB. Study of the sites and mechanisms of action of bumetanide in man. J Pharmacol Exp Ther 1977;201:251-8.
4. Imai M. Effect of bumetanide and furosemide on the thick ascending limb of Henle's loop of rabbits and rats perfused in vitro. Eur J Pharmacol 1977;41:409-16.
5. Pentikäinen PJ, Penttilä A, Neuvonen PJ, Gothoni G. Fate of [$^{14}$C]-bumetanide in man. Br J Clin Pharmacol 1977;4:39-44.
6. Pentikäinen PJ, Neuvonen PJ, Kekki M, Penttilä A. Pharmacokinetics of intravenously administered bumetanide in man. J Pharmacokinet Biopharm 1980;8:219-28.
7. Pentikäinen PJ, Pasternack A, Lampainen E, Neuvonen PJ, Penttilä A. Bumetanide kinetics in renal failure. CLIN PHARMACOL THER 1985;37:582-8.
8. Smith DE, Lau HSH. Determinants of bumetanide response in the dog: effect of probenecid. J Pharmacokinet Biopharm 1983;11:31-46.
9. Lau HSH, Shih LJ, Smith DE. Effect of probenecid on the dose-response relationship of bumetanide at steady-state. J Pharmacol Exp Ther 1983;227:51-4.
10. Odlind B, Beermann B, Lindström B. Coupling between renal tubular secretion and effect of bumetanide. CLIN PHARMACOL THER 1983;34:805-9.
11. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. J Pharmacokinet Biopharm 1979;7:1-27.
12. Vasko MR, Brown-Cartwright D, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985; 102:314-8.
13. Smith DE, Gambertoglio JG, Vincenti F, Benet LZ, Furosemide kinetics and dynamics after kidney transplant. CLIN PHARMACOL THER 1981;30:105-13.
14. Cutler RE, Blair AD. Clinical pharmacokinetics of furosemide. Clin Pharmacokinet 1979;4:279-96.
15. Brater DC, Seiwell R, Anderson S, Berdette A, Dehmer GJ, Chennavasin P. Absorption and disposition of furosemide in congestive heart failure. Kidney Int 1982;22:171-6.

16. Grahnén A, Hammarlund M, Lundqvist T. Implications of intraindividual variability in bioavailability studies of furosemide. Eur J Clin Pharmacol 1984;27:595-602.
17. Halladay SC, Sipes IG, Carter DE. Diuretic effect and metabolism of bumetanide in man. CLIN PHARMACOL THER 1977;22:179-87.
18. Marcantonio LA, Auld WHR, Skellern GG, Howes CA, Murdoch WR, Purohit R. The pharmacokinetics and pharmacodynamics of bumetanide in normal subjects. J Pharmacokinet Biopharm 1982;10:393-409.
19. Holazo AA, Colburn WA, Gustafson JH, Young RL, Parsonnet M. Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administrations to normal subjects. J Pharm Sci 1984;73:1108-13.
20. Marcantonio LA, Auld WHR, Murdoch WR, Purohit R, Skellern GG, Howes CA. The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. Br J Clin Pharmacol 1983;15:245-52.
21. Smith DE. High-performance liquid chromatographic assay for bumetanide in plasma and urine. J Pharm Sci 1982;71:520-3.
22. Tozer TN, Gambertoglio JG, Furst DE, Avery DS, Holford NHG. Volume shifts and protein binding estimates using equilibrium dialysis: application to prednisolone binding in humans. J Pharm Sci 1983;72:1442-6.
23. Wagner JG. Pharmacokinetic parameters estimated from intravenous data by uniform methods and some of their uses. J Pharmacokinet Biopharm 1977;5:161-82.
24. Metzler CM. NONLIN, a computer program for parameter estimation in nonlinear situations. Kalamazoo, Mich: The Upjohn Co, 1969.
25. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 1978;6:165-75.
26. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, Inc, 1982:45-111.
27. Øie S, Jung D. Bioavailability under variable renal clearance conditions. J Pharm Sci 1979;68:128-9.
28. Yamaoka K, Nakagawa T, Uno T. Statistical moments in pharmacokinetics. J Pharmacokinet Biopharm 1978; 6:547-58.
29. Riegelman S, Collier P. The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J Pharmacokinet Biopharm 1980;8:509-34.
30. Wagner JG. Pharmacokinetic absorption plots from oral data alone or oral/intravenous data and an exact Loo-Riegelman equation. J Pharm Sci 1983;72:838-42.
31. Proost JH. Wagner's exact Loo-Riegelman equation: the need for a criterion to choose between the linear and logarithmic trapezoidal rule. J Pharm Sci 1985; 74:793-4.
32. Holford NHG, Sheiner LB. Understanding of the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 1981;6:429-52.
33. Smith DE, Lau HSH, Fox JL. Application of effect-compartment model to bumetanide-indomethacin interaction in dogs. J Pharmacokinet Biopharm 1983; 11:355-68.
34. Brater DC, Pressley RH, Anderson SA. Mechanisms of the synergistic combination of metolazone and bumetanide. J Pharmacol Exp Ther 1985;233:70-4.
35. Rose HJ, Pruitt AW, McNay JL. Effect of experimental azotemia on renal clearance of furosemide in the dog. J Pharmacol Exp Ther 1976;196:238-47.
36. Rose HJ, O'Malley K, Pruitt AW. Depression of renal clearance of furosemide in man by azotemia. CLIN PHARMACOL THER 1977;21:141-6.
37. Kaojarern S, Day B, Brater DC. The time course of delivery of furosemide into urine: an independent determinant of overall response. Kidney Int 1982;22:69-74.
38. Hammarlund M, Paalzow LK. Acute tolerance development to the diuretic effect of furosemide in the rat. Biopharm Drug Dispos 1985;6:9-21.
39. Hammarlund MM, Odlind B, Paalzow LK. Acute tolerance development to furosemide diuresis in humans: pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther 1985;233:447-53.
40. Brater DC, Chennavasin P, Day B, Burdette A, Anderson S. Bumetanide and furosemide. CLIN PHARMACOL THER 1983;34:207-13.