Variable Furosemide Absorption and Poor Predictability of Response in Elderly Patients

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Study Objectives. To determine the between- and within-patient variability of furosemide bioavailability and natriuretic response, and whether four marketed products differ in bioavailability and response.

Design. Open-label, crossover study.

Setting. General clinical research center at an academic medical center.

Patients. Convenience sample of 17 patients age 65 ± 6 years receiving diuretics for the treatment of hypertension or congestive heart failure.

Intervention. Each patient received each of five furosemide products (one intravenous and four oral tablet formulations) twice in random order for a total of 10 treatments.

Measurements and Main Results. Measurements included absolute bioavailability using cumulative amounts of urinary furosemide collected over 8 hours after oral versus intravenous dosing, and cumulative amounts of urinary sodium. Extensive between- and within-patient variability in all measured values rendered any differences among the products neither clinically nor statistically significant. Mean (± SD) bioavailability was 49 ± 17% (range 12-112%) and coefficients of variation with different products were from 25-43%. Coefficients of variation for urinary furosemide excretion and urinary sodium excretion were also large, 25-42% and 23-51%, respectively. Multivariate analyses that incorporated between- and within-patient effects failed to reveal differences among the products for bioavailability (F=1.04, p=0.403), urinary furosemide excretion (F=1.09, p=0.371), or urinary sodium excretion (F=0.97, p=0.448). Correlation coefficients were 0.81-0.85 for the rates of sodium and furosemide excretion, and half-maximum response using a sigmoid E_{max} model did not differ among products.

Conclusion. Although furosemide concentration in urinary and natriuretic responses showed good correlation, variability in bioavailability considerably affects the drug's excretion into urine. Variability in absorption both among patients and within an individual patient is great and overwhelms any differences in bioavailability among approved furosemide products. Switching from one formulation to another will not likely result in any predictable change in patient response.

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Furosemide is one of the most widely prescribed drugs. It has been marketed generically since 1979; in 1995, 3,064,000 prescriptions for the agent were dispensed from retail pharmacies in the United States, and it ranks in the top 10 among all retail prescription drugs. Moreover, many formulations of oral furosemide are now available for clinical
administration. Despite this widespread use, few data have been forthcoming that assess differences in furosemide's bioavailability and response in patients, particularly the elderly.

Because furosemide has been cited repeatedly for its potential for bioequivalence problems, it would seem to be clinically important to determine if the various dosage forms have similar bioavailability in vivo. Any differences in bioavailability could result in changes in overall natriuretic and diuretic response and, presumably, differences in patient outcome. Alternatively, differences in bioavailability and response among products could be small relative to the overall variability among patients, and therefore, be of little clinical relevance.

Heterogeneity among patients and intrapatient variability contribute to the variability in bioavailability and bioequivalence studies of furosemide. Variation among patients derives from differences in such factors as age, glomerular filtration rate, comorbidity, and concurrent pharmacotherapy. Intrapatient variability in absorption could affect the reliability of patient response. These are the very reasons such studies should be conducted; namely, to ascertain variability of bioavailability and response in the types of patients who receive furosemide. Despite being the most common recipients of the drug, such studies have not been performed in the elderly.

Because of the potential therapeutic importance of this issue, we evaluated the variability of absorption of four tablet formulations of furosemide, approved by the Food and Drug Administration, in a group of predominantly elderly patients. Preliminary analyses of our data from a population perspective using nonlinear mixed effects modeling (NONMEM) revealed small differences in absorption disposition among generic furosemide products compared with Lasix. The analysis was performed to determine whether these population differences translate into clinically relevant differences in the extent of bioavailability and therapeutic response of individual patients.

Methods

Patients

Seventeen elderly patients between the ages of 57 and 74 years (mean 65 ± 6 yrs) who were receiving furosemide or another diuretic volunteered for the study. They were recruited from apartments that predominantly house independently living elderly persons. Previously, we have visited this site to recruit elderly persons for epidemiologic and acute interventional studies. Patients were provided details about the study and all signed informed consent for participation. The study was approved by the Indiana University–Purdue University institutional review board.

Screening physical examinations and histories were performed and screening chemistries and complete blood counts were obtained within 1 week of entering the study. Subjects excluded from the study had evidence of unstable cardiac (angina pectoris, recent myocardial infarction, New York Heart Association class IV heart failure), hepatic (cirrhosis or hepatitis), renal (estimated creatinine clearance < 20 ml/min) or endocrine disease (poorly controlled diabetes mellitus or thyroid disease), or a history of hypersensitivity to furosemide. We required that patients be capable of maintaining constant dosages of their long-term drugs throughout the study with the exceptions of acetaminophen, antacids, and laxatives. Compliance with the study protocol was closely monitored by providing 1-week supplies of drug, and weekly questioning and pill counts.

Clinical Procedures

In this crossover study patients were randomly assigned to receive each of five furosemide products twice (10 treatment periods). Treatments were assigned by random selection of randomized treatment sequences. Both intravenous and oral formulations were administered in open-label fashion. Each treatment period lasted 7 days: a 6-day run-in period with the short-term study on
Blood samples were allowed to clot and serum was collected to determine furosemide and creatinine concentrations (data not shown). Urine samples were separated into two aliquots, one to measure furosemide concentration and the other electrolyte and creatinine concentrations. Samples were frozen at -70°C before analysis and were protected from light throughout all assay procedures. To eliminate any systematic measurement error, measurements were performed in random order on all samples.

Furosemide concentrations were determined using high-performance liquid chromatography with metolazone as the internal standard, as described elsewhere. Acetonitrile 200 μl was used to deproteinize 200-μl urine aliquots. After centrifugation the supernatant was separated and 30 μl was injected directly onto the column. Injections were made using a Waters 712 WISP Automatic Sampler (Waters Associates, Milford, MA). Separation was done with a 5-μm Ultrasphere CIS column (Beckman Instruments, San Ramon, CA) eluted at 1.0 mV/min with mobile phase consisting of 33% acetonitrile and acetate buffer (pH 3.6). Detection was with a 650-15 fluorescence spectrophotometer (Perkin-Elmer, Norwalk, CT) with excitation and emission wavelengths of 344 and 410 nm, respectively. Peak areas were determined using the Chromatopac C-R3A Data Processor (Shimadzu Corp., Kyoto, Japan).

Standard curves were run for each analysis; six standard samples ranged from 1.0-20.0 pg/ml (~0.999). We used a 5.0-pg/ml external control every 12 samples. The intraday and interday coefficients of variation for urine samples were 5.11% and 5.62%, respectively.

Urinary sodium was measured with an IL943 Automatic Flame Photometer (Allied Instrumentation, Lexington, MA). The coefficient of variation was 1.0% and the limit of detection was 0.1 mEq/L. Creatinine was measured with an Autoanalyzer (Technicon Instruments Corp., Tarrytown, NY). Individual standard curves were used, and an external control deviating by more than 5% resulted in reanalysis of samples. The coefficient of variation of the assay was 0.56% and the limit of detection was 0.1 mg%.

Data Analysis

Bioavailability

We computed absolute bioavailability (F) using...
urinary data from the following equation:\(^\text{15}\):

\[
F = \frac{A_{8h,po} \cdot \text{dose}_{iv}}{A_{8h,iv} \cdot \text{dose}_{po}}
\]

where \(A_{8h,po}\) is the total amount of furosemide excreted into the urine over 8 hours after oral dosing, \(A_{8h,iv}\) is the amount of furosemide excreted after intravenous dosing, \(\text{dose}_{iv}\) is the intravenous dose (20 mg), and \(\text{dose}_{po}\) is the oral dose (40 mg). This approach assumes that both total and renal clearance of furosemide are constant between doses within an individual.

We decided to calculate furosemide's bioavailability from urine data because the drug's site of action is the intraluminal surface of the nephron and, as such, urinary amounts correlate better with response measured as sodium excretion than do serum concentrations.\(^{16,17}\) Moreover, several studies showed concordance between absolute bioavailability calculated using either plasma or urine data.\(^6,17,18\) The decision to use 8-hour cumulative data was based on previous studies that showed little difference between 8-hour cumulative excretion data and longer collection periods.\(^4,6,7,17,19\) This is consistent with the short half-life of furosemide in patients such as those studied. Examination of plots in individual patients of furosemide cumulative excretion confirmed that the 8-hour collection period was sufficient.

Response

The natriuretic response produced by a dose of furosemide in a given patient population depends on both the amount of drug reaching the tubular lumen and the rate of its delivery to the luminal site of action.\(^{16}\) It is possible therefore that formulations of the agent that deliver the same amount of drug, as reflected by the area under the plasma concentration versus time curve or cumulative urinary excretion, could therefore result in different diuretic efficiencies and overall response. We used the sigmoid maximum sodium excretion rate (\(E_{\text{max}}\)) model to describe the dependence of sodium excretion rate on urinary furosemide excretion rate.\(^{20}\) The \(E_{\text{max}}\) was assumed to be 3.11 mEq/minute,\(^{16}\) and the values of the furosemide excretion rate (\(R_{\text{furosemide}}\)) producing half-maximum response (\(E_{50}\)) and the slope factor (\(\gamma\)) were estimated from the following equation:

\[
\text{Rate of sodium excretion} = E_0 + \frac{E_{\text{max}} \cdot (R_{\text{furosemide}})^\gamma}{E_{50} + (R_{\text{furosemide}})^\gamma}
\]

where \(E_0\) is the baseline rate of sodium excretion.

The data were fit using nonlinear regression (PCNONLIN, Statistical Consultants Inc., Lexington, KY) and the optimal weighting was determined from the distribution of residuals. A weight of unity was found to be most appropriate. We defined diuretic efficiency as the total amount of sodium excreted in 8 hours divided by \(A_{8h}\). Diuretic efficiency is a function of both the \(E_{50}\) and the \(\gamma\) of the excretion response curve.

Statistical Analysis

Analysis of variance for repeated measures was used to test the statistical significance of differences in bioavailability and response among patients and furosemide products. Dependent variables were absolute bioavailability and total amounts of furosemide and sodium excreted over 8 hours. We used \(t\) tests and Pearson product-moment correlation to identify demographic variables (age, race, sex) and clinical variables (weight at onset of each study, body surface area, clearance of creatinine adjusted for body surface area) to include in each model. The effect on normality of two transformations of bioavailability was examined. However, neither logarithmic nor square of the arcsin transformations improved the normality of the bioavailability data (Shapiro-Wilk statistic = 0.97, \(p=0.15\)). We therefore performed our analysis of bioavailability without transformation. The Ryan-Einot-Gabriel-Welsch multiple \(F\) (REGWF, SAS) test was performed to ascertain whether the furosemide product means for the dependent variables differed for first and second studies independently. Variables significant at the 5% level of significance were kept in all models.

Multivariate statistics were examined to determine the statistical significance of differences among the furosemide products. A dummy variable distinguishing patients with and without congestive heart failure was retained in all models. We performed analysis of covariance on urinary sodium excretion to ascertain the effect of bioavailability in this model. Unless otherwise indicated, data are mean ± SD.

Results

The 13 women and 4 men were 64.7 ± 5.7 years of age. Ten were African-American and seven white (Table 1). They had a mean estimated creatinine clearance of 77 ± 20 ml/minute/1.73 m² and their body surface area was 1.97 ± 0.23 m². They had a variety of
Table 1. Patient Characteristics

<table>
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<tr>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Race</th>
<th>Weight (kg)</th>
<th>Height (in.)</th>
<th>Creatinine Clearance (ml/min/1.73m²)</th>
<th>Diagnoses</th>
<th>Concomitant Drugs</th>
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<td>White</td>
<td>93.6</td>
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<td>67</td>
<td>96</td>
<td>Diabetes, heart failure, peripheral vascular disease</td>
<td>Insulin, captopril, isosorbide dinitrate, pentoxyphlline</td>
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</tbody>
</table>

*These patients received furosemide 40 mg twice/day before and throughout the study.

diagnoses and were prescribed concomitant agents. The indications for diuretic therapy were hypertension in 16 patients and heart failure in 3 (2 had both disorders). All 17 patients completed all 10 treatment periods (170 treatment periods). None showed lack of compliance with study drug administration.

Baseline serum furosemide concentrations were often too low to measure. Moreover, they did not differ for patients receiving the drug twice/day from those who were receiving the drug once/day (F=0.41, p=0.89), indicating an overall lack of accumulation of drug for the two dosing schedules.

Data for absolute bioavailability and urinary excretion of furosemide and sodium appear in Table 2. None of the differences among the product means were statistically significant for any of these values (REGWF test, p>0.05). Bioavailability ranged from 12-112% and was highly variable among the products for both first
(CV 35.6%) and second exposures (CV 37.2%). Coefficients of variation for bioavailability for the first and second exposures of each product were Barr 32% and 36%, Lasix 34% and 37%, Lederle 32% and 38%, and Mylan 42% and 24%. Total amounts of urinary furosemide excreted ranged from 2.7-24.5 mg (CV 32.5%). Coefficients of variation for urinary furosemide excretion for the first and second exposures of each product were Barr 37% and 35%, oral Lasix 34% and 42%, intravenous Lasix 15% and 23%, Lederle 34% and 25%, and Mylan 43% and 29%.

Urinary excretion of sodium ranged from 17-249 mEq (CV 37.2%). Coefficients of variation for the first and second exposures of each product were Barr 41% and 39%, oral Lasix 41% and 38%, intravenous Lasix 35% and 31%, Lederle 23% and 40%, and Mylan 28% and 51%.

The box plots in Figures 1 and 2 show the variability in bioavailability and sodium excretion, respectively, for the first and second exposures of each dosage form. The legend in Figure 1 provides a guide to the interpretation of these plots. Because of the wide variability among products, differences in bioavailability were not statistically significant. Urinary sodium excretion was also highly variable. Differences in sodium excretion among products were not significant. These univariate analyses provide a sense of the marked variability in these values.

To control for interpatient variability, we examined our data using multivariate analysis of variance. Table 3 shows displays the results of the analysis of variance for repeated measures. These analyses ascertained differences in effects among the furosemide products while accounting for other factors that contribute to variability between and within patients. A final model was computed to test the hypothesis of no overall effects among the products. The products did not differ in absolute bioavailability or in urinary excretion.

Figure 1. Box and whisker plots of furosemide bioavailability for the first (upper panel) and second (lower panel) patient studies or exposures. The bar through the middle of the boxes is the median value, and the tops and bottoms of boxes are 75th and 25th percentiles, respectively. Upper and lower notches on the sides of boxes are 95% confidence intervals. Boxes have a dog-eared appearance when the upper bound of the 95% confidence interval is greater than the 75th percentile, such as for the first exposure of the Barr product. Upper and lower horizontal bars at the tips of whiskers are 95th and 5th percentiles, respectively.
excretion of furosemide or sodium. For the model of natriuresis, this conclusion did not change while controlling for differences in bioavailability among the products. Hence, we can conclude from these data that for each of these values, differences among the products were not statistically significant when administered to patients on two occasions.

The dependence of the sodium excretion rate on the furosemide excretion rate was described well by the sigmoid $E_{\text{max}}$ model (Figure 3). This figure relates the amount of diuretic at the urinary site of action to response. The data constitute all patients studied. Correlation coefficients for furosemide formulations ranged from 0.81–0.85. The estimates of the $EC_{50}$ (150

<table>
<thead>
<tr>
<th>Type of Statistical Test</th>
<th>F Value</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Absolute bioavailability$^a$</td>
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<td>Within-subject effects</td>
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<td>Urinary excretion of furosemide$^c$</td>
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<td>Within-subject effects</td>
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<td>Urinary excretion of sodium$^d$</td>
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<td>Test of no overall effects$^b$</td>
<td>0.97</td>
</tr>
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</table>

$^a$Other factors included in this model were presence of congestive heart failure and baseline creatinine clearance.

$^b$Accounts for between- and within-patient effects.

$^c$Other factors included in this model were presence of congestive heart failure, baseline creatinine clearance, sex, and body surface area.

$^d$Other factors included in this model were presence of congestive heart failure, baseline creatinine clearance, body surface area, and age.

$\pm 9$ to $198 \pm 46$ g/min) and slope factor (1.15 $\pm 0.23$ to 1.26 $\pm 0.07$) did not differ among drug products. Overall diuretic efficiencies were also comparable (0.009 $\pm 0.004$ to 0.013 $\pm 0.009$ mEq Na$^+$/mg furosemide).

**Discussion**

Although furosemide has been one of the drugs most frequently taken by elderly patients for
several decades, our study represents the first attempt to examine systematically the issue of variability between and within patients and among representative products. Earlier bioavailability studies were for the most part restricted to young, healthy volunteers, and even in such subjects furosemide absorption varied considerably. The current study strikingly emphasizes this variability in patients who had only modest severity of disease, and shows that the variability in absorption extrapolates to similar variability in response among and within individuals. The results show that in the setting of clinical care, between- and within-patient variability in bioavailability and response is so huge that it overshadows any differences among furosemide products. In view of the similar values of overall diuretic efficiency among formulations, we conclude that each of the products is equivalent in terms of both the amount and the time course of drug delivered to its site of action.

Preliminary population analyses of bioavailability data used in this study were conducted using NONMEM. Although small differences in absorption disposition were found among some generic products relative to Lasix, the results indicate that furosemide bioavailability is poor and widely variable for all products in these patients. This wide interpatient and intrapatient variability in bioavailability resulted in wide interpatient and intrapatient variability in response regardless of the product. As such, switching from one product to another will not likely improve an individual's response.

The large coefficients of variation for urinary sodium excretion indicate that a patient's response to any of these products cannot be predicted. Moreover, our bioavailability data indicate that the furosemide product prescribed does not matter. Although the Lederle drug appeared to have the greatest bioavailability and response, differences among the agents were not statistically significant. This remained the case while controlling for the effects of other factors such as the presence of congestive heart failure and creatinine clearance. Even for the Lederle drug, which appeared at least qualitatively better by rank than the other products, the percentage difference (mean ± SD) between the first and second treatments within subjects was 39 ± 37% (range 0.1–138%). Practically, this means that if 13 mg of drug were excreted into the urine with the administration of a tablet, the amount of furosemide found in the urine in the same patient after the next dose (± 1 SD) could likely be as little as 8 mg or as much as 18 mg, more than a 2-fold difference.

Many factors could contribute to this variability, some of which are specific to furosemide. Factors common to all drugs include physicochemical characteristics, tablet dissolution and product formulation, gastric pH, emptying, blood perfusion, and the timing of dosing in relation to eating. In addition, furosemide may have a specific site within the gut for absorption, that is, an absorption window. Other factors likely to affect patient response to amounts of diuretics in the urine include the presence of diseases such as congestive heart failure, variability in the capacity of the liver, gut, and kidneys to metabolize the diuretic, enterohepatic recycling of glucuronide conjugates, and differences in renal secretory capacity. In analyzing the determinants of furosemide's appearance in the urine and natriuresis, we controlled for the effects of age, body surface area, creatinine clearance, and congestive heart failure. These adjustments explained only a small portion of the variability among patients and among products. Thus, other factors are undoubtedly involved, including furosemide's time course of delivery into the urine, an individual's pharmacodynamic response, and the time of daily dosing. Hence, the variability of furosemide bioavailability and response is likely to be multifactorial.

Because we failed to find statistical differences in bioavailability among the furosemide products, it is important to examine our chance of committing a type II error. With 17 patients, it could be argued that we had insufficient power to detect clinically meaningful differences in bioavailability. We therefore performed post hoc power calculations at α = 0.05 using a standard deviation estimate from our univariate analysis of bioavailability. Our univariate power calculations indicate that we had 80% power to detect an 11% difference among furosemide products. This is the largest effect size difference for bioavailability observed in our study (53% for Lederle exposure 1 vs 42% for Barr exposure 1). However, this difference was not significant after adjusting for multiple testing.

Estimating power from multivariate models is more difficult. Unlike univariate power, which depends on the number of subjects, standard deviation (variance), and effect size, multivariate power also depends on the number of dependent
variables and the degree of within-exposure intercorrelations. Using the procedure described by Stevens, we estimated 36% power in our multivariate model. The paradox of having sufficient power univariately and poor power multivariately can be explained by the increase in the number of dependent variables tested and the weak within-exposure intercorrelation. We further estimated that the number of patients necessary for 80% power would exceed 100. Such a large study will not likely be performed because of its onerous nature and its questionable clinical relevance given the variability revealed in our study for all products tested.

We conclude that variability in furosemide absorption both among patients and within an individual patient is great and overwhelms any differences in bioavailability and response among approved furosemide products. Whether this variability could adversely affect patient outcomes compared with a more reliably absorbed product is uncertain. At the very least clinicians should be aware of this variability, as it means that from patient to patient and even within the same patient from day to day, individuals can either be responsive or not as a function of drug absorption. This coupled with patient-related pharmacodynamic factors makes it virtually impossible to predict the therapeutic expectations for an individual. Moreover, switching patients from one furosemide formulation to another will not likely result in any predictable change in response.

Would a more reliable diuretic produce a more consistent response and predictable outcomes? To date, patient outcome studies comparing diuretics differing in absorption characteristics have not been published. Bioavailability and sodium excretion studies should be performed for newer diuretics to ascertain their variability compared with furosemide. If more reliable products become or are available, the most salient issue would be to determine their effect on outcomes such as hospitalization for exacerbation of heart failure and associated costs compared with furosemide. The results of our study argue strongly for such trials.

References