

Effects of Albumin/Furosemide Mixtures on Responses to Furosemide in Hypoalbuminemic Patients

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Abstract. Hypoalbuminemic patients often have sufficient fluid accumulation to mandate diuretic therapy but are often resistant to diuresis. Studies have suggested that hypoalbuminemia itself impairs delivery of effective amounts of diuretic agent into the urine, the site of action. Therefore, administration of mixtures of albumin and loop diuretics may enhance responses. Thirteen patients with biopsy-proven cirrhosis and ascites (age, 51.2 ± 8.1 yr; Child-Pugh score, 8.5 ± 1.0 ; serum albumin concentration, 3.0 ± 0.6 g/dl) were studied in this randomized crossover study. Sodium balance was maintained throughout the study with a metabolic diet. All patients received spironolactone, but administration of all other diuretic agents was discontinued. Each patient received all of the following four treatments intravenously: (1) 40 mg of furosemide, (2) 25 g of albumin, (3) 40 mg of furosemide and 25 g of albumin pre-

mixed *ex vivo*, and (4) 40 mg of furosemide and 25 g of albumin infused simultaneously into different arms. Responses were assessed by measuring urinary sodium excretion and relating the urinary furosemide excretion rate to the sodium excretion rate. Additionally, the pharmacokinetics of furosemide were assessed. Furosemide pharmacokinetics were similar for all treatment arms. Albumin alone had negligible diuretic effects. Neither albumin regimen increased the response to furosemide. Moreover, the relationship between the urinary furosemide excretion rate and the sodium excretion rate was unaffected by albumin. In conclusion, albumin failed to enhance the diuretic effects of furosemide in cirrhotic patients with ascites. Therefore, the coadministration of albumin and furosemide for the treatment of cirrhosis, and likely other hypoalbuminemic conditions, should not be used clinically.

Different strategies have been used to alleviate diuretic resistance in hypoalbuminemic patients. Infusions of albumin itself have been used. Such trials have demonstrated negligible if any benefit (1–16). Specific to this study, recent reports suggest that albumin/diuretic coadministration results in enhanced diuresis in patients with cirrhosis or nephrotic syndrome (17–20). This strategy was derived from a study in analbuminemic rats (18). Those animals exhibited a 10-fold higher volume of distribution of furosemide than did normal animals, because there was no albumin to bind furosemide and retain it in the plasma. As a result of this large volume of distribution, insufficient concentrations of the diuretic reached secretory sites in proximal nephrons, with concomitantly little drug secreted into the urine. Therefore, negligible diuretic response ensued. When these animals were treated with a mixture of albumin and furosemide, the volume of distribution decreased, the drug was trapped in plasma and delivered to the urine, and diuresis was restored (18).

Clinical trials assessing this strategy are conflicting, and most have not been rigorously performed (13,17–20). Despite

the uncertainty of efficacy, many physicians administer furosemide/albumin mixtures to enhance diuresis in hypoalbuminemic patients, particularly those with nephrotic syndrome or cirrhosis (13). Examination of this issue among patients with nephrotic syndrome is confounded by the proteinuria of such patients, which can lead to urinary binding of diuretic agents (21). Hypoalbuminemic patients with cirrhosis thus represent a better model to study this issue. We therefore conducted a randomized crossover study to determine the effects of albumin/furosemide mixtures on the response to furosemide in cirrhotic subjects with ascites.

Materials and Methods

Patients

After institutional review board approval, 13 patients with biopsy-proven cirrhosis of varying causes gave written informed consent for participation in this study. Patient characteristics are listed in Table 1. All participants were in stable clinical condition, without evidence of active infection, gastrointestinal hemorrhage, or other acute illnesses (*e.g.*, congestive heart failure or untreated endocrinopathies) that would affect the response to a diuretic agent. All subjects were awaiting liver transplantation and had Child-Pugh class B or C cirrhosis. Patients with alcohol abstinence of <12 mo, serum creatinine concentrations of >2 mg/dl, 24-h urine protein excretion of >100 mg, or portasystemic shunts were ineligible.

Protocol

Two weeks before admission, patients who were not receiving spironolactone began to be treated with a dose of 50 mg twice daily.

Received August 8, 2000. Accepted October 11, 2000.

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1046-6673/1205-1010

Journal of the American Society of Nephrology

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Table 1. Patient demographics and clinical characteristics^a

Age (yr)	51.2 ± 8.1
Gender (M/F)	11/2
Cause of hypoalbuminemia	
hepatitis C	3
hepatitis B + C	3
alcohol	2
alcohol + hepatitis C	3
α_1 antitrypsin deficiency	1
cryptogenic	1
Child-Pugh score	8.5 ± 1.0
Child-Pugh class (B/C)	11/2
Serum albumin concentration (g/dl)	3.0 ± 0.6
Serum bilirubin concentration (mg/dl)	2.0 ± 0.7
Serum creatinine concentration (mg/dl)	0.99 ± 0.2
Serum alanine aminotransferase activity (IU/L)	70 ± 63

^a Data are mean ± SD.

This strategy was selected in preference to discontinuing spironolactone treatment for all patients because of uncertainty regarding the length of spironolactone treatment cessation needed to allow all effects to dissipate. Participants were admitted to the General Clinical Research Center at Indiana University Medical Center, where they remained until completion of the study. At the time of admission, they were placed on a metabolic diet containing 30 mEq of sodium and 60 to 80 mEq of potassium, with 3 L/d of dietary fluids. Administration of all other diuretic agents was discontinued at the time of admission. This sodium restriction allowed safe discontinuation of these diuretic agents without weight gain throughout the study. Full chemistry panel and complete blood count analyses, urinalysis, and baseline weight assessments were performed for each subject at the time of admission. Thereafter, individuals were weighed and serum electrolyte and creatinine concentrations were measured each morning. In addition, 24-h urine samples were collected each day for measurement of electrolytes and creatinine. Patients were equilibrated on the metabolic diet until they attained sodium balance, as defined by two consecutive 24-h urinary sodium excretion values that varied $\leq 20\%$ and no change in two consecutive daily weights of >0.5 kg. After sodium balance was attained, participants underwent one of the four phases of the study, in random order, as follows: (1) 25 g of albumin alone administered intravenously in 30 min, (2) 40 mg of furosemide alone administered intravenously in 30 min, (3) albumin (25 g) and furosemide (40 mg) premixed *ex vivo* for 10 min and infused intravenously in 30 min, which duplicated the method used by Inoue *et al.* (18), or (4) albumin (25 g) and furosemide (40 mg) infused intravenously, into opposite forearms simultaneously, in 30 min.

Patients fasted, except for distilled water, from midnight until 4 h after administration of the study medication. A 10 ml/kg distilled

water load was administered orally before the start of the 30-min infusion of furosemide and/or albumin, to ensure the ability to produce frequent urine samples. Urine and serum samples were collected before the dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 h after the dose. Urine losses were replaced for 8 h with equal volumes of one-half normal saline solution administered intravenously, to prevent volume depletion and the development of acute diuretic tolerance. The concentration of urinary sodium elicited by loop diuretics is reasonably well approximated by 0.45% normal saline solution; therefore, this method maintained volume status in each subject.

After finishing the first phase of the protocol, subjects continued to receive the metabolic diet until they reached sodium balance, as previously defined. The second phase of the protocol was then performed in a manner identical to the first. Similarly, the third and fourth phases of the protocol were conducted after each volunteer attained sodium balance. At least 48 h separated each phase. This design allowed individual subjects to achieve comparable states of sodium balance before each phase of the study, so that they could serve as their own control subjects. Table 2 demonstrates that the participants were in comparable clinical conditions before each phase of the study.

Analyses

Serum and urine samples were assayed for sodium, furosemide, and creatinine using techniques described in detail elsewhere (22–25). Because creatinine clearance values did not change during the study, those data are not reported. Responses were analyzed in several ways. First, total sodium excretion was compared for different treatments. Second, the sensitivity of the nephron to furosemide was determined, as described previously, by relating the urinary furosemide excretion rate to the sodium excretion rate (22–25). Third, the pharmacokinetics of furosemide were examined, because of the potential of albumin to alter these parameters. Standard model-independent methods were used to determine the pharmacokinetic parameters of interest (Win-Nonlin version 1.1; Scientific Consulting, Apex, NC). The terminal elimination rate constant (β) was determined by linear regression. The elimination half-life was determined as $t_{1/2} = 0.693/\beta$. The area under the serum concentration *versus* time curve (AUC_0^∞) was determined by a combination of linear and logarithmic trapezoidal methods, with extrapolation to infinity from the last measured serum concentration, using the terminal elimination rate constant. The clearance of furosemide was calculated as $dose/AUC_0^\infty$.

Statistical Analyses

Statistical analyses were performed using SAS software (SAS, Inc. Cary, NC). Univariate repeated-measures ANOVA models for a crossover design were used to analyze the urine excretion measures. Treatment effects were tested in the primary analysis model with control for the period of study (*i.e.*, the time the subject had been in the study). The inclusion of the period main effect accounted for the effects of metabolic diet duration on the treatment response. Person

Table 2. Documentation of sodium balance before each phase of the study^a

	Albumin	Furosemide	Furosemide + Albumin, Premixed	Furosemide + Albumin, Separate
Weight (kg)	90.2 ± 17.4	89.6 ± 17.7	89.3 ± 17.7	91 ± 17.2
Urinary sodium excretion rate (mEq/d)	24.2 ± 19.0	23.1 ± 20.8	19.6 ± 15.9	19.4 ± 18.1

^a Data are mean ± SD.

was treated in the model as a random effect, to account for the four repeated measurements obtained for each person (one with each treatment). Separate models were used for 6- and 24-h urine measurements. Because diuretic responses returned to baseline levels within 6 h (see below) and because 24-h results did not differ from 6-h findings, the 6-h data are reported. When an overall treatment effect was significant, pairwise comparisons between the treatments were tested with *P* adjustment using Sidak's multiple-comparison procedure. The effects of the baseline serum albumin concentration on the response to different treatments were tested by adding serum albumin level-treatment interaction to the primary analysis model. Albumin was tested as a continuous variable as well as a categorical variable, *i.e.*, <3 g/dl ($n = 7$) versus >3 g/dl ($n = 6$). Carryover effect was tested by adding the treatment from the previous period to the primary analysis model. *P* values of ≤ 0.05 were considered statistically significant.

Results

Response to Furosemide

The effects of albumin on the response to furosemide were assessed in three ways. First, Table 3 presents the total amounts of urine, sodium, and furosemide excreted in 6 h. Albumin alone had no effect; similarly, it had no effect on the diuretic and natriuretic effects of furosemide (Table 3 and Figure 1). It can be noted from Figure 1 that the response returned to baseline values by 6 h. Second, previous studies demonstrated that the time course of delivery of a loop diuretic to its urinary site of action is an independent determinant of the overall response (25). Figure 2 depicts the time course of furosemide delivery into the urine, wherein albumin had no effect. Finally, we and others have demonstrated that the most precise way to assess the pharmacodynamics of a loop diuretic is to relate the urinary excretion rate of the diuretic, which reflects the amount reaching the site of action, to the response as the urinary sodium excretion rate (22–25). Figure 3 demonstrates that this relationship was not affected by either method of concomitant albumin infusion. Overall, albumin infusion had no effect either on the delivery of furosemide to its site of action (Table 3 and Figure 1) or on the sensitivity of the nephron to furosemide (Table 3 and Figure 3).

Despite a wide range of serum albumin concentrations (2.1 to 4.3 g/dl), we also failed to detect any interaction between serum albumin concentrations and the response to furosemide, whether the albumin concentration was analyzed as a continuous variable or as a categorical variable ($P > 0.05$).

Furosemide Pharmacokinetics

Figure 4 demonstrates serum furosemide concentrations *versus* time, and Table 4 lists the estimated pharmacokinetic parameters. Albumin infusion would be predicted to potentially have two effects on the pharmacokinetics of furosemide. First, its binding of furosemide might result in increased AUC and decreased clearance and volume of distribution values. This did not occur in our study. Second, albumin might enhance urinary furosemide excretion, as occurred in the animal study of Inoue *et al.* (18). Table 3 demonstrates a lack of effect of albumin on the total amount of furosemide excreted into urine; Figure 2 demonstrates that albumin infusion had no effect on the time course of furosemide excretion.

Discussion

The volume status of hypoalbuminemic patients, including those with cirrhosis and ascites, can sometimes be difficult to manage, because even large doses of potent diuretics have diminished efficacy and result in complications (*e.g.*, electrolyte and acid base disturbances or renal failure) (26). Several potential mechanisms for such diuretic resistance have been suggested and include hypoalbuminemia, diminished GFR, altered pharmacokinetics and pharmacodynamics of loop diuretics, and simultaneous administration of nonsteroidal anti-inflammatory drugs (18,27–31). We specifically examined the potential role of hypoalbuminemia in affecting the pharmacokinetics and/or pharmacodynamics of furosemide. We observed no beneficial effect of albumin, arguing that this therapeutic strategy should not be used.

There has long been interest in the use of intravenously administered albumin to enhance diuresis in hypoalbuminemic patients. After salt-poor human albumin became available in 1944, several anecdotal reports suggested that albumin infusions could enhance diuresis in cirrhotic patients (4–8). In contrast, a randomized study published in 1962 demonstrated that repeated albumin infusions failed to decrease the diuretic needs of cirrhotic subjects with refractory ascites (9). Similar studies of patients with nephrotic syndrome have demonstrated no utility of albumin alone in the treatment of this disorder (13–16). Moreover, data from this study indicate no diuretic effect of albumin alone (Table 3 and Figure 1). More recently, however, Gentilini *et al.* (17) demonstrated that albumin infusion produced a 26% increase in sodium excretion caused by furosemide in hospitalized cirrhotic patients with ascites. That study did not characterize the pharmacokinetics or pharmaco-

Table 3. Effect of albumin on responses to furosemide (0 to 6 h)^a

	Albumin Alone	Furosemide Alone	Albumin + Furosemide, Separate	Albumin + Furosemide, Premixed
Urine volume (ml)	1497 ± 236	2686 ± 230	2956 ± 231	2830 ± 231
Urinary sodium excretion (mEq)	19 ± 15	154 ± 14	172 ± 15	165 ± 14
Urinary furosemide excretion (mg)		22.0 ± 1.5	22.1 ± 1.4	18.6 ± 1.5

^a Values are expressed as least-squares mean ± SEM adjusted for period. Parameters are similar for the furosemide and furosemide plus albumin phases ($P > 0.05$); parameters for the albumin phase are significantly lower than those for the other three phases ($P < 0.05$).

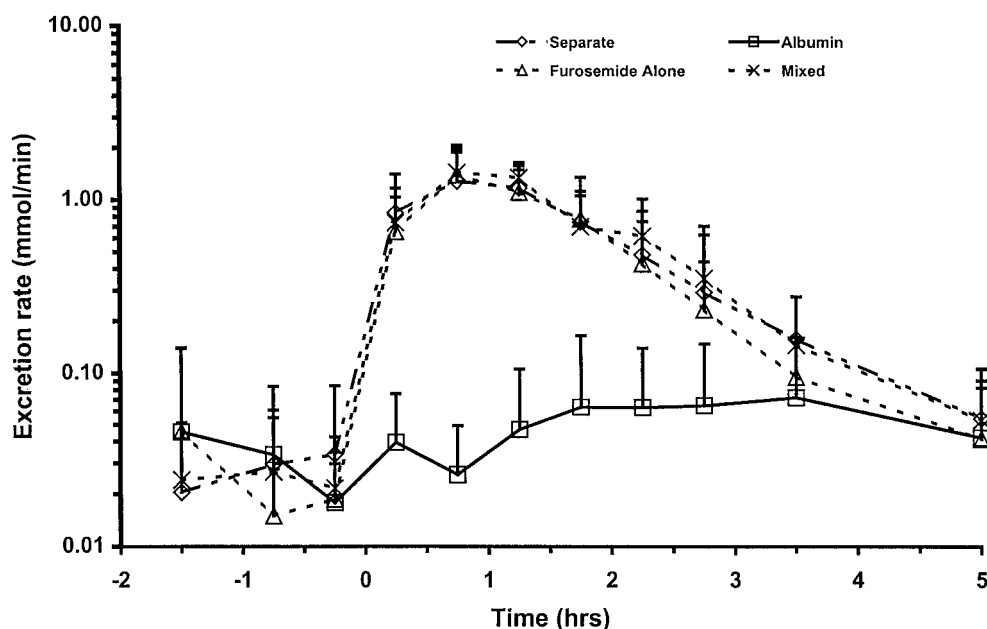


Figure 1. Urinary sodium excretion rate produced by furosemide, with and without albumin, in cirrhotic volunteers ($n = 13$).

dynamics of furosemide and therefore did not offer any mechanistic clues regarding why albumin would enhance the efficacy of furosemide. It did reinforce the uncertainty regarding the utility of albumin in enhancing diuretic responses.

Studies of patients with nephrotic syndrome have been similarly conflicting. The seminal study by Inoue *et al.* (18) in analbuminemic rats also reported the effects of an *ex vivo* mixture of furosemide and albumin in four patients with nephrotic syndrome. All patients exhibited an increase in urine volume, compared with furosemide alone. No information was provided with respect to the design of this clinical component of their study or the results in terms of sodium excretion. Akicek *et al.* (19) studied the effects of albumin alone, furosemide alone, and the combination in eight hypoalbuminemic patients with nephrotic syndrome. Each patient received each treatment, in random order, but there was no re-equilibration

between phases of the study. Albumin alone had negligible natriuretic effects (13 ± 8 mEq/4 h) and had no effect on the response to furosemide. Fliser *et al.* (20) also studied nine patients with nephrotic syndrome. Their study included dietary equilibration, and they measured the amount of furosemide that reached the urinary site of action. There was no effect on urinary furosemide levels. Albumin increased the response to furosemide by 20%. The mechanism seemed to involve an increase in renal blood flow. Those authors concluded that the effects were statistically significant but likely not clinically relevant.

On the basis of the aforementioned data for analbuminemic rats and the data presented above for patients with hypoalbuminemia, it was unclear whether the hypothesis constructed from the animal data could be extrapolated to hypoalbuminemic patients, leading to the motivation for our study. We think that patients with cirrhosis represent the best clinical model for examination of the principles underlying the potential utility of albumin/furosemide mixtures. In nephrotic syndrome, results are likely confounded by the rapid excretion of administered albumin into the urine and the ability of albumin to bind loop diuretics in the urine (21). Our data convincingly demonstrated that coadministration of albumin did not enhance the diuretic response to furosemide. Correspondingly, the pharmacokinetics and pharmacodynamics of furosemide were not altered by concomitant albumin administration (Tables 3 and 4 and Figures 2 and 4). This lack of effect has several possible explanations. First, the dose of albumin infused may not have been sufficient. We doubt that this is a reasonable explanation, because the dose of albumin used in our study was twice the amount used by Gentilini *et al.* (17) and was the same as that used by Inoue *et al.* (18). Moreover, the use of larger doses of albumin would not be practical and would be expensive. Second, it may be necessary to administer repeated doses of

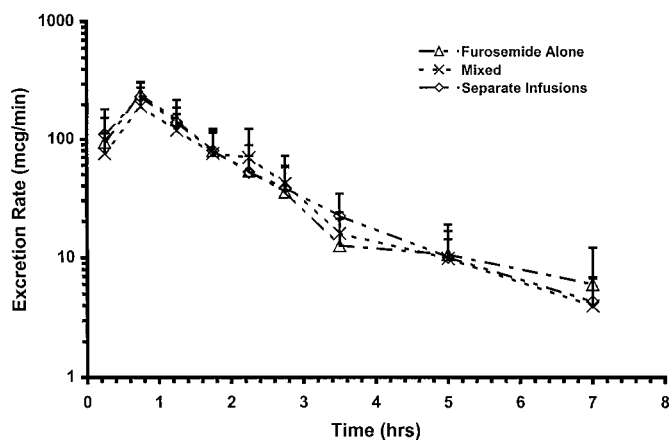


Figure 2. Urinary excretion rate of furosemide, with and without albumin.

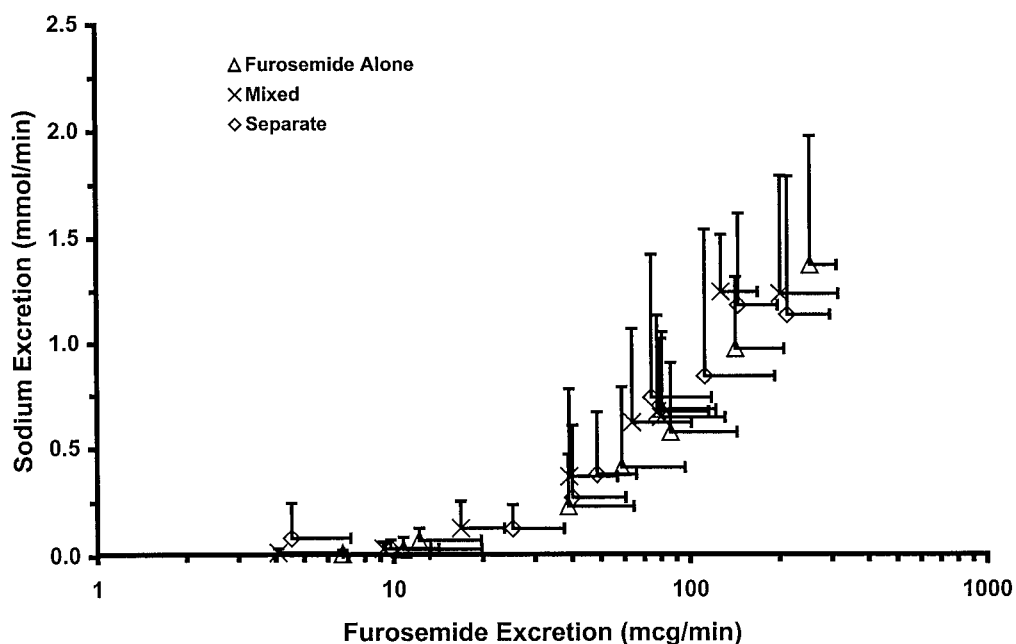


Figure 3. Relationship between the urinary furosemide excretion rate and the sodium excretion rate, with and without albumin.

albumin to produce benefits. This issue was not addressed by our study, but previous studies with repeated doses of albumin yielded mixed results (4–9). Third, it is possible that the baseline serum albumin concentration in our study population was not low enough to yield a benefit from albumin infusion. However, we consider this possibility to be unlikely, because similar albumin concentrations were observed in the patients described by Gentilini *et al.* (17) and in our patients (3.0 ± 0.7 and 3.0 ± 0.6 g/dl, respectively). The range of albumin concentrations for our patients was 2.1 to 4.3 g/dl. Therefore, we included patients with substantial hypoalbuminemia. In addition,

we tested for a relationship between diuretic response and serum albumin concentrations and found none. Fourth, the sample size may not have been sufficient for detection of a significant effect. We observed a mean difference in the 6-h urinary sodium excretion produced by furosemide with and without albumin of 9.7 mEq, with a SD of 81.7 mEq. On the basis of these data, we would need to study 563 patients to demonstrate a difference with 80% power at the 5% significance level. Even if we proved a significant effect with such a sample size, it is apparent that the magnitude of that effect would not be clinically relevant.

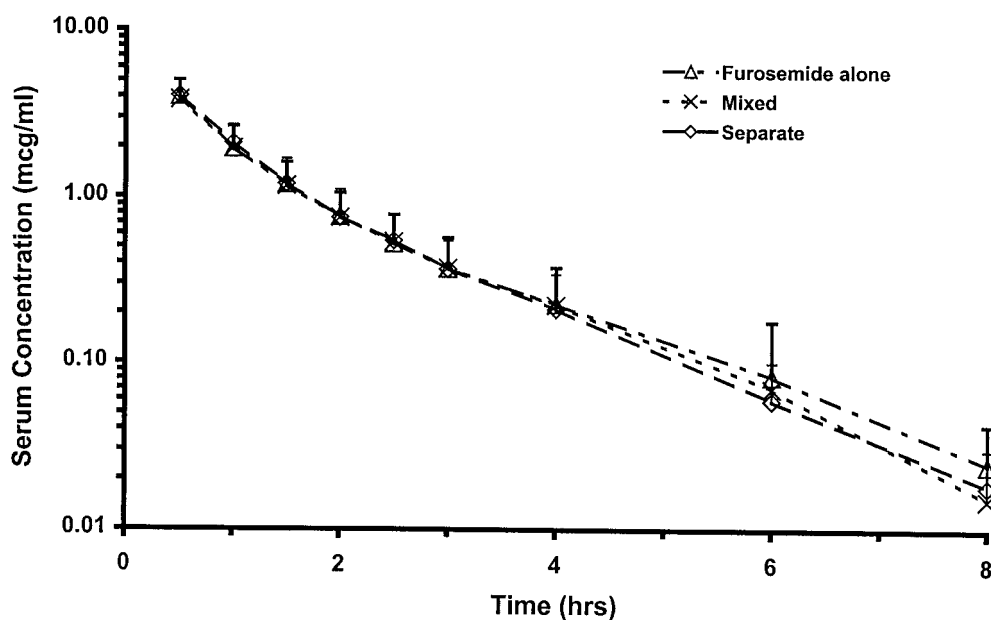


Figure 4. Serum concentration of furosemide versus time, with and without albumin.

Table 4. Effect of albumin coadministration on the pharmacokinetics of furosemide^a

	Furosemide Alone	Furosemide + Albumin, Separate	Furosemide + Albumin, Premixed
$t_{1/2}$ (h)	1.1 (1.0 to 1.2)	1.0 (0.9 to 1.1)	1.1 (1.0 to 1.2)
AUC ₀ [∞] (mg × h/L)	4.9 (4.0 to 5.8)	5.0 (4.2 to 5.7)	4.8 (4.0 to 7.6)
CL (L/h)	9.2 (7.4 to 11.0)	9.0 (7.0 to 10.9)	9.0 (7.6 to 10.5)
V _d (L)	14.2 (11.6 to 16.8)	13.3 (10.2 to 16.5)	13.6 (11.9 to 15.3)

^a Data are expressed as mean and 95% confidence interval. $t_{1/2}$, elimination half-life; AUC₀[∞], area under the curve; CL, serum clearance; V_d, volume of distribution.

Although our crossover design decreased interindividual variability, the design presents a potential risk of carryover effects. We minimized such effects by including a washout period and by attaining sodium balance before each phase of the study. Moreover, the statistical absence of any effect of previous treatment argues against carryover effects.

In conclusion, albumin administered in an *ex vivo* mixture with furosemide or administered simultaneously with furosemide did not enhance diuretic effects in patients with cirrhosis and ascites. In addition, the administration of albumin did not alter the pharmacokinetics or pharmacodynamics of furosemide. These data argue against the clinical use of this therapeutic strategy. It is likely that these results can be extrapolated to other hypoalbuminemic disorders, such as nephrotic syndrome.

Acknowledgments

This study was supported by National Institutes of Health Grants AG07631, DK37994, DK56012-01, and RR00750 (to the General Clinical Research Center).

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