

## Diuresis in the Ascitic Patient: A Randomized Controlled Trial of Three Regimens\*,†

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### ABSTRACT

To compare the efficacy of three commonly used diuretic regimens in the treatment of ascites, we randomized 90 patients to three treatment groups: *Sequential Spironolactone* (spironolactone followed by furosemide if necessary), *Combination* (spironolactone and furosemide in combination), and *Furosemide* (furosemide given alone). Diuretics were begun at a low dose by mouth and the dosage increased until a 0.4-0.8 kg daily diuresis was achieved. The clinical and laboratory findings were comparable for the three experimental groups on admission to the study. All three regimens achieved a comparable rate of diuresis. To do so was far more difficult with furosemide alone, which required repetitious upward adjustments in dosage and massive KCl supplements. The incidence of encephalopathy, hepatorenal syndrome, and marked electrolyte abnormalities was similar for the three treatment groups except that severe hyperkalemia was more frequent on combination therapy. We conclude that diuresis should be initiated with one of the two spironolactone regimens and not with furosemide as the sole agent.

Both spironolactone and furosemide are used widely, either as single agents or in combination, for the treatment of ascites. Although spironolactone alone may effect diuresis in 75% of hospitalized patients with ascites, it is usually considered a weak diuretic agent.<sup>(1-4)</sup> Perhaps for that reason, complications are infrequent with it.<sup>(5)</sup> On the other hand, furosemide is a potent "loop" diuretic and has been incriminated as a frequent cause of complications.<sup>(2,6,7)</sup>

One approach to the treatment of ascites is to begin diuretic treatment with spironolactone and add furosemide if necessary.<sup>(5)</sup> Alternatively, the two drugs have been given in combination to take advantage of their distinct pharmacologic actions.<sup>(2,8,9)</sup> Furosemide given alone has generally been reserved for the patient with refractory ascites, although it is occasionally given in low dosage in an outpatient setting.<sup>(10)</sup>

Since an estimate of the comparative efficacy of these medications, given singly or in combination, would be of practical advantage in the management of this common medical problem, we randomized 90 patients with confirmed ascites to three treatment groups: *Sequential Spironolactone* (spironolactone followed by furosemide if necessary); *Combination* (spironolactone and furosemide in combination); *Furosemide* (furosemide alone). We found that diuresis can usually be obtained with all three regimens. Furosemide, given by itself, however, was somewhat less effective and distinctly more difficult to use than either of the two spironolactone regimens.

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## Materials and Methods

### Patients

Patients with ascites were admitted to this study from Stanford University Hospital, the Veterans Administration Medical Center, Palo Alto, and Santa Clara Valley Medical Center from July 1, 1976 to July 1, 1978.

### Study Criteria

The following criteria were required for admission to the study: hospitalization, ascites confirmed by diagnostic paracentesis, and a clinical diagnosis of cirrhosis, confirmed by liver biopsy when possible. Patients were excluded from the study if they were unable to take anything by mouth or were in frank oliguric renal failure.

### Study Design

After informed consent was obtained, all patients were placed on a 87-mEq sodium, 2000-ml fluid restriction diet. Patients were then randomized to one of three treatment groups: *Sequential Spironolactone* (spironolactone followed by furosemide if diuresis did not ensue on 400 mg spironolactone), *Combination* (spironolactone and furosemide in combination), and *Furosemide* (furosemide alone). Diuretics were begun on the fourth day of the study if spontaneous diuresis had not begun. The treatment schedule for the three groups was as given in Table 1.

Medications were increased at the prescribed intervals only if diuresis had not begun with the pre-

ceding regimen. The final therapeutic program chosen was the minimum necessary to insure no more than a 0.4–0.8 kg daily weight loss and to maintain a stable weight once free from ascites. If weight loss was too rapid, or if significant presumed complications arose, reduction of dosage or discontinuation of the medication was allowed.

Patients were evaluated at the start of the study and at days 4, 7, 10, 13, 21, 28, 35, and 42. At each visit, the following laboratory data were obtained: white blood count, total bilirubin, SGOT, blood urea nitrogen (BUN), creatinine, electrolytes, albumin, and prothrombin time. In addition, the following physical findings were recorded: blood pressure, pulse, weight, liver size at the mid-clavicular line and the presence or absence of asterixis, ascites (defined as greater than 4 cm of shifting dullness), and peripheral edema. Liver biopsies and esophagrams were obtained during the study when the patient's condition permitted.

Each patient was discharged when clinically improved and followed in the Gastroenterology Clinic until the study was completed. During the patient's course, special attention was given to treatment of infection, gastrointestinal bleeding, hepatic encephalopathy, hypokalemia, and oliguric renal failure.

The study was approved by the Stanford Medical Committee on the use of Human Subjects in Research on May 13, 1976.

### Statistical Analysis

One-way analysis of variance was used to test for differences in continuous variables among the three treatment groups. When the *F* statistic was significant, differences between groups were estimated by confidence intervals, using the Student's *t*-test statistic.<sup>(11)</sup> The  $\chi^2$  statistic was used to test for differences in categorical data.<sup>(12)</sup>

### Results

#### Patient Characteristics

Ninety patients (6 from Stanford University Hospital, 36 from the Veterans Administration Medical Center, and 48 from the Santa Clara Valley Medical Center) were enrolled in the study. Thirty were randomized to *Sequential Spironolactone*, 31 to *Combination*, and 29 to *Furosemide*. Forty-four of the 90 patients had received low doses of diuretics before entry into the study. These 44 patients were evenly distributed in the three treatment groups. None had lost weight and the diuretics had been dis-

TABLE 1.

Treatment Schedule for the Three Groups<sup>a</sup>

Day	<i>Sequential Spironolactone</i> (s/f) <sup>b</sup>	<i>Combination</i> (s/f)	<i>Furosemide</i> (f)
1			
4	100/0	100/40	40
7	200/0	200/80	120–160
10	400/0	400/120	200–280
13	400/40	400/↑ <sup>c</sup>	320–400
14 on	400/↑ <sup>c</sup>	c	↑ <sup>c</sup>

<sup>a</sup> Two patients in the *Sequential Spironolactone* group and three patients in the *Combination* group received daily doses of spironolactone > 400 mg early in the study.

<sup>b</sup> Daily spironolactone dosage in mg/daily furosemide dosage in mg.

<sup>c</sup> Further daily increments of 40 mg furosemide dosage were given if necessary to ensure a diuresis.

**TABLE 2.**  
Selected Initial Clinical and Laboratory Data<sup>a</sup>

Data	Groups		
	Sequential Spirono- lactone (30)	Combi- nation (31)	Furo- semide (29)
<i>Clinical</i>			
Age (Years)	50 ± 2	52 ± 2	54 ± 2
Sex: Male (No.)	28	25	20
Female (No.)	2	6	9
Duration of ascites (Weeks)	8 ± 2	8 ± 2	14 ± 5
Weight (kg)	79.9 ± 4.0	79.1 ± 2.8	79.4 ± 2.8
Liver size (cm)	14 ± 1	14 ± 1	17 ± 1
Peripheral edema (No.)	25	24	23
Previous diuretic therapy (No.)	13	14	17
<i>Laboratory</i>			
Total bilirubin (mg/dl)	6.4 ± 1.3	6.9 ± 1.5	10.0 ± 1.9
SGOT (IU) <sup>b</sup>	54 ± 5	54 ± 6	60 ± 7
Prothrombin Time (%)	48 ± 3	49 ± 3	49 ± 4
Albumin (g/dl)	2.7 ± 0.1	2.8 ± 0.1	3.0 ± 0.1
BUN (mg/dl) <sup>c</sup>	15 ± 2	16 ± 2	14 ± 1
Creatinine (mg/dl)	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.0
Sodium (mEq/L)	134 ± 1	135 ± 1	136 ± 1
Chloride (mEq/L)	101 ± 1	102 ± 1	101 ± 1
Bicarbonate (mEq/L)	24 ± 1	24 ± 1	25 ± 1
Potassium (mEq/L)	3.8 ± 0.1	4.0 ± 0.1	3.8 ± 0.1

<sup>a</sup> Values are given as number of patients or as mean ± 1 SEM.

<sup>b</sup> Normal values for SGOT are < 20 IU.

<sup>c</sup> BUN, blood urea nitrogen.

continued. All patients received a diagnostic paracentesis of no more than 100 ml of ascitic fluid. Patients were entered into the trial an average of 2½ days after admission to the hospital.

There were no statistically significant differences among the three groups with respect to a wide variety of clinical and laboratory data obtained upon entrance to the study. Selected items for comparison are presented in Table 2. Noteworthy are the lengthy duration of ascites, the presence of peripheral edema in most patients, and the relatively normal serum electrolytes. Sixty-one of the 90 patients were icteric. There was a trend to more females in the *Combina-*

*tion* and *Furosemide* groups, but this was not statistically significant.

The clinical diagnosis was alcoholic cirrhosis in 88 patients and postnecrotic cirrhosis in two patients, one of whom was assigned to *Combination* therapy and the other to *Furosemide*. Liver biopsy was done in 37 patients and 36 of these were classified as alcoholic cirrhosis; 13 of these had superimposed alcoholic hepatitis.<sup>(13)</sup> The 37th patient was considered to have alcoholic hepatitis alone. Varices were documented in 44 patients.

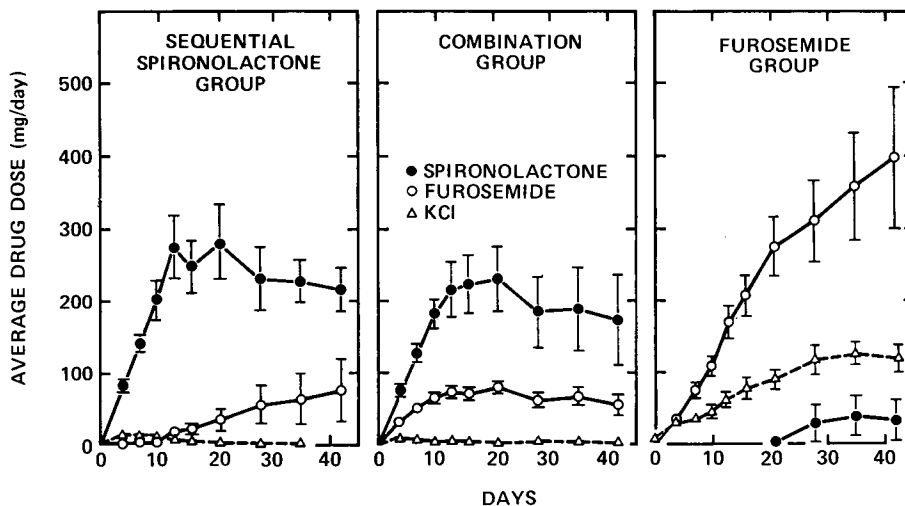
#### Mortality

Nineteen patients (21%) died during the 6-week study period (8 in the *Sequential Spironolactone* group, 7 in the *Combination* group, and 5 in the *Furosemide* group). The causes of death were hepatic failure in 11 patients, massive gastrointestinal bleeding in two patients, pulmonary embolism in one patient, aspiration and respiratory arrest in one patient, perforated duodenal ulcer with sepsis in one patient, and unknown in the remaining three patients. The times of death were randomly distributed through the 6 weeks of study.

#### Drug Dosage and Diuretic Response in Survivors

Figure 1 presents the average spironolactone, furosemide, and KCl dosage for the 6-week study period in each of the three treatment groups. Eleven of the 22 surviving patients assigned to *Sequential Spironolactone* achieved a satisfactory diuresis with this drug alone. The remaining patients required the later addition of supplemental furosemide; this explains the late rise in furosemide dosage in this group depicted in Figure 1. Remarkable is the steady rise in furosemide dosage and the marked requirement for supplemental KCl in the *Furosemide* group. Two patients in this group were given spironolactone before the 6-week study was completed. One was judged a failure by the medical house staff (even though he had lost 6 kg) and placed on spironolactone during the last 2 weeks of his course. The second patient required such massive KCl supplementation (400 mEq/day) on 440 mg of furosemide that the drug was discontinued and spironolactone substituted.

Figure 2 depicts the serial mean weights and Table 3 presents the characteristics of the diuretic response for surviving patients in each treatment group. Weight loss was generally comparable for the three groups, although those in *Furosemide* lost somewhat less. The number who lost their ascites and peripheral edema was quite comparable in the three treatment



**Figure 1.** Serial spironolactone, furosemide, and KCl dosages for the three treatment groups. The data are given as the mean dose  $\pm$  1 SEM for each observation period.

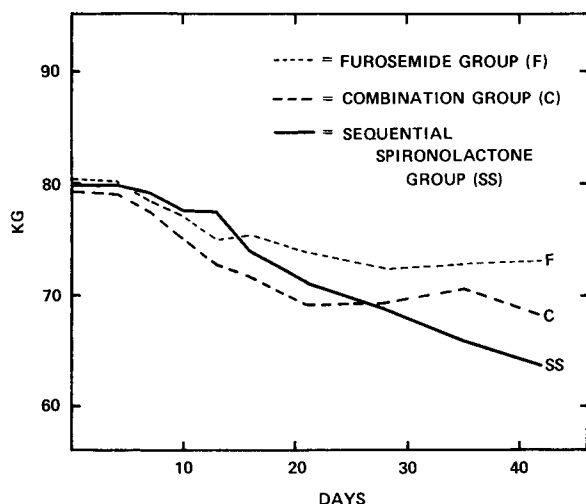
groups. Disappearance of ascites occurred somewhat sooner in the *Combination* group. Onset of diuresis was delayed in the *Sequential Spironolactone* group when compared to the others ( $p < 0.05$ ). Most patients in the *Furosemide* group required further increments in dosage, and as a consequence, reached peak dose much later than the other two groups ( $p < 0.01$ ). Typically, a patient on furosemide might begin to lose weight on 40–120 mg daily. Diuresis would then stop well before completion only to start again at 200–280 mg. Subsequent further upward adjustments were often necessary to complete the diuresis. This phenomenon was unexpected and did not necessarily correspond to loss of edema fluid first, fol-

lowed by loss of ascites. In contrast, the characteristic adjustment in dosage in the *Sequential Spironolactone* or *Combination* group was a reduction, generally because diuresis was too swift or dry weight had been achieved. Only two patients lost no weight over the 6-week study period and were judged to have “refractory” ascites. Both were in the *Furosemide* group and were receiving 1440 and 1520 mg by mouth at the end of the sixth week.

**Encephalopathy, Hepatorenal Syndrome, Azotemia, and Electrolyte Abnormalities**

Encephalopathy was noted in seven patients at entrance to the study and developed in 19 additional patients during the 6-week study. Thirteen of these 26 patients died during the study. Table 4 presents the data. Renal insufficiency (defined as BUN > 20 mg/dl or creatinine > 1.5 mg/dl) with subsequent progressive oliguric renal failure (“hepato-renal syndrome”) was noted in seven patients upon admission to the study and developed late in three additional patients (Table 4). All 10 patients died with a mean increase in BUN and serum creatinine of  $75 \pm 17$  mg/dl and  $3.6 \pm 0.7$  mg/dl, respectively, before death. There were no statistically significant differences among the three treatment groups in the incidence of encephalopathy or the hepatorenal syndrome.

Among survivors, the net increase in BUN and serum creatinine concentrations during the study is shown in Figure 3. Although the increase in BUN was most marked for the *Combination* group, differences among the three groups were not statistically signif-



**Figure 2.** Serial mean weights in kilograms for the three treatment groups.

**TABLE 3.**  
**Characteristics of the Diuretic Response in Survivors<sup>a</sup>**

	<i>Groups</i>		
	<i>Sequential Spironolactone (30)</i>	<i>Combination (31)</i>	<i>Furosemide (29)</i>
Survivors (No.)	22	24	24
Weight loss: kg (max)	14.3 ± 1.9	13.4 ± 1.4	9.5 ± 1.1
kg/day	0.43 ± 0.05	0.53 ± 0.06	0.37 ± 0.05
% body weight <sup>b</sup>	17 ± 2	17 ± 2	12 ± 2
Onset of Diuresis (Days) <sup>c</sup>	13 ± 1	9 ± 1	9 ± 1
Disappearance of ascites: No.	15	17	12
Days	26 ± 3	19 ± 2	26 ± 3
Disappearance of edema: No.	16	15	16
Days	18 ± 3	15 ± 2	17 ± 3
Refractory ascites (No.)	0	0	2
<i>Medication:</i>			
Dosage increase required after diuresis ensued (No.) <sup>d</sup>	6	3	19
Dosage reduction required after diuresis ensued (No.) <sup>d</sup>	13	16	4
Peak dosage reached (days) <sup>e</sup>	16 ± 3	10 ± 2	25 ± 3

<sup>a</sup> Values are given as number of patients or as mean ± 1 SEM.

<sup>b</sup> Observed differences between the *Sequential Spironolactone* group or the *Combination* group and the *Furosemide* group are significant at  $p < 0.05$ .

<sup>c</sup> Observed differences between the *Sequential Spironolactone* group and either the *Combination* or *Furosemide* group are significant at  $p < 0.05$ .

<sup>d</sup> Observed differences between the *Furosemide* group and either the *Sequential Spironolactone* or *Combination* group are significant at  $p < 0.001$ .

<sup>e</sup> Observed differences between the *Combination* and the *Furosemide* groups are significant at  $p < 0.001$ ; between the *Sequential Spironolactone* group and the *Furosemide* group are significant at  $p < 0.01$ .

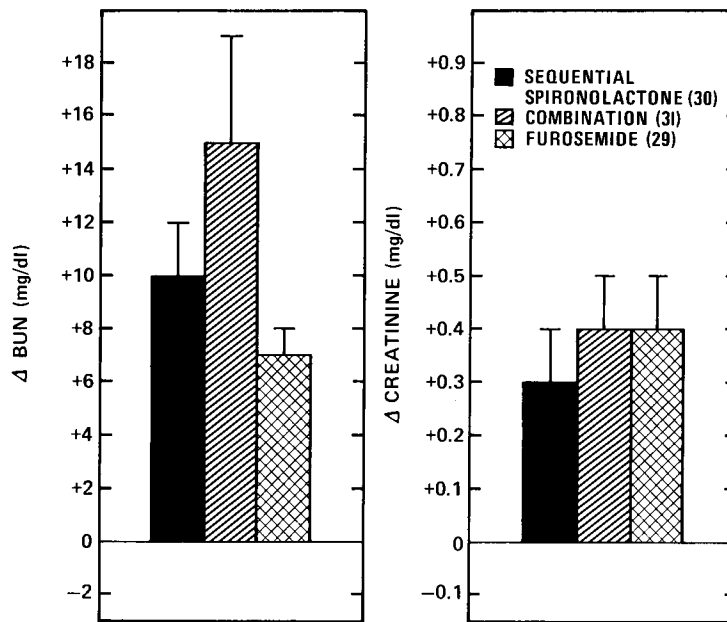
icant. Twenty-two surviving patients had at least a twofold increase in BUN during treatment and 12 of those were in the *Combination* group. The rise in BUN was readily reversed in all 22 patients when the diuretic dosage was reduced or the drug discontinued.

Figure 4 portrays the net change in serum sodium, potassium, chloride and bicarbonate concentrations during the first 3 weeks of the study. There was a fall in the serum sodium in the *Combination* group when compared to the *Furosemide* group ( $p < 0.01$ ) and little change in those assigned to *Sequential Spironolactone*. Serum potassium rose in the *Sequential Spironolactone* group when compared to those in the *Furosemide* group ( $p < 0.05$ ). The rise in serum potassium in the *Combination* group was intermediate between the other two. The changes in serum chloride generally paralleled those of serum sodium and there

**TABLE 4.**  
**Encephalopathy and the Hepatorenal Syndrome<sup>a</sup>**

	<i>Groups</i>		
	<i>Sequential Spiro- lactone (30)</i>	<i>Combi- nation (31)</i>	<i>Furo- semide (29)</i>
At entrance to study			
Encephalopathy	3	1	3
Hepatorenal syndrome	2	2	3
Development during the study			
Encephalopathy	6	8	5
Hepatorenal syndrome	1	2	0

<sup>a</sup> Values are given as number of patients.



**Figure 3.** Maximum increase in BUN and creatinine recorded during the 42-day study period among survivors. The data are given as the mean increase  $\pm 1$  SEM for the three treatment groups.

was a modest decline of bicarbonate in the *Sequential Spironolactone* and *Combination* groups when compared to the *Furosemide* group, but none of these differences reached statistical significance.

Marked hyponatremia ( $<120$  mEq/L) was noted in one patient in the *Sequential Spironolactone* group upon entrance to the study and in another patient in the *Combination* group after a 10-kg weight loss. Both patients died during the study. Severe hyperkalemia ( $>6$  mEq/L) developed in eight patients usually late in the course of the study; seven of these received *Combination* treatment ( $p < 0.01$ ). The eighth patient was in the *Sequential Spironolactone* group. In six cases, the hyperkalemia was associated with mild, reversible azotemia. In two others who died, the hepatorenal syndrome had developed. Hypokalemia of less than 2.5 mEq/L was noted in only one patient and he was in the *Furosemide* group. Hypokalemia developed with only a modest weight loss (2.6 kg) despite substantial supplementation with KCl (160 mEq/day) and responded to discontinuing furosemide.

At least one potential complication of diuretic therapy (encephalopathy, hepatorenal syndrome, or marked electrolyte abnormality) occurred in 33 patients at some time during the 42-day study. The episode was short-lived or a preterminal event in 12 patients and dictated no adjustment in protocol. In the remainder, the medications were either discontinued

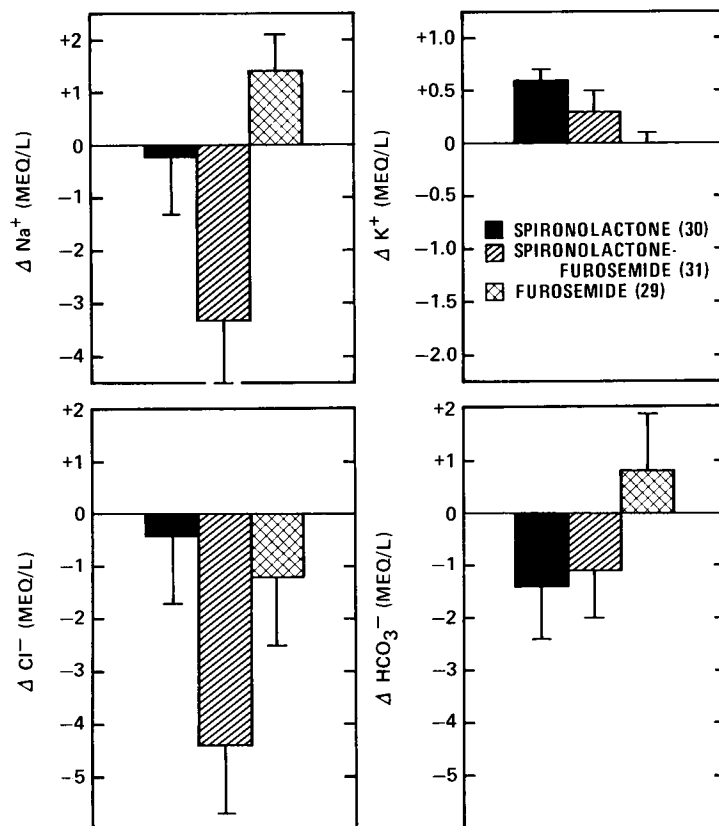
(9 patients), not started (6 patients), or maintained at a low dosage (6 patients). Severe water restriction was instituted in the two patients with marked hyponatremia.

There was one fatality in this study that can be attributed directly to the diuretic therapy. This patient was discharged from the hospital at dry weight on 400-mg spironolactone and 120-mg furosemide combination therapy. He returned severely dehydrated and encephalopathic a week after discharge. Attempts to pass a nasogastric tube in order to administer lactulose resulted in nasopharyngeal bleeding, aspiration and respiratory arrest.

#### Clinical Course and Completion of the Study

The mean duration of hospital stay was  $24 \pm 2$  days for the *Sequential Spironolactone* group,  $20 \pm 2$  days for the *Combination* group, and  $26 \pm 4$  days for the *Furosemide* group. Return of liver function towards normal, reduction of liver size, and incidence of gastrointestinal bleeding were comparable in the three treatment groups.

Four surviving patients in the *Sequential Spironolactone* group, seven in the *Combination* group, and five in the *Furosemide* group failed to complete the 42-day study period. The average duration of follow-up in these 16 patients was 25 days. Thirteen failed to return to the clinic and two discharged themselves from the hospital against medical advice.



**Figure 4.** Net change in serum sodium, potassium, chloride, and bicarbonate concentrations during the first 3 weeks of the study. The data are given as the mean change  $\pm$  1 SEM for the three treatment groups.

One developed thrombocytopenia which was considered due to furosemide and was subsequently lost to follow-up. Ascites was still present in 10 of these patients when last seen. Four of the 16 had mild azotemia on their last visit. Two have been seen at a much later date and no evidence of renal failure was found.

## Discussion

The aim of this study was to achieve a comparable rate of weight loss with three commonly used diuretic regimens in order to compare frequency of side effects, ease of administration, and relative potency. By most measures, we did achieve a comparable diuresis in the three groups. To do so was less easy than anticipated because the characteristic of the diuretic response differed among the three groups.

The onset of diuresis was delayed on the average in the *Sequential Spironolactone* group when compared to the other two. This occurred because half the patients did not lose weight on 400 mg of spirono-

lactone daily; they required supplemental furosemide which was not added to the regimen (by protocol design) until day 13 of the study. The onset of diuresis might have been accelerated in this group by either beginning treatment with a larger dose of spironolactone (200–400 mg) or adding furosemide sooner. In either case, it seems likely that a number of patients would have received more medication than they needed. We tried to avoid this by beginning at a low dose and increasing it only after maximum pharmacologic effect could be expected.<sup>(2)</sup>

Furosemide given alone proved the most difficult to use. Although the requirement for KCl supplementation was expected, the necessary amounts were large and inconvenient to administer on a routine basis. What proved most troublesome was the need to increase the dose over and over again after weight loss had begun in order to complete the diuresis. Our study does not provide an explanation for this unexpected phenomenon. A diuretic-induced decrease in GFR may have resulted in enhanced proximal nephron reabsorption of sodium chloride with a

consequent reduction in the amount delivered to the ascending loop of Henle. For that same reason, renal clearance of furosemide may have decreased, thereby preventing the achievement of effective intratubular concentration of drug. When the cirrhotic patient is not undergoing active diuresis, however, the renal clearance of furosemide is normal.<sup>(14)</sup> The steadily increasing requirement for supplemental KCl suggests that avid sodium-potassium exchange in the distal tubule under the influence of unblocked aldosterone was at least a contributing factor.<sup>(15)</sup>

Combination therapy proved the most potent regimen. Onset of diuresis was reasonably prompt, weight loss was somewhat more rapid, ascites disappeared earliest, and an increase in dose was seldom required after diuresis had begun. Presumably as a consequence, however, the fall in serum sodium and rise in BUN was most marked in this group and severe hyperkalemia occurred frequently. The latter usually arose in association with diuretic-induced azotemia and responded to discontinuing the drugs. The use of furosemide did not prevent hyperkalemia in this setting.

Complications potentially attributable to diuretic therapy occurred in 33 out of 90 (37%) of our patients. How many of these can be attributed to diuretic therapy is uncertain, because the observed rate is almost identical to the 38% noted in our previous study where 21 patients with ascites were observed for 8 weeks while withholding diuretic treatment.<sup>(5)</sup> Whatever the true rate, these complications (save for potassium abnormalities) were distributed evenly among the three treatment groups. Taken as a whole, our findings suggest that excessive rate and extent of diuresis are the reasons for most diuretic-induced complications and that the specific regimen used does not much matter.

Diuresis should be initiated in the ascitic patient with one of the two spironolactone regimens. Spironolactone given alone may be more appropriate for treatment of ambulatory patients since its diuretic action is more gentle than combination therapy. Combination therapy is an attractive alternative particularly for the hospitalized patient where frequent serum creatinine and electrolyte concentrations

can be obtained. The only short-term problem with either regimen is the development of hyperkalemia in an azotemic patient. Furosemide should not be used as the sole agent. The requirements for constant upward adjustment of dosage and massive KCl supplementation make it difficult to use.

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