A Pathophysiological Interpretation of Unresponsiveness to Spironolactone in a Stepped-care Approach to the Diuretic Treatment of Ascites in Nonazotemic Cirrhotic Patients

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It has been hypothesized that the magnitude of proximal sodium reabsorption affects the response to aldosterone antagonists in nonazotemic cirrhotic patients with ascites. To verify this hypothesis, we evaluated intrarenal sodium handling by lithium clearance in 51 nonazotemic ascitic cirrhotic patients and in 23 controls who were maintained on the same low-sodium diet (80 mmol/day). Seven of 51 cirrhotic patients underwent spontaneous diuresis, whereas 44 required diuretic treatment. Treatment was started with spironolactone at a dose of 150 mg once daily. The dose was increased to 300 mg and then to 500 mg once daily if no response ensued. Cirrhotic patients who did not experience ascites mobilization with 500 mg spironolactone were then treated with a combined diuretic regimen that included spironolactone at a fixed dose (500 mg once daily) and furosemide at an initial dose of 50 mg once daily. The dose was increased to 100, 150 and 200 mg once daily if no response was noticed. Response to diuretic treatment was defined as body weight loss greater than 700 gm every 3 days until ascites became clinically undetectable. Nonresponders (43%) to spironolactone showed lower sodium fractional excretion (0.34% ± 0.28% vs. 0.80% ± 0.50%; $p < 0.001$) because of a lower fractional sodium delivery to the distal tubule (18.2% ± 5.8% vs. 23.4% ± 7.2%; $p < 0.025$) than responders. Moreover, nonresponders showed lower distal sodium reabsorption, both in absolute terms (2,360 ± 723 μEq/min vs. 3,221 ± 960 μEq/min; $p < 0.01$) and as a percentage of filtered sodium load (17.5% ± 5.7% vs. 23.1% ± 7.6%; $p < 0.01$) despite higher values of plasma aldosterone (524 ± 542 pg/ml vs. 136 ± 213 pg/ml; $p < 0.025$).

We conclude that unresponsiveness to adequate doses of spironolactone in nonazotemic ascitic cirrhotic patients is related to a pathophysiological condition in which the role of aldosterone in renal sodium retention is limited by markedly enhanced proximal sodium reabsorption. (HEPATOLOGY 1991;14: 231-236.)

Received July 26, 1990; accepted February 6, 1991.

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31/1/29385

It is widely appreciated that aldosterone antagonists are the diuretics of choice in the treatment of ascites in cirrhotic patients (1). The gentle natriuretic effect and the potassium- and magnesium-sparing effects represent important advantages because, in ascitic cirrhotic patients, reduction of "effective plasma volume" and body potassium is usual (2, 3). Recently, it was also observed that spironolactone is more effective than hydrochlorothiazid and furosemide (4, 5). These observations have been regarded as proof of the importance of increased plasma aldosterone levels in renal sodium retention in ascitic cirrhotic patients.

Unfortunately, aldosterone antagonists do not promote effective diuresis in all ascitic cirrhotic patients, even when administered in adequate doses (4, 6-8). Although several possible determinants of unresponsiveness to aldosterone antagonists in ascitic cirrhotic patients have been characterized (9, 10), renal failure is considered the most important (11). The varied responses to therapy among azotemic ascitic cirrhotic patients has been ascribed to the differences in intrarenal sodium (Na) handling linked to renal failure. In fact, increased Na reabsorption in the renal distal tubule is thought to be the consequence of both decreased filtered sodium load and enhanced Na reabsorption in the proximal tubule (11). However, as suggested by clinical practice, water and salt retention are not controlled by spironolactone alone, and a loop diuretic must be added in many patients with adequate renal function (12, 13). Moreover, we recently observed that increased Na reabsorption in the proximal renal tubule also plays an important role in the pathogenesis of renal Na retention (14) in nonazotemic cirrhotics with ascites. Thus, as did Ring-Larsen (15) and Knauf et al. (16), we hypothesized that the magnitude of proximal Na reabsorption affects the response to distal diuretics in these patients.

To verify this hypothesis, we evaluated intrarenal Na handling in a group of nonazotemic cirrhotic patients who were about to receive stepped-care diuretic treatment based on the common guidelines to the use of diuretics in those patients.

TABLE 1. Clinical features and baseline values of nutritional status and liver function tests in cirrhotic patients who experienced spontaneous diuresis (group A) and who required diuretic treatment (group B)

Features/values	Group A (n = 7)	Group B (n = 44)	p Value
Age (yr)	49 ± 9[a]	57 ± 10	NS
First diagnosis of cirrhosis (mo)	45 ± 68	56 ± 46	NS
Ascites (first occurrence)	100%	48%	<0.001
Ascites (recurrent episodes)	0%	52%	
Large ascites	0%	34%	<0.001
Moderate or discrete ascites	100%	66%	
Peripheral edema	57%	59%	NS
Mean arterial pressure (mm Hg)	100 ± 10	94 ± 10	NS
Heart rate (beats/min)	83 ± 9	77 ± 10	NS
TSF (mm)	21.8 ± 11.5	11.0 ± 7.1	<0.025
MAMC (cm)	24.1 ± 1.6	23.3 ± 2.2	NS
Plasma Na (mmol/L) (136-145 mmol/L)[b]	138 ± 3	138 ± 4	NS
Serum albumin (gm/dl) (3.5-5 gm/dl)[b]	3.1 ± 0.6	3.1 ± 0.5	NS
Prothrombin activity (%) (>76%)[b]	54 ± 15	51 ± 14	NS
Serum bilirubin (mg/dl) (0.1-1 mg/dl)[b]	2.2 ± 1.3	2.6 ± 1.6	NS
ABT (% dose) (>9.64)[b]	7.4 ± 7.7	3.5 ± 1.6	<0.025

NS = not significant; TSF = triceps skin fold test; MAMC = mid-arm muscle circumference test; ABT = aminopyrine breath test.

[a]Data expressed as mean ± S.D.

[b]Normal range in our laboratory.

MATERIALS AND METHODS

Patients. Fifty-one patients with cirrhosis and ascites (9 women and 42 men) were enrolled in the study. Mean age was 51 ± 10 yr (range = 34 to 80 yr). Cirrhosis was established by physical examination and biochemical tests. It was confirmed by laparoscopy and/or liver histological study in 39 patients. The origin of cirrhosis was alcoholic in 44 patients, cryptogenic in 4 patients and HBV-related in 1 patient. In two patients both alcohol abuse and HBsAg were documented. Inclusion criteria were (a) normal serum urea and creatinine (< 40 mg/dl and 1.3 mg/dl, respectively); (b) total serum bilirubin less than 10 mg/dl; (c) absence of gastrointestinal bleeding, hepatic encephalopathy, infection or other complications; and (d) absence of conditions (i.e., respiratory failure or umbilical hernia) requiring rapid relief of ascites.

Twenty-three controls (12 men, 11 women) matched for age and without any evidence of liver, heart or kidney disease were studied. Informed consent was obtained from all patients and controls after full explanation of the purpose and nature of all procedures. The study conformed to the 1975 Declaration of Helsinki ethical guidelines and was approved by the local ethical committee.

Protocol. Cirrhotic patients and controls were prescribed a diet containing 80 mEq/day Na throughout the study. In both groups, 24-hr diuresis, 24-hr urinary Na excretion and body weight were monitored daily. In the 4 days after admission, patients and controls received no drugs. On day 3, nutritional status was evaluated by means of triceps skin fold and mid-arm muscle circumference tests. On the same day, the aminopyrine breath test was performed in cirrhotic patients according to the method of Hepner and Vesell (17), as previously reported (18). On day 4, no beverage containing methylxantine was allowed, and at 9 P.M., 600 mg lithium carbonate was administered to cirrhotic patients and controls. On day 5, after a 12-hr fast, an intravenous priming dose of p-aminohippurate (PAH) (8 mg/kg) was given, followed by constant infusion for at least 8 hr. The amount of PAH infused was calculated to maintain a plasma PAH concentration of approximately 1.5 mg/dl. After the initial 60 min (equilibration period), urine was collected for at least 7 hr. Blood samples were taken at the beginning, at the midpoint and at the end of the urine-collection period. Urine was collected by spontaneous voiding, but a Foley catheter was inserted in eight patients who were judged incapable of accurate urine collection. Patients remained supine throughout the study. Brachial artery pressure and heart rate were taken at the midpoint of the urine collection period. Blood samples from the beginning and the end of the urine collection period were analyzed for serum Na, lithium (Li), creatinine (Cr) and plasma PAH. Blood samples taken midway through urine collection were analyzed for plasma renin activity (PRA) and plasma aldosterone concentration (PA). Urine samples were analyzed for Na, Li, Cr and PAH concentration.

On day 5, diuretic therapy was begun in those patients who did not mobilize ascites by means of bed rest and low Na intake. Based on the common guidelines to the use of diuretics in cirrhotic patients with ascites (13), diuretic treatment was started with spironolactone at the initial dose of 150 mg once daily at 8 A.M. The dose was increased to 300 and then to 500 mg once daily if no response ensued. Cirrhotic patients who did not experience ascites mobilization with 500 mg of spironolactone were then treated with a combined diuretic regimen that included spironolactone at a fixed dose (500 mg once daily) and furosemide. The initial dose of furosemide was 50 mg once daily at 10 A.M. Subsequently, it was gradually increased (100, 150 and 200 mg once daily) if no response was observed. For the study purposes, response to bed rest and salt restriction and to spironolactone alone and to the combined diuretic treatment was defined as a body weight loss greater than 700 gm every 3 days until ascites became clinically undetectable. No drug known to affect renal function besides diuretics was prescribed during the study.

To detect adverse effects related to the proposed stepped-care diuretic treatment, plasma potassium (K) Na and Cr and serum urea level were evaluated every 2 days until almost complete mobilization of ascites was observed. Hyperkalemia and hypokalemia were defined by plasma K greater than 5.5 mmol/L and a plasma K less than 3.5 mmol/L, respectively in two consecutive serum samples. Hyponatremia was defined as plasma Na less than 130 mmol/L and by plasma Na less than 125 mmol/L in two consecutive serum samples according to a baseline plasma Na greater than 130 or less than 130 mmol/L, respectively. Azotemia was defined as a progressive increase in serum urea level and plasma Cr. Encephalopathy and gynecomastia were monitored by careful daily clinical examination. Moreover, the plasma ammonia level was evaluated every 6 days until almost complete disappearance of ascites occurred.

TABLE 2. Renal Na handling and hormonal parameters in controls, cirrhotic patients who experienced spontaneous diuresis (group A) and who required diuretic treatment (group B)

Parameters	Controls (n = 23)	Group A (n = 7)	Group B (n = 44)	p[a]	p[b]	p[c]
RPF (ml/min)	537 ± 121[d]	526 ± 88	480 ± 173	NS	NS	NS
GFR (ml/min)	108 ± 28	116 ± 27	101 ± 24	NS	NS	NS
FL Na (μEq/min)	15,201 ± 3,669	15,974 ± 3,673	13,677 ± 3,456	NS	NS	NS
FE Na (%)	1.33 ± 0.58	1.34 ± 0.47	0.60 ± 0.47	NS	<0.001	<0.005
Li clearance (ml/min)	27.0 ± 7.6	34.9 ± 8.2	20.7 ± 6.8	NS	<0.01	<0.001
FE Li (%)	25.6 ± 6.4	32.7 ± 6.5	21.2 ± 7.1	NS	<0.05	<0.025
DD Na (μEq/min)	3,779 ± 1,013	4,856 ± 1,107	2,884 ± 963	NS	<0.01	<0.001
DR Na (μEq/min)	3,590 ± 981	4,513 ± 911	2,788 ± 935	NS	<0.025	<0.01
DFR Na 1 (%)	24.1 ± 6.1	31.4 ± 6.2	20.7 ± 7.4	<0.05	NS	<0.005
DFR Na 2 (%)	94.9 ± 2.2	96.0 ± 1.0	97.2 ± 1.8	NS	<0.001	NS
PRA (ng/ml/hr)	2.34 ± 1.64	0.65 ± 0.46	5.13 ± 6.43	NS	NS	NS
PA (pg/ml)	55 ± 42	30 ± 19	304 ± 432	NS	<0.025	NS

RPF = renal plasma flow; NS = not significant; GFR = glomerular filtration rate; FL Na = filtered Na load; FE Na = fractional sodium excretion; FE Li = fractional lithium clearance.

[a]Comparison between controls and group A.

[b]Comparison between controls and group B.

[c]Comparison between group A and group B.

[d]Data expressed as mean ± S.D.

Analytical Methods. Brachial artery pressure was taken with a standard mercury sphygmomanometer. Diastolic pressure was recorded at the disappearance of Korotkoff sounds. Plasma Na, K and Li and urinary Na and Li were measured by a flame photometer (Instrumentation Laboratory model 143; Instrumentation Laboratory, Paderno Dugnano, Italy). CO_2 specific activity in the expired air was evaluated in a β-counter (Packard Tri-Carb 460-CD; Packard Instrument Co., Warrenville, IL). Plasma and urinary Cr were determined colorimetrically (19), as was PAH concentration in plasma and urine (20). PRA was determined by RIA for angiotensin I (Renin Maia Kit; Biodata, Rome, Italy); PA was also determined by RIA (Aldosterone Maia Kit; Biodata).

Calculations. The amount of radioactive CO_2 expired at 2 hr was expressed as a percentage of the amount administered according to a previously reported formula (18). Mean arterial pressure was calculated as the diastolic pressure + one third of the pulse pressure. Plasma Na, Cr and PAH were calculated as the mean of their correspondent values at the beginning and end of urine collection. Plasma Li was calculated on the basis of the correspondent values at the beginning and end of urine collection according to the formula proposed by Thomsen (21). Clearance of Na, Cr and Li were calculated by the conventional formula $CA = (UA \times V)/PA$ where *CA* is clearance of *A*, *UA* and *PA* are urine and serum or plasma concentrations of *A*, respectively, and *V* is the urinary output. Clearance of PAH and Cr were used as measures of renal plasma flow and glomerular filtration rate, respectively (22, 23).

Filtered sodium load was then calculated as plasma Na × Cr clearance. Fractional urinary excretion of Na and Li were calculated by the ratio of Na and Li clearance to Cr clearance, respectively. As previously reported (14), assuming fractional urinary Li clearance is an index of fractional distal sodium delivery, the following parameters were also evaluated: absolute distal Na delivery (DD Na) (equal to Li clearance × plasma Na in μEq/min); absolute distal Na reabsorption (DR Na) (equal to DD Na − urinary Na × urinary output in μEq/min); distal fractional Na reabsorption 1 (DFR Na 1) (equal to DR Na/FL Na %); and distal fractional Na reabsorption 2 (DFR Na 2) (equal to DR Na/DD Na %).

Statistical Analysis. Results were expressed as mean ± S.D. Comparison between cirrhotic groups and controls was carried out by ANOVA and then by the Bonferroni test. Comparison between cirrhotic subgroups was performed by ANOVA and then by Student's *t* test. Differences in proportions between groups and subgroups of patients were found using Fisher's exact test. The 5% probability level was regarded as significant.

RESULTS

Tables 1 and 2 show the main clinical and biochemical parameters of the 51 ascitic cirrhotic patients divided into two groups according to whether they required diuretic treatment (group B and group A, respectively). Considering cirrhotic patients as a whole, an inverse relationship between Li clearance and both Log. PRA and Log. PA was found ($r = -0.35$, $p < 0.01$ and $r = -0.43$, $p < 0.01$, respectively). Such a relationship was not found in controls.

Twenty-five cirrhotic patients (4 women and 21 men) from group B (57%) responded to spironolactone alone (subgroup C), whereas 19 (3 women and 16 men) (43%) did not (subgroup D).

In Tables 3 and 4, the main clinical and biochemical parameters of the two groups are shown.

It must be pointed out that two patients from subgroup D were the only cirrhotic patients who had baseline hyponatremia (plasma Na = 126 and 127 mmol/L, respectively).

Two patients (11%) who did not respond to the highest doses of spironolactone and furosemide were judged to have refractory ascites. Individual values of Li clearance in controls and in all cirrhotic subgroups are depicted in Fig. 1 according to their varied responses to therapy. Patients who required 500 mg of spironolactone had higher PA values than did those who responded to 150 to 300 mg of the drug (218 ± 230 pg/ml vs. 111 ± 207 pg/ml; $p < 0.001$).

TABLE 3. Clinical features and baseline values of nutritional status and liver function tests in cirrhotic patients who responded (subgroup C) and not responded (subgroup D) to spironolactone alone

Characteristics	Subgroup C (n = 25)	Subgroup D (n = 19)	p Value
Age (yr)	56 ± 9[a]	58 ± 11	NS
Time from first diagnosis of cirrhosis (mo)	62 ± 46	49 ± 48	NS
Ascites (first occurrence)	56%	37%	< 0.01
Ascites (recurrent episodes)	44%	63%	
Large ascites	16%	58%	< 0.001
Moderate or discrete ascites	84%	42%	
Peripheral edema	56%	48%	NS
Mean arterial pressure (mm Hg)	93 ± 9	95 ± 12	NS
Heart rate (beats/min)	75 ± 7	80 ± 12	NS
TSF (mm)	9.3 ± 3.3	13.2 ± 9.8	NS
MAMC (cm)	23.4 ± 2.4	23.1 ± 1.9	NS
Plasma Na (mmol/L) (130-140 mmol/L)[b]	137 ± 4	136 ± 4	NS
Serum albumin (gm/dl) (3.5-5 gm/dl)[b]	3.2 ± 0.5	3.0 ± 0.6	NS
Prothrombin activity (%) (> 76%)[b]	47 ± 10	55 ± 18	NS
Serum bilirubin (mg/dl) (0.1-1 mg/dl)[b]	2.9 ± 1.9	2.2 ± 1.2	NS
ABT (% dose) (> 9.64)[b]	3.6 ± 1.9	3.4 ± 1.4	NS

NS = not significant; TSF = triceps skin fold test; MAMC = mid-arm muscle circumference test; ABT = aminopyrine breath test.
[a]Data expressed as mean ± S.D.
[b]Normal range in our laboratory.

TABLE 4. Renal Na handling and hormonal parameters in controls and cirrhotic patients who responded (subgroup C) or did not respond (subgroup D) to spironolactone alone

Parameters	Subgroup C (n = 25)	Subgroup D (n = 19)	p Value
RPF (ml/min)	491 ± 184[a]	468 ± 164	NS
GFR (ml/min)	101 ± 26	100 ± 26	NS
FL Na (μEq/min)	13,941 ± 3,816	13,328 ± 2,981	NS
FE Na (%)	0.80 ± 0.50	0.34 ± 0.28	< 0.001
C Li (ml/min)	23.0 ± 6.9	17.8 ± 5.5	< 0.01
FE Li (μEq/min)	23.4 ± 7.2	18.2 ± 5.8	< 0.025
DD Na (μEq/min)	3,221 ± 979	2,439 ± 754	< 0.01
DR Na (%)	3,113 ± 960	2,360 ± 723	< 0.01
DFR Na 1 (%)	23.1 ± 7.6	17.5 ± 5.7	< 0.01
DFR Na 2 (%)	96.6 ± 1.8	97.9 ± 1.4	< 0.01
PRA (ng/ml/hr)	2.5 ± 4.7	8.6 ± 6.8	< 0.025
PA (pg/ml)	136 ± 213	524 ± 542	< 0.025

RPF = renal plasma flow; NS = not significant; GFR = glomerular filtration rate; FL Na = filtered sodium load; FE Na = fractional sodium excretion; C Li = lithium clearance; FE Li = fractional lithium clearance; DD Na = absolute distal sodium delivery; DR Na = absolute distal sodium reabsorption; DFR Na 1 = distal sodium reabsorption as a percent of filtered sodium load; DFR Na 2 = distal sodium reabsorption as a percent of distal sodium delivery.
[a]Data expressed as mean ± S.D.

It must be emphasized that in patients with refractory ascites, Li clearance and fractional urinary excretion of Li and Na and DD Na, DR NA and DFR NA 1 were dramatically reduced (12.59% ± 4.9%, 10.84% ± 2.7%, 0.16% ± 0.09%, 1,751 ± 749 μEq/min, 1,727 ± 759 Eq/min and 10.7% ± 2.8%, respectively), whereas PRA and PA were dramatically increased (16.92 ± 9.72 ng/ml/hr and 1,497 ± 335 pg/ml, respectively). However, even if we exclude the two patients with refractory ascites from subgroup D and subsequently compare the data of cirrhotic patients who responded to the combined diuretic regimen (subgroup E) with cirrhotic patients who responded to spironolactone alone (subgroup C), the same statistically significant differences in fractional urinary excretion of Li and Na and DD Na, DFR Na, PRA and PA are found.

With diuretic treatment, mean body-weight reductions of 10.362 ± 8.043 kg in 13 ± 7 days and 6.250 ± 2.202 kg in 10 ± 5 days were obtained in patients with and without peripheral edema, respectively. Mean body-weight reductions of 6.728 ± 3.978 kg in 10 ± 5 days and 11.352 ± 8.471 kg in 15 ± 8 days was obtained in cirrhotic patients who responded to spironolactone alone and in those who responded to the combined diuretic regimen, respectively.

Electrolyte derangement related to effective diuretic therapy was observed in eight patients (19%). Mild hyperkalemia occurred in four patients (in two of the patients who responded to spironolactone and in two of the patients who responded to combined diuretic regimen). In one patient of the latter group, hyperkalemia was associated with hyponatremia. One other patient of the latter group and two patients of the former group experienced mild hyponatremia. Hypokalemia was observed in one patient who responded to the combined-diuretic regimen. No cases of azotemia, encephalopathy or gynecomastia were observed. Five of eight patients who experienced adverse effects had peripheral edema. No difference in body-weight reduction (10.400 ± 7.347 vs. 8.176 ± 6.359 kg; not significant) or in the duration of diuretic therapy (12 ± 6 days vs. 14 ± 6 days; not significant) was observed between cirrhotic patients with and without electrolyte derangement.

DISCUSSION

In our study, complete ascites mobilization was achieved with spironolactone alone in 57% of patients. A serum Cr level less than 1.3 mg/dl was one of the inclusion criteria. It is known that serum Cr may overestimate renal function in cirrhotic patients. However, since all our patients had a Cr clearance greater than 65 ml/min, our results confirm that a discrete proportion of ascitic cirrhotic patients with preserved renal function did not respond to spironolactone, even when the drug was given in adequate doses.

On the basis of our previous observation of increased

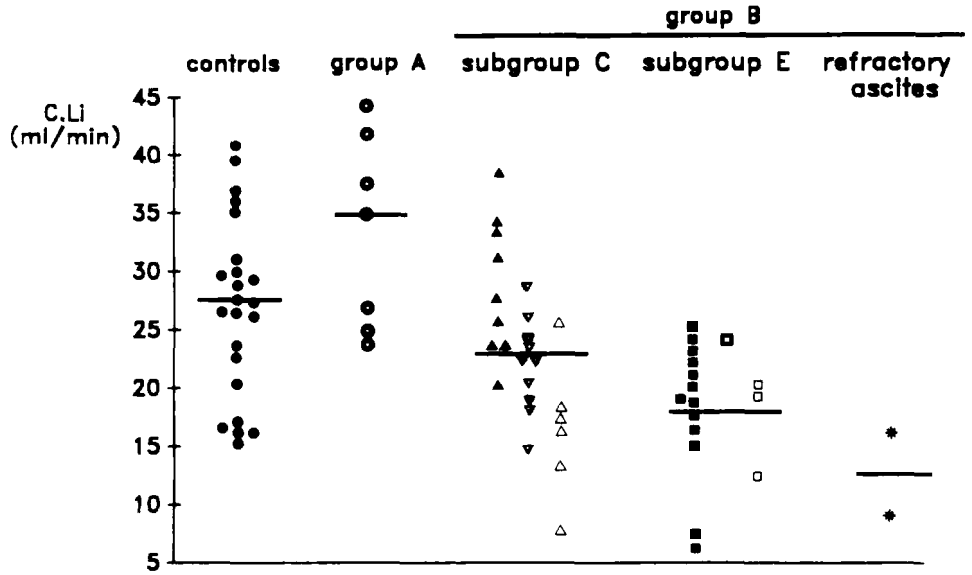

FIG. 1. Distribution of the individual values of Li clearance *(C.Li)* in controls (•), in cirrhotic patients who experienced spontaneous diuresis (group A; •), in ascitic cirrhotic patients who required diuretic treatment (group B), in ascitic cirrhotic patients who responded to spironolactone alone (subgroup C; ▲, ▼ and △ = cirrhotic patients who responded to 150, 300 and 500 mg/day spironolactone, respectively), in ascitic cirrhotic patients who responded to the combined diuretic treatment of spironolactone (500 mg/day) + furosemide (subgroup E; ■, ■ and □ = cirrhotic patients who responded to 50, 100 and 150 mg/day furosemide, respectively) and in ascitic cirrhotic patients who did not respond to the combined diuretic treatment (refractory ascites; *). Mean values of Li clearance are indicated by *bars*.

Na reabsorption in the proximal tubule in a significant proportion of nonazotemic cirrhotic patients with ascites, we applied Li clearance, a marker of proximal Na reabsorption, to characterize possible pathophysiological differences in renal Na retention between responders and nonresponders to spironolactone. However, before any considerations are made on the different pathophysiological patterns between responders and nonresponders to spironolactone alone, some methodological aspects must be exposed. It is known that no ideal marker of proximal Na reabsorption exists, and that, as discussed elsewhere (14), all proposed methods (clearance techniques and phosphate clearance) have pitfalls in their application in cirrhotic patients with ascites. Certainly, many arguments favor Li clearance as a reliable index of proximal Na reabsorption, and the method offers obvious advantages over all others for determining delivery from the proximal tubule. Nevertheless, some aspects of its accuracy are under study (24-26).

Thus experimental studies disclose that Li is also reabsorbed beyond the proximal tubule, in the loop of Henle, in the late distal tubule and in the collecting duct (27). As previously discussed (14), it has been shown that Li reabsorption beyond the loop of Henle occurs much less often in humans than in rats and dogs and only under conditions of severe sodium restriction, with values of FE Na close to 0.10% (28, 29). In addition, in contrast to experimental studies, it has been observed that an increase in Li clearance after loop diuretic administration occurs in humans under conditions of Na restriction and that a considerable part is affected in the proximal tubule (27-29). As far as cirrhotic patients with ascites are concerned, the accuracy of Li clearance may be questioned. To our knowledge, its assumption has not yet been proved, and it is still uncertain whether conditions such as reduced renal perfusion or increased vasopressin activity—which may occur in cirrhotic patients—may actually affect distal Li transport. Despite these uncertainties about the method (because FE Na in our patients was above 0.10%) we consider Li clearance a reliable index of proximal Na reabsorption on the basis of observations in normal subjects. In cirrhotic patients who required diuretic treatment, renal Na retention appears to be the result of increased Na reabsorption in the proximal tubule. This finding confirms once more our previous observation (14). However, it must be emphasized that proximal Na reabsorption may be to some extent overestimated in our patients because of the limits of Cr clearance in the assessment of glomerular filtration rate (22, 23). Moreover, when responders and nonresponders to spironolactone were considered, despite their similar values of renal plasma flow, glomerular filtration rate and FL Na, the latter subgroup demonstrated a greater reduction of FE Na consequent to markedly enhanced Na reabsorption in the proximal tubule. Nonresponders to spironolactone also presented higher PA values.

Thus one may wonder whether 500 mg/day of spironolactone was adequate in patients with the highest PA level. However, the question seems improper if PA level is considered together with all other pathophysiological findings. In fact, the finding of a greater reduction in Na reabsorption in the distal tubule in nonresponders to spironolactone suggests that the role of aldosterone in renal Na retention in these patients was limited by proximal Na reabsorption. Thus it seems unlikely that the proportion of responders would increase by administering doses of spironolactone greater than 500 mg/day. We can also hypothesize that the inhibition of

Na reabsorption in the ascending limb of Henle's loop by furosemide reset Na delivery to the aldosterone-sensitive tubular site to an extent sufficient to restore the effectiveness of spironolactone.

The influence of proximal Na reabsorption on the medical therapy of ascites in nonazotemic cirrhotic patients appears even more conspicuous if spontaneous diuresis and refractory ascites are considered. Compared with controls, proximal Na reabsorption was reduced in patients with spontaneous diuresis, whereas it was dramatically increased in patients with refractory ascites. Thus proximal Na reabsorption seems to be the main determinant of the varied response to therapy among nonazotemic cirrhotic patients with ascites. The finding of a relationship between Li clearance and PRA, which is a sensitive index of a reduced "effective" plasma volume, in cirrhotic patients but not in controls further suggests that different degrees of effective hypovolemia may occur in our patients and that it consequently may be the cause of their differing responses to therapy.

No differences were found in liver function tests, including a quantitative test such as the aminopyrine breath test, between the two subgroups. Thus the hypothesis of a difference in hepatic spironolactone metabolism between the two subgroups of patients seems unlikely.

As far as clinical considerations are concerned, it appears according to our results that a stepped-care approach to diuretic treatment in ascitic cirrhotic patients is effective in 95% of patients. It also appears that such an approach is safe, since only mild electrolyte derangement was observed.

In conclusion, in confirming that enhanced Na reabsorption in the proximal tubule seems to be the main determinant of renal Na retention in nonazotemic cirrhotic patients with ascites who did not undergo spontaneous diuresis, our study suggests that the resistance to spironolactone in nonazotemic cirrhotic patients with ascites is related to markedly enhanced Na reabsorption in the proximal renal tubule.

REFERENCES

1. Boyer TD, Warnock DG. Use of diuretics in the treatment of cirrhotic ascites. Gastroenterology 1983;84:1051-1054.
2. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. HEPATOLOGY 1988;8:1151-1157.
3. Perez GO, Oster JR. Altered potassium metabolism in liver disease. In: Epstein M, ed. The kidney in liver disease. 2nd ed. New York: Elsevier Scientific Publishers 1983:183-201.
4. Fogel MR, Sawhney VK, Neal EA, Miller RG, Knauer CM, Gregory PB. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. J Clin Gastroenterol 1981;3(Suppl 1):73-80.
5. Perez-Ayuso RM, Arroyo V, Planas R, Gaya J, Bory F, Rimola A, Rivera F. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Gastroenterology 1983;84:961-968.
6. Campra JL, Reynolds TB. Effectiveness of high dose spironolactone therapy in patients with chronic liver disease and relatively refractory ascites. Dig Dis Sci 1978;23:1025-1030.
7. Eggert RC. Spironolactone diuresis in patients with cirrhosis and ascites. Br Med J 1970;4:401-403.
8. Gregory PB, Broekelschen PH, Hill MD, Lipton AB, Knauer MC, Egger M, Miller R. Complications of diuresis in the alcoholic patient with ascites: a controlled trial. Gastroenterology 1977;73: 534-538.
9. Bernardi M, Servadei D, Trevisani F, Rusticali AG, Gasbarrini G. Importance of plasma aldosterone concentration on the natriuretic effect of spironolactone in patients with liver cirrhosis and ascites. Digestion 1985;31:189-193.
10. Medina JF, Prieto J, Guraner F, Quiroga G, Milazzo A. Effect of spironolactone on renal prostaglandin excretion in patients with liver cirrhosis and ascites. J Hepatol 1986;3:206-211.
11. Arroyo V, Gines P, Rodes J. Treatment of ascites in patients with cirrhosis of the liver. J Hepatol 1986;2:504-512.
12. Epstein O. Management aspects of cirrhosis. Practitioner 1987; 231:395-401.
13. Kandel G, Diamant NE. A clinical view of recent advances in ascites. J Clin Gastroenterol 1986;8:85-99.
14. Angeli P, Gatta A, Caregaro L, Menon F, Sacerdoti D, Merkel C, Rondana M, et al. Tubular site of renal sodium retention in ascitic liver cirrhosis evaluated by lithium clearance. Eur J Clin Invest 1990;20:111-117.
15. Ring-Larsen H. Treatment of ascites in cirrhosis. In Tygstrup N, Orlandi F. Cirrhosis of the liver: methods and fields of research. Amsterdam: Elsevier Scientific Publishers, 1987:429-436.
16. Knauf H, Wenk E, Schilmerich J, Goerg KJ, Gerok W, Leser HG, Mutschler E. Prediction of diuretic mobilization of cirrhotic ascites by pretreatment fractional sodium excretion. Klin Wochenschr 1990;68:545-551.
17. Hepner GW, Vesell ES. Assessment of aminopyrine metabolism in man by breath analysis after oral administration of [14-C]-aminopyrine. Ann Intern Med 1975;83:632-638.
18. Merkel C, Sacerdoti D, Finucci GF, Zuin R, Bazzerla G, Bolognesi M, Gatta A. Effect of nadolol on liver haemodynamics and function in patients with cirrhosis. Br J Clin Pharmacol 1986;21:713-719.
19. Bartels H, Bohmer M. Eine Mikromethode zur Kreatinibestimmung. Clin Chim Acta 1971;32:81-85.
20. Smith HW, Finkelstein N, Aliminosa L, Crawford B, Graber M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dogs and man. J Clin Invest 1945;24: 388-404.
21. Thomsen K. Lithium clearance as a measure of sodium and water delivery from the proximal tubules. Kidney Int 1990;37(Suppl 20):S10-S16.
22. Brochner-Mortensen J. Current status on assessment and measurement of glomerular filtration rate. Clin Physiol 1985;5: 1-17.
23. Schuster L, Seldin DW. Renal clearance. In: Seldin DW, Giebish G, eds. The kidney: physiology and pathophysiology. New York: Raven Press, 1985:365-395.
24. Koomans HA, Boer WH, Dorhout Mees EJ. Evaluation of lithium clearance as a marker of proximal tubule sodium handling. Kidney Int 1989;36:2-12.
25. Koomans HA, Boer WH, Dorhout Mees EJ. Lithium clearance in renal physiology: post-conference discussion and consensus. Kidney Int 1990;37(Suppl 20):S78-S79.
26. Kirchner KA. Lithium as a marker for proximal tubular delivery during salt intake and diuretic infusion. Am J Physiol 1987;253: F188-F196.
27. Atherton JC, Green SR, Hughes S, McFall V, Sharples JA, Solomon RL, Wilson L. Lithium clearance in man: effects of dietary salt intake, acute changes in extracellular volume, amiloride and furosemide. Clin Sci 1987;73:645-651.
28. Boer WH, Koomans HA, Boer WH, Dorhout Mees EJ. Lithium clearance in healthy humans suggesting lithium reabsorption beyond the proximal tubule. Kidney Int 1990;37(Suppl 20): S39-S44.
29. Cristensen S. Furosemide effect during volume expansion: evidence against lithium transport in the loop. Kidney Int 1990; 37(Suppl 20):S45-S51.