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Efficacy and safety of the stepped care medical treatment of ascites in liver cirrhosis: a randomized controlled clinical trial comparing two diets with different sodium content

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Abstract: In order to clarify debated issues of the medical treatment of ascites in cirrhosis – the usefulness of a low sodium diet and washout period preceding diuretic administration, maximal dosage of antimineralocorticoid to be reached before the addition of a loop diuretic, identifications of factors influencing treatment efficacy – 115 hospitalized patients with non-azotemic cirrhosis and ascites were recruited and randomized to receive a diet providing either 40 or 120 mmol of sodium daily. After a washout period from the outpatient diuretic regimen for 7 days (Step 1), increasing dosages of K-canrenoate (200 mg/day every 4th day up to 600 mg) were administered to patients not undergoing spontaneous diuresis (Step 2). Upon the failure of Step 2, K-canrenoate (400 mg/day) and furosemide at increasing dosage (25–50–100 mg every other day) were given (Step 3). Nine percent of patients underwent spontaneous diuresis, and 77% developed a negative sodium balance by the end of Step 2 (69% with a dosage of K-canrenoate $\leq$400 mg/day) and 93% by the end of Step 3. Two patients were withdrawn from the protocol due to diuretic side-effects. Univariate analysis showed that the type of diet did not influence the response to treatment. The washout period led to a significant increase in endogenous creatinine clearance; natremia significantly rose in hyponatremic patients. Multivariate analysis showed that creatinine clearance and plasma aldosterone were independent predictive factors of the response to treatment. The use of low-sodium diet did not enhance the efficacy of the medical treatment of non-azotemic cirrhotic ascites and a washout period from diuretics improved renal function and natremia. Antimineralocorticoids up to 400 mg/day were successful in over 2/3 of cases and the improvement in efficacy obtained by a further increase in dose was small. Endogenous creatinine clearance and plasma aldosterone significantly influenced treatment efficacy. The therapeutic regimen employed in this study was highly effective and had a very low incidence of side effects.

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Key words: ascites – cirrhosis – diet – furosemide – K-canrenoate – renal function

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A stepped care medical approach based on bed rest, low-sodium diet, and the administration of aldosterone antagonists and loop diuretics is widely accepted for the treatment of cirrhotic patients with ascites (1–3). However, there is still some disagreement on several issues. In fact, controlled clin-

ical trials failed to show greater efficacy of a low sodium diet versus an unrestricted diet when associated with diuretic agents (4, 5). Moreover, the association of severe sodium restriction with diuretic treatment may favor the occurrence of hyponatremia and renal failure (6). Aldosterone antagonists are the first choice drugs (7) and their effective dosage is directly related to the actual degree of hyperaldosteronism (8). Therefore, aldosterone antagonists are commonly given in stepwise increasing doses until a negative sodium balance is achieved. However, since the maximal dosage which it is useful to reach before the addition of a loop diuretic has not been well established, this therapeutic approach may be time consuming and lengthen the duration of hospitalization.

The aim of the present study was to evaluate the therapeutic effectiveness and the complication rate of a stepped care medical treatment, including either normo- or low-sodium diets, in non-azotemic cirrhotic patients with ascites. The influence of factors potentially affecting the success rate of the treatment was also evaluated.

Patients and methods

One hundred and sixty-nine patients with ascites consecutively admitted from January 1988 to December 1989 to three medical units were enrolled in the study. One hundred and fifteen fulfilled the criteria reported in Table 1 and were randomized using sealed envelopes by each single center and allocated to receive two different dietetic regimens containing 40 (Group A) or 120 mmol of Na^+/day (Group B), respectively. A washout period of 7 days was then started, and the diuretics taken before hospitalization (85 cases) were withheld. In patients who did not lose at least 2 kg of body weight on such a regimen (Step 1), the aldosterone antagonist K-canrenoate in the dosage of 200 mg/day was added (Step 2A). The dosage was further increased by 200 mg every 4th day, up to 600 mg/day, if the body weight decreased less than 1 kg/3 days (Step 2B). In the event of there being no diuretic response to K-canrenoate, the drug was lowered to 400 mg/day, and furosemide in an increasing dosage (25–50–100 mg every other day [Step 3]) was added (Table 2). Refractory ascites was defined when no response to the maximal combined diuretic dosage or diuretic side effects were observed.

Table 1. Criteria for admission and exclusion from the study

Admission criteria:
Liver cirrhosis with ascites
Age range 20–80
Exclusion criteria:
Peritoneal carcinosis
Bacterial peritonitis
Severe liver failure (total serum bilirubin > 170 μmol/l; prothrombin activity < 30%)
Encephalopathy grade III-IV
Recent gastrointestinal bleeding (within 15 days)
Serum creatinine ≥ 1.5 mg/dl
Intrinsic renal disease
Heart and respiratory failure
Malignancies other than hepatocellular carcinoma

Table 2. Protocol of the treatment and criteria of success

	Treatment	Loss of body weight
Step 1	Bed rest + diet	≥ 2 kg/week
Step 2a	K-canrenoate (200 mg)	≥ 1 kg/3 days
Step 2b	K-canrenoate (up to 600 mg)	≥ 1 kg/3 days
Step 3	K-canrenoate + furosemide (400 mg) (up to 100 mg)	≥ 0.7 kg/2 days

All patients were hospitalized to maintain a strict control of the compliance to the dietetic and therapeutic regimen, and to follow the clinical course thoroughly. In the presence of serum albumin concentration ≤ 25 g/l, the iv administration of human serum albumin was allowed. On admission, routine liver function tests, blood urea nitrogen, endogenous creatinine clearance (C_{cr})- which was considered representative of glomerular filtration rate –, serum and urine sodium and potassium concentrations, hemoglobin levels and albumin concentration in the ascites were determined according to current laboratory methods. Plasma aldosterone concentration was measured by radioimmunologic assay using a commercial kit (Radim S.p.A., Pomezia, Italy), and expressed as mmol/l (normal range 0.15–0.5 mmol/l). Blood urea nitrogen, creatinine clearance, serum albumin concentration, serum and urine electrolyte concentrations, and hemoglobin levels were measured again every 3 days during the follow-up period. Plasma aldosterone concentration was again determined at the end of each step. A complete set of samples for aldosterone determination was available in 84 subjects: only these cases underwent statistical evaluation concerning plasma aldosterone concentration.

Statistical analysis

The sample size was defined admitting a $\beta = 20\%$ and an $\alpha = 5\%$ error for a pre-determined difference in efficacy of the two dietetic regimens of 30%. Each single quantitative variable was expressed as mean ± standard error. The statistical significance of the variable changes during the follow-up was

evaluated by using the analysis of variance for multiple measures (Anova) or the paired Student's *t*-test. Differences between the main parameters belonging to the two randomized groups were evaluated by using Student's t-test or the chi-square test. The analysis of the predictive factors of response to treatment was performed by using logistic regression models for ordinal response data. First, univariate analysis was carried out, taking into account the following potentially predictive factors: type of diet, C_{cr}, serum sodium and potassium concentrations, urine sodium, belonging to Child-Pugh class, plasma aldosterone concentration, serum and ascites albumin concentrations, serum-ascites albumin gradient, hemoglobin level and age. The factors resulting which were significantly associated (probability level $< 5\%$) with the response variable were then tested by multivariate analysis, by means of a stepwise model selection method. The final model was described with standardized estimates and predicted probabilities.

Results

Under basal conditions, the two randomized groups of patients did not differ in terms of age, sex, etiology of cirrhosis, liver function tests, renal function, plasma aldosterone concentration, presence of edema, hepatocellular carcinoma and portal vein thrombosis (Table 3).

1. Overall influence of the diets on the effects of the stepped care medical treatment (Table 4)

The use of either the 40 mmol/day (group A) or 120 mmol/day sodium diet (group B) did not lead to statistically significant differences in the number of patients either undergoing spontaneous diuresis (6/62 vs 4/53, respectively), or requiring the highest dose of K-canrenoate (5/62 vs 6/53), or reaching Step 3 (11/62 vs 7/53). Drop-outs and refractory ascites were equally distributed between the two groups. Univariate analysis showed that the type of diet was not associated with different responses to treatment (Wilcoxon $p = 0.98$). Renal sodium excretion at the time therapeutic success was achieved is also reported in Table 4.

Table 3. Main clinical and laboratory features in the patients randomly assigned to the different diet regimens. The data refer to the finding disclosed on admission to the hospital

Dietary sodium:	40 mmol/day	120 mmol/day
Number	62	53
Age: median (range)	55 (28–80)	56 (35–80)
Sex: m/f	41/21	41/12
Pugh's class: B/C	31/31	27/26
Serum albumin: g/l	31.1±0.6	31.2±0.7
Serum sodium: mmol/l	135.07±0.6	136.4±0.5
Glomerular filtration rate: ml/min	74.5±4.1	81.1±4.7
Renal sodium excretion: mmol/day	52.7±4.2	60.2±5.0
Plasma aldosterone: nmol/l	2.08±0.27*	1.80±0.24*
Etiology: alcohol/non-alcohol: #	39/23	31/22
Hepatocellular carcinoma: #	12	12
Portal thrombosis: #	2	3
Diuretic treatment before admission: #	46	39

* plasma aldosterone determinations were available in 44 patients of group A and 47 patients of group B.
# number of observations.

Table 4. Success rate, daily renal sodium excretion at the time of reponse to treatment, and incidence of drop-outs and refractory ascites in the patients receiving diets with different Na^+ content

	Dietary sodium			
	40 mmol/day		120 mmol/day	
	% (#)	$U_{Na}V$	% (#)	$U_{Na}V$
Step 1	9.7 (6)	133.8±19.5	7.5 (4)	188.7±23.0
Step 2A	40.4 (25)	133.7±10.3	41.5 (22)	218.3±27.8*
Step 2B	25.8 (16)	199.6±16.9	30.2 (16)	218.6±15.7
Step 3	17.7 (11)	162.4±32.1	13.2 (7)	210.0±26.4
Drop-outs	1.6 (1)		1.9 (1)	
Refractory ascites	4.8 (3)		5.7 (3)	

* $p = 0.004$ with respect to patients receiving 40 mmol/day of sodium.
% (#) percentage (number) of patients undergoing diuresis at each step.

2. Effects of the washout period

During this period, 10 patients (9.3%) underwent spontaneous diuresis. The washout period led to a statistically significant improvement of renal function (Fig. 1): C_{cr} rose from 78.3 ± 3.1 to 86 ± 3 ml/min ($p < 0.001$) with a mean percentage increase of 17 ± 3.4. Such an improvement was mainly evident in those patients whose baseline C_{cr} was ≤ 50 ml/min ($n = 19$), since it changed from 38.1 ± 1.9 to 58.6 ± 4.4 ml/min ($p < 0.001$) with a mean increase of $56.2 \pm 10.5\%$. This was significantly greater than found in the cirrhotics with $C_{cr} > 50$ ml/min (from 86.7 ± 3.1 to 91.7 ± 3.2 ml/min, $p < 0.05$; increase: $8.9 \pm 2.9\%$, $p < 0.001$ with respect to patients with $C_{cr} \leq 50$ ml/min).

The C_{cr} increase found in patients receiving low-sodium diet (group A: $15.7 \pm 5\%$) was comparable to that of group B patients ($18.4 \pm 4.6\%$). However, patients with $C_{cr} > 50$ underwent a statistically significant increase of this variable only in group B.

Serum sodium concentration (Fig. 1) improved only in those patients whose baseline values were < 135 mmol/l ($n = 37$; from 130.9 ± 0.4 to 133.5 ± 0.7 mmol/l, $p < 0.001$; mean percentage increase: 2.1 ± 0.5). The extent of such an increase was similar in the two groups of patients (group A: $2.3 \pm 0.7\%$; group B: $1.6 \pm 0.6\%$, ns). No changes in

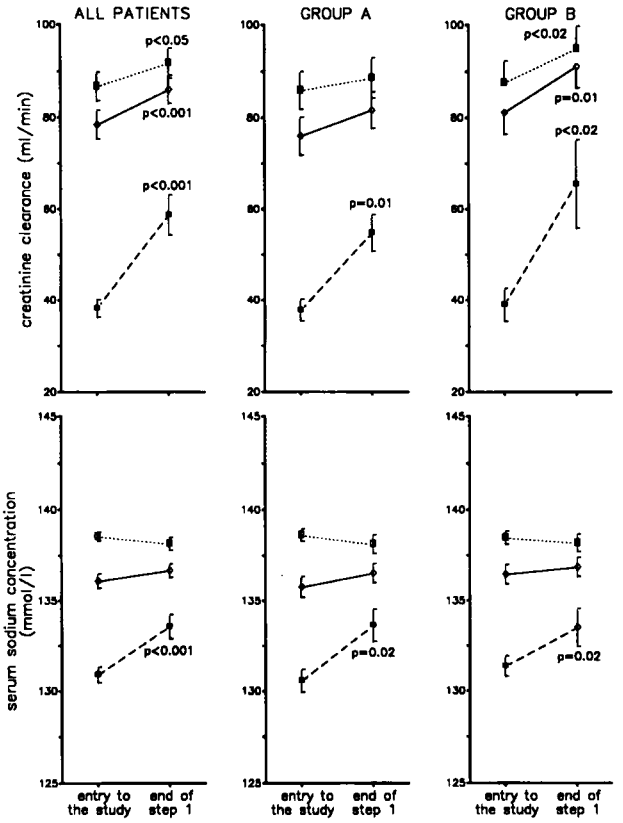

Fig. 1. Changes in endogenous creatinine clearance and serum sodium concentration which occurred during Step 1, corresponding to the period of washout from diuretics and bed rest. Data from the entire group of cirrhotics enrolled in the study (left panel), patients receiving 40 mmol of sodium/day (Group A, center panel) and patients receiving 120 mmol of sodium/day (Group B, right panel) are reported. Data are further presented in the whole group of patients belonging to each panel (o---o), in patients with baseline creatinine clearance ≤ 50 ml/min (■---■) and >50 ml/min (□···□), and in patients with serum sodium concentration <135 mmol/l (■---■) and ≥ 135 mmol/l (□···□). The levels of statistical significance of the changes which occurred during the washout period are indicated.

serum potassium concentration were found (group A: from 4.1 ± 0.05 to 4.1 ± 0.05 mmol/l; group B: from 4.2 ± 0.07 to 4.1 ± 0.06 mmol/l).

During Step 1, both renal sodium excretion and plasma aldosterone underwent reductions in both groups (Fig. 2). As under baseline conditions, these variables did not differ between groups A and B at the end of this period.

3. Overall efficacy of the diuretic administration (Table 4)

One hundred and eleven patients reached the end of the protocol. One developed severe hepatic encephalopathy during the washout period and one underwent gastrointestinal hemorrhage due to bleeding from esophageal varices during Step 2B. Diuretic side effects led to treatment withdrawal in two further cases, who developed severe hyponatremia and renal failure, respectively, during Step 3. By the end of diuretic treatment (Step 3), 107 (93%) patients showed a successful response. Thus, refractory ascites, as defined above, occurred in six cases (5.2%). At the end of Step 2A (K-canrenoate 200 mg/day) the therapeutic success was reached in 57 patients (49.6%); the further dose increases up to 600 mg/day (Step 2B) allowed us to reach a satisfactory therapeutic result in 89 cases (77.4%). It should be pointed out that with the dosage of 400 mg/day up to 79 patients (68.7%) had already achieved a satisfactory response.

4. Factors influencing the success rate of the stepped care medical treatment

Univariate analysis showed that C_{cr}, urine sodium, natremia, and plasma aldosterone concentration

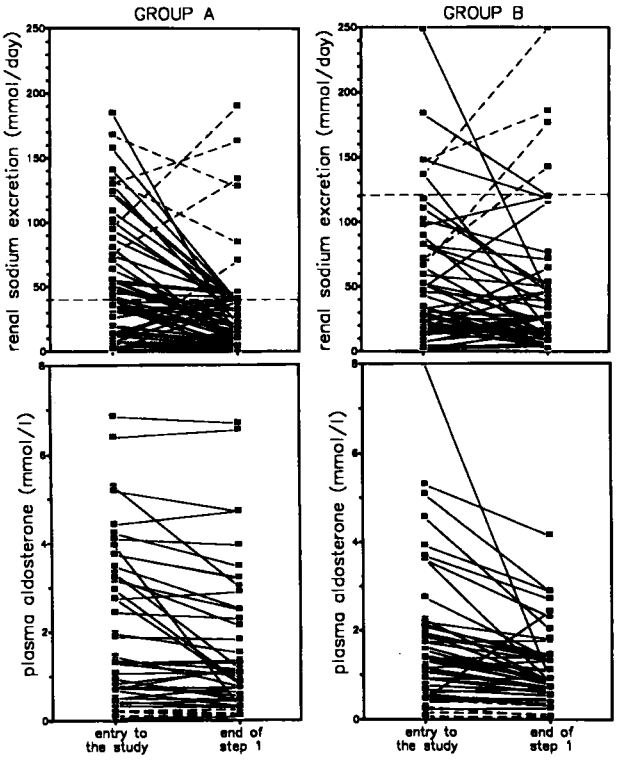

Fig. 2. Individual changes in renal sodium excretion (*top panels*) and plasma aldosterone concentration (*bottom panels*) which occurred during Step 1, corresponding to the period of washout from diuretics and bed rest. Dashed lines identify patients with spontaneous diuresis. The amounts of sodium provided by the two diets are also indicated. Renal sodium excretion decreased from 52 ± 4.2 to 31.5 ± 4.9 mmol/day ($p=0.002$) in group A and from 60.2 ± 5.0 to 49.4 ± 4 mmol/day (n.s.) in group B; plasma aldosterone decreased from 2.08 ± 0.27 to 1.67 ± 0.25 mmol/l ($p=0.011$) in group A and from 1.80 ± 0.24 to 1.17 ± 0.15 mmol/l ($p=0.008$) in group B.

were significantly associated with the observed response (Table 5). Multivariate analysis showed that only C_{cr} (standardized estimate +0.37; p=0.006) and plasma aldosterone (standardized estimate −0.26; p=0.04) were independently associated with the observed response to treatment, the former having a greater influence on the response to treatment. The signs of the estimates indicated that the greater C_{cr} and the lower plasma aldosterone, the better the response to treatment. The predictive performance of the final selection model (% of observation) was: concordant=70.3%, discordant=27.6% and tied=2.1%.

In order to achieve additional information that could be transferred to clinical practice, further analysis was carried out. By dividing the whole group of patients according to the baseline C_{cr} (≤ 50 and >50 ml/min), cirrhotics with lower C_{cr} more often reached Step 3 (36.8 vs 11.9%; $p<0.05$). Such different behavior was confined to patients in group A, while no differences were found when patients belonging to group B were analyzed (Fig. 3). It should be noted that no patients with C_{cr} ≤ 50 ml/min underwent spontaneous diuresis, irrespective of the diet received.

None of the patients with baseline plasma aldosterone concentration >0.5 mmol/l (56% of cases) underwent spontaneous diuresis. They required either high doses of K-canrenoate (Step 2B; 42.4 vs 17.6%) or reached Step 3 more often (23.4 vs 11.8%) than those with plasma levels ≤ 0.5 mmol/l ($p<0.005$). Among the patients with plasma aldosterone concentration >0.5 mmol/l, those who developed a negative sodium balance by Step 2B had a higher C_{cr} (74.8 ± 4.4 ml/min) than those requiring furosemide administration (43.3 ± 3.5 ml/min; $p<0.001$). Finally, all the cirrhotics with refractory ascites had plasma aldosterone concentration >0.5 mmol/l.

Table 5. Results of the univariate analysis showing the association of the observed response to treatment with factors (covariates) considered in the whole group of patients (n=115)

Variable	χ^2 value	p value
Creatinine clearance	11.06	0.0009
Plasma aldosterone concentration	7.15	0.0075
Urine sodium concentration	5.74	0.0166
Serum sodium concentration	4.82	0.0281
Serum potassium concentration	1.49	0.2219
Hemoglobin level	1.37	0.2414
Serum-ascites albumin gradient	0.71	0.3993
Child-Pugh class	0.48	0.4885
Ascites albumin concentration	0.42	0.5157
Serum albumin concentration	0.34	0.5602
Age	0.08	0.7772

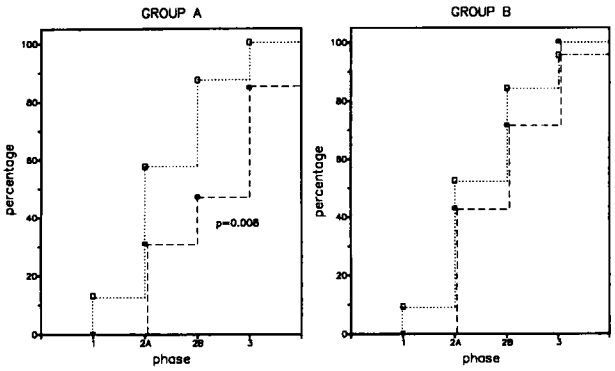

Fig. 3. Cumulative success rate at each step of the study in patients receiving 40 mmol (Group A) and 120 mmol of sodium/day (Group B), sub-grouped according to baseline creatinine clearance: ≤ 50 ml/min (■---■) and >50 ml/min (□···□). In Group A, a different distribution of the success rate with respect to Group B was disclosed (p=0.008).

5. Changes observed during treatment

By comparing the values of C_{cr}, serum sodium concentration and plasma aldosterone measured at the end of each step with the corresponding baseline values, no significant differences were found. Serum potassium concentration underwent a statistically significant increase in both groups, peaking at the end of Step 2B (group A: from 4.1 ± 0.05 to 4.4 ± 0.1 mmol/l, $p<0.005$; group B: from 4.2 ± 0.07 to 4.6 ± 0.06 mmol/l, $p<0.001$). In no case, however, did hyperkalemia develop.

In 13 cases, serum sodium concentration <130 mmol/l (minimum value: 126 mmol/l) was detected at baseline or appeared, either transiently or steadily, during treatment. These patients continued to follow the protocol: a successful response to treatment occurred at Step 2A in one patient, at 2B in three, and at Step 3 in five. The remaining four had refractory ascites because of no response at the end of Step 3. In one further case, as reported under paragraph 3, progressively increasing hyponatremia up to 120 mmol/l was considered a diuretic side effect and led to treatment withdrawal.

Discussion

This study confirmed that stepped care medical treatment of ascites in cirrhosis, evaluated in the short-term, is highly effective and safe. In fact, as a whole, it led to a satisfactory clinical response in 93% of cases, also taking into account that two withdrawals from the protocol were due to complications not attributable to the treatment. Thus, refractory ascites was only observed in 5% of patients. Such an incidence is lower than that reported by other studies (9), but it should be pointed out that patients with either renal or severe liver

failure, who often exhibit refractory ascites (2, 3), were excluded from the protocol. Based on the present experience, 68% of cirrhotic patients admitted to our units were candidates for this treatment. Since all the units involved in the study act as both community and tertiary referral centers, it is likely that a higher percentage of patients might be suitable for this treatment in general practice.

One of the goals of the study was to evaluate the usefulness of low-sodium diet in the management of cirrhotics with ascites. Our data demonstrated that sodium restriction was not associated, in the short term, with a better overall response to treatment as defined by the criteria used in the present investigation. These results confirm data from other studies, where different protocols were employed (4, 5). Moreover, the incidence of spontaneous diuresis was also similar in the two groups of patients. It cannot be excluded, however, that over a period longer than 1 week the trend towards a greater number of patients with spontaneous diuresis seen in group A might have become more evident. Since the use of a low-sodium diet should, theoretically, make the achievement of a negative sodium balance easier, this finding may be surprising and deserves comment. Along with aldosterone, renal perfusion and C_{cr} are the main factors modulating renal sodium handling in cirrhosis (10, 11). Spontaneous diuresis only ensued in patients with $C_{cr} > 50$ ml/min and plasma aldosterone concentration ≤ 0.5 mmol/l, suggesting that a preserved C_{cr} and the absence of severe secondary hyperaldosteronism are needed for the occurrence of this event. Only the diet providing 120 mmol of sodium/day led to a significant increase of C_{cr} in this subset of patients. Thus, the increase in filtered sodium load may have balanced the need to excrete a higher amount of sodium by patients of Group B.

In the present study, a low-sodium diet did not even allow us the use of lower diuretic doses to achieve a negative sodium balance. Taking into account that the relationship between plasma aldosterone concentration and renal sodium excretion has the shape of a rectangular hyperbole (12), the effect of the progressive aldosterone antagonism by anti-mineralocorticoid drugs cannot be expected to proceed in a linear way. Once effective hormone antagonism was reached, the increase in sodium excretion was of such a magnitude that it is likely that the difference of 80 mmol/day between the diets used in this study did not significantly influence the clinical response to treatment.

This study outlined the usefulness of a washout period from diuretics in improving renal function, particularly in patients presenting a poor glomerular filtration rate. Several factors could contribute to the increase of C_{cr}. First, the withdrawal of diuretic treatment, which was followed by more than 70% of patients before entry to this study. Also, the fact that hospitalization usually coincides with a greater time spent in the supine position. This may be crucial, since posture can have a great effect on the renal function of patients with cirrhosis and ascites by influencing systemic hemodynamics and the activities of the renin-aldosterone axis and the sympathoadrenergic system (13, 14).

The progressive, cumulative success rate achieved by using incremental doses of K-canrenoate was an expected finding (8) and shows that refractoriness to diuretic treatment cannot be assumed if low doses of antimineralocorticoids are employed. It should also be noted that the use of doses up to 400 mg/day led to a therapeutic success in most patients developing a negative sodium balance under K-canrenoate treatment. Further adjustments in the upper range of dosage can only provide a relatively small increase in the success rate, prolonging hospitalization and, possibly, favoring the occurrence of side-effects. Thus, 400 mg/day can be regarded as the maximal anti-mineralocorticoid dosage to be reached before the addition of loop diuretics. Whether this may also be true for long-term maintenance regimens has to be established.

Among the factors which can potentially affect the success rate of the medical treatment, C_{cr} and plasma aldosterone concentration proved to be independent predictive factors of the response to treatment. Both factors affect renal sodium handling. The former, by lowering the filtered load of sodium, enhances proximal sodium reabsorption (15), thus explaining refractoriness to K-canrenoate used alone. Marked hyperaldosteronism, as expected (8), would require high doses of antimineralocorticoid (step 2B) to counteract sodium reabsorption at the distal nephron. The need for furosemide in a number of patients with high plasma aldosterone levels was likely linked to the concomitant reduction in glomerular filtration rate. It has also recently been shown that exaggerated sodium reabsorption at the proximal convoluted tubule may be a cause of resistance to spironolactone treatment in patients with severe hyperaldosteronism and fairly well preserved renal function (16).

It should be noted that the lower success rate disclosed in patients with poor C_{cr} was confined to those receiving the low-sodium diet, suggesting that, in such a context, the avoidance of sodium restriction might prove to be beneficial.

The stepped care medical treatment used in this study was associated with a very low incidence of diuretic-induced side effects, since only two pa-

tients experienced either severe hyponatremia or pre-renal uremia. This contrast with other experiences, where diuretic-induced uremia and hyponatremia were far more frequently recorded, ranging from 5 to 27% of cases (7, 9, 17–19). Thus, the cautious administration of diuretics through a slow progressive dosage increment in order to avoid over-diuresis (20) is mandatory for the safe treatment of cirrhotic ascites. It should be pointed out that the results of this study were obtained in a selected in-patient setting, during a relatively short period of time. Whether similar results could be expected from long-term maintenance regimens in out-patients would require further investigation.

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