Liver and biliary

Salt or no salt in the treatment of cirrhotic ascites: A randomised study

A GAUTHIER, V G LEVY, A QUINTON, H MICHEL, B RUEFF, L DESCOS, J P DURBEC, J FERMANIAN, S LANCRENON, AND THE ENTAC GROUP*

From the Clinique d'hépatogastro-entérologie, Hôpital de la Conception, Marseille, Service d'hépatogastro-entérologie A, Hôpital Saint-Antoine, Paris, Services des maladies de l'appareil digestif, Hôpital Saint-André, Bordeaux, Clinique des maladies de l'appareil digestif, Hôpital Saint-Eloi, Montpellier, Service d'hépatogastro-entérologie, Hôpital Beaujon, Clichy, Service d'hépatogastro-entérologie et médecine interne, Hôpital Edouard Herriot, Lyon, INSERM U 31, Hôpital Sainte-Marguerite, Marseille, and INSERM U 88, Hôpital de la Pitié, Paris, France

SUMMARY To compare the effect of diet, cirrhotic patients with ascites were randomised into two treatment groups: (1) a low sodium diet (21 mmol) per day or (2) an unrestricted sodium intake. Both groups received effective doses of diuretics (spironolactone or, if necessary, spironolactone and furosemide). One hundred and forty patients from 12 liver units were included according to well defined criteria (group 1: 76; group 2: 64). After an initial four to seven day period of bed rest and salt restriction (21 mmol sodium pd), randomisation was done in each centre. We saw no significant difference between the two groups with respect to (1) clinical and biochemical data; (2) mortality or withdrawal (definitive or temporary) because of biochemical disturbances (group 1: 34%, group 2: 22%); (3) the time for complete disappearance of ascites was significantly shorter ($p=0.014$) for the salt restricted patients (4) actuarial survival (curves plotted up to the 120th day) was not statistically different ($p=0.18$), but division into subgroups using various prognostic factors showed that survival was significantly better for salt restricted patients without previous gastrointestinal bleeding ($p=0.02$); (5) hospitalisation time and costs were identical in both groups. We conclude that the advantage of a normal salt diet was not shown in this study.

The treatment of cirrhotic ascites usually includes a salt restricted diet and the prescription of diuretics.^{1–3} This treatment often results in clinical complications⁴ – that is, cramps, loss of appetite with consequent nutritional deterioration and/or biochemical abnormalities, hyponatremia, uraemia, hypo or hyperkalemia. It has been suggested that a normal salt diet would prevent the occurrence of short term electrolytic and renal disorders.⁵ This was not confirmed, however, by work subsequently carried out in 33 French liver units.⁶ Our study was undertaken to test the following hypotheses: (a) An

unrestricted diet in association with diuretics decreases the occurrence of short term (14 days) biochemical complications. (b) By increasing appetite, such a diet will improve nutrition and increase medium term (90 days) survival.

Methods

Twelve liver units took part in this study. The patients included had alcoholic cirrhosis, confirmed by the usual clinical and biological data: detection of hepatomegaly, spider naevi, oesophageal varices, ascites confirmed by paracentesis, serum albumin below 30 g/l. Quick time – that is, prothrombin time expressed as a percentage of prothrombin time of control subject, below 60%, observation of cirrhosis by laparoscopy and/or liver biopsy.

Ascites was confirmed by a 20 ml abdominal paracentesis enabling examination of ascitic fluid for

Address for correspondence: Professor A Gauthier, Hôpital de la Conception, 13005 Marseille, France.

*The ENTAC Group: National Inquiry for the Treatment of Cirrhotic Ascites. Co-investigators: P Bergerault (Vannes), M Bouvry (Pontoise), J P Capron (Amiens), J L Consigny (Chalon-sur-Marne), H Fraisse (Saint-Etienne), J Lafon (Aix-en-Provence), J Leblanc (Cannes), B Liberelle (Grenoble), J Roche (Grenoble).

cytology and bacteriological culture. Patients included were estimated, by clinical examination, to have at least four to five litres of ascitic fluid.

EXCLUSION CRITERIA

Patients were excluded for the following reasons: if below 20 years of age, the inability to attend regular follow up, the requirement of emergency treatment, the presence of chronic hepatic encephalopathy, haemorrhagic ascites (macroscopic appearance), tuberculosis, or extra hepatic cancer, the development of hepatocellular carcinoma during the study, a positive HBs antigen and temporary exclusion criteria persisting for more than three weeks.

Patients having one of the following disorders were temporarily excluded: gastrointestinal bleeding, acute hepatic encephalopathy, a temperature greater than 38°C, infected ascites (more than 300 leukocytes/mm³), diarrhoea, blood urea greater than 8.3 mmol/l, plasma sodium less than 130 mmol/l, plasma potassium concentration less than 3.5 or greater than 5.5 mmol/l, serum bilirubin greater than 85 µmol/l.

TREATMENT

Patients were observed initially during a four to seven day period of bed rest. Salt intake was restricted to 21 mmol and water to one litre per day. The patient was then either randomised to a treatment group, definitively excluded, or temporarily excluded. If temporarily excluded, the observation period was extended one or two weeks. If exclusion criteria remained applicable at three weeks, the patient was definitively excluded.

Both therapeutic protocols included diuretics, and differed only in diet. In group 1, sodium intake was restricted to 21 mmol/day and in group 2, it was unrestricted. The diuretics, spironolactone (Aldactone®) and furosemide (Lasix®) were used in four day increments as follows: initially 200 mg of spironolactone, increased if weight loss was less than 1 kg in total over the preceding four day period to 400 mg and then to 600 mg. If 600 mg of spironolactone was insufficient, 40 mg of furosemide was added and if necessary, increased to 80 mg. Medication was given once daily for the starting dose and if increased, divided into a twice daily regimen.

The following data were collected twice a week: weight, abdominal girth, urine volume, adverse effects of treatment, blood urea, and plasma/urine ratios of sodium and potassium. Treatment was interrupted whenever the patient's weight dropped by more than 1 kg/day, when gastrointestinal bleeding or diarrhoea occurred, if blood urea was greater than 13 mmol/l or plasma sodium below 125 mmol/l. Treatment was resumed if these dis-

orders disappeared within one week. If these abnormalities persisted for longer than one week, recurred on restarting treatment, or if treatment proved ineffective at maximum diuretic dosage patients were withdrawn and prognosis considered unfavourable.

Results were assessed on the 14th day and after three months. The assessment criteria were: disappearance of ascites assessed by clinical examination (complete disappearance, disappearance followed by relapse, partial disappearance, no disappearance), change in weight and abdominal girth, survival, assessment of nutritional status (clinically assessed as normal or obese, moderate malnutrition, severe malnutrition), appetite, the occurrence of cramps and biological tolerance – that is, biochemical parameters remaining within range specified above.

STATISTICAL METHODS

Patients were randomised between the two therapeutic protocols with stratification by centre. Mean and standard deviation were used to describe quantitative variables (our results are listed as mean $\pm$ SD in the Tables) and the two therapeutic protocols were compared by Fisher test. Percentage and χ^2 test were used to describe and compare the two therapeutic protocols for qualitative variables. For comparison of the prothrombin level, the Mann and Whitney test was used (non-parametric statistic).

Survival curves were calculated according to the method of Kaplan and Meier,⁷ Log Rank test⁸ was used to evaluate differences in survival curves. The factors likely to influence survival such as sex, age, nutritional status, previous gastrointestinal bleeding, pretreatment before randomisation were analysed.

Table 1 Clinical data before treatment

	Salt restricted diet	Unrestricted diet	
Patients (no)	76	64	
Age (years)	58.2 $\pm$ 9.5	57.3 $\pm$ 11.7	NS
Men (%)	74	83	NS
Weight (kg)	69.5 $\pm$ 12	67.9 $\pm$ 12.5	NS
Abdominal girth (cm)	102 $\pm$ 10	100 $\pm$ 12	NS
Gastrointestinal bleeding (%)	21	17	NS
Nutritional status			
Normal or obese (%)	45	42	
Moderate malnutrition (%)	47	44	NS
Severe malnutrition (%)	8	14	
Appetite			
Good (%)	27.6	35	
Medium (%)	62	55.5	NS
Poor (%)	10.4	9.5	

Results

One hundred and forty patients were included in the study: 76 had a salt restricted diet and 64 had an unrestricted diet. There were no significant differences before treatment between each group with respect to clinical (Table 1) and laboratory data (Table 2).

Patient follow up withdrawal and deaths are summarised in Figure 1. There were no significant

differences between the groups in withdrawal rate, or in the incidence of temporary interruption of the treatment (34% in group I, 22% in group II). The main clinical and biochemical data on the 14th day are shown in Table 3, and on the 90th day in Table 4.

SURVIVAL

Crude survival and actuarial curves were compared for the two groups. (a) Crude data: at 90 days, there

Table 2 Biochemical data before treatment

	Salt restricted diet	Unrestricted diet	
Patients (no)	76	64	
Serum bilirubin ($\mu\text{mol/l}$)	40.5 ± 26	34.5 ± 18.5	NS
Serum albumin (g/l)	28.5 ± 5	27.4 ± 4.5	NS
Prothrombin time expressed as a percentage of normal	Median: 53 Ranges: 27–100	Median: 56.5 Ranges: 25–100	NS
Aspartate amino transferase			
Normal (%)	41	45	
2 to 4×normal (%)	54	50	NS
More than 4×normal (%)	5	5	
Serum sodium (mmol/l)	136 ± 3	135 ± 4	NS
Serum potassium (mmol/l)	3.8 ± 0.5	3.8 ± 0.5	NS
Blood urea (mmol/l)	3.7 ± 1.7	4 ± 1.7	NS
Urinary excretion (mmol/24 h)			
Sodium	23.9 ± 36.6	38.3 ± 58.7	NS
Potassium	26.7 ± 25.8	33.5 ± 32.3	NS

Table 3 Clinical and biochemical data on 14th day of treatment

	Salt restricted diet	Unrestricted diet	
Patients under treatment	74	61	
Ascites			
Complete disappearance (%)	42	23	NS
Partial disappearance (%)	57	60.6	NS
No disappearance (%)	1	16.4	$p < 0.01$
Loss of weight (kg)	8 ± 4.3	5.4 ± 4	$p < 0.001$
Decrease in abdominal girth (cm)	9.9 ± 6	5.8 ± 4	$p < 0.001$
Appetite			
Equal or less (%)	63.5	82	
Improve (%)	36.5	18	$p < 0.02$
% of patients taking maximum spironolactone dose	12	26	$p < 0.04$
Blood urea (mmol/l)	4.7 ± 2.2	5.3 ± 5.7	NS
Difference 14th day – 1st day	$*1 \pm 1.8$	$*0.7 \pm 1.6$	NS
Serum sodium (mmol/l)	132 ± 4	133 ± 4	NS
Difference 14th day – 1st day	$\dagger 4 \pm 4.3$	$\dagger 2.4 \pm 3.6$	S ($p = 0.025$)
Serum potassium (mmol/l)	4.5 ± 0.5	4.3 ± 0.4	NS
Difference 14th day – 1st day	$*0.6 \pm 0.6$	$*0.5 \pm 0.5$	NS
Urine volume (ml/24 h)	$*699 \pm 674$	$*521 \pm 654$	NS
Urine sodium (mmol/24 h)	84.7 ± 117.5	99 ± 129.4	NS
Urine potassium (mmol/24 h)	$*29.4 \pm 44.9$	$*17.6 \pm 50.5$	NS

* representing an increase.

† a decrease from the initial value.

Fig. 1 Outcome during follow up for 140 patients in the treatment groups

were six deaths in the salt restricted groups, versus 11 deaths in the unrestricted diet ($p=0.15$). (b) Actuarial survival: curves were plotted up to the 120th day: the difference between the two groups is not statistically significant ($p=0.18$) (Fig. 2). The survival curves were compared between the two groups described in the protocol and also to subgroups defined by the various prognostic factors listed above. Among these, the only significant result was seen in the patients without previous gastrointestinal bleeding, in favour of salt restricted protocol ($p=0.02$) (Fig. 3). In this subgroup of patients, there was no difference in initial clinical and laboratory data between the two therapeutic protocol groups.

HOSPITALISATION AND COSTS

These were identical in both groups: 27.9 ± 14.8 days in group I, against 27.4 ± 15.1 in group II. Cumulative drug doses were not significantly different at three months.

Fig. 2 Actuarial curves of survival according to diet for total population

Fig. 3 Survival curves according to diet for the 113 patients with no gastrointestinal bleeding before study

Table 4 Clinical and biochemical data for patients under treatment on 90th day

	Salt restricted diet	Unrestricted diet	
Patients (no)	52	40	
Ascites disappearance			
Complete (%)	59.6	52.6	
Complete with relapse (%)	25	34.2	NS
Partial drying or failure (%)	15.4	13.2	
Loss of weight (kg)	5.9 ± 6.9	6.8 ± 5.6	NS
Decrease in abdominal girth (cm)	12 ± 9	11 ± 7	NS
Appetite			
Equal or less (%)	51.9	50	
Improved	48.1	50	NS
Nutritional status			
Equal or less (%)	71	67.5	
Improved	29	32.5	NS
Increase in blood urea (mmol/l)	$+2.14 \pm 5$	$+0.5 \pm 2$	NS
Serum sodium (mmol/l)	135.5 ± 4.3	133.4 ± 5.3	NS
Difference 90th day - 1st day	-0.6 ± 4.3	-2 ± 6	NS
Serum potassium	4.1 ± 0.5	4.2 ± 0.6	NS
Difference 90th day - 1st day	$+0.27 \pm 0.8$	$+0.52 \pm 0.7$	NS
Albumin (g/l)	32 ± 6	31.2 ± 6.6	NS
Difference 90th day - 1st day	$+3.5 \pm 7$	$+3.8 \pm 6$	NS

Discussion

The study compared a 21 mmol sodium diet and an unrestricted diet, associated with diuretics, in the treatment of cirrhotic ascites. The sodium balance was determined for each therapeutic group from salt input and output. It correlated with the observed weight loss for salt restricted patients on the 14th day and estimated a mean sodium intake for patients on a free diet of between 51 mmol and 68 mmol/day. Therefore an unrestricted diet, at least in hospital, for ascitic and probably anorectic patients, is a moderate and not a normal salt intake.

TREATMENT EFFICACY

At day 90, the resolution of ascites is identical in both groups. Disappearance of ascites occurs faster with a salt restricted diet, however, than with a free diet. This is shown by significant differences at day 14 in the number of patients without ascites, and by weight and abdominal girth differences. These differences are not found at three months (day 90). Actuarial curves of disappearance time of ascites also confirm these findings. The nutritional status that we hoped would be improved with a free, appetising diet is identical in both groups. Paradoxically, appetite seems to increase most often for salt restricted patients on the 14th day. This improvement could be related to a larger ascitic reduction in this group at this date.

TOLERANCE

Tolerance is also identical: the number of withdrawals because of biochemical disturbances during treatment, or cirrhotic complications, is similar in both groups at the 14th day and at the 90th day. Biochemical changes are similar except for a marked hyponatremia on the 14th day for salt restricted patients. This hyponatraemic tendency reported by Reynolds,¹ is however, in this study, a transient phenomenon noted at the beginning of treatment. In contrast, the marked increase in blood urea, reported by Reynolds for salt restricted patients, was not found.

SURVIVAL

The salt restricted diet tends overall to improve survival ($p=0.09$). Survival is statistically better with salt restriction for the subgroup of patients without previous gastrointestinal bleeding. The reasons why are unclear. In fact, these positive findings could be due to chance considering the repeated tests used. Moreover we could not find any explanation of this unexpected favourable effect of the salt restricted diet. This result, however, has to be confirmed in a further prospective study.

TREATMENT COSTS

Although ascites disappear significantly faster with a salt restricted diet, this has no effect on hospitalisation time (taken as an essential cost factor in this work). Drug dosage, which also affects treatment costs, does not differ significantly.

We have compared the effects of a salt restricted diet and a free salt diet, associated with diuretics, for the treatment of medium severity ascites in alcoholic cirrhotics. With an unrestricted diet, decrease of serum sodium concentration is less marked but the disappearance of ascites is also less frequent, or less significant, in the patients at 14 days. Ascite disappearance, appetite, and nutritional status are identical at three months. The beneficial effects of a salt restricted diet seen at 14 days on the following parameters weight loss, abdominal girth, clinical assessment of ascites disappearance, and appetite are transient. There is no significant difference between the two groups at three months. In conclusion, we have demonstrated a transient beneficial effect of a salt restricted diet; although not statistically significant, there was a trend towards improved survival in this group. The advantages of a free diet, suggested by Reynolds *et al*¹⁵ were not confirmed in this study.

This study was supported by INSERM grant no 650.350. We thank Dr J Kennedy for translating the manuscript.

References

- 1 Editorial. Management of hepatic ascites. *Lancet* 1978; **1**: 311-12.
- 2 Gregory PB, Fogel MR, Sawhney V, Knauer CM, Miller R. Diuresis in the ascitic patient: which is more potent, furosemide or spironolactone? *Gastroenterology* 1979; **76**: 1145.
- 3 Quintero E, Gines P, Arroyo V, *et al*. Paracentesis vs diuretics in the treatment of cirrhotics with tense ascites. *Lancet* 1985; **1**: 611.
- 4 Sherlock S, Seneviratne B, Scott A, Walker JG. Complications of diuretic therapy in hepatic cirrhosis. *Lancet* 1966; **1**: 1049-52.
- 5 Reynolds TB, Lieberman FL, Goodman AR. Advantages of treatment of ascites without sodium restriction and without complete removal of excess fluid. *Gut* 1978; **19**: 549-53.
- 6 Descos L, Gauthier AP, Levy VG, *et al*. Comparison of six treatments of ascites in patients with liver cirrhosis. *Hepatogastroenterology* 1983; **30**: 15-20.
- 7 Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Statist Assoc* 1958; **53**: 457-81.
- 8 Peto R, Peto J. Asymptotically efficient rank in variant test procedures. *J R Statist Soc Ser A* 1972; **135**: 185-207.