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ORIGINAL PAPER

Terlipressin and Albumin in Patients with Cirrhosis and Type I Hepatorenal Syndrome

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Abstract *Purpose*: Hepatorenal syndrome (HRS) is a pre-renal-like dysfunction that generally onsets in cirrhotic patients presenting ascites. We investigated the improvement of renal function in subjects with hepatorenal syndrome after terlipressin administration and the survival times after this treatment. Fifty-two patients affected by cirrhosis, with diagnosis of hepatorenal syndrome were treated with intravenous terlipressin plus albumin (group A) or with albumin alone (group B). Liver and renal function, plasma renin activity, and aldosterone plasma levels were monitored. *Results*: Patients from group A showed a significant improvement ($p < 0.001$) of renal function valued by creatinine rate compared with the results obtained in group B. The probability of survival was higher in the group A ($p < 0.0001$). *Conclusions*: Our results seem to confirm that the administration of terlipressin plus albumin improves renal function in patients with cirrhosis and type I HRS and that a reversal of hepatorenal syndrome is strongly associated with improved survival.

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Introduction

Hepatorenal syndrome (HRS) is an acute or subacute pre-renal-like dysfunction that generally onsets in cirrhotic patients presenting ascites, but may also appear during other chronic liver diseases in the presence of portal hypertension [1–3]. HRS is generally characterized by increased creatinine and azotemia concentrations, reduced diuresis, increased urine osmolarity and reduced urine sodium values without signs of organic kidney damage. HRS can be classified as type I and type II:

(a) Type I is the form typically associated in the past with the term of HRS. Left untreated, it carries a median survival of less than two weeks [1–7]; this is characterized by a rapid progressive reduction of renal function, defined by a doubling of the initial serum creatinine level to more than 2.5 mg/dl (221 micromoles/l) or a 50% reduction of initial 24 h creatinine clearance to a level of <20 ml/min in less than two weeks;
(b) Type II is a milder form that does not have a rapidly progressive course.

The International Ascites Club [2, 4] identified and classified major and minor criteria for diagnosis of HRS (Table 1): the former must be present to allow a diagnosis of HRS, while the latter only confirm this diagnosis. In recent years, treatment combining peripheral and/or splanchnic vasoactive drugs with volume expanders (e.g., albumin) has shown significant short-term efficacy, however HRS is a rare condition and it is difficult to conduct larger studies.

Table 1 Data collected in patients of group A (treated with terlipressin plus albumin) and group B (treated with albumin alone)

Group	A	B
Age (years)	59 ± 4	60 ± 3
Gender (F)	16	15
Gender (M)	10	11
Aetiology (alcohol)	3	4
Aetiology (viral hepatitis)	23	22
Duration of cirrhosis	9 ± 2	8 ± 2
Child-Pugh score	11.5 ± 1	11.2 ± 0.8
Serum creatinine (μmol/l)	248 ± 96	256 ± 105
Urine volume (ml/day)	571 ± 68	620 ± 54
Serum albumin (g/dl)	2.71 ± 0.32	2.68 ± 0.31
Serum ascites albumin rate	1.82 ± 0.36	1.78 ± 0.40
Serum sodium (mmol/l)	126 ± 5	126 ± 4
Serum potassium (mmol/l)	4 ± 0.2	4.1 ± 0.2
SBP, sepsis (number)	5	6
Unknown fever (number)	2	1
Gastrointestinal bleeding	None	None
Encephalopathy (number)	2	3
Previous paracentesis (number)	3	3
Diuretic therapy	22	23
Treatment with quinolones	None	None
Treatment with beta-blockers	4	6
Pulse rate/min	85.35 ± 9.4	88.32 ± 6.8
Central venous pressure (mmHg)	11 ± 1	10 ± 2
Mean arterial pressure (mmHg)	82 ± 2	89 ± 3
Natraemia (mEq/l)	<10	<10

There is not a significant difference ($p > 0.05$) between the values recorded in the two groups (SBP = spontaneous bacterial peritonitis)

In this paper we investigated a cohort of subjects with liver cirrhosis who came to our observation presenting reduced diuresis and renal failure with characteristic signs of HRS. The primary aim of this study was to investigate improvement of renal function during terlipressin administration. The secondary end point was to describe the possible side-effects of terlipressin and the times of survival after this treatment.

Materials and methods

We considered a total of 492 patients with cirrhosis (diagnosis was based on clinical, laboratory, and histological data), portal hypertension (diagnosis based on ultrasound and endoscopic findings) and tense ascites, who were admitted to three different units of internal medicine and hepatology at our university from December 2002 to December 2005. From this cohort we considered all patients with suspected HRS. After this diagnosis, diuretics were stopped as soon as renal failure was recognized and all patients were expanded with 1.5 l of saline solution. Infected patients were cured by antibiotic drugs before inclusion in the trial. We selected and studied 52 patients with diagnosis of type I HRS; patients were included in the study 52 patients with diagnosis of type I HRS established according to the International Ascites Club [1].

The exclusion criteria were: heart or respiratory failure, arterial hypertension, coronary and/or peripheral arterial disease, age > 75 years, or hepatocellular carcinoma.

The day of inclusion on the study was the first day of diagnosis of HRS. For inclusion, randomization divided eligible subjects at study start into group A and B individually and sequentially, in a 1:1 ratio from a computer-generated list (using SAS software version 6.12; SAS Institute Inc., Cary, North Carolina, USA): 26 subjects were assigned to treatment with terlipressin (group A) plus albumin and 26 to treatment with albumin alone (group B). We used a group of healthy subjects (all physicians and nurses at our hospital) to assess normal values of plasma renin activity and plasma aldosterone concentration. For ethical reasons a placebo group was not included in this study.

At the beginning of therapy all patients were monitored in a semi-intensive care setting with telemetry; the patients were instrumented with a central venous line. Blood

pressure was assessed non-invasively at regular intervals and cardiac rhythm was monitored continuously; urine volume was measured every 8 h. Blood samples were taken before the start of therapeutic protocol and daily, throughout treatment, to measure standard liver and renal function. Plasma aldosterone concentrations was measured using an RIA aldosterone kit (Immunotech SA, Marseille, France). Plasma renin activity was measured by immunoassay using Gamma Coat ^{125}I RIA plasma rennin activity RIT (Diarasin, Stillwater, MN, USA). We used intravenous boluses of terlipressin (Glipressin 0.5 mg; Laboratoires Ferring SpA, Milano, Italy) at the dose of 1 mg/8 h/5 days followed by 0.5 mg/8 h for two weeks plus albumin or intravenous boluses of albumin alone (Albumina Grifols 20%, 20 g of Albumin/100 ml; Barcelona, Spain). Albumin was given at a weight-based dosage (1 g/kg body weight during the first day and 20–40 g/day thereafter). In patients developing recurrence of HRS, terlipressin and albumin were administered again following the same schedule of the initial treatment. After hospital discharge, subjects were followed for three months as outpatients.

Definitions

- *Complete response*: decrease of serum creatinine to a value of 132 μmol/l (1.5 mg/dl) or lower, during treatment
- *Partial response*: decrease of 50% or greater of serum creatinine level compared with baseline values to a final value higher than 132 μmol/l (1.5 mg/dl)
- *No response*: increase or decrease of serum creatinine level of less than 50% compared with the baseline value to a final value higher than 132 μmol/l (1.5 mg/dl)
- *Recurrence*: increase of serum creatinine level of 100% or more with respect to the lowest value after therapy in subjects with complete response with a final value between 132 μmol/l (1.5 mg/dl) and 176 μmol/l (2 mg/dl) within the three-month follow-up period

At baseline, the Child-Plough score was calculated in all patients. Adverse effects to terlipressin administration were also recorded.

The study was approved by the institutional review board and ethics committee of the University of Catania and informed written consent was obtained from all the participants.

Statistical analysis

Standard descriptive statistics were used to analyze the characteristics of our cohort [mean ± standard deviation (SD), frequency, *t*-test]. Changes in serum creatinine during terlipressin administration were compared between patients with improved renal function and those without, by two-factor repeated-measures analysis of variance. We used the Pearson χ^2 test and Fisher exact test for qualitative variables. Variables reaching statistical significance in univariate analysis were included in a logistic regression model (multivariate analysis) using a software program to identify independent predictive factors of improved renal function. To assess the existence of predictive factors of survival we analyzed renal and liver function at baseline, as estimated by serum creatinine levels and Child-Plugh score. The probability of survival was estimated by the Kaplan-Meier method and compared with the log-rank test. Predictive factors of survival were analyzed by multivariate analysis using a Cox regression method. Statistical analysis of data was carried out using SPSS 11.5 (SPSS Production, Chicago, IL, USA). A two-tailed p value <0.05 was considered to be significant.

Results

The data collected from the clinical record at baseline are summarized in Table 1.

Cirrhosis was caused by viral hepatitis in 86% of patients without significant differences between the two groups. Diabetes mellitus was present in 48% of subjects. Baseline characteristics of our cohort are summarized in Table 1. Values for serum creatinine before the telipressin administration did not significantly differ between the two groups (248 ± 96 and 256 ± 104 μmol/l; $p > 0.05$).

Baseline values for plasma renin activity were similar in both groups (19.18 ± 11.72 ng/ml/h in group A and 20.01 ± 12.10 ng/ml/h in group B); these values were both higher than normal values (mean normal values 5.01 ± 1.68 ng/ml/h). Baseline plasma aldosterone concentrations did not differ between two groups (284.7 ± 48.2 ng/dl in group A and 274.4 ± 47.1 ng/dl in group B); these values were both higher than our normal values (184 ± 18.12). Only two of 26 patients given terlipressin developed side-effects (abdominal pain and suspected abdominal ischaemia) and required therapy to be stopped; all adverse events associated to terlipressin administration are recorded in Table 2. Total doses of albumin were similar in the two groups (44 ± 48 g/day in group A and 48 ± 50 in group B).

In group A 21 patients (80%) showed a complete response to the therapy, four patients (15%) showed a partial response, and one showed no response. In group B, five patients (19%) showed a complete response, 11 (16%) a partial response and 10 (30%) showed no response. Patients treated with terlipressin plus albumin showed a significant improvement, in mean overage, of renal function valued by creatinine (from 248 ± 96 to 112 ± 32 μmol/l)

Table 2 Renal function, systemic haemodynamics, activity neurohumoral system in patients receiving terlipressin plus albumin (group A) or albumin alone (group B) compared at baseline and at discharge

	Group A		Group B		*p*
	Baseline	Discharge	Baseline	Discharge	
Creatinine	248 ± 96	112 ± 32	256 ± 104	188 ± 43	<0.001
Plasma renin activity (ng/ml/h)	19.18 ± 11.72*	6.46 ± 1.24*	20.01 ± 12.10**	17.08 ± 7.12**	*<0.005 **>0.05
Plasma aldosterone (pg/ml)	284.7 ± 48.2*	64.3 ± 12.4*	274.4 ± 47.1**	234.3 ± 42.1**	*<0.0001 **>0.05
Urine volume (ml/24 h)	571 ± 68*	1.300 ± 250*	620 ± 70**	820 ± 154**	*<0.0001 **<0.05
Mean arterial pressure (mmHg)	72 ± 2*	81 ± 3*	68 ± 3**	76 ± 2**	*< 0.05 **< 0.05
Central venous pressure (cm H_2O)	11 ± 1*	15 ± 2*	10 ± 2**	13 ± 1**	*<0.05 **<0.05

* Statistical significance at baseline and discharge in Group A

** Statistical significance at baseline and discharge in Group B

compared with patients treated with albumin alone (from 256 ± 104 to 188 ± 43 μmol/l); changes of serum creatinine were significantly different ($p < 0.001$) between the two groups with worse values in patients treated with albumin alone ($p < 0.001$). At hospital discharge, mean values of serum sodium were higher than at baseline in both groups A and B (±138 and 134 mmol/l respectively) but significantly higher values were found in the group treated with terlipressin plus albumin.

In both groups A and B the body mass index (BMI) was lower at hospital discharge than at baseline. At discharge the mean plasma renin activity was significantly ($p < 0.05$) lower than at baseline in group A (6.46 ± 1.24 ng/dl/24 h) but did not significantly differ ($p > 0.05$) from the baseline values in group B (17.08 ± 7.12 ng/dl/24 h). At discharge the mean plasma aldosterone levels was significantly ($p < 0.05$) lower (64.3 ± 12.4 ng/dl) than the baseline in group A while the discharge values did not differ ($p > 0.05$) from baseline in group B (184 ± 34 ng/dl). The independent predictor factors of improved renal function were younger age ($p < 0.001$) and a Child-Pugh score no greater than 12 at study start ($p < 0.05$). Patients were followed up as outpatients until death, liver transplantation or until six months after discharge by clinical observation, evaluation of Child-Pugh score, and assessment of renal and liver function. The main causes of death were hypertensive bleeding (six patients), liver insufficiency (41), multiorgan failure (4), cerebral haemorrhage (1) without statistical difference between two groups. Mean arterial pressure and central venous pressure did not differ ($p > 0.05$) from baseline values in either group A or B. Patients were censored for the estimation of the probability of survival. In group A the estimated probability of survival was 87% at day 15, 72% at day 30, 67% at day 60, 54% at day 90, and 42% at day 180. In group B the estimated probability of survival was 53% at day 15, 42% at day 30, 21% at day 0, 18% at day 90, and 16% at day 180 (Fig. 1). Using univariate analysis and determining the *p* value by using the log-rank test, the probability of survival was significantly higher in the subjects of group A who had improved renal function during terlipressin therapy ($p < 0.0001$) (Fig. 1) with a significant statistical difference ($p < 0.05$) between the two groups (odds ratio 0.680, $p < 0.005$; 95% CI = 0.59–0.80). Using multivariate analysis the independent predictive factors of survival were improved renal function during terlipressin therapy ($r = 0.65$, $p < 0.001$) and a Child-Plough score of 12 or less at study start ($r = 0.78$, $p < 0.001$).

Discussion

Hepatorenal syndrome was considered a uniformly and rapidly fatal complication of end-stage liver disease for

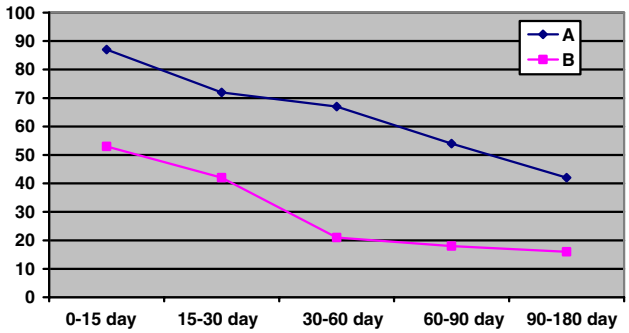

Fig. 1 The probability of survival was significantly higher in the subjects of group A who had improved renal function during terlipressin therapy ($p < 0.0001$)

many years. The best treatment for HRS is liver transplantation. However, in many Western countries, waiting lists for liver transplantation are steadily growing, so there is an increasing need to bridge severely sick patients to transplantation. Therapeutic concepts are needed to normalize renal function in patients with this syndrome.

Hepatorenal syndrome is generally regarded as a complication of end-stage liver disease but it may also onset during other chronic liver diseases [1–7]. The incidence of HRS in cirrhotic patients with ascites is around 8%, but there are peaks in cirrhotic patients presenting spontaneous bacterial peritonitis and in patients who undergo massive paracentesis during incorrect treatment for oesophageal vein haemorrhages [1–7].

The pathogenetic mechanism leading to HRS is vasoconstriction of the renal circulation, secondary to a marked arterial vasodilatation in the splanchnic vascular bed, leading a reduction in effective arterial blood volume with subsequent homeostatic activation of vasoconstrictor systems [4, 7, 8]. Type I HRS is acute, characterized by a rapid, sudden fall in glomerular filtrate and has a very high mortality rate at two weeks. Diversely, the drop in glomerular filtrate is minor and more gradual in type II HRS, where mean survival is higher and can reach weeks or months.

Splanchnic vasodilatation occurs in cirrhotic patients with ascites and determines hypovolemia caused by reflected renal vasoconstriction [3–4, 6–7]. In our work the mean plasma values of both aldosterone concentration and renin activity at hospital discharge differed significantly from their respective baseline values in both two groups; moreover these values were higher than the mean values of the control group; this confirms an effective decrease of arterial blood volume in our cirrhotic patients. This can represent the rationale for therapeutic use of a vasoconstrictor during HRS. At present, there are no drugs able to induce selective splanchnic vasoconstriction and hence improve renal haemodynamics. Results of nonrandomized studies in small series of patients with HRS suggest that long-term administration of the vasopressin analogue terlipressin may improve renal function but the management of this therapy remain is still being discussed [9–13]. Nevertheless administration of these vasopressin receptor VI antagonists, such as ornipressin and terlipressin, seems to achieve encouraging results [9–13]; other therapies using albumin plus vasoconstrictor agents such as noradrenaline seem to improve renal function in patients with HRS [14]. Ornipressin and terlipressin are usually used to treat oesophageal vein haemorrhages and may be able to augment renal perfusion and glomerular filtrate [8–13]. Some studies have shown that intravenous terlipressin and albumin are as effective in preventing a decrease in effective arterial blood volume in patients with cirrhosis treated by paracentesis for tense ascites [13, 15]. The limited number of cases cannot provide objective data that show which dose of vasoconstrictor can achieve positive results without causing side-effects; indeed, there are data which suggest that patients with a high Child-Pugh score (>11–13) may not respond to such treatment [11].

Our patients were progressively refractive to furosemide and spironlactone and hence their renal functions and general conditions deteriorated. Repeated treatment using lower daily doses of terlipressin over a longer period normalized creatinine concentrations, which remained stable over the four-month follow up. In our study, patients treated with terlipressin and albumin showed a greater improvement in renal function than patients treated with albumin alone. We administered terlipressin using lower doses over a longer period. This seems to have achieved better medium-term results without noteworthy side-effects. Although further studies are required, our results suggest possible positive results treating with low daily doses of terlipressin when HRS is suspected in patients with deteriorating renal functions who are progressively refractive to diuretic treatment.

Terlipressin was well tolerated in all patients and the incidence of adverse events during therapy was very low (Table 3). Only two of 52 patients included developed side-effects that required the therapy to be stopped. Other cardiovascular side-effects reported in the literature, such as hypertension and/or abnormalities of cardiac rhythm, were not observed. We have reported no difference in serum creatinine levels and natraemia at baseline between the patients of group A and B, but we have recorded a significant difference between group A and B at discharge, with lower sodium levels and worse values of creatinine levels in the group treated with albumin alone. Patients who showed a complete response survived longer than those who had a partial or no response.

In conclusion, our results seem to confirm the hypothesis that: (1) the administration of terlipressin plus albumin improves renal function in patients with cirrhosis and type I HRS; (2) the good results obtained in our patients can be due to a longer treatment period.

These findings are noteworthy and could be explored further in future studies.

Table 3 Adverse events during therapy

	Patients
Tachycardia	1
Chest pain	2
Diarrhoea	3
Abdomen pain	1
Bronchospasm	1
Peripheral ischaemia	1

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