Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome

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Background/Aim: Omnipressin, a vasopressin analog with potent splanchnic vasoconstrictor action, has been shown to reverse hepatorenal syndrome. However, its usefulness in clinical practice is limited by frequent ischemic complications. The aim of this study was to assess the efficacy of terlipressin, an analog of vasopressin with a low profile of side effects, plus albumin in this condition.

Methods: Nine consecutive patients with cirrhosis and hepatorenal syndrome were included in a pilot study of terlipressin (0.5–2 mg/4 h iv) therapy associated with iv albumin.

Results: Treatment (9 days, range 5–15) was associated with a marked reduction of serum creatinine (3.9±0.7 to 1.3±0.1 mg/dl, p<0.001, mean±SE). Reversal of hepatorenal syndrome (reduction of creatinine below 1.5 mg/dl) was observed in seven of the nine patients. There was a remarkable improvement in circulatory function, with an increase in mean arterial pressure (68±2 to 80±4 mmHg, p<0.05) and suppression of vasoconstrictor systems activity (plasma renin activity and plasma norepinephrine decreased from 23±12 ng/ml·h and 1549±373 pg/ml to 3.5±2 ng/ml·h and 373±98 pg/ml, respectively, p<0.01 for both). No patient developed signs of intestinal, myocardial or distal ischemia.

Conclusions: Terlipressin associated with albumin appears to be a safe and effective treatment of hepatorenal syndrome.

Keywords: Albumin; Ascites; Cirrhosis; Hepatorenal syndrome; Renal failure; Terlipressin; Vasopressin agonists.

THE MANAGEMENT of hepatorenal syndrome (HRS) constitutes a major challenge for clinicians (1). The best treatment for HRS is liver transplantation. However, this procedure is not available in all settings and not all candidates reach transplantation because of the short survival associated with HRS and the organ shortage. Therefore, there is a need for effective treatments for HRS that improve renal function and increase survival. Such treatments would be of interest not only as a bridge to liver transplantation but also as therapy for patients who are not candidates for transplantation.

Recently, it has been shown that the administration of ornipressin, a non-selective agonist of the V1 vasopressin receptors, with marked vasoconstrictor potency, improves renal function and reverses HRS (2,3). The rationale for the administration of this drug is to counteract the extreme splanchnic arterial vasodilation present in patients with cirrhosis and HRS. The vasoconstriction of the splanchnic circulation caused by ornipressin results in an improvement of circulatory function (i.e. increase in the effective arterial blood volume) which leads to a suppression of the activity of the vasoconstrictor systems (i.e. renin-angiotensin system and sympathetic nervous system) and subsequent increase of renal perfusion and glomerular filtration rate. In the two published studies on ornipressin therapy in HRS, patients were also given iv albumin either before or during the administration of the drug (2,3). Although there is no definite proof that albumin is required for the beneficial effect of ornipressin, it seems likely that albumin may contribute to the improvement of circulatory and renal function by increasing central blood volume.

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Despite its efficacy, the applicability of ornipressin administration in clinical practice is limited by the high incidence of severe side effects. In the two reports, five out of the 15 (33%) patients included required withdrawal of treatment because of ischemic complications (2,3). Terlipressin, which is also a non-selective V1 vasopressin agonist, may be an alternative to ornipressin because of a similar vasoconstrictor potency but a lower incidence of ischemic complications (4). So far, only sporadic case reports assessing the effects of terlipressin administration on renal function in patients with HRS have been published (5,6). Therefore, before planning a randomized controlled trial, it was considered important to perform a pilot study investigating the efficacy and safety of terlipressin associated with iv albumin in patients with cirrhosis and HRS. The effects of treatment on systemic hemodynamics and activity of vasoactive systems were also assessed.

Materials and Methods

Patients
Nine consecutive patients with cirrhosis and HRS admitted to the Liver Unit of Hospital Clinic of Barcelona were included in this investigation. Criteria for inclusion in the study were: type 1 HRS (six patients) or type 2 HRS with serum creatinine greater than 2 mg/dl (three patients). No patient meeting these inclusion criteria was excluded from the study. HRS was diagnosed using the criteria proposed by the International Ascites Club (7): 1) low glomerular filtration rate (GFR), as indicated by serum creatinine greater than 1.5 mg/dl; 2) absence of shock, ongoing bacterial infection, fluid losses and treatment with nephrotoxic drugs; 3) no improvement of renal function following diuretic withdrawal and plasma volume expansion; 4) proteinuria lower than 500 mg/day; and 5) no ultrasonographic evidence of parenchymal renal disease or urinary tract obstruction. Moreover, all patients had low urine output, very low urine sodium (<10 mEq/l), and urine osmolality greater than plasma osmolality. The study was approved by the Institutional Review Board of the Hospital Clinic of Barcelona and written, informed consent was obtained from all patients before the administration of treatment. In five patients the diagnosis of cirrhosis was based on histological data obtained before the diagnosis of HRS, while in the remaining four patients the diagnosis was based on clinical, biochemical and ultrasonographical findings.

The etiology of cirrhosis was alcoholic in four patients, anti-HCV positive in two, anti-HCV positive and alcoholic in two and crypto- genic in one. Six patients were male and three female. Median age was 54 years (range 42–75). All patients had moderate to severe ascites and six patients had hepatic encephalopathy (grade I in two, grade III in two, and grade IV in two) at the time of initiation of treatment. All patients had severe liver failure and a marked impairment in renal function, as indicated by high serum creatinine and BUN values, very low GFR, severe sodium retention and hyponatremia. Moreover, patients had markedly disturbed systemic hemodynamics, as indicated by arterial hypertension and overactivity of the renin-angiotensin-aldosterone system and the sympathetic nervous system (Table 1).

Study design
Once the diagnosis of HRS was made, patients were transferred to the Intensive Care Unit to ensure correct monitoring of vital signs and assessment of potential side effects of treatment. Patients were instrumented with a central venous line, a short cannula in a peripheral vein of the contralateral arm and a urinary bladder catheter. During the first days of treatment, arterial blood pressure was assessed non-invasively on an hourly basis (modular system Hewlett Packard model 56 S) and cardiac monitoring was performed continuously. Central venous pressure and urine volume were also measured every 4 h. Blood samples were taken before the start of therapy and daily or every 2 days throughout treatment to measure standard liver and renal tests. Plasma renin activity (PRA) and the plasma concentration of aldosterone, norepinephrine (NE) and atrial natriuretic peptide (ANP) were measured by RIA (3,8) in baseline conditions, 3 days after the initiation of treatment and at the end of treatment. Finally, GFR was assessed by measuring inulin clearance before and at the end of treatment, as described elsewhere (2). Terlipressin and albumin were given until the reversal of the HRS (decrease of serum creatinine below 1.5 mg/dl) or for a maximum of 15 days in case of no response to therapy. Patients showing a progressive reduction in serum creatinine and without associated complications requiring treatment in the Intensive Care Unit were then transferred to the regular ward where terlipressin and albumin treatment was continued. Terlipressin (Glypressin®, Ferring AB, Malmö, Sweden) was initially given as an iv bolus of 0.5 mg/4 h and increased in stepwise fashion every 3 days to 1 mg/4 h and 2 mg/4 h if a significant reduction in serum creatinine (equal to or greater than 1 mg/dl) was not observed. No vasoactive drugs other than terlipressin were given. Albumin (Seroalbumina Humana Grifols® 20 g of albumin per 100 ml, Instituto Grifols S.A., Barcelona, Spain) was given as an iv infusion at a dose of 1 g/kg during the first day and 20–40 g/day thereafter. Albumin infusion was stopped in patients showing an increase in central venous pressure above 15 cm H_2O.

Statistical analysis
The statistical analysis of the results was made using the paired Student’ t-test and Wilcoxon non-parametric test. Results are presented as mean ± standard error. p-values lower than 0.05 were considered as statistically significant.

Results
Eight out of the nine patients included in this protocol completed treatment with terlipressin and albumin. In the remaining patient treatment was discontinued on the fifth day of therapy, after renal function had improved (serum creatinine decreased from 4.5 mg/dl to 3 mg/dl), because of the development of acute pancreatitis. Table 1 shows the effects of terlipressin and albumin on liver and renal function, arterial pressure, heart rate, and vasoactive substances in all patients included (median duration of therapy 9 days, range 5–15). A remarkable improvement of renal function was observed during the administration of terlipressin and albumin. Serum creatinine values decreased markedly during treatment (Fig. 1). Likewise, BUN decreased and GFR increased by more than 3-fold with respect to basal values (Table 1). A reversal of HRS, as defined by a reduction in serum creatinine below 1.5 mg/dl, was observed in seven out of the nine patients. The dose of terlipressin given was 0.5 mg/4 h in four patients and 1 mg/4 h in the remaining three. The increased renal perfusion was associated with a significant increase in urine volume and serum sodium concentration. No significant changes were found in urine sodium concentration. There appeared to be no differences between patients with type 1 and type 2 HRS.
TABLE 1
Effects of terlipressin and albumin administration on renal function, systemic circulation, vasoactive factors and liver function in nine cirrhotic patients with hepatorenal syndrome (mean±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dl)</td>
<td>91±11</td>
<td>57±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>3.9±0.7</td>
<td>1.5±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium (mEq/l)</td>
<td>122±1</td>
<td>131±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.6±0.3</td>
<td>4±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min)*</td>
<td>8±2.4</td>
<td>24±3.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine volume (mlday)</td>
<td>710±101</td>
<td>1115±135</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum sodium (mEq/l)</td>
<td>3±1</td>
<td>7±1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>68±2</td>
<td>80±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate (bats/min)</td>
<td>81±4</td>
<td>83±5</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml · h)</td>
<td>23±12</td>
<td>3.5±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>342±73</td>
<td>89±29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>1549±373</td>
<td>373±98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial natriuretic peptide (fmol/ml)</td>
<td>108±19</td>
<td>158±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>32±2</td>
<td>38±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>14±6</td>
<td>15±7</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>48±5</td>
<td>43±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate. * Measured in seven patients.
Normal values of plasma renin activity, aldosterone, norepinephrine and atrial natriuretic peptide in our laboratory for healthy subjects on a low sodium diet are: 1.2±0.1 ng/ml · h, 24±2 ng/dl, 233±17 pg/ml, and 6±0.5 fmol/ml, respectively.

regarding the dose of terlipressin required to achieve a therapeutic response (0.5 mg/4 h in two patients with type 2 and two with type 1 and 1 mg/4 h in one with type 2 and two with type 1). Mean duration of treatment was 10.6 days in the four patients with type 1 and 7 days in patients with type 2. This difference was due to the fact the mean baseline serum creatinine was greater in patients with type 1 HRS compared with those with type 2 (mean±SEM: 4.8±0.8 mg/dl vs. 2.3±0.2 mg/dl, p=0.02).

The improvement in renal function was associated with a marked increase in arterial pressure and a suppression of the activity of the vasoconstrictor systems (Table 1). PRA and plasma aldosterone and norepinephrine concentration decreased to values close to those of healthy subjects at the end of treatment (Table 1 and Fig. 2). Plasma ANP levels increased significantly during therapy. As expected, serum albumin concentration increased significantly, whereas no significant changes were observed in serum bilirubin and prothrombin time. No side effects were observed during the administration of terlipressin, except for mild or moderate abdominal cramps associated with increased bowel movements in two patients. These symptoms resolved within a few hours despite the continuous administration of terlipressin and did not require specific therapy. No patient developed increased thirst.

Follow up
Three of the five candidates for liver transplantation were transplanted at 5, 12 and 99 days after the initiation of therapy and remained alive after a median follow-up of 390 days (128–530 days). None of these patients developed renal failure after transplantation. The other two patients died awaiting liver transplantation 30 and 121 days after inclusion in the study because of sepsis and liver failure. The four patients who were not transplant candidates (active alcoholism in two and old age in two) died after a median of 39 days (13–102 days). The main causes of death in these patients were gastrointestinal hemorrhage in two, and sepsis and liver failure in one patient each.

Following discontinuation of therapy, HRS did not
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Plasma Renin Activity (ng/ml-h)

Norepinephrine (pg/ml)

Fig. 2. Plasma renin activity (PRA) and plasma concentration of norepinephrine (NE) in the nine patients treated with terlipressin and iv albumin in baseline conditions (BL), at day 3, and at the end of treatment. Normal values of PRA and NE are: 1.2±0.1 ng/ml·h and 233±17 pg/ml.

Discussion

The results of the current investigation indicate that the administration of the vasopressin V1 receptor agonist terlipressin, associated with iv albumin, reverses HRS in patients with cirrhosis. This is in keeping with the results of two previous studies using ornipressin (ornithine-8-vasopressin), a drug with similar vasoconstrictor potency compared to the parent compound arginine vasopressin, the antidiuretic hormone, but with a much weaker water-retaining effect (2,3). Ornipressin treatment requires continuous iv administration because of its short half-life and is commonly associated with ischemic side effects in the splanchnic, muscular, and coronary circulations due to its marked vasoconstrictor action. In the current study, the agonist of the vasopressin receptors used was terlipressin (triglycyl-lysine-vasopressin), a synthetic derivative of vasopressin currently licensed in several countries for the management of acute variceal bleeding, which has a much greater effect on vascular vasopressin receptors (V1) than on renal vasopressin receptors (V2) (4). Terlipressin is inactive by itself but is transformed into the biologically active form, lysine-vasopressin, by the action of tissue endo- and exopeptidases (4,9). Because of this metabolism, terlipressin has a prolonged biological half-life (2–10 h) compared with other vasopressin analogues, which allows its administration as an iv bolus instead of a continuous iv infusion (4,10). Moreover, terlipressin has also been reported to induce a lower incidence of ischemic side effects compared with other vasopressin analogues. In fact, severe ischemic complications were observed in less than 5% of cases in a series of 1258 patients with cirrhosis receiving terlipressin for the management of variceal bleeding (4).

In the two studies published so far reporting the effects of prolonged ornipressin treatment in patients with cirrhosis and HRS, reversal of HRS was observed in eight out of the 15 (53%) patients treated (2,3). In five other patients (33%) ornipressin treatment had to be discontinued because of severe ischemic complications (intestinal ischemia, tongue necrosis and ventricular arrhythmias), while no beneficial effect was observed in the remaining two patients (13%). In the present study, terlipressin administration reversed HRS in seven of the nine (78%) patients included, while treatment was ineffective in only one patient (11%). No ischemic side effects were observed. One patient with alcoholic cirrhosis who had been drinking heavily before admission developed acute pancreatitis during the follow-up in the remaining four patients was 1.4 mg/dl (1.2–1.5).
study period while renal function was improving. To our knowledge, acute pancreatitis has not been reported as a side effect of terlipressin. However, because ischemia has been described as a pathogenic mechanism of acute pancreatitis (11,12), it cannot be ruled out that it was related to the administration of terlipressin. The small number of patients included in the current study and in the two previous pilot studies on ornipressin treatment does not allow a definite conclusion to be drawn about the incidence of ischemic complications related to the administration of the two drugs. It seems that the use of terlipressin is associated with a lower incidence of ischemic complications as compared with ornipressin. Nevertheless, the possibility of the development of ischemic complications in patients treated with terlipressin should always be taken into account.

A number of issues that were not addressed in this pilot study would require specific investigation in subsequent studies. First, the recommended dosage of terlipressin to be used in patients with HRS is not known. According to our results, the initial dose may be lower than that recommended for the management of variceal bleeding (2 mg/4 h) (13–16). Because most patients included in the current study showed a positive response to the administration of 0.5–1 mg/4 h and the incidence of side effects is most likely dose-dependent, it seems advisable to start with low doses and increase them up to 2 mg/4 h if there is no response. Second, the duration of treatment is also not known and probably depends on the severity of HRS. In some patients reversal of the syndrome is obtained after 5 days of treatment, whereas in others a more prolonged administration is required. A shorter treatment (2 days) is not recommended because it has been shown that it induces only a small improvement in renal function (17). If treatment is stopped when HRS has been reversed (serum creatinine lower than 1.5 mg/dl or creatinine clearance higher than 40 ml/min), recurrence of HRS is uncommon (2,3). However, if HRS recurs, a second course of treatment is probably indicated (3). Third, in the current study terlipressin was given in combination with albumin infusion to further improve the effect of the drug on effective arterial blood volume. It is very unlikely that the beneficial effect of treatment was due exclusively to the administration of albumin and not to terlipressin, because previous studies have shown that the administration of albumin alone has only minor or no effects on circulatory and renal function in patients with cirrhosis and renal dysfunction (18). Whether or not albumin is required for the beneficial effect of terlipressin on renal function is unknown and would require a prospective trial designed to answer this question.

In conclusion, the findings of the current pilot study indicate that terlipressin associated with iv albumin infusion reverses HRS in a high proportion of patients with cirrhosis with a low incidence of side effects. Large prospective placebo-controlled studies are needed to show whether this therapeutic approach improves survival in patients with HRS.

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