Terlipressin for Hepatorenal Syndrome: Novel Strategies and Future Perspectives

P. Angeli
Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy

Abstract
Type 1 hepatorenal syndrome (HRS) is a functional renal failure that often occurs in patients with cirrhosis and ascites. Type 1 HRS develops as the consequence of a severe reduction of effective circulating volume due to both extreme splanchnic arterial vasodilatation and reduction of cardiac output. Several pilot studies and two randomized control studies have shown that terlipressin plus albumin improves renal function in patients with type 1 HRS. Terlipressin plus albumin can also improve short-term survival in these patients. Terlipressin was most commonly given in intravenous boluses starting from an initial dose of 0.5–1 mg every 4 h to 3 mg every 4 h in case of nonresponse. While there is evidence that terlipressin alone may be less effective than terlipressin combined with intravenous albumin in improving renal function in patients with type 1 HRS, the best way to use terlipressin in these patients is still under evaluation. In particular, some preliminary data show that terlipressin given via continuous intravenous infusion is better tolerated than when given in intravenous boluses. Future randomized studies should confirm this difference and outline the best way to use this drug in the treatment of type 1 HRS. In any case, the available data are sufficient to state that use of terlipressin plus albumin has really changed the management of type 1 HRS in patients with advanced cirrhosis. Finally, there is some preliminary evidence suggesting that terlipressin may also be a novel therapeutic approach targeting splanchnic arterial vasodilation involved in the pathophysiology of type 2 HRS, septic shock and paracentesis-induced circulatory dysfunction, but further studies are needed in these clinical scenarios.

Copyright © 2011 S. Karger AG, Basel

Novel Strategies

Terlipressin for the Treatment of Type 1 Hepatorenal Syndrome

The administration of vasoconstrictors and albumin in patients with type 1 hepatorenal syndrome (HRS) is based on the current knowledge of the pathophysiology of this severe complication. A marked renal arterial vasoconstriction, which is the extreme renal functional abnormality that can occur in patients with cirrhosis and ascites, represents the pathophysiological basis of HRS [1]. It develops in the context of a marked
reduction of effective circulating volume, which is related to splanchnic arterial vasodilation and inadequate cardiac output [1–3] and implies an extreme overactivation of the endogenous systemic vasoconstrictors systems, namely the renin-angiotensin system, the sympathetic nervous system, and the nonosmotic release of vasopressin [1]. Splanchnic arterial vasodilatation is thought to be mainly the consequence of an increased release of endogenous vasodilators due to portal hypertension and/or hepatic failure [1]. The inadequate cardiac output can be an extreme manifestation of systolic dysfunction which represents one of the components of cirrhotic cardiomyopathy [4]. Thus, the rationale of the use of vasoconstrictors in the treatment of type 1 HRS is to counteract the splanchnic arterial vasodilation in order to improve effective circulating volume and reduce portal pressure. In this way, the final aim of this therapeutic approach is to reduce severe renal arterial vasoconstriction [5].

In small pilot perspective and retrospective studies, it has been demonstrated that the prolonged use of a vasoconstrictor derived from vasopressin, ornipressin [6, 7] or terlipressin [8–19] or of an α-agonist vasoconstrictor (midodrine plus octreotide or noradrenaline alone) [20–25] in association with human albumin is capable of recovering renal function in patients with type 1 HRS. These studies have shown that a vasoconstrictor plus albumin can recover renal function in 40–60% of the cases. In most cases, dilutional hyponatremia associated with HRS also improves during treatment. Recurrence of HRS after treatment withdrawal (a sharp increase in serum creatinine within few days) occurs in approximately 20% of patients, but retreatment is often effective.

Among vasoconstrictors, to this day, terlipressin is the most widely used in the treatment of type 1 HRS [8–19, 26]. Terlipressin has been used in more than 200 patients, either as an intravenous bolus starting from an initial dose of 0.5 mg every 4–6 h, or continuous intravenous infusion starting from an initial dose of 2 mg/day. In patients without response (no significant reduction of serum creatinine within 3 days), the initial dose of terlipressin was doubled. The maximal doses of terlipressin used in the treatment of type 1 HRS were 2 mg every 4–6 h by intravenous boluses, or 12 mg/day by continuous intravenous infusion. Complete reversal (defined by a decrease OD serum creatinine with a final value <1.5 mg/dl) or partial reversal (defined with a decrease of serum creatinine >50% with a final value ≥1.5 mg/dl) of type 1 HRS was observed in almost 59% of the patients [26]. In most studies, terlipressin has been used together with albumin starting with a priming dose of 1 g/kg BW followed by 20–40 g/day, monitoring central venous pressure. In two studies in which terlipressin was given also alone [13, 16], reversal of renal failure was lower than in the studies in which terlipressin was associated with albumin. The decrease in serum creatinine as a result of the administration of vasoconstrictors and albumin takes several days. Therefore, the length of treatment is usually 10–15 days. Despite the normalization of serum creatinine, GFR, when measured specifically [20], remains below the normal values in most responders to treatment. Up to now, two randomized controlled clinical trials comparing terlipressin and albumin with albumin alone
have been published. While both trials confirm the effectiveness of terlipressin in recovering renal function in patients with type 1 HRS, they fail in improving survival [27, 28] (table 1). Nonetheless, a systematic review of all the randomized controlled clinical trials has more recently shown that terlipressin plus albumin may prolong 15-day survival in patients with type 1 HRS [29]. This evidence stresses the meaning of the use of terlipressin and albumin as a bridge treatment towards liver transplantation (LT). In this perspective, it has been shown that this therapeutic option increases the number of patients with type 1 HRS reaching LT [26, 30], and, after LT, reduces the need for renal replacement therapy (RRT), thus improving survival [31]. Nonetheless, it appears more and more evident that in clinical practice this treatment is often used in patients with type 1 HRS who are not candidates for LT [26, 30].

The small effect of terlipressin and albumin on survival needs some further observation. First, it should be taken into account that the prognosis in these patients is not only related to a recovery of renal function but also to the degree of liver failure. A marked impairment of liver function represents a poor predictor for the response to treatment with terlipressin and albumin [16, 17] but, overall, a poor predictor for their survival [16, 17]. In particular, a Child-Pugh score >11, predicts a poor survival [13, 16, 17]. More recently, it has been shown that a serum total bilirubin ≥10 mg/dl is also a predictor of nonresponse as is an increase in arterial pressure <5 mm Hg at day 3 of treatment [32]. Thus, the severity of liver failure in patients with type 1 HRS can contribute to explain why the efficacy of terlipressin plus albumin in type 1 HRS was found to be less than 50% in patients with type 1 HRS. In addition, terlipressin is targeted on splanchnic arterial vasodilation but it has no effect on the impaired cardiac output in these patients, which has been shown to play an important role in the pathophysiology of type 1 HRS. Thus, the only effect on cardiac output of this therapeutic approach is associated with the albumin infusion. Consequently, albumin

### Table 1. Terlipressin and albumin vs. albumin in cirrhotic patients with ascites and type 1 HRS: results of two controlled trials

<table>
<thead>
<tr>
<th></th>
<th>Spanish trial (n = 45)</th>
<th>American trial (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>terlipressin and</td>
<td>terlipressin and</td>
</tr>
<tr>
<td></td>
<td>albumin</td>
<td>placebo and albumin</td>
</tr>
<tr>
<td>Response</td>
<td>43.5%*</td>
<td>34%#</td>
</tr>
<tr>
<td>at 3 months</td>
<td>8.7%</td>
<td>13%</td>
</tr>
<tr>
<td>Survival</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* p < 0.025, # p < 0.01.

Data for the Spanish trial are from Martin-Llahi et al. [28] and those for the American trial are from Sanyal et al. [27].
infusion plays an important role in the effectiveness of this new therapeutic approach to type 1 HRS. It has been shown in patients with cirrhosis and spontaneous bacterial peritonitis [33] as well in an experimental model of sepsis [34] that albumin infusion can improve not only cardiac function but also the reactivity of the arterial wall to vasoconstrictors as a result of an albumin-related reduced availability of nitric oxide. These observations can lead to another main comment. The effect of terlipressin and albumin on survival in patients with cirrhosis and type 1 HRS could have been limited by comparing this approach to albumin infusion and not to a placebo. It is too easy to hypothesize today that in the future some more complex therapeutic approaches should be tested including, for example, an inotropic agent.

Finally, it should be stressed that terlipressin can induce side effects in up to 40% of patients and that severe side effects – including myocardial infarction, arrhythmia and intestinal infarction – require discontinuation of treatment in up to 10% of patients [26]. There is some preliminary evidence showing that when terlipressin has been given as a continuous intravenous infusion, it was effective at a lower dose than when it was given as an intravenous bolus, and, as a consequence, it was much better tolerated [19]. These observations have recently been confirmed by the preliminary data of a controlled clinical study in which terlipressin given as an intravenous bolus was compared to terlipressin given as a continuous intravenous infusion in the treatment of type 1 HRS in patients with cirrhosis [35]. Despite a similar efficacy, the daily effective dose of terlipressin was lower in patients who were treated with terlipressin given by continuous intravenous infusion than in those who received terlipressin given by intravenous boluses (fig. 1). In this context it should be underlined that 10 of 14 full responders to terlipressin given as a continuous intravenous infusion responded at the initial dose of the provided schedule (2 mg/24 h). As a consequence, severe adverse effects to treatment were more frequent in patients who received terlipressin given by intravenous boluses than in those who received terlipressin via continuous intravenous infusion (fig. 2). The higher efficacy of terlipressin given as a continuous intravenous infusion as compared to terlipressin given by intravenous boluses can be explained by pharmacodynamic data on the effect of the drug on portal pressure in cirrhosis. In fact, it has been observed that continuous intravenous

**Fig. 1.** Mean effective daily dose of terlipressin. Comparison between terlipressin given by intravenous boluses and terlipressin given as continuous intravenous infusion. Data from Angeli et al. [35].
infusion of terlipressin assures a more steady profile of the lowering effect of the drug on portal pressure in patients with cirrhosis [36].

**Future Perspectives**

*Terlipressin for Treatment of Type 2 HRS*

Type 2 HRS is a more stable impairment of renal function in patients with cirrhosis and ascites. Thus, patients with type 2 HRS do not present with acute renal failure, but rather refractory ascites. As a consequence, these patients have been investigated for the treatment of refractory ascites comparing paracentesis and transjugular intrahepatic portosystemic shunt, rather than for the recovery of renal function. As a consequence, the effects of vasoconstrictors and albumin in type 2 HRS treatment have not been investigated extensively. Nevertheless, because the pathophysiology of type 2 HRS seems to be similar to that of type 1 HRS at least as far as splanchnic arterial vaso-dilation is concerned, terlipressin has been used in some pilot studies also in patients with type 2 HRS. Nonrandomized studies that enrolled a small number of patients with type 2 HRS have shown that the percentage of response to treatment in terms of recovered renal function does not, however, seem to be different from that observed in patients with type 1 HRS [37, 38], while survival appears longer (100% at 3 months).

*Terlipressin for the Treatment of Post-Paracentesis Circulatory Dysfunction*

Therapeutic paracentesis is the first-line treatment of both massive and refractory ascites [39]. The mobilization of tense ascites by paracentesis is not always safe since it can provoke further deterioration of circulatory function, namely post-paracentesis circulatory dysfunction (PPCD) [39]. The incidence of PPCD, which is defined as an increase ≥50% of plasma renin activity 1 week after the procedure, is irreversible.
and is associated with lower survival [40]. The mechanism by which paracentesis affects effective circulating volume is thought to be related to the rapid reduction of the abdominal pressure during tapping. The reduction in intra-abdominal pressure causes a similar reduction in intra-thoracic pressure with increased venous blood return to the right heart, increased cardiac output and decreased peripheral resistance. It seems that this last effect is persistent and favors a reduction of effective circulating volume [41, 42]. Thus, PPCD seems to be due to increased arterial compliance rather than to a decrease of blood volume. These observations represent the potential rationale for the use of vasoconstrictors in this clinical context. Preliminary data showed the possibility of preventing PPCD by methods other than volume expansion, e.g. administration of vasoconstrictors [43–45]. In particular, it has been shown that the administration of terlipressin (1 mg i.v. bolus just before and 1 mg i.v. bolus 8 and 16 h after paracentesis) resulted in a proportion of PPCD similar to that obtained with the albumin administration. A good tolerance to terlipressin was also noted [43]. Large randomized studies should be performed to evaluate the effects of terlipressin as well as other vasoconstrictors in patients with cirrhosis who need therapeutic paracentesis for the control of ascites.

**Septic Shock**

Vasopressin or vasopressin analogues [46, 47] are used in patients without cirrhosis but with septic shock, since these patients have marked decreases in the plasma concentrations of endogenous vasopressin. Moreover, in patients with arterial hypotension refractory to exogenous catecholamine administration, the intravenous administration of vasopressin has been shown to be capable of increasing arterial pressure [4]. In patients with cirrhosis with septic shock, the plasma concentrations of endogenous vasopressin have not yet been measured, and the effects of vasopressin or vasopressin analogues are unknown. Nevertheless, it has been shown that in rats with cirrhosis challenged with LPS, a Gram-negative bacteria product, terlipressin administration improves LPS-induced arterial hypotension through, at least in part, an inhibitory effect on the LPS-induced over-expression and over-activity of inducible nitric oxide synthase [48]. Taking into account that a similar effect on the arterial wall was observed as a consequence of albumin infusion in an experimental model of septic shock [34], it can be hypothesized that terlipressin and albumin may also be a novel approach in the treatment of patients with cirrhosis and septic shock.

**Conclusions**

The use of terlipressin and albumin in the treatment of type 1 HRS represents a landmark in the treatment of complications in patients with advanced cirrhosis. Its
rationale is closely related to our current knowledge of the pathophysiology of type 1 HRS. The use of terlipressin and albumin was proved to be effective in recovering renal function and it has also increased short-term survival in responders, making it possible to increase the number of patients who undergo LT. In addition, it has changed the outcome of LT in these patients since it reduced the post-LT need for RRT and increased post-LT survival. These results appear to be quite an encouraging development for an effective treatment of type 1 HRS. Nevertheless, it is important to recognize that recovery of renal function can be achieved in less than 50% of patients with type 1 HRS and that the recovery of renal function may be partial even in patients who are defined as full responders. This is not surprising, taking into account the complexity of the pathophysiology of type 1 HRS and the need to understand how to best use the existing approach, particularly how to best use terlipressin. Thus, in the future, a shift is needed in the treatment of type 1 HRS moving from ‘a predominant vasoconstrictor therapy’ toward a combine therapy including, for example, an inotropic agent. In addition, ongoing randomized controlled clinical trials on different modalities of the use of terlipressin in the treatment of type 1 HRS should be completed and other trials on this important issue should be planned and performed. Finally, studies should be performed in order to clarify the potential role of terlipressin and other vasoconstrictors in the treatment of type 2 HRS and septic shock as well as in the prevention of PPCD in patients with cirrhosis.

Key Messages

- The use of terlipressin and albumin is effective in recovering renal function in patients with type 1 HRS and it also increases short-term survival in responders.
- The use of terlipressin and albumin has increased the number of patients with type 1 HRS who undergo OLT and it has changed the outcome of OLT in these patients since it has reduced the post-OLT need for RRT and increased post-OLT survival.
- At the time of writing, the best way to use terlipressin in patients with type 1 HRS was still under evaluation. Preliminary data seem to suggest that terlipressin given as continuous intravenous infusion is better tolerated and cheaper than its administration as intravenous boluses.
- There are some preliminary data suggesting that terlipressin and albumin may also be a novel therapeutic approach for type 2 HRS, septic shock and paracentesis-induced circulatory dysfunction in patients with cirrhosis.

References


Paolo Angeli, MD, PhD
Department of Clinical and Experimental Medicine, University of Padova
Via Giustiniani 2
IT–35100, Padova (Italy)
Tel. +39 0498212204, Fax +39 0498218676, E-Mail pangeli@unipd.it

Terlipressin for Hepatorenal Syndrome 197