Review article: pharmacological treatment of hepatorenal syndrome

P. GINÉS, A. TORRE, C. TERRA & M. GUEVARA
Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), Instituto Reina Sofía de Investigación Nefrològica, Barcelona, Spain

SUMMARY
Hepatorenal syndrome (HRS) is a common complication of advanced cirrhosis characterized not only by renal failure but also by marked alterations in systemic haemodynamics and activity of endogenous vasoactive systems. Renal failure is due to a severe vasoconstriction of the renal circulation. The pathogenesis of HRS is not completely understood but it is probably the result of extreme underfilling of the arterial circulation secondary to arterial vasodilation located in the splanchnic circulation. As well as the renal circulation, all other extrasplanchnic vascular beds appear to be vasoconstricted. The diagnosis of HRS is currently based on the exclusion of nonfunctional causes of renal failure: prognosis of patients with HRS is very poor. Liver transplantation is the best option in selected patients, but it is not always applicable as survival expectancy is short. Vasopressor drugs with preferential effect on the splanchnic circulation (vasopressin analogues with a predominant V1 receptor effect, such as terlipressin – Glypressin®) are very effective in improving renal function, with reversal of HRS being achieved in approximately two-thirds of patients. There is no agreement as to the terlipressin treatment regimen that is associated with a greater efficacy and lower incidence of side-effects. It appears that the administration of albumin together with terlipressin improves the therapeutic response rate. The impact of treatment on the natural course of HRS remains to be assessed in prospective investigations, but it seems that the reversal of HRS is associated with improved survival. Finally, treatment of patients with HRS with terlipressin before transplantation seems to improve post-transplantation outcome.

INTRODUCTION
Renal failure is a frequent complication in patients with advanced cirrhosis. Its occurrence usually entails a poor prognosis because of the combined detrimental effect of renal and liver failure. In some instances, renal failure in cirrhosis is due to causes that also lead to renal failure in patients without liver disease, such as volume depletion, shock (haemorrhagic or septic) or administration of nephrotoxic drugs, or it may be the consequence of an intrinsic renal parenchymal disease, such as glomerulonephritis. However, in other instances renal failure in cirrhosis occurs in the absence of these aetiological factors and with a normal renal histology, a condition known as hepatorenal syndrome (HRS). This unique condition is due to an intense vasodilatation of the splanchnic circulation causing a marked vasoconstriction of the renal circulation, which leads to a severe reduction of glomerular filtration rate (GFR).1 For many years there has been no effective treatment for HRS. However, recent findings suggest that vasoconstrictor drugs are effective in improving renal function in HRS. The aim of this article is to provide an update on the pharmacological therapy of HRS.

CLASSIFICATION AND DIAGNOSIS OF HEPATORENAL SYNDROME
HRS is at the end of the clinical spectrum of abnormalities of renal function in patients with cirrhosis and
ascites. \(^2\)\(^–\)\(^5\) HRS may occur in two different clinical patterns. \(^4\)

1 Type 1 HRS is characterized by rapid and progressive impairment of renal function as defined by a 100% increase of the initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction of the initial 24-h creatinine clearance to a level lower than 20 mL/min in less than 2 weeks; in some patients, type 1 HRS develops spontaneously without any identifiable precipitating factor, while in others it occurs in close chronological relationship with some complications, particularly spontaneous bacterial peritonitis. \(^6\)

2 Type 2 HRS is characterized by a less severe and nonprogressive impairment of renal function (at least in the short term); the main clinical consequence of this type of HRS is refractory ascites.

Because of the lack of specific diagnostic tests, the diagnosis of HRS is currently made according to several criteria, as proposed by the International Ascites Club, which are based on demonstration of a marked reduction in GFR (serum creatinine > 1.5 mg/dL in the absence of diuretic therapy) and the exclusion of other causes of renal failure that may occur in patients with cirrhosis \(^4\) (Table 1).

### RATIONALE FOR THE USE OF VASOCONSTRICTOR DRUGS IN HEPATORENAL SYNDROME

The pathophysiological hallmark of HRS is a vasoconstriction of the renal circulation. \(^4\)\(^,\)\(^7\)\(^–\)\(^13\) The mechanism of this vasoconstriction is incompletely understood and possibly multifactorial, involving disturbances in the circulatory function and activity of systemic and renal vasuactive mechanisms. In the systemic circulation there is a severe arterial underfilling due to a marked arterial vasodilatation located in the splanchnic circulation, which is related to the presence of portal hypertension. By contrast, in the kidney there is marked vasoconstriction. A detailed analysis of these mechanisms and their possible role in the pathogenesis of HRS is outside the scope of this article and may be found elsewhere. \(^1\)\(^,\)\(^14\)\(^,\)\(^15\)

The theory that best fits with the observed alterations in the renal and circulatory function in HRS is the arterial vasodilatation theory, which proposes that HRS is the result of vasoconstrictor systems (i.e. the renin-angiotensin and sympathetic nervous systems) acting on the renal circulation activated as homoeostatic mechanisms to improve the extreme underfilling of the arterial circulation. \(^1\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^14\)\(^–\)\(^16\) As a result of this increased activity of the vasoconstrictor systems, renal perfusion and GFR are markedly reduced but tubular function is preserved. This is different to what occurs in acute tubular necrosis in which renal failure is associated with a markedly impaired tubular function. The vasoconstrictor systems are also responsible for the sodium retention (renin-angiotensin and sympathetic nervous systems) and impaired free water excretion (arginine vasopressin) that occur in advanced cirrhosis. \(^2\)\(^,\)\(^3\)\(^,\)\(^5\)\(^,\)\(^16\) Most available data suggest that the arterial underfilling is due to a marked vasodilatation of the splanchnic circulation related to an increased splanchnic produc-

<table>
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<tr>
<th>Table 1. Diagnostic criteria for hepatorenal syndrome. Reproduced from Arroyo et al. (^4)</th>
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<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dL or 24-h creatinine clearance lower than 40 mL/min</td>
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<tr>
<td>2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs</td>
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<tr>
<td>3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander</td>
</tr>
<tr>
<td>4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease</td>
</tr>
<tr>
<td><strong>Additional criteria</strong></td>
</tr>
<tr>
<td>1. Urine volume lower than 500 mL/day</td>
</tr>
<tr>
<td>2. Urine sodium lower than 10 mmol/L</td>
</tr>
<tr>
<td>3. Urine osmolality greater than plasma osmolality</td>
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<tr>
<td>4. Urine red blood cells less than 50 per high power field</td>
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<tr>
<td>5. Serum sodium concentration lower than 130 mmol/L</td>
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All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis, but provide supportive evidence.
tion of vasodilator substances, particularly nitric oxide. In the early phases of decompensated cirrhosis, renal perfusion is maintained within normal levels because of an increased renal synthesis of vasodilating factors (mainly prostaglandins). In the later phases of the disease, renal perfusion cannot be maintained because of the extreme arterial underfilling causing maximal activation of vasoconstrictor systems and/or decreased production of renal vasodilator factors, and HRS develops. The marked activation of vasoconstrictor systems also results in vasoconstriction of some vascular beds other than the kidneys, including lower and upper limbs and brain. The splanchnic area escapes from the effect of vasoconstrictors, probably because of a markedly enhanced local production of vasodilators. In accordance with the pathogenesis of HRS, the administration of drugs able to produce vasoconstriction of the splanchnic circulation would improve the effective arterial blood volume, suppress the activity of endogenous vasoconstrictor factors and reduce the vasoconstriction in the renal circulation. To date two types of vasoconstricting drugs have been used in patients with HRS: vasopressin analogues (terlipressin [Glypressin and ornipressin] and α-adrenergic agonists (noradrenaline [norepinephrine] and midodrine), which act on V1 vasopressin receptors and α-adrenergic receptors, respectively, present in the smooth muscle cells of the vessel wall.

EFFECTS OF VASOPRESSIN ANALOGUES

A number of nonrandomized studies published in the late 1990s and early 2000s showed that the administration of vasopressin analogues to patients with cirrhosis and HRS causes a marked improvement of renal function in a large proportion of patients. The drug most frequently used in published studies is terlipressin, which is marketed in many countries with an indication for therapy of acute oesophageal variceal bleeding in cirrhosis. Ornipressin is no longer available. The information currently available on the efficacy and safety of terlipressin in patients with HRS can be summarized as follows:

1. The administration of terlipressin (0.5–2 mg/4–6 h intravenously) is associated with an improvement in renal function in 42–92% of patients treated in different studies with an average of 63% (Table 2). Because of the lack of dose-finding studies, the therapeutic schedule of terlipressin with the best efficacy/safety ratio is unknown.

2. In most studies, treatment with terlipressin is usually maintained until serum creatinine decreases below 1.5 mg/dL (responders), or for a maximum of 15 days. It is unknown whether the continued administration of the drug after the end-point of 1.5 mg/dL of serum creatinine has been reached, is associated with a further improvement of renal function.

3. In responding patients, the improvement in urine volume tends to occur immediately after the first doses of terlipressin (within 12–24 h), while that of GFR usually occurs slowly over several days. In some cases, but not all, there is also an increased sodium excretion and improvement or normalization of serum sodium concentration. Despite the improve-

Table 2. Response rate, side-effects and survival in different series of patients with cirrhosis and hepatorenal syndrome treated with terlipressin

<table>
<thead>
<tr>
<th>Study</th>
<th>Response* (%)</th>
<th>Recurrence** (%)</th>
<th>Severe side-effects*** (%)</th>
<th>Median survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uroz et al. 2000</td>
<td>7/9 (77)</td>
<td>0/7 (0)</td>
<td>1/9 (11)</td>
<td>39</td>
</tr>
<tr>
<td>Mulkey et al. 2001</td>
<td>11/12 (92)</td>
<td>6/11 (55)</td>
<td>0/12 (0)</td>
<td>42</td>
</tr>
<tr>
<td>Moreau et al. 2002</td>
<td>53/91 (58)</td>
<td>NR</td>
<td>18/99 (18)</td>
<td>43</td>
</tr>
<tr>
<td>Colle et al. 2002</td>
<td>11/18 (61)</td>
<td>7/11 (64)</td>
<td>0/18 (0)</td>
<td>24</td>
</tr>
<tr>
<td>Halimi et al. 2002</td>
<td>13/18 (72)</td>
<td>NR</td>
<td>4/18 (22)</td>
<td>NR</td>
</tr>
<tr>
<td>Alessandria et al. 2002</td>
<td>8/11 (73)</td>
<td>8/8 (100)</td>
<td>0/11 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Ortega et al. 2002</td>
<td>14/21 (66)</td>
<td>2/12 (17)</td>
<td>1/21 (5)</td>
<td>40</td>
</tr>
<tr>
<td>Solanki et al. 2003</td>
<td>5/12 (42)</td>
<td>NR</td>
<td>3/12 (25)</td>
<td>NR</td>
</tr>
<tr>
<td>Average</td>
<td>122/192 (63)</td>
<td>23/49 (47)</td>
<td>27/200 (13)</td>
<td>38</td>
</tr>
</tbody>
</table>

* The definition of response varies between studies; ** recurrence of hepatorenal syndrome after treatment withdrawal in responder patients. Definition of recurrence also varies between studies; *** most patients presented self-limited abdominal cramps and/or diarrhoea during the administration of the first doses of terlipressin, which were not counted as severe side-effects; NR = not reported.
In most studies, intravenous albumin has been given at variable doses for the duration of therapy with terlipressin. The suggestion has been made that intravenous albumin improves the beneficial effects of terlipressin on renal function. However, this remains to be proven conclusively in prospective, randomized, comparative studies.

A consistent finding in all studies is that the recurrence of HRS after treatment withdrawal is not universal (approximately 50% of patients) (Table 2). The explanation for this is unknown. Retreatment of recurrence is effective.

The incidence of ischaemic side-effects which require the discontinuation of terlipressin is approximately 13% (Table 2). It has to be taken into account that most, if not all, studies excluded high-risk patients with ischaemic heart disease or arterial disease.

The possible beneficial effect of terlipressin on survival of patients with HRS has not been proven due to the lack of comparative studies including a control group of nontreated patients. However, the observation from several studies that responding patients had a longer survival compared to nonresponders, together with the well-known fact that the spontaneous improvement of HRS is extremely uncommon, suggests that terlipressin may actually improve survival of patients with HRS.

The above information refers mainly to type 1 HRS, as the majority of patients included in the published studies suffered from this type of HRS. Although some reports suggest that terlipressin also improves renal function in patients with type 2 HRS, its efficacy in this setting remains to be confirmed.

Patients with HRS treated with vasopressin analogues before liver transplantation have a low incidence of complications after transplantation and an excellent outcome, similar to that of patients transplanted without HRS. These findings suggest that patients with HRS should be treated with vasopressin analogues before transplantation.

EFFECTS OF $\alpha$-ADRENERGIC AGONISTS

The use of $\alpha$-adrenergic agonists in patients with cirrhosis and HRS has been investigated in two studies. In the first study, five patients with type 1 HRS were treated with the combination of midodrine (initially at a dose of 7.5 mg three times per day and increased to 12.5 mg three times per day if there was no increase in mean arterial pressure of at least 15 mmHg with the former dose), octreotide (100 µg three times daily increased to 200 µg three times daily, as explained above), and human albumin (20–40 g/day intravenously). In all five patients there was a marked improvement in circulatory function, suppression of the renin-angiotensin system and improvement of renal function compared with an historical control group of eight patients treated with dopamine plus albumin. In the second study, 12 patients with type 1 HRS were treated with noradrenaline (norepinephrine) (0.5–3 mg/h intravenously titrated to obtain an increase in mean arterial pressure of at least 10 mmHg) in combination with intravenous albumin and frusemide (furosemide) at variable doses to maintain a central venous pressure between 4 and 10 mmHg and urine output above 100 mL/4 h. Reversal of HRS was observed in 10 out of the 12 patients studied. This occurred together with a marked increase in arterial pressure and suppression of the activity of the renin-angiotensin system. In the two studies there were no side-effects except for the occurrence of a possible angina pectoris in one patient treated with noradrenaline (norepinephrine). Although there is a need for further studies including larger numbers of patients, these data suggest that $\alpha$-adrenergic agents are effective in patients with HRS.

CONCLUSIONS AND FUTURE PERSPECTIVES

In the past few years, a number of nonrandomized studies have been published assessing the efficacy of vasoconstrictor drugs in the management of HRS. The results of these studies are surprisingly consistent in that these drugs are effective in improving renal function in this condition. Nevertheless, most studies included relatively few patients and only one study was randomized. Therefore, important clinical information such as the efficacy in specific groups of patients and the effect of treatment on patient outcome is not known. The lack of prospective studies is mainly due to the fact that before this therapy was introduced there was no effective treatment for HRS and vasoconstrictor drugs were already available in clinical practice for the management of complications of cirrhosis, such as oesophageal variceal bleeding (terlipressin, ornipressin).
or circulatory support (noradrenaline [norepinephrine], midodrine). Despite this lack of information, vasoconstrictors should currently be considered the treatment of choice for patients with HRS. Compared to other potentially useful therapies for HRS, such as transjugular intrahepatic portosystemic shunt (TIPS), or the molecular adsorbent recirculating system (MARS), vasoconstrictor drugs can be given to practically all patients with HRS, regardless of the severity of liver failure, and can be used in all clinical settings.

The topics for future research in this area should include the following:

1. Effect of vasoconstrictor drugs on patient outcome compared to standard medical therapy. This would allow assessment of whether vasoconstrictors improve survival in patients with HRS, information relevant not only to patients who are candidates for liver transplantation but also to those who have contraindications to this procedure.

2. Comparison between terlipressin and \(\alpha\)-adrenergic agonists. This latter group of drugs has the potential advantage over terlipressin because of their wider availability and lower cost. Therefore, a comparison between the two types of drugs would be relevant.

3. Assessment of the potential benefit of albumin administration in combination with vasoconstrictors. There is a good rationale to assume that albumin may improve the efficacy of vasoconstrictors. However, owing to its high cost and limited availability, the efficacy of albumin should ideally be proven in prospective, comparative studies.

4. Comparison between vasoconstrictors and other potentially useful therapies for HRS, such as TIPS or MARS, in specific subsets of patients with HRS.

ACKNOWLEDGEMENTS

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