Endothelin-receptor antagonist/N-acetylcysteine combination in type 1 hepatorenal syndrome

To the Editor:

Type 1 hepatorenal syndrome (HRS) is characterized by a marked splanchnic arterial and systemic vasodilatation ultimately resulting in an acute functional renal failure. Two recent, large, randomized controlled trials confirmed that terlipressin improved renal function, only in 35% of these patients [1,2]. We report an improvement of renal function using bosentan, a nonselective endothelin-receptor antagonist, and N-acetylcysteine (NAC) association in a terlipressin/albumin unresponsive type 1 HRS case.

A 49-year-old man with post-hepatitis B cirrhosis (Child-Pugh score B8, large ascites) presented with a 3-day history of decompensation with jaundice (serum bilirubin, 61 μmol/L), coagulopathy (international normalized ratio, 2.70), grade II encephalopathy, and oligo-anuria (urine output less than 100 mL/24 h, serum creatinine, 3.85 mg/dL) after resolution of spontaneous bacterial peritonitis under adequate anti-biotherapy. Medical past history was remarkable for chronic kidney disease related to biopsy proven post-hepatitis B membranoproliferative glomerulonephritis (baseline serum creatinine, 1.70 mg/dL, proteinuria 3 g/day and hematuria 200 red blood cells/high power field). On admission, there was no evidence of shock (mean arterial pressure, 80 mm Hg), gastrointestinal bleeding, or treatment with nephrotoxic drugs. Proteinuria and hematuria were stable compared to previous renal status, and the kidneys appeared normal on ultrasonography. Urinary sodium/potassium ratio was less than one. Although the patient presented with medical history of glomerulonephritis, this current acute renal failure episode had all the features of type I HRS [3], and the decision was made to start a treatment with terlipressin and albumin. Despite 72 h intravenous terlipressin 8 mg/24 h associated with adequate intravenous fluid and albumin infusion (1 g/kg at day 1 followed by 40 g/day), the patient worsened his serum creatinine: 4.90 mg/dL urine output dropped to <10 mL/24 h, and he developed pulmonary oedema necessitating hemodialysis. Treatment including oral endothelin antagonist (bosentan, 62.5 mg twice daily) and N-acetylcysteine (150 mg/kg over 2 h, followed by a dose of 100 mg/kg daily for 5 consecutive days) was instituted leading to early clinical improvement: urine output increased to 2000 mL daily, serum creatinine decreased to baseline values (1.97 mg/dL) and dialysis could be withheld. Table 1 illustrates the end-stage liver disease score and renal parameters before and 2 weeks after the above mentioned treatment.

The intrarenal production of endothelin has been implicated in the development of renal vasoconstriction, a key step that leads to the development of HRS. However, the benefit of the use of endothelin antagonist in the management of HRS remains unclear. Bosentan prevented the development of renal failure in a rat model of acute liver failure and in-

Table 1

Effect of bosentan + N-acetylcysteine in type 1 HRS: renal and liver outcomes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Terlipressin + albumin treatment</th>
<th>Bosentan + NAC treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>90/50</td>
<td>95/50</td>
</tr>
<tr>
<td>Urine output (L/24 h)</td>
<td>&lt;0.8</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.85</td>
<td>4.90</td>
</tr>
<tr>
<td>Transaminases (ALT/AST)</td>
<td>76/64</td>
<td>116/86</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td>MELD score</td>
<td>35</td>
<td>38</td>
</tr>
</tbody>
</table>

HRS, hepatorenal syndrome, MELD, model for end-stage liver disease.

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duced a dose-related improvement of the glomerular filtration rate in humans [4,5]. In contrast, Wong et al. showed that tezosentan, another nonselective endothelin-receptor antagonist, has not been beneficial in the management of type 2 HRS in cirrhosis and reported lack of effects on renal function [6]. On the other hand, intravenous NAC has also been reported to be of some benefit in HRS [7].

Considering that both drugs seem to be safe and have some beneficial role in HRS, the combination needs to be further studied in patients with HRS.

References


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