Reversal of Type 1 Hepatorenal Syndrome With the Administration of Midodrine and Octreotide

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The aim of the study was to verify the effects of the administration of an inhibitor of the release of endogenous vasodilators together with a vasoconstrictor agent in patients with hepatorenal syndrome (HRS). This new medical perspective was compared with a traditional medical approach for HRS, such as the infusion of nonpressor doses of dopamine to produce renal vasodilation. Thirteen patients with type 1 HRS were enrolled in the study. Five of them were treated with the oral administration of midodrine and the parenteral administration of octreotide. In addition, the patients received 50 to 100 mL of 20% human albumin solution daily for 20 days. Midodrine and octreotide were dosed to obtain a stable increase of at least 15 mm Hg of mean arterial pressure. Eight patients were treated with the intravenous administration of nonpressor doses of dopamine (2-4 μg/kg/min) and the same daily amount of albumin. After 20 days of treatment with midodrine and octreotide, an impressive improvement in renal plasma flow (RPF), glomerular filtration rate, and urinary sodium excretion was observed in patients. This was accompanied by a significant reduction in plasma renin activity, plasma vasopressin, and plasma glucagon. No side effects were observed. Three patients were discharged from the hospital. One of them successfully underwent liver transplantation. One of the two remaining patients is still alive after 472 days with a preserved renal function, and the other died from terminal liver failure after 76 days. Seven out of eight patients who were treated with dopamine experienced a progressive deterioration in renal function and died during the first 12 days. Only one patient recovered renal function and underwent liver transplantation. In conclusion, the long-term administration of midodrine and octreotide seems to be an effective and safe treatment of type 1 HRS in patients with cirrhosis. (HEPATOLOGY 1999;29:1690-1697.)

Hepatorenal syndrome (HRS) occurs in 18% of cirrhotic patients with ascites. HRS is characterized by intense vasoconstriction, low glomerular filtration rate (GFR), preserved tubular function, and normal renal histology.1 The diagnostic criteria of HRS have been recently reviewed, and HRS has been classified on a clinical basis into two different types: type 1 characterized by rapidly progressive renal function impairment and type 2 in which renal failure does not have a rapidly progressive course.2 From a pathophysiological point of view HRS is considered to be the extreme expression of a reduced effective circulating volume because of arterial vasodilation, particularly in the splanchnic area.3 Consequently, the extreme increase in the activity of both renin-angiotensin and sympathetic nervous system as well as the elevated circulating levels of endothelin are the most likely cause of HRS.4-9

The prognosis of HRS is poor1 and all the therapeutic approaches have so far been discouraging.6-9 Gonwa et al.10 have reported a good long-term survival after orthotopic liver transplantation (OLTX) in cirrhotic patients with HRS. However, other investigators reported a significant reduction in survival after OLTX in cirrhotic patients with preoperative renal failure.11 Thus, the reversal of HRS with a medical therapeutic approach is also a very important tool in patients who are waiting for OLTX. Most attempts to pharmacologically reverse HRS have consisted in the intravenous administration of vasodilators (i.e., dopamine, misoprostol, and aminophylline) or drugs that inhibit the synthesis or the effects of endogenous vasoconstrictors (i.e., captoril, saralasin, thromboxane inhibitors, and endothelin antagonist). However, none of these attempts resulted in an effective and reproducible improvement of renal hemodynamics and function.6-9

Recently, the administration of vasoconstrictor drugs such as ornipressin or terlipressin to correct arterial vasodilation has been put forward in the treatment of HRS.12-15 But, the results of the acute administration of these drugs remain still controversial.12,15 In this respect, we observed that the acute administration of midodrine, an orally available α-adrenergic drug, to cirrhotic patients with ascites results in an improvement in systemic hemodynamics, renal perfusion, and renal function only in patients without HRS. In patients with HRS the drug failed to improve systemic hemodynamics and no significant renal effect was observed.16 The lack of response to midodrine as well as to other vasoconstrictors in cirrhotics with HRS is not surprising, because an impaired arterial
reactivity to endogenous and exogenous vasoconstrictors has
been described in these patients. Arterial vasodilatation as
well as the reduced arterial response to vasoconstrictors is
related to an increased level of both endothelial (i.e., prostacy-
clin and nitric oxide) and nonendothelial vasodilators (i.e.,
glucagon), mainly in the splanchnic area. Experimental
studies have shown that the responsiveness to vasoconstric-
tors of the mesenteric artery may be normalized by the
inhibition either of glucagon or nitric oxide (NO) synthesis may induce per se renal failure in patients or in
animals with cirrhosis, because these compounds counteract
the action of vasoconstrictors on renal perfusion. In accord-
ance with these observations the aim of the study was
to inhibit glucagon release was based on clinical and experi-
mental evidence showing that the inhibition of prostacyclin or NO
once the diagnosis of type 1 HRS had been made, on the morning
of midodrine and octreotide in patients with type 1 HRS.

In five patients admitted to our department from January 1997 to
January 1998, a two-drug combined therapy was initiated with
octreotide and midodrine. The doses of octreotide and midodrine
were titrated to obtain an increase in mean arterial pressure of
at least 15 mm Hg. Octreotide was administered subcutaneously at
an initial dose of 2 µg/kg/min. The dose was increased to 4 µg/kg/min after 48 hours if
no response was observed. In addition, an amount of 20 to 40 g/d of albumin was infused.

In five patients admitted to our department from January 1996 to January 1997, after the baseline
evaluation, dopamine was infused intravenously at an initial dose of
2 µg/kg/min. The dose was increased to 4 µg/kg/min after 48 hours if
no response was observed. In addition, an amount of 20 to 40 g/d of albumin was infused.

Arterial blood pressure and heart rate (HR) were evaluated in all
patients every 6 hours throughout the study. Arterial blood pressure
was recorded by means of a manual sphygmomanometer.

Basic Management. Throughout the study, sodium and fluid intake
was restricted and maintained at a carefully controlled level (40
mEq/die and 1 L/die, respectively). If, despite this mainstay of basic
treatment, patients developed tense ascites a 3-L paracentesis was
performed to reduce intraabdominal pressure. Paracentesis was
then followed by plasma volume expansion with 8 go fh u m a n albumin
dose of albumin. If, despite this mainstay of basic

Analytical Methods and Assays. Analytical methods for measure-
ments of plasma and urinary PAH and inulin concentrations, as well
as serum sodium and potassium concentrations, have been previously described. Urine AGL and GGT as well as plasma and urine LYS
measurements were performed by methods previously described.

PRA and plasma levels of PAH, ADH, and atrial natriuretic peptide

PATIENTS AND METHODS

Patients. From January 1996 to January 1998 fifteen consecutive
cirrhotic patients with ascites and type 1 HRS admitted to our
department were enrolled in the study. The diagnosis of cirrhosis
was based on liver histology (10 cases) or clinical and laboratory
findings (5 cases). The cause of the liver disease was alcoholic in 6
patients, hepatitis C virus related in 8, and hepatitis B virus related in
1. The criteria of inclusion were (1) an absence of recent
complications or (2) an absence of HCC at the time of the study. One
patient with heart disease and one with diabetes mellitus were
excluded from the study. All patients had moderate to severe ascites
on day 1 and then 40 g/d of human albumin for at least 4 days); (4)
presor doses of dopamine to produce renal vasodilatation.

Study Design. During the first 5 days after inclusion into the study,
patients did not receive diuretics or other drugs with known effects
on systemic and renal hemodynamics and/or on renal function. A short
cannula in a peripheral vein and a urinary bladder catheter
were applied to each patient and serum urea, serum creatinine,
serum sodium concentration, liver tests, 24-hour diuresis, 24-hour
natriuresis, and body weight were monitored daily. A central venous
line was inserted in 10 patients.

Once the diagnosis of type 1 HRS had been made, on the morning
of the sixth day, after overnight fasting, an intravenous priming dose

of paraminohippurate (PAH) (PAH 7.8 mg/kg body weight; Mo-
nico, Venice, Italy) and inulin (Inulnet 52.5 mg/kg body weight;
Laevosan-Gesellesschaft, Linz, Austria) was given, followed by
constant infusion of a solution containing 1.33 g/dL of inulin and
0.33 g/dL of PAH for at least 8 hours. The rate of constant infusion
was calculated on the basis of the creatinine clearance (ClCr.)
of each patient. After an equilibration period of 60 minutes, urine
samples were collected for two 4-hour periods (baseline clearance
periods). Urine volume was recorded and aliquots were separated to
measure inulin, PAH, and sodium concentration. In the middle of
each baseline clearance period, blood samples were taken from the
central venous line to measure inulin, PAH, lithium, and sodium
clearance. Urinary enzymes were also evaluated to exclude
tubular damage more readily. The ratio of urinary excretion of
glucagon release was based on clinical and experimental
data showing that the inhibition of prostacyclin or NO
synthesis may induce per se renal failure in patients or in
animals with cirrhosis, because these compounds counteract
the action of vasoconstrictors on renal perfusion. In accord-
ance with these observations the aim of the study was
to assess the effects on renal hemodynamics and function of
increasing arterial pressure by the combined administration
of midodrine and octreotide in patients with type 1 HRS.
These effects were compared with those of a traditional
medical approach, such as the infusion of nonpressor doses of
dopamine to produce renal vasodilatation.

In the middle of the urine collection, blood samples were obtained to measure plasma renin activity (PRA), plasma aldoste-

rone concentration (PA), plasma antidiuretic hormone (ADH)
concentration, plasma atrial natriuretic peptide concentration, and
serum nitrate and nitrate levels (NOx). Renal plasma flow (RPF),
GFR, urinary sodium excretion (UNaV), and FE Na; PRA, plasma
concentration of aldosterone and ADH, and serum concentration of
NOx were reevaluated on day 10 and 20 after the initiation of
the medical therapy.

Medical Therapeutic Approaches. In eight patients admitted to our
department from January 1996 to January 1997, after the baseline
evaluation, dopamine was infused intravenously at an initial dose of
2 µg/kg/min. The dose was increased to 4 µg/kg/min after 48 hours if
no response was observed. In addition, an amount of 20 to 40 g/d of

of midodrine and octreotide in patients with type 1 HRS.

Basic Management. Throughout the study, sodium and fluid intake
was restricted and maintained at a carefully controlled level (40
mEq/die and 1 L/die, respectively). If, despite this mainstay of basic
therapy, patients developed tense ascites a 3-L paracentesis was
performed to reduce intraabdominal pressure. Paracentesis was
then followed by plasma volume expansion with 8 g of human albumin
for each liter of removed ascites.

Following the initiation of the pharmacological treatment for
HRS, hemodialysis was performed only in patients with symptoms
of uremia or to prevent life-threatening emergencies, such as acute
pulmonary edema, from occurring.

Analytical Methods and Assays. Analytical methods for measure-
ments of plasma and urinary PAH and inulin concentrations, as well
as serum sodium and lithium concentrations, have been previously described. Urine AGL and GGT as well as plasma and urine LYS
measurements were performed by methods previously described.

PRA and plasma levels of PAH, ADH, and atrial natriuretic peptide
were evaluated by means of radioimmunoassay (RIA) with methods described in detail elsewhere. The serum concentration of NOx was measured by means of a colorimetric assay kit based on a simple two-step process as described previously. The first step is the conversion of nitrate to nitrite using nitrate reductase. The second step is the addition of the Griess reagents, which convert nitrite into a deep purple azo compound (Alexis Biochemical, Laufelfingen, Switzerland).

Calculations. UNaV, clearance of PAH, inulin, and sodium were calculated by means of conventional formulas previously reported. Clearance of PAH and inulin were used as measures of RPF and GFR, respectively.

Mean arterial pressure (MAP) was evaluated as the diastolic pressure plus one third of the pulse pressure.

According to our previous study, urinary excretion of AGL and GGT were corrected by GFR, while urinary excretion of LYS was expressed as fractional clearance of LYS.

Statistical Analysis. Baseline data of MAP, HR, RPF, GFR, FENa, and UNaV represent the arithmetic means of the different measurements performed during each clearance period. Data of MAP and HR after dopamine or midodrine and octreotide administration represent the arithmetic means of the different measurements obtained during each drug clearance period. All results were expressed as means ± SEM. Differences for each variable before and after treatment administration was determined by means of analysis of variance for repeated measures (ANOVA). Student’s t test for paired samples and the Bonferroni test were then used to analyze means of each variable before and after treatment. Analysis of survival was performed by means of log rank-test. The 5% probability level was regarded as significant.

RESULTS

In Table 1 the data of systemic hemodynamics, liver function tests, renal function, and hormonal parameters in eight patients treated with dopamine (group A) and in five patients treated with midodrine and octreotide (group B) are reported. No significant difference was observed between the two groups.

After the initiation of pharmacological treatment, three out of eight patients of group A required hemodialysis to control the symptoms of uremia. All these patients had hemodynamic instability during hemodialysis and all died before the fourth dialysis. Two hemodialyses were performed in one out of five patients of group B to control symptoms of uremia without any worsening of systemic hemodynamics. A 3-L paracentesis was performed to relieve tense ascites in two patients of group A and two patients of group B.

Four patients of group A died within 5 to 7 days of treatment. Causes of death were shock (1 patient), gastrointestinal hemorrhage (1 patient), and terminal liver failure (2 patients). Three more patients died after 10, 11, and 12 days, respectively, for terminal liver failure (1 patient) and gastrointestinal hemorrhage (2 patients). The remaining patient completed the study and was transplanted 14 days after the discontinuation of treatment. She died 15 days after OLTX of fungal infection. As far as renal hemodynamics and function is concerned, a progressive worsening was observed in patients of group A considered as a whole (Table 2). In particular, serum creatinine continued to increase progressively or remained at very high levels in all patients except for the one who was finally transplanted (Fig. 1).

All patients of group B completed the study period. Two patients were treated with initial doses of midodrine and octreotide, whereas the other three patients required the highest doses of the drugs. An increase in MAP of at least 15 mm Hg, which was the empirical aim of the pharmacological treatment, was obtained in all patients throughout the study and was accompanied by a significant decrease in HR, PRA plasma serum concentration of aldosterone, ADH, and NO. Likewise, a progressive improvement in RPF, GFR and UNaV was observed in patients of group B. Individual data of the pattern of serum creatinine during the treatment are reported in Fig. 1. Three patients were discharged from the hospital and they continued the treatment at home. One of them was transplanted 44 days later while under treatment, and now he is still alive and shows a good renal function after 20 months from OLTX. Another patient discontinued the treatment after 2 months and he is still alive (472 days) with a degree of renal failure (serum creatinine 1.8 mg/dL), which is the same as he had before the onset of type 1 HRS. The remaining patient discontinued the treatment after 2 months and died 15 days after this owing to liver failure. One of the two patients who were not discharged from the hospital discontinued the treatment after 2 months. She was transplanted 20 days later and is still alive and with a normal renal function after 8 months from OLTX. The remaining patient died after 29 days of treatment from pneumonia when the renal function was almost totally recovered. One-month survival was significantly higher in patients of group B (Fig. 2).

As far as urinary excretion of renal tubular enzymes is concerned, an increase of UAGL/GFR, UGGT/GFR, and ClfLVS was observed in both groups of patients at day 5 after the initiation of treatment. Thereafter, a further increase in these parameters was observed in patients of group A whereas a normalization was observed in patients of group B (Fig. 3).

No significant side effects were observed in patients of group A. In those of group B, two patients experienced tingling and goosebumps and one patient suffered from diarrhea. Side effects did not require the discontinuation of therapy.

### TABLE 1. Clinical Parameters, Baseline Systemic Hemodynamics, Serum Sodium Concentration, and Renal and Liver Function Tests in Patients With HRS Treated With Nonpressor Doses of Dopamine (Group A) and With Midodrine and Octreotide (Group B)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 8)</th>
<th>Group B (n = 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 3</td>
<td>62 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of cirrhosis (alcoholic, HCV, HBV)</td>
<td>3/4/1</td>
<td>2/3/0</td>
<td>NS</td>
</tr>
<tr>
<td>Time from the appearance of ascites (yr)</td>
<td>2.7 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>NS</td>
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<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>0/1/7</td>
<td>0/1/4</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of peripheral edema (yes/no)</td>
<td>4/4</td>
<td>2/3</td>
<td>NS</td>
</tr>
<tr>
<td>Ascites (moderate/severe)</td>
<td>3/5</td>
<td>2/5</td>
<td>NS</td>
</tr>
<tr>
<td>Encephalopathy (yes/no)</td>
<td>3/5</td>
<td>1/4</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of type 2 HRS before the onset of type 1 HRS (yes/no)</td>
<td>4/4</td>
<td>2/3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum urea (mg·dl⁻¹)</td>
<td>167 ± 32</td>
<td>208 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.6 ± 0.6</td>
<td>5.0 ± 0.9</td>
<td>NS</td>
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<tr>
<td>Serum sodium (mEq/L)</td>
<td>128 ± 3</td>
<td>130 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.9 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>42.8 ± 5.4</td>
<td>44.4 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>6.1 ± 2.0</td>
<td>4.3 ± 1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. P values are the comparison between patients of group A and group B (Student’s t test for unpaired data and Fisher’s exact test).

Abbreviations: NS, not significant; HCV, hepatitis C virus; HBV, hepatitis B virus.
### Table 2. Effects of Nonpressor Doses of Dopamine (Group A) and Midodrine Plus Octreotide (Group B) on Systemic Hemodynamics, Renal Hemodynamics, Renal Function, Hormonal Parameters, and Liver Function Tests

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>5 days</th>
<th>10 days</th>
<th>20 days</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>78.9 ± 3.6</td>
<td>74.9 ± 2.1</td>
<td>79.1 ± 5.2</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>75.9 ± 3.0</td>
<td>90.9 ± 5.2</td>
<td>96.9 ± 6.5*</td>
<td>96.6 ± 4.7*</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>84 ± 5</td>
<td>92 ± 3</td>
<td>91 ± 5</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>84 ± 6</td>
<td>70 ± 5†</td>
<td>76 ± 3</td>
<td>76 ± 3</td>
<td>P &lt; .025</td>
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<tr>
<td><strong>Renal plasma flow (mL/min)</strong></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>80.92 ± 14.86</td>
<td>49.55 ± 5.37</td>
<td>67.70 ± 30.90</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>60.60 ± 16.02</td>
<td>81.75 ± 25.37</td>
<td>181.13 ± 46.20*</td>
<td>264.47 ± 71.18*</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (mL/min)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>14.48 ± 3.65</td>
<td>8.53 ± 1.74</td>
<td>11.60 ± 7.17</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>10.40 ± 3.67</td>
<td>16.11 ± 5.32</td>
<td>33.95 ± 4.22‡</td>
<td>46.06 ± 9.61*</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Serum sodium (mEq/L)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>5.0 ± 1.9</td>
<td>25.8 ± 7.9</td>
<td>44.6 ± 9.2‡</td>
<td>45.6 ± 8.8‡</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>13.61 ± 1.06</td>
<td>13.35 ± 1.27</td>
<td>16.83 ± 4.42</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Plasma renin activity (ng/mL/h)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>5.0 ± 1.9</td>
<td>25.8 ± 7.9</td>
<td>44.6 ± 9.2‡</td>
<td>45.6 ± 8.8‡</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>16.83 ± 1.66</td>
<td>7.78 ± 0.78∥</td>
<td>5.17 ± 0.52§</td>
<td>3.91 ± 0.74∥</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Plasma aldosterone (pg/mL)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>1,208.8 ± 140.9</td>
<td>1,174.4 ± 149.2</td>
<td>1,250.7 ± 274.9</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>1,349.2 ± 289.7</td>
<td>636.4 ± 108.9*</td>
<td>378.8 ± 53.7*</td>
<td>191.6 ± 35.7*</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Plasma ADH (pg/mL)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>3.55 ± 0.31</td>
<td>3.57 ± 0.82</td>
<td>3.17 ± 0.73</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>4.16 ± 0.82</td>
<td>2.84 ± 0.27</td>
<td>0.76 ± 0.08*</td>
<td>0.48 ± 0.08*</td>
<td>P &lt; .001</td>
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<tr>
<td><strong>Plasma ANP (pg/mL)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>65.2 ± 5.2</td>
<td>74.5 ± 4.8*</td>
<td>84.2 ± 8.7</td>
<td>—</td>
<td>P &lt; .025</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>61.6 ± 6.3</td>
<td>79.2 ± 5.2¶</td>
<td>81.6 ± 3.6*</td>
<td>81.0 ± 5.2‡</td>
<td>P &lt; .001</td>
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<tr>
<td><strong>Urinary sodium excretion (mEq/d)</strong></td>
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<tr>
<td>Group A (n = 8)</td>
<td>6.6 ± 0.9</td>
<td>18.7 ± 5.9</td>
<td>23.0 ± 10.7</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>5.0 ± 1.9</td>
<td>25.8 ± 7.9</td>
<td>44.6 ± 9.2‡</td>
<td>45.6 ± 8.8‡</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Plasma creatinine (µmol/L)</strong></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>457.5 ± 41.4</td>
<td>468.4 ± 24.5</td>
<td>514.7 ± 61.4</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>523.8 ± 73.9</td>
<td>284.4 ± 26.6*</td>
<td>225.6 ± 20.6*</td>
<td>182.6 ± 23.9*</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td><strong>Serum urea (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (n = 8)</td>
<td>167 ± 32</td>
<td>189 ± 29</td>
<td>187 ± 65</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>208 ± 22</td>
<td>192 ± 30</td>
<td>144 ± 20</td>
<td>110 ± 14*</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td><strong>Serum creatinine (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>3.6 ± 0.6</td>
<td>5.5 ± 0.8</td>
<td>5.1 ± 1.5</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>5.0 ± 0.8</td>
<td>4.6 ± 1.3</td>
<td>3.3 ± 0.7*</td>
<td>1.8 ± 0.1*</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td><strong>Serum sodium (mEq/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (n = 8)</td>
<td>128 ± 3</td>
<td>127 ± 2</td>
<td>133 ± 3</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>130 ± 3</td>
<td>139 ± 2</td>
<td>140 ± 1</td>
<td>139 ± 1*</td>
<td>P &lt; .025</td>
</tr>
<tr>
<td><strong>Serum albumin (g/dL)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Group A (n = 8)</td>
<td>2.9 ± 0.1</td>
<td>3.5 ± 0.1§</td>
<td>3.5 ± 0.1¶</td>
<td>—</td>
<td>P &lt; .025</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>3.0 ± 0.1</td>
<td>3.7 ± 0.2</td>
<td>3.9 ± 0.1‡</td>
<td>3.9 ± 0.1*</td>
<td>P &lt; .005</td>
</tr>
<tr>
<td><strong>Serum bilirubin (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (n = 8)</td>
<td>6.1 ± 2.0</td>
<td>7.5 ± 2.3</td>
<td>7.9 ± 4.7</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>4.3 ± 1.3</td>
<td>4.7 ± 1.5</td>
<td>5.9 ± 1.6</td>
<td>6.2 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prothrombin activity (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (n = 8)</td>
<td>42.8 ± 5.4</td>
<td>34.0 ± 4.8</td>
<td>40.0 ± 11.6</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>44.4 ± 8.0</td>
<td>40.8 ± 4.7</td>
<td>38.2 ± 5.8</td>
<td>40.6 ± 7.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Data of group A at day 10 are relative to the four survived patients. All P values are compared with baseline values by means of the Bonferroni test. Abbreviations: ANOVA, analysis of variance; NS, not significant; ANP, atrial natriuretic peptide; PA, plasma aldosterone concentration, FeNa, fractional sodium excretion.

*P < .05.
†P < .001.
‡P < .025.
§P < .001.
∥P < .005.
¶P < .0025.
Type 1 HRS is a serious complication of advanced cirrhosis with an almost universally fatal outcome. No medical treatment is currently available and liver transplantation represents the only therapeutic option for cirrhotic patients with HRS. However, the outcome from OLTX in these patients is compromised in terms of postoperative morbidity and mortality to such an extent that it has been stated that cirrhotic patients with ascites should be transplanted before the development of HRS. Moreover, in patients with type 1 HRS, the applicability of OLTX is very unlikely, because survival after the onset of renal failure is extremely short.

Our observations outline two very important points in the management of cirrhotic patients with HRS. The pattern of urinary excretion of renal tubular enzymes in our patients confirms that subclinical tubular damage may occur in HRS probably as a result of intense renal vasoconstriction. Tubular damage is reversible to some extent, but if renal ischemia cannot be resolved therapeutically, the laboratory features of acute renal failure could change from those associated with type 1 HRS to those of acute tubular necrosis, namely UNaV greater than 10 mEq/L. This observation, which was previously supported by histological findings, further underlines the urgency for performing OLTX in patients with HRS and could contribute, together with the use of nephrotoxic drugs such as cyclosporine, towards explaining why the recovery of renal function after OLTX is often delayed and incomplete in these patients.

However, the major contribution of the study is that the combined long-term administration of midodrine, an oral \( \alpha \)-adrenergic agent, and octreotide, an inhibitor of the release of powerful gastrointestinal vasodilator peptides such as glucagon and vasoactive intestinal peptide, led to an improvement in renal perfusion after 10 days and in its almost complete normalization after 20 days. As a consequence, the life expectancy was increased significantly compared with that obtained with other pharmacological approaches to reverse HRS. In our study in particular, 1-month survival in patients treated with midodrine and octreotide was significantly improved compared with that of patients treated with nonpressor doses of dopamine. The improvement in renal perfusion and renal function in patients treated with midodrine and octreotide was associated with an increase in mean arterial pressure and a decrease in HR. Thus, our data support the vasodilation theory, which proposed that HRS is the result of a marked decrease in effective circulating volume owing to arterial vasodilatation. The concomitant decrease that was observed in PRA and the plasma concentration of aldosterone and ADH further supports this interpretation. On the basis of a previous study that showed that an increase in glomerular filtration rate may be obtained by the...
it could be argued that the efficacy of our treatment may be related to the prolonged plasma volume expansion by intravenous administration of albumin, rather than to the administration of midodrine and octreotide. But two observations rendered this hypothesis extremely unlikely. The same plasma volume regimen did not prevent the progressive decline of renal function in most patients treated with nonpressor doses of dopamine. Moreover, midodrine alone was shown to increase RPF, GFR, and UNaV in patients with cirrhosis and ascites without HRS. Even if in the same study no significant effects on renal hemodynamics and function were observed in cirrhotic patients with ascites and HRS, it was just on the basis of these results that we changed our pharmacological approach to HRS. The lack of response to midodrine alone as well as to other vasoconstrictors in cirrhotics with HRS is not surprising, because an extremely impaired arterial reactivity to endogenous and exogenous vasoconstrictors has been described in these patients. The reduced arterial responsiveness to vasoconstrictors is related to an increased level of endogenous vasodilators, mainly in the splanchnic area and may be normalized by the inhibition of their release.

On the basis of this clinical and experimental evidence we hypothesized that the combined administration of an arterial vasoconstrictor and an inhibitor of glucagon release may increase the effectiveness of the former in the treatment of HRS. The choice to use an inhibitor of the release of glucagon in our patients was justified by the potential risk of further deteriorating renal hemodynamics and function by inhibiting the release of prostacyclin or NO. In particular, octreotide was proven to be effective in reducing splanchnic hyperemia and portal pressure reducing cardiac output and increasing mean arterial pressure in patients with cirrhosis. Moreover, octreotide, unlike other inhibitors of glucagon release (i.e., somatostatin) has no effect on renal hemodynamics and function. Unlike recent studies on the therapy of HRS with vasoconstrictors alone, no adverse ischemic effects were observed in our patients. This finding, together with the marked reduction of NOx and plasma levels of glucagon, further support the hypothesis that octreotide contributed toward normalizing the response of vasodilated splanchnic arterial vessels to midodrine, thereby avoiding its potential extraspahnic vascular effects. All these considerations allow us to state that the pharmacological approach we proposed may represent what Epstein called “a specific intervention to counteract the arterial vasodilation in patients with cirrhosis.” The suitability of this therapeutic approach for HRS should be proven in prospective, controlled studies in a large series of patients.

As far as the inhibition of endogenous vasodilators is concerned, whereas the decrease of glucagon release by means of octreotide was a foreseen event, the decrease of plasma NOx represented an unexpected and intriguing finding. It has been observed that midodrine reduces NOx probably as a consequence of the drug-induced improvement of systemic hemodynamics in cirrhotic patients with ascites, and that octreotide has no direct effect on NOx in these patients. Thus, the most likely hypothesis is that the reduction of NOx in our patients was owing to the correction of the hyperdynamic circulation and thus to a decrease in the shear stress. Nevertheless, the possibility that midodrine

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Figure 3: (A) The ratio of urinary excretion of γ-glutamyl transpeptidase to GFR, (B) the ratio of urinary excretion of α-glucosidase to GFR, and (C) the fractional clearance of lysozyme in cirrhotic patients with type 1 HRS treated with nonpressor doses of dopamine (group A) or with midodrine and octreotide (group B); d 5, d 10, and d 20 signify times after the initiation of treatment; dotted line, upper limit of normal range in our laboratory; *P < .05; **P < .025; ***P < .001; ****P < .005 compared with basal values by means of the Bonferroni test.
and/or octreotide may directly reduce the release of NO in patients with advanced cirrhosis needs further investigation.

Few pharmacokinetic data exist on midodrine and octreotide in cirrhotic patients with HRS. In the current study, drugs were dosed empirically to obtain a stable elevation in MAP of at least 15 mm Hg. It should be noted that the maximum dosage of octreotide used in the study was the same as that administered to cirrhotic patients with gastrointestinal hemorrhage by Besson. As far as midodrine dosage is concerned, the highest dose used in the study was not so different from that administered acutely in cirrhotic patients with ascites in our previous study. Finally, considering the modalities of administration of midodrine and octreotide, it should also be pointed out that three patients were able to continue the therapy for HRS at home. To our knowledge, this is the very first time that this event has been highlighted, thereby underlining another advantage of the drugs that were chosen for the treatment of HRS in the current study.

In conclusion, our study shows that the prolonged administration of midodrine and octreotide combined with plasma volume expansion by means of albumin is a promising therapeutic perspective in the treatment of type 1 HRS. Even if further investigations are required to confirm the effectiveness and safety of this therapeutic approach, it should be considered because no other effective treatment except for OLTX exists as yet, and the survival after the onset of type 1 HRS is often too short in patients already placed on a waiting list for liver transplantation.

Acknowledgment: The Authors are indebted to Stefania Magrini and Marina Canapero for the preparation of the manuscript.

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