Treatment with terlipressin as a bridge to liver transplantation in a patient with hepatorenal syndrome

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Abstract

Hepatorenal syndrome is a rapidly lethal complication of cirrhosis. The present case provides further evidence of the efficacy of terlipressin in this context even with concomitant treatment with propranolol. A 56 year old male with HBV related cirrhosis developed renal failure characteristic of hepatorenal syndrome. He was also taking propranolol for primary prophylaxis of variceal bleeding. Terlipressin 6 mg/day was administered during haemodialysis and after 1 week plasma creatinine dropped from 6,2 to 2,8 mg%. Daily urinary volume, plasma sodium and natriuresis dramatically increased during the treatment. Discontinuation of the treatment led to a rapid relapse of renal failure (plasma creatinine from 1,8 to 2,2 mg%) and the drug was readministered until a successful liver transplantation could be performed 1 month after the beginning of the treatment. The patient has now a near normal renal function 3 months after transplantation. (Acta gastroenterol. belg., **1998**, 61, **268-270**).

Hepatorenal syndrome (MRS) is a severe complication of liver cirrhosis. It develops in 39% of the patients followed-up for 5 years and its associated mortality is extremely high since median survival after the diagnosis is only 1,7 week (1). To date, the unique effective treatment remains liver transplantation, which despite increased perioperative morbidity, allows the recovery of renal function with a minimal impact on survival compared to patients without HRS (2). However, from a practical point of view, few patients will benefit from liver transplantation due to the high early mortality associated with HRS and the time required to get a liver on waiting lists. Therefore, the best management for these patients should be a medical treatment that allows renal function recovery while they are waiting for liver replacement. Unfortunately, among most of the treatments tried in this condition, none disclosed a clear benefit in pilot studies and no randomized trials are actually published in this setting. Recent uncontrolled series have reported the potential benefit of prostaglandins (3), ornipressin or terlipressin (4-6) and TIPS in the management of HRS (7). The present case provides additional evidence that the long-term use of terlipressin in a patient with HRS is able to nearly normalise renal function until liver transplantation, even in the case of concomitant administration of beta-blockers.

Case report

A 56 year old man with HBV associated cirrhosis, oesophageal varices and ascites was registered as candidate for liver transplantation in January 1997. At that time, he was taking 80 mg propranolol for primary prophylaxis of variceal bleeding, 100 mg spironolactone and 40 mg furosemide for the control of ascites. On clinical examination he had moderate ascites, plasma creatinine (pCreat) was 1,3 mg%, plasma sodium 124 mEq/L and the Pugh score was 10/15. By the end of April 1997 he developed tense ascites, pCreat was 1,9 mg%, diuretics were continued at the same dosage and total paracentesis was performed. Three weeks later he was readmitted with encephalopathy and renal failure (pCreat 6,3 mg%, urea 178 mg%). Extensive work-up ruled out any precipitating event (no evidence of digestive haemorrhage ; negative blood, ascites and urine cultures ; patent portal vein and no liver tumor at ultrasound examination, and no ingestion of nephrotoxic agents). Urinary sodium excretion was 2 mEq/24h for 200 ml urines collected during 24 hours. Despite albumin (500 ml) and saline (2000 ml) infusion for 48h, renal function did not improve and haemodialysis was started with a diagnosis of HRS (8). Diuretics were discontinued, propranolol was kept at the same dosage and terlipressin 2 mg tid was begun. Haemodialysis could be stopped after two sessions due to a decrease in pCreat and increased diuresis. After 7 days of terlipressin pCreat was 2,4 mg%, urea 139 mg%, urinary volume 900 ml/day and urinary sodium 24 mEq/L (Fig. 1 & 2). In addition, systolic blood pressure increased from 95 mmHg before the treatment to 110 mmHg during 6 mg/day terlipressin administration. No complication of the treatment was observed and the drug was continued for another week with a resultant pCreat of 1,8 mg%. Stopping drug administration at that time resulted in a rapid relapse of renal failure (pCreat 2,2 mg% and urinary volume 450 ml/24h within 2 days) and decrease in systolic blood pressure (90 mmHg). Terlipressin was again administered (1 mg bid for two days and 2 mg bid thereafter) with improvement of kidney function and stabilisation of systolic blood pressure around 100 mmHg until a successful liver transplantation could be performed 2 weeks ater. No delay in cyclosporine administration

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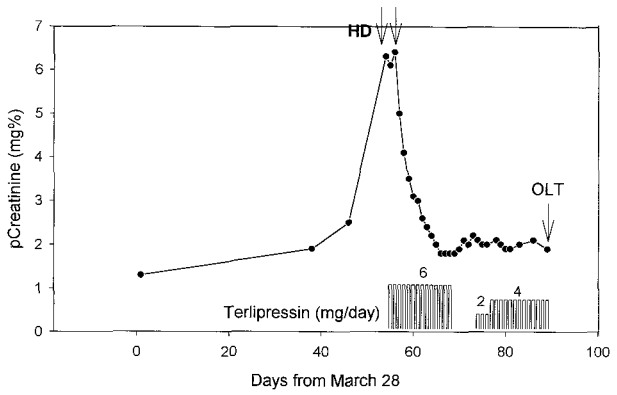

Fig. 1. — Course of plasma creatinine (black circles) with respect to terlipressin administration (vertical bars). HD (haemodialysis). OLT (orthotopic liver transplantation).

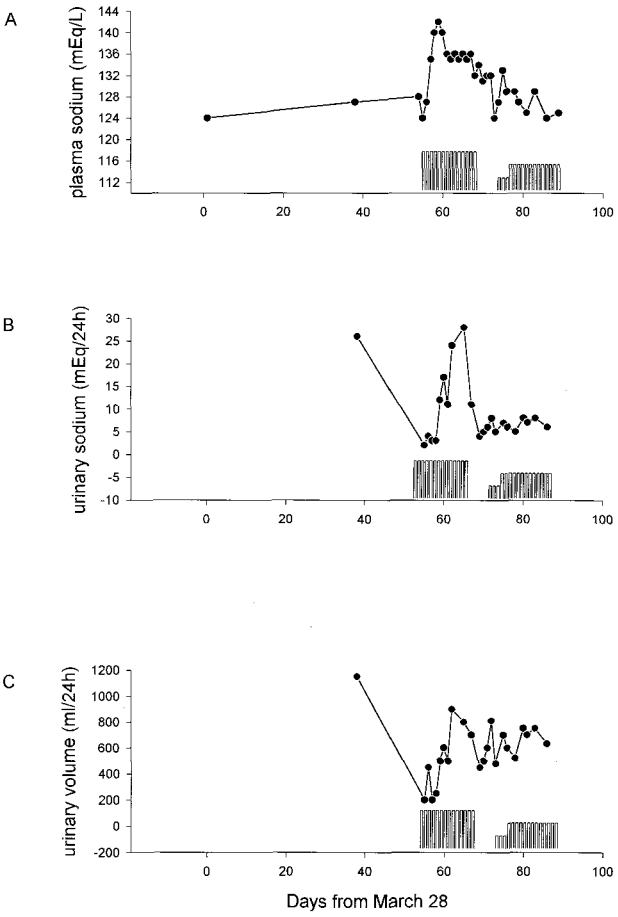

Fig. 2. — Course of plasma sodium (A, black circles), urinary sodium (B, black circles) and daily urinary volume (C, black circles) before and during terlipressin administration (vertical bars). For terlipressin doses see fig. 1.

was required and the patient has currently 1,4 mg% pCreat 3 months after transplantation without any complication. Evolution of natriuresis, urinary volume and plasma sodium concentration before and during terlipressin administration are depicted in Fig. 2.

Discussion

The present case shows that chronic administration of terlipressin was effective in the treatment of HRS and allowed a successful liver transplantation without any delay in the administration of cyclosporine. Moreover, nearly one month of intravenous administration was proved clinically safe. The novel finding of the current report compared to the two ones recently published (5,6), is that the same beneficial effects were obtained in a patient concomitantly treated with another vasoactive drug, namely, propranolol. Since both drugs, terlipressin and propranolol decrease cardiac index, their combination may have adversely affected renal perfusion in this patient. It was clearly not the case. In fact, despite propranolol administration the patient dramatically improved its renal function that allowed the discontinuation of haemodialysis. It was recently shown that acute administration of terlipressin in patients taking beta-blockers lead to additional systemic increase in systemic vascular resistances and mean arterial pressure, and an additional decrease in hepatic venous pressure gradient and azygos blood flow (9). Both effects may, indeed, influence circulating levels of neuro-humoral factors that regulate sodium and water retention and vascular reactivity in the kidney, such as the renin-angiotensin system (RAS) and the sympathetic tone assessed by norepinephrine plasma levels (NE). The current beneficial effect of ornipressin or terlipressin is attributed to splanchnic vasoconstriction without such a consequence on the renal circulation. This leads to a decrease in the RAS and NE levels, in parallel with an increase in atrial natriuretic peptide (5). The resultant is a redistribution of circulating blood flow to the kidney associated with a reduction of sodium retention and increased glomerular filtration rate. These effects were clearly obtained in our patient who disclosed increase in mean arterial pressure, increased natriuresis and daily urinary volume, and definite improvement in renal function. Interestingly, plasma sodium, urinary sodium and systolic blood pressure were dependent on the daily dose of terlipressin. Indeed, after stopping the drug, readministration of lower doses (2 followed by 4 mg) were not able to provide the effects of 6 mg daily concerning these parameters. Another explanation would rely on progressive vasopressin receptors desensitisation.

Spontaneous improvement of HRS in this patient could reasonably be ruled out since it has scarcely been reported (1), and discontinuation of terlipressin after 2 weeks led to a rapid relapse of renal failure, decrease in daily urinary volume and natriuresis that was reversed by drug readministration. Nevertheless, it is clear that these results must now be confirmed in randomised trials.

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