Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome : a pilot study

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Abstract

Background : **Hepatorenal syndrome (HRS) is a severe complication of liver cirrhosis. Recently, ornipressin, a potent splanchnic vasoconstrictor, was reported to improve renal function in patients with HRS. However, this treatment is associated with a high incidence of vascular complications. Terlipressin is thought to be as effective as ornipressin with less systemic complications.**

Aims : **To evaluate the effectiveness and safety of terlipressin administration in cirrhotic patients with type 1 HRS.**

Patients : **Twelve consecutive patients fulfilling HRS criteria of the International Ascites Club were included in the study. Median plasma creatinine and sodium, urine volume and sodium before treatment were 3,4 mg% {2,5-4,0} ; 127 mEq/l {124-130}, 500 ml/24h {100-1031} and 7 mEq/24h {1-17}.**

Methods : **Terlipressin was administered iv 2 mg bid in 8 patients and tid in 4 others for at least one week and up to 2 months.**

Results : **After one week of treatment median plasma creatinine decreased to 1.8 mg% {1.3-2.1} together with an increase in urine volume, sodium excretion, creatinine and free-water clearance. Three patients underwent successful liver transplantation with a near normal renal function after 34, 36 and 111 days. The 9 other patients died during follow-up (4 from sepsis, 2 from digestive bleeding and 3 from liver failure). No ischaemic complications were encountered during the treatment.**

Conclusions : **Long-term terlipressin administration is safe and effective to control type 1 HRS. However, it does not cure the underlying disease and therefore, may only be considered as a bridge to a definitive treatment as liver transplantation.** (Acta gastroenterol. belg., **2001**, 64, **15-19**).

Key words : cirrhosis, portal hypertension, vasoconstrictors, renal failure, liver transplantation, sodium.

Introduction

Hepatorenal syndrome (HRS) is the most common type of renal failure in patients with cirrhosis. Its natural history is currently well defined and the pathophysiology of HRS adequately fits with the arterial underfilling theory (1,2). Excessive splanchnic vasodilatation in the context of portal hypertension leads to systemic vascular underfilling. As a consequence, the renin — angiotensin — aldosterone axis is stimulated, systemic vasoconstrictors as norepinephrin are released and a non osmotic release of anti-diuretic hormone occurs. The net result is sodium and water retention which helps to maintain an effective circulating volume. When splanchnic vasodilatation further increases, in spite of a maximal stimulation of the vasoconstrictor systems, vascular underfilling worsens, inducing renal vasoconstriction and a decrease of the glomerular filtration rate which ultimately leads to the development of HRS (2). This renal impairment often occurs rapidly over days (type 1) and is associated with a very poor prognosis, the median survival being less than 2 weeks (1).

As a splanchnic vasoconstrictor, ornipressin, together with plasma volume expansion is able to improve renal function in patients with type 1 HRS and normalises the overactivity of renin-angiotensin and sympathetic nervous systems (3,4). However, the use of ornipressin in this setting is often associated with severe ischaemic complications which jeopardise long-term administration of the drug (4). As an alternative, terlipressin, a long-acting analog of vasopressin, has less side effects, is also able to improve renal function after a short administration course and was reported to reverse HRS in two patients (5-7). It is however not known if long-term administration of terlipressin can be beneficial for these patients. The aim of the present study was to assess the effectiveness and safety of long-term terlipressin administration in the treatment of HRS type 1.

Patients and methods

Patients

Twelve consecutive cirrhotic patients with a type 1 HRS admitted between September 1997 and March 1999 were included in this prospective study. Informed consent was obtained from all patients or their relatives before inclusion. The diagnosis of cirrhosis was based on liver biopsy in 10 patients and on clinical, biochemical and radiological data in two patients. Liver biopsy was performed by the transjugular route allowing also the measurement of hepatic venous pressure gradient. The diagnosis of HRS was performed according to the criteria of the International Ascites Club (2). Briefly, all patients had plasma creatinine levels above 2.0 mg/dL. After a complete systematic bacteriological workup (urine, ascites and blood cultures), infections could be ruled out. None of the patients had a history of nephrotoxic drug intake, recent gastrointestinal bleeding and all had portal hypertension. Microscopic examination of the

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urine sediment ruled out any glomerulopathy or tubulopathy. From the day of suspected diagnosis of HRS, diuretics were stopped and isotonic saline (1500 ml/day) and albumin (60 gr/day) administered for 2 days. Under this regimen, none of the patients improved their renal function, even more one patient had to be haemodialysed. None of the patients had contraindication to terlipressin administration (coronary disease, uncontrolled arterial hypertension, cerebral or peripheral vasculopathy, respiratory disorders and medical history of epileptic spasms). Four patients were under beta-blockers for primary or secondary prevention of variceal bleeding. Patients clinical and biological characteristics are given in Table 1.

Table 1. — **Clinical, biological and haemodynamic characteristics of the 12 patients before treatment initiation. Data are expressed as medians with their 95% confidence interval**

Age (years)	53,5 (44,8 – 60,2)
Sex (male/female)	10 / 2
Etiology of cirrhosis (alcoholic/non alcoholic)	9 / 3
Alcoholic hepatitis (n)	5
Hepatocellular carcinoma (n)	3
Child class (B/C)	2 / 10
Ascites (moderate/tense)	6 / 6
Encephalopathy (none/moderate/severe)	1 / 11 / 0
Total bilirubin (mg/dl)	6,2 (1,7 – 20,5)
Prothrombin Time (%)	38 (24 – 58)
Albumin (g/dl)	2,9 (2,4 – 3,4)
Mean arterial pressure (mmHg)	76 (68 – 83)
Heart rate (beats/min)	91 (74 – 110)
Hepatic venous pressure gradient (mmHg)	18,5 (10,9 – 30,5)
Plasma creatinine (mg/dl)	3,4 (2,5 – 4,0)
Blood urea nitrogen (mg/dl)	134 (91 – 191)
Plasma Sodium (mEq/l)	127 (124 – 130)
Urine volume (ml/24h)	500 (100 – 1031)
Urine Sodium (mEq/24h)	7 (1-17)
Creatinine clearance (ml/min)	11 (7 – 24)

Methods

Once the definite diagnosis of HRS established, namely in the absence of renal function improvement after plasma volume expansion, patients were treated intravenously with terlipressin (Glypressine®, Ferring, Wevelgem, Belgium) via a large calibre vein (injection over 1 minute). Administration schedule for terlipressin was 2 mg tid in the four first patients and 2 mg bid in the eight subsequent patients. This dose is less than what is recommended for variceal bleeding (2 mg four times a day) and was given for one week. After one week, doses were tapered to maintain plasma creatinine at the lowest and steady levels obtained with the higher doses. After at least two days of steady plasma creatinine levels under the lowest dose of terlipressin (1 or 2 mg/day) the treatment was stopped. If renal function deteriorated again, terlipressin was reintroduced at the lowest dose used before stopping the drug. During the first days of the treatment a concomitant infusion of albumin (0,5-1g/kg per day) was maintained in all patients. The details of the treatment are depicted in Table 2. Blood pressure and heart rate were monitored 3 times a day. Clinical records, blood electrolytes and renal function were followed every day. Patients were not treated in the Intensive Care Unit. Twenty-four hours urine collection for daily electrolyte and creatinine excretion were determined before terlipressin administration and as far as possible, every three days during the treatment (it is our policy not to use bladder catheters in cirrhotic patients). The free water clearance in electrolytes was calculated by using the formula of Burton Rose (8), taking into account urine sodium, potassium and volume, and plasma sodium (C_{H2O} = Vol x (1 – U_{Na+K} / PNa), were C_{H2O} is the free-water clearance, Vol the 24 hours urine volume, U_{Na+K} the sum of daily urine sodium and potassium excretion, PNa the plasma sodium concentration).

Statistical analysis

Data are expressed as medians with their 95% confidence intervals. Statistical comparisons were performed with the paired Wilcoxon rank test. The survival curve was constructed according to the Kaplan-Meier method, patients undergoing liver transplantation were censored alive at the time of surgery. Significance was considered at a p value < 0,05.

Results

Biological and haemodynamic response to terlipressin

All patients presented a significant decrease in plasma creatinine after starting terlipressin. The effect was obvious after 2 days of treatment and often maximal by day 7 (Table 3 and Fig. 1). In the patient initially managed by haemodialysis, extra-renal epuration could be stopped after 3 days of terlipressin. Plasma creatinine dropped below 2 mg/dL in 9 patients and in 11 out of 12 patients after 1 week and 2 weeks of treatment, respectively. The response to terlipressin was the same whatever the initial administration regimen (6 or 4 mg/day). The only patient who responded poorly had an hepatocellular carcinoma with portal vein thrombosis. The treatment also resulted in a significant increase in sodium plasma levels and a slight increase in mean arterial pressure (Table 3). In seven patients the daily urines could be collected after a week of treatment and compared to those obtained before treatment. In these patients, daily urine volume, creatinine clearance, daily sodium excretion and free water clearance significantly increased during terlipressin administration (Table 4).

Clinical response to terlipressin and follow-up

One patient presented abdominal cramps during the first injection of terlipressin, this symptom did not recur during the subsequent injections. In three patients slight hypernatremia (149, 150, 151 mEq/l) developed, all

Table 2. — **Details of the first two weeks of treatment (medians with their 95% confidence interval)**

Days	0	2	4	6	8	10	12	14
Albumin infusion (g/day)	40 (12-60)	40 (12-60)	20 (0-60)	0 (0-48)	0	0	0	0
Dose of Terlipressin (mg/day)	4 (4-6)	4 (4-6)	4 (4-6)	4 (2-6)	4 (1-6)	2 (0-4)	2 (0-3,5)	2 (0-2)

Table 3. — **Time course of systemic haemodynamics, plasma creatinine and plasma sodium during the first two weeks of treatment (medians with their 95% confidence interval). ¶ p < 0,05 compared to day 0 value**

Days	0	2	4	6	8	10	12	14
HR (bts/min)	91 (74-110)	85 (75-105)	80 (75-100)	84 (62-102)	85 (75-98)	86 (77-100)	85 (79-100)	84 (68-100)
MAP (mmHg)	76 (68-83)	83 ¶ (74-93)	78 ¶ (73-89)	80 ¶ (73-97)	80 (73-88)	83 (73-90)	87 ¶ (77-95)	75 (73-98)
Creatinine (mg/dl)	3,4 (2,5-4,0)	2,7 ¶ (2,0-3,1)	2,1 ¶ (1,7-2,6)	1,8 ¶ (1,5-2,3)	1,8 ¶ (1,3-2,1)	1,6 ¶ (1,2-2,1)	1,6 ¶ (1,3-2,0)	1,6 ¶ (1,2-2,0)
Sodium (mEq/l)	127 (124-130)	132 ¶ (128-137)	137 ¶ (132-143)	135 ¶ (131-140)	136 ¶ (130-142)	137 ¶ (129-141)	135 ¶ (127-139)	133 (124-143)

HR : heart rate, MAP : mean arterial pressure.

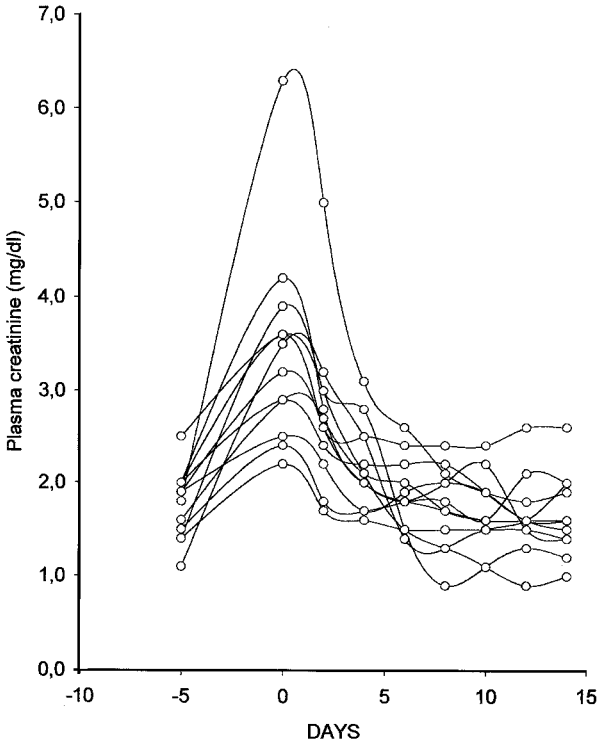

Fig. 1. — Time course of plasma creatinine in twelve patients with HRS type 1. Before the development of HRS (Day -5), baseline values after failure of plasma expansion (Day 0) and thereafter during terlipressin administration (up to Day 14).

three also had severe diarrhoea subsequent to lactitol administration. No overt ischaemic complication was observed during the study. The median duration of the treatment was 26 days, with a minimum of 8 days and a maximum of 68 days. In 9 patients who had a stable renal function after a median terlipressin treatment of 17 days (8-26), we tried to stop the medication. In 4, the treatment had to be restarted within 4 days because of recurrent renal failure. In 1 of these patients a second attempt to stop terlipressin failed again after 47 days, and it is only after 68 days of treatment that discontinuation was successful. Therefore, a complete and sustained withdrawal of terlipressin without recurrence of HRS was obtained in 6 out of 12 patients. Nine patients eventually died from other complications of cirrhosis : bacterial sepsis in 4 patients, digestive bleeding in 2 patients and liver failure in 3 patients. Orthotopic liver transplantation was performed in three patients 34, 36 and 111 days after the beginning of the treatment. One patient was still under terlipressin at the time of transplantation. All three patients had a preoperative plasma creatinine below 2 mg/dL and below 1.6 mg/dL at day 3 postoperatively, which allowed safe introduction of cylosporine in the immunosuppressive regimen. They are still alive in good condition 12, 14 and 30 months after transplantation. The survival curve of the whole population discloses a median survival time of 42 (35-49) days (Fig. 2).

Discussion

The present study shows that long-term terlipressin administration dramatically improves renal function in cirrhotic patients with type 1 HRS. Importantly, terlipressin is easy to administer and no severe ischaemic complication occurred during the treatment even when the drug was administered for up to two months. Recent evidence was provided that the splanchnic vasoconstrictor, ornipressin, is able to reverse HRS in cirrhotic

Table 4. — **Effects of terlipressin and albumin infusion on renal function. Data from 7 patients for whom 24 hours urine collection was available between 5 and 8 days after treatment initiation**

	Before treatment	After one week	P
Urine volume (ml/24h)	500 (100-1031)	1160 (500-2712)	< 0,05
Creatinine clearance (ml/min)	11 (7-24)	33 (15-43)	< 0,05
Urine Sodium (mEq/24h)	7 (1-17)	38 (5-283)	< 0,05
Free water clearance (ml/24h)	201 (60-546)	413 (193-900)	< 0,05

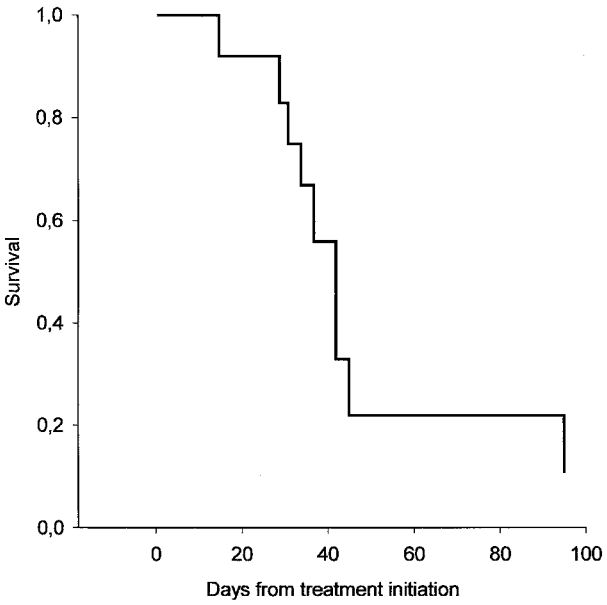

Fig. 2. — Kaplan-Meier survival plot from the initiation of terlipressin treatment. Three patients underwent liver transplantation and were censored alive at the time of surgery. The median survival rate was 42 days.

patients (4,9). Both short-term and long-term administration of this compound induces the normalisation of the increased renin activity, aldosterone and norepinephrine plasma levels together with an increase in atrial natriuretic peptide plasma levels (3,4). However, it is only the long-term administration of ornipressin which is associated with a prominent effect on renal function, ie increase in glomerular filtration rate, urine volume and normalisation of serum creatinine, and an increase of mean arterial pressure (4). Similar results were subsequently reported by using ornipressin (10,11) and other splanchnic vasoconstrictors as mitodrine in combination with octreotide (12). However, the major drawbacks of ornipressin treatment are the need for continuous infusion with careful surveillance of the dose administered and the high rate of side effects, especially those related to ischaemia. Indeed, in at least 30% of the patients with long-term ornipressin administration for HRS, the treatment had to be discontinued in relation to ischaemia-related side effects as ischaemic colitis, cardiac arrhythmia's or tongue ischaemia (4,10). Thus far, an effective treatment of HRS which is not associated with so severe side effects is clearly needed. In this context, terlipressin, another synthetic analog of vasopressin, is known to be safer, at least in the setting of variceal bleeding (13). Recently, Hadengue et al, showed that 2 days terlipressin treatment is also able to decrease renin activity and aldosterone plasma levels as well as improving creatinine clearance and urine output in patients with HRS (7). In addition, two cases were reported describing patients with HRS in whom long-term administration of terlipressin allowed safe liver transplantation without side effects (5,6). The present prospective study extends these observations to a larger number of patients with HRS. As for the previous studies, it is extremely unlikely that the improvement in renal function observed in these patients would be related to plasma volume expansion or a so called placebo effect. Indeed, all patients fulfilled the recently published criteria for the diagnosis of HRS (2) and each of them failed to respond to plasma volume expansion with albumin and isotonic saline for at least 2 days. In addition, spontaneous recovery from HRS is known to be less than 5% (1). Therefore, the observed improvement in renal function is most likely to be related to terlipressin administration although the definitive demonstration of this effect should be confirmed in a randomised trial.

Three major messages can be taken from the present study. The first is that terlipressin administration in the case of HRS leads to a dramatic improvement of renal function in all patients, similar to that observed in the studies using ornipressin (4,10). The major differences are related to the safety of the drug and its ease of administration. No severe ischaemic complications were observed, even when terlipressin was administered for months, Intensive Care Unit surveillance is not necessary, and a regimen of 2 mg bid was as effective as 2 mg tid during the first week of treatment. Afterwards, for those patients in whom the drug could not be discontinued, the daily dose of terlipressin was 1 to 2 mg once a day, a regimen that can easily be managed on an outpatient basis. The second point is that terlipressin treatment rapidly normalises plasma sodium levels. Hyponatraemia is associated with and is one of the predictive factors of HRS development (1). This observation was not reported in trials using ornipressin, even if a non significant trend towards an increase in plasma sodium is described (4,10). This finding may be related to the specificity of terlipressin's binding to V1 or V2 receptors, the receptors of vasopressin. V1 receptors are involved in smooth muscle contraction and are particu-

larly abundant in the splanchnic area, while V2 receptors are mainly located in the kidney and responsible for the anti-diuretic action of vasopressin. Since terlipressin has less affinity than ornipressin for V2 receptors (14), the increase in plasma sodium may be more pronounced under terlipressin treatment due to less anti-diuretic effect and, therefore, to an increased water clearance as it was shown in the present study. This peculiar effect of terlipressin should be kept in mind as 3 out of 12 patients developed slight hypernatraemia in the presence of lactitol induced diarrhoea. On the other side, this means that specific V1 agonists might be useful for treating cirrhosis associated hyponatraemia while anti-V2 molecules which are currently under development for the treatment of hyponatraemia in other diseases (15) might be deleterious in this setting, due to the decrease in effective blood volume that they may induce. The third major message seems obvious but has to be underlined. It is that the treatment of HRS with terlipressin does not cure the underlying disease. Indeed, the median survival rate after the treatment was presently of 42 days, which is dramatically improved compared to the 12 days reported in the single study published to date concerning the natural history of HRS (1). However, the 3 months mortality rate was still 100% for those patients who were not transplant candidates or those who could not benefit of liver transplantation. All died from other causes than HRS, namely bacterial infections, gastrointestinal bleeding or liver failure. This probably means that HRS is an ultimate expression of terminal liver failure or portal hypertension and that only patients suitable for liver transplantation would benefit from terlipressin treatment as a bridge towards a definitive cure of hepatocellular failure and portal hypertension.

Finally, it should be considered that some new therapeutic modalities including splanchnic vasoconstriction (4,10,12,16), but also portal decompression with TIPS (17,18) or anti-oxidant therapy (19) allow patients with HRS to benefit from a survival delay. These new treatments will have to be compared in the future to determine the best strategy with less side effects and maximal impact on survival.

ADDENDUM : During the reviewing process another pilot study dealing with the treatment of hepatorenal syndrome with terlipressin was published (J. Uriz et al, J Hepatol 2000 ; 33 : 43-48). The present article confirms the safety of terlipressin administration in the treatment of hepatorenal syndrome using lower doses than those recommended for variceal bleeding. In addition, we show that retreatment and administration of terlipressin for months upon relapse is feasible without side-effects and may allow patients to undergo liver transplantation.

References

1. GINES A., ESCORSELL A., GINES P. *et al.* Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*, 1993, **105** : 229-236.
2. ARROYO V., GINES P., GERBES A.L. *et al.* Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology*, 1996, **23** : 164-176.
3. LENZ K., HORTNAGL H., DRUML W. *et al.* Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. Effects on renal hemodynamics and atrial natriuretic factor. *Gastroenterology*, 1991, **101** : 1060-1067.
4. GUEVARA M., GINES P., FERNANDEZ-ESPARRACH G. *et al.* Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology*, 1998, **27** : 35-41.
5. GANNE CARRIE N., HADENGUE A., MATHURIN P., DURAND F., ERLINGER S., BENHAMOU J.P. Hepatorenal syndrome. Long-term treatment with terlipressin as a bridge to liver transplantation. *Dig. Dis. Sci.*, 1996, **41** : 1054-1056.
6. LE MOINE O., EL NAWAR A., JAGODZINSKI R. *et al.* Treatment with terlipressin as a bridge to liver transplantation in a patient with hepatorenal syndrome. *Acta Gastroenterol. Belg.*, 1998, **61** : 268-270.
7. HADENGUE A, GADANO A, MOREAU R. *et al.* Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J. Hepatol.*, 1998, **29** : 565-570.
8. ROSE B.D. New approach to disturbances in the plasma sodium concentration. *Am. J. Med.*, 1986, **81** : 1033-1039.
9. LENZ K., DRUML W., KLEINBERGER G. *et al.* Enhancement of renal function with ornipressin in a patient with decompensated cirrhosis. *Gut*, 1985, **26** : 1385-1386.
10. GULBERG V., BILZER M., GERBES A.L. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology*, 1999, **30** : 870-875.
11. EISENMAN A., ARMALI Z., ENAT R., BANKIR L., BARUCH Y. Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. *J. Intern. Med.*, 1999, **246** : 183-190.
12. ANGELI P., VOLPIN R., GERUNDA G. *et al.* Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology*, 1999, **29** : 1690-1697.
13. D'AMICO G., TRAINA M., VIZZINI G. *et al.* Terlipressin or vasopressin plus transdermal nitroglycerin in a treatment strategy for digestive bleeding in cirrhosis. A randomized clinical trial. *J. Hepatol.*, 1994, **20** : 206-212.
14. BERNADICH C., BANDI J.C., MELIN P., BOSCH J. Effects of F-180, a new selective vasoconstrictor peptide, compared with terlipressin and vasopressin on systemic and splanchnic hemodynamics in a rat model of portal hypertension. *Hepatology*, 1998, **27** : 351-356.
15. MAYINGER B., HENSEN J. Nonpeptide vasopressin antagonists : a new group of hormone blockers entering the scene. *Exp. Clin. Endocrinol. Diabetes*, 1999, **107** : 157-165.
16. KAFFY F., BORDERIE C., CHAGNEAU C.*et al.* Octreotide in the treatment of the hepatorenal syndrome in cirrhotic patients [letter]. *J. Hepatol.*, 1999, **30** : 174
17. BRENSING K.A., TEXTOR J., STRUNK H., KLEHR H.U., SCHILD H., SAUERBRUCH T. Transjugular intrahepatic portosystemic stent-shunt for hepatorenal syndrome. *Lancet*, 1997, **349** : 697-698.
18. GUEVARA M., GINES P., BANDI J.C. *et al.* Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome : effects on renal function and vasoactive systems. *Hepatology*, 1998, **28** : 416-422.
19. HOLT S., GOODIER D., MARLEY R. *et al.* Improvement in renal function in hepatorenal syndrome with N-acetylcysteine [letter]. *Lancet*, 1999, **353** : 294-295.