Treatment of hepatorenal syndrome with TERLIPRESSIN

By Klaus-D. Döhler, Curatis Pharma GmbH, D-30625 Hannover, Germany

Hepatorenal syndrome is a functional renal disorder that occurs in cirrhotic patients with advanced liver disease and ascites. Hepatorenal syndrome is caused by marked hypoperfusion of the kidneys as the result of renal vasoconstriction, which is thought to be the extreme manifestation of an underfilling of the arterial circulation. This circulatory dysfunction is the consequence of arterial vasodilation in the splanchnic circulation. The cause for this splanchnic vasodilation is thought to be due to systemic and locally acting vasodilators like nitrogen oxide (NO), glucagon, calcitonin-gene-related peptide (CGRP), substance P, vasoactive intestinal peptide (VIP), tumor necrosis factor (TNF), adrenomedullin and the non-adrenergic, non-cholinergic neurotransmitter system.

Splanchnic vasodilatation leads to reduced vascular resistance and to increased blood volume in the mesenterial blood vessels. This blood pooling generates hypovolemia in the central and arterial system with decreased systolic and diastolic blood pressure, initiating compensatory activation of the renin-angiotensin-aldosteron system (RAAS) and the sympathetic nervous system (SNS). This compensatory mechanism induces renal vasoconstriction which is followed by hypoperfusion of vital organs, worsening of renal hemodynamics and occurrance of renal failure.

Hypoperfusion of the kidneys leads to sodium and water retention and to impaired glomerular filtration rate. Hepatorenal syndrome Typ I is associated with a very low survival expectancy and with a mortality rate of up to 80 % within one month.

There is no established drug therapy yet for the treatment of hepatorenal syndrome. Preliminary studies, however, have shown that the administration of splanchnic vasoconstrictors such as terlipressin in combination with volume expanders improved renal function in patients with hepatorenal syndrome and may be used to bridge the time until liver transplantation can be performed.

Splanchnic vasoconstriction reduces blood flow into the portal vein and, thus, reduces portal venous pressure. In consequence, blood flow through porto-caval shunts is reduced, central and arterial hypovolaemia is corrected and activation of the RAAS and the SNS are reduced, leading to lower intrahepatic and intrarenal resistance. The result is an improvement of organ perfusion – including perfusion of the kidneys and the liver – and an improvement of the hyperdynamic cardiovascular situation.

Application of the splanchnic vasoconstrictor terlipressin has shown in a number of studies to improve kidney function in patients with hepatorenal syndrom (1-22). Terlipressin has been shown

- to reduce serum levels of creatinine below 1,5 mg/dl (14, 20) and
- to improve the cardiovascular situation *via* an increase in mean arterial blood pressure and *via* inhibition of plasma renin activity and lowering of plasma levels of aldosterone and noradrenalin (20),
- to stimulate glomerular filtration rate *via* vasoconstriction of the renal glomerular vessels (2, 14, 16, 18, 20), and
- to stimulate natriuresis (16, 18) and urine excretion (14, 16, 18), parameters which improve hepatorenal syndrome (9 – 11, 14 – 16, 18, 20).

Of particular interest is the observation that in many of these patients, treated with terlipressin and volume expanders, the improved cardiovascular situation persisted and hepatorenal syndrome did not recur following discontinuation of the treatment (2), thus raising important questions about the mechanism by which hepatorenal syndrome follows a progressive course in most untreated cases.

[#1] Hepatorenal syndrome in cirrhosis: pathogenesis and treatment.

Arroyo V, Guevara M, Ginès P.

Liver Unit, Institute of Digestive Disease, Hospital Clinic, University of Barcelona, Villaroel 170, 08036 Barcelona, Spain. arroyo@medicina.ub.es

Gastroenterology 2002 May;122(6):1658-76

Publication Types:

- Review
- Review, Tutorial

PMID: 12016430 [PubMed - indexed for MEDLINE]

[#2] Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem.

Arroyo V, Jimenez W

Institute of Digestive Diseases and Hormonal Laboratory, Hospital Clinic Universitari, University of Barcelona, Spain. arroyo@medicina.ub.es

J Hepatol 32 (1 Suppl): 157-170, 2000

The pathophysiology of circulatory and renal dysfunction in cirrhosis and the treatment of ascites and related conditions (hepatorenal syndrome and spontaneous bacterial peritonitis) have been research topics of major interest during the last two decades. However, many aspects of these problems remain unclear and will constitute major areas of investigation in the next millennium. The pathogenesis of sodium retention, the most prevalent renal function abnormality of cirrhosis, is only partially known. In approximately one third of patients with ascites, sodium retention occurs despite normal activity of the renin-aldosterone and sympathetic nervous systems and increased circulating plasma levels of natriuretic peptides and activity of the so-called natriuretic hormone. These patients present an impairment in circulatory function which, although less intense, is similar to that of patients with increased activity of the renin-aldosterone and sympathetic nervous systems, suggesting that antinatriuretic factors more sensitive to changes in circulatory function that these systems may be important in the pathogenesis of sodium retention in cirrhosis. The development of drugs that inhibit the tubular effect of antidiuretic hormone and increase renal water excretion without affecting urine solute excretion has opened a field of great interest for the management of water retention and dilutional hyponatremia in cirrhosis. Two families of drugs, the V2 vasopressin receptor antagonists and the kappa-opioid agonists, have been shown to improve free water clearance and correct dilutional hyponatremia in human and experimental cirrhosis with ascites. The first type of drugs blocks the tubular effect of antidiuretic hormone and the second inhibits antidiuretic hormone secretion by the neurohypophysis. On the other hand, two new treatments have also been proved to reverse hepatorenal syndrome in cirrhosis. The most interesting one is that based on the simultaneous administration of plasma volume expansion and vasoconstrictors. The second is transjugular intrahepatic porto-systemic shunt. The long-term

administration (1-3 weeks) of analogs of vasopressin (ornipressin or terlipressin) or other vasoconstrictors together with plasma volume expansion with albumin is associated with a dramatic improvement in circulatory function and normalization of serum creatinine concentration in patients with severe hepatorenal syndrome. Of interest is the observation that in many of these patients, hepatorenal syndrome does not recur following discontinuation of the treatment, thus raising important questions about the mechanism by which hepatorenal syndrome follows a progressive course in most untreated cases. The pathogenesis of circulatory dysfunction in cirrhosis and the role of local mechanisms in the development of the splanchnic arteriolar vasodilation associated with portal hypertension will continue as important topics in clinical and basic research in Hepatology. Of special interest is the study of the mechanism by which circulatory function further deteriorates following complications such as severe bacterial infection or therapeutic interventions such as therapeutic paracentesis, and the adverse consequences of the impairment in circulatory function on renal and hepatic hemodynamics. Finally, although major advances have been made concerning the treatment and secondary prophylaxis of spontaneous bacterial peritonitis in cirrhosis, many aspects of the pathogenesis of this infection remain unclear. The mechanism of bacterial translocation and of the colonization of bacteria in the ascitic fluid are particularly important to design adequate measures for primary prophylaxis of this severe bacterial infection.

[#3] Hepatorenal syndrome.

Bataller R, Gines P, Arroyo V, Rodes J.

Liver Unit, Institut de Malalties Digestives, Hospital Clinic, Barcelona, Spain.

Clin Liver Dis 2000 May;4(2):487-507

Hepatorenal syndrome is a functional renal failure that occurs in cirrhotic patients with advanced liver disease and ascites. The diagnostic criteria and clinical types of this syndrome have recently been revised. Hepatorenal syndrome is caused by marked hypoperfusion of the kidney as the result of renal vasoconstriction, which is thought to be the extreme manifestation of an underfilling of the arterial circulation. This circulatory dysfunction is the consequence of arterial vasodilation in the splanchnic circulation. Liver transplantation is the best treatment for HRS, but its applicability is low because of the short survival of these patients. New therapies, such as the use of systemic vasoconstrictors or TIPS, seem promising, but prospective investigations are needed to delineate their role in the management of cirrhotic patients with HRS.

Publication Types:

- Review
- Review, Tutorial

PMID: 11232202 [PubMed - indexed for MEDLINE]

[#4] Effect of terlipressine (glypressine) on hepatorenal syndrome (HRS) in cirrhotic patients: Results of a pilot study.

Bonnard Ph., Bernard B., Halimi Ch., Mathurin Ph., Demontis R., di Martino V., Henry-Biabaud E., Mofredj A., Poynard T., Cadranel JF.

Gastroenterology 114 (4), A 1214, 1998 (abstract).

[#5] Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis.

Cardenas A, Gines P, Uriz J, Bessa X, Salmeron JM, Mas A, Ortega R, Calahorra B, De Las Heras D, Bosch J, Arroyo V, Rodes J.

Hepatology 2001 Oct;34(4 Pt 1):671-6

Liver Unit, Institut de Malalties Digestives, Hospital Clinic, University of Barcelona, Spain.

To assess the incidence, clinical course, predictive factors, and prognosis of renal failure in patients with cirrhosis and gastrointestinal bleeding, 175 consecutive episodes of gastrointestinal bleeding in 161 patients were analyzed. Renal failure occurred in 20 (11%) episodes and was transient in 8 episodes and nontransient in 12. Renal failure was more common in patients with cirrhosis than in a control population of bleeding patients without cirrhosis matched by age and severity of the bleeding episode. Among 39 clinical and laboratory variables obtained at admission or during hospitalization related with the bleeding episode or with liver and renal function, the presence of hypovolemic shock, number of packed red blood cells transfused, Child-Pugh class at admission, and baseline platelet count were independent predictors of renal failure. The development of renal failure and hypovolemic shock was the only independent predictors of in-hospital mortality. Mortality rate among the 20 episodes with renal failure was 55% (11 deaths) as compared with only 3% (5 deaths) in the 155 episodes without renal failure (P <.01). The development of nontransient renal failure entailed a much greater mortality as compared with transient renal failure (10 of 12 [83%] vs. 1 of 8 [12%]; P <.01). In conclusion, renal failure is a common event in patients with cirrhosis and gastrointestinal bleeding, the occurrence of which is mainly related to the severity of bleeding and baseline liver function. Renal failure is a strong predictor of mortality in patients with cirrhosis and gastrointestinal bleeding.

PMID: 11584362 [PubMed - indexed for MEDLINE]

[#6] Hepatorenal syndrome.

Cardenas A, Uriz J, Gines P, Arroyo V.

Liver Unit, Institut de Malalties Digestives, Hospital Clinic, Barcelona, Spain.

Liver Transpl 2000 Jul;6(4 Suppl 1):S63-71

Publication Types:

- Review
- Review, Tutorial

PMID: 10915194 [PubMed - indexed for MEDLINE]

[#7] Terlipressin may influence the outcome of hepatorenal syndrome complicating alcoholic hepatitis.

Cervoni JP, Lecomte T, Cellier C, Auroux J, Simon C, Landi B, Gadano A, Barbier JP.

Service d'Hepato-Gastroenterologie, Hopital Laennec, Paris, France.

Am J Gastroenterol 1997 Nov;92(11):2113-4

Hepatorenal syndrome is a frequent complication associated with extremely short survival in cirrhotic patients with alcoholic hepatitis. Vasopressin analogs have been reported to induce transient regression of hepatorenal syndrome in patients with cirrhosis. However, treatment withdrawal was followed by early recurrences in every case. We report the case of a 68-yr-old woman with severe alcoholic hepatitis complicated by hepatorenal syndrome. Terlipressin induced a prolonged recovery of renal function that was associated with improvement in hepatic function.

Publication Types:

- Review
- Review of Reported Cases

PMID: 9362205 [PubMed - indexed for MEDLINE]

[#8] Review article: pharmacological treatment of the hepatorenal syndrome in cirrhotic patients.

Dagher L, Patch D, Marley R, Moore K, Burroughs A.

Department of Liver Transplantation and Hepatobiliary Medicine, Royal Free Hospital, London, UK.

Aliment Pharmacol Ther 2000 May;14(5):515-21

Renal failure is common in patients who are dying from end-stage cirrhosis, developing in 40-80% of all patients. Where there is no anatomical or pathological cause for the renal failure, it is termed the hepatorenal syndrome. When the hepatorenal syndrome develops, it will only recover when there is some degree of improvement in liver function. Thus for most patients this will occur only after liver transplantation, although the transplantation mortality is increased in this group. Hepatorenal syndrome is a common complication of alcoholic hepatitis, and this group is unusual in that with time and abstinence, significant recovery of liver function may occur. There is therefore a need for supportive therapy to allow time for some recovery of liver function in patients with alcoholic hepatitis and hepatorenal syndrome. Similarly, patients may need support whilst waiting for liver transplantation. This article reviews the pathophysiology and treatment of hepatorenal syndrome.

Publication Types:

- Review
- Review, Tutorial

PMID: 10792112 [PubMed - indexed for MEDLINE]

[#9] Restoration of the uricosuric effect of probenecid after triglycylvasopressine administration in a gouty patient.

Decaux G, Soupart A, Musch W, Hannotier P, Prospert F.

Hopital Universitaire Erasme, Universite Libre de Bruxelles, Belgium.

Clin Nephrol 1998 Oct;50(4):262-5

A 35-year-old patient with severe gout and mild renal insufficiency presented very low urinary urate excretion. Volume expansion induced by fludrocortisone combined or not with a uricosuric drug (Benzbromarone) was unable to significantly increase his urate excretion. A combined Probenecid (PB) and Pyrazinamide (PZA) test was performed. These drugs being considered to affect renal tubular reabsorption or secretion. No significant modification of uric acid fractional excretion (FE.uric acid) was observed after PB and PZA. When the same test was performed after the administration of Triglycyl-lysine vasopressine (TGLV), a potent V1 receptor stimulator, we observed a three fold increase in FE.uric acid after PB intake (from 6 to 18%) followed by a decrease after PZA (from 18 to 5.6%). When TGLV was administered alone their was no significant modification of uric acid fractional excretion. We propose that

TGLV decrease proximal tubular urate reabsorption that could only be detected when postsecretory reabsorption is blocked by an uricosuric drug.

PMID: 9799074 [PubMed - indexed for MEDLINE]

[#10] Hepatorenal syndrome in cirrhotic patients: terlipressine is a safe and efficient treatment; propranolol and digitalic treatments: precipitating and preventing factors?

Duhamel C, Mauillon J, Berkelmans I, Bourienne A, Tranvouez JL.

Am. J. Gastroenterol. 95, 2984-2985, 2000

Publication Types:

- Letter

PMID: 11051385 [PubMed - indexed for MEDLINE]

[#11] Natriuretic response to the combination of atrial natriuretic peptide and terlipressin in patients with cirrhosis and refractory ascites.

Gadano A, Moreau R, Vachiery F, Soupison T, Yang S, Cailmail S, Sogni P, Hadengue A, Durand F, Valla D, Lebrec D.

Laboratoire d'Hemodynamique Splanchnique, Unite de Recherches de Physiopathologie Hepatique, INSERM U-24, Hopital Beaujon, Clichy, France.

J Hepatol 1997 Jun;26(6):1229-34

BACKGROUND/AIMS: Refractory ascites, which occurs in certain patients with cirrhosis, is associated with a blunted natriuretic response to exogenous atrial natriuretic peptide (ANP). Since this blunting seems to be related to ANP-induced arterial hypotension, a vasoconstrictor, such as terlipressin (a vasopressin analogue), may restore natriuresis to exogenous ANP. Moreover, since cirrhosis-elicited vasodilation is thought to play a role in sodium retention, a vasoconstriction caused by terlipressin alone may lead to an increase in sodium excretion. This study aimed to evaluate the natriuretic response to either a combination of ANP with terlipressin or terlipressin alone in patients with cirrhosis and refractory ascites. METHODS: Sixteen consecutive patients with cirrhosis and refractory ascites were randomly assigned to receive either a combination of terlipressin (1-2 mg, i.v. bolus) with ANP (35 ng/kg, i.v. bolus followed by 15 ng x kg(-1) x min(-1) for 60 min) (n=8) or terlipressin alone (1-2 mg, i.v. bolus) (n=8). Sodium excretion and urine output, systemic, splanchnic and renal hemodynamics and renal oxygen consumption were measured before and during treatments. RESULTS: Combined therapy did not change arterial pressure but significantly increased urinary sodium excretion and urine output. These effects were associated with a significant increase in glomerular filtration rate and a decrease in renal oxygen consumption. Terlipressin alone significantly increased arterial pressure but did not change urinary sodium excretion or urine output.

Moreover, terlipressin did not change either glomerular filtration rate or renal oxygen consumption. CONCLUSIONS: The combination of exogenous ANP with terlipressin, but not terlipressin alone, increases sodium excretion in patients with cirrhosis and refractory ascites.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9210608 [PubMed - indexed for MEDLINE]

[#12] Hepatorenal syndrome. Long-term treatment with terlipressin as a bridge to liver transplantation.

Ganne-Carrie N, Hadengue A, Mathurin P, Durand F, Erlinger S, Benhamou JP.

Service d'Hepatologie, Hopital Beaujon, Clichy, France.

Dig Dis Sci 1996 Jun;41(6):1054-6

In patients with hepatorenal syndrome (HRS), 4-hr administration of a vasopressin analog has recently been shown to benefit renal blood flow and renal function. However, long-term effects and tolerance of this treatment have not been reported. We report a case of HRS that was controlled by the vasopressin analog, terlipressin. Because HRS repeatedly relapsed when treatment was discontinued, terlipressin, 2 mg/day was administered for 67 days, until liver transplantation could be performed in a patient with normal renal function. Except for limited cutaneous necrosis at an injection point, prolonged treatment with this vasopressin analog was well tolerated.

PMID: 8654133 [PubMed - indexed for MEDLINE]

[#13] Disease of the month: Hepatorenal syndrome.

Gines P, Arroyo V.

Liver Unit, Institut de Malalties Digestives, Hospital Clinic, Barcelona, Catalunya, Spain.
gines@medicina.ub.es

J Am Soc Nephrol 1999 Aug;10(8):1833-1839

Publication Types:
- Review
- Review, Tutorial

PMID: 10446954 [PubMed - indexed for MEDLINE]

[#14] Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome.

Hadengue A, Gadano A, Moreau R, Giostra E, Durand F, Valla D, Erlinger S, Lebrec D

Laboratoire d'Hemodynamique Splanchnique et de Biologie Vasculaire, INSERM and Service d'Hepatologie, Hopital Beaujon, Clichy, France.

J Hepatol 29(4): 565-70, 1998 (Oct)

BACKGROUND/AIMS: A treatment to induce a sustained increase in glomerular filtration rate in patients with hepatorenal syndrome has not yet been identified. Thus, the aim of the present study was to investigate the effects of terlipressin for 2 days on the glomerular filtration rate in patients with cirrhosis and hepatorenal syndrome.

METHODS: A double-blind, cross-over randomized study was performed in nine patients. Patients received terlipressin (2 mg/day for 2 days) and a placebo for 2 days in a randomized order.

RESULTS: Terlipressin administration significantly increased creatinine clearance (from 15+/-2 ml/min to 27+/-4 ml/min) and urine output (from 628+/-67 ml/day to 811+/-76 ml/day), but did not significantly change urinary sodium concentrations. Urinary sodium excretion was not significantly different after placebo administration (0.6+/-0.1 mmol/24 h) and terlipressin administration (9.3+/-7.2 mmol/24 h). Terlipressin administration significantly decreased plasma concentrations of renin and aldosterone but not atrial natriuretic peptide levels. Placebo elicited no significant effects.

CONCLUSIONS: This study shows that 2-day terlipressin administration increases the glomerular filtration rate in patients with cirrhosis and hepatorenal syndrome.

[#15] A discussion of how terlipressin limits mortality in cases of bleeding oesophageal varices.

Lebrec D

Laboratoire d'Hemodynamique Splanchnique et de Biologie Vasculaire, Unite de Recherches de Physiopathologie Hepatique (INSERM), Hopital Beaujon, Clichy, France.

Eur J Gastroenterol Hepatol 10(7): 549-552, 1998 (Jul)

Bleeding oesophageal varices (BOV) are a potentially life-threatening complication of portal hypertension. While endoscopic sclerotherapy and banding ligation are often employed in an attempt to arrest bleeding, the use of vasoactive pharmacological agents to control haemorrhage has a number of advantages. While many of the available vasoactive agents control acute bleeding and may exert a beneficial influence over hepatic haemodynamics, terlipressin (triglycyl lysine-vasopressin) is the only agent that has been shown actually to decrease mortality in cases of BOV. It is hypothesized that this increase in survival rate is due to the apparently unique multifactorial influence of terlipressin over variceal haemostasis and blood flow, hepatic and gastric haemodynamics and renal function, combined with the likelihood of only minimal adverse events.

[#16] Treatment with terlipressin as a bridge to liver transplantation in a patient with hepatorenal syndrome.

Le Moine O, el Nawar A, Jagodzinski R, Bourgeois N, Adler M, Gelin M, Cremer M

Department of Gastroenterology, Hopital Erasme, Universite Libre de Bruxelles, Belgium.

Acta Gastroenterol Belg 61(2): 268-270, 1998 (Apr-Jun)

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.

[#17] Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study.

Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichai P, Abergel A, Halimi C, Pauwels M, Bronowicki JP, Giostra E, Fleurot C, Gurnot D, Nouel O, Renard P, Rivoal M, Blanc P, Coumaros D, Ducloux S, Levy S, Pariente A, Perarnau JM, Roche J, Scribe-Outtas M, Valla D, Bernard B, Samuel D, Butel J, Hadengue A, Platek A, Lebrec D, Cadranel JF.

INSERM U-481 et Service d'Hepatologie, Hopital Beaujon, Clichy, France; Service d'Hepato-Gastroenterologie, Groupe Hospitalier Pitie-Salpetriere, Paris, France; Service de Gastroenterologie, Centre Hospitalier, Le Havre, France; Service d'Hepato-Gastroenterologie, Hopital Fontenoy, Chartres, France; Centre Hepato-Biliaire, Hopital Paul Brousse, Villejuif, France; Service d'Hepato-Gastroenterologie, CHU Hotel-Dieu, Clermont-Ferrand, France; Service d'Hepato-Gastroenterologie, Centre Hospitalier, Senlis, France; Service de Medecine B, Centre Hospitalier, Abbeville, France; Service d'Hepato-Gastroenterologie, CHU Nancy-Brabois, Vandoeuvre-les-Nancy, France; Unite de Greffe, HUG-Hopital Cantonal, Geneve, Switzerland; Service d'Anesthesie-Reanimation, CHU de Bordeaux, Centre Medico-Chirurgical de la Maison du Haut Leveque, Groupe Hospitalier Sud, Pessac, France; Service de Gastroenterologie, Centre Hospitalier Jean Coulon, Gourdon, France; Service d'Hepato-Gastroenterologie, Centre Hospitalier la Beauche, Saint-Brieuc, France; Service d'Hepato-Gastroenterologie, Centre Hospitalier Victor Dupouy, Argenteuil, France; Service d'Anesthesie-Reanimation-Urgences, Etablissement Public de Sante, Arpajon, France; Service d'Hepato-Gastroenterologie, Hopital Saint-Eloi, Montpellier, France; Service d'Hepato-Gastroenterologie, CHU-Hopital Civil, Strasbourg, France; Service d'Alcoologie, CHU-Hopital Jean Minjoz, Besancon, France; Service d'Hepato-Gastroenterologie, Hopital Robert Debre, CHU de Reims, Reims, France; Service d'Hepato-Gastroenterologie, Centre Hospitalier, Pau, France; Service de Medecine B, CHR Notre-Dame de Bon-Secours, Metz, France; Service de Medecine Interne, Centre Hospitalier, Roanne, France; Service d'Hepato-Gastroenterologie, Centre Hospitalier, Ussel, France; and Unite d' Hepatologie, Centre Hospitalier Laennec, Creil, France.

Gastroenterology 2002 Apr; 122(4): 923-930

Background & Aims: Type 1 hepatorenal syndrome (HRS) is a severe complication of cirrhosis associated with a short median survival time (<2 weeks). Although the administration of terlipressin improves renal function, its effect on survival is unknown. This study investigated predictive factors of survival in patients with type 1 HRS treated with terlipressin. METHODS: Ninety-nine patients with type 1 HRS treated with terlipressin in 24 centers were retrospectively studied. Terlipressin-induced improved renal function was defined as a decrease in serum creatinine value to <130 &mgr;mol/L or a decrease of at least 20% at the end of treatment. RESULTS: At inclusion, the Child-Pugh score was 11.8 +/- 1.6 (mean +/- SD). Terlipressin (3.2 +/- 1.3 mg/day) was administered for 11 +/- 12 days. Renal function improved in 58% of patients (serum creatinine decreased by 46% +/- 17% from 272 +/- 114 &mgr;mol/L). Median survival time was 21 days. Survival rate was 40% at 1 month. Multivariate analysis showed that improved renal function and Child-Pugh score </=11 at inclusion were independent predictive factors of survival (P < 0.0001 and 0.02, respectively). Thirteen patients underwent liver transplantation (92 +/- 95 days after HRS onset), 10 of whom had received terlipressin and had had improved renal function. CONCLUSIONS: This retrospective uncontrolled study shows that in patients with type 1 HRS, terlipressin-induced improved renal function is associated with an increase in survival. Thus, a randomized trial investigating the effect of terlipressin on survival in patients with type 1 HRS should be performed.

PMID: 11910344 [PubMed - as supplied by publisher]

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

Mulkay JP, Louis H, Donckier V, Bourgeois N, Adler M, Deviere J, Le Moine O.

Department of Gastroenterology, Hopital Erasme, Universite Libre de Bruxelles (ULB), Brussels, Belgium.

Acta Gastroenterol Belg 64 (1): 15-19, 2001

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/24 h (100-1031) and 7 mEq/24 h (1-17).

METHODS: Terlipressin was administered i.v. 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.

[#19] Hepatorenal Syndrome.

Planas R, Bataller R, Rodes J.

Liver Section, Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet, 08916 Badalona, Spain.

Curr Treat Options Gastroenterol 2000 Dec;3(6):445-450

The management of the hepatorenal syndrome (HRS) constitutes a major challenge for clinicians. Because HRS is a functional disorder due to advanced liver disease and is associated with a very low survival expectancy, orthotopic liver transplantation (OLT) is the only effective and permanent treatment for patients with HRS. However, OLT is not applicable to all cirrhotic patients despite the presence of HRS. In addition, because of the poor prognosis of HRS and the prolonged waiting lists in most transplant centers a significant proportion of these patients may die before OLT is possible. Therefore, there is a need for effective therapies for HRS that improve renal function and increase survival. Such treatments are of interest not only as a bridge to OLT but also as a therapy for patients who are not candidates for transplantation. Preliminary studies have suggested that the administration of splanchnic vasoconstrictors such as terlipressin in combination with volume expanders or the insertion of transjugular intrahepatic portosystemic shunts (TIPS) may improve renal function in patients with HRS. However, before these treatments are widely recommended further studies are necessary.

PMID: 11096604 [PubMed - as supplied by publisher]

[#20] Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome.

Uriz J, Gines P, Cardenas A, Sort P, Jimenez W, Salmeron JM, Bataller R, Mas A, Navasa M, Arroyo V, Rodes J

Institut de Malalties Digestives, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomediques August Pi-Sunyer, Catalunya, Spain.

J Hepatol 33 (1): 43-48, 2000 (Jul)

BACKGROUND/AIM: Ornipressin, a vasopressin analog with potent splanchnic vasoconstrictor action, has been shown to reverse hepatorenal syndrome. However, its usefulness in clinical practice is limited by frequent ischemic complications. The aim of this study was to assess the efficacy of terlipressin, an analog of vasopressin with a low profile of side effects, plus albumin in this condition.

METHODS: Nine consecutive patients with cirrhosis and hepatorenal syndrome were included in a pilot study of terlipressin (0.5-2 mg/4 h i.v.) therapy associated with iv albumin.

RESULTS: Treatment (9 days, range 5-15) was associated with a marked reduction of serum creatinine (3.9+/-0.7 to 1.3+/-0.1 mg/dl, p<0.001, mean+/-SE). Reversal of hepatorenal syndrome (reduction of creatinine below 1.5 mg/dl) was observed in seven of the nine patients. There was a remarkable improvement in circulatory function, with an increase in mean arterial pressure (68+/-2 to 80+/-4 mmHg, p<0.05) and suppression of vasoconstrictor systems activity (plasma renin activity and plasma norepinephrine decreased from 23+/-12 ng/ml x h and 1549+/-373 pg/ml to 3.5+/-2 ng/ml x h and 373+/-98 pg/ml, respectively, p<0.01 for both). No patient developed signs of intestinal, myocardial or distal ischemia.

CONCLUSIONS: Terlipressin associated with albumin appears to be a safe and effective treatment of hepatorenal syndrome.

[#21] Increased plasma levels of neuropeptide Y in hepatorenal syndrome.

Uriz J, Ginès P, Ortega R, Jimenez W, Cardenas A, Calahorra B, Sort P, Fernandez J, Bataller R, Arroyo V, Rivera F, Rodes J.

Liver Unit, Institut de Malalties Digestives, Hospital Clinic, Barcelona, Spain

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Background/Aims: To investigate the relationship between neuropeptide Y (NPY), a potent renal vasoconstrictor peptide released upon marked stimulations of sympathetic nervous system (SNS), and renal and circulatory function in cirrhosis.Methods: Plasma levels of NPY (radioimmunoassay) and norepinephrine and renal function parameters were determined in 17 healthy controls, nine patients with cirrhosis without ascites, and 37 patients with cirrhosis and ascites, of whom 12 had hepatorenal syndrome (HRS).Results: Patients with ascites showed circulating levels of NPY similar to those of patients without ascites and controls (73plus minus4, 76plus minus4 and 68plus minus4pmol/l, respectively; NS). However, patients with HRS had significantly increased levels of NPY with respect to the other groups (110plus minus6pmol/l; P<0.001). NPY levels correlated inversely with renal plasma flow and glomerular filtration rate and directly with norepinephrine. In patients with HRS (n=6) treatment with terlipressin and albumin was associated with a marked improvement in circulatory and renal function and marked suppression of NPY and norepinephrine levels.Conclusions: Patients with HRS have increased levels of NPY which are related to circulatory dysfunction and SNS activation and may contribute to renal vasoconstriction.

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[#22] Das hepatorenale Syndrom; Pathophysiologie, Diagnostik und Therapie.

von Schrenck T., Wolf G.

Deutsches Ärzteblatt 43, A2858-A2862, 2000 (review).

[#23] New challenge of hepatorenal syndrome: prevention and treatment.

Wong F, Blendis L.

Division of Gastroenterology, Department of Medicine, The Toronto General Hospital, University of Toronto, Ontario, Canada.

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Hepatorenal syndrome (HRS) remains one of the major therapeutic challenges in hepatology today. The pathogenesis is complex, but the final common pathway seems to be that sinusoidal portal hypertension, in the presence of severe hepatic decompensation, leads to splanchnic and systemic vasodilatation and decreased effective arterial blood volume. Renal vasoconstriction increases concomitantly, renal hemodynamics worsens, and renal failure occurs. Renal failure was shown 15 years ago to be potentially reversible after liver transplantation. This potential reversibility together with increased understanding of the pathogenesis has led to successful preliminary attempts to reverse HRS nonsurgically with combinations of splanchnic vasoconstrictors and colloid volume expansion, insertion of transjugular intrahepatic portovenous shunt radiologically, and improved forms of dialysis. Recent classification of HRS into the acute onset or severe type 1 with virtually 100% mortality and the more insidious less severe type II promises to shed more light on the pathogenesis of HRS, especially on the currently unrecognized precipitating factors. It is hoped that this classification will be included in the necessary and carefully performed clinical trials, which should lead to clearer indications for the available therapies. The challenge now is to use all this information to improve our management of cirrhotic patients to prevent occurrence of HRS in the future.

Publication Types:

- Review
- Review, Tutorial

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