Terlipressin and Hyponatremia

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A new study published in the October issue of the journal *Hepatology* (Solà et al. 2010) and being frequently cited in news media and popular science panels found that patients with severe portal-hypertensive bleeding who are treated with terlipressin may experience an acute reduction of sodium in their blood. This reduction in serum sodium, known as hyponatremia, can cause adverse reactions such as neurological complications. The reduction in serum sodium is rapidly reversible upon terlipressin withdrawal. The authors suggest that serum sodium levels should be closely monitored in these patients and caution that use of solutions with high sodium content to treat this condition may cause a too rapid recovery of sodium, leading to adverse events.

The serum sodium concentration has long been known to be of value in determining the prognosis of patients with cirrhosis (Arroyo et al. 1976). In the early stages of cirrhosis, serum sodium concentrations are within the normal range, but they progressively decrease in the later stages and hypervolemic hyponatremia develops in a considerable proportion of patients. This condition is characterized by low serum sodium concentrations in patients with an expanded extracellular volume as well as ascites and edema. Hypervolemic hyponatremia is due to an increased secretion of antidiuretic hormone (vasopressin) secondary to the circulatory dysfunction that is characteristic of advanced cirrhosis (Schrier 2006).

Two receptor subtypes (V_{1A} and V_2) mediate vasopressin's major physiologic effects. V_{1A} receptors are located on vascular smooth muscle cells and cardiac myocytes, affecting vascular tone and myocardial function (Finley et al. 2008). V_2 receptors are located on cells lining the kidney's collecting ducts. Activation of the V_2 receptor inserts vasopressin-sensitive water channels in the cell membrane, promoting the reabsorption of water and elaboration of a concentrated urine. Excessive reuptake of electrolyte-free water into the blood circulation may lead to hyponatremia.

Studies of the natural history of cirrhosis show that patients with cirrhosis and hyponatremia have a poor short-term prognosis and that the prognostic value of the serum sodium concentration is independent of the prognostic value of liver-function tests (Llach et al. 1988). A number of reports have extended these observations to patients on the liver-transplant waiting list, and they have shown that incorporation of the serum sodium concentration into the MELD score improves the accuracy of the MELD score alone in assessing short-term mortality (Kim et al. 2008). However, the degree of improvement varies among studies. Whether hyponatremia is deleterious by itself or is just a surrogate marker of more advanced liver disease is unknown and warrants investigation (Cardenas & Ginès 2008).

Terlipressin is a vasopressin analog in which the V_{1A}-receptor affinity has been increased and the V_2-receptor affinity has been decreased as compared to vasopressin. Therefore, terlipressin has stronger vasoconstrictive effects than vasopressin and less effects on water reabsorption in the kidney collecting ducts. The vasoconstrictive effects of terlipressin on splanchnic vessels moves blood volume from the splanchnic vessels into the central blood circulation and – thus – increases blood flow to the kidneys. Terlipressin's vasoconstrictive effect on postglomerular blood vessels leads to an increased glomerular filtration pressure and – thus – to increased diuresis.

Because of its reduced V_2-receptor affinity terlipressin by itself should have little effect on water reabsorption in the collecting ducts. However, terlipressin is slowly metabolized in the liver to vasopressin. Since vasopressin has quite strong agonistic effects on V_2-receptors the possibility cannot be excluded that terlipressin may stimulate water reabsorption

indirectly via its conversion to vasopressin and, thus, cause hyponatremia.

Literature references of studies in which terlipressin caused hyponatremia:

1. Douriez et al. (1993) observed severe hyponatremia after repeated administration of terlipressin. This publication is in French.

2. Feu et al (1996) observed five cases of hyponatraemia among 80 patients in the terlipressin group compared with three among 81 treated with somatostatin.

3. Escorsell et al. (2000) observed four cases of hyponatraemia in 105 patients treated with terlipressin compared with no cases in the sclerotherapy group.

4. Dunwoodie & Jowett (2007) described a 46-year-old woman with bleeding esophageal varices who received five dosages of 2 mg terlipressin within 26 hours and developed a tonic-clonic seizure and serum sodium was found to have decreased from 132 to 115 mmol/L.

5. Bruha et al. (2009) treated 15 patients with bleeding esophageal varices with 1 mg terlipressin every 4 hours for 5 days and another 10 patients for 10 days. Serum sodium levels decreased in both groups, but returned to normal after discontinuation of terlipressin treatment.

6. Krag et al. (2010) reported that among 62 patients with bleeding esophageal varices who were treated in their department with high-dose short-term terlipressin of 2 mg/4 h at mean 1.7 days (range 1 - 6 days) serum sodium levels decreased from 136 ± 6 to 130 ± 7. The same research group has shown previously (Krag et al. 2008) that in patients with ascites under water load terlipressin increases aquaporin-2 excretion which is a clear indication for a V_2 receptor effect.

7. Hyun et al. (2010) experienced one case of hyponatremia induced by infusion of terlipressin which resulted in generalized seizure. On admission, the patient's sodium level was 141 mmol/L but, 4 days after the initiation of terlipressin, it plummeted to 114 mmol/L, with serum osmolality also having fallen to 243 mOsm/kg. Hyponatremia could not be corrected despite correction with hypertonic saline but, after withdrawal of terlipressin, the serum sodium level showed a dramatic increase almost to the normal range the following day.

8. A retrospective study by Solà et al., published in the October 2010 issue of the journal Hepatology, found that patients with severe portal-hypertensive bleeding who are treated with terlipressin may experience acute hyponatremia. This reduction in serum sodium can cause adverse reactions such as neurological complications, and is rapidly reversible upon terlipressin withdrawal. Researchers noted a significant reduction in serum sodium concentration during terlipressin treatment (from 134.9 mEq/L at baseline to 130.5 mEq/L at day 5 of treatment). A reduction of sodium in the blood was found in 67% of patients with 31% having a moderate decrease (5-10 mEq/L) and 36% experiencing a marked decrease in serum sodium (greater than 10mEq/L). Only 19 patients out of a total of 58 were determined to have no change in serum sodium levels.

   A decrease in serum sodium concentration was more common in patients in whom treatment with terlipressin was effective in the control of bleeding. Among the 40 patients in whom treatment with

terlipressin was effective, 78% (31 patients) developed either moderate or marked reduction in serum sodium concentration compared to 44% (eight patients) in whom treatment failed ($P < 0.013$). Patients who developed hyponatremia had less advanced liver disease at baseline, as indicated by lower MELD scores and higher baseline serum sodium concentration, compared to those of patients who did not develop hyponatremia.

Overall, 17 of the 58 patients (29%) died during hospitalization. There was an inverse relationship between changes in serum sodium concentration during treatment with terlipressin and survival. The in-hospital mortality rate of patients categorized according to changes in serum sodium was 53% for patients with no or minor changes in serum sodium, 28% for patients with moderate reduction, and 10% for patients with marked reduction in serum sodium concentrations ($P < 0.0016$). Thus, patients who developed hyponatremia in this setting had a better prognosis compared to those who did not develop hyponatremia.

The authors interpret these findings that the development of an acute reduction in serum sodium levels might be related to the degree of occupancy of renal V_2 vasopressin receptors before the initiation of treatment with terlipressin. In patients with very advanced liver disease and low serum sodium levels, the renal V_2 receptors are likely to be occupied by endogenous vasopressin. Therefore, the administration of a drug with agonistic effect on the V_2 receptors may not have significant antidiuretic effect because the receptors would be occupied already by the endogenous ligand. By contrast, in patients with less severe liver dysfunction and normal serum sodium levels, terlipressin would cause solute-free water retention because V_2 vasopressin receptors are not occupied by endogenous vasopressin.

A clinical situation like variceal bleeding, characterized by pharmacological antidiuresis together with administration of hypotonic fluids, would strongly favor the development of acute hyponatremia. The observation that hyponatremia is very uncommon during treatment with terlipressin for hepatorenal syndrome (Llahi et a. 2008; Sanyal et al, 2008), a situation characterized by high levels of vasopressin, is consistent with the authors' hypothesis. In fact, in a review of 50 patients with hepatorenal syndrome, treated with terlipressin plus albumin in the authors' hospital unit over the last years, only five of the 50 patients (10%) developed hyponatremia (Nazar et al. 2010).

The frequency of reduction in serum sodium concentration (67%), observed in this study of Solà et al., is much higher than that reported in randomized studies comparing terlipressin with other therapeutic methods in patients with acute variceal bleeding, which ranges between 0% and 6%. Several factors may account for this difference, including the definition and methods used to report hyponatremia as well as the population of patients studied. The population of patients in the current study (Solà et al. 2010) was very select, and included only patients with severe bleeding who failed to respond or had recurrent bleeding under somatostatin treatment, whereas randomized studies included a nonselected population of patients.

Literature references of studies in which serum levels of sodium were elevated after treatment with terlipressin:

1. Uriz et al. 2000 showed in Table 1 of their publication that terlipressin plus albumin significantly elevated (not reduced) serum levels of sodium in patients with hepatorenal syndrome (HRS).

2. Ortega et al. (2002) showed that terlipressin plus albumin significantly elevated serum levels of sodium in patients with HRS. Treatment of these patients with terlipressin alone (without albumin) had no effect on serum sodium levels.

3. In the largest study ever made with terlipressin in hepatorenal syndrome – the OT-0401-study by Orphan Therapeutics (Sanyal et al. 2008) - an analysis of changes in serum sodium levels was made in a by-day analysis from baseline to Day 13 (includes only patients still receiving study treatment). Terlipressin-treated patients demonstrated statistically significant increases in serum sodium (4-5 mmol/L) and serum chloride (4-5 mmol/L) on days 3 to 6 compared to placebo-treated patients (unpublished). In addition, within group statistically significant increases in sodium occurred in terlipressin-treated patients from days 1 to 11 (again, includes only patients still receiving study treatment). There was one adverse event report of hyponatremia in a terlipressin-treated patient and none in placebo-treated patients.

4. Prakoso et al. presented abstracts at the American Liver Meeting (AASLD 2007) and at the Congress of the International Liver Transplantation Society 2008, where they show, that treatment with terlipressin improved serum sodium levels in patients with advanced liver failure and isolated hyponatremia, allowing the majority of these patients to be listed for liver transplant.

5. Kalambokis et al. (2010) studied fifteen nonazotemic cirrhotic patients (Child-Pugh B/C: 6/9) after an oral water intake of 20 ml/kg within 40 min and measured water excretion over 5 h at baseline on day 1, and after a bolus infusion (2 mg) of terlipressin on day 3. Terlipressin was shown to increase water excretion during a water load test without hyponatremia suggesting that the administration of arterial vasoconstrictors could improve the prognosis of these patients.

No change in serum sodium levels after treatment with terlipressin:

1. In the Barcelona TAHRS study (Martín-Llahí et al. 2008) on patients with hepatorenal syndrome there were no statistically significant changes in serum sodium levels after terlipressin treatment compared to the control group in the by-day analysis during treatment nor were there any statistically significant changes within the treatment group. There were no adverse event reports of hyponatremia in terlipressin-treated patients.

Conclusion:

Explanations for the different effects of terlipressin on serum sodium levels, as reported in the literature, should consider age of the patient and advanced stage of the disease. Normal aging is accompanied by many changes in the regulatory systems that control sodium and water balance (Miller 1998). Consequently, the older person is at an increased risk for clinically significant alterations in sodium and water balance, especially hyponatremia. In liver cirrhosis serum sodium concentrations progressively

decrease in the later stages of the disease and hypervolemic hyponatremia develops in a considerable proportion of these patients.

These observations emphasize the importance of monitoring sodium and potassium levels during treatment. The various adverse events of terlipressin must be evaluated, however, against the fact that the 2-week survival rate for untreated HRS-1 is less than 50% and in patients with bleeding esophageal varices the 6-week mortality is still about 20%.

References:

Arroyo V, Rodés J, Gutiérrez-Lizárraga MA, Revert L.: Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976;21:249-256.

Bruha R, Marecek Z, Prochaza V, Lata J, Spicak J, Ehrmann J, et al.: Double-blind randomized multicenter study comparing the efficacy and safety of 10-day to 5-day terlipressin treatment of bleeding esophageal varices. Hepatogastroenterology 2009;56:390-394.

Cárdenas A, Ginès, P: Predicting Mortality in Cirrhosis — Serum Sodium Helps. NEJM 2008;359;1060-1062.

Dunwoodie E, Jowett S.: Terlipressin causing a hyponatraemic seizure. Scand J Gastroenterol. 2007;42:665.

Douriez E, Mollard P, Laval C, Albengres E, Laporte JP, Tillement JP.: [Severe hyponatremia after repeated administration of terlipressin] [Article in French]. Therapie. 1993 Sep-Oct;48(5):518-519.

Escorsell A, Ruiz del Arbol L, Planas R, Albillos A, Ban˜ares R, Cale`s P, et al.: Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. Hepatology 2000;32:471-476.

Feu F, Ruiz del Arbol L, Bañares R, Planas R, Bosch J.: Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. Variceal Bleeding Study Group. Gastroenterology. 1996 Nov;111(5):1291-1299.

Finley JJ 4th, Konstam MA, Udelson JE.: Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. Circulation. 2008 Jul 22;118(4):410-421.

Hyun JJ, Seo YS, Lee KG, Keum B, Yim HJ, Jeen YT, Chun HJ, Um SH, Kim CD, Ryu HS.: Terlipressin-induced hyponatremic seizure. Scand J Gastroenterol. 2010 Apr;45(4):501-504.

Kalambokis GN, Pappas K, Baltayiannis G, Katsanou A, Tsianos EV.: Effects of terlipressin on water excretion after oral water load test in nonazotemic cirrhotic patients with ascites without hyponatremia. Scand J Gastroenterol. 2010 Aug 9

Kim WR, Biggins SW, Kremers WK, et al.: Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-26.

Krag A, Bendtsen F, Pedersen E, Holstein-Rathlou N, Moller S.: Effects of terlipressin on the aquaretic system: evidence of antidiuretic effects. Am J Physiol Renal Physiol 2008;295:F1295-F1300.

Krag A, Hobolth , Møller S, Bendtsen F.: Hyponatraemia during terlipressin therapy. Gut 2010 59: 417-418.

Llach J, Ginès P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482-487.

Martín-Llahí M, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, Soriano G, Terra C, Fábrega E, Arroyo V, Rodés J, Ginès P; TAHRS Investigators.: Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology. 2008 May;134(5):1352-1359.

Miller M.: Hyponatremia: age-related risk factors and therapy decisions. Geriatrics. 1998 Jul;53(7):32-3, 37-8, 41-2 passim.

Nazar A, Pereira GH, Guevara M, Martin-Llahi M, Pepin MN, Marinelli M, et al.: Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2010;51:219-226.

Ortega R, Ginès P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jiménez W, Arroyo V, Rodés J.: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology. 2002 Oct;36(4 Pt 1):941-8.

Prakoso E, Jamias JD, James MW, Koorey, DJ, Strasser SI, McCaughan GW, Shackel NA: Terlipressin Therapy for Renal Dysfunction and Hyponatremia in Patients with Liver Failure. AASLD 2007, abstract 815.

Prakoso E, Koorey DJ, Strasser SS, Shackel NA, McCaughan GW: TERLIPRESSIN SIGNIFICANTLY IMPROVES ISOLATED HYPONATREMIA IN PATIENTS WITH LIVER FAILURE. Int. Liver Transpl. Soc. 2008, abstract P-237.

Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Gülberg V, Sigal S, Teuber P; Terlipressin Study Group: A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology. 2008 May;134(5):1360-1368.

Schrier RW.: Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. Am J Med. 2006 Jul;119(7 Suppl 1):S47-553.

Solà E, Lens S, Guevara M, Martín-Llahí M, Fagundes C, Pereira G, Pavesi M, Fernández J, González-Abraldes J, Escorsell A, Mas A, Bosch J, Arroyo V, Ginès P.: Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology. 2010 Aug 5. [Epub ahead of print]

Uriz J, Ginès P, Cárdenas A, Sort P, Jiménez W, Salmerón JM, Bataller R, Mas A, Navasa M, Arroyo V, Rodés J.: Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol. 2000 Jul;33(1):43-48.

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