Hyponatremia in cirrhosis: clinical features and management

Marta MARTÍN-LLAHÍ, Mónica GUEVARA, Pere GINÈS
Liver Unit, Hospital Clinic, IDIBAPS, University of Barcelona, Spain.

SUMMARY

The presence of dilutional hyponatremia has a poor prognosis for survival in patients with cirrhosis and ascites. Effective and safe treatments are needed to improve prognosis in patients with cirrhosis and dilutional hyponatremia. The initial approach to management includes fluid restriction, low sodium diet, and minimizing the use of diuretics. In addition, the use of hypertonic saline should be avoided in patients with cirrhosis and dilutional hyponatremia. Furthermore, patients should be placed on the top of the list for liver transplantation if they are appropriate candidates. Although V₂ arginine vasopressin receptor antagonists that selectively enhance solute-free water excretion in patients with cirrhosis seem very promising, two points must be considered in relation to the available data. First, although the results of phase-2 studies are encouraging, the efficacy and safety of these compounds should be further evaluated. Second, the clinical utility of these agents in cirrhosis has only been assessed in short-term studies. The long-term effects of these drugs remain unknown. Future research with these compounds should not only focus on the effects on serum sodium, but also on treatment and prevention of recurrence of ascites. In addition, the possible beneficial effects of these drugs in the prevention of hepatic encephalopathy would be worth studying.

The clinical course of patients with cirrhosis is frequently complicated by the development of abnormalities in renal function and electrolyte levels. Hyponatremia is the most common disorder of the latter. In some patients, hyponatremia develops because of important losses of extracellular fluid, either from the gastrointestinal tract (due to diarrhea and/or vomiting) or from the kidney (due to diuretics because of the administration of excessive doses of diuretics). This condition characterized by low serum sodium concentrations, contracted blood volume, lack of edema and ascites, signs of dehydration and pre-renal failure, is known as "true hyponatremia". Serum sodium levels usually improve after correcting the cause or withholding diuretics and replacing fluid losses with the i.v. administration of saline solution. However, in most patients with advanced cirrhosis hyponatremia develops in the setting of an expanded extracellular fluid volume and in the absence of significant sodium loss. This condition is characterized by low serum sodium concentrations, expanded blood volume (although the effective blood volume is low due to the existence of marked arterial vasodilation in the splanchnic circulation), expanded extracellular fluid volume with ascites and edema, and no signs of dehydration. This condition is known as "dilutional hyponatremia" and is due to marked impairment in renal solute-free water excretion, resulting in a disproportionate renal retention of water compared to that of sodium causing a decrease in serum sodium levels despite the increased total body sodium from the marked renal sodium retention. The aim of the current article is to review the clinical features, prognostic significance, and management of hyponatremia in cirrhosis. This review mostly refers to dilutional hyponatremia, which is more common during liver disease.

Definition and epidemiology

Dilutional hyponatremia in cirrhosis is defined as a reduction in serum sodium concentrations to below 130 mEq/L with expanded extracellular fluid volume in the form of ascites and/or edema. Therenal capacity to eliminate solute-free water is usually markedly impaired. It should be emphasized, however, that the 130 mEq/L level of serum sodium used to define hyponatremia is arbitrary and many patients with cirrhosis and

Reprints: P. GINÈS, Liver Unit, Hospital Clinic, Villarol 170, Barcelona 08036, Spain.
E-mail: pgines@clinic.ub.es

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ascites with serum sodium above this cut-off but below normal levels (between 130 and 135 mEq/L) have an impaired ability to eliminate solute-free water. Because the impairment in solute-free water excretion in cirrhosis is usually progressive, patients with serum sodium concentrations between 130 and 135 mEq/L frequently develop hyponatremia (serum sodium lower than 130 mEq/L) during the course of their disease.

Hyponatremia is usually a late event in cirrhosis and occurs chronologically after the development of sodium retention and ascites. Although there are no longitudinal studies assessing the occurrence of hyponatremia in patients with ascites, most patients develop this complication during the course of the disease. Data from cross-sectional studies indicate that approximately 30-35% of hospitalized patients with cirrhosis and ascites have hyponatremia [2-4]. In patients with refractory ascites or hepatorenal syndrome, this proportion increases to 40 to 60% [5].

Pathogenesis

The pathogenesis of dilutional hyponatremia in cirrhosis is complex and involves several renal and extra-renal factors, including a reduced delivery of filtrate to the ascending limb of the loop of Henle, reduced renal synthesis of prostaglandins, and non-osmotic hypersecretion of arginine vasopressin [1, 6, 7]. A detailed discussion of the pathogenesis of hyponatremia in cirrhosis is outside of the scope of this review and can be found elsewhere [8, 9]. Definitive data about the relative importance of these factors in the pathogenesis of solute-free water retention and subsequent hyponatremia in patients with cirrhosis is lacking. However, from the results obtained in studies using specific antagonists of the tubular effect of arginine vasopressin (V2 antagonists), suggest that hypersecretion of arginine vasopressin probably plays a major role, particularly in patients without renal failure [10-13]. In patients with renal failure besides arginine vasopressin, a reduced distal delivery of filtrate due to decreased filtered load and increased sodium and water reabsorption in the proximal tubule also probably play an important role in the impairment of solute-free water excretion.

Cerebral adaptation to hyponatremia

The brain can be severely affected by hyponatremia, including the following effects.

Regulation of the osmolality of the extracellular fluid is very important because it strongly influences the state of hydration (and subsequent cell volume) of all cells. Therefore, plasma osmolality is tightly regulated to prevent marked shifts of water from the intracellular to the extracellular space or vice versa. Despite this regulation, all the cells in the body have defense mechanisms against sudden changes in the osmolality of the extracellular fluid, especially brain cells because the expansion of brain tissue in case of brain edema is limited by the skull [14].

When serum sodium increases (which leads to an increase in the osmolality of the extracellular fluid), water moves out to the cell to maintain an osmotic equilibrium between the intracellular and the extracellular space. This shift causes cell dehydration and shrinkage. On the other hand, when serum sodium falls, water moves into the cells to attain an osmotic balance between the extracellular and the intracellular space. The consequence of this is cell swelling and intracerebral edema [14], in most cells, including brain cells, cell swelling leads to extrusion of intracellular solutes to decrease intracellular osmolality and to match that of plasma. If solutes are extruded an osmolar equilibrium will be reached between the brain and plasma. If solute extrusion is inadequate water will continue to influx into cells increasing intracranial pressure, causing cerebral edema, and eventually tentorial herniation. The mechanisms responsible for protecting the brain from edema have been extensively studied in experimental animals. Immediately after the development of hyponatremia there is a rapid loss (within 24 hrs) of intracellular electrolytes, causing a reduction in intracellular osmolality [15-18]. Then there is a progressive reduction of the intracellular content of organic compounds, known as organic osmolytes which are involved in the long-term adaptation to osmotic changes. These osmolytes include glutamine, glutamate, taurine, and myo-inositol and account for about one third of the intracellular solute loss in chronic hyponatremia [18, 19].

After recovery of hyponatremia there is a regain of electrolytes and osmolytes; sodium and chloride correct quickly while the organic osmolytes take longer [20]. When correction of hyponatremia occurs rapidly (either from aggressive treatment or water restriction alone) lack of adaptation may lead to the osmotic demyelination syndrome [21, 22]. In this severe complication, also known as central pontine myelinolysis, shrinkage of cerebral tissues leads to demyelination of the pontine and extrapontine neurons. This is associated with severe neurological complications such as quadriplegia, pseudobulbar palsy, seizures, and coma [22].

There is almost no information on the functional changes in the brains of patients with cirrhosis and dilutional hyponatremia. A recent study showed a marked reduction in the brain concentration of organic osmolytes in these patients compared to patients without dilutional hyponatremia, indicating that this defense mechanism against brain edema is operational during cirrhosis [23].

Clinical Consequences

There is very limited information on the clinical consequences of dilutional hyponatremia during cirrhosis. Most of the clinical symptoms associated with hyponatremia in patients without liver disease are related to the central nervous system. Because patients with advanced cirrhosis often have hepatic encephalopathy, it is impossible to differentiate between the neurological symptoms due to hyponatremia and hepatic encephalopathy. Ife hyponatremia can be reversed with antagonists of the V2 receptors of arginine vasopressin the signs and symptoms directly related to low serum sodium levels could be identified. However in this paper, the clinical implications of dilutional hyponatremia in cirrhosis are discussed on the basis of the current information and divided into three categories: 1/ clinical consequences of hyponatremia on the central nervous system; 2/ relationship between hyponatremia and hepatic encephalopathy; and 3/ clinical consequences of a sudden increase in serum sodium levels on the central nervous system.

In patients without liver disease, although hyponatremia can produce different disturbances involving almost all body systems, the most relevant and potentially severe involve the central nervous system and are related to cerebral edema from the movement of water from the plasma and cerebrospinal fluid into brain cells. The clinical features of hyponatremia depend on the rapidity and the severity of the decrease in serum sodium concentrations. On one hand, acute severe hyponatremia, which occurs when there is a marked decrease in
serum sodium in less than 48 hours, causes cerebral edema that can lead to coma, irreversible neurological damage, and even death from respiratory failure from temporal cerebral herniation and brainstem compression. Symptoms usually do not appear until serum sodium concentrations fall below 120 mEq/L [24-29]. On the other hand, the gradual development of hyponatremia over several days or weeks is often associated with relatively mild symptoms despite severe degrees of hypoosmolality. In this situation, patients develop the adaptive cerebral mechanisms against hyponatremia that have been described in the previous section to reduce the impact of hypoosmolality on brain cells [24].

In patients with cirrhosis, dilutional hyponatremia usually develops slowly although occasionally patients may present with an acute onset of this condition. Moreover, in most patients the degree of hyponatremia is mild, with serum sodium levels ranging from 125 to 130 mEq/L. Although there is no detailed assessment of symptoms associated with dilutional hyponatremia in cirrhosis, severe neurological complications, such as seizures, coma, severe brain damage, brain-stem herniation, or death are uncommon in cirrhosis [23]. One clinical consequence of dilutional hyponatremia in cirrhosis that has not received much attention until recently is the possible relationship between hyponatremia and hepatic encephalopathy. It has been suggested that hyponatremia could act as predisposing factor of hepatic encephalopathy by producing metabolic changes in brain cells [30]. There are several lines of evidence suggesting this pathogenic relationship. First, hyponatremia has been identified as a risk factor of hepatic encephalopathy in patients treated with transjugular intrahepatic portosystemic shunts [31, 32]. Second, in patients with ascites receiving diuretics, pre-treatment hyponatremia is associated with an increased risk of hepatic encephalopathy (figure 1). Third, the administration of hypertonic saline, to prevent hyponatremia and maintain serum sodium levels between 145-155 mEq/L, is associated with a reduced incidence and severity of episodes of intracranial hypertension (due to cerebral edema) in patients with acute liver failure and hepatic encephalopathy grade III or IV [33]. Finally, hepatic encephalopathy is more common in patients with hyponatremia than in those without, although this may also be related to more advanced liver failure in the former compared to the latter [23]. Figures 2 and 3 describe two patients with cirrhosis who developed hepatic encephalopathy in close chronological relationship with hyponatremia. If hyponatremia could be reversed with arginine vasopressin V2 receptor antagonists, the relationship between hyponatremia and hepatic encephalopathy could probably be clarified.

The last type of clinical consequences related to hyponatremia that may occur in patients with cirrhosis are neurological complications due to a sudden normalization of serum sodium levels. To our knowledge, this has only been described in hyponatremic cirrhotic patients undergoing liver transplantation [33-37]. Approximately one third of cirrhotic patients with hyponatremia at transplantation develop neurological complications during the postoperative period, a figure which is three times greater than in patients transplanted without hyponatremia. The most common neurological complications in patients transplanted with hyponatremia are altered mental status, seizures, and/or focal motor disorders. However, 10-15% of patients develop central pontine myelinolysis, [33-37]. To date, there is no effective therapy to prevent the occurrence of central pontine myelinolysis in hyponatremic patients undergoing liver transplantation. The use of hypertonic saline solutions before transplantation has been proposed but its efficacy has not been tested in prospective studies. The new vasopressin V2 receptor antagonists could have a beneficial effect in these cases by increasing serum sodium concentrations before transplantation. However, this needs to be demonstrated in prospective, randomized studies.

**Prognosis**

It is well known that impaired renal capacity to excrete solute-free water and hyponatremia are associated with a poor short-term prognosis in patients with cirrhosis [38-42]. Recent studies have extended these observations by showing that serum sodium concentration is an important predictive factor of mortality in patients with cirrhosis awaiting liver transplantation and that its prognostic value is independent of that of the MELD score [43-45]. Specifically, it has been shown that serum sodium concentration adds to the prognostic accuracy of the MELD score in the assessment of mortality of patients with cirrhosis awaiting liver transplantation [43, 45].

**Management**

**Non pharmacologic therapy**

The most widely accepted therapy for dilutional hyponatremia in cirrhosis and other water-retaining states is restricting fluids to 1 liter/day to prevent further increase in total body water [1, 13]. Unfortunately, fluid restriction in patients with cirrhosis and dilutional hyponatremia does not raise serum sodium levels, but it probably prevents them from lowering further [13]. Administration of hypertonic saline solution is not recommended because additional expansion of extracellular fluid can worsen edema and ascites and its effect in increasing serum sodium is very modest [13, 46]. In addition to water restriction, patients must also follow a low-sodium diet because they have marked sodium retention.
Pharmacological therapy

Pharmacological approaches to the management of dilutional hyponatremia in cirrhosis have focused on inhibiting the actions of arginine vasopressin. One of the first drugs used for dilutional hyponatremia was demeclocycline, a tetracycline that inhibits the tubular effect of arginine vasopressin thereby increasing solute-free water clearance and serum sodium concentration [47, 48]. One of the drawbacks of this agent was the development of renal failure and it was therefore abandoned in patients with cirrhosis [48, 49].

In recent years, non-peptide antagonists of the V2 receptors of arginine vasopressin have become available and are being tested in phase II clinical trials. In 1992, Yamamura et al. [50] reported on an orally effective non-peptidic V2 receptor antagonist, OPC 31260 that 100 times more selective for V2 than for V1 receptors. Recently, several other non-peptide V2 receptor antagonists including SR 121463, conivaptan, tolvaptan, RWJ-351647, and VPA 985, with more affinity than OPC 31260 for V2 receptors, have also been extensively studied in experimental cirrhosis. V2 receptor antagonists have demonstrated the potential of VPA 985 as a therapeutic agent in patients with cirrhosis and ascites. The administration of diuretics induced a positive natriuretic response (not shown) that was associated with a reduction in serum sodium concentration and development of hepatic encephalopathy. Serum creatinine concentration increased slightly. There was a chronological relationship between the decline in serum sodium concentration and the occurrence of hepatic encephalopathy. No other known etiological factors of hepatic encephalopathy could be identified.

In 1998 Inoue et al. [10] examined the therapeutic effect of OPC 31260 in patients with cirrhosis and ascites. The administration of 30 mg/day p.o. to eight patients with cirrhosis and ascites without hyponatremia was associated with an increase in urine volume and solute-free water clearance at 2 and 4 hours, respectively, and a decrease in urine osmolality 2 hours after administration. However, since patients did not have hyponatremia at baseline, the effect on serum sodium was not assessed. Furthermore, neither the normal serum sodium increase, nor urinary sodium excretion changed. In 2002, Guyader et al. [11] reported the pharmacodynamics, safety, and pharmacokinetics of increasing single doses of VPA 985 (25-300 mg) in 27 patients with cirrhosis and ascites in a phase II randomized, double-blind, placebo-controlled trials. VPA 985 produced a marked dose-related increase in urinary output and a dose-related decrease in urine osmolality when given at 300 mg/day. Urine volume increased significantly with the 300 mg dose. Solute-free water clearance increased to levels above 3 mL/min for doses 100 mg and higher. In addition, significant increases in urine sodium excretion and serum osmolality, sodium, and vasopressin levels were observed. In this pharmacodynamic study the authors only demonstrated the potential of VPA 985 as a therapeutic agent for water retention in cirrhosis. But since the main end-point was to evaluate the safety and efficacy of this compound, they did not examine its role in managing patients with dilutional hyponatremia; in fact all patients had serum sodium levels above 130mEq/L. Both agents (VPA 985 and OPC 31260) in

V2 RECEPTOR ANTAGONISTS IN HUMAN CIRRHOSIS

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the above mentioned studies were clinically well tolerated and did not produce any significant side effects or changes in systemic hemodynamics.

Two multicenter, randomized, placebo-controlled trials published in 2003 evaluated the use of VPA 985 in cirrhotic patients with dilutional hyponatremia. In the first trial Wong et al. [55], investigated the effects of VPA 985 on serum sodium during a 7 day period in 44 hospitalized patients with dilutional hyponatremia (33 with cirrhosis, 5 with congestive heart failure and 5 with SIADH). Patients with cirrhosis and congestive heart failure were kept on diuretics and an escalating dose of VPA 985 ranging from 50-500 mg/day was given. VPA 985 had a significant aquaretic response compared with placebo in patients receiving diuretics as well as in those patients who were not (SIADH group). There was a dose-related increase in the net fluid volume (urine output minus fluid intake) and solute-free water clearance leading to significant increases in serum sodium and serum osmolality (Figure 4 and 5). Unfortunately, there was a high drop-out rate (12 patients or 27%; six due to dehydration and the other half due to other reasons). The highest doses of the drug (250-500 mg/day) were poorly tolerated and associated with dehydration, as assessed by systemic postural hypotension, increased thirst and marked sodium elevation. As a result, half of the patients on the 500 mg/day dose had the medication withheld several occasions. VPA 985 was most effective and safe when given at a dose of 125-250 mg/day. The second study by Gerbes et al. [13], included 60 patients with cirrhosis and dilutional hyponatremia on fluid restriction who were randomly assigned to receive 100 or 200 mg/day of VPA 985 or placebo for 7 days. There was a significant dose-dependent increase in serum sodium concentrations as well as a significant reduction in urine osmolality and body weight in both groups receiving VPA 985 whereas no changes in these parameters were found in the placebo arm (Figure 6). Complete response defined as a serum sodium ≥ 136 mEq/L was observed in 27% in the 100 mg dose and 50% in the 200 mg dose. Thirst was the main side effect in the 200 mg group, but not in the other groups. Two problems with this study were the small number of patients in each group (around 20) and that the effects of VPA 985 were only evaluated until serum sodium normalized without information on long-term response. The effects of the V2 receptor antagonists in cirrhotic patients with ascites are summarized in Table I.

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**Fig. 4** – Twenty-four hours free water clearance (upper) and net fluid volume (urine output minus fluid intake) (right) in patients with hyponatremia treated with placebo or the V2-receptor antagonist VPA985. (U) Placebo; (z) 25 mg twice daily; (A) 125 mg twice daily; (P) 250 mg twice daily. *, P<0.05 versus placebo. ***, P<0.01 versus 25 mg twice per day; #, P<0.05 versus 125 mg twice per day. (Reproduced with permission from Wong et al. Hepatology 2003;37:182-91).

**Clairance de l'eau libre des 24h (haut) et balance hydrique nette (diurèse moins apports hydriques de 24h) (droite) chez des malades avec hyponatrémie traités par placebo ou l'antagoniste des récepteurs V2 VPA985. (U) Placebo ; (z) 25 mg deux fois par jour ; (A) 125 mg deux fois par jour ; (P) 250 mg deux fois par jour. *, P < 0,05 versus placebo. ***, P < 0,01 versus 25 mg deux fois par jour ; #, P < 0,05 versus 125 mg deux fois par jour. (Reproduit avec la permission de Wong et al. Hepatology 2003;37:182-91).**

**Fig. 5** – Serum osmolality (upper) and serum sodium concentration (lower) in patients with hyponatremia treated with placebo or the V-2 receptor antagonist VPA 985. (U) Placebo; (z) 25 mg twice daily; (A) 125 mg twice daily; (P) 250 mg twice daily. (Reproduced with permission from Wong et al. Hepatology 2003;37:182-91).

**Sérum osmolalité (haut) et concentration sérique de sodium (bas) chez des patients avec hyponatrémie traités par placebo ou antagoniste des récepteurs V2 VPA985. (U) Placebo ; (z) 25 mg deux fois par jour ; (A) 125 mg deux fois par jour ; (P) 250 mg deux fois par jour. (Reproduit avec la permission de Wong et al. Hepatology 2003;37:182-91).**
Table I. – Published clinical studies of V2 receptor antagonists in patients with cirrhosis.

**Etudes cliniques réalisées avec les antagonistes des récepteurs V2 chez les malades cirrhotiques.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Compound</th>
<th>Dose</th>
<th>Subjects</th>
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<th>Results</th>
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<tr>
<td>Inoue et al.</td>
<td>OPC-31260</td>
<td>30 mg, single dose</td>
<td>Cirrhotics with ascites and peripheral oedema (8) vs healthy subjects (6)</td>
<td>14</td>
<td>• Increased urine flow</td>
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<td>• Lowered urinary osmolality</td>
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<td>• Increased free water clearance</td>
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<td>Decaux et al.</td>
<td>VPA-985</td>
<td>50, 100 mg</td>
<td>Hyponatremic cirrhotics with ascites (5) and SIADH patients (6)</td>
<td>11</td>
<td>• Increased serum sodium</td>
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<td>• Increased urine volume</td>
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<td>• Decreased urine osmolality</td>
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<td>Guyader et al.</td>
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<td>25, 50, 100, 200, 300 mg</td>
<td>Cirrhotics with ascites</td>
<td>25</td>
<td>• Increased serum sodium</td>
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<td>• Increased free water clearance</td>
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<td>Wong et al.</td>
<td>VPA-985</td>
<td>25, 125, 250 mg</td>
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<td>• Increased serum sodium</td>
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<td>Cirrhotics with hyponatremia</td>
<td>60</td>
<td>• Reduction in body weight</td>
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<td>• Normalization of serum sodium</td>
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<td>• Reduction in urine osmolality</td>
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Numbers into brackets correspond to references.

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**REFERENCES**


