BRIEF OBSERVATION

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Limited Efficacy of Tolvaptan in Patients with Cirrhosis and Severe Hyponatremia: Real-Life Experience

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ABSTRACT

BACKGROUND: Vaptans, vasopressin selective V2-receptor antagonists, represent the first pharmacologic approach to the treatment of hypervolemic hyponatremia in cirrhosis. However, information on the use of vaptans for patients with cirrhosis and hyponatremia in a real-life scenario is limited. Therefore, this study evaluated the effect of tolvaptan on serum sodium in patients with cirrhosis and severe hypervolemic hyponatremia.

METHODS: Nine patients with cirrhosis and serum sodium $\leq$125 mEq/L were included.

RESULTS: Only 2 of the 9 patients (22%) gained an increase in serum sodium >130 mEq/L that persisted throughout treatment. In the remaining patients, serum sodium did not change or increased during the first days but decreased thereafter despite continuation of treatment. Only 1 patient developed hyperkalemia as a side effect.

CONCLUSIONS: The efficacy of tolvaptan in patients with cirrhosis and severe hypervolemic hyponatremia seems to be limited.

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KEYWORDS: Cirrhosis; Hypervolemic hyponatremia; Hyponatremia; Tolvaptan; Vasopressin

Hyponatremia is a common complication of cirrhosis that entails a poor prognosis.[1,2] In most cases, hyponatremia in cirrhosis is hypervolemic because it occurs in the setting of an expanded extracellular fluid volume. The main factor responsible for the impairment of renal solute-free water excretion is an increased release of vasopressin (arginine vasopressin) as a compensatory response to the impaired effective arterial blood volume that occurs in advanced cirrhosis.[2-4] Arginine vasopressin acts on collecting duct cells of the kidney, causing an increased reabsorption of water through water channels of the aquaporin system.[3,4]

In recent years, a family of drugs, vaptans, that selectively antagonize the vasopressin V2 receptors in the kidney, were developed. Vaptans can increase solute-free water excretion and increase serum sodium in subjects with euvolemic and hypervolemic hyponatremia.[5] One of these drugs, tolvaptan, was approved by the Food and Drug Administration (FDA) for the management of hyponatremia associated with cirrhosis, heart failure, and syndrome of inappropriate antidiuretic hormone secretion.[6-9] The existing information on its efficacy in cirrhosis in clinical practice is

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limited, and most data stem from pivotal trials[7-9] that included patients with hypervolemic hyponatremia of various origins, and the number of patients with cirrhosis was low.

PATIENTS AND METHODS

The objective of this study was to analyze the efficacy of tolvaptan in improving serum sodium concentration in 9 patients with cirrhosis and severe hyponatremia treated in 2 academic centers in Europe: the Hospital Clínic in Barcelona, Spain, and the Clinica Medica in Padova, Italy. Severe hyponatremia was defined as serum sodium ≤125 mEq/L unresponsive to fluid restriction of 1 L/d and without diuretic therapy. Patients with significant comorbidities or hepatocellular carcinoma were excluded. Patients with hyponatremia and ongoing bacterial infections, gastrointestinal bleeding, hepatic encephalopathy grade ≥II, type 1 hepatorenal syndrome, or hemodynamic instability were considered for treatment only after resolution of these complications. Tolvaptan was given on a compassionate-use basis, because tolvaptan was approved by the European Medicines Agency for hyponatremia in heart failure and syndrome of inappropriate antidiuretic hormone secretion and not in cirrhosis. The inclusion of patients in the study was finalized when the FDA raised a safety alert indicating the potential risk of tolvaptan to induce liver injury.

Tolvaptan was administered following the guidelines proposed by the FDA. All patients were hospitalized during the titration phase. During this phase, serum sodium was measured every 8 hours during the first day of treatment and daily thereafter. To avoid a rapid increase in serum sodium concentration, fluid intake was not restricted during treatment. Tolvaptan was started at 15 mg/d, and the dose was increased in a stepwise fashion to 30 and 60 mg/d if serum sodium levels did not increase ≥5 mEq/L in 24 hours and were still <135 mEq/L. The effective dose of tolvaptan, defined as the dose leading to an increase of serum sodium ≥5 mEq/L with a value ≥130 mEq/L, was maintained until the end of treatment. If serum sodium increased >140 mEq/L, treatment was stopped, and it could be restarted when serum sodium decreased <135 mEq/L. If serum sodium increased ≥8 mEq/ in 24 hours, treatment was discontinued for 24 hours. Treatment also was stopped in patients who developed side effects.

CLINICAL SIGNIFICANCE

- Vaptans represent the first pharmacologic approach to the treatment of hypervolemic hyponatremia in patients with cirrhosis.
- Information on the use of vaptans in patients with cirrhosis in a real-life scenario is scarce.
- The efficacy of tolvaptan in patients with cirrhosis and severe hypervolemic hyponatremia in a real-life setting seems to be limited, because only 2 of the 9 patients included in this study had a complete response to treatment.

RESULTS

The baseline characteristics of patients are shown in Table 1. Baseline median serum sodium concentration was 121 mEq/L (117-125 mEq/L). All patients had severe ascites without significant impairment of kidney function. Four patients were on the waiting list for liver transplantation.

In 2 of the 9 patients, serum sodium increased during treatment >130 mEq/L, to 133 and 140 mEq/L, respectively, and this increase persisted until the end of treatment. In 2 other patients, serum sodium levels reached ≥130 mEq/L during the first days of tolvaptan (132 and 130 mEq/L, respectively), but then decreased despite continuation of treatment. End of treatment values in these patients were 120 and 124 mEq/L, respectively. In the remaining 5 patients, serum sodium increased slightly or did not increase at all during treatment (end of treatment values were 117, 120, 121, 128, and 129 mEq/L). Overall, a positive response (increase of serum sodium ≥5 mEq/L with a value that persisted ≥130 mEq/L throughout treatment) occurred in only 2 of the 9 patients (22%). Figure shows the individual values of serum sodium during treatment in all patients included. There were no significant changes in liver and kidney function, mean arterial pressure, heart rate, urine volume, urine sodium, and plasma osmolality (Table 2).

Overall, median treatment duration was 16 days (5-40 days). Reasons for stopping therapy were lack of response (n = 4), liver transplant (n = 1), side effects (n = 1; recurrent hyperkalemia), and complications of cirrhosis (n = 2; type 1 hepatorenal syndrome and septic shock). No patient developed hypernatremia or a rapid increase in serum sodium (>8 mEq/L within 24 hours).

Table 1 Demographic and Clinical Data and Liver and Kidney Function of Patients Included

Age (y)	65 (55-70)
Gender, male	4 (44%)
Alcoholic cirrhosis	5 (56%)
Previous ascites	9 (100%)
Previous hepatic encephalopathy	3 (38%)
Serum bilirubin (mg/dL)	2.7 (1.2-9.4)
Serum albumin (g/L)	28 (21-38)
INR	1.6 (1.2-2.3)
Serum sodium (mEq/L)	121 (117-125)
Serum creatinine (mg/dL)	0.9 (0.7-1.2)
Leukocyte count (10^9 cells/L)	6.5 (2.7-9.9)
Platelet count (10^9 cells/L)	98 (33-162)
Child Pugh score	8 (5-10)
MELD score	18 (9-29)

Data are expressed as number and percentage or median and range.
INR = International normalized ratio; MELD = model for end-stage liver disease.