Original Research Article

Tolvaptan, an oral vasopressin antagonist, in treatment of Hyponatremia in Cirrhosis

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Received:- 17/11/23
Revised:- 18/12/23
Accepted:- 24/02/24

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ABSTRACT

Background & Aims: Tolvaptan is a vasopressin V2-receptorv antagonist that improves serum sodium concentration by increasing renal solute-free water excretion. Specific data on the safety and efficacy of tolvaptan in patients with cirrhosis and hyponatremia has not been exclusively evaluated. **Methods:** This Study examined cirrhotic patients with hyponatremia who received 15 mg oral tolvaptan (n = 24; increased to 30 or60 mg if needed)orplacebo (n = 21) once-dailyfor30 days. At base-line, 44% had mild hyponatremia (serum sodium 130–134 mmol/L), 56% had marked hyponatremia (serum sodium <130 mmol/L). **Results:** Tolvaptan was effective in raising serum sodium. Average daily area under the curve for serum sodium was significantly greater in the tolvaptan group from baseline to day 4 ($p<0.0001$)and day 30($p<0.0001$). This superiority was maintained after stratification by baseline hyponatremia (mild and marked). Hyponatremia recurred 7 days after discontinuation of tolvaptan. Mean mental component summary scores of the SF-12 health surveyimproved from baseline to day 30 in the tolvaptan group butnot the placebo group (4.68vs. 0.08, p= 0.02). Major side effects due to tolvaptan were dry mouth and thirst. Gastrointestinal bleeding occurred in 10% and 2% of patients in the tolvaptan and placebo group, respectively (p= 0.11). Adverse event rates, withdrawals, and deaths were similar in both groups. **Conclusions:** One month of tolvaptan therapy improved serum sodium levels and patient-reported health status in cirrhotic patients with hyponatremia. Hyponatremia recurred in tolvaptan-treated patients after discontinuation.

Introduction

Patients with cirrhosis may retain fluids due to an abnormal regulation of extracellular fluid volume leading to increased renal sodium and solute-free water re-absorption. In some patients, excessive solute-free water retention may lead to hyponatremia occurring in the setting of this expanded extracellular fluid volume. This type of hyponatremia is known as dilutional or hypervolemic hyponatremia and usually occurs in patients with advanced cirrhosis[5,9]. In cirrhosis, splanchnic vasodilation secondary to sinusoidal portal hypertension leads to arterial under-filling, which in turn unloads high-pressure baroreceptors that stimulates a non-osmotic hypersecretion of arginine vasopressin(AVP), thereby leading to solute-free water retention and hyponatremia[8,9].

Hyponatremia in cirrhosis has been linked to hepatic encephalopathy, impaired quality of life, and poor short-term prognosis[13,14]. Fluid restrictions to 1–1.5 liters per day had been, until recently, the only available method for managing hypervolemic hyponatremia. However, this method has very limited efficacy in improving serum sodium levels [2,16]. Other treatments, such as demeclocycline or urea, are not approved by the Food and Drug Administration (FDA) or by the European Medicines Agency(EMEA), are slow to correct serum sodium, and are potentially nephrotoxic in cirrhosis[1,17,19]. The administration of hypertonic saline solution is not recommended because

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How to cite this article:
Jayaswal M, Kumar V, Agarwal A K, Tolvaptan, an oral vasopressin antagonist, in treatment of Hyponatremia in Cirrhosis

additional expansion of the extracellular fluid worsens edema and ascites and,with over-rapid correction, can induce osmotic demyelination [8,17]. Most importantly, none of the prior therapeutic options addresses the underlying pathophysiology of the hyponatremia, which is related to increased AVP levels. Oral selective antagonists of AVP that bind to the V2 receptor of the principal cells of the renal collecting ducts are effective in increasing serum sodium levels in hypervolemic hyponatremia[18].

Tolvaptan, an orally active, selective, nonpeptide V2 antagonist, induces the excretion of electrolyte-free water without increasing the total level of electrolyte excretion. This agent is approved for the treatment of dilutional hyponatremia associated with SIADH, cardiac failure or cirrhosis by the FDA in the United States, for SIADH by the EMEA in Europe, and for diuretic-resistant volume overload in heart failure by the Ministry ofHealth in Japan. Pivotal studies of tolvaptan enrolled patients with hyponatremia due to SIADH, cardiac failure, and cirrhosis have been conducted. The results of these pivotal studies indicate that tolvaptan effectively improves serum sodium levels in these patients [10,11]. In these studies, no evaluation was performed on the disease responsible for hyponatremia. Thus,there is lack of data on the specific effects of tolvaptan inpatients with cirrhosis and hyponatremia. Given that tolvaptan is the only oral vaptan approved for management of hyponatremia, its efficacy in the population of patients with cirrhosis is of interest to practicing clinicians. Therefore, the current study reports a sub-analysis of the tolvaptan pivotal studies evaluating the efficacy and safety of tolvaptan in patients with cirrhosis and hyponatremia.

Patients and methods

Patients

This report represents an analysis of patients with cirrhosis enrolled in two prospective, multicenter, randomized, placebo-controlled, double-blind, phase 3 studies.

Inclusion criteria: Patients aged 18 years or older, with non acute hypervolemic hyponatremiadue to cirrhosis, were eligible. Patients with hypovolemic hyponatremia were excluded. Patients with ascites underwent a sodium restricted diet of 90 mmol/day and were kept on diuretics .Hyponatremia was classified as either mild (baseline serum sodium concentration of 130–134 mmol/L) or marked (baseline serum sodium concentration of<130 mmol/L). Patients with a serum sodium <120 mmol/L without significant neurological impairment.

Exclusioncriteria: Patients with a serum sodium <120 mmol/L if they had associated significant neurological impairment severe cardiopulmonary disease; cerebrovascular accident; multiple strokes; SBP<90 mmHg; severe pulmonary hypertension; urinary tract obstruction; uncontrolled diabetes mellitus; progressive or episodic neurological disease; or a serum creatinine>3.5 mg/dl (309lmol per liter).Terminally ill patients with little chance of short-term survival were also excluded.

Study design

Study was conducted between June , 2019 and February, 2020 at PMCH/Patna . All patients enrolled in the study provided written informed consent. Eligible patients were centrally randomized using random permuted blocks and stratified according to the severity of their hyponatremia (marked[<130 mmol/L] or mild [130–134 mmol/L]). Patients were randomized in a 1:1ratio to receive oral tolvaptan or visually identical placebo once daily in the morning for 30 days. Treatment with lithium chloride, demeclocycline, or urea was not permitted. Fluid restriction was at the discretion of the investigator, but generally recommended to be avoided during study drug titration. Hospitalization wasrequired on day 1 only; most patients were discharged by day 5 .On day 1, patients received a 15 mg oral tablet of tolvaptan or matching placebo. Based on the patient's serum sodium and a regimen designed to correct the sodium slowly, the dose of study drug was increased from 15 to 30 mg and from 30 to 60 mg, during the first 4 days of therapy and at the investigators' discretion throughout the 30-day treatment. If serum sodium was less than136 mmol/L and had increased by less than5 mmol/L during the prior 24 h, the dose was increased. If serum sodium concentration exceeded 145 mmol/L,increased by more than 8 mmol/L during 8 h on day 1, or increased by more than12 mmol/L during 24 h, investigators withheld the next day's dose or increased the patient's fluid intake.

Study assessments

Patients were assessed at baseline, 8 h after the first dose of study drug, and on days 2, 3, 4, 11, 18, 30, and 37. Study drug was stopped at day 30. At day37, the effect of stopping the study drug on serum sodium was assessed.

Primary endpoints :

The absolute serum sodium concentrations at each visit; percentage of patients with normalized serum sodium (>135 mmol/L) at day 4 and day 30; time to normalization of serum sodium concentration; and categorical serums odium concentrations at day 4 and day 30 .

Secondary endpoints

Changes in fluid intake and output on day 1, change in body weight on day 1, and fluid restriction or use of intravenous saline as rescue therapy. Clinical outcomes such as effect of ascites resolution, changes in degree of hepatic encephalopathy and changes in renal function were not a focus of this study and were not specifically evaluated.

Adverse events

Adverse events and laboratory abnormalities were monitored throughout the 30 days of the study and the 7day follow-up period. Patients could spontaneously report adverse events . Seriousness and severity of each event and the probability of an association between the study drug and the adverse event were assessed.

Statistical analysis

The two primary end points, the changes in average daily serum sodium concentration from baseline to day 4 and from baseline to day 30, were calculated as change in serum sodium concentration in the two treatment groups were compared using an analysis of covariance (ANCOVA) model with treatment group and base-line stratification as factors and baseline serum sodium as covariate. The percent-age of patients with normalized serum sodium (>135 mmol/L) and the percentage of patients requiring fluid restriction were analyzed with the Cochran–Mantel–Haenszel test, stratified by baseline stratification factors. Categorical changes in hyponatremia severity were analyzed using the Cochran–Mantel–Haenszel meanscore test with a modified Ridit score (van Elteren test). This analysis was performed separately for patients with mild and marked hyponatremia at baseline.Post-treatment categories were normal (135–145 mmol/L), mild, and marked Hyponatremia .The time to normalization of the serum sodium concentration was analyzed with the use of a log-rank test. Using an analysis of variance model,with treatment group and baseline stratification as factors, fluid loss, fluid intake,and fluid balance (total intake minus total output) on day 1 was analyzed.

	Tolvaptan n=24	Placebo n=21
Degree of hyponatremia (mmol/ml)		
Mild (130-134mmol/L)	n=11	n= 09
Marked (<130mmol/L)	n=13	n= 12
eGFR (ml/min/1.73m^2)	76.3	67.7
S. Creatinine (mg/dl)	1.0	1.1
Prothrombin time (sec.)	15	15

Results

Study patients

The demographic and baseline characteristics of patients in the two treatment groups were similar. Liver and renal function tests, as well as serum sodium concentration at the time of randomization, are shown . Sodium levels between 131–135 meq/L are not uncommon in patients with Child A cirrhosis as impairment of solute-free water excretion can develop in those with mild ascites and edema[5,9]. About half of these subjects had mild and half more severe hyponatremia. In those with the lowest sodium levels, it is possible that other factors (concomitant CHF, iatrogenic causes) may have contributed to the severity of hyponatremia. Prior to study treatment, 98% of patients in the tolvaptan group and 100% of patients in the placebo group were taking diuretics (spironolactone and/or furosemide). The majority of patients were on a moderate dose (spironolactone <200 mg/day and furosemide <80 mg/day). 17 (72.6%) out of the 24 patients randomized to tolvaptan and 14 (66.7%) out of 21 patients randomized to placebo completed the 30-day study period and the 7-day follow-up.

Effect of treatment on serum sodium concentration :

The absolute change in serum sodium

from baseline to day 4 and from baseline to day 30 was significantly greater in the tolvaptan group than in the placebo group . This effect was seen both in the mild and marked hyponatremic patients (See Table). The statistically significant difference between tolvaptan and placebo in increasing the absolute value of serum sodium from baseline today 4, and from baseline to day 30 was generally maintained when patients were categorized by baseline hyponatremia, eGFRand serum creatinine. However, the absolute change in serum sodium for tolvaptan versus placebo at day 30 in patients with marked hyponatremia and for those with an eGFR of <60 ml/min did not achieve statistical significance (p= 0.0840 and p= 0.0576, respectively). This analysis was not significant at day 30 in patients with serum creatinine>1.5 mg/dl(p= 0.27), although only 5tolvaptan- and 3 placebo-treated subjects were available for this subgroup's analysis. Although not tested for significance of the difference, the nominal changes in serum sodium were greater in those with more severe hyponatremia, but lesser in those with more severe renal insufficiency.

Urine output and fluid intake on day 1 was significantly greater in the tolvaptan group, and fluid balance on day 1 was significantly more negative compared to placebo. When patients were stratified by eGFR, the significantly greater negative fluid balance in the tolvaptan group persisted in both the high and low eGFR groups, although a greater net difference in fluid balance was apparent for those with preserved renal function, as compared with those whose eGFR was <60 ml/min. The percentage of patients on fluid restriction at day 1 was not significantly different between treatment groups, nor was the change in bodyweight at day 1. No patients required intravenous saline as rescue therapy for hyponatremia. Responder analyses, based on normalization of serum sodium(>135 mmol/L), were pre-specified using the last observation carried forward principle

Absolute change in serum sodium (mmol/L)

All patients	n=24	n=21	*p* value
Day 4	4.7	0.3	
Day 30	4.2	1.3	
Mild hyponatremia	n=11	n=9	
Day 4	3.7	-0.2	
Day 30	3.1	-0.3	
Marked hyponatremia	n=13	n=12	
Day 4	5.6	0.8	
Day 30	5.0	2.6	
eGFR>60ml/mim	n=13	n=8	
Day 4	5.1	1.7	
Day 30	5.1	2.3	
eGFR<60 ml/min	n=9	n=12	
Day 4	4.0	-0.7	
Day 30	3.4	0.7	
SCr<1.5mg/dl	n=19	n=17	
Day 4	4.7	0.70	
Day 30	4.4	1.5	
SCr>1.5mg/dl	n=5	n=3	
Day 4	4.4	-0.5	
Day 30	4.1	1.4	

Safety

Overall adverse events occurred in 87.5% of tolvaptan patient and 80.9% of placebo patients. Treatment-emergent adverse events occurred

in more than 5% of patients in either group . The most common treatment-emergent adverse event seen in both groups was ascites, whereas the most common emergent adverse events in the tolvaptan group were thirst, dry mouth, and hyperkalemia. Treatment-emergent serious adverse events occurred in 37.5 %of tolvaptan patients and 33.3 % of placebo patients.

The most common disorder sresulting in discontinuation were hepatobiliary (hepatic failure in one patient on tolvaptan, hepatorenal syndrome in one patient on placebo, and veno-occlusive liver disease in one patient on placebo), renal and urinary disorders (nocturia in one patient on tolvaptan, acute renal failure in three patients on placebo),and nervous system (hepatic encephalopathy in two patients on tolvaptan, and hepatic encephalopathy in one patient on placebo). Throughout the study, potentially clinically significant increases in serum creatinine (defined as serum creatinine>1.5 mg/dl) occurred in 12.5 % of patients in the tolvaptan group and 14.3% of patients in the placebo group. Among the 24 patients in the tolvaptan group, there were 3deaths due to treatment-emergent adverse events that started before the 7-day follow-up visit. Among the 21 patients in the placebo group, there were two such deaths. In the tolvaptan group, the deaths were due to hepatic failure, hepatic encephalopathy, and respiratory failure. The deaths in the placebo group were due to intestinal ischemia and hepatorenal syndrome, each in a single subject.

The desirable rate of correction of sodium concentration (<0.5 mmol/L/h) was not exceeded during the first 24 h in any patient. None of the patients in the tolvaptan group or the placebo group developed hypernatremia (serum sodium >145 mmol/L). Fewer patients in the tolvaptan group had potentially clinically significant increases in potassium, heart rate, and blood pressure. Slightly more patients in the tolvaptan group had potentially clinically significant changes in serum bilirubin (>2.0 mg/dl)(65%vs.60%). The two groups had similar changes in creatinine clearance during the study .Gastrointestinal bleeding events occurred in 3 out of 24(12.5%) patients receiving tolvaptan and in one out of 21 (4%)patients on placebo . Among patients receiving tolvaptan, 2 had evidence of upper gastrointestinal hemorrhage and concomitant esophageal varices and one patient had a self-limited episode of bright red blood per rectum attributed to hemorrhoids. The patient on placebo who bled had a gingival hemorrhage and concomitant esophageal varices that were not considered as the cause of hemorrhage. No deaths related to gastrointestinal bleeding occurred in either group.

Discussion

The use of the oral vasopressin V2 receptor antagonist tolvaptan for 30 daysincreases serum sodium concentration in hyponatremic patients with cirrhosis. The administration of tolvaptan was also associated with a significant increase in urine output and fluid intake and a negative fluid balance 24 h after the initial dose when compared to placebo.

This analysis is unique in the sense that it specifically evaluates,in cirrhotic patients, the safety and efficacy of the only approved oral vaptan for hyponatremia in this population. The absolute value of serum sodium was higher in the tolvaptan group compared to the placebo group from baseline to day 4 and from baseline to day 30.Tolvaptan was superior to placebo in raising serum sodium levels at all time points from day 1 to day 30 and brought more patients into the normal range more quickly.

Both the increase in serum sodium levels while on drug and the drop of serum sodium levels after stopping tolvaptan indicate that V2 receptor antagonism in patients with cirrhosis leads to solute-free water excretion and improvement of serum sodium levels. Previous studies indicated that the use of other V2 receptor antagonists in patients with cirrhosis, ascites, and hypervolemic hyponatremia is efficacious in improving serum sodium levels[6,12,16,20]. In addition, other studstudies have shown reduction in body weight probably due to a decrease in ascites and edema[3,20]. The current study was performed for a longer period of time than previous studies with similar results and indicates that the initial response to tolvaptan could occur regardless of the baseline serum sodium level and be maintained throughout the 30 days.ies have shown reduction in body weight probably due to a decrease in ascites and edema[3,20]. The current study was performed for a longer period of time than previous studies with similar results and indicates that the initial response to tolvaptan could occur regardless of the baseline serum sodium level and be maintained throughout the 30 days.

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