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A STUDY ON TOLVAPTAN, AN ORAL VASOPRESSIN ANTAGONIST, IN TREATMENT OF HYPONATREMIA IN CIRRHOSIS

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ABSTRACT

Tolvaptan is a vasopressin V2-receptorantagonist that improves serum sodium concentration byincreasing renal solute-free water excretion. Specific data onthe safety and efficacy of tolvaptan in patients with cirrhosisand hyponatremia has not been exclusively evaluated.

Methods: This Study examined cirrhotic patients with hyponatremiawho received 15 mg oral tolvaptan (n = 30; increased to 30 or60 mg ifneeded)orplacebo (n = 25) once-dailyfor30 days.Atbase-line, 46% had mild hyponatremia (serum sodium 130–134 mmol/L), 54% had marked hyponatremia (serum sodium <130 mmol/L).

Results: Tolvaptan was effective in raising serum sodium. Patients treated with tolvaptan showed greater increase in serum sodium level. This superiority was maintained afterstratification by baseline hyponatremia (mild and marked).Hyponatremia recurred 7 days after discontinuation of tolvaptan. Major side effectsdue to tolvaptan were dry mouth and thirst. Gastrointestinalbleeding occurred in 10% and 2% of patients in the tolvaptanand placebo group, respectively . Adverse event rates,withdrawals, and deaths were similar in both groups.

Conclusions:One month of tolvaptan therapy improved serumsodium levels and patient-reported health status in cirrhoticpatients 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 renalsodium 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 hyponatremiais 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 stimulate 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 poorshort-term prognosis[13,14].Restricting fluids to 1–1.5 liters per day had been, untilrecently, the only available method for managing hypervolemic hyponatremia. However, this method has very limited efficacyin improving serum sodium levels [2,16]. Other treatments, such as demeclocycline or urea, are not approved by the Food andDrug 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 hypertonicsaline solution is not recommended because additional expansion of the extracellular fluid worsens edema and ascites and,with over-rapid correction, can induce osmotic demyelination[8,17]. Mostimportantly, 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 receptorof the principal cells of the renal collecting ducts are effective inincreasing 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 isapproved for the treatment of dilutional hyponatremia associated with SIADH, cardiac failure or cirrhosis by the FDA in theUnited 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 cirrhosishave been conducted. The results of these pivotal studies indicate that tolvaptan effectively improves serum sodium levelsin these patients [10,11]. Inthese studies, no evaluation wasperformed 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 tolvaptanis the only oral vaptan approved for management of hyponatremia, its efficacy in the population of patients with cirrhosis is ofinterest to practicing clinicians. Therefore, the current studyreports 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 study represents an analysis of patients with cirrhosis enrolled in two prospective, multicenter, randomized, placebo-controlled, double-blind, phase 3 studies.

Patients aged 18 years or older, with nonacute hypervolemic hyponatremia due 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 were included.

Exclusion criteria: 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 episodicneurological disease; or a serum creatinine>3.5 mg/dl (309mol per liter).Terminally ill patients with little chance of short-term survival were also excluded.

Study design

Study was conducted between September 2017 to August 2018 at Department Of Medicine, Patna Medical College & Hospital, 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 notpermitted. Fluid restriction was at the discretion of the investigator, but generallyrecommended 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 thesodium 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, thedose 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 increasedthe patient's fluid intake.

Study assessments

Patients were assessed at baseline, 8 h after the first dose of study drug, and ondays 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 withnormalized serum sodium (>135 mmol/L) at day 4 and day 30; time to normalization of serum sodium concentration; and categorical serumsodium concentrations at day 4 and day 30 .

Secondary endpoints included: changes in fluid intake and output on day 1, change in body weighton day 1, and fluid restriction or use of intravenous saline as rescue therapy. Clinical outcomes such as effect of ascites resolution, changes in degreeof hepatic encephalopathy and changes in renal function were not a focus of thisstudy 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 associationbetween the study drug and the adverse event were assessed.

Statistical analysis

The two primary end points, the changes in average daily serum sodiumconcentration from baseline to day 4 and from baseline to day 30, were calculatedas changein serum sodium concentration in the two treatment groups were comparedusing 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 percentageof patients requiring fluid restriction were analyzed with the Cochran–Mantel–Haenszel test, stratified by baseline stratification factors. Categorical changes inhyponatremia 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 markedHyponatremia .The time to normalization of the serum sodium concentrationwas 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.

Table 1.

	Tolvaptan n=30	Placebo n=24
Degree of hyponatremia (mmol/ml)		
Mild (130-134mmol/L)	n=14	n= 11
Marked (<130mmol/L)	n=16	n= 14
eGFR (ml/min/1.73m2)	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 in Table 1 . 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 withmild 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 (concomitantCHF, 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) . 22 (73.3%) out of the 30 patients randomized to tolvaptan and 17 (68 %) out of 25 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 2). The statistically significant difference between tolvaptan and placebo in increasing the absolute value of serum sodium from baseline to day 4, and from baseline to day 30 was generally maintained when patients were categorized by baseline hyponatremia,eGFR and 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= 0.0930 andp= 0.0616, respectively). This analysis was not significant at day 30 in patients with serum creatinine>1.5 mg/dl (p= 0.29), although only 5 tolvaptan- 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 body weight 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=30	n=25	p value
Day 4	4.8+/-4.3	0.3+/-3.7	<0.0001
Day 30	4.2+/-4.6	1.3+/-5.9	0.001
Mild hyponatremia	n=14	n=11	
Day 4	3.7+/-2.8	-0.2+/-3.4	<0.0001
Day 30	3.2+/-3.9	-0.3+/-4.8	0.006
Marked hyponatremia	n=16	n=14	
Day 4	5.5+/-4.9	0.7+/-4.0	<0.001
Day 30	4.9+/-4.8	2.6+/-6.2	0.09
eGFR>60ml/mim	n=16	n=10	
Day 4	5.2+/-4.0	1.7+/-4.4	0.0005
Day 30	5.1+/-3.8	2.3+/-6.5	0.04
eGFR<60 ml/min	n=12	n=14	
Day 4	4.1+/-3.8	-0.7+/-2.9	<0.0001
Day 30	3.5+/-4.9	0.7+/-5.5	0.06

SCr<1.5mg/dl	n=22	n=19	
Day 4	4.8+/-3.9	0.69+/-3.7	<0.0001
Day 30	4.5+/-4.4	1.6+/-5.9	0.007
SCr>1.5mg/dl	n=8	n=6	
Day 4	4.4+/-4.6	-0.5+/-3.3	0.04
Day 30	4.2+/-4.4	1.3+/-5.7	0.29

Safety

Overall adverse events occurred in 87.5% of tolvaptan patient and 80.9% of placebo patients. Treatment-emergent adverseevents 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 disordersresulting in discontinuation werehepatobiliary (hepatic failurein one patient on tolvaptan,hepatorenal syndrome in one patient on placebo, and venoocclusiveliver disease in one patient onplacebo), renal and urinary disorders (nocturia in one patienton tolvaptan, acute renal failure in three patients on placebo),and nervous system (hepatic encephalopathy in two patients ontolvaptan, and hepaticencephalopathy in one patient on placebo). Throughout the study, potentially clinically significantincreases in serum creatinine (defined as serum creatinine>1.5 mg/dl) occurred in 12.5 % of patients in the tolvaptangroupand 14.3% of patients in the placebo group.Among the 30 patients in the tolvaptan group, there were 4 deaths due to treatment-emergent adverse events that startedbefore the 7-day follow-up visit. Among the 25patients in the placebo group, there were 3 such deaths. In the tolvaptangroup, 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 4 out of 30 (13.3 %) patients receiving tolvaptan and in one out of 25 (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 ofthe oral vasopressin V2 receptor antagonist tolvaptan for 30 days increases 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 patientsinto the normal range more quickly.

Both the increase inserum sodium levels while on drug and the drop of serumsodiumlevels 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 studiesindicated 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 studies 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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