Vasopressin V2-receptor antagonists in patients with cirrhosis, ascites and hyponatremia

Shahid Habib and Thomas D. Boyer

Abstract: Hyponatremia is a common problem in patients with advanced cirrhosis. It develops slowly (paralleling the rate of progression of the liver disease) and usually produces no neurological symptoms, although it may exacerbate hepatic encephalopathy. For patients awaiting liver transplantation a low serum sodium level is a strong predictor of pretransplant mortality, independent of the Model for End-stage Liver Disease score (MELD). The pathogenesis of hyponatremia is related to the hemodynamic changes and secondary neurohormonal adaptations that occur in patients with cirrhosis and ascites. The nonosmotic release of arginine vasopressin is the principle cause of the hyponatremia and vasopressin-receptor antagonists are a new class of drugs recently approved for treatment of cirrhotic hyponatremia. In this article we review the safety and efficacy of V2-receptor antagonists in patients with cirrhosis, ascites and hyponatremia.

Keywords: ascites, cirrhosis, hepatorenal syndrome, hyponatremia, lixivaptan, portal hypertension, satavaptan, tolvaptan, vasopressin

Introduction

Disorders of water and electrolyte metabolism are common in patients with cirrhosis. In one large series the prevalence of hyponatremia in patients with cirrhosis and a serum sodium level less than 135 mmol/liter was 57% in hospitalized patients and 40% in outpatients. A total of 21% of patients with cirrhosis had serum sodium levels less than or equal to 130 mmol/liter [Boyer, 2010; Angeli *et al.* 2006]. Although hyponatremia is well tolerated in this population other problems associated with hyponatremia include severe ascites that is more difficult to treat, more frequent hepatic encephalopathy, hepatorenal syndrome and increased mortality. For example, patients with a serum sodium level less than or equal to 130 mmol/liter, despite the presence of severe ascites, were more likely not to be taking diuretics compared with those with higher serum sodium levels, suggesting diuretics had been stopped in the former group because of hyponatremia [Angeli *et al.* 2006]. Hyponatremia is an independent predictor of mortality over and above the Model for End-stage Liver Disease (MELD) score in patients awaiting liver transplantation and is also

predictive of post liver transplantation outcome [Kim *et al.* 2008; Hackworth *et al.* 2009]. The complications in the immediate post-transplantation period which are associated with pretransplant hyponatremia include increased risk of neurological problems, renal failure, infections, acute rejection, and higher mortality [Hackworth *et al.* 2009].

Pathogenesis of hyponatremia in cirrhosis

Hyponatremia is the most common electrolyte disorder in patients with cirrhosis. Classification of hyponatremia includes hypovolemic, euvolemic, and hypervolemic hyponatremia. The latter is also known as dilutional hyponatremia. Hypovolemic hyponatremia accounts for 10% of all cases of hyponatremia in patients with cirrhosis [Angeli *et al.* 2006]. Hypervolemic or dilutional hyponatremia is by far the most common cause of this disorder. In approximately 50% of patients with cirrhosis and hyponatremia contributing factors could be identified, such as hemorrhage, infection, or medications [Ginès and Guevara, 2008].

Ther Adv Gastroenterol

[2012] 5(3) 189–197

DOI: 10.1177/
1756283X12437357

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Figure 1. Pathogenesis of hyponatremia in cirrhosis.

AVP, arginine vasopressin; NO, nitric oxide; PG, prostaglandins; PHTN, portal hypertension; RAS, renin angiotensin system, SVR, systemic vascular resistance.

Hypovolemic hyponatremia develops as a result of volume losses of extracellular fluid resulting in a decreased intravascular volume. This usually happens because of over diuresis, free water loss from the gastrointestinal (GI) tract, and decreased fluid intake. These patients show signs of dehydration and prerenal azotemia. Additionally, they have little peripheral edema and lack significant ascites. Hepatic encephalopathy is a common finding in this situation. Hypervolemic hyponatremia develops in the setting of increased extracellular fluid volume. This clinically manifests with dependent edema, anasarca, and ascites. Plasma volume in such patients is increased in absolute values but effective blood volume is reduced because of dilatation of the arterial circulation, in particular the splanchnic circulation. This is part of the hyperdynamic circulation which includes arterial vasodilation and increased cardiac output. Patients are hypotensive and there is activation

of neurohumoral systems, including increased secretions of norepinephrine, renin and angiotensin, and vasopressin (antidiuretic hormone [ADH]) (Figure 1). The above-mentioned neurohormonal changes compensate for the reduced effective plasma volume [Schrier *et al.* 1988]

Not all patients with cirrhosis and fluid retention develop hyponatremia. A higher percentage of patients with hyponatremia have decreased liver size, higher blood levels of plasma renin activity, aldosterone, antidiuretic hormone, and norepinephrine. Reduced free water excretion is the principal abnormality. Factors that are involved in the reduced free-water clearance in cirrhosis include

- (1) Increased nonosmotic release and decreased clearance of vasopressin [Ginès *et al.* 1998].
- (2) Decreased glomerular filtration rate and excessive proximal tubular sodium

reabsorption resulting in impaired free water excretion.

- (3) Increased expression of aquaporin 2 water channels independent of vasopressin concentration in patients with decompensated cirrhosis with ascites [Chung *et al.* 2010].

Treatment of hyponatremia

Hyponatremia is difficult to treat. Fluid restriction is the mainstay of treatment. However, this is very difficult for patients and physicians. It is important to identify and address correctable factors such as medications or infections that may be contributing to the hyponatremia. Furthermore, fluid restriction by itself is not very effective in improving serum sodium levels. In one report serum sodium failed to rise over 7 days with water restriction (1.5 liters daily) in patients who were hospitalized and had been receiving diuretics [Wong *et al.* 2003]. Even if the serum sodium rises, the rate of increase is usually slow and if the hyponatremia is severe, less than 125 mmol/liter, prolonged hospitalization may be required. As a result of hyponatremia, diuretics are usually stopped, leading to worsening of ascites. More rapid correction can be achieved with hypertonic saline, which will worsen the fluid retention and increase the risk of development of hypernatremia and osmotic demyelination. A number of other agents have been used to treat hyponatremia, including demeclocycline, urea and κ opioids with variable results. Adverse events (AEs) were found to be quite significant with these agents [Ginès and Cardenas, 2008]. The development of a new class of drugs that are receptor antagonists of vasopressin has led to the hope that a new and effective therapy is now available for patients with cirrhosis and hyponatremia.

Vasopressin-receptor antagonists

Vasopressin-receptor antagonists (VPAs) are a new class of drugs. These drugs block the action of vasopressin at one of its receptor sites. Vasopressin has several physiological functions in addition to its antidiuretic effects. Three different types of vasopressin receptors have been identified which are V1a, V1b also called V3, and V2 [Lemmens-Gruber and Kamyar, 2006]. All of these receptors are very similar in size and amino acid sequence. The classical vascular smooth muscle cell contraction, platelet aggregation, and hepatic glycogenolysis actions of

vasopressin are mediated by V1a receptors. V2 receptors are expressed in the principal cells of renal collecting ducts. Vasopressin exerts its antidiuretic effect by binding to these V2 receptors located on the basolateral membrane of the principal cells. Activation of the V2 receptors stimulates the Gs-coupled adenylyl cyclase system that promotes the formation of cyclic adenosine monophosphate (cAMP) [Ginès *et al.* 2008; Kumar and Berl, 2008]. The cyclic nucleotide in turn activates serine threonine kinase, and protein kinase A. The post-cAMP events that mediate the increase in water permeability are related to the presence of a member of the water channel family that is exclusively expressed in the collecting duct principal cells called aquaporin 2 (AQP2). AQP2, following phosphorylation by protein kinase A, moves to the luminal membrane thereby increasing water reabsorption and leading to a fall in serum sodium [Boyer, 2010].

VPAs, termed 'vaptans', are classified based on their receptors: nonselective V1/V2-receptor antagonists, including conivaptan, approved for use in euvolemic hyponatremia; selective V1a-receptor antagonists, including relcovaptan; selective V1b-receptor antagonists which are useful in the treatment of emotional and psychiatric disorders; they also may be of benefit in the treatment of disorders such as cerebral ischemia, stroke, Raynaud's disease, and dysmenorrhoea; selective V2-receptor antagonists, including tolvaptan, lixivaptan, and satavaptan, used for the treatment of hyponatremia related to cirrhosis, congestive heart failure (CHF), and syndrome of inappropriate antidiuretic hormone (SIADH) [Lemmens-Gruber and Kamyar, 2006]. Not all of these drugs are currently used in cirrhosis. Tolvaptan (Samsca) is an oral V2 receptor antagonist and has been approved by the US Food and Drug Administration (FDA) for use in patients with CHF or cirrhosis and hyponatremia, and is also used in patients with SIADH. Conivaptan (Vaprisol) is also approved by the US FDA for treatment of euvolemic hyponatremia.

Drugs such as tolvaptan and other V2-receptor antagonists bind to the V2 receptor, blocking the effect of vasopressin, leading to a decrease in AQP2 channels in the luminal membrane, and an increase in solute-free water clearance and correction of hyponatremia. In addition, this group of drugs causes mild natriuresis and an increase in urine output, resulting in more rapid weight

loss compared with patients not receiving the drug [Boyer, 2010; Ginès *et al.* 2008].

Clinical efficacy

Clinical efficacy of vasopressin receptor blockers has been evaluated in euvolemic and hypervolemic hyponatremia. A meta-analysis by Rozen-Zvi and colleagues evaluated overall efficacy of vaptans in patients with hyponatremia of all etiologies (CHF, cirrhosis, and SIADH) [Rozen-Zvi *et al.* 2010]. Fifteen trials were included evaluating early response in 1125 patients and late response in 549 patients. Response rates were high in trials assessing mostly patients with euvolemic hyponatremia and those assessing mostly patients with hypervolemic hyponatremia, with greater effect observed in the former. Change from baseline serum sodium level was significantly increased in early [weighted mean difference 5.27 mEq/liter; 95% confidence interval (CI) 4.27–6.26, 13 trials] and late response evaluation trials (weighted mean difference 3.49 mEq/liter; 95% CI 2.56–4.41, eight trials). Although there was an increased rate of rapid sodium correction [relative risk (RR) 2.52; 95% CI 1.26–5.08, eight trials] with vasopressin antagonists, hypernatremia rates were not significantly higher compared with controls (RR 2.21; 95% CI 0.61–7.96, five trials). AEs including mortality were not increased, and there were no reports of osmotic demyelination syndrome.

Data on the use of VPAs in the setting of cirrhosis with hyponatremia are limited (Table 1) [Berl *et al.* 2010; Ginès *et al.* 2008, 2010; Gerbes *et al.* 2003; Ku *et al.* 2009; Rozen-Zvi *et al.* 2010; Schrier *et al.* 2006; Wong *et al.* 2003, 2009, 2010, 2012]. Tolvaptan is the only drug that has been approved for treatment of cirrhotic hyponatremia. This approval relied on the SALT 1 and SALT 2 trials that also included patients with CHF and SIADH [Schrier, 2009]. Patients with cirrhosis in these trials were small in number and the trials did not differentiate between the different causes of hyponatremia. Trials evaluating satavaptan included only patients with cirrhosis and ascites, whereas a trial evaluating lixivaptan included patients with cirrhosis (77%), CHF, and SIADH [Wong *et al.* 2003]. Other trials evaluated lixivaptan in all the above-mentioned conditions but benefits in those with cirrhosis are based on subgroup analysis ($n = 60$) [Gerbes *et al.* 2003]. Satavaptan is the most studied drug in patients

with cirrhosis and ascites. The results of all published trials evaluating efficacy in patients with cirrhosis and hyponatremia are summarized in Table 1. Vaptans have shown the following clinical effects:

- (1) All V2-receptor antagonists in short-term use improved serum sodium concentration in both mild (serum sodium ≥ 130 mmol/liter) and marked (serum sodium < 130 mmol/liter) hyponatremia, increased urine output, and decreased urine osmolality.
- (2) The effect of tolvaptan on hyponatremia is marked in patients with serum sodium less than 130 mmol/liter, and there is a trend for the final serum sodium level in patients with cirrhosis to be lower than that in patients with hyponatremia due to SIADH or CHF.
- (3) Time to correction of hyponatremia ranged between 1 and 8 days with vaptans, which is significantly shorter compared with patients receiving placebo.
- (4) The proportion of patients developing hypernatremia (serum sodium > 145 mmol/liter) was 0–27%. Use of lixivaptan in higher doses (250 mg twice a day) was associated with a higher rate of hypernatremia, 50%.
- (5) The proportion of patients in whom serum sodium was corrected at a faster rate than planned (>8 mmol/liter/day) ranged from 1% to 14%.
- (6) Long-term use of satavaptan and tolvaptan has been studied and both are effective in increasing serum sodium concentration. However, the tolvaptan trial (SALTWATER) was open label and lacked a placebo control.
- (7) The effect of all of the vaptans on hyponatremia is short lived with a fall in serum sodium within a few days of discontinuation of the drug.
- (8) Satavaptan use was associated with a reduction in and better control of ascites, but it failed to show any benefit in reducing the need for large volume paracentesis.
- (9) Satavaptan use was associated with higher mortality and serious AEs compared with placebo in one trial requiring premature termination of the trial and withdrawal of the drug from further trials.

Table 1. Summary of published trials evaluating efficacy of vasopressin-receptor antagonists (VPAs) in patients with cirrhosis and hyponatremia

Vasopressin antagonists	Author	Year	Patients with cirrhosis (%)	Patients (N)	Serum Na at inclusion (mmol/liter)	Diuretic use	Duration of treatment	Proportion (%) of patients achieving serum Na >135	Mean (Mn)/median (Md) change in serum Na (mmol/liter)	Proportion (%) of patients with rapid change ($\geq$ 8mmol/liter/day)	Proportion (%) of patients achieving serum Na $\geq$ 145
Satavaptan ^{††}	Ginès	2008	100	110	$\leq$ 130	yes	14 days	P 26 versus T 50–82	(Mn) P 1.3 versus T 6.6	P 14 versus T 14	P 0 versus T 0–4
Satavaptan ^{††}	Ginès	2010	100	148	>130	yes	14 days	ND	(Md) P 0.1 versus T 2.5*	P 6 versus T 11	P 3.2 versus T 27.3
Satavaptan ^{††}	Wong	2010	100	151	<135 [‡]	yes	12 weeks	ND	Significant increase	ND	ND
Satavaptan ^{††}	Wong	2012	100	462	<135 [‡]	yes	52 weeks [□]	ND	ND	P 0.04 versus T 0.09	P 9.6 versus T 15.2
Satavaptan ^{††}	Wong	2012	100	496	<135 [‡]	yes	52 weeks [¶]	ND	ND	P 0 versus T 1.8	P 3.6 versus T 9.5
Satavaptan ^{††}	Wong	2012	100	240	<135 [‡]	yes	52 weeks [#]	ND	ND	P 1 versus T 2	P 5.1 versus T 13
Tolvaptan ^{§§}	Berl	2010	20	111	<130 (53%) ^{\$}	no	1.9 years	Tm 60 versus Ts 45	4.2**	4.5**	7**
Tolvaptan ^{††}	Schrier	2006	23	205	<130 (52%) ^{\$}	no	30 days	P 25 versus T 53	(Mn) P 5.4 versus T 7.2	1.8**	P ND versus T 1.8
Tolvaptan ^{††}	Schrier	2006	30	243	<130 (48%) ^{\$}	no	30 days	P 25 versus T 58	(Mn) P 6.3 versus T 6.9	1.8**	P ND versus T 1.8
Lixivaptan (VPA985) ^{††}	Gerbes	2003	100	60	115–132	no	7 days	P 0 versus T 50*	(Mn) P 0 versus T 2–5	ND	ND
Lixivaptan (VPA985) ^{††}	Wong	2003	100	44	<130	yes	7 days	ND	(Mn) P –1 versus T 7§	9**	P 0 versus T 8–50

* $p < 0.05$ all doses versus placebo.

\$Other group included patients with mild hyponatremia (130–134 mmol/liter).

[‡]Study also included patients with serum Na $\geq$ 135.[§] $p = 0.003$ in group with 250 mg twice a day; in other groups rise was statistically insignificant.[□]Patients completed study period, placebo = 55.8%, treatment = 59.9%.[¶]Patients completed study period, placebo = 22.5%, treatment = 21.1%.[#]Patients completed study period, placebo=15%, treatment = 21.7%.

**Response was documented cumulatively in treated patient only.

^{††}Randomized placebo-controlled and blinded trial.^{§§}Open-label study.

Md, median; Mn, mean; ND, not documented; P, placebo; T, treatment; Tm, treatment group mild hyponatremia (130–134 mmol/liter); Ts, treatment group significant hyponatremia (<130 mmol/liter).

Adverse events

Short-term use

In a meta-analysis by Rozen-Zvi and colleagues, mortality was reported in five trials of the use of vaptans in 794 patients with hyponatremia and different diseases [Rozen-Zvi *et al.* 2010]. A total of 49 deaths were reported overall without a significant difference between the treated group and the control group (RR 0.79; 95% CI 0.44–1.42), without significant heterogeneity. There was also no difference in the number of AEs (RR 1.05; 95% CI 0.96–1.15), serious AEs (RR 0.95; 95% CI 0.75–1.21), and AEs requiring drug discontinuation (RR 0.98; 95% CI 0.67–1.44). Major AEs reported included thirst and infusion site reactions. This meta-analysis did not find any examples of osmotic demyelination syndrome, or increased incidence of orthostatic hypotension.

Satavaptan use was found to be associated with a higher rate of acute renal failure, defined as doubling of serum creatinine, compared with placebo (14.8% *versus* 2.7%) and a higher rate of asymptomatic orthostatic hypotension, defined as a drop in systolic blood pressure of more than 20 mmHg, compared with placebo (16.7% *versus* 3%). Thirst was reported in 13.9% of the satavaptan group compared with none in the placebo group. There was no increase in mortality in the satavaptan group compared with the placebo group. Hyponatremia (serum sodium > 145 mmol/liter) was seen more often (27.3%) in patients receiving a larger dose (25 mg) of satavaptan [Ginès *et al.* 2008, 2010].

In the SALT 1 and SALT 2 trials evaluating tolvaptan, the overall occurrence of AEs and serious AEs was similar in both groups. Thirst and dry mouth were common in the treated group (14%) compared with placebo (5%). More patients in the tolvaptan group developed constipation. None of the patients in either group developed acute renal dysfunction. The occurrence of hypotension was similar in both groups [Schrier *et al.* 2006].

In trials evaluating safety and efficacy of lixivaptan, thirst was the most common side effect especially in patients receiving a larger dose (200 mg/day). Renal impairment was seen in 20% of study patients and was similar to placebo. No patient developed neurological complications [Gerbes *et al.* 2003; Ku *et al.* 2009; Wong *et al.* 2003].

Long-term use

With long-term use (52 weeks) of satavaptan in patients with cirrhosis and ascites who are receiving diuretics, the incidence of major complications of cirrhosis was no different than placebo. Overall, treatment-related AEs were seen in 85–88% of satavaptan-treated patients and in 86–87% of patients receiving placebo. Serious AEs were also similar between groups (satavaptan 47–60% *versus* placebo 50–55%). Discontinuation rates were also similar [Wong *et al.* 2009]. However, when analyzing individual AEs, long-term use of satavaptan compared with placebo was associated with significant increases in aspartate aminotransferase (11.6% *versus* 6%), alanine aminotransferase (9.5% *versus* 3%), and bilirubin (8.8% *versus* 4.8% levels). Higher rates of GI bleeding in the satavaptan group compared with placebo were also observed (upper GI bleeding 10.9% *versus* 6%, lower GI bleeding 3.3% *versus* 1.8%). There was also an increase in renal events in the satavaptan group compared with placebo (30.9% *versus* 24.7%). The incidences of hepatorenal syndrome and hyperkalemia were similar in both groups. More patients in the satavaptan group died (29.4%) compared with the placebo group (21.7%). The relative risk for all-cause mortality during or after treatment was 1.47 (95% CI 1.01–2.15, $p = 0.049$). Most deaths were associated with complications of cirrhosis. The incidence of treatment-related fatal outcome was significantly higher in the satavaptan group and this outcome led to withdrawal of the drug [Wong *et al.* 2009]. Long-term use of satavaptan alone without concurrent use of diuretics in patients with cirrhosis and refractory ascites was not associated with higher mortality in one trial [Wong *et al.* 2012].

In the SALTWATER extension of SALT 1 and SALT 2, the efficacy and safety of long-term use of tolvaptan was evaluated [Berl *et al.* 2010]. The original causes of hyponatremia were CHF 30%, cirrhosis 18%, and SIADH 52%. Mean follow-up time on tolvaptan therapy was 1.9 years. A total of 105 patients out of 111 experienced an AE. AEs that occurred in more than 10% of patients (drug related or unrelated) included peripheral edema (25 patients), hyponatremia (23 patients), anemia (20 patients), diarrhea (19 patients), urinary tract infection (18 patients), nausea (17 patients), fatigue (15 patients), hypokalemia (14 patients), headache (14 patients), ascites (13 patients), hypotension (13 patients), pneumonia (13 patients), cardiac failure (12 patients), thirst (12 patients), and dizziness (12 patients). A total of 19 patients (17%)

died during the 212 patient-years of exposure – nine deaths per 100 patient-years of exposure. Nineteen patients withdrew because of a treatment-emergent AE. Six of the 19 patients who withdrew from the study due to AEs subsequently died (cardiac failure – two patients, bleeding esophageal varices, hepatic cirrhosis, cerebral hemorrhage, and GI hemorrhage). An additional 13 patients died as a result of an AE without being withdrawn from the study (cardiac failure – three patients, renal failure – two patients, hepatorenal syndrome, cardiorespiratory arrest, cardiac arrest, pneumonia, cerebral hemorrhage, respiratory failure, sepsis, and urosepsis) [Berl *et al.* 2010]. Since there were no controls, it is hard to assess whether the use of tolvaptan was associated with an increase in mortality.

Monitoring for drug-related adverse events

The AE most feared in the use of these drugs is a too rapid rise in serum sodium (>12 mmol/liter/24 h) leading to hypernatremia, osmotic demyelination, and central nervous system injury. Osmotic demyelination was not observed in any of the published trials. The proportion of patients achieving hypernatremia ranged from 0% to 50% and this was observed with all three V2-receptor antagonists. Therefore, the FDA has included a black box warning that initiation of therapy should occur in an inpatient setting with close monitoring of serum sodium. Also, as patients with cirrhosis may be at risk from more side effects and are at lower risk for neurological complications, slower rates of increase are recommended by the FDA. Patients with cirrhosis tolerate hyponatremia with minimal neurological sequelae and therefore use of tolvaptan should be limited to those with serum sodium levels less than 125 mmol/liter. Daily or every other day serum sodium levels should be determined while patients are receiving tolvaptan. All three V2-receptor antagonists cause a diuresis which if excessive could lead to renal insufficiency, especially when used for longer duration with concurrent use of diuretics. Monitoring of renal function should be performed when patients receive any of the vaptans. One side effect of major concern is the increased risk of variceal bleeding, and perhaps GI tract bleeding in general, as was seen in the trials with satavaptan. There is no way to monitor for this risk but patients with known high risk varices or a past history of variceal or GI tract bleeding are poor candidates for the long-term use of vaptans until

further evidence is available. Long-term outpatient studies using vaptans in concert with diuretics are needed before the true benefit of the vaptans for the treatment of cirrhotic hyponatremia is known.

Conclusions and recommendations

- (1) All three V2-receptor antagonists, lixivaptan, satavaptan, and tolvaptan, have been studied in patients with cirrhosis, ascites, and hyponatremia, and have shown beneficial effects in correcting hyponatremia when used short term. Satavaptan and tolvaptan have also shown beneficial effects when used long term, although the data are limited.
- (2) Tolvaptan has been approved by the US FDA for use in patients with cirrhosis and hyponatremia in addition to hyponatremia associated with CHF and SIADH.
- (3) Not every patient with cirrhosis, ascites, and hyponatremia needs V2 receptor antagonist treatment, and use of tolvaptan should be reserved for patients with marked hyponatremia, that is a serum sodium level less than 125 mmol/liter.
- (4) The dose of tolvaptan should be low to start with and gradually titrated based on response of the serum sodium level to achieve a level of more than 130 mmol/liter.
- (5) Concurrent use of vaptans and diuretics may be associated with more effective diuresis but at a cost of more AEs. Pending further studies the concurrent use of diuretics and tolvaptan should be limited.
- (6) The use of satavaptan is associated with higher rates of GI tract hemorrhage.
- (7) Long-term use of satavaptan in combination with diuretics was associated with higher mortality leading to concern about the long-term use of other vaptans with diuretics in patients with cirrhosis. Satavaptan has been withdrawn and therefore is not available. Although long-term follow up of patients receiving tolvaptan suggests this drug is safe, most patients did not have cirrhosis and usage of diuretics in this patient population was not defined. Pending further studies, the use of tolvaptan should be for a short period of time and limited to inpatients align with cirrhosis and severe

hyponatremia. Long-term use is not recommended until further controlled trials are completed assessing the risk and benefit.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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