ORIGINAL ARTICLE

Use of tolvaptan in patients hospitalized for worsening chronic heart failure with severe hyponatremia: The initial experience at a single-center in Turkey

Kronik kalp yetersizliğinin kötüleşmesi nedeniyle hastaneye yatırılan ciddi hiponatremik hastalarda tolvaptan kullanımı: Türkiye'de tek merkezden ilk deneyim

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ABSTRACT

Objective: The aim of the present study was to assess the efficacy and safety of tolvaptan for severe hyponatremia (SH) in hypervolemic heart failure (HF) patients within daily clinical practice.

Methods: We restrospectively reviewed our database on tolvaptan as an add-on treatment in hypervolemic patients admitted to our clinic due to deterioration of HF and having hyponatremia resistant to standard therapy. Severe hyponatremia was defined as serum sodium concentration ≤125 mEq/L. The database included demographic, clinical, laboratory, and echocardiographic findings on admission, and numerous outcome measures for oral tolvaptan treatment were used to assess its efficacy and safety.

Results: The study group consisted of 56 hypervolemic HF patients with severe hyponatremia (25 female and 31 male) with mean age of 66 years. All patients received a single dose of tolvaptan 15 mg daily for an average of 3.2 days due to severe hyponatremia. Sodium and potassium concentrations, fluid intake, and urine volume increased ($p<0.0001$, $p=0.037$, $p<0.0001$, and $p<0.0001$, respectively), whereas furosemide dosage, body weight, heart rate, systolic and diastolic blood pressure, and New York Heart Association class decreased significantly in response to tolvaptan treatment, without a rise in serum creatinine or urea concentrations ($p<0.0001$, $p<0.0001$, $p=0.001$, $p<0.049$, $p<0.009$ ve $p=0.001$, respectively).

Conclusion: In this retrospective, single-centered study conducted in a small group of Turkish patients, short-term treatment with low-dose tolvaptan added to standard therapy of hypervolemic HF patients with severe hyponatremia was well tolerated with a low rate of major side effects and was effective in correcting severe hyponatremia.

ÖZET

Amaç: Hipervolemik kalp yetersizliği (KY) olan hastalardaki ciddi hiponatremide tolvaptan'ın etkinlik ve güvenilirliğini değerlendirmek.

Yöntemler: KY'nin kötüleşmesi nedeniyle kliniğimize yatırılan hipervolemik hastalarda standart tedaviye dirençli hiponatreminin tolvaptan eklenerek tedavisi için oluşturulan bir veritabanı geriye dönük olarak tarandı. Serum sodyum düzeyinin ≤125 mEq/L ciddi hiponatremi olarak tanımlandı. Bu veritabanı, hastaneye yatış sırasındaki demografik, klinik, laboratuvar ve ekokardiyografik bulguları içermekteydi. Oral tolvaptan tedavisinin etkinlik ve güvenilirliğini değerlendirmek amacıyla tolvaptan tedavisiyle ilgili bilgiler ile serum elektrolitleri dahil çok sayıda sonlanım ölçütü de kaydedildi.

Bulgular: Toplam 56 (25 kadın, 31 erkek, ortalama yaş 66) ciddi hiponatremisi olan hipervolemik kalp yetersizlikli hasta dahil edildi. Tüm hastalar ciddi hiponatremi nedeniyle ortalama 3.2 gün boyunca günde 15 mg'lık tek doz tolvaptan aldı. Tolvaptan tedavisiyle serum üre ve kreatinin düzeylerinde bir artış olmaksızın sodyum ve potasyum düzeyleri, sıvı alımı ve idrar hacmi anlamlı artarken (sırasıyla, $p<0.0001$, $p=0.037$, $p<0.0001$ ve $p<0.0001$) furosemit dozu, vücut ağırlığı, nabız sayısı, sistolik ve diyastolik kan basınçları ile New York Kalp Cemiyeti fonksiyonel sınıfı anlamlı biçimde azaldı (sırasıyla, $p<0.0001$, $p<0.0001$, $p=0.001$, $p<0.049$, $p<0.009$ ve $p=0.001$).

Sonuç: Bu küçük, geriye dönük, tek merkezli ve Türk popülâsyonunda ilk olan çalışmada, hipervolemik kalp yetersizlikli hastalardaki ciddi hiponatremi için standart tedaviye ek olarak verilen kısa süreli, düşük doz tolvaptan, düşük bir majör yan etki oranıyla iyi tolere edildi ve ciddi hiponatreminin düzeltilmesinde etkili oldu.

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Heart failure (HF) is a major public health problem that leads to frequent hospital admissions with clinical picture of volume overload in both intravascular and extracellular spaces.[1] Patients who experience HF usually have history of progressive fluid retention with hyponatremia, causing increase in body weight, which exacerbates symptoms and leads to hospitalization.[2,3] This condition of volume overload reflects a state of marked neurohormonal activation and, importantly, activation of water-retaining hormone arginine vasopressin. Among hospitalized patients with decompensated HF, hyponatremia occurs with prevalence of 8% to 27%, depending on data source (e.g., clinical trials or registries) and threshold used to define low serum sodium,[3–6] and is regarded as a poor prognostic indicator.[7]

Abbreviations:

ACEI	*Angiotensin-converting enzyme inhibitor*
ARB	*Angiotensin receptor blocker*
eGFR	*Estimated glomerular filtration rate*
HF	*Heart failure*
NYHA	*New York Heart Association*
SH	*Severe hyponatremia*

Non-potassium-sparing diuretics (i.e., particularly loop diuretics) are still the first-line treatment to improve hypervolemic state, but patients sometimes have inadequate improvement.[2,3,8–11] The Acute Decompensated Heart Failure Registry (ADHERE) study reported diuretic resistance to be approximately 30%.[12] Furthermore, use of diuretics may lead to frequent and important side effects, including hypotension, electrolyte imbalance, such as hyponatremia or hypokalemia, and worsening renal function.[2]

Evidence suggests that vasopressin receptor antagonists increase diuresis without significantly affecting serum potassium, blood pressure, or renal function. In addition, by optimizing HF treatment through the specific effect of such an agent on diuresis, it may be possible to reduce dose of loop diuretics, and thereby avoid some adverse effects of high dose, such as renal dysfunction and hearing loss.[13] Ultimately, in contrast to angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers, left ventricular dysfunction can be prevented with vasopressin antagonists, which are able to reduce volume retention and correct hyponatremia in HF patients.[1]

Tolvaptan is a non-peptide vasopressin V2-receptor antagonist.[10] Several HF studies have demonstrated that oral tolvaptan alone or added to conventional diuretic therapy produced significant decrease in body weight and edema, and increased serum sodium concentrations without leading to electrolyte imbalance or worsening kidney function.[2,8,10,13–15] Accordingly, the latest European Society of Cardiology Guidelines for HF recommended tolvaptan use to treat resistant hyponatremic HF patients.[9]

Management of hypervolemic hyponatremic HF is challenging and data indicate that there is a need for new therapies, particularly in patients with resistance to loop diuretics or electrolyte imbalance due to their use.[13] According to New York Heart Association (NYHA) classification of severity, HF patients have increased vasopressin level, which is due to an increase in angiotensin II level and activation of a baroreceptor, and a reduction in vasopressin degradation due to liver/kidney dysfunction.[16,17] This vasopressin increase is especially prominent in NYHA class III-IV HF patients.[16] Elevated vasopressin level can lower HF clinical status via free water retention by V2-receptors in renal collecting ducts and increase in systemic vascular vasoconstriction via V1 receptors in vascular smooth muscle. Consequently, this excessive water retention results in intravascular and extravascular congestion, and increase in total body fluid volume. This condition can lead to hypervolemic hyponatremia, particularly in patients with tendency for hyponatremia due to use of loop diuretics. In addition, hypervolemic hyponatremia is associated with re-hospitalization, prolonged hospitalization, increased cost, and mortality.[2,3,11,16] Tolvaptan effectively causes additional volume deprivation by opposing pathophysiological mechanisms of fluid retention.[11,13,18]

The present retrospective study aimed to determine the efficacy and safety of short-term, low-dose oral tolvaptan for hyponatremia refractory to standard treatments in hospitalized Turkish patients with decompensated HF and hypervolemia.

METHODS

Retrospective review of a prospectively collected database on tolvaptan as add-on treatment to standard therapy in severe hyponatremic patients hospitalized for worsening chronic HF at the cardiology clinic of a university hospital between November 2014 and November 2015 was performed. The study protocol was approved by the local ethics committee. The study was conducted according to the World Medical Asso-

ciation Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

In the present study, severe hyponatremia was defined as serum sodium level ≤125 mEq/L and maximum prescribed dose of tolvaptan was 15 mg daily for no more than 7 days, according to the regulations of the "Notifications on Health Practices" in Turkey. Insurance-approved dose of tolvaptan is 15 mg daily and indication is irrespective of existence of severe hyponatremia (<125 mEq/L) in hospitalized patients.

The study included adult patients (aged ≥18 years) who received oral tolvaptan for hyponatremia refractory to standard treatments administered following hospitalization for worsening decompensated HF with volume overload based on observation of jugular venous distention, dyspnea, rales, hepatomegaly, or peripheral edema. In this study cohort, tolvaptan was not used as first option drug. Tolvaptan was added to standard treatments when they failed and/or serum sodium level decreased (refractory hyponatremia). Initial dose of tolvaptan was determined by the attending physician, taking hemodynamics and degree of congestion of the patient into consideration, and was maintained during study period. Use of tolvaptan ceased if patient's hyponatremia and clinical condition improved.

Exclusion criteria included hypovolemia; acute coronary syndrome during previous 3 months; cardiac surgery during previous 3 months; mechanical cardiac support, such as ventricular assist devices, intra-aortic balloon pumping, extracorporeal membranous oxygenation, mechanical ventilation, or any combination of these devices; biventricular pacemaker placement during previous 3 months; comorbid conditions with expected survival <6 months; severe stenotic valvular disease; end-stage renal failure with dialysis or hemofiltration; pregnancy; and serum sodium concentration >125 mEq/L.

Data analyzed included demographic, clinical, laboratory, and echocardiographic findings at admission. Baseline demographic data consisted of age, gender, height, weight, and body mass index. Clinical data included medical history, congestive symptoms, cardiovascular findings, NYHA functional class, etiology and type of HF, and pharmacological treatments used for HF at admission. Laboratory data comprised hemoglobin, serum sodium, potassium urea, creatinine, and albumin concentrations; total protein; and estimated glomerular filtration rate (eGFR) at admission. Anemia was defined as hemoglobin concentration <13 g/dL in males and <12 g/dL in females.[9] Echocardiographic parameters were measured at admission via standard comprehensive M-mode and 2-dimensional echocardiography, performed by expert echocardiologists. Echocardiographic data included left atrial dimension, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left ventricular ejection fraction calculated using biplane Simpson method from apical 4- and 2-chamber views.

Data on tolvaptan treatment, including duration of both hospitalization and tolvaptan treatment, tolvaptan dose, and treatment outcome were also included. To analyze efficacy of tolvaptan, serum sodium, potassium, creatinine, and urea concentrations; concomitant furosemide dosage; fluid intake; urine volume; body weight; heart rate; systolic and diastolic blood pressure assessed at admission (baseline), 24 hours before initiation of tolvaptan (day 0), on days 1, 3, 5, and 7 of tolvaptan treatment, and at discharge were recorded. NYHA functional class in each patient at admission and discharge was also recorded.

Primary outcomes in this study were change in serum sodium, potassium, creatinine, and urea concentrations, and concomitant furosemide dosage, fluid intake, urine volume, body weight, heart rate, systolic and diastolic blood pressure at discharge compared with day 0, and change in NYHA functional class at discharge compared with baseline. To analyze the safety of tolvaptan treatment, side effects of tolvaptan — the study's secondary outcome — were recorded.

Statistical analysis

Statistical analysis was performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Power analysis was not performed. Categorical parameters are presented as frequency and percentage, and continuous variables as mean±SD. Wilcoxon test, paired t-test, or simple repeated measure analysis of variance was used to compare measurements at different time points. Pearson's correlation analysis was used to assess relationships between measurements at baseline, day 0, day 7, and at discharge. All statistical tests were 2-tailed and level of statistical significance was set at $p<0.05$.

RESULTS

Patient characteristics at admission

Among all patients (n=64) hospitalized for HF, 56 with HF and severe hyponatremia met study criteria according to prospectively collected data on tolvaptan use. A total of 8 patients were excluded due to hypovolemia. Among the 56 patients included in the study, 49 (87.5%) had a history of hospitalization for HF. The patients had apparent congestive symptoms, and 71.4% had jugular venous distention, 100% had dyspnea, 71.4% had rales, 48.2% had hepatomegaly, and 100% had edema/peripheral tibial edema. Mean duration of HF was 7±4 years.

In total, etiology of HF was ischemic heart disease in 60.7% of the patients, valvular heart disease in 28.6%, and cardiomyopathy in 7.1%. Among the patients, 58.9% had both right and left HF. Mean ejection fraction was 40±13%.

All patients were administered loop diuretics on admission and mean home furosemide dose was 55±28 mg. In all, 73% of the patients received beta-blockers, approximately 68% received ACEI/angiotensin receptor blocker (ARB), and 43% received spironolactone. Additionally, 30% of the patients received oral digoxin, whereas only 18% received ivabradine for heart rate control. Moreover, 30% of the patients were administered inotropic support during treatment. Table 1 provides a summary of demographic and clinical characteristics of the patients at admission.

Patient characteristics and outcome measures of tolvaptan treatment

The average length of hospitalization for HF was 10±5 days (range: 4–25 days). All hypervolemic hyponatremic patients received single daily dose of 15 mg tolvaptan if serum sodium concentration was ≤125 mEq/L despite standard in-hospital treatment (lifestyle modification, drug therapy, device therapy, as indicated). Tolvaptan was added to standard treatments, including both non-pharmacological (salt restriction) and pharmacological methods (ACEI, ARB, beta-blocker, spironolactone, digoxin, ivabradine, and inotropic agents) as required, according to recent guidelines. Mean duration of tolvaptan treatment was 3.2±2 days (range: 1–7 days). Tolvaptan treatment was maintained by the attending physician, taking hemodynamics and degree of individual patient's congestion into consideration. Tolvaptan was withdrawn by the physician when patient's hyponatremia and clinical condition improved. Figure 1 illustrates course of mean serum sodium, potassium, creatinine, and urea concentrations from baseline to discharge,

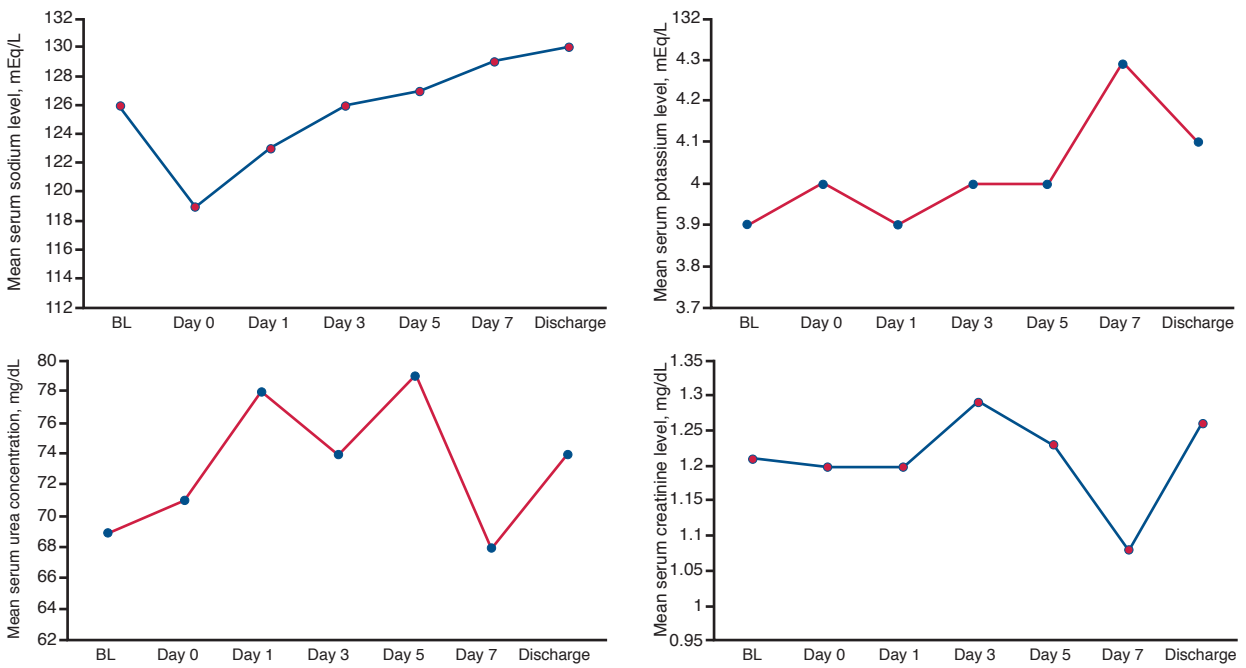

Figure 1. The course of mean serum sodium, potassium, creatinine, and urea concentrations from baseline to discharge.

Table 1. Clinicodemographic characteristics and laboratory data of the study patients at admission

Patient characteristics	Values		
	n	%	Mean±SD
Demographic			
Age (years)			66±11
Height (cm)			163±7
Weight (kg)			78±13
BMI (kg/m^2)			29.2±4.2
Medical history			
Prior hospitalization for HF	49	87.5	
Pacemaker/ICD/CRT	17	30.4	
Atrial fibrillation	21	37.5	
HT	34	60.7	
DM	26	46.4	
Hyperlipidemia	12	21.4	
Smoking	15	26.8	
Cerebrovascular accident	7	12.5	
Chronic kidney disease	18	32.1	
Previous MI	41	73.2	
CAD	41	73.2	
Congestive symptoms			
Rales	40	71.4	
Jugular venous distention	40	71.4	
Dyspnea	56	100	
Hepatomegaly	27	48.2	
Edema/peripheral tibial edema	56	100	
Cardiovascular examination			
Heart rate (beats per minute)			79±13
Systolic blood pressure (mmHg)			116±20
Diastolic blood pressure (mmHg)			65±8
NYHA functional class			
II	5	8.9	
III	34	60.7	
IV	17	30.4	
Etiology of HF			
Ischemic	34	60.7	
Cardiomyopathy	4	7.1	
Valvular	16	28.6	
Arrhythmia	0	0	
Hypertensive	2	3.6	
Type of HF			
Right HF	13	23.2	
Left HF	10	17.9	
Right and left HF	33	58.9	

Table 1 (cont.). Clinicodemographic characteristics and laboratory data of the study patients at admission

Patient characteristics	Values		
	n	%	Mean±SD
Pharmacological treatments			
Loop diuretics	56	100	
Beta-blockers	41	73.2	
ACEI/ARB	38	67.9	
Spironolactone	24	42.9	
Digoxin	17	30.4	
Ivabradine	10	17.9	
Inotropic agents	17	30.4	
Laboratory findings			
Hemoglobin (g/dL)			10.9±1.7
Serum urea (mg/dL)			69±41
Serum creatinine (mg/dL)			1.21±0.59
Estimated glomerular filtration rate (eGFR), (mL/min/1.73 m^2)			49±14
Serum sodium (mEq/L)			126±8
Serum potassium (mEq/LW)			3.9±0.7
Total protein (g/dL)			6.3±0.9
Serum albumin (g/dL)			3.3±0.5
Echocardiographic findings			
Left atrial dimension (mm)			51±10
LVEDD (mm)			53±9
LVESD (mm)			41±11
LV ejection fraction (%)			40±13

BMI: Body mass index; HF: Heart failure; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronization therapy; HT: Hypertension; DM: Diabetes Mellitus; MI: Myocardial infarction; CAD: Coronary artery disease; NYHA: New York Heart Association; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LV: Left ventricle; SD: Standard deviation.

and Figure 2 shows mean concomitant furosemide dosage, fluid intake, urine volume, and body weight from baseline to discharge. Heart rate, and systolic and diastolic blood pressure change from baseline to discharge can be seen in Figure 3.

In terms of primary outcomes, from day 0 of tolvaptan treatment to discharge, serum sodium and potassium concentrations, fluid intake, and urine volume increased significantly ($p<0.0001$, $p=0.037$, $p<0.0001$, and $p<0.0001$, respectively), whereas concomitant furosemide dosage, body weight, heart

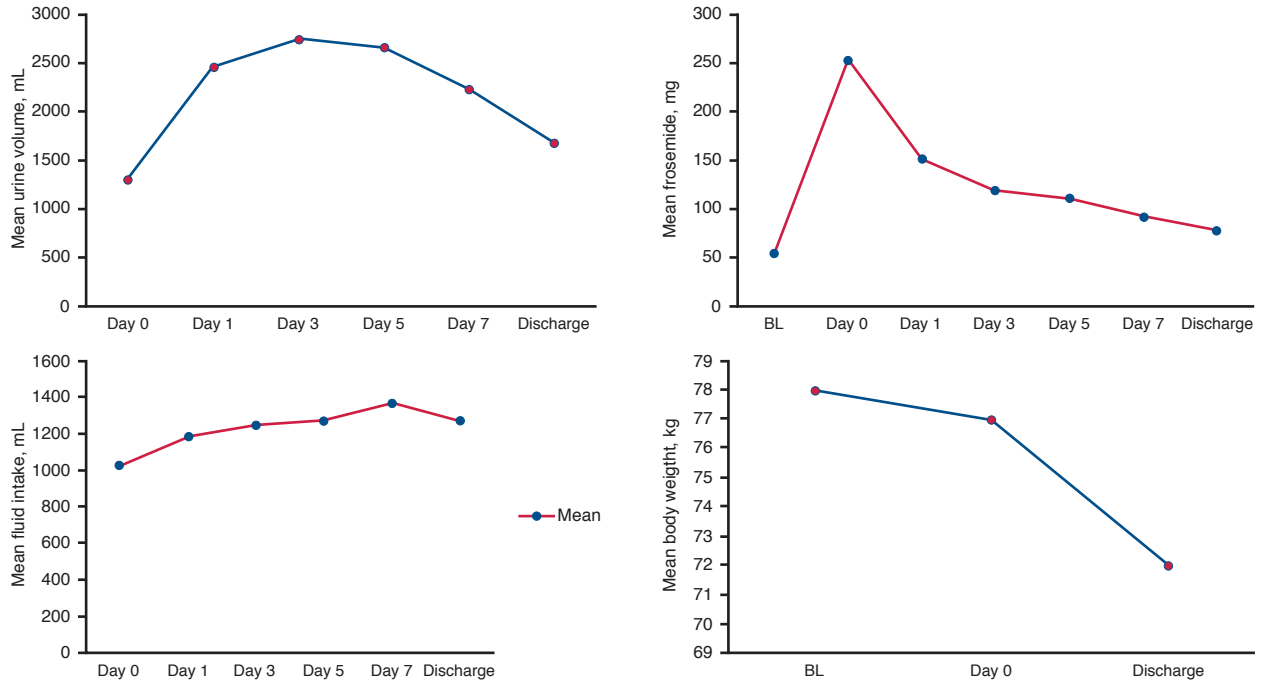

Figure 2. The course of mean concomitant furosemide dosage, fluid intake, urine volume, and body weight from baseline to discharge.

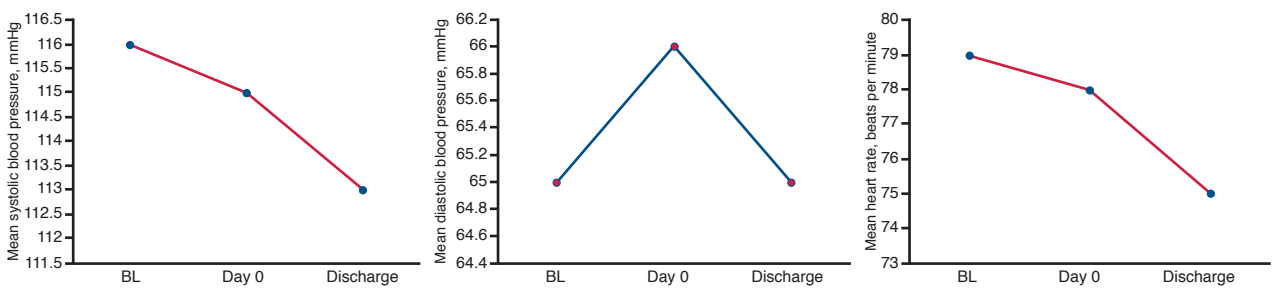

Figure 3. Heart rate and systolic and diastolic blood pressure changes from baseline to discharge.

rate, systolic and diastolic blood pressure, and NYHA functional class decreased significantly (p<0.0001, p<0.0001, p=0.001, p<0.049, p<0.009, and p=0.001, respectively). Serum creatinine and urea concentrations also decreased, but not significantly (p=0.112 and p=0.193, respectively) (Table 2). Among the 56 patients, 14 (25%) had serum sodium concentration >125 mEq/L^{-1} after only 1 day of tolvaptan treatment versus 23 patients (41%) after 3 days of treatment. In the remaining 19 patients (34%), serum sodium concentration increased to >125 mEq/L^{-1} after 5 days or 7 days of tolvaptan treatment.

Change in NYHA functional class from admission to discharge was analyzed. At admission, 51 (91.1%) of the patients were NYHA class III or IV, whereas only 13 (23.2%) patients were NYHA class III and none were class IV at discharge (Table 3). First quartile, median, and third quartile percentiles for NYHA class at admission were 3, 3, and 4, respectively, versus 2, 2, and 2, respectively, at discharge,. Median percentiles for NYHA class at discharge were significantly lower than at admission (p=0.001).

In bivariate analyses, correlation analyses were performed for each value (at admission, day 0, and discharge) of investigational parameters, duration of hospitalization, and duration of tolvaptan treatment (Table 4). Among study parameters, serum sodium concentration was significantly correlated with dura-

Table 2. Change in selected laboratory parameters and clinical characteristics with tolvaptan treatment (If data were not available for all study participants, the number for which data were present is shown in parenthesis.)

Parameters	At day 0	At discharge	*p*
	Mean±SD	Mean±SD	
Serum urea (mg/dL)	70.4±40.7	73.6±40.6	0.112
Serum creatinine (mg/dL)	1.22±0.56	1.26±0.58	0.193
Serum sodium (mEq/L)	119.2±4.7	130±3.4	<0.001
Serum potassium (mEq/L)	3.96±0.43	4.1±0.48	0.037
Concomitant furosemide dosage (mg/day)	252.5±129.5	79.3±32.1	<0.001
Fluid intake (mL/day)	1025.5±226.4	1271.4±195.8	<0.001
Urine volume (mL/day)	1305.8±378.7	1676.1±385.9	<0.001
Body weight (kg)	76.7±12.5	71.9±12.2	<0.001
Heart rate (beats per minute)	77.8±9.5	74.8±8.5	0.001
Systolic blood pressure (mmHg)	114.5±12.3	112.7±9.1	0.049
Diastolic blood pressure (mmHg)	66.1±5.6	64.8±6.4	0.009
New York Heart Association functional class (median)	3.21±0.59 (baseline)	2.04±0.66	0.001

SD: Standard deviation.

Table 3. Change in NYHA functional class from admission to discharge

	New York Heart Association class at admission						Total	
	II		III		IV			
	n	%	n	%	n	%	n	%
New York Heart Association class at discharge								
I	3	60.0	8	23.5	0	0.0	11	19.6
II	2	40.0	25	73.5	5	29.4	32	57.1
III	0	0.0	1	2.9	12	70.6	13	23.2
Total	5	100	34	100	17	100	56	100

tion of both hospitalization and duration of tolvaptan treatment, whereas heart rate was significantly correlated with duration of tolvaptan treatment. There was significant negative correlation between duration of hospitalization and serum sodium level at admission, on day 0, and at discharge (r=–.721 and p=0.000, r=–.554 and p=0.000, and r=–.447 and p=0.001, respectively); however, only serum sodium concentration at admission and on day 0 were negatively correlated with duration of tolvaptan treatment (r=–.495 and p=0.000, and r=–.390 and p=0.003, respectively). Furthermore, heart rate on day 0 and at discharge was negatively correlated with duration of tolvaptan treatment (r=–.303 and p=0.023, and r=–.328 and p=0.014, respectively).

Safety of tolvaptan treatment, as secondary outcome, was analyzed based on observed side effects of treatment; in all, 10 patients had only 1 side effect, 5 patients had 2 side effects, and 4 patients had 3 side effects. Thirst, dry mouth, and muscle cramps were most common adverse effects (14.3%, 14.3%, and 12.5%, respectively) (Table 5). None of these patients discontinued drug use due to side effects.

DISCUSSION

This study represented real-life experience of tolvaptan treatment in decompensated HF patients from Turkey with hypervolemia and hyponatremia. This retrospective study examined efficacy and safety of short-term, oral tolvaptan (at fixed low dose) added

Table 4. Significant results of bivariate analyses showing correlations between primary investigational parameters and length of hospitalization and tolvaptan treatment

		Length of hospitalization	Length of tolvaptan treatment
Serum sodium level at admission	r	-0.721	-0.495
	p	0.000	0.000
Serum sodium level at day 0	r	-0.554	-0.390
	p	0.000	0.003
Serum sodium level at discharge	r	-0.447	-0.233
	p	0.001	0.084
Heart rate at admission	r	0.040	-0.193
	p	0.767	0.155
Heart rate at day 0	r	-0.012	-0.303
	p	0.929	0.023
Heart rate at discharge	r	0.010	-0.328
	p	0.940	0.014

to standard treatments for severe SH in hospitalized patients with decompensated HF and volume overload. We found that addition of tolvaptan to patients with hypervolemic HF and SH significantly increased serum sodium concentrations and urine volume, and significantly reduced furosemide dose and body weight. Furthermore, symptoms of HF significantly improved, based on observed improvement in NYHA functional class and cardiovascular parameters, and tolvaptan was associated with low incidence of major side effects. Present findings indicate that short-term, low-dose adjuvant tolvaptan treatment is safe and effective for treating SH in hypervolemic HF patients, and that tolvaptan, which is commercially available in Turkey, should be considered a useful therapeutic alternative for the management of hypervolemic hyponatremic HF patients.

Several studies from the United States, Europe, India, and Japan have investigated the efficacy and safety of tolvaptan in hypervolemic hyponatremic HF patients;[1–3,5,8,10,13–15] however, to the best our knowledge, the present study is the first to evaluate the efficacy and safety of tolvaptan in Turkish HF patients. In the present retrospective observational study, tolvaptan added to standard treatments yielded results similar to those reported earlier.[14,19–26] In the current study, low-dose tolvaptan treatment for mean of 3.2 days corrected hyponatremia, increased diuresis, decreased body weight, improved symptoms associated with volume overload, and improved serum potassium concentration, fluid intake, blood pressure, heart rate, and renal function. Of note, while reduction in systolic blood pressure was statistically significant, it was not clinically significant. Furthermore, diastolic blood pressure was stable. Present findings are important because they demonstrate that low-dose tolvaptan is effective, even with very short-term use; however, persistence of its therapeutic effect on serum sodium concentration in decompensated HF patients was not determined, due to lack of post-hospitalization follow-up. Moreover, tolvaptan treatment in the present study resulted in reduction in daily furosemide dosage during hospitalization and at discharge, which is consistent with earlier studies.[2,3] In addition, it can be said that there was increase in serum potassium level due to decreasing dose of furosemide. Decrease in heart rate was seen when tolvaptan was added to standard treatment. Heart rate reduction may have been due to decreasing volume load of the patients. Decrease in sympathetic activity may also have contributed to decrease in heart rate due to decreased congestion.

Table 5. Tolvaptan-related adverse effects

Side effects	n	%
Thirst	8	14.3
Dry mouth	8	14.3
Nausea/vomiting	2	3.6
Muscle cramps	7	12.5

A number of disease-and treatment-related factors have been investigated in tolvaptan use for de-

compensated HF patients.[27–30] Rales, pedal edema, hyponatremia, lower creatinine clearance, higher brain natriuretic peptide, not using beta-blocker, and worse health status have been reported as independent risk factors for rehospitalization and death.[30] Toda et al.[31] investigated predictors of response to tolvaptan in patients with acute decompensated HF and reported that eGFR, urine osmolality, and kidney size were significantly greater in responders than in non-responders; however, kidney size was independently associated with responders based on multivariate analysis. Tolvaptan treatment was also reported to be independent factor in improving renal function.[32] In the present study, analysis of relationship between primary study parameters and duration of both hospitalization and tolvaptan treatment showed that low serum sodium concentration at admission, on day 0, and at discharge was associated with duration of hospitalization. Similarly, as serum sodium concentration at admission and on day 0 decreased, duration of tolvaptan treatment increased. On the other hand, as heart rate on day 0 and at discharge decreased, duration of tolvaptan treatment increased.

Although tolvaptan is a safe treatment in decompensated HF patients with hypervolemia and hyponatremia, there is potential risk for side effects, such as thirst and dehydration.[9] As expected based on earlier reports,[1–3,9,10,13] thirst and dry mouth were most common side effects observed in the present study; renal dysfunction — based on elevated serum creatinine concentration — was observed in 7 (12.5%) patients, even though most of these 7 patients had elevated serum creatinine concentration at admission, which is suggestive of pre-existing loss of renal functional reserve, and only 2 (3.6%) patients had progressive deterioration of renal function after completion of treatment. This adverse effect is not unusual and is consistent with earlier reports.[1,10] Nonetheless, hypernatremia (>145 mEq/L^{-1}) was not observed in any of the present study patients, in contrast to the literature.[1,10] It is most likely that short-term, low-dose administration of tolvaptan did not produce hypernatremia in the present study cohort.

Study limitations

The present study has several limitations, including retrospective design, small study population, and lack of control group to test the strength of our findings. Moreover, power analysis was not performed and duration of tolvaptan treatment was not standardized. Lastly, the present study included roughly selected patients from a single-center and it was not possible to use higher doses of tolvaptan due to reimbursement restrictions based on Turkish regulations. Combined, these limitations reduce the power of the findings and limit their generalizability; however, multicenter, prospective, randomized, controlled trials on the efficacy and safety of standardized tolvaptan treatment in large cohorts of selected patients continue to be published.[5,19–24]

Conclusion

The present findings demonstrate that in Turkish hypervolemic HF patients with SH, short-term treatment with low-dose tolvaptan added to standard treatments was well tolerated and effectively corrected SH with low rate of major adverse effects. Based on these findings, we think that tolvaptan should be considered a useful therapeutic alternative in the management of hypervolemic hyponatremic HF patients.

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REFERENCES

1. Patra S, Kumar B, Harlalka KK, Jain A, Bhanuprakash HM, Sadananda KS, et al. Short term efficacy and safety of low dose tolvaptan in patients with acute decompensated heart failure with hyponatremia: a prospective observational pilot study from a single center in South India. Heart Views 2014;15:1–5. [CrossRef]
2. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, et al; Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291:1963–71. [CrossRef]
3. Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail 2013;19:390–7. [CrossRef]

4. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Arch Intern Med 2007;167:1998–2005.
5. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–31. [CrossRef]
6. Sato N, Gheorghiade M, Kajimoto K, Munakata R, Minami Y, Mizuno M, et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol 2013;111:1019–25. [CrossRef]
7. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, et al; OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 2007;28:980–¬8.
8. Watanabe K, Dohi K, Sugimoto T, Yamada T, Sato Y, Ichikawa K, et al. Short-term effects of low-dose tolvaptan on hemodynamic parameters in patients with chronic heart failure. J Cardiol 2012;60:462–9. [CrossRef]
9. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847. [CrossRef]
10. Kinugawa K, Sato N, Inomata T, Shimakawa T, Iwatake N, Mizuguchi K. Efficacy and safety of tolvaptan in heart failure patients with volume overload. Circ J 2014;78:844–52.
11. Çavuşoğlu Y, Altay H, Ekmekçi A, Eren M, Küçükoğlu MS, Nalbantgil S, et al. Practical approaches for the treatment of chronic heart failure: Frequently asked questions, overlooked points and controversial issues in current clinical practice. Anatol J Cardiol 2015;15 Suppl 2:1–60. [CrossRef]
12. Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynne J, Mills RM, et al; ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. Cardiology 2009;113:12–9. [CrossRef]
13. Udelson JE, Bilsker M, Hauptman PJ, Sequeira R, Thomas I, O'Brien T, et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. J Card Fail 2011;17:973–81. [CrossRef]
14. Salterain-Gonzalez N, Esteban-Fernández A, García-López M, Lavilla-Royo FJ, Gavira-Gómez JJ. Efficacy of tolvaptan in patients hospitalized for heart failure with refractory hyponatremia. Clinical experience in daily practice. Rev Esp Cardiol (Engl Ed) 2013;66:503–4. [CrossRef]
15. Rodríguez-de Muñoz YM, Sánchez-Lázaro IJ, Almenar-Bonet L, Martínez-Dolz L, Rodríguez-Serrano M, Salvador-Sanz A. Use of tolvaptan in patients with hyponatremia due to heart failure: initial experience. Rev Esp Cardiol (Engl Ed) 2013;66:319–21. [CrossRef]
16. Nakamura T, Funayama H, Yoshimura A, Tsuruya Y, Saito M, Kawakami M, et al. Possible vascular role of increased plasma arginine vasopressin in congestive heart failure. Int J Cardiol 2006;106:191–5. [CrossRef]
17. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. J Am Coll Cardiol 2015;65:480–92.
18. Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, Yamashita T, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther 1998;287:860–7.
19. Imamura T, Kinugawa K, Ohtani T, Sakata Y, Higo T, Kinugawa S, et al. Assessment of quality of life during long-term treatment of tolvaptan in refractory heart failure: design and rationale of the AQUA-TLV study. Int Heart J 2014;55:264–7.
20. Torres VE, Meijer E, Bae KT, Chapman AB, Devuyst O, Gansevoort RT, et al. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. Am J Kidney Dis 2011;57:692–9. [CrossRef]
21. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST). Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–43. [CrossRef]
22. Gheorghiade M, Gottlieb SS, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, et al; Tolvaptan Investigators. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. Am J Cardiol 2006;97:1064–7. [CrossRef]
23. Matsue Y, Suzuki M, Nagahori W, Yoshida K, Onishi Y, Satoh Y, et al. Clinical effectiveness of tolvaptan in patients with acute decompensated heart failure and renal failure: design and rationale of the AQUAMARINE study. Cardiovasc Drugs Ther 2014;28:73–7. [CrossRef]
24. Matsuzaki M, Hori M, Izumi T, Fukunami M; Tolvaptan Investigators. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). Cardiovasc Drugs Ther 2011;25 Suppl 1:S33–45. [CrossRef]

25. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099–112. [CrossRef]
26. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, et al; Tolvaptan Investigators. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;107:2690–6. [CrossRef]
27. Vaduganathan M, Ambrosy AP, Greene SJ, Mentz RJ, Subacius HP, Maggioni AP, et al; EVEREST trial investigators. Predictive value of low relative lymphocyte count in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Circ Heart Fail 2012;5:750–8. [CrossRef]
28. Greene SJ, Harinstein ME, Vaduganathan M, Subačius H, Konstam MA, Zannad F, et al; EVEREST Trial Investigators. Prognostic value of monocyte count in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial). Am J Cardiol 2012;110:1657–62. [CrossRef]
29. Greene SJ, Vaduganathan M, Wilcox JE, Harinstein ME, Maggioni AP, Subacius H, et al; EVEREST Trial Investigators. The prognostic significance of heart rate in patients hospitalized for heart failure with reduced ejection fraction in sinus rhythm: insights from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial. JACC Heart Fail 2013;1:488–96. [CrossRef]
30. Dunlay SM, Gheorghiade M, Reid KJ, Allen LA, Chan PS, Hauptman PJ, et al. Critical elements of clinical follow-up after hospital discharge for heart failure: insights from the EVEREST trial. Eur J Heart Fail 2010;12:367–74. [CrossRef]
31. Toda H, Nakamura K, Nakahama M, Wada T, Watanabe A, Hashimoto K, et al; Tolvaptan Registry Investigators. Clinical characteristics of responders to treatment with tolvaptan in patients with acute decompensated heart failure: Importance of preserved kidney size. J Cardiol 2016;67:177–83. [CrossRef]
32. Matsue Y, Suzuki M, Seya M, Iwatsuka R, Mizukami A, Nagahori W, et al. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure in high-risk population. J Cardiol 2013;61:169–74.

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