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ORIGINAL ARTICLE

Tolvaptan Increases Serum Sodium in Pediatric Patients With Heart Failure

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Abstract This study aimed to evaluate the use of tolvaptan in a consecutive series of pediatric patients with heart failure. Patients 18 years of age or younger with heart failure prescribed tolvaptan between January 2009 and October 2011 were retrospectively identified at Children's Medical Center Dallas. Laboratory parameters, urine output, fluid balance, and concurrent medications were recorded at baseline and at specified intervals after a single dose of tolvaptan. The 28 patients in the study had a median age of 2 years (range 1 month–18 years). The median tolvaptan dose administered was 0.3 mg/kg (range 0.1–1.3 mg/kg). The study patients had a median baseline serum sodium concentration of 127 mmol/L, and the increases in sodium were 2.5 mmol/L at 12 h, 5 mmol/L at 24 h, 4 mmol/L at 48 h, and 5 mmol/L at 72 h (all $p < 0.001$). Urine output was increased at 24 h ($p < 0.001$) and 48 h ($p = 0.03$), and fluid balance changes were significantly different at 24 h ($p = 0.004$). The changes in potassium, blood urea nitrogen, and serum creatinine were not significant at any interval. When controlling for traditional diuretic therapy, increases in serum sodium concentration and urine output remained statistically significant. A single dose of tolvaptan increased serum sodium concentrations for the majority in this small series of pediatric patients with heart failure. These results suggest that tolvaptan can be safely and effectively administered to pediatric patients. Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of its use further.

Keywords Diuretics · Heart failure · Hyponatremia · Pediatrics · Sodium

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Introduction

Hyponatremia is a common electrolyte abnormality found in patients with heart failure. Data from adult studies indicate that hyponatremia significantly increases hospital length of stay, morbidity, and mortality [5, 9, 11, 13, 14, 20].

The pathophysiology of hyponatremia in heart failure is multifactorial and not completely understood. Both prolonged activation of the renin–angiotensin–aldosterone system and activation of the sympathetic nervous system contribute to a decrease in free water excretion. Additionally, patients with heart failure have chronically elevated levels of arginine vasopressin, which contributes to further free water retention. Finally, many of the common diuretic therapies initiated to relieve heart failure symptoms potentiate hyponatremia by blocking sodium reabsorption in the kidney [2, 6–9, 11].

An emerging treatment of hyponatremia is the use of vasopressin receptor antagonists [3, 6, 9, 11]. Tolvaptan, an oral selective vasopressin V_2-receptor antagonist, was approved in 2009 for the treatment of clinically significant euvolemic or hypervolemic hyponatremia in adult patients with heart failure, cirrhosis, or syndrome of inappropriate antidiuretic hormone (SIADH) [16].

Antagonism of V_2-receptors blocks free water reabsorption by preventing the insertion of aquaporin 2 into the luminal membrane of the renal collecting duct. Consequently, free water is excreted, increasing serum sodium concentration and decreasing urine osmolality [3, 6, 15, 21]. The efficacy and safety of tolvaptan are well documented in adult patients, but to date, no studies or case reports of its use in pediatric patients with heart failure have been published [1, 4, 12, 19]. Therefore, the primary purpose of this study was to analyze the use of tolvaptan in a series of pediatric patients with heart failure.

Methods

Study Population

This single-center, retrospective study investigated pediatric patients who received tolvaptan between January 2009 and October 2011 while admitted to Children's Medical Center Dallas. Patients who received tolvaptan were identified through the electronic medical record. The patients enrolled in the study were 18 years of age or younger and had a diagnosis of heart failure. Patients were excluded from the study if they received tolvaptan for an indication other than heart failure (i.e., SIADH) or had incomplete data for evaluation of outcomes. This study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center.

Data Collection

The demographic data collected included gender, race, age, weight, height, and primary and secondary diagnoses. The clinical data collected included tolvaptan doses, timing of administrations, and method of administrations (tablet or solution). Laboratory values including serum sodium, serum potassium, blood urea nitrogen (BUN), and serum creatinine (SCr) were collected to evaluate efficacy and safety. Additionally, fluid balance and urine output (UOP) were calculated for the 24 h before tolvaptan administration and for 24 and 48 h after tolvaptan administration. Total daily dose and route of administration of selected concurrent medications were recorded for the 24 h before and after tolvaptan administration. These medications included diuretics (loop, thiazide, potassium-sparing, and metolazone), angiotensin-converting enzyme (ACE) inhibitors, digoxin, sodium supplements, and potassium supplements.

Efficacy was defined by changes in serum sodium at 12, 24, 48, and 72 h and UOP at 24 and 48 h after tolvaptan administration. Additionally, we evaluated safety by analyzing changes in potassium at 12, 24, 48, and 72 h and changes in BUN and SCr after tolvaptan administration. All outcomes were evaluated after the first dose of tolvaptan. Laboratory values were accepted if they were within 6 h (before or after) of the designated interval.

Statistical Analysis

Baseline patient and tolvaptan dosing characteristics were summarized by the use of medians and ranges for continuous variables and percentages for categorical variables. Estimates and significance tests of changes from baseline were established using mixed linear regression models specified with a discrete time factor and first-order autocorrelated residuals to account for correlation of repeated measurements within patients. Similarly, estimates and significance tests of changes from baseline controlling for changes in diuretic therapy were established using mixed linear regression models specified with an additional three-level factor for diuretic therapy change (decrease, no change, increase) and a time × diuretic therapy change interaction.

To estimate the within-subjects relationship between serum sodium and urine output while controlling for subjects effects, we fit a linear growth model of serum sodium with factors for time, urine output, and urine output at baseline, again assuming first-order autocorrelated residuals. We used SAS/STAT, version 9.2: SAS Institute Inc. Cary, NC, USA for all analyses. A p value lower than 0.05 indicated statistical significance.

Results

Patient Characteristics

During the study period, 36 patients were identified as having received tolvaptan, and 28 of these patients met the inclusion criteria. The majority of excluded patients had a diagnosis of SIADH, and one patient was excluded due to a lack of data. According to the demographic shown in Table 1, 11 patients

Table 1 Summary of patient demographics

Age (years)	2 (0.1–18)
Weight (kg)	12 (4–190)
Females	15 (53.6)
Race	
Hispanic	11 (39.3)
White	10 (35.7)
Black	3 (10.7)
Other	4 (14.3)

Values are expressed as median (range) or n (%)

(39 %) were Hispanic. The median age of the patients was 2 years (range 1 month–18 years), and 22 patients were 5 years of age or younger. The majority of the patients had heart failure secondary to failed single-ventricle physiology or dilated cardiomyopathy, and one patient developed heart failure after chemotherapy treatment.

Within 24 h before or after tolvaptan administration, 27 patients (96 %) received concurrent loop diuretic therapy (furosemide or bumetanide), and 15 patients (54 %) received a thiazide diuretic (chlorothiazide). Half (50 %) of the patients received spironolactone, and two patients (7 %) received metolazone. After tolvaptan administration, five patients had an increase in their traditional diuretic regimen, whereas six patients had a decrease in their diuretic regimen. Sodium replacement therapy was administered to six patients (21 %). Information regarding concurrent medications is summarized in Table 2.

Tolvaptan Dosing and Administration

The median single dose of tolvaptan administered was 3.8 mg (range 0.8–30 mg), and the median weight-based dose was 0.3 mg/kg (range 0.1–1.3 mg/kg). Partial or full tablets were administered to 17 patients (60.7 %) depending on their dose, and 11 patients received their dose as a solution after a crushed tablet was dissolved in water. Multiple doses of tolvaptan were given to 20 patients, 15 of whom received an additional dose within 72 h after their first dose of tolvaptan. Of these 15 patients, 3 had a dose increase and 2 had a dose decrease. During the study period, 318 doses of tolvaptan were administered, with a single patient receiving 100 doses.

Table 2 Concurrent diuretic therapy with tolvaptan administration

Medications	Daily dose range
Loop diuretic (mg/kg)	
Intravenous bumetanide ($n = 2$)	0.2
Intravenous furosemide ($n = 18$)	0.5–3.8
Oral furosemide ($n = 9$)	1–6.1
Thiazide diuretic (mg/kg)	
Intravenous chlorothiazide ($n = 11$)	1.9–15.5
Oral chlorothiazide ($n = 4$)	9.9–21.5
Spironolactone (mg/kg) ($n = 14$)	0.3–3.1
Metolazone (mg/kg) ($n = 2$)	0.2–0.3
ACE inhibitor (mg/kg)	
Oral enalapril ($n = 8$)	0.2–0.8
Oral lisinopril ($n = 1$)	0.2
Digoxin, mcg/kg ($n = 8$)	1.3–10
Sodium supplement (mmol/kg) ($n = 6$)	1–3.1
Potassium supplement (mmol/kg) ($n = 11$)	0.5–4

ACE angiotensin-converting enzyme

Efficacy and Safety

Changes in serum sodium and UOP were evaluated for all the patients. The study population had a median baseline sodium concentration of 127 mmol/L. The increases in sodium concentration were 2.5 mmol/L at 12 h, 5 mmol/L at 24 h, 4 mmol/L at 48 h, and 5 mmol/L at 72 h (Fig. 1). The changes in sodium from baseline were statistically significant at each subsequent time (all $p < 0.001$). The median baseline UOP was 2.49 mL/kg/h, and the increases in UOP at 24 h (3.96) ($p < 0.001$) and 48 h (3.25) ($p = 0.03$) were statistically significant (Fig. 2). For each UOP increase of 1 mL/kg/h, a sodium increase of 0.77 mmol/L ($p = 0.045$) was observed (Fig. 3). Fluid balance changes were significantly different at 24 h ($p = 0.004$). Changes in potassium, BUN, and SCr were not significant at any interval (Table 3). When controlling for all the patients as if they had no change in traditional diuretic therapy, the increases in sodium still were statistically significant at 24 h ($p < 0.001$), 48 h ($p < 0.008$), and 72 h ($p < 0.01$). Additionally, increases in UOP remained significant.

Discussion

Hyponatremia in heart failure can have detrimental effects on patient outcomes, increasing short- and long-term morbidity and mortality. Recognition and proper management of hyponatremia are crucial [5, 9, 11, 13, 14, 20].

In the current study, a single dose of tolvaptan increased serum sodium concentrations for the majority in this small

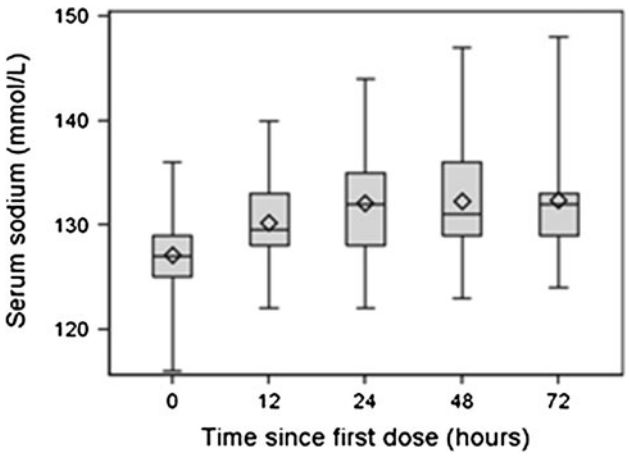

Fig. 1 Serum sodium concentration at baseline, then 12, 24, 48, and 72 h after the first tolvaptan dose. *Boxes* extend from the 25th to the 75th percentile of values. *Whiskers* extend to the extremes. The median is marked with a *horizontal line*, and the mean is marked by a *diamond*. The median sodium concentration was 127 mmol/L at baseline, then 129.5 mmol/L at 12 h, 132 mmol/L at 24 h, 131 mmol/L at 48 h, and 132 mmol/L at 72 h (all $p < 0.001$)

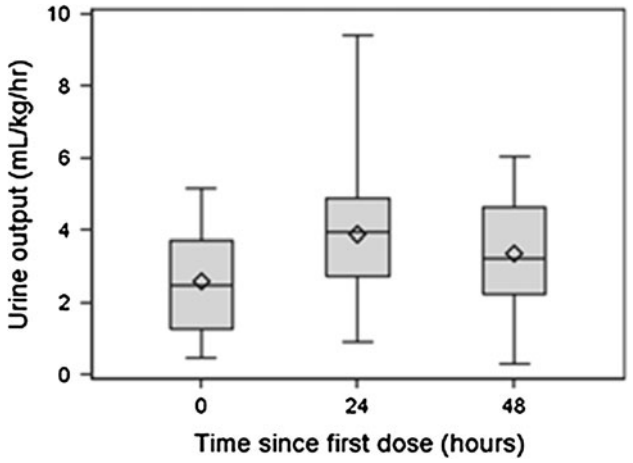

Fig. 2 Urine output at baseline, then 24 and 48 h after the first tolvaptan dose. *Boxes* extend from the 25th to the 75th percentile of values. *Whiskers* extend to the extremes. The median is marked with a *horizontal line*, and the mean is marked by a *diamond*. The median baseline urine output was 2.49 mL/kg/h, and the output increased to 3.96 mL/kg/h at 24 h ($p < 0.001$) and to 3.25 mL/kg/h at 48 h ($p = 0.03$)

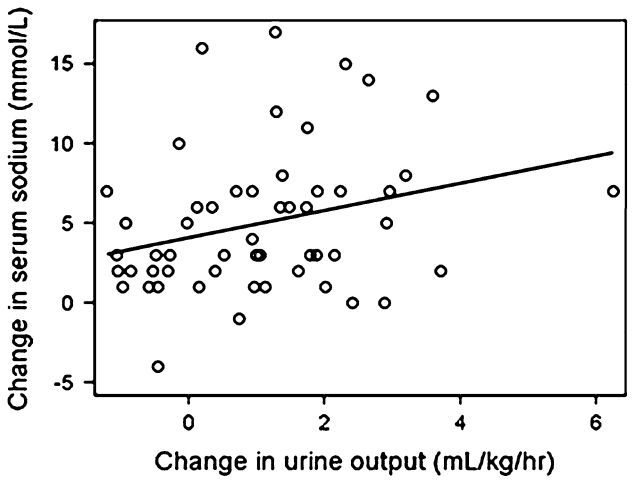

Fig. 3 Change from baseline in serum sodium versus change from baseline in urine output shown by a *linear regression line*. The *slope*, estimated using a linear growth model, is 0.77 mmol/L of serum sodium per mL/kg/h of urine output ($p = 0.045$)

series of pediatric patients with heart failure. In addition, UOP increased significantly, and the effect was not secondary to a change in traditional diuretic therapy.

Studies in adult patients with heart failure have shown normalization of serum sodium and a decrease in body weight after treatment with tolvaptan [1, 4, 12, 19]. No studies using tolvaptan for the treatment of hyponatremia in pediatric patients with heart failure have been published. Evidence of vasopressin receptor antagonist use in pediatrics is limited to case reports and a retrospective study describing the use of intravenous conivaptan, a vasopressin V_{1a} and V_2-receptor antagonist [10, 17, 18]. Conivaptan has been used successfully for a 13-year-old boy with lymphoma who experienced hyponatremia due to SIADH and for a 4-month-old infant with hyponatremia secondary to heart failure [17, 18]. In a cohort of critically ill patients younger than 6 months, patients with cardiac disease experienced increased serum sodium concentrations after administration of conivaptan [10].

Table 3 Efficacy and safety outcomes

Outcomes	Patients	Median (range)	*p* value[a]
Baseline sodium (mmol/L)	28	127 (116–136)	
At 12 h	16	129.5 (122–140)	<0.001
At 24 h	26	132 (122–144)	<0.001
At 48 h	27	131 (123–147)	<0.001
At 72 h	26	132 (124–148)	<0.001
Baseline UOP (mL/kg/h)	28	2.49 (0.48–5.16)	
At 24 h	28	3.96 (0.91–9.42)	<0.001
At 48 h	28	3.25 (0.32–6.05)	0.03
Baseline fluid balance (mL)	28	+304 (−2,672 – +859)	
At 24 h	28	+25 (−8,186 – +430)	0.004
At 48 h	28	+111 (−4,560 – +696)	0.18
Baseline potassium (mmol/L)	26	3.9 (2.6–5.3)	
At 12 h	16	3.8 (2.7–5.2)	0.94
At 24 h	25	3.8 (2.5–5.3)	0.57
At 48 h	26	3.8 (2.6–5.6)	0.76
At 72 h	25	4.1 (2.2–6.5)	0.28
Baseline BUN (mmol/L)	28	6.4 (1.8–14.6)	
At 24 h	27	6.1 (1.8–12.9)	0.63
Baseline SCr (μmol/L)	28	44.2 (17.7–114.9)	
At 24 h	27	44.2 (17.7–123.8)	0.66

UOP urine output, *BUN* blood urea nitrogen, *SCr* serum creatinine

[a] *p* values for tests of difference from baseline in repeated measures regression models

Previous approaches for the treatment of hyponatremia have included fluid restriction, modification of traditional diuretic therapy, and sodium supplementation. The majority of patients with heart failure require diuretic therapy to manage their fluid status, but traditional diuretic therapies may be limited by electrolyte abnormalities. The use of diuretics can exacerbate hyponatremia by limiting the kidney's ability to excrete free water [8]. Therefore, tolvaptan can help to correct hyponatremia while achieving euvolemia with minimal effects on other electrolytes by enhancing the excretion of free water.

We also wanted to determine whether the rise in serum sodium concentration is correlated with the increase in free water excretion. Due to the retrospective nature of this

study, we were not able to calculate the free water clearance in these patients. However, we did analyze the relationship between the increase in urine output as a surrogate for free water excretion and the rise in serum sodium concentration (Fig. 3). The positive correlation suggests that the mechanism for the increase in serum sodium concentration was related to the increase in free water excretion.

The limiting factors for the use of tolvaptan include hyperkalemia and the development of the osmotic demyelinating syndrome from rapid correction of hyponatremia [16]. In our study, no significant increases in potassium were observed although the patients received concomitant ACE inhibitors, spironolactone, or potassium supplements.

The risk of osmotic demyelination syndrome is associated with rapid correction of sodium concentration. One patient with a baseline sodium of 122 mmol/L did have a sodium level of 139 mmol/L 29 h later. However, this increase in sodium was not likely a result of tolvaptan alone. The patient received a 1-mmol/kg dose of oral sodium chloride before receiving tolvaptan, then received a total of 2 mmol/kg of sodium chloride before the 24-h level was drawn. Therefore, the sodium level before the patient received tolvaptan was likely higher than the recorded baseline value, and further sodium supplementation increased the sodium in addition to the tolvaptan. No adverse events were reported for this patient, and no other patient experienced a sodium increase greater than 12 mmol/L within 24 h based on the collected laboratory values.

Due to the retrospective design of the study, several limitations are noted. Because dosing for pediatric patients has not been established, dosing recommendations were extrapolated from adult data. In addition to the variable intended dosing, the exact dose of tolvaptan administered may not have been accurate due to the methods of administration. A commercial dosage form suitable for pediatric patients is not available, thereby making administration of tolvaptan for these patients challenging. Our hospital stocks the 15-mg tablets, which are triangular and difficult to split for partial doses [16]. Additionally, the dose drawn up from the water solution may not have been accurate due to limited solubility.

Another limitation noted in the data analysis was that not all the patients had laboratory values drawn at the designated outcome interval, so values were recorded within 6 h of the specified time. Finally, to maximize the number of subjects, we chose to examine outcomes after a patient's first dose of tolvaptan. Because 15 patients received another dose of tolvaptan within 72 h after their initial dose, changes in sodium and UOP may be reflective of multiple doses.

Hyponatremia in heart failure is multifactorial, and tolvaptan alleviates only one component of this complicated disease state, which could explain why some patients did not have a clinically significant increase in their serum sodium levels. This small retrospective study further supports the fact that tolvaptan is a newer medication now available in our armamentarium for the management of heart failure. Given the limitations, it is difficult to determine the extent of tolvaptan's effect on correction of hyponatremia, but our data suggest that tolvaptan can be safely delivered at a dosage of 0.3–0.5 mg/kg, with an expected increase in serum sodium and UOP. A prospective, randomized controlled trial is planned to evaluate further the safety and efficacy of tolvaptan use for pediatric patients.

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