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Short communication

Vasopressin antagonism for decompensated right-sided heart failure☆

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ABSTRACT

Background: Targeted treatment for decompensated right heart failure (RHF) with or without left heart failure is lacking. Vasopressin antagonists (vaptans) may offer an option by increasing urine output and fluid mobilization when used in acute decompensated RHF without impacting blood pressure or renal function, both common complications of loop diuretics.

Methods and results: We searched electronic medical records from 2 institutions over 4 years for patients with RHF treated with vaptans. Urine output, creatinine, BUN and sodium, 1 day pre- versus 1 day post-vaptan initiation were compared. Baseline (admission) pre-vaptan values for patients with RHF who met inclusion criteria ($n = 112$) were RAP, median (interquartile range) = 19 (13–24) mmHg; cardiac index, mean ± standard deviation = 1.8 ± 0.4 L/min/m2; BNP, 1078 (523–1690) pg/ml; creatinine clearance of 51 (39–69) ml/min, BUN, 37 (26–54) mg/dl, and serum [Na+] 132 (126–135) mEq/L. Most patients ($n = 103/112$) received intravenous inotrope (prior to vaptan, $n = 91$). Overall length of stay was 27 (16–43) days. Vaptan treatment (90% tolvaptan, 10% conivaptan) was associated with increased 24 h urine output, 1517 (906–2394) vs 2337 (1425–3744) mL, $p = 0.005$, and [Na+], 127 (124–130) vs 130 (126–135) mEq/L, $p = 0.001$, without significant change in Cr or BUN. Furosemide IV dose equivalent decreased or remained unchanged in 75% of patients at 24 h and 64% at 72 h compared to the 24 h prior to vaptan use.

Conclusion: Vaptans were associated with a significant increase in urine output and serum sodium with an apparent reduction or stabilization of furosemide equivalent dosing in the early treatment period in patients with decompensated RHF. Vaptans may offer a management option for patients failing conventional diuretic-based treatment.

1. Introduction

Advanced right-sided heart failure (RHF) with or without left-sided heart failure is associated with an adverse prognosis [1]. Conventional management with loop diuretic therapy is often complicated by the development of renal failure [2]. Additionally, the lack of specific treatment guidelines for RHF makes clinical management more challenging.

Vasopressin antagonists (vaptans) which lead to filtration and excretion of free water with less intravascular volume contraction and subsequent prerenal azotemia compared with loop diuretics [3], could be a valuable adjunctive treatment option for patients with RHF. This class of drug has shown utility in the treatment of dyspnea [4] and leads to increased urine output in patients with left-sided HF [5], especially in the presence of comorbid conditions such as chronic kidney disease [6] and low serum sodium [7] but has not been investigated for treatment of acute or chronic RHF. Therefore, the purpose of this retrospective study was to investigate the effect of vaptans in patients hospitalized with clinical and echocardiographic evidence for RHF as an in-hospital treatment option mediated by increasing urine output and fluid mobilization without negatively impacting renal function.

2. Methods

Electronic medical records were used to identify patients receiving at least one dose of tolvaptan or conivaptan with ICD-9 codes for HF at two institutions from June 2011–February 2014. Baseline echocardiographic, hemodynamic, and laboratory data obtained prior to vaptan initiation were recorded. Patients were included if they met ≥2 of the following RHF criteria: echocardiographic evidence of moderate or severe right ventricular dysfunction/enlargement; tricuspid annular plane systolic excursion <1.6 cm or

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Table 1
Baseline variables of patients with right-sided heart failure receiving vaptan. $N = 112$.

Baseline (Admission) variables	Values[a]
Age, years	57.8 ± 14.6
Male	81 (72)
Caucasian	81 (72)
Non-ischemic cardiomyopathy	52 (46)
Left ventricular ejection fraction percent	18 (13–35)
EF > 50%	15 (13)
Left ventricular assist device	47 (42)
LVAD prior to vaptan	28 (25)
Intra-aortic balloon pump	19 (17)
Cardiac index, L/min/m^2	1.8 ± 0.4
Right atrial pressure, mmHg	19 (13–24)
Brain natriuretic peptide, pg/mL	1078 (523–1690)
Serum sodium, mEq/L	132 (126–135)
Serum creatinine, mg/dL	1.4 (1.0–1.8)
Creatinine clearance, ml/min	51 (39–69)
BUN, mg/dL	37 (26–54)
Albumin, g/dL	3.7 ± 0.6
Total bilirubin, g/dL	1.4 (0.7–2.1)
ALT, u/L	40 (26–81)
AST, u/L	43 (30–83)
Continuous inotrope[c]	103 (92)
Prior to vaptan	89 (80)
Initiated ±24 h vaptan initiation	8 (7)
Loop diuretic home dose, mg[b]	60 (40–80)
Thiazide diuretic	40 (36)
Beta blocker	9 (8)
ACEI or ARB	68 (61)

[a] Values are mean ± standard deviation; n (%); or median (interquartile range) unless otherwise indicated.
[b] All loop diuretic doses were converted to furosemide intravenous equivalent.
[c] Continuous inotrope = dobutamine ($n = 79$) milrinone ($n = 23$) or both ($n = 1$).

inferior vena cava collapse <50% with sniff; central venous pressure to pulmonary capillary wedge pressure ratio >0.63 or right atrial pressure (RAP) >15 mmHg; total bilirubin >2.0 mg/dL; presence of ascites, JVD, or pitting edema; and RHF risk score [8] >4 or need for inotrope/nitric oxide use for ≥2 weeks post left ventricular assist device (LVAD) implantation. Patients were excluded if they received vaptan treatment for euvolemic hyponatremia or neurologic etiologies or were admitted with acute myocardial infarction, pulmonary embolism, myocarditis, or sepsis.

The primary endpoint was change in 24-hour urine output (UOP) after initiation of vaptan. Secondary endpoints for efficacy and safety included diuretic dose (furosemide IV total daily dose equivalents) and change in serum sodium, creatinine, and blood urea nitrogen (BUN) on the day prior to and following vaptan initiation and at similar 72-hour time points. Parametric and nonparametric data are presented as mean ± standard deviation or median (interquartile range), respectively. Sign Test compared values over time.

3. Results

A total of 112 patients met inclusion criteria for RHF and vaptan administration (Table 1). Most patients were Caucasian (72%) and male (72%) with a mean age of 57.8 ± 14.6 years and median left ventricular ejection fraction of 18% (13–35). The most common RHF qualifying criteria were right ventricular dysfunction (79%), lack of IVC collapse (78%), TAPSE <1.6 cm (71%), and RAP >15 mmHg (48%). The median hospital length of stay was 27 (16–43) days; 91 (81%) patients were admitted to an ICU during the hospitalization for a median duration of 192 (96–440) hours. Twenty-three (21%) patients died prior to discharge (10 within 30 days of admission). Tolvaptan was the primary vaptan used (90%, with 91% of doses ranging from 15 to 30 mg) and the remaining patients received conivaptan (10%, with 91% of doses ranging from 20 to 30 mg daily). At the time of vaptan initiation, the numbers of patients with serum sodium <130 and <125 mEq/L were 104 and 58 respectively. The median time to initiation of vaptan therapy was hospital day 12 (5–19); the median duration of vaptan therapy was 3 (1–5) days. A total of 47 patients received a left ventricular assist device (LVAD) during the study period. In 19 (40%) of these patients, the first dose of vaptan was given 6 (3–16) days prior to LVAD implantation; the remaining 28 were initiated after LVAD implantation at 10 (5–18) days post-surgery.

Vaptan treatment was associated with increased 24 h urine output, 1517 (906–2394) vs 2337 (1425–3744) mL, $p = 0.005$ and serum sodium, 127 (124–130) vs 130 (126–135) mEq/L, $p = 0.001$. Change in serum sodium was greater for patients with pre-vaptan values <129 mEq/L than pretreatment values ≥129 mEq/L, 125 (123–127) mEq/L to 130 (125–135) vs 130 (128–132) to 130 (126–134), $p = 0.026$, by Mann-Whitney U test on change scores. The dose of diuretics (furosemide equivalent) decreased or remained unchanged in 75% of patients at 24 h and 64% at 72 h compared to the 24 h prior to vaptan use. There were no significant changes in serum creatinine, 1.33 (1.02–1.93) vs 1.27 (0.99–1.78) md/dL, $p = 0.141$ or BUN, 35.5 (24.7–53.2) vs 36.0 (24.0–55.0) md/dL, $p = 1.00$. All efficacy and safety data were consistent at 72 h pre- and post-vaptan exposure (Table 2). An additional post-hoc analysis showed no difference in efficacy (change in weight or serum sodium) or safety outcomes (change in serum creatinine) when patients with inotrope and/or LVAD prior to receiving vaptan therapy ($n = 89$) were compared with patients on neither therapy ($n = 23$).

4. Discussion

The use of vaptans for left heart failure has been extensively evaluated [9]. Across different studies, urine output increases and dyspnea appears to improve. In contrast, there is a paucity of literature on the effect of this class of drug in right heart failure except for a small series and case report [10]. This represents a significant gap in knowledge as fluid management in right heart failure (with or without left heart failure) can be challenging. Loop diuretics may be associated with worsening renal function and there are few studies to guide approach to right sided volume overload.

In the current analysis, vaptan use was associated with significant increase in urine output and serum sodium, and an apparent reduction or stabilization of furosemide equivalent dosing in the early treatment period in patients with decompensated RHF (including patients on left ventricular assist devices) without causing renal injury or rapid correction of hyponatremia. These benefits were observed within 24 h of drug administration and remained consistent after 3 days of treatment.

Table 2
Vaptan effects at 24 h and 72 h post exposure.*

Outcome	24 h Pre-vaptan initiation	24 h Post-vaptan initiation	*P*	72 h Pre-vaptan initiation	72 h Post-vaptan initiation	*P*
24 h-urine output (mL)	1517 (906–2394)	2337 (1425–3744)	0.005	1567 (1115–2642)	2192 (1495–2894)	0.019
Serum sodium (mEq/L)	127 (124–130)	130 (126–135)	0.001	128 (126–130)	132 (129–134)	<0.001
Serum creatinine (mg/dL)	1.33 (1.02–1.93)	1.27 (0.99–1.78)	0.141	1.23 (0.95–1.76)	1.24 (0.80–1.70)	1.00
BUN (mg/dL)	35.5 (24.7–53.2)	36.0 (24.0–55.0)	1.00	30.7 (21.0–54.0)	36.0 (19.5–49.3)	1.00

*Values are median (interquartile range).

5. Study limitations

The study is limited by its retrospective design, lack of randomization, and multiple criteria that could be used to define right heart failure. In addition, most of the patients received a limited course of vaptan treatment, so efficacy and safety results may only apply to a short-term regimen. We cannot definitively state why the clinician chose to use a vaptan, nor which vaptan (tolvaptan or conivaptan). Nevertheless, our study suggests vaptan administration may improve diuresis in patients experiencing RHF without renal adverse effects. A pilot, randomized, controlled trial of vaptans in this cohort appears warranted.

Conflict of interest

Drs. Joseph and Hauptman have served as consultants to Otsuka America Pharmaceutical Inc. The other authors report no relationships that could be construed as a conflict of interest.

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