Abstract and Introduction

Abstract

Objectives: This study sought to assess the acute hemodynamic effect of vasopressin V_2 receptor antagonism.
Background: In decompensated heart failure (HF), tolvaptan, a vasopressin V_2 receptor antagonist, has been shown to improve congestion. It has not yet been established whether these improvements maybe associated with the hemodynamic effects of tolvaptan.
Methods: A total of 181 patients with advanced HF on standard therapy were randomized to double-blind treatment with tolvaptan at a single oral dose (15, 30, or 60 mg) or placebo.
Results: Tolvaptan at all doses significantly reduced pulmonary capillary wedge pressure (-6.4 ± 4.1 mm Hg, -5.7 ± 4.6 mm Hg, -5.7 ± 4.3 mm Hg, and -4.2 ± 4.6 mm Hg for the 15-mg, 30-mg, 60-mg, and placebo groups, respectively; $p < 0.05$ for all tolvaptan vs. placebo). Tolvaptan also reduced right atrial pressure (-4.4 ± 6.9 mm Hg [$p < 0.05$], -4.3 ± 4.0 mm Hg [$p < 0.05$], -3.5 ± 3.6 mm Hg, and -3.0 ± 3.0 mm Hg for the 15-mg, 30-mg, 60-mg, and placebo groups, respectively) and pulmonary artery pressure (-5.6 ± 4.2 mm Hg, -5.5 ± 4.1 mm Hg, -5.2 ± 6.1 mm Hg, and -3.0 ± 4.7 mm Hg for the 15-mg, 30-mg, 60-mg, and placebo groups, respectively;$p < 0.05$). Tolvaptan increased urine output by 3 h in a dose-dependent manner ($p < 0.0001$), without changes in renal function.
Conclusions: In patients with advanced HF, tolvaptan resulted in favorable but modest changes in filling pressures associated with a significant increase in urine output. These data provide mechanistic support for the symptomatic improvements noted with tolvaptan in patients with decompensated HF.

Introduction

Vasopressin plasma concentrations are known to be elevated in patients with heart failure (HF) and left ventricular (LV) systolic dysfunction, and may lead to fluid retention and hemodynamic abnormalities.[1-4] Inhibition of vasopressin at the V_2 receptors in the kidney through use of a selective antagonist (tolvaptan) has been shown to be associated with increased urine output and reductions in body weight in patients with HF.[5-8] Recent studies also have shown that the effects of tolvaptan on fluid volume are associated with symptomatic improvements in patients hospitalized with worsening HF, without affecting outcomes.[8]

Relatively little is known about the impact of vasopressin V_2 receptor antagonism on hemodynamic parameters. The ECLIPSE (EffeCt of toLvaptan on hemodynamIc Parameters in Subjects with hEart failure) study was designed to evaluate the hemodynamic effects of vasopressin V2 receptor inhibition in a randomized, prospective, placebo-controlled trial of patients with advanced HF.

Methods

Patient Eligibility

Patients eligible for entry into the baseline evaluation phase of this trial were required to be more than 18 years of age and have symptomatic HF (New York Heart Association functional class III or IV) of at least 3 months' duration caused by LV ejection fraction <40%. Patients were required to be on standard background therapy for HF for at least 1 month. Exclusion criteria included a supine systolic blood pressure <90 mm Hg or serum creatinine ≥3.0 mg/dl.

Study Design

The protocol for this study and the consent form were approved by the Institutional Review Boards/Ethics Committees at all participating sites, and all patients signed an informed consent form. Patients entered a baseline inpatient phase in which a pulmonary artery catheter was inserted. Patients received their daily dose of concomitant background medications at least 2 h before catheter insertion. Patients then entered a 2- to 20-h stabilization period. After this stabilization period, final eligibility criteria for entry into the randomized, double-blind treatment phase included pulmonary capillary wedge pressure (PCWP) >18 mm Hg on 2 successive readings at least 10 min apart during the 2 h before study drug administration.

Patients eligible by baseline hemodynamic criteria were randomized to receive a double-blind oral dose of placebo or 1 of 3 doses of tolvaptan (15, 30, or 60 mg) in a 1:1:1:1 ratio. The doses of tolvaptan used in this study were selected to provide data on hemodynamics from the doses expected to be used clinically in keeping with the EVEREST (Efficacy of

Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial of patients with decompensated HF,[7,8] as well as the SALT (Study of Ascending Levels of Tolvaptan in Hyponatremia) trials in patients with hyponatremia.[9]

Hemodynamic and renal parameters and vital signs were measured at multiple time points over an 8-h assessment period. Background diuretics and other cardiac medications were held during this time period, and fluid was restricted to 250 ml every 2 h from the time of insertion of the pulmonary artery catheter throughout the treatment period.

An independent technical review committee was established to assess individual subject pressure tracing data in a blinded manner to determine evaluable datasets. A safety oversight committee monitored the safety of study subjects in a blinded manner.

Statistical Analysis

The primary efficacy end point was the PCWP peak change from baseline within 3 to 8 h after treatment administration. A sample size of 45 patients per group (180 patients total) was calculated assuming a standard deviation of 5 mm Hg for the PCWP peak change. The power of the study to detect a difference of 3 mm Hg was set at 80%.

Secondary efficacy parameters included area under the curve(AUC) for the change from baseline PCWP and other hemodynamic parameters over an 8-h evaluation period and renal and electrolyte parameters.

All patients with valid baseline PCWP and at least 1 post-drug measurement were included in the primary analysis of peak change in PCWP. An analysis of covariance (ANCOVA) model with terms of treatment and country, and with baseline PCWP as a covariate, was applied to the data of the primary efficacy variable for the 60-mg, 30-mg, and placebo groups. A comparison between a tolvaptan dose (30 or 60 mg) versus placebo was significant if both the F-test of the treatment effect of the ANCOVA model and the *t* test of the contrast statement of the ANCOVA model between the tolvaptan dose and placebo were significant. The comparison between tolvaptan 15 mg and placebo of the primary efficacy variable was considered as secondary and was conducted by using a *t* test in a contrast statement of ANCOVA. The area under the curve for change from baseline in PCWP over 8 h post-dose was derived using the trapezoidal rule.

Results

Baseline Characteristics of the Population Sample

The demographic and baseline hemodynamic characteristics of the study population are shown in Table 1 . Patients were enrolled at 48 study centers in the U.S., Romania, and Bulgaria. Of the 306 patients who were screened, 181 patients met the baseline hemodynamic entry criteria and were randomized into the double-blind treatment phase. Angiotensin-converting enzyme inhibitors were used as background therapy in 89.6% of placebo-treated patients and 87.8% of those randomized to tolvaptan, whereas 97.9% and 95.0% were on beta-adrenergic blockers, respectively.

Table 1. Baseline Demographics and Hemodynamics

	Tolvaptan			
	15 mg (n = 44)	**30 mg (n = 43)**	**60 mg (n = 46)**	**Placebo (n = 48)**
Demographics				
Gender, n (%), male	32 (72.7)	36 (83.7)	36 (78.3)	40 (83.3)
Race, n (%), Caucasian	32 (72.7)	31 (72.1)	31 (67.4)	34 (70.8)
Age (yrs), mean (SD)	60.3 (11.7)	59.7 (13.4)	61.0 (11.9)	58.9 (14.0)
History of hypertension, n (%)	31 (70.5)	28 (65.1)	29 (63.0)	33 (68.8)
ICD, n (%)	10 (22.7)	21 (48.6)	19 (41.3)	16 (33.3)
CRT, n (%)	1 (2.3)	7 (16.3)	6 (13.0)	6 (12.5)
Diabetes mellitus, n (%)	23 (52.3)	15 (34.9)	16 (34.8)	17 (35.4)
Hypercholesterolemia, n (%)	29 (65.9)	30 (69.8)	30 (65.2)	29 (60.4)
Peripheral vascular disease, n (%)	7 (15.9)	6 (14.0)	11 (23.9)	8 (16.7)

Previous PTCA, n (%)	16 (36.4)	13 (30.2)	15 (32.6)	11 (22.9)
Previous CABG, n (%)	14 (31.8)	19 (44.2)	10 (21.7)	14 (29.2)
Previous MI, n (%)	22 (50.0)	27 (62.8)	23 (50.0)	26 (54.2)
Ischemic HF etiology, n (%)	24 (54.5)	20 (69.8)	25 (54.3)	26 (54.2)
Previous HF hospitalization, n (%)	37 (84.1)	33 (76.7)	38 (82.6)	44 (91.7)
Ejection fraction (%), mean (SD)	23 (8)	23 (9)	24 (7)	24 (9)
Diuretics, n (%)	42 (95.5)	43 (100.0)	45 (97.8)	48 (100.0)
Beta-blockers, n (%)	43 (97.7)	38 (88.4)	44 (95.7)	47 (97.9)
ACE-I/ARB, n (%)	39 (88.6)	37 (86.0)	40 (87.0)	43 (89.6)
Baseline				
PCWP (mm Hg), mean (SE)	26.3 (1.1)	24.3 (0.8)	25.0 (1.0)	24.8 (0.7)
RAP (mm Hg), mean (SE)	14.6 (0.9)	12.6 (1.2)	13.2 (1.0)	12.6 (0.7)
PAP (mm Hg), mean (SE)	37.2 (1.5)	35.3 (1.5)	36.9 (1.4)	37.6 (1.3)

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PTCA = percutaneous transluminal coronary angioplasty; RAP = right atrial pressure.

Effect of Tolvaptan on Hemodynamic Measurements

The effects of the vasopressin receptor antagonist tolvaptan on hemodynamic parameters in the study population are shown in Table 2 . These values represent the pre-specified end point using the peak change in these values between 3 to 8 h after study drug administration.

Table 2. Effects of Tolvaptan on Hemodynamic Parameters

	Tolvaptan			
	15 mg	**30 mg**	**60 mg**	**Placebo**
PCWP, mm Hg	–6.38 ± 4.12†	–5.67 ± 4.58 *	–5.71 ± 4.35 *	–4.16 ± 4.57
CI, $l \cdot min^{1} \cdot m^{2}$	0.32 ± 0.48	0.50 ± 0.46	0.55 ± 0.56	0.42 ± 0.39
PVR, $dyn \cdot s \cdot cm^{5}$	–40.94 ± 109.13	–98.71 ± 146.67	–108.3 ± 117.02	–42.04 ± 117.09
SVR, $dyn \cdot s \cdot cm^{5}$	–237.5 ± 476.5	–344.7 ± 330.2	–355.2 ± 409.5	–327.2 ± 434.3
PAP, mm Hg	–5.60 ± 4.23†	–5.54 ± 4.12 *	–5.24 ± 6.11 *	–3.01 ± 4.73
RAP, mm Hg	–4.35 ± 6.92†	–4.30 ± 4.02 *	–3.49 ± 3.61	–3.03 ± 3.01

Values are mean ± SD. *$p < 0.05$, †$p < 0.01$ versus placebo.
CI = cardiac index; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; other abbreviations as in Table 1.

The pair-wise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from 3 to 8 h post-dose ($p = 0.003$, $p = 0.044$, and $p = 0.033$, respectively) (Fig. 1A). The primary intention-to-treat statistical analysis for the overall comparison among the treatment groups of placebo and of 30 and 60 mg tolvaptan, to assess distinct responses between these doses, approached statistical significance(*F*-test, $p = 0.056$). The AUC0-8 h for the change from baseline in PCWP was also assessed. The 15-mg-tolvaptan group was the only tolvaptan dose group that was statistically significantly different from placebo, with the 30-mg group showing a statistical trend.

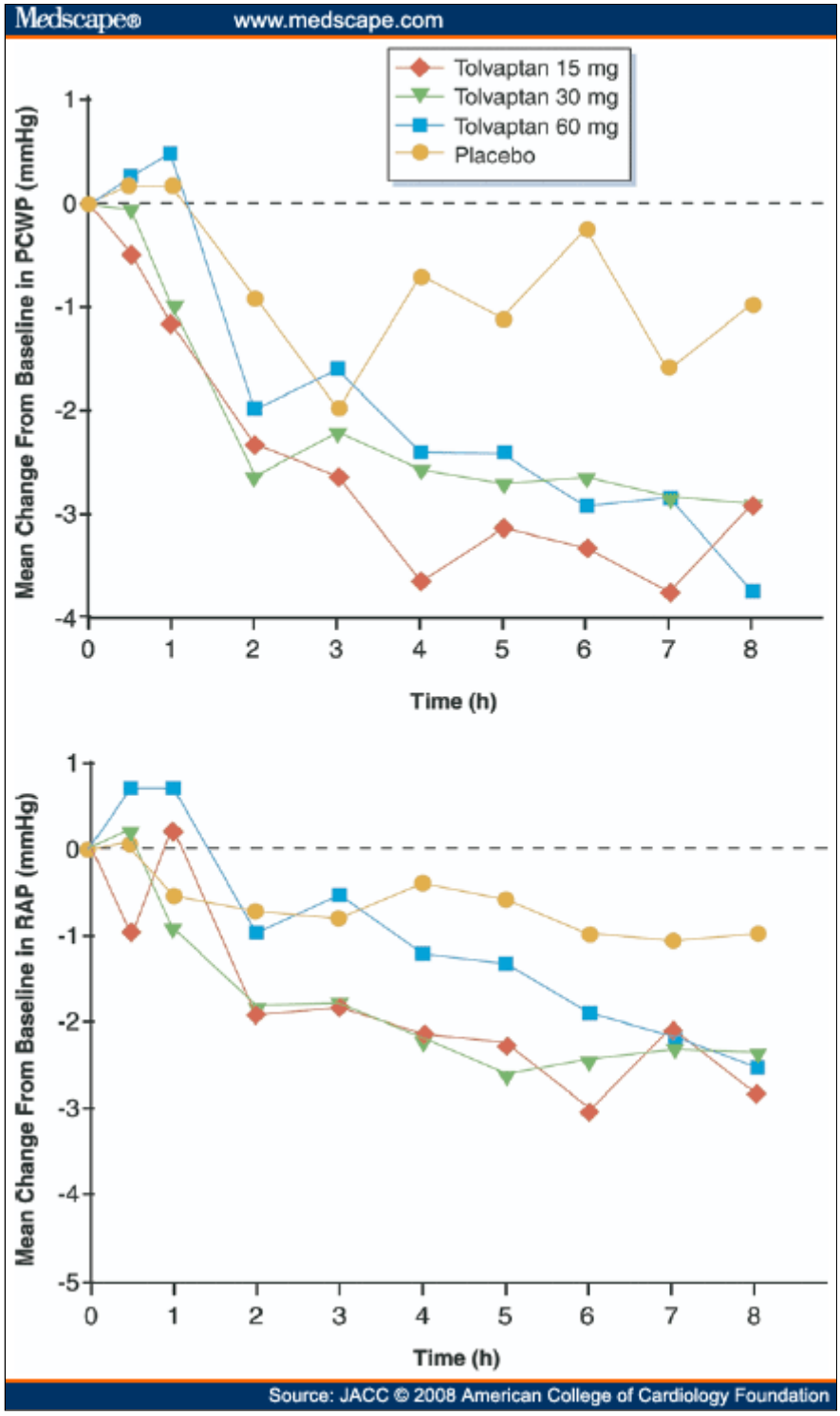

Fig 1. Mean Change from Baseline in PCWP and RAPs (Top) Mean change from baseline in pulmonary capillary wedge pressure (PCWP) out to 8 h after treatment administration. The pairwise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from 3 to 8 h post-dose, the pre-specified time period for assessment. (Bottom) Mean change from baseline in right atrial pressure (RAP) in the 4 treatment groups. The tolvaptan 15- and 30-mg doses resulted in statistically significant reductions in peak change in RAP as compared with placebo.

All tolvaptan doses produced statistically significantly greater changes than placebo in peak change in pulmonary artery pressure (Table 2). Tolvaptan 15- and 30-mg doses also resulted in statistically significant reductions in peak change in right atrial pressure as compared with placebo (Fig. 1B). No significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were observed after tolvaptan administration compared with placebo.

Table 2. Effects of Tolvaptan on Hemodynamic Parameters

	Tolvaptan	Placebo

	15 mg	30 mg	60 mg	
PCWP, mm Hg	–6.38 ± 4.12†	–5.67 ± 4.58 *	–5.71 ± 4.35 *	–4.16 ± 4.57
CI, $l \cdot min^{1} \cdot m^{2}$	0.32 ± 0.48	0.50 ± 0.46	0.55 ± 0.56	0.42 ± 0.39
PVR, $dyn \cdot s \cdot cm^{5}$	–40.94 ± 109.13	–98.71 ± 146.67	–108.3 ± 117.02	–42.04 ± 117.09
SVR, $dyn \cdot s \cdot cm^{5}$	–237.5 ± 476.5	–344.7 ± 330.2	–355.2 ± 409.5	–327.2 ± 434.3
PAP, mm Hg	–5.60 ± 4.23†	–5.54 ± 4.12 *	–5.24 ± 6.11 *	–3.01 ± 4.73
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Values are mean ± SD. *$p < 0.05$, †$p < 0.01$ versus placebo.
CI = cardiac index; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; other abbreviations as in Table 1.

Effects of Tolvaptan on Renal and Electrolyte Parameters

During the 12-h study period, urine output in the tolvaptan-treated groups was substantially greater than that in the placebo-treated group (Fig. 2A). The single dose of tolvaptan produced a dose-dependent increase in urine output ($p < 0.0001$ for all tolvaptan groups vs. placebo). Urine osmolality was significantly reduced by all doses of tolvaptan relative to placebo ($p < 0.0001$ for all tolvaptan groups vs. placebo) (Fig. 2B). Free water clearance was also significantly greater for all tolvaptan doses relative to placebo at all time points. Plasma osmolality showed a small but significant increase in all of the tolvaptan-treated groups compared with placebo (Fig. 3). Serum sodium levels showed a dose-related modest increase compared with placebo (1.2 ± 2.5 mEq/l, 3.3 ± 3.9 mEq/l, 4.6 ± 4.9 mEq/l, and-0.7 ± 3.2 mEq/l for the tolvaptan 15-mg, 30-mg,60-mg, and placebo groups, respectively), and potassium levels were not different from placebo in any of the tolvaptan dosing groups.

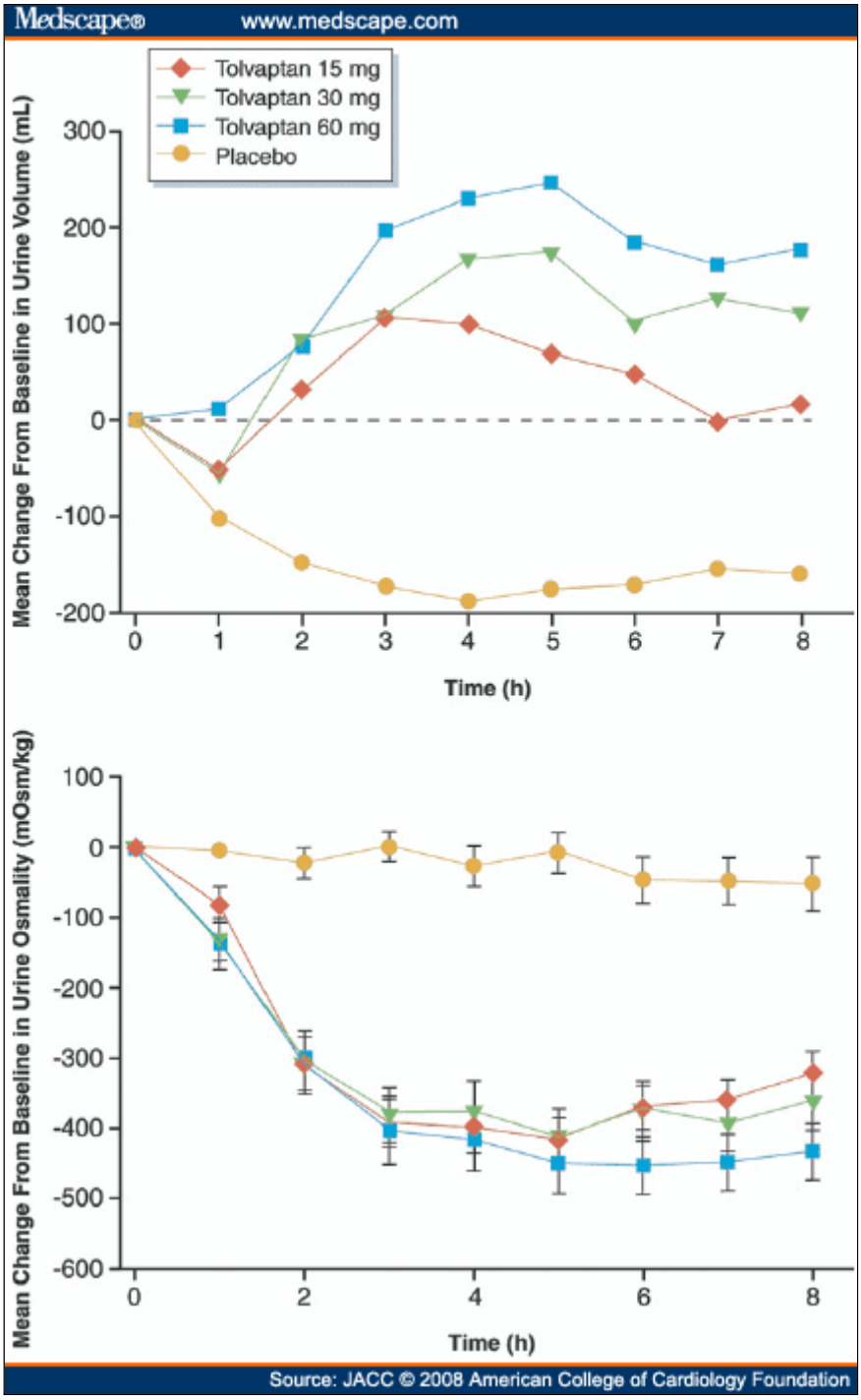

Fig 2. Mean Change From Baseline in Urine Volume and Osmolality (Top) Mean change from baseline in urine volume in the first 8 h after treatment administration. A dose-dependent increase in urine output was observed among the tolvaptan-treated groups. (Bottom) Mean change from baseline in urine osmolality in the first 8 h after dosing. Urine osmolality was significantly reduced by all doses of tolvaptan relative to placebo ($p < 0.0001$ for all tolvaptan groups vs. placebo).

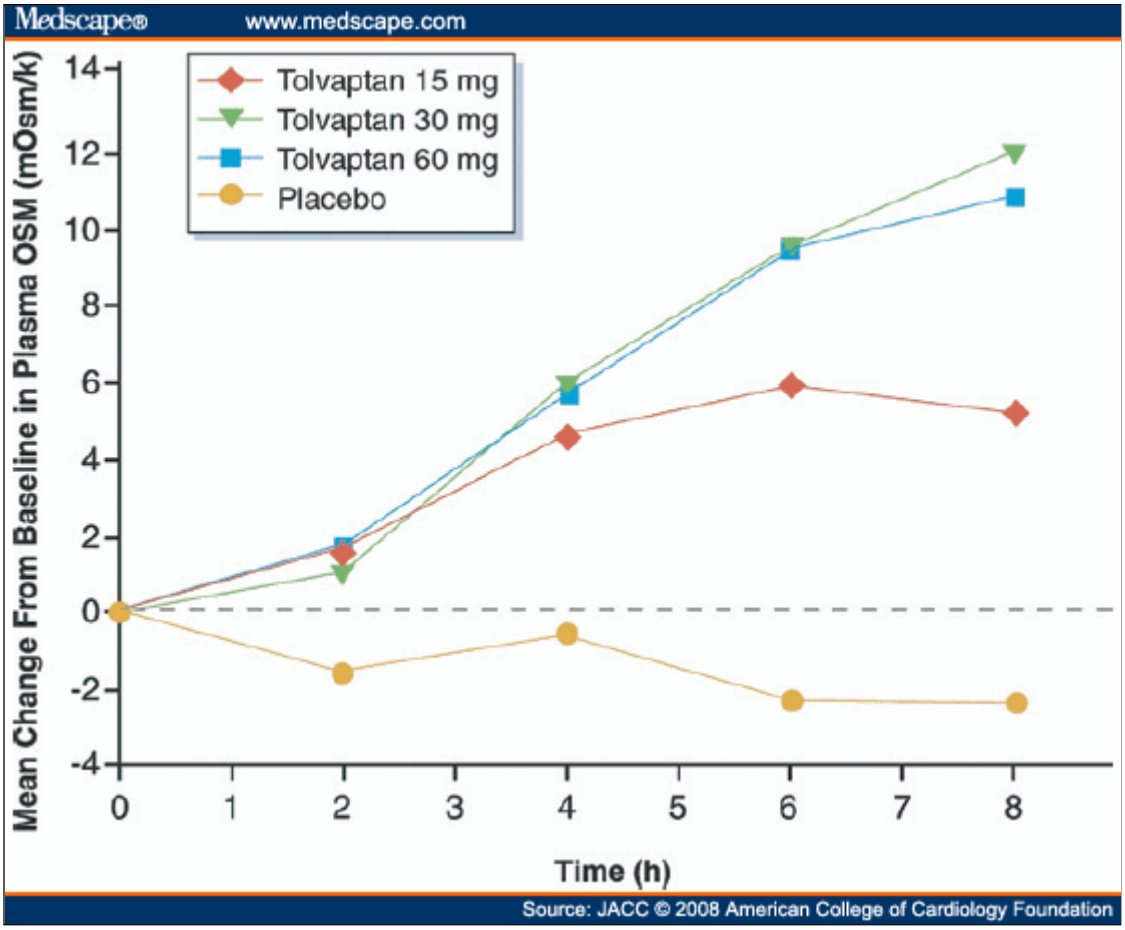

Fig 3. Changes in Plasma OsmolalityMean change from baseline in plasma osmolality (OSM) in the 4 treatment groups. A significant increase was observed in all of the tolvaptan dosing groups ($p < 0.0005$ for all tolvaptan groups vs. placebo at 4 h and later).

No significant changes in serum creatinine, blood urea nitrogen, serum potassium, and vital signs were observed after study drug administration.

Adverse Events

Acute tolvaptan therapy was well tolerated relative to placebo. Patient-reported adverse events in this short-term study occurred in 45.5%, 44.2%, 54.3%, and 33.3% of the 15-, 30-, and 60-mg tolvaptan and placebo groups, respectively. The most commonly reported event was catheter site pain, which occurred in 4.5%of the tolvaptan-treated patients and 6.3% of the placebo patients. There were no drug-related deaths.

Discussion

The results of this prospective, multicenter, randomized, double-blind, placebo-controlled trial suggest that antagonism of the vasopressin V_2 receptor with a single dose of tolvaptan in patients with advanced HF results in favorable although modest changes in hemodynamics associated with an increase in urine output. The magnitude of the enhanced urine output was dose-dependent, whereas the changes in filling pressures and pulmonary artery pressures were not dependent on dose. Urine osmolality decreased and free water clearance increased after tolvaptan treatment compared with placebo, consistent with antagonism of renal V_2 vasopressin receptors. These results occurred with no clinically significant associated changes in electrolytes, blood pressure, or heart rate. These data provide a potential underlying mechanism for the short-term clinical effects noted in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial.[8]

In the EVEREST trial, 4,133 patients admitted to the hospital with decompensated HF were randomized to treatment with tolvaptan 30 mg per day or to placebo, in addition to standard therapy, soon after admission. More patients receiving tolvaptan reported improvement in dyspnea compared with patients randomized to placebo at day 1 after enrollment ($p < 0.001$).[8] The data reported herein from the ECLIPSE trial suggest that the favorable changes in symptomatic end points observed in the EVEREST trial during tolvaptan treatment were at least in part related to the improved though modest

changes in central hemodynamics, which were in turn associated with the volume loss from the increased urine output.

In the contemporary era, several nonpeptide vasopressin antagonists have been studied. Conivaptan, a dual V_1/V_2 receptor antagonist, was shown in a single-dose, dose-ranging trial, with a design similar to the present study, to be associated with reductions in filling pressure and dose-dependent increases in urine output in stable patients with advanced HF.[10] The data from the ECLIPSE trial show similar reductions in filling pressure and dose-dependent increase in urine output, and in addition reductions in pulmonary artery pressure. Taken together, the data suggest that the predominant clinical effects are mediated by V_2 receptor antagonism, even for the dual-receptor antagonist conivaptan.

The magnitude of change in PCWP after a single oral dose of tolvaptan in this study was modest relative to placebo. Indeed, the magnitude of PCWP reduction is less than that reported for many vasoactive or other agents in studies of acute hemodynamic effects in HF patients, such as tezosentan,[11,12] levosimendan,[13] or nesiritide.[14] However, a greater magnitude of PCWP change may come with a cost in terms of greater risk of hypotension. An excess of hypotension has not been reported in the published tolvaptan data, now involving several thousand patients with decompensated HF.[7,8]

To the extent that the results from the ECLIPSE trial in patients with stable though advanced HF can be extrapolated to the EVEREST population, the data suggest that even modest short-term reduction in PCWP can be associated with identifiable improvement in dyspnea, using vasopressin receptor antagonism. Given the modest PCWP reduction, it is possible that the slight increase in plasma osmolality observed in this data set might also contribute to relief of dyspnea though osmotic mechanisms (as suggested by studies of high-dose furosemide with hypertonic saline in decompensated HF patients [15]) possibly resulting in diminution of interstitial lung water.

There are limitations to this dataset and to the conclusions that may be drawn from it. The patients in this study had advanced symptomatic HF and were selected to have abnormal baseline hemodynamics. Thus the generalizability to all patients with decompensated HF, in whom treatment with tolvaptan would potentially be started concomitant with intravenous diuretics and other acute therapies, is not certain. The reported safety issues and effects on renal and electrolyte parameters in this study are the consequence only of single-dose administration. The safety of repeated dosing chronically on all of these parameters has been reported in the large EVEREST patient database.[7,8]

Hence, antagonism of the vasopressin V_2 receptor with a single dose of tolvaptan in patients with advanced HF results in favorable although modest changes in hemodynamics associated with a dose-dependent increase in urine output, and an increase in free water clearance, with no short-term changes in potassium or renal function. The results provide a potential mechanistic explanation for the short-term favorable effects of tolvaptan on symptoms such as dyspnea in patients with decompensated HF as reported in the EVEREST trial.

Appendix

For a list of the Executive Steering Committee, Independent Technical Review Committee, Safety Oversight Committee, and the Clinical Sites and Investigators, please see the online version of this article.

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Abbreviation Notes
ANCOVA = analysis of covariance; AUC = area under the curve; HF = heart failure; LV = left ventricular; PCWP = pulmonary capillary wedge pressure

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