

Efficacy and Safety of the Vasopressin V1A/V2-Receptor Antagonist Conivaptan in Acute Decompensated Heart Failure: A Dose-Ranging Pilot Study

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ABSTRACT

Background: Hospitalization for acute decompensated heart failure (ADHF) involves substantial morbidity and mortality. Current management strategies have major limitations, and there has been little progress in the development of newer therapies. Arginine vasopressin—receptor antagonists may have promise in the treatment of ADHF in view of their ability to facilitate diuresis. This pilot study was designed to evaluate the efficacy and safety of intravenous conivaptan, a dual arginine vasopressin V_{1A}/V₂-receptor antagonist, in treating ADHF.

Methods and Results: In a double-blind, multicenter trial, 170 patients hospitalized for worsening heart failure and given standard therapy were randomly assigned to treatment with conivaptan (20-mg loading dose followed by 2 successive 24-hour continuous infusions of 40, 80, or 120 mg/d) or placebo. The conivaptan and placebo groups did not differ significantly in patient or clinician assessments of global and respiratory status at 48 hours. There was no evidence of worsening heart failure in any group. Conivaptan at each dosage increased urine output significantly more than placebo at 24 hours ($P \leq .02$), with the difference averaging 1.0 to 1.5 L. Decreases in mean body weight with conivaptan 40 and 80 mg/d (~ 1 – 2 kg) paralleled the increases in urine output but did not reach statistical significance. Conivaptan was well tolerated and not associated with clinically important changes in vital signs, electrolyte disturbances, or cardiac rhythm. The most common adverse events were infusion-site reactions.

Conclusion: When added to standard therapy for ADHF, conivaptan safely improves urine output. Further study of this compound in ADHF may be warranted, especially in view of the limitations of current treatment for this syndrome. (*J Cardiac Fail* 2008;14:641–647)

Key Words: Acute heart failure, aquaresis, diuresis.

Acute decompensated heart failure (ADHF) is the primary diagnosis for approximately 1 million hospitalizations in the United States and the secondary diagnosis for approximately 2 million hospitalizations.¹ Hospitalization

for ADHF is also associated with substantial morbidity and mortality.² In the Acute Decompensated Heart Failure National Registry, the in-hospital mortality for this condition was 4%,³ and in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study, the 60-day mortality in patients hospitalized for ADHF was 9.6%.⁴ Depending on the patient population, the combined risk of death or rehospitalization within 60 to 90 days of discharge for ADHF is between 30% and 70%.^{4–6} Within 6 months of discharge, approximately half of patients hospitalized for heart failure require readmission.⁷ It is clear that better treatment for ADHF is needed.

Diuretics are the first-line therapy for pulmonary congestion or peripheral edema secondary to fluid overload.⁸ Despite providing rapid symptomatic relief and reducing volume overload, diuretics may promote neurohormonal

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activation, worsen renal function, and induce electrolyte disturbances.⁹ Diuretics clearly have not been successful based on the current dismal outcomes in ADHF, with or without the adjunctive use of vasodilators and inotropes, as reported in the Acute Decompensated Heart Failure National Registry.³

Despite the poor outcomes and potential pitfalls associated with current treatments for ADHF, recent progress has been limited. Nesiritide provides modest additional symptom relief,^{10,11} whereas other vasodilators such as endothelin antagonists have not been shown to improve outcome compared with standard therapy.^{12,13} Inotropes such as milrinone may be harmful.⁴ Nonpharmacologic treatment directed at fluid removal with ultrafiltration (UF), however, has been shown to reduce readmission rates after hospitalization for ADHF.¹⁴ Therefore, ADHF remains open to additional pharmacologic treatment, especially one directed at fluid removal, in addition to or in place of conventional diuretics. Arginine vasopressin (AVP)–receptor antagonists may represent one such therapy.

Patients with heart failure often have an elevated level of AVP, a neurohormone produced in response to changes in plasma osmolality or in the presence of various central stimuli, hypovolemia, or hypotension.^{15–19} Excessive AVP signaling could contribute to chronic heart failure by mechanisms that include vasoconstriction and left ventricular hypertrophy or remodeling through vasopressin V_{1A}-receptor effects and water retention by the kidneys through V₂-receptor effects.²⁰ Both the vasoconstrictive and water-retaining effects of excessive vasopressin secretion could contribute to ADHF. In theory, therefore, inhibition of AVP signaling may represent a new option for treating patients with ADHF.

The AVP-receptor antagonist conivaptan has strong affinity for and binds potently to both AVP V_{1A} and V₂ receptors in vitro and in vivo.²¹ In an experimental model of heart failure, conivaptan improved hemodynamics and increased free water clearance.²² In patients with symptomatic heart failure (New York Heart Association class III and IV), a single dose of intravenous conivaptan significantly reduced pulmonary capillary wedge pressure and right atrial pressure ($P < .05$ for both measures vs placebo) and significantly increased urine output ($P < .001$ vs placebo).²³

Antagonism of the V₂ receptor in the renal collecting ducts results in the primary pharmacodynamic effect of conivaptan—aquaresis, the solute-free, electrolyte-sparing excretion of water.²⁴ In a clinical study of conivaptan in patients with hyponatremia, significant aquaresis was demonstrated by an increase in free water clearance, which resulted in significant increases in serum sodium concentration ($[Na^+]$).²⁵ Conivaptan is approved for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients but is not approved for the treatment of heart failure.

The potential therapeutic benefit of conivaptan in patients with heart failure²³ prompted this pilot study to evaluate the efficacy and safety of conivaptan in alleviating the signs and symptoms of congestion in patients with ADHF.

Materials and Methods

Patients

Eligible men and women were at least 18 years of age, were hospitalized for treatment of worsening heart failure (indicated by increasing dyspnea), had evidence of pulmonary congestion, had visual analog scale (VAS) scores greater than 50 mm on assessments of global and respiratory symptoms, and had provided written informed consent.

Excluded from the trial were patients with obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; a need for mechanical ventilatory or circulatory assistance within 2 days before enrollment; supraventricular or ventricular arrhythmia likely to require treatment within 48 hours after study entry; clinical evidence of digitalis toxicity; sustained systolic blood pressure > 180 or < 85 mm Hg; serum potassium concentration ($[K^+]$) < 3.5 or > 5.5 mmol/L; serum creatinine > 3 mg/dL; any disorder other than heart failure that was the primary cause of dyspnea or tachypnea; or any disorder other than heart failure that could complicate protocol-specified measurements or be life threatening within 48 hours after study entry.

Patients were also excluded from the study if they had any of the following in the 2 hours before randomization: treatment with an oral diuretic or vasodilator, bolus administration of an intravenous diuretic or vasodilator, continuous infusion of an intravenous diuretic, or initiation of or a change in the infusion rate of vasodilators or positive inotropes. Diuretic use was otherwise not restricted.

Study Procedures

The protocol and informed consent document were approved by each investigator's independent ethics committee. In this randomized, double-blind, placebo-controlled study (conducted at 35 centers in the United States, South Africa, and Israel), 170 patients were assigned to 1 of 4 treatments: placebo, conivaptan 40 mg/d, conivaptan 80 mg/d, or conivaptan 120 mg/d; each was administered as 2 successive 24-hour continuous intravenous infusions. A 30-minute infusion of a loading dose of either conivaptan 20 mg (active-therapy groups) or placebo was followed by the first continuous infusion.

Vital signs were recorded at baseline, at 1, 2, 4, 6, 12, 24, 36, 48, and 72 hours after the start of study drug administration, and on study day 30. Blood samples were collected for measurement of serum Na^+ , K^+ , magnesium (Mg^{2+}), creatinine, and blood urea nitrogen concentrations before infusion (baseline), 24, 48, and 72 hours after treatment began, and 30 days posttreatment. Blood and urine samples for clinical laboratory evaluation were obtained at baseline, after completion of treatment, and on day 30. For determination of AVP and conivaptan plasma concentrations, blood samples were collected at baseline and 24 and 48 hours after the start of treatment. Electrocardiograms (ECGs) were also obtained at baseline and 24 and 48 hours after the start of treatment.

Efficacy Measures

Key efficacy variables were the area under the curve (AUC) change from baseline at 48 hours in patient-assessed severity of respiratory symptoms and global status (measured according to a VAS score ranging from 0 [best possible status/symptoms absent] to 100 [worst possible status/most severe symptoms]), the total urine output at 72 hours, the total daily urine output at

24, 48, and 72 hours, and the change from baseline in body weight at 24, 48, and 72 hours. Patient and clinician global assessments and dyspnea assessments, change from baseline in respiratory rate, total daily fluid intake, and a comparison of 9 clinical signs of heart failure with baseline findings were also recorded. The following clinical signs of heart failure were evaluated: elevated jugular venous pressure, pulmonary rales, pleural effusion, third heart sound, cardiac murmur, hepatomegaly, ascites, leg edema, and presacral edema.

Statistical Analysis

A 2-sided analysis of covariance was used to analyze differences among treatment groups in AUC change from baseline in respiratory VAS, global VAS, and body weight; baseline values were included as covariates. Intergroup differences in urine output measures underwent an analysis of variance. Continuous variables were summarized by descriptive statistics and discrete variables, by frequency and percentage. The threshold of significance in the comparative efficacy analyses was .05.

Safety Assessments

Safety was evaluated by the incidence and severity of treatment-emergent adverse events (AEs); change from baseline in vital signs, physical examination findings, and ECG findings; and clinical laboratory results.

Results

Baseline Characteristics

Of 170 randomized patients, 162 received the study drug and had at least 1 efficacy assessment; 143 completed treatment (Fig 1). Of the 27 patients who discontinued treatment, 11 did so because of AEs (1 patient each in the placebo and conivaptan 40-mg groups, 4 patients in the 80-mg group, and 5 patients in the 120-mg group). Other reasons for study discontinuation included lack of compliance (3 patients), lack of efficacy (3 patients), administrative (8 patients), and withdrawn consent (2 patients).

Among patients who received study treatment, 63% were men, and the mean age was 63.5 years. A total of 91% had chronic New York Heart Association class III/IV heart

failure, and mean left ventricular ejection fraction was 29.5%. The concomitant use of medications for heart failure was common and similar in each group (Table 1).

Efficacy

Respiratory and global VAS scores indicated no significant difference between conivaptan and placebo in AUC change from baseline at 48 hours. Conivaptan and placebo did not differ significantly in change from baseline in the global and dyspnea assessments by patients and clinicians. A small mean decrease in respiratory rate occurred in each group, again with no significant differences between conivaptan and placebo in changes from baseline. Neither worsening nor improvement in heart failure was evident in any group.

The total urine output (AUC) at 72 hours was significantly greater with each conivaptan dosage than with placebo (Fig 2); a statistically significant dose–response relationship was observed ($P = .003$). All conivaptan-treated groups demonstrated significantly greater total mean daily urine output at 24 hours ($P \leq .02$ vs placebo). Urine output was also significantly greater with conivaptan 80 or 120 mg/d at 48 hours ($P \leq .004$) and with 40 mg/d at 72 hours ($P = .046$) than with placebo (Fig 3). Mean body weight decreased from baseline in all groups at 24, 48, and 72 hours. The decreases in body weight with conivaptan 40 and 80 mg/d ranged from 0.7 to 2 kg greater than with placebo. These changes paralleled the increases in urine output but did not reach statistical significance compared with placebo (Fig 4). Mean daily fluid intake was approximately 0.1 to 0.4 L higher in the conivaptan groups than in the placebo group, except during the 48- to 72-hour evaluations among patients taking conivaptan 40 or 80 mg/d. Clinical signs of heart failure were improved consistently in all groups on day 30.

Other Findings

With both conivaptan 40 and 80 mg/d, the median plasma conivaptan concentrations at 24 hours were similar to those at 48 hours; with conivaptan 120 mg/d, the median

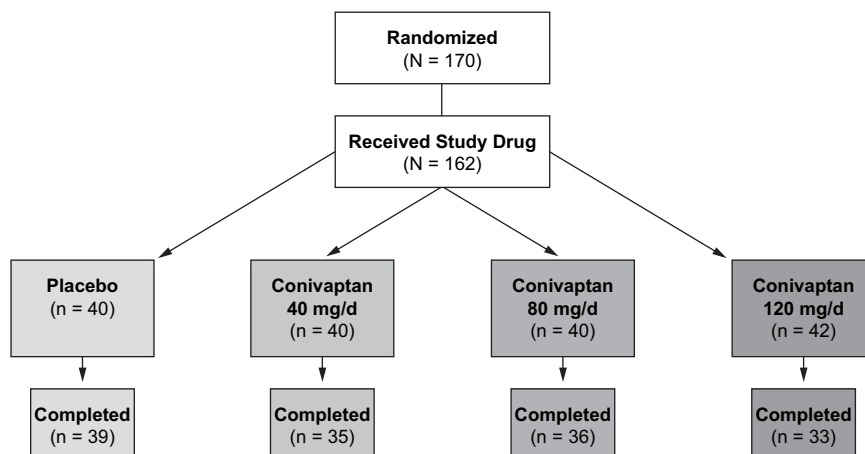


Fig. 1. Disposition of patients.

Table 1. Demographic and Baseline Characteristics

Characteristic	Placebo (n = 40)	Conivaptan 40 mg/d(n = 40)	Conivaptan 80 mg/d(n = 40)	Conivaptan 120 mg/d(n = 42)
Sex, no. (%)				
Male	24 (60)	22 (55)	24 (60)	32 (76)
Female	16 (40)	18 (45)	16 (40)	10 (24)
Race, no. (%)				
White	27 (68)	24 (60)	23 (58)	31 (74)
Black	10 (25)	12 (30)	7 (18)	8 (19)
Hispanic	1 (2)	4 (10)	8 (20)	2 (5)
Asian	1 (2)	0	0	1 (2)
Other	1 (2)	0	2 (5)	0
Age, y*	63.8 (18.0)	60.7 (14.2)	67.2 (12.0)	62.3 (11.6)
Weight, kg*	87.3 (22.1)	97.4 (29.2)	88.2 (24.6)	91.0 (21.3)
NYHA class, no. (%)				
I	0	1 (2)	0	0
II	3 (8)	3 (8)	4 (10)	3 (7)
III	18 (45)	12 (30)	14 (35)	18 (43)
IV	19 (48)	24 (60)	22 (55)	21 (50)
Type of heart failure				
Ischemic	20 (50)	15 (38)	21 (52)	20 (48)
Idiopathic	9 (22)	14 (35)	12 (30)	13 (31)
Hypertensive	5 (12)	8 (20)	4 (10)	6 (14)
Other	6 (15)	3 (8)	3 (8)	3 (7)
Concomitant heart failure medication, no. (%) [†]				
ACE inhibitors	31 (78)	31 (78)	32 (80)	29 (69)
Angiotensin receptor blockers	4 (10)	2 (5)	7 (18)	9 (21)
β-blockers	31 (78)	25 (62)	27 (68)	31 (74)
Calcium channel blockers	9 (22)	4 (10)	4 (10)	6 (14)
Digoxin	24 (60)	19 (48)	13 (32)	21 (50)
Diuretics				
Furosemide	30 (75)	31 (78)	38 (95)	36 (86)
Hydralazine	3 (8)	4 (10)	3 (8)	1 (2)
Metolazone	3 (8)	6 (15)	4 (10)	4 (10)
Spironolactone	15 (38)	14 (35)	15 (38)	12 (29)
Torsemide	5 (12)	3 (8)	0	3 (7)
Nesiritide	2 (5)	6 (15)	5 (12)	5 (12)
Vasodilators	18 (45)	16 (40)	12 (30)	15 (36)
Baseline serum [Mg ²⁺],*	mmol/L 0.80 (0.17)	0.85 (0.12)	0.83 (0.14)	0.84 (0.10)
Baseline serum [K ⁺],*	mmol/L 4.24 (0.52)	4.09 (0.55)	4.11 (0.47)	4.23 (0.55)
	(n = 37)	(n = 33)	(n = 37)	(n = 35)
LVEF (%) ^{**‡}	25.8 (14.8)	29.8 (14.8)	32.2 (17.1)	30.2 (15.5)

NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction.

*Mean (+mn; standard deviation).

[†]Heart failure medications used by ≥ 10% of any treatment group.

[‡]Only from patients who had an LVEF assessment as part of routine care.

concentration was higher at 48 hours (845 ng/mL) than at 24 hours (574 ng/mL). With the exception of conivaptan 40 mg/d at 48 hours, all doses of conivaptan were associated with significantly higher plasma AVP levels compared with placebo (Table 2). The mean increases from baseline in AVP, which ranged from 0.2 to 1.8 pg/mL and seemed to be dose dependent, however, were not clinically significant.

The mean increase in serum [Na⁺] at 24, 48, and 72 hours was significantly higher in each of the conivaptan groups compared with the placebo group ($P \leq .036$), with the largest increases occurring in the higher dose groups. At 48 hours, conivaptan increased serum [Na⁺] by 1.38 to 2.40 mmol/L, with a placebo-corrected change of 2.25 to 3.27 mmol/L.

Safety and Tolerability

There were 18 deaths among the study population (5 patients given placebo, 3 patients given conivaptan 40 mg/d, 3 patients given conivaptan 80 mg/d, and 7 patients given

conivaptan 120 mg/d). Of these deaths, 14 were related to cardiac failure or pulmonary complications, 1 was due to multisystem organ failure, 1 was due to sepsis, 1 was due to dead bowel and disseminated intravascular coagulation, and 1 was due to end-stage renal disease. Six deaths occurred during initial hospitalization (in 1 patient given placebo, 1 patient given conivaptan 40 mg/d, 1 patient given 80 mg/d, and 3 patients given 120 mg/d); 5 deaths resulted from events that began after hospitalization but before day 30 (in 1 patient given conivaptan 40 mg/d and 4 patients given conivaptan 120 mg/d); and 7 deaths resulted from events that began after the day 30 assessment (in 4 patients given placebo, 1 patient given conivaptan 40 mg/d, and 2 patients given 80 mg/d). Only 1 death, in a patient given conivaptan 120 mg/d, was considered possibly related to treatment. That patient demonstrated ventricular tachycardia during treatment and died of ventricular fibrillation the next day (after discontinuation of conivaptan).

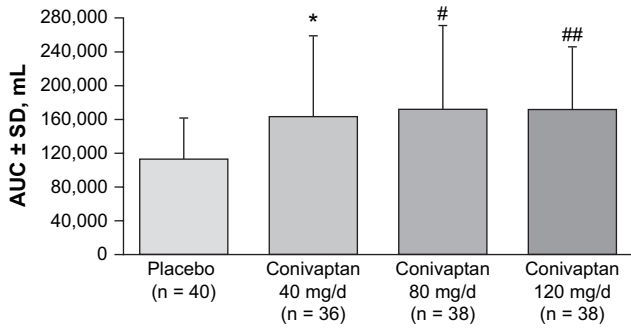


Fig. 2. Total urine output at 72 hours. **P* = .016; #*P* = .002; ##*P* = .001 versus placebo. AUC, area under the curve; SD, standard deviation.

Given conivaptan’s mechanism of action and the importance of hemodynamic stability when treating ADHF, any changes in blood pressure could be clinically relevant. Evaluations for hypotension and hypertension revealed no significant differences between the conivaptan and placebo groups. At 48 hours, mean changes from baseline in systolic blood pressure were -4.9 mm Hg, -8.6 mm Hg, and -4.3 mm Hg among patients given conivaptan 40 mg/d, 80 mg/d, and 120 mg/d, respectively. Mean changes in diastolic pressure were -1.8 mm Hg, -5.2 mm Hg, and -6.0 mm Hg in the 3 dose groups, respectively. Among patients given placebo, mean changes in systolic and diastolic pressures were -8.8 mm Hg and -6.1 mm Hg. The ECG findings at baseline and at 24 and 48 hours after study drug infusion were abnormal in 89% of patients in each treatment group. Only 4 patients with a normal ECG at baseline had an abnormal ECG after baseline. Conivaptan was not associated with any clinically significant changes in heart rate. At 48 hours, the mean changes from baseline in heart rate ranged from -4.3 and 1.0 beats/min among all conivaptan groups and -2.0 beats/min among those given placebo.

Most reported AEs were mild or moderate, and the most common AEs that occurred in all conivaptan groups at

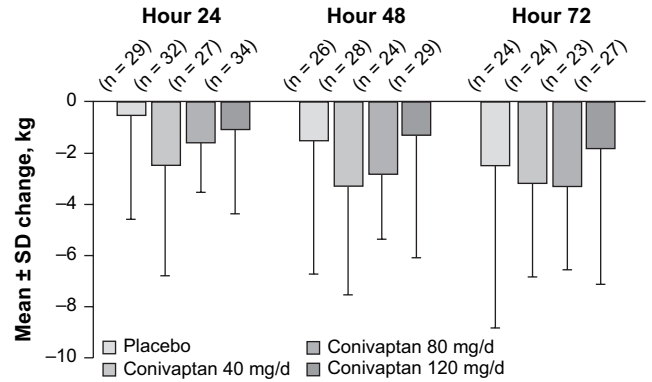


Fig. 4. Mean change from baseline in body weight. SD, standard deviation.

a higher incidence than with placebo were related to infusion-site reactions (Table 3). Other than infusion-related events, the incidence of AEs associated with all doses of conivaptan was similar to that observed with placebo. Among patients given conivaptan, AEs potentially related to study treatment affected between 40% and 60% of all groups and seemed to be dose-dependent. Except for infusion-site reactions, none of these treatment-related AEs occurred in more than 2 patients in any group. Most infusion-related AEs were mild; 3 patients given conivaptan 120 mg/d and 1 patient in each of the other groups had severe reactions.

Hepatic AEs were noted in 1 patient given placebo and in 2 patients each given conivaptan 40 and 120 mg/d; none of these events were serious or led to changes in study drug administration. Renal AEs occurred in 7 patients (18%) given placebo, 11 patients (28%) given conivaptan 40 mg/d, 9 patients (22%) given conivaptan 80 mg/d, and 7 patients (17%) given conivaptan 120 mg/d. One patient (2%) taking conivaptan 80 mg/d discontinued treatment because of an acute exacerbation of chronic renal failure. Thrombocytopenia was observed in 2 patients (5%) given placebo and in 1 patient (2%) given conivaptan 40 mg/d; none of the events were judged related to treatment.

The incidence of any clinically significant abnormality in hematologic and clinical chemistry tests was similar in the study groups and ranged from 24% with conivaptan 120 mg/d to 38% with placebo. Clinically significant elevations in blood urea nitrogen were noted in 7 of 40 patients (18%) in the placebo group, and in 8 of 40 patients (20%) given conivaptan 40 mg/d, 7 of 40 patients (18%) given conivaptan 80 mg/d, and 4 of 42 patients (10%) given conivaptan 120 mg/d. Serum creatinine elevations of clinical consequence were recorded in 7 patients (18%) in the placebo group, and in 7 patients (18%), 6 patients (15%), and 7 patients (17%) in the respective conivaptan groups. At 24 and 48 hours, respectively, mean \pm mn; standard deviation increases from baseline in serum $[Mg^{2+}]$ were significantly greater with conivaptan 120 mg/d ($0.07 \pm mn; 0.11$ mmol/L, $0.14 \pm mn; 0.27$ mmol/L) than with placebo ($0.03 \pm mn; 0.12$ mmol/L, $0.06 \pm mn; 0.17$ mmol/L; *P* < .05). A significant mean \pm mn; standard deviation increase

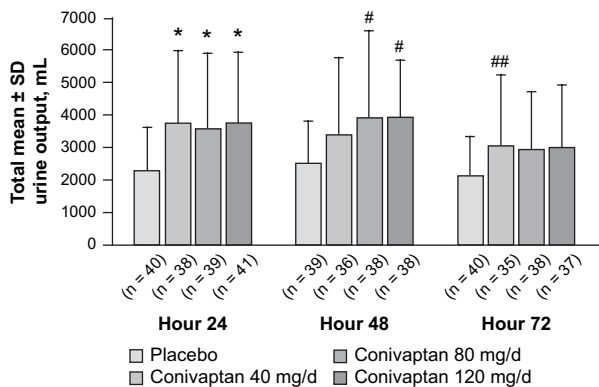


Fig. 3. Total mean daily urine output at 24, 48, and 72 hours. **P* ≤ .02; #*P* ≤ .004; ##*P* = .046 versus placebo. SD, standard deviation.

Table 2. Change From Baseline in Plasma Arginine Vasopressin

Plasma AVP, pg/mL*	Placebo (n = 40)	Conivaptan 40 mg/d (n = 40)	Conivaptan 80 mg/d (n = 40)	Conivaptan 120 mg/d (n = 42)
Baseline	2.14 (1.76)	2.79 (5.67)	2.21 (1.91)	2.13 (1.81)
Hour 24	1.56 (1.47)	2.76 (2.47) [†]	2.59 (1.46) [†]	3.78 (2.14) [‡]
Hour 48	1.73 (2.39)	3.00 (3.65)	3.07 (1.66) [†]	3.93 (2.06) [‡]

AVP, arginine vasopressin.

*Mean (+mn; standard deviation).

[†]*P* < .05.

[‡]*P* < .001.

from baseline in serum $[K^+]$ was observed at 72 hours with conivaptan 120 mg/d (0.32 +mn; 0.68 mmol/L) compared with placebo (0.07 +mn; 0.61 mmol/L; *P* = .039). None of the increases in serum $[Mg^{2+}]$ and $[K^+]$, however, were clinically relevant.

Discussion

In this pilot study in patients with ADHF, conivaptan was effective in producing a significant increase in urine output compared with standard care at each dose studied. On average, treatment with conivaptan produced a total increase in urine output of 1.0 to 1.5 L in 24 hours. Both placebo and

conivaptan groups received oral loop diuretic therapy; thus, the effect of conivaptan was seen in addition to, not in place of, standard therapy. Changes in body weight paralleled the increases in urine output and seemed to be clinically relevant with the 40- and 80-mg/d doses, although not significantly different compared with placebo. Conivaptan did not alleviate signs and symptoms of heart failure to a degree greater than placebo, as indicated by global and respiratory VAS scores.

Patients treated with conivaptan did not seem to be at increased risk for any major disturbance in blood chemistry, nor were there any cardiovascular complications, such as hypotension or atrial arrhythmias, including atrial fibrillation. This is important in view of the negative impact such complications have had on short-term outcomes in studies of other agents.^{4,26} In particular, because excessive hypotension has been linked to poor outcome, and because the contemporary treatment of heart failure focuses on agents that interrupt signaling of the renin-angiotensin-aldosterone system and sympathetic nervous system, it was important to demonstrate the safety of an agent that could, in theory, induce hypotension by way of V_{1A} -receptor antagonism.²⁷ As noted, clinically significant hypotension was not seen in this study, which included severely ill patients, most of whom were receiving angiotensin-converting enzyme inhibitors and β -adrenergic blockers, which suggests that a combined V_{1A}/V_2 blocker carries a low risk of causing clinically meaningful decreases in blood pressure in this population. Without specific hemodynamic measurements, however, it is not possible to determine whether there were any changes in cardiac output or systemic vascular resistance in response to conivaptan.

Most AEs with conivaptan were mild infusion-site reactions, with few necessitating discontinuation of treatment. These reactions are believed to be due to the polypropylene glycol buffer in which the compound is dissolved. The percentage of patients who discontinued participation because of AEs was highest among those given the highest conivaptan dose. This group also seemed to have been more ill than the other groups, as reflected in their higher multifactorial mortality at 30-day follow-up. The overall safety profiles for conivaptan 40 and 80 mg/d were similar.

This pilot study demonstrated a dissociation between diuretic efficacy and symptom scores in response to conivaptan. These findings are similar to those reported in the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial, which demonstrated that although

Table 3. Summary of Adverse Events

Event, no. (%)	Placebo (n = 40)	Conivaptan 40 mg/d (n = 40)	Conivaptan 80 mg/d (n = 40)	Conivaptan 120 mg/d (n = 42)
Deaths*	1 (2.5)	2 (5.0)	1 (2.5)	6 (14.3)
Patients with serious AEs	7 (17.5)	4 (10.0)	5 (12.5)	10 (23.8)
Discontinuations due to AEs	1 (2.5)	2 (5.0)	3 (7.5)	6 (14.3)
Patients with treatment-related AEs	10 (25.0)	16 (40.0)	20 (50.0)	25 (59.5)
Most common AEs [†]				
Infusion-site phlebitis	2 (5.0)	7 (17.5)	13 (32.5)	14 (33.3)
Exacerbated dyspnea	5 (12.5)	7 (17.5)	7 (17.5)	5 (11.9)
Hyperkalemia	2 (5.0)	5 (12.5)	2 (5.0)	1 (2.4)
Injection-site cellulitis	0	4 (10.0)	2 (5.0)	3 (7.1)
Headache	3 (7.5)	2 (5.0)	1 (2.5)	4 (9.5)
Limb pain	0	3 (7.5)	2 (5.0)	2 (4.8)
Hypnatremia	0	2 (5.0)	3 (7.5)	2 (4.8)
Cough	2 (5.0)	3 (7.5)	1 (2.5)	1 (2.4)
Dizziness	2 (5.0)	3 (7.5)	0	1 (2.4)
Hematuria	1 (2.5)	1 (2.5)	3 (7.5)	0
Infusion-site erythema	0	0	3 (7.5)	1 (2.4)
Decreased blood magnesium	0	1 (2.5)	3 (7.5)	0
Decreased urine sodium	0	1 (2.5)	3 (7.5)	0
Infusion-site tenderness	0	0	3 (7.5)	0

AE, adverse event.

*At 30-day follow-up, excluding 1 patient who died of an event that began more than 30 days after randomization.

[†]Occurring in $\geq 7.5\%$ of any group taking conivaptan and at a higher incidence than with placebo.

UF had no benefit compared with loop diuretic treatment on symptoms, treatment with UF was associated with improvement in fluid balance.¹⁴ In the UNLOAD trial, treatment with UF also led to a significantly lower readmission rate at 90 days than conventional diuretic-based therapy. The results in the UNLOAD trial demonstrate the relative importance of clinical decongestion over symptomatic assessments in predicting short-term outcomes. However, short- and long-term treatment of ADHF with tolvaptan, a selective V₂-receptor antagonist, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan trial was also associated with greater weight loss than with usual care, but no change in clinical status or outcomes.^{10,11} The difference in weight loss with tolvaptan compared with standard care alone was considerably less than that observed with UF in UNLOAD, and patients in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan did receive furosemide.^{10,11,14} Why the 2 trials with different approaches to fluid removal had different results is therefore open to many possible explanations.

Conclusions

The results of this pilot study suggest that conivaptan at doses of 40 and 80 mg/d increases urine output and, except for local infusion-site reactions, is well tolerated in patients with ADHF. The clinical impact of this facilitated diuresis would require further study in appropriately powered investigations. Conivaptan, in theory, may also benefit patients with ADHF by relieving vasoconstriction. Given the safety and demonstrable benefit of conivaptan as an adjunct to standard diuretic therapy in this pilot trial, further study of this compound in ADHF would seem reasonable, particularly in high-risk populations who currently do not respond well to conventional treatment.

References

1. Congestive heart failure in the United States: a new epidemic. Data Fact Sheet. <http://library.thinkquest.org/27533/>. Available at: facts.html Accessed August 2, 2007.
2. Felker GM, Adams KF Jr, Konstam MA, O'Connor CM, Gheorghide M. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. *Am Heart J* 2003;145(Suppl 2):S18–25.
3. Fonarow GC. ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med* 2003;4(suppl 7):S21–30.
4. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;287:1541–7.
5. Gheorghide M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, et al. International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. *Circulation* 2005;112:3958–68.
6. Vinson JM, Rich MW, Sperry JC, Shah AS, McNamara T. Early readmission of elderly patients with congestive heart failure. *J Am Geriatr Soc* 1990;38:1290–5.
7. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99–104.
8. Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2006;12:10–38.
9. Gheorghide M. The clinical effects of vasopressin receptor antagonists in heart failure. *Cleve Clin J Med* 2006;73(Suppl 2):S24–9.
10. Gheorghide 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) Investigators. 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.
11. Konstam MA, Gheorghide 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.
12. Sharma M, Teerlink JR. A rational approach for the treatment of acute heart failure: current strategies and future options. *Curr Opin Cardiol* 2004;19:254–63.
13. Cheng JW. Tezosentan in the management of decompensated heart failure. *Cardiol Rev* 2005;13:28–34.
14. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al, for the UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;49:675–83.
15. Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med* 1981;305:263–6.
16. Riegger GA, Liebau G, Kochsiek K. Antidiuretic hormone in congestive heart failure. *Am J Med* 1982;72:49–52.
17. Goldsmith SR, Francis GS, Cowley AW Jr, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1983;1:1385–90.
18. Wong LL, Verbalis JG. Systemic diseases associated with disorders of water homeostasis. *Endocrinol Metab Clin North Am* 2002;31:121–40.
19. Goldsmith SR. Vasopressin antagonists in CHF: ready for clinical trials? *Cardiovasc Res* 2002;54:13–5.
20. Goldsmith SR, Gheorghide M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol* 2005;46:1785–91.
21. Tahara A, Tomura Y, Wada K-I, Kusayama T, Tsukada J, Takanashi M, et al. Pharmacological profile of YM087, a novel potent nonpeptide vasopressin V_{1A} and V₂ receptor antagonist, in vitro and in vivo. *J Pharmacol Exp Ther* 1997;282:301–8.
22. Yatsu T, Tomura Y, Tahara A, Wada K, Kusayama T, Tsukada J, et al. Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V_{1A} and V₂ receptor antagonist, in dogs with pacing-induced congestive heart failure. *Eur J Pharmacol* 1999;376:239–46.
23. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazizadeh M, Thomas I, et al. Acute hemodynamic effects of conivaptan, a dual V_{1A} and V₂ vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417–23.
24. Burnier M, Fricker AF, Hayoz D, Nussberger J. Pharmacokinetic and pharmacodynamic effects of YM087, a combined V₁/V₂ vasopressin receptor antagonist in normal subjects. *Eur J Clin Pharmacol* 1999;55:633–7.
25. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvoletic and hypervolemic hyponatremia. *Am J Nephrol* 2007;27:447–57.
26. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA* 2007;297:1883–91.
27. Chatterjee K. Neurohormonal activation in congestive heart failure and the role of vasopressin. *Am J Cardiol* 2005;95(Suppl):8B–13B.