Acute Hemodynamic Effects of Conivaptan, a Dual V1A and V2 Vasopressin Receptor Antagonist, in Patients With Advanced Heart Failure

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Background—Arginine vasopressin may contribute to abnormalities in hemodynamics and fluid balance in heart failure through its actions on V1A (vascular and myocardial effects) and V2 receptors (renal effects). Inhibiting the action of vasopressin may be beneficial in patients with heart failure.

Methods and Results—A total of 142 patients with symptomatic heart failure (New York Heart Association class III and IV) were randomized to double-blind, short-term treatment with conivaptan, a dual V1A/V2 vasopressin receptor antagonist, at a single intravenous dose (10, 20, or 40 mg) or placebo. Compared with placebo, conivaptan at 20 and 40 mg significantly reduced pulmonary capillary wedge pressure (−2.6±0.7, −5.4±0.7, and −4.6±0.7 mm Hg for placebo and 20 and 40 mg groups, respectively; P<0.05) and right atrial pressure (−2.0±0.4, −3.7±0.4, and −3.5±0.4 mm Hg for placebo and 20 and 40 mg groups, respectively; P<0.05) during the 3- to 6-hour interval after intravenous administration. Conivaptan significantly increased urine output in a dose-dependent manner (−11±17, 68±17, 152±19, and 176±18 mL/hour for placebo and 10, 20, and 40 mg groups, respectively; P<0.001) during the first 4 hours after the dose. Changes in cardiac index, systemic and pulmonary vascular resistance, blood pressure, and heart rate did not significantly differ from placebo.

Conclusions—In patients with advanced heart failure, vasopressin receptor antagonism with conivaptan resulted in favorable changes in hemodynamics and urine output without affecting blood pressure or heart rate. These data suggest that vasopressin is functionally significant in advanced heart failure and that further investigations are warranted to examine the effects of conivaptan on symptom relief and natural history in such patients. (Circulation. 2001;104:2417-2423.)

Key Words: heart failure ■ hemodynamics ■ hormones

Arginine vasopressin is a peptide hormone with significant cardiovascular and renal effects.1-3 These effects are mediated through at least 2 receptor subtypes: the V1A receptor, which is found on vascular smooth muscle cells and in the myocardium, and V2 receptors, which are found in the distal tubule of the kidney.2,3 Stimulation of the V1A receptor results in vasoconstriction in the peripheral and coronary circulations and has other effects, including increasing intracellular calcium levels in cardiac myocytes.2-4 Recent studies have also demonstrated that arginine vasopressin increases the rate of protein synthesis in the myocardium, leading to myocyte hypertrophy, a direct effect mediated by the V1A receptor.5-7 The V2 receptor mediates renal water retention and is predominantly responsible for the antidiuretic effect of this hormone.2,3

Under normal circumstances, vasopressin release is predominantly influenced by small changes in plasma osmolality, resulting in tight regulation of serum osmolality and serum sodium levels.3 In heart failure and left ventricular (LV) dysfunction, however, numerous nonosmotic mechanisms assume a more prominent role in the control of vasopressin release.3,8 These mechanisms include baroreceptors sensing changes in intra-arterial plasma volume and neurohormonal influences on vasopressin release.1,3

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Vasopressin levels are often elevated in patients with heart failure and LV dysfunction, and they seem to be associated with adverse cardiovascular outcomes in the setting of LV dysfunction after myocardial infarction. These data suggest that vasopressin may contribute to the circulatory response in patients with heart failure and may also play a role in the development and progression of heart failure. Many of the prior studies examining vasopressin levels in patients with heart failure or LV dysfunction were performed in patients off of background medications and in an era before the widespread use of ACE inhibitors and β-adrenergic blockers as standard background therapy. In the current study, we evaluated the hemodynamic effects of conivaptan, a combined V₁A and V₂ vasopressin receptor antagonist, in a randomized, prospective, placebo-controlled trial of patients with advanced heart failure.

Methods

Patient Eligibility

Patients eligible for entry into the baseline evaluation phase of this multicenter trial were required to be 18 to 90 years of age and have symptomatic heart failure (New York Heart Association class III or IV) of at least 3 months duration due to LV systolic dysfunction. Patients were required to be on standard background therapy for heart failure, including at least 1 month of therapy with a loop diuretic and an ACE inhibitor (unless intolerance to such agents had been demonstrated) and, optionally, digoxin and/or a β-adrenergic blocker and/or spironolactone. Exclusion criteria included a supine systolic blood pressure <90 mm Hg or uncontrolled hypertension, uncontrolled bradycardia or tachyarrhythmias, pacemaker or defibrillator implantation <60 days before screening, acute coronary syndrome within 1 month of screening, severe obstructive pulmonary disease, significant uncorrected valvular or congenital heart disease, obstructive cardiomyopathy, or significant renal impairment (defined as a serum creatinine >2.5 mg/dL or creatinine clearance <30 mL/min). Patients on continuous intravenous inotropic therapy and those patients who had conivaptan plasma concentrations determined at 1, 3, 8, 12, and 24 to 48 hours after starting the intravenous infusion. Plasma samples were assayed for conivaptan by a validated liquid chromatography-tandem mass spectrometry method in the positive ionization mode. Pharmacokinetic parameters were determined using a nonlinear mixed effects modeling approach with NONMEM (version V, level 1.1, University of California at San Francisco).

Study Design

The protocol for this study and the consent form were approved by the Institutional Review Boards at all participating sites in this multicenter trial, and all patients signed the informed consent form. Patients who provided informed consent, met all inclusion criteria, and no one in the study criteria within the prior 30 days were held during this time period, and fluid was restricted to 250 mL every 2 hours from the time of insertion of the pulmonary artery catheter throughout the treatment period.

The analysis of conivaptan pharmacokinetics included 104 patients who had conivaptan plasma concentrations determined at 1, 3, 8, 12, and 24 to 48 hours after starting the intravenous infusion. Plasma samples were assayed for conivaptan by a validated liquid chromatography-tandem mass spectrometry method in the positive ionization mode. Pharmacokinetic parameters were determined using a nonlinear mixed effects modeling approach with NONMEM (version V, level 1.1, University of California at San Francisco).

Statistical Analysis

The sample size of 35 patients per group (140 patients total) was calculated assuming a standard deviation of 3 mm Hg for the PCWP peak change. The power of the study to detect a difference of 3 mm Hg in the PCWP peak change from baseline within 3 to 6 hours after treatment administration was set at 95% (with a 2-sided error rate of 0.05 adjusted for multiple comparison using Dunnett’s approach).

The prespecified primary efficacy parameters were (1) peak change from baseline (the average of 2 qualifying baseline values) in PCWP at 3 to 6 hours after the start of study medication infusion and (2) area under the curve (AUC) for the change from baseline PCWP over the 12-hour evaluation period. Secondary efficacy parameters included peak change at 3 to 6 hours in cardiac index, systemic and pulmonary vascular resistance, right atrial pressure, and renal and electrolyte parameters (urine output, effective and free water clearance).

All patients with valid baseline PCWP and at least one post-drug measurement were included in the primary analysis of peak change in PCWP. Treatment comparisons were done using an ANCOVA that accounted for treatment effect, baseline β-blocker use, and baseline PCWP. Analysis of AUC and other parameters was conducted using a similar model. AUC was defined by the last PCWP measurement obtained before study drug administration and all consecutive measurements obtained after the infusion through the end of the 12-hour treatment phase. The AUC was corrected for baseline and calculated using the linear trapezoidal rule.

Results

Baseline Characteristics of the Population

The demographic and baseline hemodynamic characteristics of the study population are shown in Table 1. Patients were enrolled at 26 study centers in North America. Of 193 patients who met study criteria and underwent placement of a pulmonary artery catheter, 142 patients met the baseline hemodynamic entry criteria and were randomized into the...
double-blind treatment phase. Randomized patients were ≈60 years of age; ≈75% were men; and ≈40% were not white. The majority of patients were in New York Heart Association functional class III, and the average LV ejection fraction within the randomization groups ranged from 21% to 26%. Approximately 45% of patients had ischemic heart disease as the underlying cause of heart failure. ACE inhibitors were used as background therapy in 84% of placebo-treated patients and 86% of those randomized to conivaptan, whereas 50% and 44% were on β-adrenergic blockers, respectively. Baseline demographic and hemodynamic characteristics were similar between placebo-treated and conivaptan-treated patients.

### Effect of Conivaptan on Hemodynamic Measurements

The effects of the vasopressin receptor antagonist conivaptan on hemodynamic parameters in the study population are shown in Table 2. These values represent the prespecified end point using the peak change in these values between 3 to 6 hours after study drug administration. PCWP was significantly reduced compared with placebo in both the 20 and 40 mg conivaptan dosing groups, as was right atrial pressure (Table 2 and Figure 2).

The effect of conivaptan on PCWP was sustained for ≈8 hours after study drug administration, and PCWP remained below baseline after 12 hours (Figure 2). The AUCs for

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### TABLE 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=38)</th>
<th>Conivaptan 10 mg (n=37)</th>
<th>Conivaptan 20 mg (n=32)</th>
<th>Conivaptan 40 mg (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±2</td>
<td>58±2</td>
<td>56±2</td>
<td>59±2</td>
</tr>
<tr>
<td>Men, %</td>
<td>82</td>
<td>70</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>24 (63)</td>
<td>17 (46)</td>
<td>20 (63)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>12 (32)</td>
<td>17 (46)</td>
<td>11 (34)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>2 (5)</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td>III</td>
<td>35 (92)</td>
<td>33 (89)</td>
<td>28 (87)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3 (8)</td>
<td>4 (11)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±4</td>
<td>26±1</td>
<td>21±2</td>
<td>22±2</td>
</tr>
<tr>
<td>Cause of HF,* n (%)</td>
<td>Ischemic</td>
<td>18 (47)</td>
<td>17 (46)</td>
<td>13 (41)</td>
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<tr>
<td></td>
<td>Hypertensive</td>
<td>7 (18)</td>
<td>8 (22)</td>
<td>6 (19)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic/dilated</td>
<td>17 (45)</td>
<td>18 (49)</td>
<td>14 (44)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Baseline hemodynamics</td>
<td>PCWP, mm Hg</td>
<td>23±1</td>
<td>26±1</td>
<td>23±1</td>
</tr>
<tr>
<td></td>
<td>CI, L · min⁻¹ · m⁻²</td>
<td>2.1±0.1</td>
<td>2.0±0.1</td>
<td>2.0±0.1</td>
</tr>
<tr>
<td></td>
<td>SBP, mm Hg</td>
<td>125±4</td>
<td>121±3</td>
<td>120±3</td>
</tr>
<tr>
<td></td>
<td>SVR, dynes · s⁻¹ · cm⁻²</td>
<td>1533±82</td>
<td>1625±80</td>
<td>1628±105</td>
</tr>
<tr>
<td>Median plasma AVP, pg/mL</td>
<td>2.7</td>
<td>2.1</td>
<td>2.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Baseline serum</td>
<td>Osmolality, mOsmol/kg</td>
<td>293±2 (n=35)</td>
<td>290±1 (n=33)</td>
<td>291±1 (n=30)</td>
</tr>
<tr>
<td></td>
<td>Sodium, mEq/L</td>
<td>137±1 (n=36)</td>
<td>137±1 (n=37)</td>
<td>138±1 (n=31)</td>
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<tr>
<td></td>
<td>Creatinine, mg/dL</td>
<td>1.2±0.1 (n=35)</td>
<td>1.1±0.1 (n=36)</td>
<td>1.1±0.1 (n=31)</td>
</tr>
<tr>
<td>Background medications, %</td>
<td>ACE inhibitor</td>
<td>84</td>
<td>87</td>
<td>81</td>
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<tr>
<td></td>
<td>Loop diuretic</td>
<td>100</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>β-Blocker</td>
<td>50</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>32</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>84</td>
<td>84</td>
<td>75</td>
</tr>
</tbody>
</table>

Values are mean±SE or as indicated. ACE indicates angiotensin-converting enzyme; AVP, arginine vasopressin; CI, cardiac index; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; and SVR, systemic vascular resistance.

*Patients could be classified into more than one category.
PCWP and right atrial pressure versus time curves through
the 12-hour evaluation period demonstrated significant
differences from placebo ($P<0.05$) in the 20 and 40 mg
conivaptan groups (Figure 3). Mean±SE AUCs
(in mm Hg×hours) for PCWP were $-3.9±7$ for placebo,
$-22.9±7$ for 10 mg, $-29.8±8$ for 20 mg, and $-26.8±7$ for
40 mg; for right atrial pressure, they were $-0.9±5$ for
placebo, $-4.0±5$ for 10 mg, $-17.9±5$ for 20 mg, and
$-21.2±5$ for 40 mg. These effects on PCWP and right atrial
pressure were not affected by the presence or absence of
$\beta$-blockers in background therapy.

There were no statistically significant changes in cardiac
index, pulmonary artery pressures, mean arterial pressures,
 systemic or pulmonary vascular resistance, or heart rate
 across the groups.

### Effects of Conivaptan on Renal and Electrolyte Parameters

During the 12-hour study period, urine output in the
conivaptan-treated groups was substantially greater than that
in the placebo-treated group (Figure 4). The single dose of
conivaptan produced a dose-dependent increase in urine
output, which peaked at 2 to 3 hours after the dose. Mean
change from baseline in urine flow rates $0$ to $4$ hours after
infusion were $-11.3±17$, $68.9±17$, $152.2±19$, and
$176.2±18$ mL/hour for placebo, $10$ mg, $20$ mg, and $40$ mg
dosing groups, respectively ($P<0.001$). Urine osmolality was
significantly reduced by all doses of conivaptan relative to
placebo. Values (mean±SE) for placebo, $10$, $20$, and $40$ mg
groups were $-2.2±28$, $-249.8±27$, $-279.6±32$, and
$-319.3±26$ mOsmol/kg, respectively ($P=0.0001$ for all
conivaptan groups versus placebo). Serum osmolality, serum

### Table 2. Effect of Conivaptan on Hemodynamic Parameters (Peak Change at 3–6 hours)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP, mm Hg</td>
<td>$-2.6±0.7$</td>
<td>$-3.7±0.7$</td>
<td>$-5.4±0.7^*$</td>
<td>$-4.6±0.7^*$</td>
</tr>
<tr>
<td>CI, L⋅min$^{-1}$⋅m$^{-2}$</td>
<td>$0.3±0.1$</td>
<td>$0.2±0.1$</td>
<td>$0.4±0.1$</td>
<td>$0.2±0.1$</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>$-4.1±1.3$</td>
<td>$-5.4±1.3$</td>
<td>$-6.0±1.4$</td>
<td>$-4.2±1.3$</td>
</tr>
<tr>
<td>PVR, dynes⋅s⋅cm$^{-5}$</td>
<td>$-53.4±14.9$</td>
<td>$-38.0±15.1$</td>
<td>$-59.1±16$</td>
<td>$-36.1±15.3$</td>
</tr>
<tr>
<td>SVR, dynes⋅s⋅cm$^{-5}$</td>
<td>$-185.2±43.8$</td>
<td>$-182.3±44.5$</td>
<td>$-284.2±47.1$</td>
<td>$-128.9±45$</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>$-4.2±1.1$</td>
<td>$-6.0±1.1$</td>
<td>$-5.9±1.2$</td>
<td>$-6.3±1.1$</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>$-2.0±0.4$</td>
<td>$-2.0±0.4$</td>
<td>$-3.7±0.4^*$</td>
<td>$-3.5±0.4^*$</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>$-2.4±1.0$</td>
<td>$-1.1±1.0$</td>
<td>$-1.9±1.1$</td>
<td>$-0.4±1.1$</td>
</tr>
</tbody>
</table>

$^*P<0.05$, $^P<0.01$.

Values are mean±SE. CI indicates cardiac index; HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary arterial systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; and SVR, systemic vascular resistance.

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**Figure 2.** A, Time course of changes in PCWP over the 12-hour period after short-term treatment with 1 of 3 doses of conivaptan or placebo. Changes were significant at the 20-mg dose ($P<0.01$) and the 40-mg dose ($P<0.05$). B, Time course of changes in right atrial pressure (RAP) over the 12-hour period after short-term treatment with 1 of 3 doses of conivaptan or placebo. Changes were significant at the 20-mg dose ($P<0.01$) and the 40-mg dose ($P<0.05$).

**Figure 3.** Changes in AUCs for PCWP vs time plots over the 12-hour measurement period for the groups randomized to different doses of conivaptan or placebo.
sodium, and potassium levels were not greatly different from placebo in any of the conivaptan dosing groups (Table 3).

**Vasopressin Levels and Relation of Hemodynamic and Renal Parameters to Baseline Measurements**

Median plasma arginine vasopressin levels were 2.7, 2.1, 2.9, and 2.2 pg/mL in the placebo, 10 mg, 20 mg, and 40 mg groups, respectively. Plasma levels of arginine vasopressin were not significantly changed at 12 hours after study drug administration, except for a slight increase in the 40-mg randomization group (to 5.0 pg/mL).

In conivaptan-treated patients, there were no statistically significant correlations between the changes in PCWP or changes in urine output at 0 to 4 hours and baseline arginine vasopressin levels (r = −0.1 and r = −0.2, respectively). There were also no statistically significant correlations between changes in PCWP or changes in urine output at 0 to 4 hours and baseline serum sodium levels in conivaptan-treated patients (r = −0.2 and r = −0.0, respectively).

**Adverse Events**

Acute conivaptan therapy was well tolerated, and there were fewer adverse events reported after conivaptan than after placebo treatment. Patient-reported adverse events in this short-term study occurred in 63.2%, 59.5%, 56.3%, and 60.0% of the placebo, 10 mg, 20 mg, and 40 mg groups, respectively. The most commonly reported event was headache, which occurred in 7.9% of the placebo patients and 5.8% of the conivaptan-treated patients. There were no drug-related deaths or other serious adverse events.

**Conivaptan Pharmacokinetics**

Conivaptan pharmacokinetics were best described by a 2-compartment model with Michaelis-Menten elimination. Typical values for the maximum rate of elimination (V$_{\text{max}}$), Michaelis-Menten constant (K$_{\text{m}}$), and intrinsic metabolic clearance (V$_{\text{max}}$/K$_{\text{m}}$) were 5.08±1.89 mg/h, 289±151 ng/mL, and 17.6±6.5 L/h, respectively. The typical terminal half-life value was 7.80 hours (range, 5 to 12 hours). As shown in Figure 5, maximum plasma concentration (C$_{\text{max}}$) ranged from ~100 ng/mL at the lowest dose up to 1100 ng/mL at the highest dose, and AUCs were in the range of 600 to 4000 ng·h·mL$^{-1}$.

**Discussion**

The data from this multicenter, randomized, double-blind, placebo-controlled trial demonstrate that short-term antagonism of V$_{1A}$ and V$_2$ vasopressin receptors with conivaptan produced favorable hemodynamic and renal effects in patients with advanced heart failure. Decreases in PCWP and right atrial pressure were accompanied by substantial increases in urine output, without affecting systemic blood pressure, heart rate, or serum electrolytes. Arginine vasopressin levels observed in this population of heart failure patients treated with contemporary background therapies were similar to those measured in some previous studies,$^{12,14–16}$ but lower

**TABLE 3. Effect of Conivaptan on Renal and Electrolyte Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine output (0–4 hr),* mL/hr</td>
<td>−11.2±17.3</td>
<td>68.9±17.4†</td>
<td>152.2±19.2‡</td>
<td>176.2±17.8‡</td>
</tr>
<tr>
<td>Urine osmolality (0–4 hr),* mOsmol/kg</td>
<td>−2.2±27.9</td>
<td>−249.8±26.9§</td>
<td>−279.6±31.7§</td>
<td>−319.3±25.8§</td>
</tr>
<tr>
<td>Serum sodium (at 4 hr),† mEq/L</td>
<td>−0.4±0.7</td>
<td>0.5±0.5</td>
<td>0.8±0.7</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Serum osmolality (at 4 hr),† mOsmol/kg</td>
<td>−2.4±1.5</td>
<td>1.8±0.9</td>
<td>3.0±1.1</td>
<td>1.9±1.8</td>
</tr>
<tr>
<td>Serum potassium (at 4 hr),† mEq/L</td>
<td>−0.2±0.1</td>
<td>−0.1±0.2</td>
<td>0.1±0.1</td>
<td>−0.1±0.1</td>
</tr>
</tbody>
</table>

Values are *mean±SE or †mean±SE, change from baseline.

§P<0.001; †P=0.0001.
than levels observed in other studies. Of interest, there was no correlation between baseline vasopressin levels or potential markers of excessive secretion (serum sodium concentration) and conivaptan-induced changes in hemodynamics or urine output. The hemodynamic and renal effects observed with vasopressin receptor antagonism suggest that vasopressin remains functionally important in the current era of advanced heart failure. Moreover, the lack of significant correlation between conivaptan effects and baseline vasopressin or serum sodium levels suggest that the potential therapeutic application of this approach may be generalizable beyond patients with hyponatremia and very elevated vasopressin levels, as might have been expected from prior studies.

Numerous studies over the years have examined the role of vasopressin in patients with heart failure. In 1968, Yamane, using an older assay system, reported that 50% of patients with advanced heart failure had elevated vasopressin levels. Using more modern radioimmunoassay techniques, Goldsmith et al found that mean levels of plasma arginine vasopressin were substantially higher in heart failure patients than control patients. In a baseline analysis of the Studies of Left Ventricular Dysfunction (SOLVD) population before randomization to enalapril or placebo, Francis et al reported that patients with asymptomatic LV dysfunction had elevated arginine vasopressin levels compared with control patients, whereas patients with symptomatic mild-to-moderate heart failure had even higher arginine vasopressin levels. Rouleau and colleagues reported on the prognostic value of vasopressin levels in the Survival and Ventricular Enlargement (SAVE) population of post-myocardial infarction patients with LV dysfunction. Vasopressin levels 1 month after myocardial infarction were independently associated with adverse long-term cardiovascular outcomes, including heart failure, recurrent myocardial infarction, and death. Other studies have documented dysregulation of vasopressin levels in the heart failure state. Lack of suppression of vasopressin levels with a water load, as well as exaggerated release in response to an osmotic load, have been reported.

Prior investigations of vasopressin receptor antagonism in heart failure have generally been small, single-center studies with agents that were ultimately found not suitable for development. Creager and colleagues studied patients with heart failure undergoing short-term V₁ receptor antagonism and found reductions in systemic vascular resistance and increases in cardiac output. The change in systemic vascular resistance after acute V₁ receptor antagonism was correlated with the baseline value, suggesting the possibility of partial agonism of this agent in patients with initially low systemic vascular resistance. Nicod et al reported on 10 patients with advanced heart failure, only one of whom had elevated vasopressin levels at baseline. Reduction in systemic vascular resistance with acute V₁ receptor antagonism was seen in that patient alone. Mulini et al studied a rat model of post-myocardial infarction heart failure in rats with both small and extensive myocardial infarction. Combined V₁/V₂ receptor antagonism resulted in reductions in systemic vascular resistance with increases in cardiac output, as well as a substantial increase in urine output.

The present study is the first in the contemporary era of heart failure therapy to examine the short-term acute effect of dual vasopressin receptor antagonism in a placebo-controlled format. The favorable hemodynamic and renal effects noted in this study suggest that further development of this approach may be warranted. Studies examining long-term oral therapy with this agent and its effects on functional capacity and other potential indicators of long-term effects are ongoing.

Conivaptan is a combined vasopressin receptor antagonist with in vitro binding affinities (Ki) of 6.30 nM/L (3.36 ng/mL) and 1.10 nM/L (0.59 ng/mL) for human V₁A and V₂ receptors, respectively. It is 98.5% bound to plasma proteins. Conivaptan has demonstrated efficacy in animal models of altered cardiac function and volume overload. Intravenous administration of conivaptan (0.1 mg/kg) was shown to produce hemodynamic improvement and marked aquaretics in a canine model of congestive heart failure induced by rapid right ventricular pacing. Investigations with conivaptan in receptor assay systems and animal models suggested substantial antagonism of both the V₁A and V₂ receptors. In the present study however, there was no significant change in systemic vascular resistance nor an increase in cardiac output to suggest vasodilatory effects consequent to antagonism of V₁A receptors in the peripheral vasculature. The absence of a reduction in peripheral resistance suggests that the favorable effect of conivaptan on filling pressures may have been secondary to the enhanced urine output. However, the lack of close similarity between observed PCWP changes and the observed urine output changes (PCWP changes seemed to level off at the 40-mg dose, whereas urine output increased with dose) suggests that reductions in PCWP and right atrial pressure may not have been solely due to V₂ receptor antagonism and increases in urine output. It is possible that direct antagonism of V₁A receptors within the myocardium influenced the observed reductions in filling pressures, although that possibility cannot be further examined with this data set. Further investigations in humans with longer-term studies may help to clarify this point.

The important role of neurohormonal activation in the progression of heart failure and LV dysfunction is well established. That vasopressin may contribute importantly to this process is supported by prior studies demonstrating elevated arginine vasopressin levels in the absence of background heart failure therapy. Studies demonstrating the prognostic implications of elevated arginine vasopressin levels in the setting of LV dysfunction and evidence of neurohormonal “cross-talk” in that vasopressin potentiates the synthesis of endothelin and the release and/or effects of angiotensin II. It is conceivable that in the setting of neurohormonal blockade with ACE inhibitors, β-blockers, and aldosterone antagonists, other neurohormones such as vasopressin and endothelin begin to play a more prominent role in the subsequent progression of heart failure and LV dysfunction. The current results documenting favorable short-term hemodynamic and renal effects of combined V₁A and V₂ vasopressin receptor antagonism, as well as the lack of relation of these effects to baseline markers of vasopressin.
activation, suggest that vasopressin receptor antagonism may have a future role as part of more comprehensive neurohormonal blockade for heart failure patients. Ongoing studies will document the effect of more prolonged oral therapy with this agent on symptoms and mechanistic markers such as LV remodeling and, ultimately, the effect of vasopressin blockade on the natural history of patients with heart failure and LV dysfunction.

References

Acute Hemodynamic Effects of Conivaptan, a Dual V1A and V2 Vasopressin Receptor Antagonist, in Patients With Advanced Heart Failure

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Circulation. 2001;104:2417-2423
doi: 10.1161/hc4501.099313

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/20/2417