Assessment of the Efficacy and Safety of Intravenous Conivaptan in Euvolemic and Hypervolemic Hyponatremia

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Key Words
Aquesis · Arginine vasopressin · Conivaptan · Euvolemia · Hypervolemia · Sodium · Water balance

Abstract
Background: Most cases of hyponatremia – serum sodium concentration ([Na⁺]) <135 mEq/l (<135 m M ) – are associated with an elevated plasma arginine vasopressin level. This study investigated the efficacy and tolerability of intravenous conivaptan (YM087), a vasopressin V 1A /V 2 -receptor antagonist, in treating euvolemic and hypervolemic hyponatremia. Methods: Eighty-four hospitalized patients with euvolemic or hypervolemic hyponatremia (serum [Na⁺] 115 to <130 mEq/l) were randomly assigned to receive intravenous placebo or conivaptan administered as a 30-min, 20-mg loading dose followed by a 96-hour infusion of either 40 or 80 mg/day. The primary efficacy measure was change in serum [Na⁺], measured by the baseline-adjusted area under the [Na⁺]-time curve. The secondary measures included time from first dose to a confirmed ≥4 mEq/l serum [Na⁺] increase, total time patients had serum [Na⁺] ≥4 mEq/l higher than baseline, change in serum [Na⁺] from baseline to the end of treatment, and number of patients with a confirmed ≥6 mEq/l increase in serum [Na⁺] or normal [Na⁺] (≥135 mEq/l). Results: Both conivaptan doses increased area under the [Na⁺]-time curve during the 4-day treatment (p < 0.0001 vs. placebo). From baseline to the end of treatment, the least-squares mean ± standard error serum [Na⁺] increase associated with placebo was 0.8 ± 0.8 mEq/l; with conivaptan 40 mg/day, 6.3 ± 0.7 mEq/l; and with conivaptan 80 mg/day, 9.4 ± 0.8 mEq/l. Conivaptan significantly improved all secondary efficacy measures (p < 0.001 vs. placebo, both doses). Conivaptan was generally well tolerated, although infusion-site reactions led to the withdrawal of 1 (3%) and 4 (15%) of patients given conivaptan 40 and 80 mg/day, respectively. Conclusion: Among patients with euvolemic or hypervolemic hyponatremia, 4-day intravenous infusion of conivaptan 40 mg/day significantly increased serum [Na⁺] and was well tolerated.

Introduction

Hyponatremia, defined by a serum sodium concentration ([Na⁺]) <135 mEq/l (<135 m M ) [1–3], is a common electrolyte disturbance occurring in up to 15% of hospitalized patients [4]. The disorder is seen frequently in the elderly or chronically ill patients and can be associated with substantial morbidity and mortality [2, 3, 5, 6]. In addition, as serum [Na⁺] decreases, either too far or too...
rapidly, the risk of morbidity and death increases in patients with a variety of underlying disorders [7–10].

Fluid restriction is the mainstay of treatment for patients with chronic (developing over a period >48 h) asymptomatic hyponatremia [3, 11]. Hypertonic saline and loop diuretics are therapeutic measures often used in patients with symptomatic hyponatremia or those who fail to respond to fluid restriction [3, 11]. A desirable goal for all therapies is a controlled increase of serum [Na+] (up to a maximum of 12 mEq/l per day) to avoid adverse effects associated with overly rapid correction [3, 11]. Existing therapies are suboptimal, however, because of their adverse effects and slow and unpredictable correction of serum [Na+] [1, 3, 5]. Therefore, new treatments for hyponatremia that elevate the serum [Na+] reliably and safely would be desirable.

Arginine vasopressin (AVP) plays a critical role in the regulation of body water and its serum concentration is elevated in most cases of dilutional hyponatremia [10, 12]. AVP binding to V2 receptors on kidney collecting duct epithelial cells increases apical cell membrane water permeability, which stimulates water reabsorption, thereby decreasing serum [Na+] [12, 13]. Thus, a potentially valuable pharmacologic approach for correcting dilutional hyponatremia is AVP-receptor antagonism to block this antidiuretic cascade.

Conivaptan (YM087) is a high-affinity nonpeptide antagonist of AVP V2 and V1A receptors that produces aquarexia, the renal excretion of solute-free water that is electrolyte sparing [13, 14]. Orally and intravenously administered conivaptan increased plasma osmolality (P_{osm}) and decreased urine osmolality (U_{osm}) and AVP-induced skin vasoconstriction in normal individuals [15]. In patients with advanced heart failure (New York Heart Association class III or IV), a single intravenous dose of conivaptan markedly increased urine output and significantly reduced pulmonary capillary wedge pressure [16].

Conivaptan is the first AVP-receptor antagonist approved for the treatment of dilutional hyponatremia. Several V2-receptor antagonists have also been evaluated for the treatment of other edematous disorders, including heart failure (lixivaptan and tolvaptan) [17, 18] and cirrhosis (lixivaptan, OPC-31260, and RW-351647) [19–21]. The V2-receptor antagonists may also hold promise in the treatment of polycystic kidney disease; a phase 3 clinical trial is underway to determine the efficacy and safety of tolvaptan in patients with autosomal dominant polycystic kidney disease [22].

Intravenous conivaptan (20 and 40 mg/day) is approved for the treatment of euvoletic and hypervolemic hyponatremia in hospitalized patients [23]. Intravenous conivaptan is not indicated for the treatment of congestive heart failure (CHF). The objective of the current study was to evaluate the efficacy and tolerability of intravenous conivaptan (40 and 80 mg/day) in the treatment of euvoletic and hypervolemic hyponatremia.

Methods

Patients

Eligible patients were men or women 18 years of age or older with a serum [Na+] 115 to <130 mEq/l, P_{osm} <290 mOsmol/kg H2O, fasting blood glucose <275 mg/dl (<15 mmol/l), and volume status of euvoletic (absence of pitting edema or ascites) or hypervolemic (edema), as determined by clinical assessment. The major exclusion criteria were hypovolemic hyponatremia, as indicated by clinical evidence of volume depletion or dehydration; a supine systolic blood pressure <85 mm Hg, significant ororthostatic hypotension (systolic blood pressure <80 mm Hg on standing or a decrease of >20 mm Hg from supine to standing), or uncontrolled hypertension; and uncontrolled bradyarrhythmia or tachyarrhythmia necessitating emergent pacemaker implantation or treatment. Medications known to interact with cytochrome P450 3A4 were prohibited, as were AVP, oxytocin, desmopressin and other medications used to treat hyponatremia (specifically, lithium salts, urea, and demeclocycline). Also excluded were patients expected to have hyponatremia necessitating emergent treatment during the study.

Study Design

The protocol and consent form were approved by the institutional review boards or ethics committees at all participating sites. In this multicenter, double-blind, placebo-controlled study, 84 patients with euvoletic or hypervolemic hyponatremia were randomly assigned to continuous infusions of placebo, conivaptan 40 mg/day, or conivaptan 80 mg/day for 4 days. Patients were assessed 6–9 days after completion of the treatment.

Following screening, eligible patients entered a single-blind placebo baseline phase and received a 20- to 28-hour infusion of placebo (5% dextrose and water, D5W) to establish baseline values for a number of study parameters, including serum [Na+], serum and urine electrolytes, free water clearance (FWC), U_{osm} and P_{osm}, and thirst index. Patients whose serum [Na+] was ≥133 mEq/l by the end of the baseline phase were not randomly assigned to treatment.

For the double-blind treatment phase, patients were stratified by volume status (i.e., euvoletic or hypervolemic) and randomly assigned to receive placebo or 1 of 2 dosage regimens of conivaptan, each administered as a 30-min intravenous infusion (loading dose) followed by a 96-hour continuous infusion. Conivaptan was given as a 20-mg loading dose (diluted in D5W to a total volume of 100 ml) on day 1 followed by either 40 or 80 mg/day (diluted in D5W up to a total volume of 250 ml) continuous infusion on days 1 through 4. The placebo group received a 100-ml loading dose of D3W on day 1 followed by continuous infusion of 250 ml D5W.
for 4 days. Blood samples were obtained at hours 4, 6, 10, and 24 on each day for the assessment of serum [Na\(^+\)] levels and other parameters. Patients were instructed to maintain their 24-hour sodium intake, caloric consumption, and caffeine intake at levels consistent with those observed at baseline. The protocol limited daily fluid intake to no more than 2.0 l (not including water from food).

**Study Endpoints**

The primary efficacy parameter was the change from baseline in serum [Na\(^+\)] during the course of treatment, measured by the baseline-adjusted area under the [Na\(^+\)]-time curve (AUC) from the beginning through the end of treatment. The 4 secondary efficacy parameters were (1) the time from the first dose to a confirmed ≥4 mEq/l increase from baseline in serum [Na\(^+\)]; (2) the total time from the first dose to the end of treatment during which patients had a serum [Na\(^+\)] ≥4 mEq/l higher than that observed at baseline; (3) the change in serum [Na\(^+\)] from baseline to the end of treatment (defined as the average of measurements taken at hours 4, 6, 10, and 24 on the last day of treatment); and (4) the number of patients who achieved a confirmed ≥6 mLq/l increase from baseline in serum [Na\(^+\)] or a normal serum [Na\(^+\)] (≥135 mEq/l). The secondary endpoints are based directly on serum [Na\(^+\)] measurements and include thresholds of change that correspond to a clinically meaningful increase in serum [Na\(^+\)] (i.e., ≥4 mEq/l) and a 5% increase from a typical baseline of 120 mEq/l (i.e., ≥6 mEq/l). Thus, these endpoints offer a direct, simple, and accurate method of assessing how quickly and for how long clinically meaningful efficacy was achieved with conivaptan.

Other efficacy parameters included the change from baseline in FWC and effective water clearance (EWC), net fluid loss, Urine Na, Urine K, and plasma AVP, aldosterone, epinephrine, and norepinephrine levels and renin activity. FWC and EWC were calculated as follows:

\[
FWC = V \left(1 - \frac{U_{\text{osm}}}{P_{\text{osm}}} \right)
\]

and

\[
EWC = V \left(1 - \frac{\text{Urine}[\text{Na}^+] + \text{Urine}[\text{K}^+]}{\text{Serum}[\text{Na}^+] + \text{Serum}[\text{K}^+]} \right),
\]

where V = urine volume and [K\(^+\)] = potassium concentration.

**Sample Size**

Eighty-four patients (28 per group) were considered adequate to provide 90% power to detect a 104 mEq/l h/l change in the baseline-adjusted AUC through 4 days, calculated using the t test formula for 2 independent groups and assuming a dropout rate of 20% [24].

**Statistical Analyses**

The efficacy analyses were conducted using a modified intent-to-treat approach and included all randomized patients who had at least 1 baseline serum [Na\(^+\)] measurement, received at least 1 dose of study medication, and had at least 1 valid efficacy measurement. The effect of treatment on baseline-adjusted AUC was determined according to an analysis of covariance model, in which the treatment, treatment center, and each patient’s volume status (euvolemic or hypervolemic) were the factors and the baseline serum [Na\(^+\)] was the covariate. The threshold of statistical significance of the interactions between treatment and baseline serum [Na\(^+\)], treatment center, and volume status was 0.1. The baseline serum [Na\(^+\)] for each patient was the average of all measurements during a 24-hour baseline period. The statistical comparisons between conivaptan and placebo were performed with Dunnett’s two-sided multiple test (threshold of significance, 0.05) [25, 26].

The log-rank test and the Cox proportional hazards model were used for between-group comparisons for the time from first dose to a confirmed ≥4 mEq/l increase from baseline in serum [Na\(^+\)]. The total time from first dose to treatment end during which patients had a ≥4 mEq/l increase from baseline in serum [Na\(^+\)] and changes in the serum [Na\(^+\)] from baseline were analyzed using the analysis of covariance model. The number of patients with a ≥6 mEq/l increase from baseline in serum [Na\(^+\)] or normal serum [Na\(^+\)] (≥135 mEq/l) at any time during treatment was analyzed using the Cochran-Mantel-Haenszel procedure, stratified by volume status. All other efficacy parameters were summarized using descriptive statistics.

**Results**

**Treatment and Follow-Up**

Of 104 patients who entered the placebo baseline period, 88 patients were randomized and 84 patients received 4-day intravenous treatment with placebo, conivaptan 40 mg/day, or conivaptan 80 mg/day (fig. 1).

The study population was evenly divided between men and women; the mean age was 74 years (table 1). The proportions of patients with euvolemic and hypervolemic hyponatremia were equivalent across the 3 groups; two thirds of the population had euvolemic hyponatremia. The median duration of hyponatremia was comparable in the 3 groups (3–5 days). The most common single causes of dilutional hyponatremia were CHF and syndrome of inappropriate antidiuretic hormone secretion. There were no differences between the groups regarding mean baseline serum [Na\(^+\)], other baseline characteristics, or comorbidity.
Primary and Secondary Efficacy Outcomes

Conivaptan 40 and 80 mg/day produced significantly greater mean increases in baseline-adjusted serum [Na⁺] AUC than did placebo throughout the study (p < 0.001 for both conivaptan groups; table 2). However, the difference between the 40 and 80 mg/day groups was not statistically significant.

A mean serum [Na⁺] increase ≥4 mEq/l occurred by hour 24 in the group given conivaptan 40 mg/day and by hour 10 in the group given 80 mg/day, whereas the placebo group did not demonstrate this increase after a 4-day infusion (table 2; fig. 2). At hour 24 during the treatment phase, the least squares (LS) mean ± SE increase from baseline in serum [Na⁺] was significantly higher with conivaptan 40 mg/day (6.4 ± 0.7 mEq/l) and 80 mg/day (8.1 ± 0.7 mEq/l) compared with placebo (0.4 ± 0.7 mEq/l; p < 0.001 for both groups). Similar results were observed at hour 48. At hour 72, patients in the conivaptan 40 and 80 mg/day groups experienced significantly higher increases from baseline in serum [Na⁺] (6.9 ± 0.8 mEq/l and 8.8 ± 0.7 mEq/l, respectively) than the placebo group (1.9 ± 0.8 mEq/l; p < 0.001 for both conivaptan groups).

Both conivaptan doses were significantly superior to placebo in each efficacy outcome measure (table 2). The median time to a confirmed ≥4 mEq/l increase in serum [Na⁺] (for those who achieved this increase) was approximately 24 h in each conivaptan group. The 9 placebo patients who achieved a confirmed increase of ≥4 mEq/l did so only at the end of the 4-day study; therefore, the median event time could not be estimated. The total time that serum [Na⁺] was at least 4 mEq/l above baseline was significantly longer in both conivaptan groups than in the placebo group (p < 0.001 vs. placebo). The LS mean change from baseline in serum [Na⁺] at the end of treatment was significantly greater among patients given conivaptan than among those given placebo (p < 0.001 for both conivaptan groups). Compared with those given placebo, significantly more patients in both conivaptan groups achieved a confirmed normal serum [Na⁺] or an increase of ≥6 mEq/l from baseline (p < 0.001). Increases in serum [Na⁺] from baseline were maintained 6–9 days after the treatment period (table 3).

Other Outcomes

Conivaptan 40 or 80 mg/day increased the FWC and EWC, whereas placebo did not (table 3; fig. 3), demonstrating conivaptan’s aquaretic effect. The greatest increase in FWC occurred on study day 1 in both conivaptan groups and corresponded to the largest increase in serum [Na⁺]. Consistent with the change in water clearance, P_{osm} increased from baseline with conivaptan on
study day 1, while both $U_{osm}$ and urine [Na$^+$] decreased (table 3). Conivaptan did not cause clinically significant changes in serum [K$^+$].

Fourteen (54%) patients given conivaptan 80 mg/day, 11 (38%) given 40 mg/day, and 6 (21%) given placebo violated the 2 liters/day fluid restriction during the treatment period. Despite this, serum [Na$^+$] continued to increase faster in the 2 conivaptan groups than in the placebo group during the treatment phase.

Both conivaptan doses caused a greater increase in net fluid loss on study days 1 and 2. Compared with placebo, conivaptan 40 and 80 mg/day were associated with greater body weight reduction on days 1 (~0.1, ~1.8, and ~1.2 kg, respectively) and 4 (0, ~0.4, and ~1.7 kg, respectively).

Plasma aldosterone, epinephrine, and norepinephrine concentrations were similar in the placebo and conivaptan groups. Patients given conivaptan 80 mg/day demonstrated higher plasma renin activity than those given placebo or conivaptan 40 mg/day. Unlike patients given placebo, those who received conivaptan 40 and 80 mg/day demonstrated a small dose-dependent increase from baseline on day 4 in plasma AVP concentration (~0.3, 0.5, and 1.5 pg/ml, respectively).

### Safety and Tolerability

The incidence of death in all groups did not appear dose related (table 4). The number of patients with serious AEs and the rates of discontinuation for any reason were
comparable in the 3 groups. The rate of discontinuation due to AEs among patients given conivaptan 80 mg/day was 19.2%, versus 6.9% among those given conivaptan 40 mg/day and 10.3% among those given placebo. Drug-related, treatment-emergent AEs were observed in 55.2 and 65.4% of patients given conivaptan 40 and 80 mg/day, respectively, compared with 24.1% of patients given placebo.

Conivaptan was associated with a greater incidence of AEs than was placebo. The most common AEs included infusion-site reactions, hypotension, postural hypotension, pyrexia, hyperkalemia, and infusion-site thrombo-

### Table 2. Efficacy outcomes of treatment with intravenous conivaptan 40 or 80 mg/day

<table>
<thead>
<tr>
<th>Study endpoints</th>
<th>Placebo (n = 29)</th>
<th>IV conivaptan 40 mg/day (n = 29)</th>
<th>IV conivaptan 80 mg/day (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in baseline adjusted serum sodium AUC, LS mean (SE) mEq · h/l</td>
<td>12.9 (61.2)</td>
<td>490.9 (56.8)*</td>
<td>716.6 (60.4)*</td>
</tr>
<tr>
<td>Secondary efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total time during treatment phase that patients had serum [Na⁺] ≥4 mEq/l from baseline, median h (95% CI)</td>
<td>NE</td>
<td>23.7 (10.0, 24.0)*</td>
<td>23.4 (6.0, 24.0)*</td>
</tr>
<tr>
<td>Change in serum [Na⁺] from baseline to end of treatment, LS mean (SE) h</td>
<td>14.2 (5.25)</td>
<td>53.2 (5.17)*</td>
<td>72.7 (5.43)*</td>
</tr>
<tr>
<td>Patients with an increase in serum [Na⁺] ≥6 mEq/l or a serum [Na⁺] ≥135 mEq/l</td>
<td>0.8 (0.80)</td>
<td>6.3 (0.74)*</td>
<td>9.4 (0.79)*</td>
</tr>
</tbody>
</table>

CI = Confidence interval; NE = not estimable. * p < 0.001.

### Table 3. Assessments of treatment with intravenous conivaptan 40 or 80 mg/day

<table>
<thead>
<tr>
<th>Study endpoints</th>
<th>Placebo (n = 29)</th>
<th>IV conivaptan 40 mg/day (n = 29)</th>
<th>IV conivaptan 80 mg/day (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum [Na⁺] from baseline to 6–9 days after the end of treatment, mean (SD) mEq/l</td>
<td>5.2 (5.1); n = 17</td>
<td>8.1 (5.5); n = 13</td>
<td>4.7 (7.9); n = 20</td>
</tr>
<tr>
<td>Change from baseline in FWC on day 1, LS mean (SE) ml</td>
<td>−306.3 (341.79)</td>
<td>1,837.1 (357.62)*</td>
<td>1,763.0 (374.88)*</td>
</tr>
<tr>
<td>Change from baseline in EWC on day 1, LS mean (SE) ml</td>
<td>−244.6 (368.17)</td>
<td>1,733.2 (390.33)*</td>
<td>1,860.0 (400.38)*</td>
</tr>
<tr>
<td>Change from baseline in P_omp on day 4, mean (SD) mOsm/kg</td>
<td>2.3 (7.88)</td>
<td>14.0 (16.32)</td>
<td>19.6 (10.69)</td>
</tr>
<tr>
<td>Change from baseline in U_omp on day 1, mean (SD) mOsm/kg</td>
<td>64.7 (188.54)</td>
<td>−488.6 (337.59)</td>
<td>−318.7 (155.05)</td>
</tr>
<tr>
<td>Change from baseline in urine [Na⁺] on day 1, mean (SD) mEq/l</td>
<td>6.5 (19.34)</td>
<td>−36.7 (42.96)</td>
<td>−28.6 (31.18)</td>
</tr>
<tr>
<td>Change from baseline in serum [K⁺] at hour 24 on day 1, mean (SD) mEq/l</td>
<td>0.00 (0.35)</td>
<td>0.11 (0.39)</td>
<td>−0.04 (0.67)</td>
</tr>
<tr>
<td>Change from baseline in serum [K⁺] at hour 24 on day 4, mean (SD) mEq/l</td>
<td>0.08 (0.66)</td>
<td>0.31 (0.50)</td>
<td>0.15 (0.60)</td>
</tr>
</tbody>
</table>

* p < 0.001; *+ p = 0.002; *++ p = 0.001.
Intravenous Conivaptan in Hyponatremia

**Fig. 2.** Mean serum [Na⁺] (a) and mean change (LS) from baseline in serum [Na⁺] (b) at baseline (hour 0) and each measurement time. T bars indicate SE. *p = 0.025; †p = 0.034; ‡p = 0.002; §p = 0.008; ||p < 0.001.

**Fig. 3.** Effect of conivaptan on the mean change (LS) from baseline in FWC (a) and EWC (b) during treatment. T bars indicate SE. a *p < 0.001; †p = 0.03; ‡p = 0.01. b *p = 0.001; †p = 0.002; §p = 0.05.
sis (table 4). The pyrexia appeared to be associated with infusion-site reactions. Transient hypotension was an expected pharmacodynamic effect of conivaptan because of aquarexis resulting in volume contraction. The evaluation of hypotension was not defined in the protocol, and investigators determined the incidence, severity, and duration of such events at their discretion. The investigators did not withdraw any patient given conivaptan from the study because of hypotension. No patient given conivaptan discontinued treatment, required pharmacologic intervention, or had complications because of hypotension.

Significantly more patients in the groups given conivaptan experienced infusion-site reactions than those in the placebo group. Infusion-site reactions led to discontinuation in 1/29 (3.4%) and 4/26 (15.4%) patients receiving 40 and 80 mg/day, respectively, compared with none in the placebo group.

Six patients (1 given placebo, 2 given conivaptan 40 mg/day, and 3 given conivaptan 80 mg/day) developed renal dysfunction or worsened renal function, all of whom had a history of heart disease or CHF (ischemic, hypertensive, or idiopathic). Two of these patients entered the study with preexisting renal insufficiency or renal failure. Two patients, 1 given placebo and 1 given conivaptan 80 mg/day, died in the poststudy phase, when the cardiac event myocardial infarction contributed to their death. The other 4 patients exhibited mild or moderate transient increases in blood urea nitrogen or creatinine measurements, or both, that resolved shortly after cessation of treatment.

One patient given conivaptan 40 mg/day with a history of gall bladder carcinoma with metastasis in the liver had significantly elevated liver enzymes and white blood cell levels on study day 2 and subsequently died from liver failure and concurrent Gram-negative sepsis. The abnormalities in liver function were believed to be due to the gall bladder carcinoma and unlikely related to the conivaptan therapy. One patient given conivaptan 80 mg/day had elevated liver enzyme levels during the course

### Table 4. Summary of AEs, discontinuations, and changes from baseline in systolic and diastolic blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 29)</th>
<th>IV conivaptan 40 mg/day (n = 29)</th>
<th>IV conivaptan 80 mg/day (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>4 (13.8%)</td>
<td>1 (3.4%)</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Patients with 1 or more serious AEs</td>
<td>6 (20.7%)</td>
<td>8 (27.6%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Discontinuations (all)</td>
<td>6 (20.7%)</td>
<td>7 (24.1%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Discontinuations (AEs)</td>
<td>3 (10.3%)</td>
<td>2 (6.9%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Patients with 1 or more drug-related AEs</td>
<td>7 (24.1%)</td>
<td>16 (55.2%)</td>
<td>17 (65.4%)</td>
</tr>
</tbody>
</table>

**Most common AEs**

- Injection-site phlebitis
- Hypotension
- Postural hypotension
- Injection-site inflammation
- Pyrexia
- Hyperkalemia
- Injection-site thrombosis

**Changes from baseline in blood pressure, mean (SD) mm Hg**

**Supine systolic blood pressure**

- Baseline 122 (20)
- Day 1 change from baseline 4.0 (17)
- End of treatment change from baseline 8.3 (17)

**Supine diastolic blood pressure**

- Baseline 71 (13)
- Day 1 change from baseline 2.3 (9.7)
- End of treatment change from baseline 0.8 (10)

### Table 4 continued

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 29)</th>
<th>IV 40 mg/day (n = 29)</th>
<th>IV 80 mg/day (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection-site phlebitis</strong></td>
<td>2 (6.9%)</td>
<td>7 (24.1%)</td>
<td>8 (30.8%)</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>2 (6.9%)</td>
<td>4 (13.8%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td><strong>Postural hypotension</strong></td>
<td>0</td>
<td>4 (13.8%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td><strong>Injection-site inflammation</strong></td>
<td>0</td>
<td>2 (6.9%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td><strong>Pyrexia</strong></td>
<td>0</td>
<td>3 (10.3%)</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
<td>1 (3.4%)</td>
<td>0</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td><strong>Injection-site thrombosis</strong></td>
<td>0</td>
<td>3 (10.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*p = 0.004; + p = 0.008.

*Events occurring in ≥10% of any treatment group.
Hyponatremia

In hospitalized patients with euvoletic or hyponatremia, conivaptan (40 and 80 mg/day) significantly increased baseline-adjusted serum [Na⁺] AUC and was significantly more effective than placebo in improving all 4 secondary efficacy outcomes. The differences in efficacy between the 40- and 80-mg/day dosages were not statistically significant, however. Conivaptan raised serum [Na⁺] within 6 h after the drug was administered, and this increase continued through the infusion period, with clinically relevant increases by hour 24. In contrast, patients given placebo who also underwent fluid restriction did not demonstrate any significant changes in serum [Na⁺].

The increases in serum [Na⁺] were a result of the marked increases in free water excretion that resulted from the aquaretics produced by conivaptan’s V₂-receptor antagonism. This is confirmed by the changes in EWC, which reflect the drug’s primary pharmacodynamic effect. As expected, the aquaretics resulted not only in increased serum [Na⁺] but also increased P_o,sm and reduced body weight. The changes in EWC were most marked during the first 24 h of conivaptan administration and are consistent with the predominant increase in serum [Na⁺] that occurs at that time. One possible reason for the more marked aquaretics in the first 24 h is that most of the excess free water in patients with dilutional hyponatremia may be more easily mobilized with the initial V₂-receptor antagonism, while the subsequent free water excretion may be limited by systemic and intrarenal hemodynamic factors activated by the initial aquaretics. Another explanation for larger changes in EWC within the first 24 h may be that the bolus loading dose on day 1, in combination with the following continuous infusion, produced a higher maximum drug concentration and increased free concentrations of conivaptan, which is highly protein bound [23].

A potential secondary benefit of conivaptan was also observed as a result of the aquaretics, namely, the increased serum [Na⁺] in the conivaptan treatment groups despite their higher incidence of fluid-restriction violations when compared with the placebo group. This indicates that patients given conivaptan were able to tolerate greater fluid intake with less detrimental effects of water retention than would have otherwise been the case. This finding is particularly important for hospitalized patients, who frequently have an obligate requirement for fluid administration.

Conivaptan was generally well tolerated, particularly the 40 mg/day dosage. Although the study was small, the incidences of deaths, serious AEs, and discontinuations for any reason were comparable among patients given conivaptan or placebo. Discontinuations due to AEs were higher among patients given conivaptan 80 mg/day and were largely attributed to local infusion-site reactions. To minimize the risk of vascular irritation, conivaptan should be administered through large veins and the infusion site should be changed every 24 h [23].

Although drug-related treatment-emergent AEs occurred more frequently among patients receiving conivaptan and appeared to be dose related, infusion-site reactions did not account for all of these events. Hypotension and renal dysfunction were also more frequent among patients given conivaptan. The former is of interest because conivaptan is an antagonist of both V₁A and V₂ receptors, and V₁A receptors are responsible for the vasopressor response to AVP by virtue of increasing vascular smooth muscle contraction. None of the patients given conivaptan had hypotension of a sufficient magnitude to lead them to withdraw from the study, however, and the overall blood pressure changes with conivaptan were not
clinically significant. In addition, only increased orthostatic symptoms were noted predominantly after the first day of conivaptan therapy, after maximum exposure to conivaptan had passed. These blood pressure results were coincident with increases in blood urea nitrogen and creatinine, consistent with causation of all of these effects by the contraction of the extracellular and intravascular fluid spaces associated with aquaresis.

Neurologic symptoms secondary to osmotic demyelination from overly rapid correction of hyponatremia were notably absent in this study. The study protocol called for the cessation of conivaptan treatment if the correction of serum $[Na^+]$ exceeded 12 mEq/l in the first 24 h. This limit was exceeded in only 2 patients, and no neurologic symptoms related to overly rapid correction of serum $[Na^+]$ were noted in any patients. Although the risk of overly rapid correction exists with conivaptan treatment, as it does with hypertonic saline, it appears to be rare in view of the magnitude of aquaresis produced by these doses, and this risk can be managed through the cessation of therapy coupled with increased free water intake.

The results from this study suggest that conivaptan 40 mg/day produces a prompt aquaresis with consequent increases in serum $[Na^+]$ in patients with euvolemic or hypervolemic hyponatremia. The corrections in serum $[Na^+]$ were significant and clinically relevant. In addition to increased serum $[Na^+]$, patients given conivaptan were able to tolerate an increased volume of fluid and therefore had a lesser need for fluid restriction. Thus, conivaptan will likely address an important clinical need for reliable and well-tolerated treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients.

Appendix

In addition to the authors, the following investigators and institutions participated in this clinical trial: Rajiv Agarwal, Indiana University, Richard Roudebush VA Medical Center, Indianapolis, Ind.; Lidia Arcavi, Kaplan Medical Center, Rechovot, Israel; Harry Colfer, Nisus Research, Northern Michigan Hospital, Petoskey, Mich.; Jalal Ghali, Cardiac Centers of Louisiana, LLC, Shreveport, La.; Mark Gottfried, Pulmonary Associates, PA, Phoenix, Ariz.; Thomas Gray, Pretoria East Hospital, Pretoria, South Africa; Lukas Haragsim, University of Oklahoma Health Sciences Center, Oklahoma City, Okla.; Steven Jennison, Prairie Education and Research Cooperative, Springfield, Ill.; Murray Katz, Southern Arizona VA Health Care System Hospital, Tucson, Ariz.; Mark Klapolz, St. Vincent’s Hospital and Medical Center, New York, N.Y.; Norberto Kriyov, Rambam Medical Center, Haifa, Israel; Barton Levine, VAGLAHS West Los Angeles, Los Angeles, Calif.; Stephen Mallon, University of Miami, Jackson Memorial Medical Center, Miami, Fla.; Alon Tomas Marmor, Rebeka Sfeif Government Hospital, Heart Institute, Safed, Israel; Hussein Pahad, Milpark Hospital, Johannesburg, South Africa; Mark Paller, University of Minnesota Research Services Organization, Minneapolis, Minn.; Leonardo Reisin, Barzilai Medical Center, Ashkelon, Israel; David Ross, Plantation General Hospital, Plantation, Fla.; Rene Roux, Bureau des Internisthes, Drummondville, Canada; Yoram Shenker, University of Wisconsin-Madison Clinical Science Center/Hospital, Madison, Wisc.; Timothy Sole, Frere Hospital, East London, South Africa; Johann Viljoen, G07 Medi-Clinic, Bloemfontein, South Africa.

References

Intravenous Conivaptan in Hyponatremia


