Aquaretic Effect of Lixivaptan, an Oral, Non-Peptide, Selective V2 Receptor Vasopressin Antagonist, in New York Heart Association Functional Class II and III Chronic Heart Failure Patients

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OBJECTIVES
The purpose of this study was to examine the renal effects of a V2 receptor arginine vasopressin (AVP) antagonist in heart failure.

BACKGROUND
Arginine vasopressin has been implicated in the renal water retention and dilutional hyponatremia associated with chronic heart failure.

METHODS
We examined the effects of the oral, non-peptide, selective V2 receptor antagonist lixivaptan in 42 diuretic-requiring patients with mild-to-moderate heart failure in a randomized, double-blind, placebo-controlled, ascending single-dose study. After overnight fluid deprivation, patients received single-blind placebo on day –1 (baseline) and double-blind study medication (placebo [n = 12] or lixivaptan 10, 30, 75, 150, 250, or 400 mg [n = 5 per dose group]) on day 1, followed by 4 h of continued fluid restriction and additional 20 h with ad libitum fluid intake.

RESULTS
At all but the 10-mg dose, lixivaptan produced a significant and dose-related increase in urine volume over 4 h, compared with placebo. During 24 h, increases in urine volume ranged from 1.8 l with placebo to 3.9 l after the 400-mg lixivaptan dose (p < 0.01). These increases in urine volumes were accompanied by significant increases in solute-free water excretion. At higher doses, serum sodium was significantly increased; AVP antagonism was well tolerated in these patients.

CONCLUSIONS
These observations confirm a role for AVP in the renal water retention associated with heart failure and suggest that the V2 receptor antagonist lixivaptan may be a promising therapeutic agent for the treatment of heart failure. (J Am Coll Cardiol 2006;47:1615–21) © 2006 by the American College of Cardiology Foundation

A major cause of morbidity and mortality in chronic heart failure (CHF) relates to the renal sodium and water retention characteristic of patients with symptomatic disease (1). Currently available diuretic therapy may initiate or exacerbate the dilutional hyponatremia associated with heart failure. In this context, it should be noted that hyponatremia is an indicator of poor prognosis in heart failure patients (2,3). An agent that can increase solute-free water excretion may thus facilitate diuresis, prevent or correct hyponatremia, and possibly improve outcome in patients with heart failure.

The role of arginine vasopressin (AVP) in the water retention and dilutional hyponatremia of heart failure remains controversial. Observations from experimental models support a role for AVP in the renal pathophysiology of heart failure (4–6). Moreover, plasma AVP concentrations are usually elevated in patients with heart failure and correlate, in general, with the clinical and hemodynamic severity of the disease (7–10), suggesting an important role for AVP in disease progression. Szatalowicz et al. (7) were the first to document detectable plasma AVP concentrations in over 80% of hyponatremic heart failure patients, despite a degree of hypo-osmolality that would normally suppress AVP to undetectable levels in healthy subjects. However, the ability to fully elucidate the role of AVP in heart failure and the potential benefits of antagonizing it has awaited the development of orally active, non-peptide AVP receptor antagonists (11,12). In this regard, renal or V2 receptor AVP antagonists have been shown to reverse water retention and hyponatremia and to decrease renal medullary aquaporin-2 (AQP-2) in experimental CHF (13,14). The effects of such agents in human heart failure have been incompletely studied.

Lixivaptan (or VPA-985) (Cardiokine Inc., Philadelphia, Pennsylvania) is a potent, orally active, non-peptide competitive AVP antagonist that is selective for the V2 receptor (15). To further evaluate the role of the V2 receptor in heart failure and to determine the pharmacological potential of this specific agent, we evaluated the effects of lixivaptan on solute-free water excretion and on other parameters in 42 New York Heart Association (NYHA) functional class II or III heart failure patients.

METHODS
This was a randomized, double-blind, placebo-controlled, ascending, single-dose safety, efficacy, and tolerability study.
of lixivaptan in patients with chronic symptomatic heart failure requiring diuretic therapy. Subjects were enrolled at two centers: the University of Colorado Health Sciences Center and the University of Iowa Hospitals and Clinics. The investigational review boards and the General Clinical Research Center (GCRC) scientific advisory committees of each participating institution approved the study protocol, and all patients provided written informed consent.

**Subjects.** Adult men or women with NYHA functional class II or III systolic heart failure (left ventricular ejection fraction ≤35% documented within three months of study enrollment), serum sodium concentration of 120 to 140 mmol/l, and serum potassium concentration in the normal range were eligible for the study. Patients were excluded from study for a variety of medical reasons including a systolic blood pressure of ≤90 mm Hg, hypertrophic obstructive or restrictive cardiomyopathy, significant valvular obstruction, sustained ventricular tachycardia, or ventricular fibrillation within 30 days, recent myocardial infarction or cardiac surgery, intrinsic renal or hepatic insufficiency, or the inability to withhold heart failure medications other than digitalis for at least 48 h before study drug administration. Subjects with study drug dose administration. However, if a patient was not used, because of potential for infection, albeit small for measurement of urine volume, electrolytes, creatinine, and osmolality were also performed on both days. Urine was collected in timed increments of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h to examine the time course of effect of the study medication. Neurohormones, including plasma renin activity, aldosterone, norepinephrine, endothelin-1, and atrial natriuretic peptide, were measured at 0, 2, 4, 8, and 24 h. After patients had been supine for at least 30 min, plasma AVP levels were assessed at 0, 0.5, 1, 2, 4, 8, 12, and 24 h. Food and fluids, including water, were prohibited for 8 h before and 4 h after the mock or study drug dose administration. However, if a patient urinated >3 h during the 4-h post-dose period on day 1 or if the investigator thought that patient safety would be compromised by a continued fast, the patients were allowed free access to water before the 4-h time point.

**Statistical methods.** Kruskal-Wallis tests were performed to examine the equivalence of dose groups on baseline characteristics. After normalizing transformations were applied to adjust for skewness, mixed model longitudinal data analysis was performed using SAS PROC MIXED (SAS Institute, Cary, North Carolina) to determine the effects of dose, time, and day (baseline [day −1] and placebo vs. active treatment) on urine volume, urine flow, urine osmolality, solute-free water clearance, serum osmolality, serum sodium, and plasma vasopressin concentration. For each dependent variable, the best fitting model was determined by the smallest value of Akaike’s information criterion. The Tukey-Kramer multiple comparison adjustment for p values was applied to all longitudinal data analysis. Differences among dose groups between day −1 and placebo vs. active treatment) on urine volume on day −1 and day 1), serum electrolytes, osmolality, creatinine, and urea nitrogen were measured at 0, 1, 2, 4, 8, 12, and 24 h of the study period. Twenty-four-hour regular urine collections (bladder catheters were not used, because of potential for infection, albeit small) for measurement of urine volume, electrolytes, creatinine, and osmolality were also performed on both days. Urine was collected in timed increments of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h to examine the time course of effect of the study medication. Neurohormones, including plasma renin activity, aldosterone, norepinephrine, endothelin-1, and atrial natriuretic peptide, were measured at 0, 2, 4, 8, and 24 h. After patients had been supine for at least 30 min, plasma AVP levels were assessed at 0, 0.5, 1, 2, 4, 8, 12, and 24 h. Food and fluids, including water, were prohibited for 8 h before and 4 h after the mock or study drug dose administration. However, if a patient urinated >3 h during the 4-h post-dose period on day 1 or if the investigator thought that patient safety would be compromised by a continued fast, the patients were allowed free access to water before the 4-h time point.

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RESULTS

Demographics and baseline characteristics of patients. Forty-two patients with congestive heart failure enrolled in and completed the study. Given the randomization scheme of 5 active to 2 placebo subjects per dose group, a total of 12 patients were allocated to the placebo group. The baseline demographic characteristics of these patients, by dose group, are presented in Table 1. Although there were differences in race, gender, and age between the groups, the baseline control urine data was comparable (not shown).

Effect on urine flow. Baseline (day −1) urine volume did not change significantly during 24 h of observation in patients assigned to the six different doses groups; there was however a slight, although insignificant, increase during the 6-to-8-h period, which corresponded to the postprandial period. On day 1, significant dose-related increases in urine volume were observed at lixivaptan doses greater than 10 mg. This effect was particularly apparent at all doses greater than 10 mg during the first 4 h (data not shown). During 24 h, increases in urine volume ranged from 1.8 l with placebo to 3.9 l after the 400-mg dose of lixivaptan (p < 0.01).

Urinary flow rate was increased for all doses groups (Fig. 1). At hour 1, urinary flow was significantly greater with doses of 75 mg (p < 0.05), 250 mg (p < 0.01), and 400 mg (p < 0.01) as compared with placebo. Urine flow rate was significantly greater at 2 h with doses of 30, 75, 150, 250, and 400 mg (all p < 0.001) compared with the placebo. At hour 4, urine flow remained significantly higher with doses of 250 mg (p < 0.001) and 400 mg (p < 0.001) as compared with placebo. Urine flow rate remained significantly higher with a dose of 400 mg (p < 0.01) as compared with the placebo until hour 8. Significant differences in urine flow rate occurred at 2 h between baseline (day −1) and treatment period (day 1) for 30 mg and higher doses (all p < 0.001). At hour 4, urine flow rate remained significantly higher with the 250-mg (p < 0.001) and 400-mg (p < 0.001) doses as compared with the baseline study day. Urine flow rate was still significantly higher with the 400-mg dose (p < 0.01) at 6 and 8 h as compared with the baseline.

Effect on urinary osmolality. At baseline, urinary osmolality was on average elevated consistent with the water-retaining nature of these subjects. Significant reductions in urinary osmolality were achieved in all patients administered lixivaptan as compared with the placebo group. This decrease and its duration was dose-related (linear p < 0.001 for dose response). By hour 1, urine osmolality decreased significantly with doses of 30 mg (p < 0.01), 150 mg (p < 0.05), 250 mg (p < 0.001), and 400 mg (p < 0.01) compared with placebo. The minimal urine osmolality values were achieved within the first 2 h after drug administration for all groups 10 mg and higher with the greatest response with a dose of 400 mg. At hour 4, urine osmolality remained significantly lower with doses of 75, 150, 250, and 400 mg (all p < 0.001) as compared with placebo. At 6 h, urine osmolality remained significantly lower with a dose of 400 mg (p < 0.01) as compared with placebo. Urine osmolality was significantly lower with doses of 30 mg (p < 0.001), 75 mg (p < 0.01), 150 mg (p < 0.001), 250 mg (p < 0.01), and 400 mg (p < 0.001) during the treatment period (day 1) as compared with day −1 at hour 2. Urine osmolality remained significantly lower with doses of 75 mg (p < 0.05), 150 mg (p < 0.01), 250 mg (p < 0.001), and 400 mg (p < 0.001) as compared with placebo.

Table 1. Characteristics of the CHF Patients by Dose Group

<table>
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<tr>
<th>Characteristics</th>
<th>Placebo (n = 12)</th>
<th>10 mg (n = 5)</th>
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<th>150 mg (n = 5)</th>
<th>250 mg (n = 5)</th>
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<td>3</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

CHF = chronic heart failure; NYHA = New York Heart Association; SD = standard deviation.

0.001) at hour 4 and remained lower with doses of 150 mg (p < 0.01), 250 mg (p < 0.01), and 400 mg (p < 0.001) at hour 6 as compared with baseline (day 1).

No significant differences were observed for urinary sodium, potassium, chloride, magnesium, or urea nitrogen excretion (data not shown).

**Effect on solute-free water excretion.** Lixivaptan dramatically increased solute-free water excretion during the first 2-h period after study drug administration as compared with the placebo (Fig. 2). During the 0-to-2-h period, solute-free water excretion was significantly greater with doses of 30 mg (p < 0.05), 75 mg (p < 0.001), 150 mg (p < 0.001), 250 mg (p < 0.01), and 400 mg (p < 0.001) compared with placebo. Solute-free water excretion was significantly greater during the 2-to-4-h period with doses of 10 mg (p < 0.05), 30 mg (p < 0.05), and 75, 150, 250, 400 mg (all p < 0.001) compared with the placebo. During the 4-to-6-h period, solute-free water excretion remained significantly greater with doses of 250 mg (p < 0.01) and 400 mg (p < 0.01) compared with the placebo. Although solute-free water excretion remained positive for the 250- and 400-mg doses, the effect did not reach significance at the 6-to-8-h period. Peak effects ranged from 3 ml/min after 30 mg to 5.7 ml/min after 400 mg; this peak effect occurred within the first 2-h period after administration. Compared with baseline (day −1), solute-free water excretion was significantly greater with doses of 30 mg (p < 0.001), 75 mg (p < 0.01), 150 mg (p < 0.001), 250 mg (p < 0.01), and 400 mg (p < 0.001) during the first 2-h period and during the 2-to-4-h period with doses of 10 mg (p < 0.05), 30 mg.
(p < 0.05), 75 mg (p < 0.05), 150 mg (p < 0.001), 250 mg (p < 0.05), and 400 mg (p < 0.05) during the treatment period (day 1).

**Effect on serum osmolality, serum sodium, and serum electrolytes.** At hour 2, serum osmolality was significantly higher with doses of 150 mg (p < 0.01) and 400 mg (p < 0.05) compared with the placebo. Serum osmolality was also significantly higher with a dose of 400 mg at hour 4 (p < 0.01) and hour 8 (p < 0.05) compared with the placebo. A significantly higher serum osmolality occurred on the treatment period (day 1) as compared with baseline (day −1) at doses of 75 mg (p < 0.05), 150 mg (p < 0.05), and 250 mg (p < 0.05) at hour 2. At hour 4, serum osmolality remained significantly higher with doses of 75 mg (p < 0.05), 250 mg (p < 0.01), and 400 mg (p < 0.05) compared with the baseline (day −1).

At hour 2, serum sodium concentration was significantly higher with doses of 150 mg (p < 0.05) and 250 mg (p < 0.05), and at hour 4 with doses of 150 mg (p < 0.001) and 250 mg (p < 0.05) compared with baseline (day −1). After active study drug administration, no significant differences were seen in serum chloride, magnesium, blood urea nitrogen, and potassium concentrations when compared with placebo or baseline (day −1) (data not shown).

**Effect on plasma concentration of vasopressin and other hormones.** At time 0.5 h, plasma AVP concentrations were similar for all doses. By 2 h, a dose of 400 mg was associated with an increase in AVP concentration as com-

![Figure 2.](image-url)
pared with placebo (2.21 ± 1.04 vs. 0.83 ± 0.64 pg/ml, p < 0.05). Arginine vasopressin concentration increased significantly with doses of 150 mg (p < 0.05), 250 mg (p < 0.001), and 400 mg (p < 0.001) as compared with placebo at hour 4. Moreover, AVP concentrations were significantly higher with doses of 250 mg and 400 mg from 2 to 8 h compared with baseline (day −1) (p < 0.05). However, the maximum AVP concentration after study drug administration did not exceed 3.5 pg/ml, on average, or 6.6 pg/ml in any individual patient. No significant differences occurred for plasma renin, aldosterone, atrial natriuretic peptide, endothelin-1, and norepinephrine as compared with placebo or baseline (day −1) (data not shown).

**Tolerability and adverse effects.** The study medication was well tolerated in these heart failure patients. There were no serious adverse events reported. Four events were considered potentially serious (two possibly study drug related, tachyarrhythmia and bradyarrhythmia) but resolved with appropriate medical intervention. The most frequent adverse events of any sort included diarrhea (three), headache (two), dizziness (three), orthostatic tachycardia (two), dry mouth (two), and flatulence (two). There were no consistent positive or negative trends in clinical chemistry, ECGs, or vital signs.

**DISCUSSION**

This study represents the most extensive evaluation of the renal and biochemical effects of an AVP antagonist in water-retaining heart failure patients. These findings demonstrate a dose-related increase in urine volume, urine flow rate, and solute-free water excretion, compatible with the expected aquaretic effect of a V2 receptor antagonist. At higher doses, serum sodium concentration was increased within the normal range. There was no increase in urinary solute excretion or neurohormonal activation (with the exception of plasma AVP) and no decrease in renal function, as measured by blood urea nitrogen and serum creatinine (data not shown). The increase in plasma AVP occurred only at the higher doses of study medication and remained within the “physiologic” range seen in heart failure patients. These findings suggest a role for AVP in the water retention associated with heart failure and demonstrate the potential utility of AVP antagonists for its treatment.

Our earlier preliminary report provided evidence that this V2 receptor antagonist was associated with a dose-dependent decrease in the excretion of urinary AQP-2, the AVP-sensitive water channel expressed in collecting duct cells within the kidney (17). This observation suggests the mechanism of action of the AVP antagonist, whereby blockade of the renal V2 receptor results in decreased trafficking of AQP-2 to the apical membrane and a reduction in the distal reabsorption of water.

There were several important controls in this randomized trial including the day −1 and placebo results. Because fluid intake was restricted for 4 h after V2 antagonist adminis-

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thirds from intracellular volume and only one-third from ECF potentially blunting any neurohormonal stimulation. The small number of patients could have also contributed to no detectable changes in neurohormones, except vasopres-
in, which is very sensitive to an increase (1% to 2%) in plasma osmolality.

In summary, this study implicates AVP in the water retention seen in heart failure and supports ongoing clinical research evaluating the safety and efficacy of V2 receptor antagonists in heart failure patients. The potential use of these agents as aquaretic agents is supported by the present observations. The effect of such agents on heart failure outcomes requires evaluation in large-scale morbidity and mortality studies.

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