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Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure

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Abstract

Diuretics are frequently required to treat fluid retention in patients with congestive heart failure (CHF). Unfortunately, they can lead to a decline in renal function, electrolyte depletion, and neurohumoral activation. Arginine vasopressin (AVP) promotes renal water reabsorption via the V_2 receptor, and its levels are increased in CHF. This study was designed to assess the effects of a single oral dose of tolvaptan, a selective V_2-receptor blocker, in the absence of other medications, on renal function in human CHF and to compare this to the effects of a single oral dose of furosemide. We hypothesized that V_2-receptor antagonism would yield a diuresis comparable to furosemide but would not adversely affect renal hemodynamics, plasma electrolyte concentration, or neurohumoral activation in stable human CHF. Renal and neurohumoral effects of tolvaptan and furosemide were assessed in an open-label, randomized, placebo-controlled crossover study in 14 patients with NYHA II-III CHF. Patients received placebo or 30 mg of tolvaptan on *day 1* and were crossed over to the other medication on *day 3*. On *day 5*, all subjects received 80 mg of furosemide. Tolvaptan and furosemide induced similar diuretic responses. Unlike tolvaptan, furosemide increased urinary sodium and potassium excretion and decreased renal blood flow. Tolvaptan, furosemide, and placebo did not differ with respect to mean arterial pressure, glomerular filtration rate, or serum sodium and potassium. We conclude that tolvaptan is an effective aquaretic with no adverse effects on renal hemodynamics or serum electrolytes in patients with mild to moderate heart failure.

Keywords

congestive heart failure; V_2-receptor antagonism; aquaretics

A hallmark of Congestive heart failure (CHF) is avid sodium and water retention by the kidney in response to decreases in cardiac output and arterial pressure and activation of sodium-and water-retaining hormones. Because fluid retention further increases the load on

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an already failing heart, congestive symptoms such as dyspnea and peripheral edema consequently develop. Indeed, the major reason for hospitalization for acute decompensated heart failure is congestive symptoms; thus therapies to reduce this complication of heart failure are of high priority.

Loop diuretics have for decades been a mainstay to treat congestion by inhibiting sodium reabsorption in the loop of Henle with the secondary action of passively increasing the excretion of water. As saluretics, loop diuretics may become less efficient in the setting of hyponatremia and may worsen hyponatremia. Furthermore, despite the widespread and long history of use of diuretics in CHF, some detrimental actions of diuretics continue to emerge. Importantly, by increasing distal tubular delivery of sodium, loop diuretics activate the tubuloglomerular feedback mechanism, which causes vasoconstriction of the afferent arteriole and a reduction in renal blood flow (RBF) (3,13,26). Thus loop diuretics may compromise renal function, which has been identified in retrospective analyses as a powerful predictive factor for CHF mortality (6). Potassium-wasting diuretics, which have been associated with increased mortality, can also lead to serum potassium depletion, which, in turn, can promote arrhythmias (4,5). This has prompted efforts to develop more physiological strategies to treat volume overload.

Similar to other neurohormones that are activated in CHF, circulating arginine vasopressin (AVP) is elevated in patients with CHF (12). AVP, a nonapeptide, is secreted by the posterior pituitary gland in response to reduced cardiopulmonary blood volume, reduced systolic blood pressure, or increased plasma osmolality. AVP acts via three receptor types: V_{1A}, V_{1B} (or V_3), and V_2. V_{1A} receptors are located in vascular smooth muscle cells, where they mediate vasoconstriction, and in the myocardium, where they may affect hypertrophy (24). V_{1B} receptors are located in the anterior pituitary and mediate adrenocorticotropin release. V_2 receptors are located in the renal collecting duct, where AVP binding to the V_2 receptor leads to a rise in intracellular cAMP. This promotes renal water reabsorption via translocation of intracellular vesicles containing the water channel aquaporin-2 into the apical plasma membrane and increased transcription of aquaporin-2 (19). Taken together, it would appear as though blocking the renal effects of AVP with a selective V_2-receptor antagonist would produce a diuresis and maintain renal function by antagonizing elevated endogenous AVP levels rather than unphysiologically blocking sodium reabsorption.

Tolvaptan, which is named OPC-41061 in earlier literature, is a modified benzazepine derivative that acts as a selective V_2-receptor antagonist (Fig. 1). Its synthesis has been described in detail by Kondo et al. (14). The potent aquaretic properties of this V_2 antagonist in rats and its pharmacological profile were reported by Yamamura et al. (27). Its oral availability now permits studies in humans that address the physiological significance of the V_2 receptor in human CHF and also the development of a V_2 antagonist as therapeutic agents.

Gheorghiade and colleagues (9) performed the first human studies using this V_2 antagonist in patients with CHF. In a double-blind, placebo-controlled study, these investigators examined the effects of V_2 antagonism in humans with CHF. They found that, on the first day, V_2-blocked patients had an increase in urine volume, and this was accompanied by a decrease in weight that was maintained throughout the study. In a subsequent study, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV), these investigators also again found that V_2-receptor antagonism improved congestion with a decrease in body weight without causing electrolyte abnormalities or worsening renal function (8).

To date, the role of V_2 receptors in the regulation of renal function in human CHF remains poorly defined. Therefore, the objective of the present study was to define the role of V_2 receptors in renal hemodynamics as well as in the control of regulation of water and sodium excretion. We also compared the renal response of V_2-receptor antagonism with the response to acute furosemide. We hypothesized that V_2-receptor antagonism would have a diuretic effect comparable to furosemide but would not impair renal hemodynamics or induce plasma electrolyte abnormalities in humans with stable CHF.

METHODS

Study population

The study was performed in 14 patients with chronic HF. Inclusion criteria were New York Heart Association class II–III and left ventricular ejection fraction of <40%, assessed within 1 yr by two-dimensional echocardiography, radionuclide ventriculogram, or angiography. Exclusion criteria included systolic blood pressure <95 mmHg, serum creatinine level >1.5 mg/dl, serum potassium <3.5 mmol/l, hemoglobin <10.0 g/dl, malignancy, urinary tract obstruction, myocardial infarction/unstable angina/cardiac surgery within 60 days of screening, and HF secondary to uncorrected thyroid disease, amyloidosis, or hypertrophic cardiomyopathy. Furthermore, patients who could not be taken off diuretics, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors were to be removed from the study. The study was conducted under the Investigational New Drug Exemption of the US Food and Drug Administration, 21 Code of Federal Regulations, Part 312. The study was performed in compliance with Good Clinical Practice regulations and the ethical principles of the Declaration of Helsinki. The protocol and informed consent form were approved by the institutional review board of each investigational center, and informed consent was obtained from all participants.

Study design and protocol

The study was designed as a randomized, placebo-controlled crossover study. All subjects received an oral dose that assessed the effects of tolvaptan (Otsuka), furosemide, or placebo. Fifteen days before the start of the study, patients underwent a full physical exam, a 12-lead electrocardiogram, and serum chemistries. They were put on a controlled diet of 2 g of sodium/day, and ACE inhibitors other than captopril were discontinued and replaced with captopril (12.5 or 25 mg, 3 times daily). Bladder ultrasounds were also performed to assess for full emptying of the bladder. Three days before the study, patients were admitted, and captopril, diuretics, β-blockers, and aspirin were discontinued. On study *day 1*, patients received either a single dose of placebo or 30 mg of tolvaptan and were crossed over to the other medication on *day 3*. On *day 5*, all subjects received 80 mg of furosemide. *Days 2* and *4* were washout periods. On the evenings of *days −1*, *2*, and *4*, all subjects received 600 mg of lithium carbonate at 10 PM. Grapefruit, caffeine, alcohol, and tobacco products were prohibited. Two hours before the administration of the study drug (tolvaptan, placebo, or furosemide), the subjects drank four glasses of distilled water (237 ml/glass), serum chemistries and electrocardiograms were obtained, and a urinary catheter was inserted if necessary. Loading doses, followed by continuous infusions of inulin and PAH were given starting 1.5 h before administration of the study drug. The patients remained in a recumbent position, except for voiding, from 2 h before until 9 h after administration of the study drug.

Mean arterial pressure (MAP), heart rate, and blood samples were obtained at baseline and every hour after dosing for 9 h. Blood for neurohumoral assays was obtained 30 min before and 2.5 h after study drug administration. Urine was voided (or catheter emptied) at baseline and every 30 min after dosing, the volume was determined, and samples were collected for

further analyses. Fluid replacement with oral distilled water was given at a 1:1 ratio, based on voided urine volume, starting 1 h after drug dosing and continuing for 8 h.

The glomerular filtration rate (GFR) was calculated by inulin clearance and effective renal plasma flow (ERPF) by PAH clearance. RBF was calculated from ERPF and hematocrit according to the formula RBF = ERPF/(1 − hematocrit). Renal vascular resistance (RVR) was estimated as MAP divided by RBF. The lithium clearance technique was employed to estimate the proximal and distal fractional reabsorption of sodium. Proximal fractional reabsorption was calculated by the following formula: [1 − (lithium clearance/GFR)] × 100. Distal fractional reabsorption of sodium was calculated by this formula: [(lithium clearance − sodium clearance)/lithium clearance] × 100. Electrolytes, inulin, and PAH were determined by well-established methodologies (7). Urine osmolality was measured by freezing-point depression using an automatic microosmometer. Plasma neurohormones were measured by standard radioimmunoassays in blood samples obtained at 0.5 h predose and 2.5 h postdose, with the patient in the supine position before voiding (3a).

Statistical analysis

Tests on the overall mean of repeated-measures data were conducted using a longitudinal analysis model with terms of sequence, subject within sequence, treatment, and period for comparison between tolvaptan and placebo, and a model with terms of subject and treatment for comparisons between tolvaptan and furosemide, as well as placebo and furosemide. In all these models, an autoregression structure is assumed for the repeated observations on a subject within a treatment period. A P value <0.05 was considered statistically significant.

RESULTS

Patient characteristics at baseline are presented in Table 1. *MAP.* There were no significant changes in MAP or heart rate with placebo, tolvaptan, or furosemide, and there were no differences among treatments.

Renal function

Both tolvaptan and furosemide significantly increased urine flow compared with placebo; however, there was no significant difference in urine flow between tolvaptan and furosemide (Fig. 2*A*). Furosemide significantly increased urinary sodium excretion compared with placebo and tolvaptan, whereas there was no difference between placebo and tolvaptan (Fig. 2*B*). The same was true for sodium clearance. Similarly, furosemide increased urinary potassium excretion compared with placebo. In contrast, there was no difference between tolvaptan and placebo (Fig. 2*C*). Again, the same was true for potassium clearance. Urine osmolality was lower with tolvaptan compared with placebo and tended to be lower compared with furosemide. Furosemide also decreased urine osmolality compared with placebo (Fig. 2*D*). Furosemide significantly decreased RBF compared with placebo and tolvaptan, whereas there was no difference between placebo and tolvaptan (Fig. 2*E*). Similarly, there was a trend for furosemide to cause a reduction in ERPF (P = 0.053). There were no changes in GFR among the three different groups (Fig. 2*F*). There were also no changes in RVR.

Furthermore, no significant differences were found among the three treatments with respect to proximal fractional reabsorption of sodium (daily weighted averages: placebo: 0.76 ± 0.18, tolvaptan: 0.74 ± 0.20, furosemide: 0.73 ± 0.11). In contrast, furosemide decreased distal fractional reabsorption of sodium compared with placebo (P = 0.0056) and compared with tolvaptan (P = 0.0233), but there was no significant difference when tolvaptan and

placebo were compared (daily weighted averages: placebo: 0.95 ± 0.04, tolvaptan: 0.94 ± 0.04, furosemide: 0.75 ± 0.42).

Plasma electrolytes

Tolvaptan did not significantly change plasma sodium concentration, whereas furosemide tended to decrease it. However, there were no significant differences among groups (Fig. 3). There were no significant differences in plasma potassium concentration among groups (Fig. 4).

Neurohumoral function

There were no significant differences with respect to neurohormonal concentrations when tolvaptan was compared with either placebo or furosemide. Furosemide did cause a statistically significant increase in plasma renin activity and norepinephrine compared with placebo; however, there were no significant changes in the other neurohormones (Table 2).

DISCUSSION

We report here for the first time the renal effects of acute V_2-receptor antagonism compared with furosemide in patients with mild to moderate CHF and preserved renal function. Acute V_2-receptor blockade produced a diuresis equivalent to furosemide but without natriuresis and without decreasing RBF. Furthermore, whereas furosemide was associated with an increase in potassium excretion, the pure aquaresis associated with tolvaptan did not increase urinary potassium excretion compared with placebo.

Renal hemodynamics

Acute V_2-receptor blockade also significantly increased RBF compared with furosemide, whereas furosemide decreased RBF compared with placebo. However, in this setting no differences could be seen with regard to GFR. The preserved GFR despite decreased RBF with furosemide could occur via vasoconstriction of the efferent arteriole of the glomerulus, leading to an increased filtration fraction.

An emerging concept is that the cardiorenal syndrome may, in part, be a consequence of excessive renal vasoconstriction with a reduction in GFR, which may contribute to the diuretic resistance seen in this syndrome. Excessive use of loop diuretics may contribute to such adverse renal effects. Thus the differential actions of V_2-receptor blockade compared with furosemide should be further explored, especially in the acute setting of patients hospitalized for acute decompensated CHF at risk for worsening renal function.

Renal electrolytes

As expected, tolvaptan acted as a pure aquaretic. Conversely, furosemide led to a significant natriuresis and also increased urinary potassium excretion compared with placebo. This aquaretic vs. natriuretic response was further confirmed utilizing the lithium clearance technique to assess sodium handling by the nephron. Here V_2 blockade demonstrated no change in either proximal or distal fractional reabsorption of sodium in contrast to a decrease in sodium reabsorption beyond the proximal tubule with furosemide. It is well established that by inhibiting sodium reabsorption in the loop of Henle, furosemide increases sodium delivery to the distal tubule with an associated increase in distal sodium reabsorption. Indeed, loop diuretic use can increase the thiazide-sensitive Na^+/Cl^- cotransporter abundance in the distal tubule and lead to hypertrophy and hyperplasia of cells of the distal collecting duct (1,22). It will be interesting to see whether the cardiorenal syndrome is associated with these functional and structural changes and whether the use of tolvaptan induces these potentially counterproductive changes.

As Fig. 3 suggests, the serum sodium concentration tended to decrease from baseline with furosemide, whereas this was not seen with tolvaptan treatment. In contrast, no such trend was observed for serum potassium (Fig. 4). It is clinically well known that furosemide is natriuretic and that it also causes potassium loss. Given the nature of this study, it was conducted for only a brief period of time, and therefore no substantial changes in serum electrolytes were expected. Long-term use of V_2 blockade with and without potassium-wasting diuretics should be examined carefully as the issue of potassium wasting by loop diuretics is of increasing importance given a recent retrospective analysis of the Studies Of Left Ventricular Dysfunction trial (5). This analysis revealed that CHF patients taking a "potassium-sparing" diuretic had a reduced risk of death from or hospitalization for worsening CHF and a reduced risk of all-cause or cardiovascular death. Thus as a potassium sparing diuretic, chronic use of a V_2 antagonist warrants further evaluation as a potential therapy for not only decreasing congestion but also for decreasing mortality. The impact of chronic oral use of tolvaptan on mortality is currently being tested in the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial (10).

Hyponatremia in CHF patients is associated with increased mortality (16). As discussed by Goldsmith (11) in a recent review, this hyponatremia can arise from *1*) a dilutional hypervolemic hyponatremia secondary to water retention promoted by AVP and/or *2*) solute losses from standard diuretic therapy. Thus vasopressin antagonists such as tolvaptan may be especially useful in the treatment of CHF patients with hypervolemic hyponatremia.

Neurohormones

In this study, V_2 antagonism had no acute, negative effects on the neurohumoral system compared with PLC. The long-term effects of V_2-receptor blockade on neurohumoral systems still need to be studied, especially in combination with other cardiovascular medications. This could be of particular relevance to the renin-angiotensin-aldosterone system and adrenergic nervous system, given that furosemide, but not tolvaptan, increased plasma renin activity and norepinephrine compared with placebo.

Perspective/outlook

This study looked exclusively at the effects of the selective V_2-receptor antagonist tolvaptan or furosemide on renal function. Subjects with stable CHF in this study had ACE inhibitors, diuretics, and β-blockers discontinued before the study. It would be expected that, e.g., an ACE inhibitor or angiotensin II type 1-receptor (AT_1) antagonist could influence renal hemodynamics and neurohumoral activation. Indeed, Chen et al. (3) reported that the AT_1-receptor antagonist losartan prevented the furosemide-induced decrease in GFR, reduced aldosterone, and further increased urine flow and urinary sodium excretion. With respect to tolvaptan, the impact of comedication has been partly addressed in the two clinical trials by Gheorghiade and colleagues (8,9). These investigators found no change in serum creatinine, blood urea nitrogen, or serum electrolytes when tolvaptan was given chronically to these patients, who were on standard therapy and even other diuretics. Other parameters of renal function such as RBF, RVR, GFR, and ERPF were not measured. Although the effects of combined tolvaptan and ACE inhibitor therapy should be addressed further, the data thus far suggest that renal function is not harmed.

Of note, CHF is a syndrome that is characterized not only by fluid retention but also by avid sodium retention. Therefore, tolvaptan as an aquaretic likely will have to be combined with a natriuretic drug. It will be especially interesting to see whether the combination with an aldosterone antagonist might be efficacious, as both available aldosterone antagonists have been shown to decrease mortality in clinical trials (20,21). Furthermore, thiazides and

thiazide-like diuretics, which act on the distal tubule, frequently are not potent enough to control fluid status in more advanced stages of HF, and patients have to be switched to loop diuretics. A combination of a thiazide with tolvaptan may be able to delay this necessity. Future studies to explore these different diuretic strategies and their impact on functional and structural changes in the kidney appear warranted.

Another issue of interest when a selective V_2-receptor blocker is given is the impact on the unblocked V_{1A} receptor. A theoretical problem could arise because the circulating AVP, which can no longer bind to the V_2 receptor, is available to bind to the V_{1A} receptor, which mediates vasoconstriction. This study was neither intended nor designed to address this issue, but it may indirectly suggest that excess activation of V_{1A} receptors did not occur acutely given that no changes were noted in MAP or RVR when tolvaptan was compared with placebo. Another issue that may need to be addressed in the future is the possibility that excessive V_{1A}-receptor activation causes hypertrophy of cardiac myocytes. An in vitro study of neonatal rat cardiac myocytes suggested that vasopressin could induce hypertrophic growth of myocytes via the V_{1A} receptor (18). The physiology of combined V_{1A}- and V_2-receptor antagonism is currently under study (2,23,25).

An important limitation of the present study is that it was a single-dose study, and therefore it is not possible to extrapolate these results to long-term administration. Ongoing clinical trials like the EVEREST trial will help us to define the properties of tolvaptan as a chronic therapy (10).

In summary, acute V_2-receptor blockade in human CHF with tolvaptan enhanced aquaresis without adversely affecting renal hemodynamics, urinary sodium or potassium excretion, serum electrolytes, or neurohumoral systems. This study was directed only at the renal physiological effects of V_2-receptor antagonism in stable patients with mild to moderate heart failure and preserved renal function. More studies are needed to evaluate the effects of V_2-receptor blockade on renal function in patients with more severe CHF, in patients with renal insufficiency, and in patients on standard medications, particularly ACE inhibitors.

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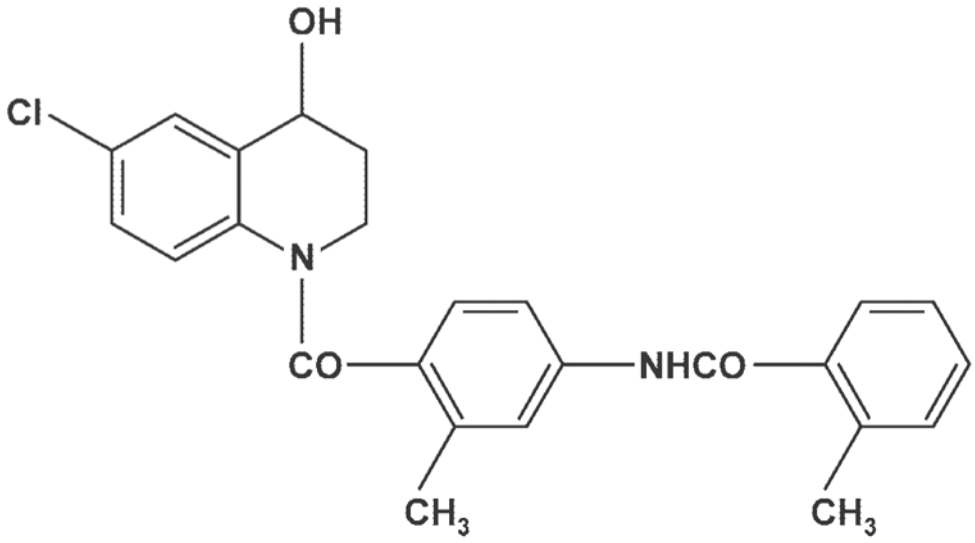

Fig. 1.
Chemical structure of tolvaptan. The chloride on the 7 position of the benzazepine and the methyl group on the 2 position of the aminobenzoyl moiety give tolvaptan good oral availability (14).

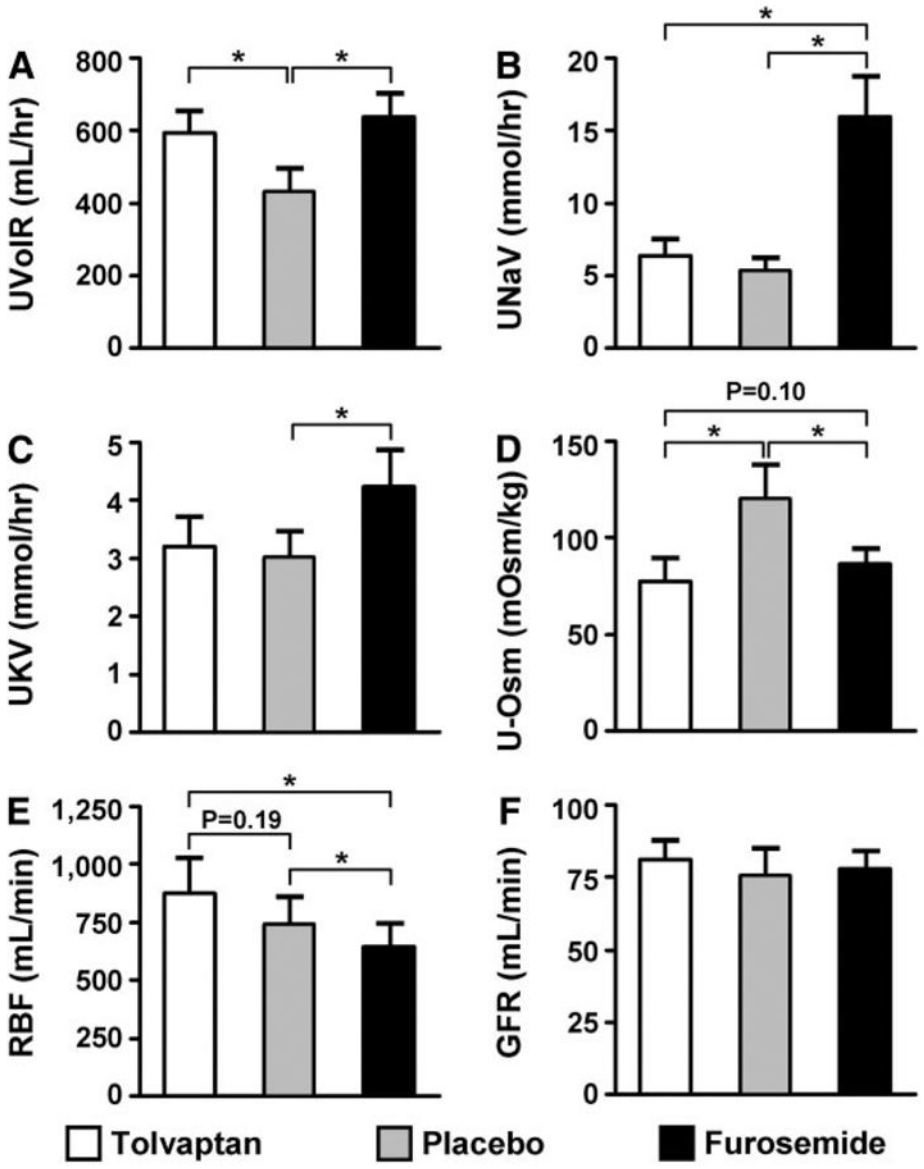

Fig. 2.

Effect of tolvaptan, placebo, and furosemide on urine flow ($U_{Vol}R$; *A*), urinary sodium excretion ($U_{Na}V$; *B*), urinary potassium excretion ($U_{K}V$; *C*), urine osmolality (U-Osm; *D*), renal blood flow (RBF; *E*), and glomerular filtration rate (GFR; *F*). Bars represent weighted averages ± SE over an observation period of 9 h. **P* < 0.05.

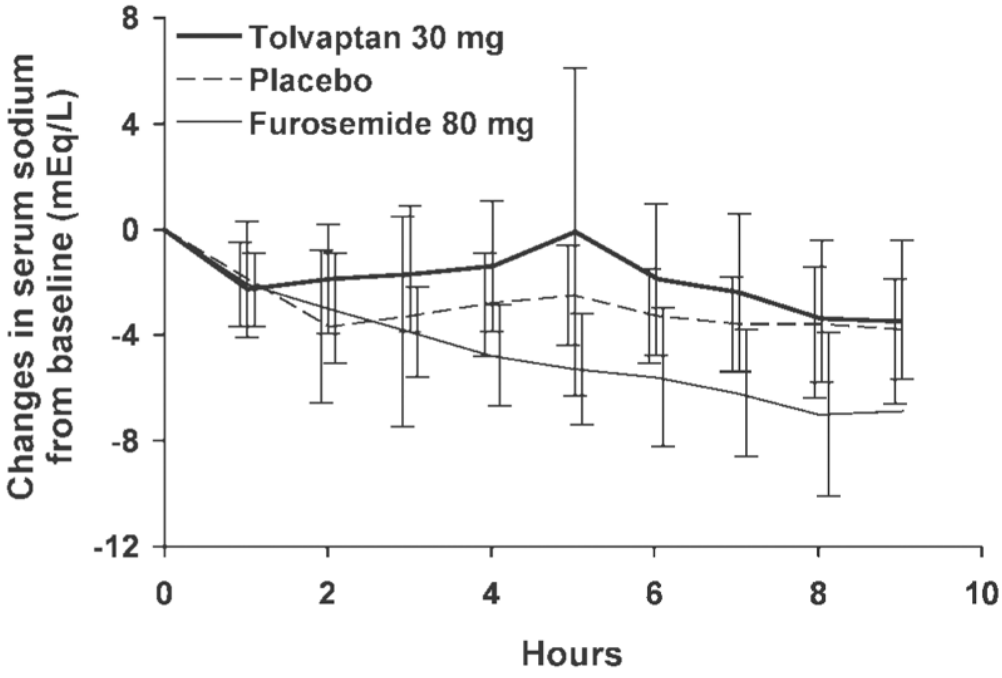

Fig. 3.
Changes in serum sodium concentration from baseline. Thick line, tolvaptan; dashed line, placebo; thin line, furosemide.

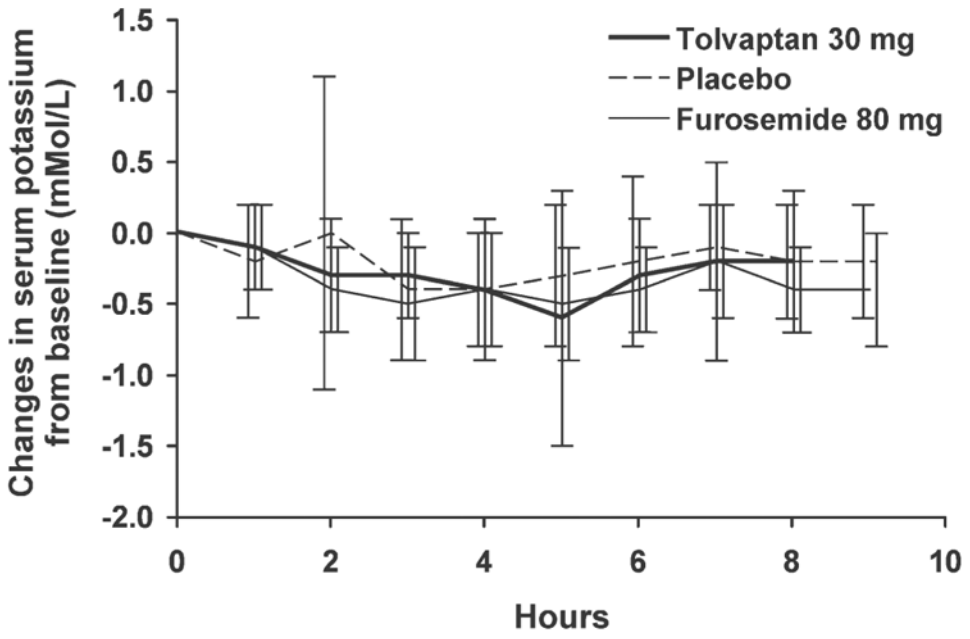

Fig. 4.
Changes in serum potassium concentration from baseline. Thick line, tolvaptan; dashed line, placebo; thin line, furosemide.

Table 1

Demographic characteristics of patients

Age, yr	56±8
Male/female, *n* (%)	10/4 (71/29)
Caucasian, *n* (%)	7 (50)
LVEF	34±3

Values are means ± SE except for left ventricular ejection fraction (LVEF; % ± SE); *n* = 14.

Table 2

Neurohumoral changes compared among groups

	TLV vs. Pl	Furo vs. Pl	TLV vs. Furo
Arginine vasopressin, pg/ml	$P = 0.44$	$P = 0.51$	$P = 0.94$
Plasma renin activity, $ng \cdot ml^{-1} \cdot h^{-1}$	$P = 0.24$	$P = 0.02$*	$P = 0.13$
Aldosterone, ng/dl	$P = 0.20$	$P = 0.08$	$P = 0.10$
Atrial natriuretic peptide, pg/ml	$P = 0.28$	$P = 0.11$	$P = 0.95$
B-type natriuretic peptide, pg/ml	$P = 0.57$	$P = 0.36$	$P = 0.43$
Norepinephrine, pg/ml	$P = 0.24$	$P = 0.005$*	$P = 0.13$

TLV, tolvaptan; Furo, furosemide; Pl, placebo.

*Increase with Furo compared with Pl.