

Tolvaptan for the treatment of hyponatremia and congestive heart failure

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Tolvaptan is an oral, once-daily nonpeptide arginine vasopressin V₂-receptor antagonist under development for the treatment of hyponatremia and congestive heart failure. In Phase II clinical trials, tolvaptan, in addition to standard therapy, increased fluid loss, resulting in decreased body weight and improved edema and serum sodium without affecting blood pressure, heart rate or renal function in patients with heart failure. The compound appeared to be well tolerated and dose-dependent adverse events were generally related to its pharmacological activity, such as thirst and dry mouth. In patients with hyponatremia, tolvaptan appears to be more effective than fluid restriction at improving sodium levels without an increase in adverse events. An international Phase III outcome study; Efficacy of Vasopressin antagonism in hEaRt failure outcome Study with Tolvaptan (EVEREST), evaluating the long-term efficacy and safety of tolvaptan in patients hospitalized with worsening heart failure, is currently ongoing.

Vasopressin, also known as arginine vasopressin (AVP) or antidiuretic hormone (ADH), is a neuro-peptide produced in the supraoptic and paraventricular nuclei of the hypothalamus, where it is transported to the pituitary gland and released into the bloodstream. Secretion of this hormone from hypothalamic neurons is regulated by baroreceptors and osmoreceptors, which can be affected by factors such as malignancies, drugs, cardiopulmonary disease, CNS disorders and endocrinopathies.

Two receptors have been isolated: the V₁ receptor (further divided into V_{1a} [1,2] and V_{1b} [3,4]), localized in the vasculature, the uterus and the brain; and the V₂ receptor [5,6], primarily localized in the collecting duct of the renal nephron where it mediates changes in water permeability. A decrease in blood pressure, as well as an increase in plasma osmolality, leads to marked increases in AVP blood levels. AVP causes vasoconstriction via cyclic adenosine monophosphate (cAMP)-independent V₁ receptors, and promotes water reabsorption in the kidneys by increasing intracellular cAMP and translocating aquaporin-2 from intracellular vesicles to the apical plasma membranes [7]. Absence of vasopressin, or its blockade by antagonists, leads to excretion of large volumes of very dilute urine and an increase in plasma sodium concentration if water intake is unchanged.

It has been shown that various disorders, including congestive heart failure (CHF), liver cirrhosis and syndrome of inappropriate secretion of antidiuretic hormone (SIADH), are associated with increased AVP secretion resulting in abnormal fluid retention [8]. Electrolyte imbalances

with unclear etiologies, in particular hyponatremia, often occur in such patients. The use of loop diuretics to treat these patients sometimes promotes an inappropriate loss of electrolytes and thus exacerbates hyponatremia and other electrolyte imbalances, resulting in neurological and cardiac complications [9,10]. As AVP V₂ receptor antagonists could promote free-water excretion without disturbing electrolytic balance, it has been hypothesized that they would be clinically useful for the treatment of diseases associated with hyponatremia or fluid retention.

The first nonpeptide vasopressin antagonists were discovered in the early 1990s. Tolvaptan (OPC-41061) is a potent, highly selective and orally effective nonpeptide AVP V₂ receptor antagonist, and is currently in development for the treatment of CHF, hyponatremia and polycystic kidney disease.

Chemical structure

Tolvaptan is a benzazepine derivative and the result of structural optimization of OPC-31260, the first nonpeptide V₂ receptor antagonist discovered [11]. Tolvaptan (OPC-41061) is chemically described as $\text{5-}[(7\text{-chloro-}2,3,4,5\text{-tetrahydro-}5\text{-hydroxy-}1H\text{-}1\text{-benzazepin-}1\text{-yl)carbonyl]}\text{-}o\text{-tolu-m-toluidide}$. The chemical structure of tolvaptan is shown in Figure 1.

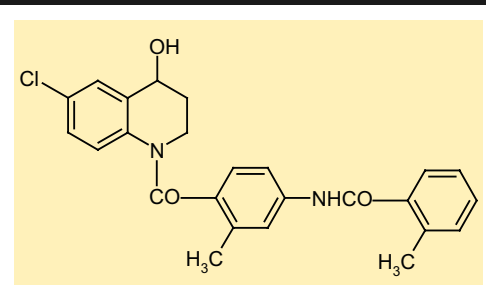
Pharmacodynamics

The pharmacodynamics of tolvaptan in healthy male and female volunteers have been assessed in two single-center, double-blind, randomized, placebo-controlled, ascending single-dose studies

Keywords: aquaresis, arginine, congestive heart failure, hyponatremia, tolvaptan, vasopressin

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Figure 1. Chemical structure of tolvaptan, $\bar{S}$ -4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-o-tolu-m-toluidide, an orally active, selective vasopressin V_2 receptor antagonist.



that were conducted in fasted healthy subjects. The evaluated doses ranged between 60 and 480 mg. For the 0–24 h interval following administration of tolvaptan, serum potassium and creatinine clearance, and urinary sodium and potassium excretion, and osmolality were not different compared with the placebo group. Increases, throughout 0–24 h, were seen in mean serum sodium concentrations (4–6 mEq/l), plasma osmolality (approximately 8 mOsm/kg) and free water clearance (approximately 6 ml/min). Mean urine concentrations of sodium and potassium were decreased to less than 20 mEq/l, and mean urine osmolality was decreased to less than 100 mOsm/kg. None of the pharmacodynamic parameters demonstrated a dose-dependent response as it appears that V_2 receptors were completely inhibited for at least 24 h post-dose at doses greater than or equal to 180 mg. Mean maximal urinary excretion rate and mean urine excretion from 0–24 h post-dose appeared to plateau at approximately 12 ml/min and 11.5 l, respectively. Only total urine volume excretion (0–72 h post-dose) increased linearly with dose. As plasma tolvaptan concentrations increased, the duration of enhanced urine excretion also increased.

Pharmacokinetics

Tolvaptan is rapidly absorbed into the systemic circulation, with a peak concentration (C_{max}) approximately 2–3 h following single oral administration [12]. The pharmacokinetics of tolvaptan are linear over a broad range (5–480 mg).

In patients with heart failure (HF) and volume expansion, the apparent total clearance of tolvaptan was approximately twofold lower in HF patients than in the healthy subjects [12]. The half-life of tolvaptan is 6–8 h.

Tolvaptan is primarily metabolized via the cytochrome (CYP) P450 isoenzyme CYP3A4. Coadministration of ketoconazole increased C_{max} levels by 248% and increased the area under the plasma concentration versus time curve by 440% [13]. Tolvaptan coadministration does not affect pharmacokinetics of amiodarone [13] or warfarin [14].

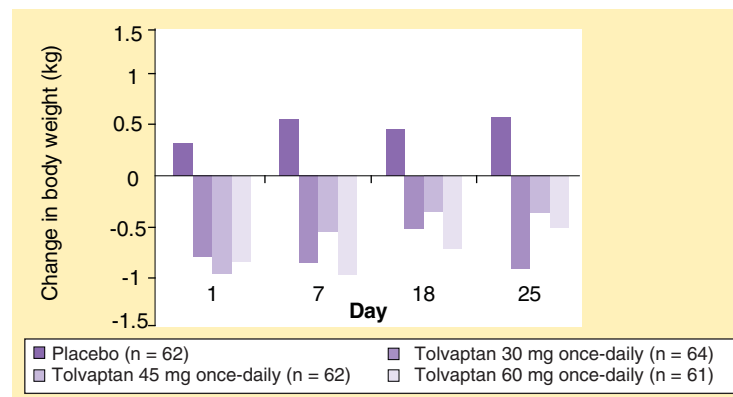
Clinical efficacy

The effects of tolvaptan have been studied in patients with HF and hypervolemic and euvolemic hyponatremia.

Phase II clinical trials in CHF

The effects of tolvaptan were first studied in a multicenter, randomized, placebo-controlled, double-blind, dose-ranging Phase II study (Study 156–98–252) in patients with CHF on stable diuretic doses [14]. A total of 254 patients were randomized to three doses of oral tolvaptan (30, 45 and 60 mg once-daily) or placebo, and treated for 25 days. Patients with either normal or compromised left-ventricular function were enrolled in the study. The four treatment groups were balanced with regard to age, sex, race, New York Heart Association (NYHA) functional class and background therapy. The primary end point was body weight changes over time, and secondary objectives included peripheral edema, urinary sodium excretion, urine volume and osmolality. Tolvaptan significantly reduced body weight from baseline compared with placebo on the first day. This effect was also maintained throughout the study ($p < 0.001$; Figure 2). As expected, tolvaptan treatment significantly increased urine volume and decreased urine osmolality compared with placebo ($p < 0.001$; Figure 3). Tolvaptan treatment also appeared to reduce edema in patients with moderate-to-severe edema at baseline. Importantly, no significant changes in heart rate, blood pressure, serum potassium, or renal function were observed in association with tolvaptan therapy.

The Acute and Chronic Therapeutic Impact of a Vasopressin antagonist in Congestive Heart Failure (ACTIV CHF) trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging Phase II feasibility trial that compared the use of three oral, once-daily doses of tolvaptan with placebo [15]. This study was designed to evaluate the short- and intermediate-term effects of tolvaptan in patients hospitalized with HF. In this study, 319 patients admitted for worsening HF and with signs or

Figure 2. Study 156-97-252.

Mean decreases from baseline in body weight were observed on day 1 of treatment at all doses and maintained throughout the study (all patients). These differences were statistically significant from that of placebo at each time point ($p < 0.001$).

symptoms of congestion were randomized to receive tolvaptan 30, 60 or 90 mg or placebo, respectively, in addition to standard therapy for an inpatient period of up to 10 days, followed by a 7-week outpatient period.

The study had two primary end points to assess both the acute (in-hospital) and the intermediate-term (60 days after hospital discharge) effects of tolvaptan. The inpatient end point was body weight changes 24 h after first administration of the study drug. The outpatient end point was worsening HF (defined as rehospitalization, unscheduled visit for HF or death) at 60 days

after randomization. Secondary end points included changes in dyspnea, jugular venous distention, rales, edema, serum electrolyte levels, use of diuretics, patient- and physician-assessed symptom scales, body weight (at discharge and outpatient) and urine volume (inpatient).

All doses of tolvaptan resulted in significant reductions in body weight at day 1, discharge and 60 days postdischarge (Figure 4). Urine volumes were also significantly higher for all tolvaptan groups when compared with placebo. Only nonstatistically significant trends were observed for improvements in signs and symptoms (edema, dyspnea and jugular venous distention) after 1 day of treatment and at discharge. Although no significant differences in worsening HF were observed, intriguing trends towards improved survival were seen in the overall population and particularly in patients with increased mortality risk (e.g., hyponatremia, elevated blood urea nitrogen [BUN] and severe congestion) (Figure 5).

The effects of tolvaptan on cardiac remodeling have also been studied in the recently completed Multicenter Evaluation of Tolvaptan Effects On Remodeling (METEOR) study [16]. The study demonstrated only nonstatistically significant trends toward improved cardiac volumes after 1 year of treatment. However, a nominal p-value was observed in a non-prespecified analysis of time to death or worsening HF.

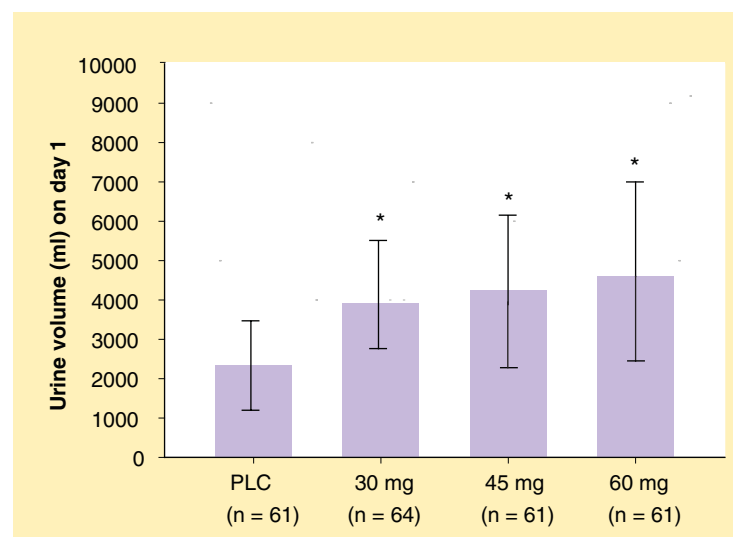
Unlike furosemide, tolvaptan also appears to increase urine volume without unfavorable changes in renal hemodynamics or sodium and potassium excretion [17].

While the effects of tolvaptan on fluid balance have been extensively studied, its impact on hemodynamics (e.g., the pulmonary capillary wedge pressure [PCWP]) has not yet been elucidated. This is currently being tested in an ongoing international trial (the ECT of tolvaptan on hemodynamic parameters in Subjects with hEart failure [ECLIPSE] trial).

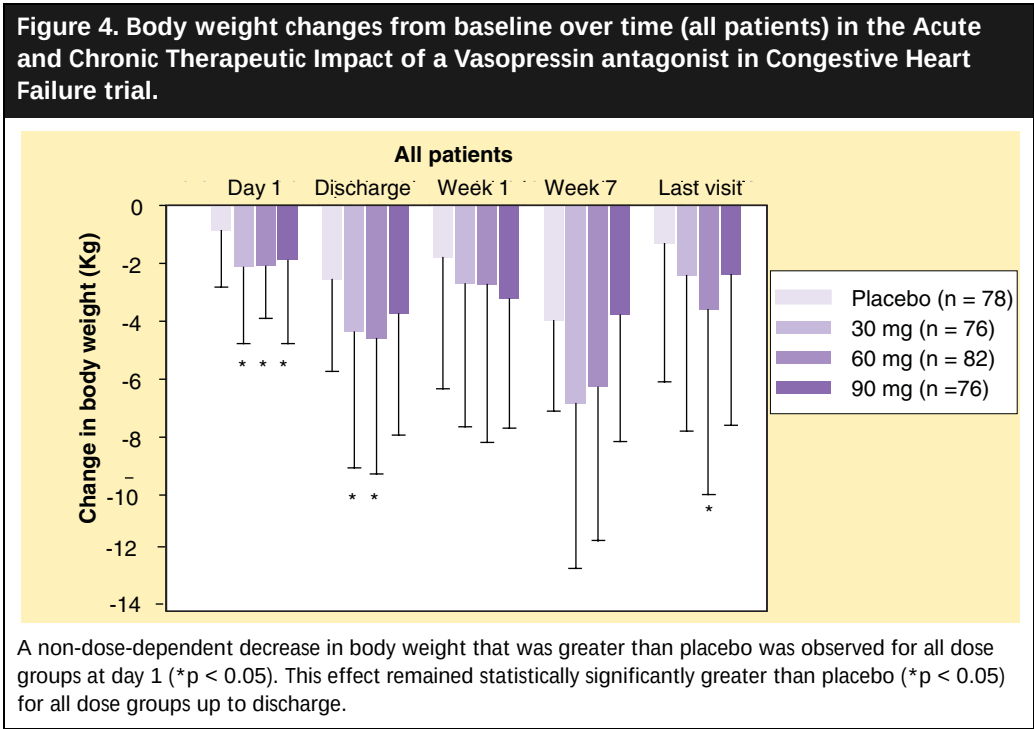
Phase II clinical trials in hyponatremia

The effects of tolvaptan in patients with euvolemic and hypervolemic hyponatremia were assessed in a Phase II study and in subanalyses of the two CHF studies mentioned previously.

A multicenter, prospective, randomized, open-label, active-controlled trial was designed to evaluate the effects of dose titration of tolvaptan without fluid restriction versus placebo with fluid restriction on serum sodium concentration in hyponatremic patients [18]. A total of 28 hospitalized patients with

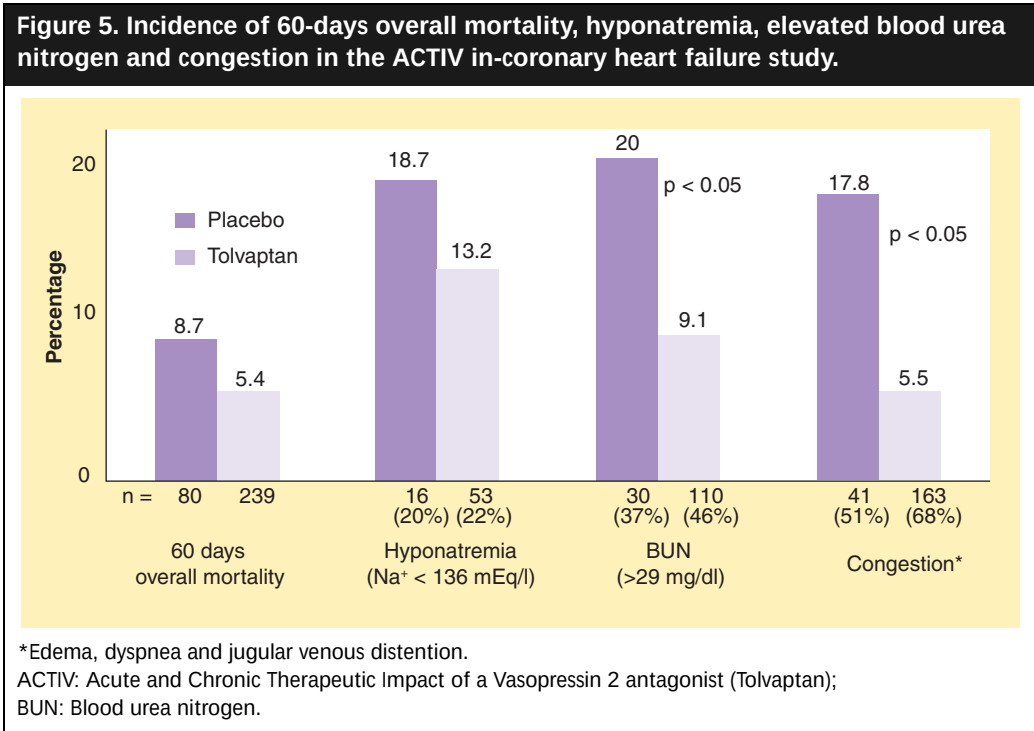
Figure 3. Study 156-97-252.

Total urine output (ml/24 h) on day 1 of treatment in all patients. An increase in urine volume that was statistically significantly than placebo ($p < 0.001$) was observed for all dose groups.



euvolemic or hypervolemic hyponatremia (serum sodium <135 mmol/l) were enrolled in this study. Patients were randomized 2:1 to tolvaptan alone (n = 17) or placebo plus 1200 ml/day of fluid restriction (n = 11) for up to 27 days and follow-up continued up to 65 days. Tolvaptan dosing was initiated on the smallest dose (10 mg/day)

and then continued on subsequent days using up-titration doses (15, 30, 45 and 60 mg/day, respectively), as needed to achieve serum sodium concentrations within normal ranges. The primary end point was to determine if tolvaptan normalized serum sodium or caused an increase of 10% or greater from baseline to



the last inpatient assessment. The secondary end points were changes in urine volume, urine osmolality, urine sodium concentration, body weight, total fluid intake, free-water clearance and thirst score from baseline to the last inpatient assessment.

Patients treated with tolvaptan achieved significantly greater increases in mean serum sodium levels from baseline compared with the fluid-restricted patients, which persisted through the last inpatient visit. Urine osmolality and urine sodium were lower in the tolvaptan-treated patients. As expected, urine output and fluid intake were significantly increased in the tolvaptan group. In this study, tolvaptan appeared to be more effective than fluid restriction in correcting hyponatremia in hospitalized patients, without an increase in adverse events.

A subanalysis of the 156–98–252 and ACTIV CHF studies looked at the subset of patients with hyponatremia at baseline. In both studies, tolvaptan appeared to significantly improve serum sodium levels, often leading to normalization, after the first dose. This effect also was sustained over time and lasted for 25 days in the 156–98–252 study and up to 60 days post-discharge in the ACTIV CHF study.

Phase III studies: congestive heart failure

The hypothesis that tolvaptan, in addition to standard therapy, might improve patient status in the short term and favorably impact outcomes (mortality and morbidity) in the long term is being tested in the Efficacy of Vasopressin antagonism in hEaRt failure outcome Study with Tolvaptan (EVEREST) trial [19]. This is an international, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the long-term efficacy and safety of oral tolvaptan 30 mg once-daily in patients hospitalized with worsening HF. Patients are eligible for inclusion if they have a reduced left-ventricular ejection fraction ($\leq 40\%$) and are hospitalized for worsening HF, and have signs of volume expansion and NYHA class III/IV symptoms. Patients are randomized 1:1 to oral tolvaptan (30 mg once daily) or a matching placebo for a minimum of 60 days.

The design of the trial has previously been described in detail [19]. Briefly, EVEREST consists of a main outcome study and two embedded studies designed to assess the acute effects on patient status. The main study has two coprimary end points: time to all-cause mortality and time to first cardiovascular mortality, or HF

hospitalization. A composite end point of patient-assessed global clinical status and body weight changes at day 7 or earlier if discharged is used as the primary end point in the embedded study. Other clinical end points include changes from baseline in body weight on first day of inpatient treatment, edema score, serum sodium, dyspnea and Kansas City Clinical Questionnaire overall summary score at outpatient week 1.

EVEREST was to be continued until at least 1065 deaths occurred. The first patient was enrolled on October 7th, 2003, and the study was recently completed with a total of 4133 patients.

Phase III studies: hyponatremia

The effects of tolvaptan in patients with euvoletic and hypervolemic hyponatremia have been tested in two identical pivotal Phase III studies: Sodium Assessment with increasing Levels of Tolvaptan in hyponatremia (SALT)-1 and -2. These trials represent the largest placebo-controlled studies to date in these populations. The multicenter, international, randomized, placebo-controlled trials evaluated the clinical efficacy and safety of serum sodium correction using tolvaptan versus placebo. Data respectively from 205 (SALT-1) and 243 (SALT-2) consenting patients with hyposmolar hyponatremia (<135 mEq/l) were collected. Excluded were acute (e.g., fluid overload, pain or head trauma) and treatable etiologies (e.g., hypothyroidism and hypoadrenalism). Randomization was stratified by degree (50% each of severe [<130 mEq/l] or mild [130 – 134 mEq/l]) and etiology of hyponatremia ($<50\%$ CHF-related). Oral tolvaptan or placebo (1:1) given for 30 days beginning at 15 mg daily was titrated to 30 or 60 mg daily guided by serum sodium and symptomatic response. Patients drank according to thirst, in general. At day 30, the patients returned to usual therapies, with monitoring of serum sodium and patient status at day 37.

Two primary end points were used: correction of hyponatremia by day 4 and day 30, expressed as average daily area under concentration curve (AUC) in change from baseline of serum sodium. Secondary end points included percent normalized (>135 mEq/l), time to normalization, change in serum sodium, categorical change, percent requiring fluid restriction, fluid I/O and balance, change in body weight for hypervolemic patients, change in Short Form (SF)12 item and hyponatremia questionnaires, and percent requiring hyponatremia rescue (saline infusion). Analyses

were performed for total population and severity subgroups. The studies have been completed and the results submitted for publication.

Safety & tolerability

The most frequent adverse events across study populations in clinical trials conducted to date were generally related to the pharmacological mechanism of action of tolvaptan and include excess thirst, frequent urination and dry mouth. Other commonly reported adverse events in tolvaptan-treated patients include headache, fatigue, myalgia and dizziness. In clinical trials conducted in patients with HF and/or hyponatremia, no significant differences were observed in heart rates, blood pressure, renal function, potassium concentration or vasopressin levels in patients receiving tolvaptan versus placebo.

Rapid aquaresis can lead to severe volume depletion and renal failure, particularly when patients are not able to respond to thirst. It is expected that care should be maintained during the initiation of therapy to ensure that patients reach steady-state volume equilibrium without becoming volume depleted.

Regulatory affairs

Tolvaptan is being developed by the Otsuka Maryland Research Institute (OMRI, MD, USA). OMRI filed an Investigational New Drug application for tolvaptan to the Cardiorenal Division of the US FDA for the treatment of patients with CHF in May 1996. Subsequently, in September 1997, OMRI submitted an Investigational New Drug application for tolvaptan to the Metabolic and Endocrine Division of the US FDA for the treatment of patients with hyponatremia of any origin.

Conclusions

Tolvaptan is an orally active, selective AVP V_2 -receptor antagonist. By selectively blocking the V_2 receptor, tolvaptan increases free water excretion without affecting electrolyte balance.

Results from Phase II clinical trials indicate that tolvaptan treatment is well tolerated. Its use was associated with significant increases in urine volume without affecting renal function or fluid balances, resulting in body weight loss and improvements in serum sodium concentrations. Trends toward improvement in symptom scores have been observed, but have not reached statistical significance. Favorable trends in mortality have also been shown in the ACTIV CHF study conducted in patients

hospitalized with worsening CHF. Improvement and often normalization of serum sodium levels in patients with hyponatremia has also been observed. Confirmation of these promising results is expected from the ongoing Phase III SALT program, focused on hyponatremia of any origin, and the EVEREST trial looking at outcomes and patient status in acute HF syndromes.

In conclusion, owing to its mechanism of action, tolvaptan may become a useful addition to the available armamentarium in the treatment of CHF and a new, more efficacious and safer approach to the treatment of patients with euvolemic and hypervolemic hyponatremia.

Future perspective

In many respects, vasopressin antagonists represent a unique class of therapeutic agents due to their potential role in both the short- and long-term treatment of patients with hyponatremia and patients hospitalized with worsening HF. In the short-term, as 'aquaretics', vasopressin antagonists should offer the possibility of added efficacy in relieving congestion and improving symptoms with minimal side effects in combination with standard medical therapy. In the long-term, as neurohormonal antagonists, vasopressin antagonists follow in the footsteps of several well-established drug therapies in patients with HF, and should offer the possibility of improved outcome particularly in patients with worsening HF.

The recently completed EVEREST trial will be the first large-scale (>4000 patients randomized) prospective evaluation of a neurohormonal antagonist in patients hospitalized with worsening HF. Similarly, the recently completed SALT trials will provide an unprecedented evaluation of the safety and efficacy of an oral vasopressin antagonist in patients with hyponatremia.

Information resources

Relevant further reading: acute heart failure syndromes

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Executive summary**Mechanism of action**

- Tolvaptan is an arginine vasopressin (AVP) receptor antagonist that selectively blocks the AVP type 2 (V_2) receptors in the kidney.
- Antagonism of the V_2 receptor results in water diuresis (aquaresis).

Pharmacokinetic properties

- Tolvaptan has high V_2 receptor selectivity.
- A drug elimination half-life conducive to once-daily dosing.
- Linear pharmacokinetics over the therapeutic dose range.

Clinical efficacy

- Increased urine output.
- Reductions in body weight in fluid-overloaded patients.
- Improvements in signs and symptoms of congestion.
- Improvement in serum sodium levels in hyponatremic patients.

Safety & tolerability

- Increased thirst, dry mouth and polyuria.
- No effect on heart rate, blood pressure or renal function.

Drug interactions

- Tolvaptan is primarily metabolized via the cytochrome P450 (CYP) isoenzyme CYP3A4.
- Coadministration of ketaconazole increases C_{max} levels and the area under the plasma concentration versus time curve.
- Tolvaptan coadministration does not affect the pharmacokinetics of amiodarone or warfarin.

Dosage & administration

- Dose titration from 15, 30 and 60 mg oral once-daily in hyponatremia based on sodium levels.
- 30 mg fixed oral once-daily dose in coronary heart failure.

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