**INTRODUCTION**

Hyponatremia is the most common electrolyte abnormality in patients who are admitted to the hospital. Affecting 5.5% of patients,1 hyponatremia is manifested as a decrease in serum sodium levels, accompanied by symptoms ranging from nausea to seizures and coma. The presence and degree of these symptoms are dependent on the rate of the decrease in sodium as well as the absolute sodium concentration. Hyponatremia is not a primary diagnosis; it is commonly associated with the syndrome of inappropriate antidiuretic hormone (SIADH), excessive hydration during exercise, nephritic syndrome, cirrhosis, heart failure (HF), and the use of certain drugs.2

Although the etiology of hyponatremia may be diverse, nearly all causes can be related to the hormone arginine vasopressin (AVP). AVP is normally secreted by the anterior hypothalamus in response to an increased plasma osmolality or a decrease in blood volume or blood pressure (BP). After AVP is released, it stimulates several subtypes of AVP receptors throughout the body. Table 1 shows the location and physiological effect of receptor activation. Hyponatremia associated with SIADH results from the incomplete suppression of AVP resulting from a variety of causes, whereas hyponatremia associated with HF results from an increased AVP secretion secondary to decreased effective arterial blood volume that is independent of the sodium concentration.2

Aside from its direct consequences, the presence of hyponatremia is often a poor prognostic factor in several disease states, including HF. Short-term data from the OPTIMIZE–HF registry (Organized Program To Initiate life-saving treatment in hospitalized patients with Heart Failure) indicate that hyponatremic patients who are admitted to the hospital for HF experience a higher mortality risk during a hospital stay and in the first two to three months after discharge.3 Evaluating patients who were admitted with HF and preserved ejection fraction, Rusinaru et al. determined that the presence of hyponatremia upon admission was associated with increased one-year, three-year, and seven-year mortality rates when compared with patients with normal sodium levels. Further, patients with sodium levels that remained uncorrected at hospital discharge experienced worse survival rates than patients whose sodium levels were corrected before discharge.4

Until recently, the treatment of hyponatremia had focused largely on sodium replacement and water restriction. However, because most episodes of hypo-

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**Table 1 Vasopressin Receptor Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Anatomic Location</th>
<th>Physiological Effect</th>
</tr>
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<tbody>
<tr>
<td>V1a</td>
<td>Vascular smooth muscle, Adrenal gland, Myometrium, Bladder, Adipocytes, Hepatocytes, Platelets, Kidney (medullary interstitial cells, vasa recta, collecting duct epithelial cells), Spleen, Testis, Central nervous system</td>
<td>Platelet aggregation, Vasconstriction, Inotropic stimulation, Myocardial protein synthesis</td>
</tr>
<tr>
<td>V1b</td>
<td>Anterior pituitary, Brain, Pancreas, Adrenal medulla</td>
<td>Pituitary ACTH secretion</td>
</tr>
<tr>
<td>V2</td>
<td>Kidney (renal collecting duct, thick ascending limb epithelial cells), Vascular endothelium</td>
<td>Antidiuresis, Von Willenbrand factor and factor VIII release</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone.

Hyponatremia involve dysregulation of AVP, the pursuit of an AVP receptor antagonist has been a target of drug development for the last 30 years. Early attempts at developing an antagonist focused on a peptide analogue of AVP. Although initial trials seemed promising, trials in humans demonstrated that these molecules were partial AVP receptor agonists and further research was abandoned. More recently, nonpeptide, small-molecule AVP receptor antagonists have been introduced.

The first drug in this group, called the “vaptans,” was released in 2005. Conivaptan (Vaprisol, Astellas Pharma US) is an intravenous (IV) AVP antagonist with activity at the V₁₆ and V₂ receptors. The FDA approved conivaptan for the treatment of patients with euvolemic and hypervolemic hyponatremia. Its use is limited to hospitalized patients for no more than four days, largely because it has significant cytochrome P450 drug interactions.

Although this drug class increases serum sodium concentrations, there is still a need for an oral agent that is safe and effective for long-term use. The recent approval of tolvaptan (Samsca, Otsuka) may be able to fill this gap.

**CHEMICAL AND PHYSICAL PROPERTIES**

Tolvaptan is the first oral AVP antagonist. The 15-mg and 30-mg blue tablets are stamped with the label OTSUKA and the strength.

**MECHANISM OF ACTION**

Tolvaptan is a vasopressin antagonist that has a greater affinity and selectivity for the V₂ receptor than endogenous AVP. Antagonism at the V₂ receptor causes a decrease in the number of aquaporin-2 channels in the renal collecting tubules, resulting in decreased water reabsorption, a net increase in free water excretion (aquaresis), and an increase in serum sodium concentrations. This decrease in free water is not associated with an increased excretion of sodium or potassium ions; the increase in serum sodium concentration is solely a result of aquaresis.

**PHARMACOKINETICS**

**Absorption and Distribution**

The absolute bioavailability of a dose of tolvaptan is unknown, but at least 40% of the drug is absorbed after oral administration. The onset of effect is two to four hours after a dose is taken, and peak effects occur four to eight hours after administration. Taking tolvaptan with food does not appear to affect the drug’s bioavailability or its onset or duration of effect.

After tolvaptan is absorbed, it is 99% bound to circulating plasma proteins. The volume of distribution is approximately 3 L/kg, and it is increased in patients with moderate-to-severe hepatic impairment and HF; however, this does not affect the patient’s response to the drug. Renal impairment is not known to affect the distribution of tolvaptan.

**Metabolism and Excretion**

Tolvaptan is eliminated by the liver almost entirely by CYP 3A4 to inactive metabolites, and it is a substrate and inhibitor of P-glycoprotein. The terminal-phase half-life is 12 hours; however, increased serum sodium concentrations persist at 24 hours post-dose despite a return to baseline free water excretion. Although clearance is decreased in moderate and severe hepatic impairment and HF, these alterations do not appear to have a clinical effect. Renal impairment does not affect the excretion of tolvaptan.

**INDICATIONS**

Tolvaptan was approved for use in the U.S. in May 2009 for patients with hypervolemic and euvolemic hyponatremia, including those with HF, cirrhosis, and SIADH. In this case, hyponatremia is defined as a serum sodium level of less than 125 mEq/L. Patients with a serum sodium level of 125 to 134 mEq/L may be treated if they have symptoms and have not responded to fluid restriction.

**CLINICAL EFFICACY**

The efficacy of tolvaptan was evaluated in two sets of phase 3 clinical trials: the Study of Ascending Levels of Tolvaptan in Hyponatremia (the SALT trials) and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (the EVEREST Program). The SALT Trials

Two randomized, placebo-controlled, double-blind trials were conducted in parallel to assess the outpatient use of tolvaptan for hyponatremia secondary to various causes. The drug’s safety and reversibility of effect were also assessed. SALT-1 and SALT-2 were identical in methodology but were run in parallel in order to satisfy regulatory requirements. Patients were enrolled in the trials if they were 18 years of age or older and had euvolemic or hypervolemic hyponatremia (sodium levels below 135 mEq/L) secondary to HF, cirrhosis, or SIADH.

Patients were excluded from the SALT trials if they:

- exhibited a reversible cause of hyponatremia.
- had neurological pathology, including psychogenic polydipsia, progressive or episodic neurological disease (including cerebrovascular accidents), or neurological impairment, accompanied by a serum sodium level below 120 mEq/L.
- had a cardiopulmonary factor such as hemodynamic instability, myocardial infarction (MI), ventricular tachycardia or fibrillation, severe angina, or severe pulmonary hypertension.
- had undergone recent surgery.
- had a serum creatinine (Cr) level above 5 mg/dL, a Child–Pugh Score above 10, or urinary tract obstruction.
- had uncontrolled diabetes mellitus.
- could not tolerate sudden shifts in fluid volumes and pressures.
- had a small chance of short-term survival.

The authors predetermined that more than 50% of the study population needed to have marked hyponatremia (sodium level below 130 mEq/L), and no causative disease could represent more than half of the study population.

Enrolled patients were stratified according to the severity of hyponatremia. They initially received either tolvaptan or matching placebo for 30 days. The dose was initiated at 15 mg orally once daily and then titrated to a maximum of 60 mg once daily according to a protocol that provided for gradual correction of serum sodium (no more than a 12-mEq/L increase in 24 hours and an absolute serum sodium concentration not higher than 145 mEq/L). All patients...
were admitted to the hospital at the time of randomization, and most patients were discharged from the hospital by day 4. Active treatment ended at day 30, and patients were reassessed at day 37.

Primary outcomes were a change in the area under the curve (AUC) of the serum concentration of sodium from randomization to day 4 and from randomization to day 30. Prespecified secondary endpoints included a change in the AUC concentration of sodium in patients with marked hyponatremia, an absolute change in serum sodium levels, time to normalization of sodium concentrations, percentage of patients with normal sodium levels at days 4 and 30, and categorical serum sodium levels (i.e., normal, mild, or marked) for patients with obvious hyponatremia at randomization.

Other endpoints included fluid intake and output on day 1, a change in body weight on day 1 if patients were hypervolemic at randomization, fluid restriction or the use of IV saline rescue therapy, and a change from baseline in the physical component summary and mental component summary of the Medical Outcomes Study 12-item Short Form (SF-12) General Health Survey.

The SALT-1 trial enrolled 102 patients in the tolvaptan arm and 103 patients in the placebo arm. SALT-2 enrolled 123 patients in the tolvaptan arm and 120 patients in the placebo arm. Except for height, patients enrolled in each study group in both trials were similar in demographic and clinical characteristics, including the cause of hyponatremia.

In SALT-1, 77.5% of patients receiving the study drug and 63.1% of patients receiving placebo completed the entire 37-day study. In SALT-2, 74.8% of patients receiving the study drug and 74.2% of patients in the placebo arm completed the entire 37-day study.

Adverse events were similar between the two treatment groups in both trials. The most common adverse events attributed to tolvaptan were thirst (14% vs. 5% with placebo, respectively, and dry mouth, 13% vs. 4%, respectively).

Tolvaptan resulted in significant improvement of the primary endpoint of the trial, an increase in the AUC concentration of sodium at days 4 and 30 (Table 2). In the analysis of the secondary endpoints, fewer tolvaptan patients than placebo patients had marked hyponatremia at days 4 and 30. Patients who received tolvaptan had significantly increased urine output and significantly greater net fluid loss on day 1 \( (P < 0.001 \text{ for all comparisons}) \). Even though improved sodium and fluid status was noted, there was no significant difference in the number of patients requiring fluid restriction \( (P = 0.08 \text{ for each study}) \).

In terms of health status measures, no difference in the Physical Component Summary was noted. A significant difference in the Mental Component Summary was noted for the combined analysis of SALT-1 and SALT-2 \( (P = 0.02) \) and for the combined scores of patients with marked hyponatremia from both studies \( (P = 0.04) \). A difference was observed in the analysis of all patients enrolled in SALT-1 \( (P = 0.04) \), but no difference was observed in patients enrolled in SALT-2.

In summary, tolvaptan was effective in increasing serum sodium levels in patients with diverse disease states in the outpatient setting and serum sodium returned to baseline levels after tolvaptan was discontinued. The SALT studies were not designed to show a survival benefit or long-term safety.

### The EVEREST Clinical Status Trials

The EVEREST Program, a prospective, randomized, double-blind, placebo-controlled study, was conducted at 359 sites in North America, South America, and Europe. The program consisted of three trials: two short-term studies assessed the effects of tolvaptan on outcomes and clinical status, and a third study evaluated long-term outcomes of all patients from the short-term trials.

### Table 2 Changes in the Area under the Curve (AUC) of the Serum Concentration of Sodium in the SALT Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>SALT-1</th>
<th>SALT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change (mEq/L)( ^{‡} ) for all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>3.62 ± 2.68</td>
<td>0.25 ± 2.08</td>
</tr>
<tr>
<td>Day 30</td>
<td>6.22 ± 4.10</td>
<td>1.66 ± 3.59</td>
</tr>
</tbody>
</table>

\( ^{‡} \text{SALT = Study of Ascending Levels of Tolvaptan in Hyponatremia.} \)

\( ^{‡} \text{All values are mean ± standard deviation.} \)

\( ^{‡} P < 0.001 \text{ for all comparisons.} \)
Within 48 hours of hospitalization, enrolled patients were randomly assigned to receive either tolvaptan 30 mg orally daily or placebo along with standard HF therapy, including angiotensin-converting enzyme (ACE)–inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, diuretics, digoxin, and hydralazine plus nitrates. The intervention continued until the end of the long-term study.8

Patients were evaluated for the primary endpoint of the composite score of changes in self-assessed global clinical status and body weight from baseline to day 7 or at discharge, whichever occurred first. Secondary endpoints included:

- patient-assessed dyspnea at day 1 if dyspnea was present at baseline.
- global clinical status at day 7 or at discharge.
- body weight at days 1 and 7 or at discharge.
- peripheral edema at day 7 or upon discharge if edema was present at baseline.

Patients were continuously assessed for adverse events throughout the trial. Vital signs were monitored daily during hospitalization, and blood chemistry profiles were evaluated on inpatient day 1, day 7, and at discharge. Electrocardiograms were evaluated on days 1, 3, 6, 8, and upon discharge.8

EVEREST enrolled 4,133 patients; 2,048 patients were assigned to trial A (1,018 received tolvaptan; 1,030 received placebo) and 2,085 patients were assigned to trial B (1,054 received tolvaptan; 1,031 received placebo). The two groups in each trial were similar in terms of baseline demographic and clinical characteristics. Before day 7 or discharge from the hospital, 54 patients in trial A and 50 patients in trial B discontinued treatment. Of these, 12 patients receiving tolvaptan and four patients receiving placebo discontinued treatment because of unspecified adverse reactions.8

In terms of the primary endpoint, patients in both trials A and B showed statistically significant improvements in composite global clinical status and body weight at day 7 or at discharge (P < 0.001 for both trials). More patients with baseline dyspnea receiving tolvaptan showed improvement at day 1 (76.74% vs. 70.61%; P = 0.001 for trial A; 72.06% vs. 65.32%; P = 0.001 for trial B). In both trials, changes in global clinical status were similar for both tolvaptan and placebo (P = 0.51 for trial A; P = 0.52 for trial B).

Greater body weight reductions were associated with tolvaptan at days 1 and 7 or at discharge in both trials (P < 0.001 for all comparisons). Changes in pedal edema at day 7 or at discharge were significantly greater in the tolvaptan arm in trial B (P = 0.02) but were not statistically significant in trial A (P = 0.07).8

For the safety analysis, patients receiving tolvaptan experienced more treatment-emergent adverse events, dry mouth, and thirst. No significant differences were noted in BP, heart rate, renal failure, electrolyte abnormalities, or liver function abnormalities throughout the study. A post hoc analysis revealed a significantly greater decrease in dyspnea, rales, orthopnea, jugular venous distention, and furosemide dose in the tolvaptan arm during the inpatient stay.8

The EVEREST Clinical Status Trials demonstrated tolvaptan’s short-term ability to decrease body weight and dyspnea in hospitalized patients with HF when the drug was used with standard therapy but did not show an improvement in global clinical status. This study did not measure long-term data on clinical status or mortality.

**The EVEREST Outcome Trial**

The EVEREST Outcome Trial, which included all patients who had been randomized in the first set of trials, was designed to evaluate the long-term effects of tolvaptan therapy on clinical outcomes. Patients had to meet the same inclusion and exclusion criteria as for the short-term trials. After randomization, patients continued in the study for a minimum of 60 days during an initial inpatient hospitalization and a follow-up period. Follow-up extended until death, the predetermined end of the study, or patient withdrawal. Patients were observed for a median period of 9.9 months.

Primary endpoints included all-cause mortality and a composite of cardiovascular death and hospitalization for HF. All-cause mortality was subject to superiority and non-inferiority analyses, whereas only a superiority analysis was performed on the composite endpoint.

Secondary endpoints included:

- the composite of cardiovascular mortality or hospitalization.
- cardiovascular mortality.
- the incidence of clinically worsened HF.
- a change in body weight at day 1.
- sodium level at day 7 or at discharge if the baseline sodium level was below 134 mmol/L (134 mEq/L).
- edema at day 7 or discharge if edema was present at baseline.
- dyspnea on day 1 if dyspnea was present at baseline.
- the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at outpatient week 1.

Tertiary endpoints were a change in KCCQ domains at outpatient weeks 1 and 24 and at the end of treatment.

Patients were randomly assigned in a fashion identical to that of the short-term trials. In this study, 2,072 patients received tolvaptan and 2,061 patients received placebo. Adverse events caused 137 patients in the tolvaptan group and 115 patients in the placebo group to withdraw from the study. Thirst was the only adverse event to occur more frequently with tolvaptan in seven patients compared with none of the patients receiving placebo (P = 0.02).

In the analysis of all-cause mortality, tolvaptan did not show statistical superiority to placebo. In the tolvaptan group, 537 patients (25.9%) died; in the placebo group, 543 patients (26.3%) died (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.87–1.11; P = 0.68). In the non-inferiority analysis, however, tolvaptan did demonstrate that it was not worse than standard treatment (P < 0.001). Tolvaptan therapy did not improve the composite endpoint of cardiovascular death and hospitalization for HF (HR, 1.04; 95% CI, 0.95–1.14; P = 0.55).

For the secondary endpoints, tolvaptan did not cause a statistically significant difference in the composite of cardiovascular mortality or hospitalization, cardiovascular mortality, or the incidence of clinically worsened HF. However, in patients with dyspnea, significantly more patients who received tolvaptan reported decreased dyspnea at day 1 (74.3% vs. 68.0%, P < 0.001).
Tolvaptan use also resulted in significantly decreased body weight at day 1 ($P < 0.001$) and pedal edema at day 7 ($P = 0.003$). Larger increases in serum sodium were also observed with tolvaptan (mean [standard deviation], tolvaptan, 5.49 mEq/L [5.77 mEq/L], placebo 1.85 mEq/L [5.10 mEq/L], $P < 0.001$). This effect was observed starting on day 1 and continued through week 40 of the trial.

No changes in the KCCQ overall summary score were observed at week 1; however, significant increases were observed at the study’s end for the quality-of-life domain ($P = 0.003$), the social limitation domain ($P = 0.05$), and the overall summary score ($P = 0.02$) at the last on-treatment assessment at the end of the study.

Adverse events resulted in discontinuation of the study drug by 6.5% of tolvaptan patients and by 5.5% of placebo patients. The only adverse event that occurred more often with tolvaptan was thirst ($P = 0.02$). There were no significant differences noted in the rates of renal failure or hypotension, and similar downward trends in BP and heart rate were noted in both groups throughout the study period.

The EVEREST Outcome Trial did not demonstrate the superiority of tolvaptan to standard treatment in terms of mortality or rehospitalization but did confirm that this therapy was not inferior to standard treatment. Tolvaptan was also superior to placebo in terms of dyspnea, pedal edema, and quality of life.

**DOSEAGE**

**Adults**

Patients beginning tolvaptan treatment should be hospitalized to ensure appropriate therapeutic monitoring. The starting dose is 15 mg orally once daily without regard to meals. The dose should be titrated no more than once every 24 hours to a maximum of 60 mg daily. Fluid restriction should not be instituted for the first 24 hours of therapy to avoid rapid correction of the sodium level.

**Special Populations**

**Extremes of age.** No data are available regarding the use of tolvaptan in pediatric patients, and the drug is not approved for these patients. Dosage adjustments are not necessary for elderly patients.

**Organ dysfunction.** No dosage adjustments are necessary for patients with hepatic or cardiac dysfunction. Tolvaptan has been studied in patients with renal impairment, and there is no need for dosage adjustments in patients with a creatinine clearance (CrCl) of 10 mL/minute or greater. The drug has not been studied in patients with a CrCl below 10 mL/minute. Because of the drug’s mechanism of action, no benefit is expected in anuric patients; tolvaptan should not be used in these individuals.

**DRUG INTERACTIONS**

Although tolvaptan is associated with many drug interactions, the magnitude of these interactions is much smaller than that observed with conivaptan. Despite weaker interactions, tolvaptan is still contraindicated with strong CYP 3A4 inhibitors (e.g., clarithromycin, ketoconazole, itraconazole, and many protease inhibitors) and the drug may be less effective when used with potent CYP 3A4 inducers such as rifampin.

Dose reductions should be considered when tolvaptan is used with P-glycoprotein inhibitors such as cyclosporine. Tolvaptan may increase the concentrations of digoxin, but it does not alter the pharmacokinetics of warfarin (Coumadin, Bristol-Myers Squibb) or amiodarone (Cardarone, Wyeth). The pharmacokinetic properties of tolvaptan are not altered by lovastatin (Mevacor, Merck) or digoxin.

When tolvaptan is given concomitantly with furosemide (Lasix, Sanofi-Aventis) or hydrochlorothiazide, urine volumes are similar to those of tolvaptan administration alone. Tolvaptan may increase the rate of hyperkalemia when it is given with ACE-inhibitors, type II ARBs, and potassium-sparing diuretics.

**CONCLUSION**

Tolvaptan is the first oral vasopressin antagonist. Clinical trials have demonstrated its efficacy in normalizing serum sodium concentrations in a wide range of illnesses and its ability to decrease dyspnea and edema in patients with HF without causing renal failure. In view of these data, the drug should be considered to be an appropriate treatment option in patients with SIADH. However, tolvaptan has not yet shown a mortality benefit in patients with HF and should not be considered a component of standard pharmacotherapy for the disease. Future research may be able to identify a longer-term mortality benefit, or a specific subset of HF patients who may experience decreased mortality.

**REFERENCES**