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# TOLVAPTAN: A NEW APPROACH TO THE MANAGEMENT OF EUVOLEMIC AND HYPERVOLEMIC HYPONATREMIA

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Hyponatremia is the most common electrolyte disorder in the United States, occurring in approximately 15 to 20% of hospitalized patients.[1] Hyponatremia is classified as hypovolemic, euvolemic or hypervolemic, depending on the amount of fluid and solute. Hyponatremia is associated with morbidity and mortality among patients with heart and liver disease, neurological disorders, as well as syndrome of inappropriate anti-diuretic hormone secretion (SIADH).[2] This is significant because correction of the electrolyte imbalance in situations, such as chronic heart failure (CHF), liver cirrhosis and SIADH, can have drastic implications in the improvement and management of these disease states.

Chronic heart failure, liver cirrhosis, and SIADH are examples of conditions that are characterized by abnormal water retention mediated by arginine vasopressin (AVP) release inappropriate to plasma tonicity.[3] AVP produces its anti-diuretic effect on the kidneys through interactions with aquaporin 2 channels.[4] Systemic blood volume is an important non-osmotic trigger for AVP secretion.[4] Other non-osmotic triggers for AVP release include nausea and hypoglycemia.[4] Osmotic stimuli for AVP release occur through osmoreceptor detection of blood osmolality **(Figure 1)**. Subsequently, low plasma osmolality leads to the release of AVP, while high plasma osmolality inhibits AVP secretion.[4] An osmotic stimulus for AVP release that may have significant implications in CHF is atrial natriuretic peptide (ANP). ANP is released upon atrial stretch receptor activation which occurs during periods of volume expansion. High levels of ANP have been observed in hyponatremic patients and may contribute to hyponatremia by increasing natriuresis and solute depletion.[5]

Vasopressin mediates its effects through interactions with several receptors that have multiple actions throughout the body **(Table 1)**. There are 3 receptor subtypes, $V_{1A}$, $V_{1B}$, and $V_{2,}$ which differ based on localization and signal transduction pathways. AVP binds to $V_{1A}$ receptors on vascular smooth muscle, leading to peripheral vasoconstriction, an increase of intracellular calcium within myocytes, and direct myocardial muscle stimulation.[6] AVP activity at $V_{1B}$ receptors occurs at the pituitary gland and mediates the release of adrenocorticotropic hormone (ACTH).[7] $V_2$ receptors in the kidney are the primary receptors responsible for the anti-diuretic effects of vasopressin.

Tolvaptan (tôl vâp´ tân) is an oral, non-peptide $V_2$ receptor antagonist manufactured by Otsuka Pharmaceutical Company. Tolvaptan is currently being studied for use in euvolemic and hyper-

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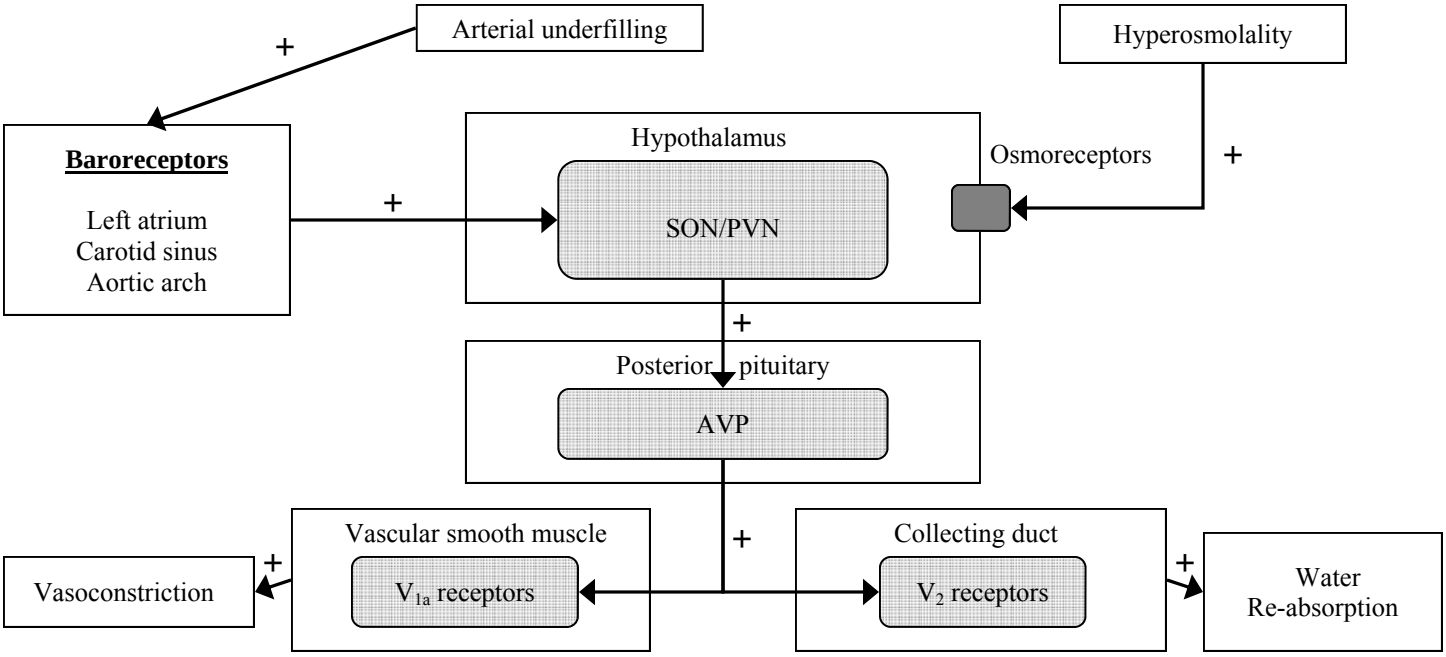
**Figure 1. Process of water regulation by vasopressin**




Osmoreceptors residing in the anteroventral third ventricle region of the hypothalamus detect increased serum osmolality thereby stimulating the production of AVP. Baroreceptors located in the left atrium, carotid sinus, and aortic arch detect arterial underfilling which stimulate neurons in the SON and PVN to produce AVP (the atrial receptors are mediated by the vagus nerve rather than blood pressure). The neurons of the SON and PVN project into the posterior pituitary gland where AVP is initially stored and then released into the circulation. $V_{1a}$ receptors located in the vascular smooth muscle sense increased levels of AVP and cause vasoconstriction. AVP also stimulates $V_2$ receptors located in the collecting duct of the kidney which cause free water absorption.

volemic hyponatremia associated with CHF, cirrhosis, or SIADH. Ultimately, tolvaptan increases excretion of free water resulting in serum sodium concentration increases.[2] Tolvaptan is different from its AVP receptor antagonist predecessor, conivaptan (Travisol®), in that it is selective for $V_2$ receptors and is able to be given orally. This article will discuss the clinical pharmacology, efficacy and tolerability of tolvaptan.

## Clinical Pharmacology

AVP receptor antagonism provides a promising mechanism for a new class of drugs designed to manage hyponatremic disorders. This class of drugs increases serum sodium concentrations and promotes aquaresis with good tolerability.[8] Tolvaptan exerts its effects through $V_2$ receptors of the distal nephron. $V_2$ receptors are coupled to aquaporin channels in the apical membrane of the renal collecting ducts. These

**Table 1. Vasopressin receptor location and function**

| Receptor | Localization | Function |
|---|---|---|
| $V_{1A}$ | Vascular smooth muscle | Vasoconstriction, myocardial hypertrophy |
| $V_{1B}$* | Anterior pituitary | ACTH release |
| $V_2$ | Basolateral membrane of collecting tubule | Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis |
| | Vascular endothelium and vascular smooth muscle | Vasodilation |

*Termed $V_3$ in some references ACTH, adrenocorticotropin hormone; AQP2, aquaporin-2 Adapted from Janicic N, et al.[1]

receptors are integral to maintain plasma osmolality within the normal range. As expected from this class of drugs, the primary pharmacodynamic effect of $V_2$ antagonism is excretion of free water.

**Clinical Evidence**

*Tolvaptan in CHF, cirrhosis and SIADH*

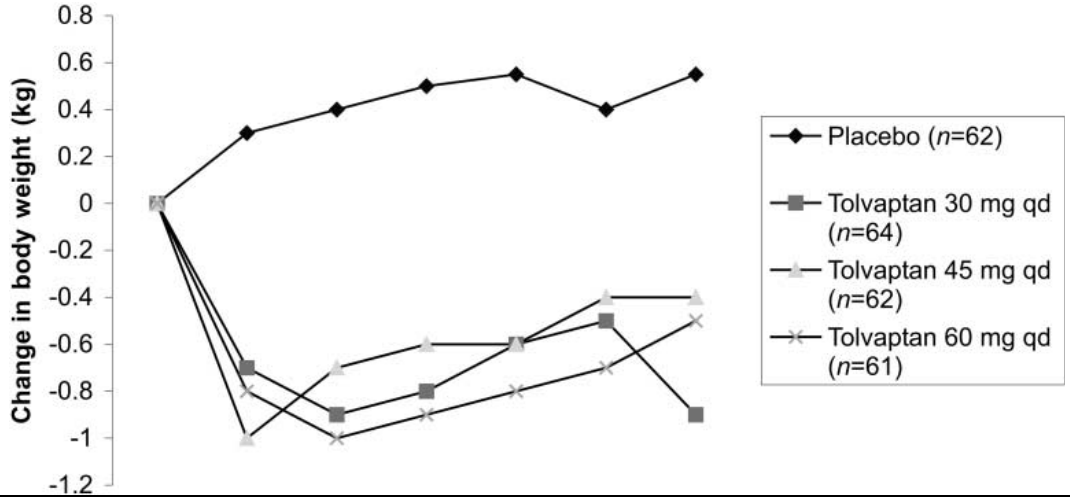
In the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT 1 and SALT 2)[2], patients with serum sodium concentrations < 135 mmol/L were randomly assigned to tolvaptan or placebo for 30 days. The study was double-blinded with 15 mg of tolvaptan administered orally with dose adjustments to 30 mg or 60 mg as needed. The mean age was 62 years, 42% of the patients were women, and the 2 groups were roughly equal at 225 and 223 subjects for tolvaptan and placebo, respectively. The source of hyponatremia could be linked to CHF in 31% of patients, cirrhosis in 27% of patients and SIADH or other causes in 42% of patients. Mean baseline serum sodium concentrations in the two groups was 129 mmol/L. Serum sodium levels were measured on days 4 and 30, revealing an increase in serum sodium of 4 mmol/L and 6 mmol/L, on respective days, in the tolvaptan treated group. The placebo treated group showed no increase in serum sodium at day 4 and an increase of 2 mmol/L at day 30 ($p<0.001$). Results further showed that in the tolvaptan group, > 40% of patients had a normal serum sodium by day 4 and approximately 55% of patients by day 30. The placebo treated group had approximately 10% of patients reach normal serum sodium levels by day 4 and 25% by day 30 ($p<0.001$).[2]

The most prevalent adverse effects were dry mouth and thirst. There were 14 deaths in the tolvaptan group and 13 deaths in the placebo group during a mean follow-up of 37 days. The authors concluded that vasopressin antagonists can correct hyponatremia, but the effect on mortality should still be explored.[2]

*Tolvaptan in CHF NYHA class II and III*

Gheorghiade et al.[9] studied the efficacy of tolvaptan in 254 patients with CHF NYHA class II or III, who were not on fluid restriction. Patients were maintained on stable doses of furosemide and randomized to receive 30, 45, or 60 mg tolvaptan or placebo once daily for 25 days. After 24 hours, the tolvaptan treated patients lost 0.8 kg on average versus the placebo group who gained 0.32 kg. **(Figure 2)** The weight loss was similar in all dosage groups and continued with no added weight loss over the remainder of the study period. At the conclusion of the 25 day study period, tolvaptan was shown to have significantly increased urine output, reduce body weight, and improve clinical signs and symptoms of heart failure. Additionally, the tolvaptan treated group demonstrated normalization of serum sodium levels and reduction of edema, whereas the placebo group did not. Hypernatremia was documented in 5, 6, 11, and 13% of patients in the placebo, tolvaptan 30 mg, 45 mg , and 60 mg groups. Polyuria, thirst, and dry mouth were the most common adverse effects. The authors concluded that tolvaptan provided a moderate effect on weight loss and demonstrated a normalization of serum sodium levels without sig-

**Figure 2. Changes in body weight**




Significant (P=0.001) decreases in body weight were observed primarily on the first day of treatment with all three doses of tolvaptan compared with placebo. These reductions persisted throughout the 25 days of the study. Adapted from ref. Gheorghiade et al.[9]

nificant hypernatremia.[9]

*Tolvaptan in CHF exacerbation*

In the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure trial (ACTIV in CHF), 319 patients from multiple centers across the United States were randomized to receive tolvaptan at doses of 30, 60, or 90 mg per day or placebo for 60 days. The patients had ejection fractions < 40% and were hospitalized for acute CHF exacerbation. The primary endpoint was in-hospital weight loss at 24 hours. The tolvaptan treated group demonstrated greater weight loss than the placebo group: −1.80 (−3.85 to −0.50), −2.10 (−3.10 to −0.85), −2.05 (−2.80 to −0.60), and −0.60 (−1.60 to 0.00) kg for the groups receiving tolvaptan 30, 60, and 90 mg, and placebo (p=.002, .002, and .009 for the 3 tolvaptan groups compared with the placebo group) Additional secondary endpoints were worsening heart failure or unexpected hospital visits for CHF exacerbations over the 60 day period. These endpoints were not significantly different.[10]

*Tolvaptan versus fluid restriction*

Fluid restriction has served as a fundamental strategy in the correction of hyponatremia. In a randomized, double-blind study by Gheorghiade et al.[11], treatment with tolvaptan was compared to fluid restriction when attempting to achieve normal serum sodium concentrations, defined as concentrations >135 mmol/L or > 10% increase from baseline. The treatment group received tolvaptan alone at 10 mg/day with increases to 60 mg/day as needed, whereas the fluid restriction group did not consume more than 1,200 ml/day in addition to placebo. Treatment continued for 27 days with a total of 65 days of follow up. At the last in-patient visit, the tolvaptan group demonstrated an increase in serum sodium of 5.7 mmol/L compared to 1.0 mmol/L in the fluid restriction group (p=0.006). Tolvaptan appeared to be more effective than fluid restriction in the normalization of serum sodium. Adverse effects were similar in both groups.[11]

*Tolvaptan and cardiovascular mortality*

In one of the more anticipated studies to include tolvaptan, Konstam et al.[12] investigated the mortality benefits in The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST). The trial consisted of 4,133 patients who were randomized to tolvaptan 30 mg daily or placebo within 48 hours of hospital admission, for a minimum of 60 days in addition to standard therapy. The primary endpoints were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Data was collected for 28 months with a median follow-up of 9.9 months. During the follow-up period, 537 patients (25.9%) in the tolvaptan treated group and 543 patients (26.3%) in the placebo group died (HR 0.98; 95% confidence interval [CI], 0.87-1.11; p=.68). The rate of cardiovascular death or hospitalization for heart failure occurred in 871 (42%) patients in the tolvaptan group and 829 (40.2%) patients in the placebo group (HR 1.04; 95% CI, 0.95-1.14; p=.55). There were also no differences in the secondary endpoints of cardiovascular death, cardiovascular hospitalization and worsening heart failure. However, in the short term, tolvaptan did provide added body weight reduction and relief of dyspnea on days 1 and 7 after admission, in lieu of discharge.[13] Adverse effects were similar between tolvaptan and placebo groups, and no signs of hypotension or worsening renal dysfunction were reported.[13]

**Adverse Effects**

Tolvaptan was generally well tolerated during clinical trials. The most common adverse effects were dry mouth, thirst and polyuria. A summary of the important adverse effects is included in **Table 2**.

**Cost and Dosing**

Tolvaptan is currently not marketed in the United States and is undergoing phase III clinical trials. Specifics pertaining to cost and availability are not available at this time. In two clinical trials for the treatment of euvolemic and hypervolemic hyponatremia, tolvaptan was initiated at 15 mg by mouth once daily. The dose can be increased to 30 mg, then 60 mg per day as needed based on serum sodium levels.[2] In addition, patients hospitalized with acute decompensated heart failure were randomized to receive 30 mg by mouth daily within 48 hours of admission for a minimum of 60 days.

**Summary**

Tolvaptan is a new approach to the management of hyponatremia. It provides an effective and tolerable alternative to the current utilization of fluid

**Table 2. Summary of adverse events in clinical trials**

| Adverse event | Tolvaptan (%) | Placebo (%) |
|---|---|---|
| Thirst | 14 | 5 |
| Dry Mouth | 13 | 4 |
| Ascites | 6 | 6 |
| Constipation | 7 | 2 |
| Diarrhea | 5 | 6 |
| Nausea | 8 | 6 |
| Vomiting | 3 | 9 |
| Fatigue | 5 | 5 |
| Peripheral edema | 7 | 7 |
| Weakness | 9 | 5 |
| Urinary tract infections | 6 | 4 |
| Hyperglycemia | 5 | 1 |
| Hyperkalemia | 5 | 5 |
| Dizziness | 7 | 5 |
| Headache | 7 | 7 |
| Urinary frequency | 7 | 3 |
| Hypotension | 7 | 6 |

retention, hypertonic 3% saline and pharmacological modalities such as demeclocycline, urea and lithium which are often associated with poor patient compliance and limited variability.[14] The evidence supports the short term benefits of symptom relief associated with diuresis; however, reduction in mortality and CHF-related morbidity have not been elucidated. If approved, it remains to be seen where tolvaptan will reside within the armamentarium of strategies employed to combat CHF. Further research is needed to uncover the benefits that this class of drugs may provide.

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## DRUG UPDATE

**Pregabalin (Lyrica®)** - *Pfizer, Inc.*

In June 2007, pregabalin was the first drug approved by the FDA for the management of fibromyalgia. Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA) that acts through binding to the $\alpha_2$-$\delta$ subunit of calcium channels. Pregabalin has anxiolytic, analgesic, and antiepileptic properties. As such, pregabalin is also indicated for neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, and adjuctive therapy for adults with partial onset seizures. Starting dose for the treatment of fibromyalgia is 150 mg daily in divided doses. Target dose is 300 to 450 mg per day in 2 divided doses. The dose should be adjusted in patients with reduced renal function. The most common adverse effects include dizziness, somnolence, dry mouth, edema, blurred vision, and weight gain. Pregabalin is a Schedule V controlled substance.

**Budesonide:Formoterol (Symbicort®)** - *AstraZeneca*

Budesonide:formoterol is now available for use. Budesonide:formoterol is a combination of a corticosteroid and a long acting beta-2 agonist administered by oral inhalation via metered-dose inhaler (MDI) approved by the FDA in July 2006. Historically, budesonide (Pulmicort®) and formoterol (Foradil®) have been administered as dry powder inhalers, but this combination product is administered as a MDI. Budesonide:formoterol is indicated for long-term maintenance treatment of asthma. Depending on asthma severity, the recommended dose is 2 inhalations of Symbicort® 80/4.5 (80 mg of budesonide and 4.5 mcg of formoterol per inhalation) or Symbicort® 160/4.5 (160 mg of budesonide and 4.5 mcg of formoterol per inhalation) twice daily. Budesonide:formoterol has not been proven safe and effective in children less than 12 years.

**Armodafinil (Nuvigil®)** *Cephalon, Inc.*

Armodafinil is a single isomer of the parent drug, modafanil (Provigil®), that was recently approved by the FDA for treating excessive sleepiness associated with narcolepsy, shift work sleep disorder (SWSD), or obstructive sleep apnea/hypopnea syndrome (OSA/HS). Armodafinil is classified as a C-IV controlled substance. Armodafinil may increase excitatory glutaminergic transmission in the thalamus and hippocampus, thus promoting wakefulness. The approved dose is 150 mg or 250 mg daily in the morning for OSA/HS and narcolepsy; for SWSD, 150 mg 1 hour before shift work starts. The most common adverse effects in clinical trials were headache, nausea, dizziness, insomnia, and anxiety.

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