

Conivaptan HCl for Injection (Vaprisol): A Vasopressin Antagonist for the Management of Euvolemic Hyponatremia

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INTRODUCTION

Hyponatremia, a common electrolyte disorder, is defined as a serum sodium level of less than 135 milliequivalents per liter (mEq/L).¹ The estimated prevalence of hyponatremia in the U.S. ranges from 3.2 to 6.1 million persons per year.²

About 1% of patients have an acute and symptomatic presentation of hyponatremia, and 4% are reported to have an acute presentation but no symptoms.² Another 15% to 20% of patients have chronic and symptomatic hyponatremia, and 75% to 80% of patients have chronic hyponatremia but are asymptomatic.²

Most patients have asymptomatic hyponatremia; however, when symptoms appear, sodium levels usually drop below 120 mEq/L. Usually, symptoms are non-specific, such as headache, lethargy, and nausea. In severe cases, neurological manifestations, including seizures and coma, may occur.³

Hyponatremia is common in hospital and ambulatory settings.^{4,5} The prevalence of hyponatremia in nursing-home residents was studied in a retrospective and prospective record review at a Veterans Affairs facility.⁵ Of 119 patients studied, 18% of patients were found to be hyponatremic according to random serum sodium levels, and a 12-month screening series revealed that 53% of patients had experienced at least one

episode of hyponatremia during the study period.⁵

An acute and symptomatic episode of hyponatremia may be associated with morbidity and mortality. Mortality rates as high as 17.9% have been reported in hospitalized patients.⁶ Even in patients with mild chronic hyponatremia, who are normally considered asymptomatic, the morbidity rate is high.⁷

The incidence of falling was higher in patients with a mean serum sodium level of 126 ± 5 mEq/L (21.3%) than in those without hyponatremia (5.3%). The adjusted odds ratio was 67, with a 95% confidence interval (CI) of 7.5 to 607 ($P < 0.001$).⁷

In addition to the morbidity and mortality associated with hyponatremia, this condition is costly to treat. The direct costs of managing hyponatremia range from \$1.6 to \$3.6 billion per year in the U.S.²

WATER AND SODIUM BALANCE

Total body water and sodium homeostasis are interdependent. Sodium is primarily an extracellular ion, and an increase in serum sodium results in increased tonicity of the plasma, which stimulates the thirst center and arginine vasopressin secretion from the posterior pituitary gland in the hypothalamus of the brain.^{3,8}

Arginine vasopressin, also known as antidiuretic hormone (ADH), acts on the vasopressin 2 (V_2) receptors in the collecting ducts of renal tubules, causing an increase in water reabsorption and in the production of concentrated urine. This mechanism is mediated by cellular membrane transport proteins called *aquaporins*.⁹ The opposite result occurs with decreased extracellular sodium: inhibition of the thirst center and arginine vasopressin secretion, leading to diuresis.^{3,8}

CLASSIFICATION OF HYPONATREMIA

There are three types of hyponatremia, as defined by the water volume:^{8,10}

- hypervolemic (edematous, or increased water)
- hypovolemic (volume-depleted)
- euvolemic (normal volume)

Hypervolemic hyponatremia is identified by an increase in total body water and sodium; there is more water than sodium, with the excess of water resulting in edema. Clinically, this type may be present in patients with congestive heart failure or liver or kidney disease. It is evident from the patient's history and physical examination.^{3,10}

Hypovolemic hyponatremia is caused by a deficit in total body water and a greater loss of total body sodium.

Patients with euvolemic hyponatremia have normal or nearly normal total body sodium levels.¹⁰

To distinguish between hypovolemic and euvolemic hyponatremia, physicians assess plasma osmolality and urinary sodium concentrations.¹⁰ Plasma osmolality can be normal, high, or low. Measuring the urinary sodium concentration is beneficial in patients with low plasma osmolality.

The presence of *normal* plasma osmolality (280–300 mOsm/kg) and hyponatremia can be caused by *pseudohyponatremia*. Pseudohyponatremia is present when large-molecular-weight particles circulate in the plasma, such as during hypertriglyceridemic and hyperproteinemic states. These patients usually have euvolemic hyponatremia, because osmolality is unchanged; however, sodium levels appear falsely decreased.

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High plasma osmolality and hyponatremia may be present in cases of severe hyperglycemia, resulting in an increased osmotic pull of glucose molecules, leading to dilution of plasma. Osmotic diuresis from glucose then results in hypovolemic hyponatremia.

Low plasma osmolality can be present in hypovolemic or euvolemic hyponatremia; therefore, the health care provider must know the concentration of urinary sodium in order to differentiate hypovolemic from euvolemic hyponatremia.

Concentrated urine or excess renal sodium loss can be identified if the urinary sodium concentration is high, defined as more than 30 mEq/L of sodium. In these cases, hyponatremia is euvolemic and may be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism, or medications.

Low urinary sodium concentrations are present in patients with hypovolemic hyponatremia. In this case, the body attempts to conserve sodium. This state occurs in severe burns, gastrointestinal (GI) losses from vomiting or diarrhea, or in acute water overload. The use of diuretics may also induce a state of hypovolemia.^{3,8,10}

TREATMENT

The management of hyponatremia depends on the severity of symptoms and the etiology.

Acute severe hyponatremia (a serum sodium level below 125 mEq/L) that develops within 48 hours may be associated with neurological symptoms, such as cerebral edema; therapy with hypertonic saline is required.¹¹

In patients with chronic euvolemic hyponatremia, the mainstay of therapy is fluid restriction to less than 1 to 1.5 liters (L) per day.¹² Demeclocycline (Declomycin, Wyeth), an antibiotic, may also be beneficial in patients with SIADH.¹³

In patients with hypervolemic hyponatremia, fluid restriction and loop diuretics are used.¹⁴

The latest approach to management of hyponatremia is a development of a new class of medications called arginine vasopressin receptor antagonists, known as *aquaretics*. The first medication of this class was approved by the Food and Drug Administration (FDA) for treating

euvolemic hyponatremia in a setting of SIADH, hypothyroidism, adrenal insufficiency, or pulmonary disorders in hospitalized patients.¹⁵ Conivaptan (Vaprisol, YM-087, Astellas) was originally developed by Yamanouchi Pharmaceuticals and was approved in December 2005. Although this agent has been studied primarily in patients with hypervolemic hyponatremia, it is currently approved only for euvolemic hyponatremia and only in the injectable form.

PHARMACOLOGY

Conivaptan, a derivative of the benzazepines, is a nonpeptide, dual-vasopressin antagonist with a high affinity for human vasopressin receptors V_{1A} and V_2 .¹⁶⁻²³ Vasopressin receptors are found on the vascular smooth muscle cells, the myocardium, and the distal tubule of the kidney.²⁴

The pharmacological effect of conivaptan in hyponatremia is carried out by the antagonism of V_2 receptors, located in the renal collecting ducts. The V_2 receptors are coupled to aquaporin channels in the apical membrane of the collecting ducts. These receptors help to maintain plasma osmolality within the normal range.

The antagonism of V_2 receptors results in *aquaresis*, or an increase in free water excretion or effective water clearance, net fluid loss, increased urine output, and decreased urine osmolality.²¹ Conivaptan is thought to enhance free water excretion with less effect on electrolyte balance, when compared with a diuretic such as furosemide (Lasix, Sanofi-Aventis), based on animal data and case reports.^{21,25} Conivaptan also constricts blood vessels via vascular V_{1A} receptors.^{26,27}

PHARMACOKINETICS

Conivaptan is currently approved as an intravenous (IV) infusion.¹⁵ Pharmacokinetic parameters following an IV infusion of 40–80 mg/day and oral administration are nonlinear, and inhibition by the drug of its own metabolism seems to be the major cause of the nonlinearity.^{15,28}

Because of these nonlinear pharmacokinetic properties, the absolute bioavailability of conivaptan has not been established; however, Burner et al. reported that after a single oral dose of

conivaptan 60 mg, oral bioavailability ranged from 34% to 55% in six healthy volunteers with a 90% CI ranging from 28% to 60%.²⁸

The mean termination elimination half-life after IV administration of conivaptan was five hours, and the mean clearance was 15.2 L/hour.¹⁵ Conivaptan binds to plasma proteins at a rate of 99% over a concentration range of 10 to 1,000 ng/ml.

The hepatic cytochrome P450 (CYP 450) 3A4 enzyme system is responsible for conivaptan's metabolism.¹⁵ Four metabolites have been identified. The pharmacological activity of the metabolites at the V_{1A} and V_2 receptors is minimal. Most of the drug is excreted in the feces (83%). The effects of hepatic or renal impairment on the pharmacokinetics of IV conivaptan have not been systematically evaluated.

EFFICACY IN CLINICAL TRIALS

Euvolemic Hyponatremia

Conivaptan has been approved by the FDA only as an injection, but some studies have involved the oral form. Following is a summary of studies including both oral and injectable formulations.

Verbalis et al.^{29,30}

The effects of conivaptan on serum sodium levels in patients with SIADH and congestive heart failure were reported in two publications. A randomized, double-blind, multicenter, placebo-controlled, parallel-group study enrolled participants 18 years of age or older. Their serum sodium concentrations ranged between 115 and 130 mEq/L. The patients were given placebo or a 20-mg bolus injection of conivaptan, followed by a continuous infusion of 40 mg/day or 80 mg/day for four days.

The primary efficacy measure was a change in serum sodium area-under-the-curve (AUC) concentrations from the baseline value over the treatment period.

Secondary outcomes included change in serum sodium levels from the baseline at day four, the time from the first dose to achieve a 4-mEq/L increase in serum sodium, the number of patients achieving more than a 6-mEq/L change in serum sodium or normal serum sodium, and effective water clearance. Baseline serum sodium levels were equivalent among the three groups and ranged from

123.3 ± 4.7 to 124.8 ± 3.4 mEq/L.

The least square mean change in serum sodium AUC concentrations to day four was statistically significantly higher in patients receiving conivaptan 40 mg/day (490.9 ± 56.8 mEq/L per hour) and in patients receiving 80 mg/day (716.6 ± 60.5 mEq/L per hour), compared with those receiving placebo (12.9 ± 61.2 mEq/L per hour) ($P < 0.001$).

The least square mean change in serum sodium concentrations at the fourth day was 6.8 ± 0.8 mEq/L with conivaptan 40 mg/day, 9 ± 0.8 mEq/L with 80 mg/day, and 2 ± 0.8 mEq/L with placebo ($P < 0.001$).

The median time from the first dose to an increase of 4 mEq/L in the serum sodium level was 23.7 hours with 40 mg/day and 23.4 hours with 80 mg/day, compared with placebo ($P < 0.001$). In the 40-mg/day group, 69% of patients achieved more than 6 mEq/L or a normal serum sodium concentration ($P < 0.01$). In the group receiving 80 mg/day, 88.5% of patients showed the same findings, compared with 20.7% of those receiving placebo ($P < 0.001$).

The mean change from baseline in effective water clearance on the first day was 1,984 ± 1,559.4 ml with conivaptan 40 mg/day, 1,759.4 ± 1,748.3 ml with 80 mg/day, and -332.3 ± 434.1 ml with placebo ($P < 0.05$).

Gross et al.³¹

The efficacy of oral conivaptan was evaluated in patients with euvoletic and hypervolemic hyponatremia as well as in some patients with heart failure. The randomized, double-blind study was conducted in 17 European medical centers and enrolled 52 euvoletic and 31 hypervolemic hyponatremic patients. Serum sodium levels ranged between 115 and 130 mEq/L, and plasma osmolality was less than 290 mOsm/kg H₂O. Patients were assigned to receive placebo, conivaptan 40 mg, or conivaptan 80 mg/day in two divided oral doses for five days.

Conivaptan demonstrated dose-dependent increases in serum sodium concentrations and effective water clearance ($P < 0.05$).

The primary outcome, the mean least square change from baseline to the end-of-study in serum sodium, as measured by the area-under-the-sodium time curve, revealed a dose-dependent in-

crease in this parameter. For 80 mg, it was 952.7 ± 85.7 mEq/L per hour; for 40 mg, it was 634.2 ± .2 mEq/L per hour; and for placebo, it was only 87.5 ± 80.8 mEq/L per hour ($P = 0.0001$).

Ghali et al.³²⁻³⁴

In a similar study, the efficacy of the same oral dose of conivaptan was evaluated in 74 euvoletic and hypervolemic patients with hyponatremia. This study revealed the same dose-dependent increase in serum sodium concentrations. A significant increase in serum sodium levels was demonstrated by the mean change in serum sodium on day five with conivaptan 80 mg/day (7.9 ± 1 mEq), with 40 mg/day (6.4 ± 1 mEq), and with placebo (3.9 ± 1.1 mEq) ($P < 0.05$).

These study results have now been published,³³ and the combined results of all of these trials with oral and IV conivaptan are available in abstract form.³⁴

Decaux³⁵

Decaux reported two patients with symptomatic hyponatremia, caused by SIADH, who were treated with oral conivaptan therapy for three months. The treatment was compared with therapeutic water restriction, urea, and furosemide.

The first patient was a 45-year-old man with history of seizure disorders who had been treated with phenytoin (e.g., Dilantin, Pfizer). He also had SIADH resulting from post-traumatic subdural hematoma for several years. His serum sodium level at nadir was 108 mmol/L. Hyponatremia was successfully treated with water restriction while he was hospitalized, but it returned after fluid restriction was abandoned.

When the serum sodium level fell below 120 mmol/L, the patient had a recurrent seizure. Fluid restriction, combined with urea 30 g daily, increased the serum sodium concentration from 125 to 130 mmol/L.

Similar results were achieved when therapy was supplemented with furosemide 30 mg/day, sodium chloride 3 g/day, and potassium chloride 1 g/day. With these combined therapies, the sodium level rose from 132 to 140 mmol/L and was maintained for three years.

For three months, this patient was subsequently treated with conivaptan 20 mg

twice daily, and his serum sodium level was steadily maintained at average of 138 mmol/L. After conivaptan was discontinued, hyponatremia returned but at a lower rate than previously. The patient was being treated with fluid restriction and urea, resulting in a serum sodium level above 135 mmol/L.

Another patient was a 55-year-old woman with chronic SIADH following a meningeal hemorrhage. She had been previously treated with fluid restriction and urea, followed by furosemide. Her serum sodium level ranged from 127 to 137 mmol/L. After a three-month trial of conivaptan at 20 mg twice daily, her average serum sodium was maintained at 135 mmol/L or greater. Following therapy with conivaptan, maximum diuresis occurred during the first four hours. There were no clinically significant changes in blood pressure or in pulse rate during treatment.

In both patients, urine osmolality decreased and urine flow increased following conivaptan therapy. Conivaptan was effective in these two cases of chronic symptomatic hyponatremia secondary to SIADH.

Martinaz-Castelao³⁶

In an open-label titration study, patients with SIADH with serum sodium levels below 132 mEq/L were given oral conivaptan 20, 40, or 80 mg daily. Serum sodium levels were normalized in all five patients, with an increase in free-water clearance and a reduction in urine osmolality. After conivaptan was discontinued, hyponatremia recurred in all of the patients.

Congestive Heart Failure

Various neuroendocrine hormones are involved in regulating heart function. Among them, arginine vasopressin is responsible for volume homeostasis, controlled by V₂ receptors, and for vascular tone, regulated by V_{1A} receptors. It has been proposed that excessive arginine vasopressin activity might contribute to the development of hyponatremia and edema in patients with heart failure.²⁷

Physiological actions associated with stimulation of the V_{1A} receptor include arteriolar vasoconstriction, increased systemic vascular resistance (SVR), increased afterload, and myocardial hypertrophy.²⁷

Physiologic effects resulting from V_2 receptor stimulation include sodium and water retention, increased preload, increased pulmonary capillary wedge pressure (PCWP), and increased left ventricular filling pressure.²⁷ Currently, the benefit of vasopressin antagonists in the treatment of heart failure remains uncertain; however, the evidence is accumulating.

Udelson et al.²⁴

The hemodynamic effects of conivaptan were evaluated in 142 patients with symptomatic heart failure of New York Heart Association (NYHA) class III and IV. In a double-blind study, the patients were randomly assigned to receive placebo or a single IV dose of conivaptan 10 mg, 20 mg, or 40 mg. PCWP was significantly lower in patients given 20 mg and 40 mg of conivaptan (-5.4 ± 0.7 and -4.6 ± 0.7 mm Hg, respectively), compared with placebo (-2.6 ± 0.7 mm Hg) ($P < 0.05$).

During the three- to six-hour interval after IV administration, right atrial pressure was lower in patients receiving conivaptan 20 mg (-3.7 ± 0.4 mm Hg) and 40 mg (-3.5 ± 0.4 mm Hg), compared with those receiving placebo (-2.0 ± 0.4 mm Hg) ($P < 0.05$).

During the first four hours after the dose was given, conivaptan significantly increased urine output in a dose-dependent manner: 10 mg, 68 ± 17 ml/hour; 20 mg, 152 ± 19 ml/hour; 40 mg, 176 ± 18 ml/hour; and placebo, -11 ± 17 ml/hour ($P < 0.001$).

Changes in cardiac index, SVR, pulmonary vascular resistance (PVR), blood pressure, and heart rate did not differ among patients receiving conivaptan and placebo.

Russell et al.³⁷

ADVANCE (A Dose evaluation of a Vasopressin Antagonist in CHF patients undergoing Exercise) was a multicenter, double-blind, placebo-controlled, randomized trial designed to investigate the effect of conivaptan on functional capacity in patients with heart failure. The study enrolled 345 patients with NYHA class II to IV symptoms who were being treated with standard pharmacotherapy for heart failure. Three oral doses of conivaptan were compared with placebo for 12 weeks.

Currently, only the methodology of this unique trial has been published. More results are anticipated in the future.

SAFETY

Adverse Effects

Reactions at the Infusion Site

The most common adverse drug effects (ADEs) related to conivaptan are infusion-site reactions during IV administration, possibly as a result of propylene glycol, which is irritating to the veins.¹⁵ These reactions occur at a frequency of 52.5% in conivaptan patients, compared with 3.3% in placebo-treated patients.

Most of these reactions have been mild, but when serious reactions occurred, they resulted in discontinuation of therapy. The most frequent events at the infusion site were general reactions (20.2%), phlebitis (15.8%), pain (7.7%), cannula reactions (5.5%), erythema (4.9%), and swelling (2.7%).

Peripheral Edema

Peripheral edema has been reported in 5.5% of patients. Conivaptan must be diluted in dextrose 5% solution and administered diluted via large veins. The infusion site should be rotated every 24 hours.

Cardiovascular Events

The most frequent cardiovascular ADEs were orthostatic hypotension (5.5%), hypertension (5.5%), atrial fibrillation (2.7%), and hypotension (2.7%). If hypovolemia or hypotension develops, the drug should be discontinued, followed by frequent monitoring of volume status and vital signs.

Metabolic and Renal Events

The most common metabolic and renal disorder abnormalities in patients treated with conivaptan included hypokalemia (9.8%), thirst (9.8%), frequent daytime urination (6%), polyuria (4.9%), hypoglycemia (3.3%), hyponatremia (3.3%), hyperglycemia (2.7%), hypomagnesemia (2.2%), and dehydration (2.2%). Serum sodium concentrations and volume status should be monitored frequently.

Neurological Events

The most frequent neurological ad-

verse reactions were headache (12%), confusion (3.8%), and insomnia (3.3%). If the serum sodium level continues to rise, conivaptan infusion should be stopped and the patient's neurological status should be re-evaluated before conivaptan is continued.

Gastrointestinal Events

Common GI ADEs included nausea and vomiting (6.6%), diarrhea (5.5%), constipation (4.9%), and dry mouth (4.4%).

Drug Interactions

Because conivaptan is a substrate of the CYP450 3A4 enzyme system, coadministration of inhibitors of this isoenzyme may lead to elevated conivaptan plasma concentrations. In its own right, conivaptan is a potent inhibitor of CYP 3A4, and it can increase the concentration of other drugs that are metabolized by this enzyme system.

The manufacturer warns against the concomitant use of potent CYP450 3A4 inhibitors, including ketoconazole (Nizoral, Janssen), itraconazole (Sporanox, Janssen) clarithromycin (Biaxin, Abbott), ritonavir (Norvir, Abbott), and indinavir sulfate (Crixivan, Merck).¹⁵

Administration of oral conivaptan 40 mg twice daily with amlodipine besylate (Norvasc, Pfizer) resulted in a two-fold increase in the AUC concentration and increased half-life of amlodipine. Therefore, the concomitant use of conivaptan and calcium-channel blockers such as amlodipine should be closely monitored, or the combination should be avoided.

The combined use of IV conivaptan and midazolam should be avoided, because the AUC concentration of midazolam may be increased by two-fold to three-fold when these agents are used together.

The coadministration of conivaptan and HMG-CoA reductase inhibitors (statins) such as simvastatin (Zocor, Merck) should also be avoided because the AUC concentration of the statin is increased by three-fold.

Digoxin (Lanoxin, GlaxoSmithKline), when taken with oral conivaptan, results in a 30% reduction in clearance of digoxin. Therefore, if digoxin is administered with conivaptan, digoxin plasma levels should be closely monitored.

The effect of IV conivaptan on the pharmacokinetics or the pharmaco-

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dynamics of warfarin (Coumadin, Bristol-Myers Squibb) has not been evaluated. However, oral conivaptan, given at a dose of 40 mg twice daily in addition to warfarin, did not result in any pharmacokinetic or pharmacodynamic interactions.

Other actual and potential drug–drug and drug–food interactions should be anticipated and screened for before co-administration of other medications with conivaptan.

DOSAGE AND ADMINISTRATION

The IV dose is 20 mg delivered over 30 minutes, followed by a 20- to 40-mg continuous infusion over 24 hours through a large vein. The site of administration must be rotated every 24 hours because of a high incidence of infusion-site reactions in more than 50% of patients.

The total duration of administration of conivaptan should not exceed four days. In clinical trials, serum sodium levels on day four following administration of 40 mg of IV conivaptan increased by about 7 mEq/L. Treatment also resulted in significant aquaresis.

COST

According to the manufacturer, conivaptan costs about \$315 per 20-mg ampule.³⁸

CONCLUSION

Conivaptan is a member of a new class of drugs called vasopressin antagonists. These agents regulate volume homeostasis via V₂ receptors, and they regulate vascular tone via V_{1A} receptors.

Currently, the use of conivaptan is approved for patients with euvolemic hyponatremia whose serum sodium concentrations range from 115 to 130 mEq/L. The advent of this agent represents a significant achievement for the management of this type of hyponatremia. Conivaptan is also being studied in patients with heart failure.

Conivaptan, even with its good efficacy, should be used cautiously because it is a potent CYP450 3A4 enzyme inhibitor. Its use with other CYP450 3A4 inhibitors and substrates should be avoided or closely monitored.

Despite its potential for side effects, its likelihood of drug–drug interactions, and its high cost, conivaptan represents an exciting new class of drugs for the

management of sodium and water balance. However, careful clinical assessment of the patient and an accurate diagnosis of euvolemic hyponatremia are necessary before therapy is prescribed.

Conivaptan should be reserved for those patients who have not responded to the conventional management of euvolemic hyponatremia.

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