

WHITEPAPER

The State of Hyponatremia in the Critically ill Patient

1. UNDERSTANDING VOLUME STATUS AND HYPONATREMIA

Hyponatremia, defined as serum sodium levels <135 mEq/L, is the most common electrolyte abnormality in hospitalized patients.¹ Recent studies have shown that over 30% of patients admitted to the ICU already have true hyponatremia.² In another study, 18% of patients entering the ICU without hyponatremia will develop the condition while in intensive care.³ Overall, almost 50% of neurological and critically ill patients are admitted with or will develop hyponatremia during a hospital stay.^{2,3}

There are three distinct classifications of hyponatremic patients: hypovolemic, euvolemic and hypervolemic hyponatremia. These three classifications of hyponatremia are further defined by a patient's fluid volume: volume overloaded or volume depleted.

All three types of hyponatremia involve deficient sodium levels relative to total body water. Because the cause of each type of hyponatremia varies, treatment plans must be specific to the type of hyponatremia.



2. TAILORING YOUR HYPONATREMIA TREATMENT APPROACH

The treatment course for hyponatremia should be dependent upon the patient's volume status, serum sodium level and condition.

When faced with hyponatremia in the critical care setting, physicians should consider stabilizing hyponatremic patients early. Once hyponatremia is verified with the serum sodium level results, the patient's volume status should be established. With volume depleted (hypovolemic) patients, fluid and solutes can be replaced with hypertonic and isotonic saline, whereas, volume overloaded patients (euvolemic and hypervolemic) can be more challenging to manage and treat.⁴ After a hyponatremia diagnosis, physicians can set a target serum sodium treatment goal and then determine therapy, administer therapy and closely monitor serum sodium and urine output.

1. Diagnose hyponatremia appropriately

2. Set target serum sodium goal

3. Determine and administer therapy

4. Closely monitor sodium and urine output

3. ACCURATELY DIAGNOSE HYPONATREMIA

The signs and symptoms of hyponatremia depend on several factors including the severity of the hyponatremia, duration and any underlying diseases that may affect its clinical presentation. Patients may present with the following symptoms:⁵

Classification	Serum Sodium	Neurological Symptoms
Severe	<125 mmol/L	Vomiting, seizures, obtundation, deep somnolence, respiratory distress, coma
Moderate	<130 mmol/L	Nausea, delirium or confusion, weakness, disorientation, altered mental status, weakness, depressed reflexes, gait instability, falling
Mild or Asymptomatic	<135 mmol/L	Headache, irritability, difficulty concentrating, altered mood, gait irregularities

One of the difficulties in diagnosing hyponatremia is that many patients appear asymptomatic. Although a patient may appear asymptomatic, this may only be a situational finding.⁶ A case-control study of 122 elderly patients with chronic asymptomatic hyponatremia (mean serum sodium of 126 mEq/L) suggested that asymptomatic patients, particularly neurological patients, may show symptoms such as gait disturbances that would otherwise be undetectable if a patient was left in the bed.⁷

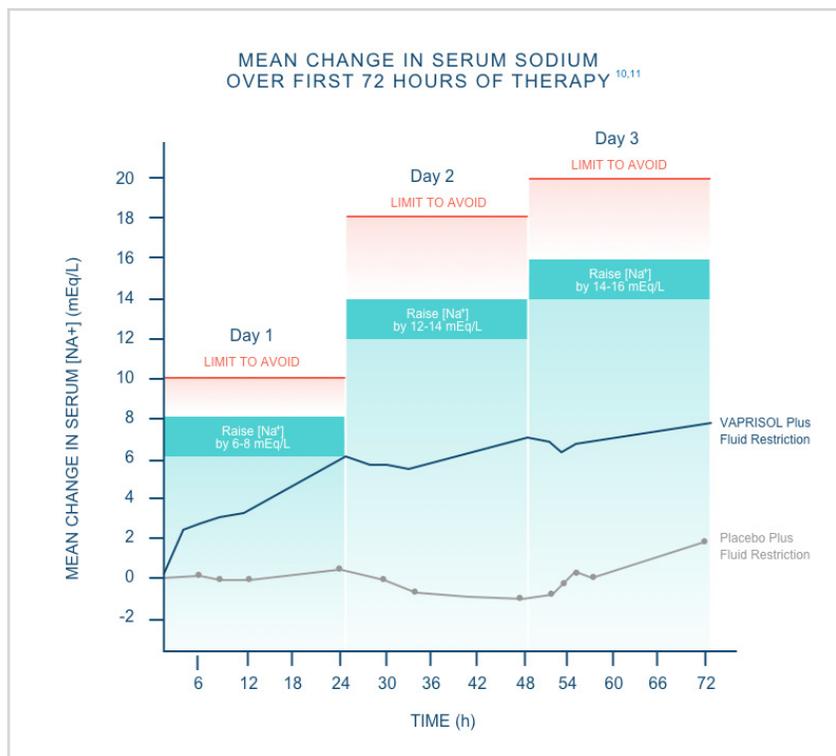
In addition to identifying the symptoms and severity of hyponatremia, a treatment approach should consider whether the hyponatremia is acute (occurring over 24-48 hours) or chronic (>48 hours). Acute hyponatremia is generally much more symptomatic than chronic hyponatremia. The mainstay of therapy for this group with an acute drop in serum sodium is prompt administration of hypertonic saline to rapidly address neurological symptoms. Slower rates of correction should be used in severe hyponatremia that is subacute or chronic.⁸

4. SET TARGET SERUM SODIUM GOAL

To avoid iatrogenic injury, physicians must have a clear understanding of why the serum sodium concentration level falls and why it rises in hyponatremic patients. It is equally important to understand how the brain responds to a changing serum sodium concentration, as well as what the goals of therapy should be and how to achieve them.⁹

The Sterns “rule of sixes” is an easy-to-remember therapeutic goal to increase serum [Na⁺] by 6 mEq/L to improve symptoms of hyponatremia. In other words, for all patients, the rule emphasizes that symptom improvement can be achieved with a serum [Na⁺] correction of 6 mEq/L. “Six a day makes sense for safety; so give six in six hours for severe symptoms and stop.”⁹

A patient’s serum sodium concentration should be increased gradually to prevent complications of untreated hyponatremia while avoiding overcorrection that comes with the increased risk of an iatrogenic brain injury. The brain is vulnerable to injury if the serum sodium concentration is normalized too rapidly. Evidence for the optimal approach to management of acute or chronic hyponatremia comes from clinical observational studies and from experimental models; no randomized trials have been performed comparing treatments.¹⁰



Results from a double-blind, placebo-controlled, randomized, multicenter study in patients with euvolemic or hypervolemic hyponatremia (serum sodium 115-130 mEq/L), reflected in line graphs,¹¹ show the primary efficacy endpoint, of which was changed from baseline in serum sodium concentrations during the course of treatment, measured by the baseline-adjusted area under the sodium-time curve (AUC) from the beginning through the end of treatment. Fluid restricted to ≤ 2.0 L/day in all patients. The mean baseline serum sodium concentrations in patients treated with VAPRISOL or placebo were 123.3 mEq/L and 124.3 mEq/L, respectively.

Warnings and Precautions

Hypovolemia or hypotension: For patients who develop hypovolemia or hypotension while receiving VAPRISOL, VAPRISOL should be discontinued, and volume status and vital signs should be frequently monitored. Once the patient is again euvolemic and is no longer hypotensive, VAPRISOL may be resumed at a reduced dose if the patient remains hyponatremic.

5. DETERMINE AND ADMINISTER THERAPY

Approaches to treatment of hyponatremia may include restricting fluids or discontinuing drugs that are associated with low sodium. Common agents to treat hyponatremia include normal saline, hypertonic saline, demeclocycline, salt tablets, diuretics and vasopressin receptor antagonists (vaptans).¹² Hypertonic saline solution must be administered with extreme caution because excessively slow or rapid sodium correction can lead to severe neurologic adverse effects.¹³

Salt tablets may seem to be an intuitive treatment but are rarely useful for patients who can't take an oral medication, or for euvolemic and hypervolemic hyponatremia where the issue is total body water and not salt content. Isotonic saline is used to treat acute hypovolemic hyponatremia, but may result in overly rapid correction, particularly in elderly patients.¹²

In the euvolemic and hypervolemic, mild to moderate, acute, symptomatic hyponatremia patient in the critical care setting, conivaptan combined with fluid restriction provides improved response over fluid restriction alone in the first 24 hours.^{11,14}

Another consideration for treatment of any hyponatremic patient is the method of delivery. Because hyponatremia is common in ICU patients, physicians must consider delivery in their treatment options for patients who are on a ventilator, or are not able to receive oral medications. These conditions limit treatment options to fluid restriction or agents given by IV such as hypertonic saline, diuretics or conivaptan.¹²

Vaptans

Vasopressin receptor antagonists, also known as “vaptans,” bind to the vasopressin receptor and thus prevent binding of vasopressin, directly addressing the cause of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). Two drugs in this class—conivaptan and tolvaptan—have received U.S. Food and Drug Administration (FDA) approval for patients with euvolemic or hypervolemic hyponatremia. Vaptans promote excretion of water only, without the loss of electrolytes as seen in diuretics.¹⁵

Vaptans are an aquaretic class of agents that remove free water while not disturbing electrolytes.¹⁶

Vaprisol is administered intravenously and reversibly binds to both V1a and V2 receptors. Its intravenous delivery makes it particularly useful in the ICU setting. It is administered as a 20 mg loading dose in 30 minutes followed by a continuous intravenous infusion of 20 mg over 24 hours for up to four days, if needed. Conivaptan can be titrated up to 40 mg, if needed. A 10 mg dose is recommended for patients with severe liver impairment.¹¹

When Vaprisol is administered as a 24-hour continuous infusion, the physician has control in the rate of serum sodium increase.

A clinical trial found that conivaptan combined with fluid restriction raised serum sodium levels in 69% to 88.5% of treated patients.¹⁴ Clinical trials of intravenous conivaptan in euvolemic and hypervolemic patients found the drug effectively raised mean serum sodium in 24 hours.^{14,17}

Vaprisol is the only IV vaptan approved to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia. It is a premixed formula in 100 mL of D5W and a defined daily dose (10 mg, 20 mg, 40 mg). Vaprisol has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication.¹¹

Tolvaptan binds to the V2 receptor and is administered orally, commonly in outpatient settings, although it must be initiated and reinitiated in a hospital. Patients taking tolvaptan experienced a greater increase in serum sodium concentration than those taking a placebo, with the sharpest rise seen in those with the lowest baseline levels. In 2% of cases, the serum sodium concentration level increased greater than 12 mEq/L at 24 hours, exceeding the maximum recommended rate of <10 mEq/L.^{10,18} Tolvaptan should be avoided in patients with underlying liver disease.¹⁸

6. MONITOR VOLUME STATUS TOWARDS TARGET TREATMENT LEVEL

In most patients with hyponatremia, the ability to excrete dilute urine is only temporarily or reversibly impaired. Once the cause of water retention ends, the excretion of dilute urine can increase the serum sodium concentration, sometimes by much more than the clinician intends or expects.⁹

In mild to moderate hyponatremia, when Vaprisol is partnered with fluid restriction, patients can achieve proven response day one.^{14,17}

ADVERSE REACTIONS

The most common adverse reactions experienced by patients treated with Vaprisol are infusion site reactions (including phlebitis), pyrexia, hypokalemia, headache and orthostatic hypotension.¹¹

In general therapy, unless the urine is maximally dilute, it is recommended that patients should be fluid restricted. For patients in the ICU, this can mean careful attention to unintended sources of electrolyte-free water such as tube feedings and IV medications that are administered in D5W. As some of these are unavoidable, it may be necessary to administer 300 mL 3% saline (150 mEq of sodium) to compensate for every liter of free water.⁹

Monitor volume status and serum sodium frequently for target treatment level and rate of rise.

Use this as your guide to the safe rate of rise.¹⁰

	+	
1st 24 Hrs	Raise [Na+] by 6-7 mEq/L	Limit** <10 mEq/L
	+	
1st 48 Hrs	Raise [Na+] by 12-14 mEq/L	Limit** <18 mEq/L
	+	
1st 72 Hrs	Raise [Na+] by 14-16 mEq/L	Limit** <20 mEq/L

*Limits not to be exceeded to avoid iatrogenic injury

With any therapy, a rapid rise in serum sodium levels has been linked to osmotic demyelination, a complex disorder that can result one to several days after a rapid correction of hyponatremia.¹⁹ A sharp increase in sodium concentration does not allow the brain sufficient time to reverse the adaptations made in chronic hyponatremia, particularly the extrusion of solutes.²⁰

7. HYPONATREMIA TREATMENT ALGORITHM BASED ON NEUROLOGICAL SYMPTOMS

The table below describes the 3 levels of hyponatremia along with various treatment options.*

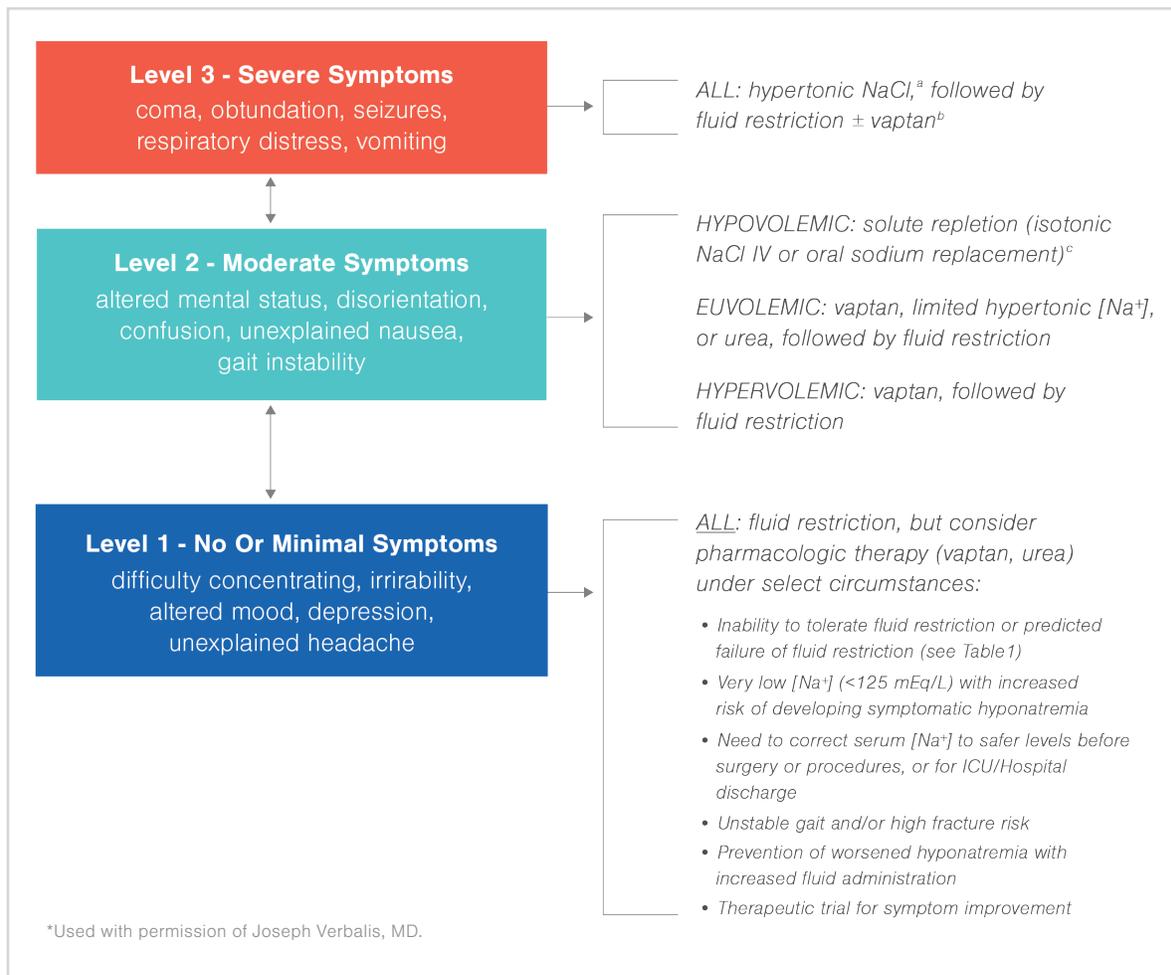


TABLE 1.*

General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

General recommendations:

- Restrict all intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/d below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of the likely failure of fluid restriction:

- High urine osmolality (>500 mOsm/kg H₂O).
- Sum of the urine Na⁺ and K⁺ concentrations exceeds the serum Na⁺ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na⁺ concentration <2 mEq/L/d in 24-48 hours on a fluid restriction of 1 L/d.

a) Some authors recommend simultaneous treatment with desmopressin to limit speed of correction.

b) No active therapy should be started within 24 hours of hypertonic saline to decrease the chance of overly rapid correction of [Na⁺] and risk of ODS.

c) With isotonic NaCl infusion, serum [Na⁺] must be followed closely to prevent overly rapid correction and risk of ODS due to secondary water diuresis.

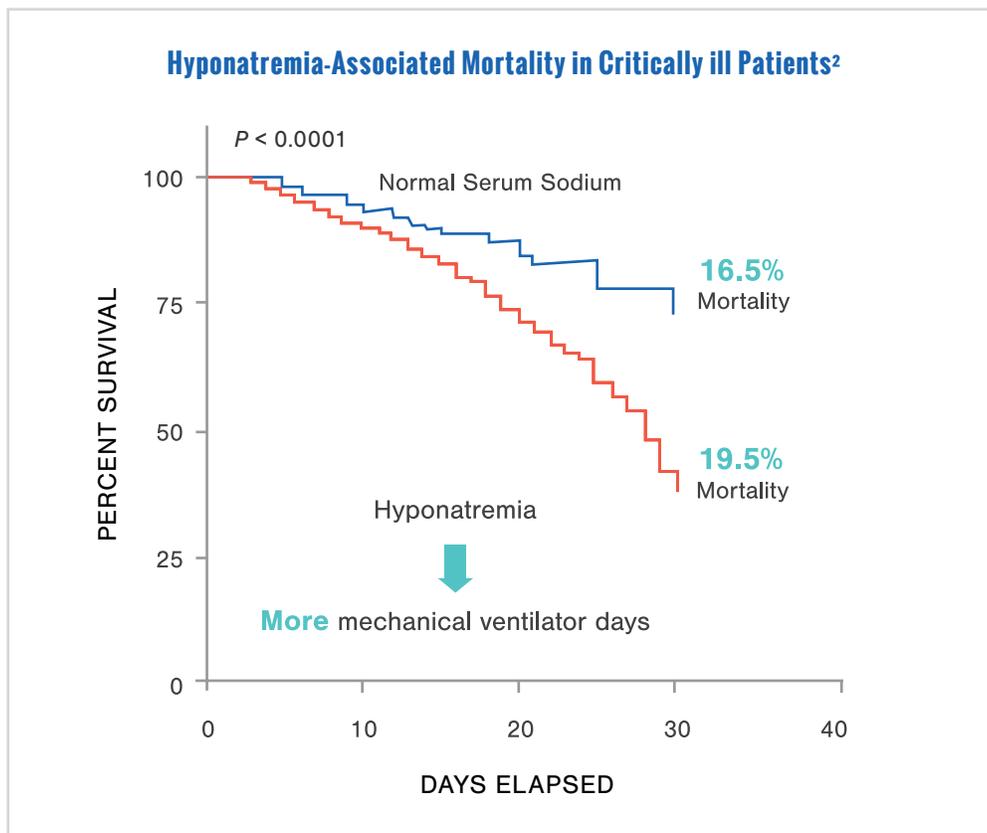
8. RISK OF MORTALITY IN HYPONATREMIC PATIENTS

Critically ill patients are diagnosed with hyponatremia more often than hypernatremia and as a result, severe outcomes are more often seen with hyponatremic patients.²¹

An observational cross-sectional study by Mahmoud et al. showed that hyponatremia increased mortality and length of stay for critically ill patients. Of 600 patients, 132 (22%) acquired dysnatremia, 111 patients (18.5%) acquired hyponatremia, while only 21 patients (3.5%) acquired hypernatremia. The relative risk (RR) of developing hyponatremia increased with increasing age more than 50 years (RR 2), presence of fever (RR 2.7), administration of hypotonic fluid therapy (RR 2.4), use of diuretics (RR 4.8), presence of renal impairment (RR 2.9) and advanced liver disease (RR 2.3). Compared with normonatremic patients, hyponatremia was associated with increased ICU-mortality (RR 2.52), and with increased ICU-LOS (RR 1.8).³

**Over 30% of patients admitted to the ICU have hyponatremia.²
18% will develop hyponatremia while in the ICU.³**

In an observational, prospective 12-month study by Padhi et al., ICU patients with hyponatremia spent a longer time in the ICU ($P = 0.02$), had longer mechanical ventilator days ($P = 0.03$) and had an increased mortality rate (19.5%); ($P < 0.0001$), than patients in the normal serum sodium group (16.5%).²



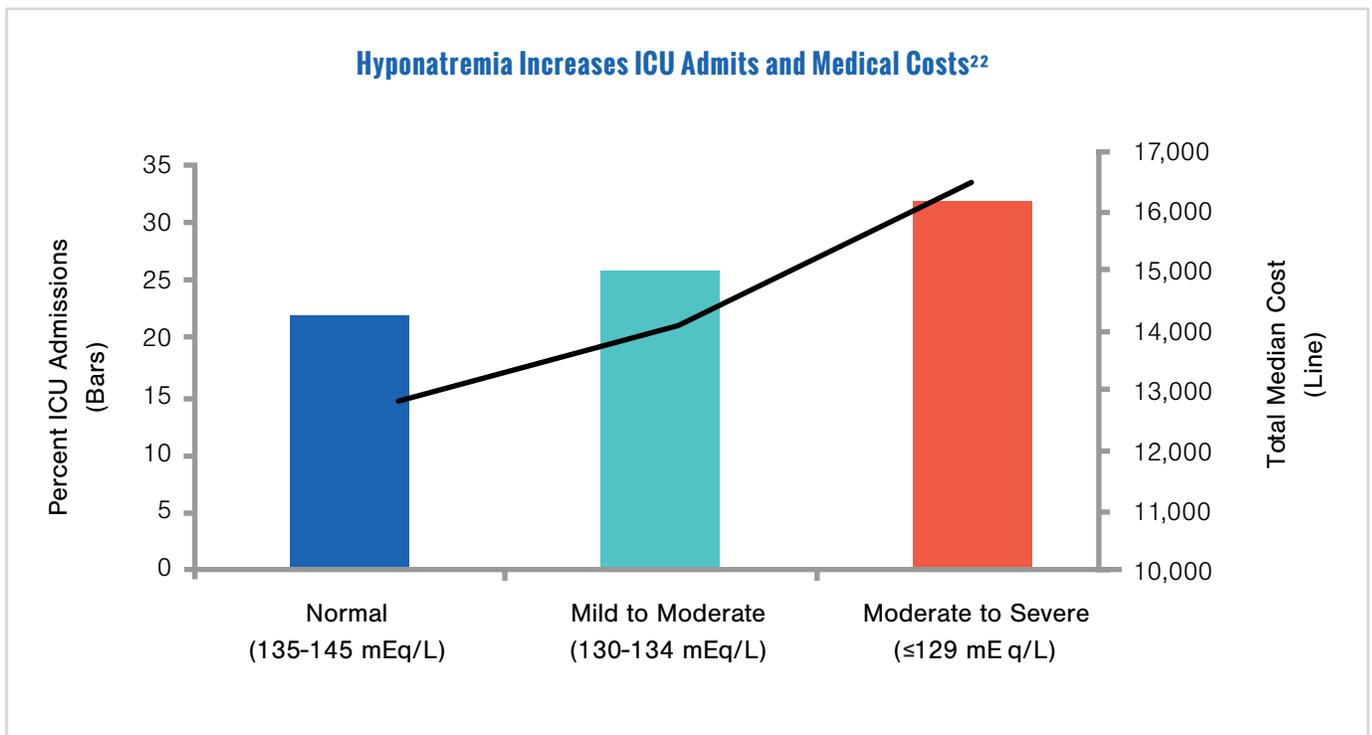
9. ECONOMIC IMPACT OF HYPONATREMIA

To examine the economic impact of hyponatremia upon admission, a retrospective cohort study was undertaken by identifying all inpatient admissions of adults with a serum sodium <134 mEq/L at a university hospital from January 2004 through May 2005.²²

Extrapolating the increased cost from a single center study to a 2003 national inpatient admission and hospital charge dataset, it was estimated that patients with hyponatremia incur 1.4 million additional bed days and have additional costs of \$1.1 billion per year, which were primarily borne by the hospitals themselves, as reimbursement methods usually are unable to bill patients or payers. Investigators concluded that hyponatremia upon admission was associated with longer LOS, more frequent ICU admissions, and higher total medical care costs.²²

Compared with non-hyponatremic patients, patients with a primary diagnosis of hyponatremia use a greater amount of hospital resources and represent a challenge to hospital profitability due to the increased likelihood of 30-day readmission.²³ Despite the significant risks posed by low serum sodium and ready access to effective therapies, more than 75% of patients hospitalized with hyponatremia leave the hospital still hyponatremic.²⁴

More than 75% of patients hospitalized with hyponatremia leave the hospital still hyponatremic.²⁴



10. VAPRISOL TREATMENT GUIDELINES¹¹

Vaprisol, a premixed intravenous solution - 20mg/100mL D5W

Indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.

Hyponatremia

Load: 20 mg IV infusion over 30 minutes; and THEN

20 mg IV as continuous infusion over 24-hour period for 2-4 days

After initial day of treatment, may increase to 40 mg/day, if necessary.

Monitor serum sodium and volume status frequently; a significant increase in serum sodium (>10 mEq/L/24 hours) may result in serious neurologic effects.¹⁰

Renal Impairment

Mild and Moderate Renal Impairment (CLcr 30-80 mL/minute): No dosage adjustment required

Severe Renal Impairment (CLcr <30 mL/minute): Not recommended

Hepatic Impairment

Mild Hepatic Impairment: No dosage adjustment required

Moderate (Child-Pugh Class B) and Severe (Child-Pugh Class C) Hepatic Impairment: Initiate with loading dose of 10 mg IV infused over 30 minutes, followed by 10 mg/day as a continuous infusion (ie, over 24 hrs) for 2-4 days; may titrate up to 20 mg/day if serum sodium is not rising at desired rate.

IMPORTANT SAFETY INFORMATION AND IMPORTANT LIMITATIONS

Vaprisol (conivaptan hydrochloride) Injection

(1) Indication

(2) Important Safety Information

Indication: VAPRISOL is indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.

Important Limitations: VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication. It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

VAPRISOL is contraindicated in patients with hypovolemic hyponatremia. The coadministration of VAPRISOL with potent CYP3A inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. In addition, no benefit can be expected in patients unable to make urine.

WARNINGS & PRECAUTIONS

Hyponatremia associated with heart failure: Safety data on the use of VAPRISOL in these patients are limited. Consider other treatment options.

Overly rapid correction of serum sodium: Monitor serum sodium, volume and neurologic status and if the patient develops an undesirably rapid rate of rise of serum, VAPRISOL should be discontinued. If serum sodium concentration continues to rise, VAPRISOL should not be resumed. Serious neurologic sequelae, including osmotic demyelination syndrome, can result from over rapid correction of serum sodium. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction should be used.

Hypovolemia or Hypotension: For patients who develop hypovolemia or hypotension while receiving VAPRISOL, VAPRISOL should be discontinued, and volume status and vital signs should be monitored.

Infusion site reactions: Serious reactions have occurred. Administer through large veins and change infusion site every 24 hours.

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 10\%$) are infusion site reactions (including phlebitis), pyrexia, hypokalemia, headache and orthostatic hypotension.

DRUG INTERACTIONS

Potent CYP3A inhibitors may increase the exposure of conivaptan and are contraindicated. Generally avoid CYP3A substrates. Exposure to coadministered digoxin may increase digoxin levels and should be monitored.

USE IN SPECIAL POPULATIONS

Use in Patients with Hepatic Impairment

In patients with moderate to severe hepatic impairment, initiate VAPRISOL with a loading dose of 10 mg over 30 minutes followed by 10 mg/day as a continuous infusion for 2 to 4 days. If no rise in serum sodium, VAPRISOL may be titrated upward to 20 mg/day.

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