Contemporary Management of Hyponatremia

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Hyponatremia, a common electrolyte imbalance, generally is defined as a serum sodium concentration of less than 135 mEq/L. Patients with acute or moderate to severe hyponatremia may present with neurologic signs and symptoms, and may be at risk for long-term complications. However, even patients with mild, chronic forms of the disorder may be at risk for significant morbidity, making recognition and appropriate treatment essential.

Classification and Epidemiology

Hyponatremia can be classified by rate of onset, as either acute (i.e., rapid-onset) or chronic, and by the degree of sodium deficit—mild (125-130 mEq/L), moderate (115-125 mEq/L), or severe (110-115 mEq/L). Estimates of the prevalence of hyponatremia vary, ranging from less than 1% to 45%, depending on the setting and the population studied. High rates of hyponatremia have been reported in hospitalized patients, with about 40% having low sodium levels either at hospital admission or during a hospital stay. In a retrospective study, Wald et al reviewed the discharge records of 53,236 hospital admissions for which serum sodium was recorded, along with information on mortality, length of stay, and patient disposition at time of hospital discharge. At the time of admission, low serum sodium levels (referred to as community-acquired hyponatremia) were present in 37.9% of hospitalizations. Hyponatremia worsened during the hospital stay for 5.7% of these hospitalizations. Hospital-acquired hyponatremia (in which serum sodium levels were within normal range at the time of admission) occurred in 38.2% of hospitalizations. In a similar analysis, using data from the American College of Surgeons National Surgical Quality Improvement Program, Leung et al identified 75,423 patients with hyponatremia out of a cohort of 964,263 adults undergoing major surgery, for a prevalence of about 8%.
The prevalence of hyponatremia also has been assessed in specific patient populations, including patients with heart failure, cancer, and cirrhosis. In an analysis of data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Patients with Heart Failure) registry, Gheorghiade et al reported that 9,368 of 47,647 patients with heart failure (19.7%) had hyponatremia at study entry.6 Klein et al reported a somewhat higher prevalence of hyponatremia—256 of 943 patients with heart failure (27%)—in the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study.7 More recently, Shchekochikhin et al conducted a retrospective analysis of 5,347 patients with heart failure who were admitted to a single institution over a 7-year period.10 The authors identified community-acquired hyponatremia in 19.4% of the admitted patients; another 30.2% of the patients who had normal sodium levels at admission developed hyponatremia during their hospital stay.

Among patients with cancer, Doshi et al reported hyponatremia in 1,596 of 3,357 patients (47%) admitted to a single institution over a 3-month period.5 Among patients with cirrhosis, higher rates of hyponatremia have been reported. In a prospective study evaluating 997 patients with cirrhosis from 28 hospitals and clinics, 49.5% of those patients had hyponatremia. When only hospitalized patients were considered, 57.4% had hyponatremia. For outpatients, the prevalence was 40.2%.11

The Clinical Burden

Hyponatremia has been associated with significant morbidity and mortality, regardless of severity. A study reported that the lower the hospital admission serum sodium level, the greater the risk for poorer outcomes, including in-hospital mortality, need for discharge to short- or long-term care facilities, and longer hospital stays.6 Compared with patients admitted with a serum sodium of 138 to 142 mEq/L, those with a serum sodium less than 138 mEq/L had an adjusted odds ratio (OR) for in-hospital mortality of 1.52 (95% confidence interval [CI], 1.36-1.69). As serum sodium levels decreased, the risks for all 3 outcomes increased, and all differed significantly from risks of patients with normal-range sodium levels. Among 3,075 patients admitted to the hospital with a serum sodium of 128 to 132 mEq/L, there were 151 in-hospital deaths, for an OR of 1.99 (95% CI, 1.65-2.40) relative to patients with normal levels. This risk for in-hospital death increased to 2.46 (95% CI, 1.38 to 4.90) for those with sodium levels 122 mEq/L or lower. Similar results were seen for hospital length of stay, with an OR of 1.09 (95% CI, 1.05-1.14) for hyponatremic patients.

For patients who acquired hyponatremia during their hospital stay, the OR for in-hospital mortality was 1.66 (95% CI, 1.39-1.98) compared with patients without hyponatremia. The rate of discharge to a care facility and the need for a longer hospital stay also were both significantly increased among patients with hospital-acquired hyponatremia.

The effects of hyponatremia on surgical outcomes also have been investigated. A large cohort trial included 964,263 patients undergoing major surgery over a 5-year period and compared outcomes between patients with preoperative hyponatremia (75,423 patients) and those with normal-range serum sodium (888,840 patients).7 The primary outcome of the study was 30-day mortality. The types of surgery varied, with most procedures (about 70%) described as general surgery. A total of 15,630 deaths occurred within 30 days of surgery. The risk for death was highest among patients with moderate to severe hyponatremia (sodium <130 mEq/L), with an OR of 1.72 (95% CI, 1.58-1.88) compared with those with normal-range sodium levels. The risk also was significantly increased among patients with mild preoperative hyponatremia (sodium 130-134 mEq/L) (OR, 1.38; 95% CI, 1.32-1.45). Secondary outcomes, such as major coronary events, wound infection, and pneumonia, also were significantly increased among patients with preoperative hyponatremia.

Crestanello and colleagues investigated the effects of hyponatremia in a cardiac surgery population. Among 4,850 patients who underwent cardiac surgery, hyponatremia was seen in 59% during hospitalization after surgery.12 Both 1-year and 5-year mortalities were increased in the presence of postoperative hyponatremia—15.6% and 39.4%, versus 7.9% and 25.0% in patients with normal-range sodium levels, respectively (P<0.001). In addition, hospital length of stay was prolonged significantly (10.7 vs 7.0 days), with significantly higher rates of operative, infectious, pulmonary, and renal complications (P<0.001 for all comparisons).

Poorer outcomes also have been reported among hyponatremic hospitalized patients with heart failure, liver disease, and cancer.5,10,13 In-hospital mortality, length of stay, in-hospital worsening of kidney function, and need for discharge to a short- or long-term care facility were significantly increased in the presence of hyponatremia, whether present at hospital admission or acquired during the hospital stay. The risk for death among patients with liver disease also may be increased in the presence of hyponatremia.13 In a study of nearly 14,000 patients who had severe liver disease and were awaiting liver transplantation, the risk for death increased by 5% for every unit decrease in serum sodium when levels were between 125 and 140 mEq/L. Increases in mortality and hospital length of stay also have been reported in cancer patients with hyponatremia, whether the hyponatremia was mild, moderate, or severe, compared with patients with normal sodium levels.5
Mild hyponatremia also may increase the risk for falls and fractures, especially in elderly individuals. In a series of patients admitted for hip fractures secondary to a fall, Kengne et al reported that 13% (67 of 513 patients) had mild asymptomatic hyponatremia (mean serum sodium level 131 mEq/L), compared with 3.9% (20 of 513) of a similar group of patients without a fracture.14 Although the exact mechanism of the relationship of hyponatremia to falls is unclear, low sodium levels have been suggested to cause impairment of both gait (balance and posture) and attention compared with normal sodium levels.

Beyond hyponatremia’s effects on general health, this disorder has a significant economic impact.15 Treatment for hyponatremia in the United States, in either inpatient or outpatient settings, has been estimated to cost between $1.6 billion and $3.6 billion annually. In a retrospective analysis, Amin estimated significantly higher health care costs for hospitalized patients with hyponatremia than for non-hyponatremic patients—$15,281 versus $13,439 (P<0.001).16 This cost difference was seen for several subgroups based on reasons for admission, including community-acquired pneumonia, heart failure, and chronic obstructive pulmonary disease.

Mechanisms of Water–Sodium Balance

The balance of both water and sodium is important for the regulation of plasma osmolality and blood volume.1 Water in the body is divided between the extracellular (approximately 33%) and intracellular (approximately 67%) compartments.17 Sodium (and its associated anions) is the major determinant of the osmotic pressure and volume of extracellular fluids (ECFs); therefore, any changes in total body content of sodium can result in changes in ECF osmolality. Similarly, intracellular osmotic pressure primarily is determined by potassium. Normally, the osmolality of the intracellular fluid (ICF) and ECF is the same, maintained by the free exchange of water between the 2 compartments and a balance of the solutes sodium and potassium (referred to as effective osmoles).18,19 However, changes in the osmolality of the ECF will influence this free-water exchange between the 2 compartments. Hypertonicity of the ECFs (as with excessive sodium) will result in a decrease in ICF volume (ie, a shift in free water to the extracellular compartment). Hypotonicity (as with low sodium) will cause an increase in ICF volume (ie, a shift in free water to the intracellular compartment). This increase in ICF volume is especially important in cerebral tissues, where an increase in cell volume can result in significant cellular damage.

Other mechanisms also can affect the water–sodium balance. Water retention or metabolism is controlled primarily by arginine vasopressin (AVP or antidiuretic hormone), a peptide produced by the pituitary gland in response to osmotic and non-osmotic changes.19-21 An increase in plasma osmolality results in stimulation of AVP secretion by osmo-receptors in the anterior hypothalamus, causing antidiuresis and reabsorption of water into the circulation. This, along with stimulation of thirst, results in a decrease in water excretion and an increase in water intake.21,22 When plasma osmolality is below a biologically preset threshold (approximately 280 mOsm/kg), AVP levels usually are undetectable, allowing for excretion of free water and normalization of osmolality.20,21 Secretion of AVP also is stimulated via a more potent non-osmotic mechanism—arterial stretch baroreceptors—in response to a reduction in blood pressure or blood volume of approximately 8% to 10%. Although osmotic mechanisms generally control AVP secretion over non-osmotic mechanisms, under certain pathophysiologic conditions, such as cardiac failure or liver cirrhosis, pressure and volume responses for AVP secretion predominate and allow for elevated AVP levels despite low plasma osmolality, resulting in hyponatremia.

Causes of Hyponatremia

Hyponatremia usually results when there is a loss of balance between intake and excretion of water, or from renal or extra-renal sodium loss.22 Initial evaluation of a patient with hyponatremia generally includes plasma or serum osmolality and volume status to determine the type of hyponatremia and to identify possible causes (Tables 1 and 2).18,23 Plasma osmolality, which is normally between 280 and 295 mOsm/kg with normal hydration, can determine whether the hyponatremia is isotonic, hypertonic, or hypotonic.

Hypotonic Hyponatremia

Hypotonic hyponatremia is the most common type and also is associated with critical illnesses.24 It can be further classified based on ECF status (including urine osmolality and sodium) as hypovolemic, euvoletic, or hypervolemic.23

Hypovolemic hyponatremia results in reductions in both total body water (decreased ECF) and, to a certain extent, total body sodium.18,23 Urine osmolality is elevated (>450 mOsm/kg). Urine sodium measures can indicate the cause of water and sodium loss. Urine sodium of less than 20 mEq/L suggests extra-renal loss, such as diarrhea, vomiting, excessive sweating, or blood loss.1,24 High urine sodium levels (>20 mEq/L) indicate renal loss of sodium and water as a cause, such as diuretic use, adrenal insufficiency, or certain nephropathies.

Euvoletic hyponatremia presents with clinically normal ECF volume and is the most common of the hypotonic hyponatremias.18,24 Although total body water is increased, it is not enough to cause edema, making the patient appear clinically euvoletic.2 Euvoletic
Hyponatremia is most commonly the result of the syndrome of inappropriate antidiuretic hormone (SIADH), in which water intake exceeds excretion by the kidney. Urine osmolality generally is higher than 100 mOsm/kg and urine sodium levels are high (>20 mEq/L). Euvolemic hyponatremia also can result from primary polydipsia (water intake >20 L/d) or very low-solute diets. In this case, urine osmolality is less than 100 mOsm/L and the urine sodium level is low (<20 mEq/L).

Hypervolemic hyponatremia is associated with excess total body sodium, along with a greater expansion of total body water, resulting in hyponatremia with clinically evident edema. The increase in total body water results from a reduction in water excretion by the kidneys—a response to a decrease in effective circulating blood volume. Conditions associated with hypervolemic hyponatremia include heart failure, cirrhosis, and nephrotic syndrome. Urine osmolality is higher than 100 mOsm/kg, with a urine sodium concentration of less than 20 mEq/L.1

Clinical Presentation

Symptoms of hyponatremia vary greatly, depending on the type and degree of hyponatremia and the rate of onset. Hypovolemic hyponatremia typically causes signs of dehydration, such as dry mucous membranes, tachycardia, and hypotension. Hypervolemic hyponatremia can cause peripheral or pulmonary edema; these are not present with euvolemic hyponatremia. Symptoms of hyponatremia also differ depending on the degree of sodium loss. Individuals with mild (>125-130 mEq/L) and chronic hyponatremia generally are asymptomatic. However, it has been suggested that symptoms of mild hyponatremia may be too subtle to notice, yet result in significant morbidity among certain patient groups, such as the elderly. Moderate to severe hyponatremia or rapid-onset (<48 h) hyponatremia may present with neurologic symptoms ranging from confusion, agitation, or impaired mental function to seizures and coma if sodium levels fall to less than 115 mEq/L. The rate of change in sodium levels may be especially important because a rapid drop in sodium does not allow the cells of the brain time to adapt to the change in osmolality, resulting in cerebral edema as water moves intracellularly. Although solutes such as sodium and potassium move from the brain cells to the extracellular space quickly, other solutes (organic solutes such as taurine, creatine, and glutamine) are slower, requiring up to 48 hours to completely compensate for the fluid shift. Onset of hyponatremia over several days, even if severe, allows time for this adaptation process and reduces the risk for cerebral edema.

### Treatment of Hyponatremia

Treatment of hypertonic or isotonic hyponatremia generally consists of addressing the underlying cause of the sodium decrease. For example, hypertonic hyponatremia secondary to hyperglycemia may resolve with a reduction in blood glucose. For isotonic hyponatremia (an artifactual decrease in serum sodium concentrations), appropriate laboratory assessment is needed to determine the true serum sodium concentration. The following section relates primarily to the treatment of hypotonic hyponatremia.

### Sodium Chloride Infusions

Because of the risk for cerebral edema and death, acute symptomatic, severe hyponatremia is considered a medical emergency. Although prompt treatment is needed, too rapid a correction of serum sodium levels should be avoided because of the risk for osmotic demyelination or central pontine demyelination, a potentially severe neurologic complication. However, cerebral edema and severe neurologic symptoms generally can be reduced or stopped with only a small increase in serum sodium—about a 5% increase for cerebral edema.

### Table 1. Types of Hyponatremia by Plasma Osmolality

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<tr>
<th>Isotonic</th>
<th>Hypertonic</th>
<th>Hypotonic</th>
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<tr>
<td>• Pseudohyponatremia due to an artifactual reduction in sodium that is caused by elevation of the nonaqueous, non-sodium portion of plasma by proteins and lipids relative to the aqueous portion, with no true reduction in total sodium</td>
<td>• Elevation in plasma osmolality due to presence of effective osmoles (eg, glucose, mannitol, sorbitol) and movement of water from intracellular to extracellular spaces</td>
<td>• Excess water relative to effective osmoles (solute) in extracellular space that is caused by either a decrease in total body solute (depletion) or an increase in total body water (dilution)</td>
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<tr>
<td>• No movement of water between extracellular and intracellular spaces</td>
<td>• Result is a reduction in serum sodium with elevated osmolality</td>
<td>• Plasma osmolality: &lt;280 mOsm/kg</td>
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<tr>
<td>• Plasma osmolality: normal range</td>
<td>• Plasma osmolality: &gt;295 mOsm/kg</td>
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Based on references 18, 23, and 24.
and a 3 to 7 mEq/L increase for seizures. Therefore, an initial rate of correction of 1 to 2 mEq/L per hour for several hours has been recommended for patients with severe symptoms. This rate can be reduced once symptoms begin to subside or a serum sodium level of 125 to 130 mEq/L (or lower if starting level is ≤ 100 mEq/L) is achieved. Other researchers have recommended slowing the infusion rate when a sodium level of 118 to 120 mEq/L has been reached and the patient is asymptomatic.23 Regardless, the sodium level should not be increased by more than 8 to 12 mEq/L in the first 24 hours, because correction rates higher than this are associated with an increased risk for osmotic demyelination.1,22,23,26 A more conservative limit of 6 mEq/L also has been advocated.22,30 Several methods for calculation of the infusion rate for sodium chloride are available. One method calculates the rate of infusion based on total body water, the change in sodium per liter of solution infused, the target sodium increase, and the desired rate of sodium correction (Table 3).1,22,23,26 (For general management strategies, see Table 4.)

There is some concern regarding the use of hypertonic sodium chloride infusions, such as 3% sodium chloride, for correction of hyponatremia. These infusions can rapidly correct serum sodium in emergent situations and may be needed when isotonic infusions are not appropriate, such as for SIADH. However, there is a risk for too rapid a correction with hypertonic solutions, with the potential for osmotic demyelination. One approach to avoid overcorrection in severe chronic hyponatremia that has been described in the literature is the use of desmopressin (2 to 4 mcg given every 8 hours) with 3% sodium chloride. Desmopressin, which prevents water diuresis that may occur in some patients with severe chronic hyponatremia, helps decrease the likelihood of overcorrection of sodium. However, this strategy has not been supported by some authors due to concerns that it might worsen hyponatremia, rather than correcting the imbalance, and increase the risk for pulmonary edema from sodium and water retention. Overall, for the treatment of severe hyponatremia, the risks and benefits associated with any approach to sodium correction should be considered. In nonemergent situations when patients are asymptomatic or have mild to moderate symptoms, 0.9% sodium chloride may be used to slowly correct sodium levels as well as to replace deficits in ECF volume for those who are hypovolemic.

**FLUID RESTRICTION**

For patients with nonemergent euvoletic or hypervolemic hypertonic hyponatremia, fluid restriction has been recommended, along with identification and correction of underlying causes. Fluid intake usually is restricted to no more than 1,200 mL per day, so that urine output and insensible losses exceed intake, resulting in a negative water balance. For example, in a patient with a urine output of 550 mL per day, with 200 mL of insensible losses, fluid should be restricted to less than 750 mL per day.

**DRUG THERAPY**

**Conventional Therapies.** For some patients with chronic forms of hyponatremia, such as hyponatremia secondary to SIADH, fluid restriction may be difficult to maintain, necessitating drug therapy. Demeclocycline is a tetracycline derivative that inhibits tubular AVP activity, leading to a decrease in plasma osmolality and an increase in serum sodium levels. When used for hyponatremia, the dose ranges from 600 to 1,200 mg daily in divided doses. Lithium carbonate also has been used and has an effect that is similar to that of demeclocycline, increasing water clearance and serum sodium levels. Doses have ranged from 900 to 1,200 mg per day. However, because of its adverse effect profile and less consistent effects, the use of

<table>
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<th>Table 2. Common Etiologies for Hyponatremia</th>
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<td><strong>Isotonic</strong></td>
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<tr>
<td>• Marked hyperlipidemia</td>
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<td>• Marked hyperproteinemia</td>
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SIADH, syndrome of inappropriate antidiuretic hormone

Based on references 17, 18, and 23.
Diuretics have been used in the treatment of hypervolemic hyponatremia in addition to fluid restriction to help reduce volume overload in patients with underlying causes such as heart failure. Although loop diuretics are more potent for producing diuresis, thiazide diuretics are more likely to cause hyponatremia, possibly secondary to impairment of renal diluting mechanisms. The risk for hyponatremia is lower with loop diuretics because these agents affect both renal concentrating and diluting mechanisms.

**Arginine Vasopressin Receptor Antagonists.** The AVP receptor antagonists are a newer class of agents approved for the treatment of hypervolemic or euvolemic hypotonic hyponatremia in addition to fluid restriction to help reduce volume overload in patients with underlying causes such as heart failure. Although loop diuretics are more potent for producing diuresis, thiazide diuretics are more likely to cause hyponatremia, possibly secondary to impairment of renal diluting mechanisms. The risk for hyponatremia is lower with loop diuretics because these agents affect both renal concentrating and diluting mechanisms.

**Tolvaptan is an orally administered AVP receptor antagonist of the V₂ receptor that is indicated for the treatment of euvoletic or hypervolemic hyponatremia in symptomatic patients who have failed fluid restriction.** In the SALT-1 and SALT-2 (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2) trials, tolvaptan resulted in greater increases in serum sodium compared with placebo within 8 hours of first treatment among patients with hyponatremia secondary to heart failure, cirrhosis, or SIADH. By day 4, significantly more patients had normalization of serum sodium levels with tolvaptan than with placebo.

Conivaptan is a parenteral AVP receptor antagonist of the V₂ and V₁a receptors that also is indicated for the treatment of euvolemic or hypervolemic hyponatremia. In a study involving 84 patients with hypervolemic or euvolemic hyponatremia (serum sodium 115-130 mEq/L) given conivaptan 20 mg as an intravenous loading dose followed by a 40- or 80-mg continuous infusion per day for 4 days, conivaptan resulted in significantly greater increases in serum sodium concentrations compared with placebo. Increases of 4 mEq/L over baseline with conivaptan were seen within the first 24 hours; this effect did not occur with placebo. At 72 hours, increases with conivaptan were 6.9 and 8.8 mEq/L over baseline, whereas serum sodium was increased by 1.9 mEq/L with placebo. In this study and both SALT trials, patients with hypovolemic hyponatremia were excluded from participation.

For both tolvaptan and conivaptan, close monitoring of serum sodium levels is necessary to avoid too
Although tolvaptan is an oral agent, therapy should be initiated in the hospital setting to allow for sodium monitoring. In addition, because of the potential for serious liver injury, use of tolvaptan should be limited to 30 days.

**Summary**

Hyponatremia can result in significant morbidity and mortality, making its recognition and appropriate treatment essential. Prompt treatment of hyponatremia is critical if severe sodium deficits are present, or if the onset is rapid, to avoid cerebral edema and progressive neurologic effects. Sodium chloride infusion is the most commonly used treatment for acute hyponatremia. For more chronic hyponatremia, other therapies, such as fluid restriction or agents that inhibit the actions of AVP, can be used.

**Table 4. General Management Strategies for Hypotonic Hyponatremia**

<table>
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<tr>
<th>Treatment</th>
<th>Clinical Issues</th>
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| Sodium chloride infusion | 3% or 0.9% solution  
*Euvolemic and hypervolemic patients: may require hypertonic sodium chloride (3%) to avoid volume overload and worsening of hyponatremia  
Hypovolemic patients: may require 0.9% sodium chloride to replace extracellular fluid*  
*Rate of correction depends on severity of symptoms but should not exceed 6-8 mEq/L in 24 h to lessen risk for osmotic demyelination*  
*Euvolemic and hypervolemic patients: may require hypertonic sodium chloride (3%) to avoid volume overload and worsening of hyponatremia  
Hypovolemic patients: may require 0.9% sodium chloride to replace extracellular fluid*  
| Fluid restriction | 1,200 mL/d or less (intake should be less than urine output and insensible losses combined)  
*All fluids need to be restricted  
*Slow onset  
*Compliance difficult  
*Increase in serum sodium generally small (1-2 mEq/L per day)  
*May require addition of sodium chloride and/or loop diuretics*  
| Demeclocycline | 600-1,200 mg/d in divided doses  
*Slow onset (3-6 d)  
*Expensive  
*Potential for nephrotoxicity, especially with concurrent liver disease*  
| Lithium | 900-1,200 mg/d  
*Slow onset  
*Less predictable effects*  
| Conivaptan | 20 mg IV bolus followed by 20 mg as continuous infusion over 24 h for up to 4 d; up to 40 mg/d may be administered*  
*Only indicated for euvolemic or hypervolemic hyponatremia  
*Avoid increases of serum sodium >12 mEq/L per 24 h  
*Potential for drug interactions via CYP3A4 isoenzymes*  
| Tolvaptan | 15 mg once daily titrated to a maximum of 60 mg once daily  
*Only indicated for euvolemic or hypervolemic hyponatremia  
*Therapy should be initiated in the hospital to allow for close monitoring of serum sodium levels  
*Avoid increases of serum sodium >12 mEq/L per 24 h  
*Potential for drug interactions via CYP3A4 isoenzymes*  

*Although higher doses have been used in clinical trials, the maximum dose per product labeling is 40 mg over 24 hours.  
Based on references 1, 26, and 30-34.*
References


