Rational Management of Hospitalized Patients with Hyponatremia:
Application to Patient Cases

FREQUENTLY ASKED QUESTIONS ABOUT MANAGING HYPONATREMIA

The management of hyponatremia in hospitalized patients is the focus of a series of learning opportunities planned by ASHP Advantage. The learning opportunities are designed to build on each other to provide practical strategies for managing the electrolyte disorder safely and effectively in various types of hospitalized patients.

A live symposium with case scenarios on the optimal management of hospitalized patients with hyponatremia was conducted on December 9, 2013, during the 48th ASHP Midyear Clinical Meeting and Exhibition in Orlando, Florida. In addition, a live webinar with a similar format was conducted on January 29, 2014. Frequently asked questions (FAQs) submitted during these live activities were later addressed by Initiative Chair Joseph F. Dasta, M.S., FCCM, FCCP, and faculty member, Jodie L. Pepin, Pharm.D., in another live webinar on March 4. Those FAQs also serve as the basis for two e-newsletters that are part of the educational initiative. The March 2014 issue focused on the impact of fluctuations in serum sodium concentration on patient outcomes and barriers to and strategies for improving the management of hyponatremia in hospitalized patients. This issue focuses on the use of arginine vasopressin (AVP) receptor antagonists (also known as vaptans) to manage hyponatremia in hospitalized patients with heart failure, a patient population that can be especially challenging. The role of protocols, algorithms, and standardized order sets in managing this electrolyte disorder in hospitalized patients also is discussed.

Other learning opportunities in the series include the following:

- On-demand web-based activity based on the January 29 webinar, which provides 1 hour of continuing pharmacy education.
- A faculty roundtable discussion exploring important issues related to the management of hyponatremia in hospitalized patients and led by Professor Joseph Dasta.

For more information and to access these learning opportunities, go to the web portal at www.ashpadvantage.com/hyponatremiacases. The activities are supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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FREQUENTLY ASKED QUESTIONS

Question: Patients with heart failure often present with chronic hyponatremia. What are some key points to keep in mind in identifying the best treatment option for these patients?

Hyponatremia (usually defined as a serum sodium concentration less than 135 mEq/L) is the most common electrolyte abnormality in hospitalized patients.1-3 The hyponatremia associated with heart failure usually is hypervolemic, with increased total body water and total body sodium, and characterized by edema.4 The hyponatremia in these patients typically is chronic and must be corrected slowly to avoid osmotic demyelination syndrome, a brain demyelinating disease that results in significant morbidity and mortality.2,5 The volume status of the patient should be considered, and treatments that exacerbate hypervolemia should be avoided.

Patients with heart failure and hypervolemic hyponatremia often are difficult to treat because they are volume overloaded despite the use of diuretic therapy. Initial efforts should include fluid restriction and optimization of diuretic therapy, which may provide modest improvement in hyponatremia. Improved outcomes have been reported by using hypertonic saline infusions in combination with large doses of loop diuretics instead of diuretics alone.6 Serum sodium should be monitored frequently if this approach is used.

The introduction of AVP receptor antagonists expanded the therapeutic options for managing hyponatremia. These agents antagonize the vasopressin V2 receptors in the renal collecting ducts, which promotes aquareisis (i.e., increased free water excretion without a substantial effect on electrolyte excretion), the formation of a highly hypotonic urine, and increases in serum sodium concentration. Fluid restriction should be avoided during vaptan therapy.7

Vaptans are an attractive therapeutic option in patients with heart failure and hypervolemic hyponatremia, although studies demonstrating improved outcomes and guidelines for use of the drugs in these patients are not available. Therapy must be initiated in a hospital setting where the serum sodium concentration can be monitored closely. The decision to use vaptans in this patient population is based on clinical judgment, taking into consideration the need for an alternative to conventional therapy, safety factors, and availability of resources for outpatient continuation of therapy initiated in a hospital setting.

Question: What differences between conivaptan and tolvaptan might influence product selection for hospitalized patients with hyponatremia?

Conivaptan antagonizes the vasopressin V1a and V2 receptors. Tolvaptan is a selective antagonist of vasopressin V2 receptors. The predominant pharmacodynamic effects of both drugs in patients with hyponatremia are mediated by V2 receptor antagonism in the renal collecting ducts, which increases urine volume and decreases urine osmolality.8 The clinical significance of vasopressin V1a receptor antagonism by conivaptan is unclear.9

Conivaptan was approved by the Food and Drug Administration (FDA) in 2004 to raise serum sodium concentration in hospitalized patients with euvolemic and hypervolemic hyponatremia.10 Euvolemic hyponatremia is characterized by an increase in total body water with no change in total body sodium.4 Tolvaptan was approved by FDA in 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and
syndrome of inappropriate antidiuretic hormone (SIADH). In patients with SIADH, plasma AVP concentrations are inappropriately elevated, resulting in impaired renal water excretion, increased total body water, and hyponatremia.\textsuperscript{11,12}

The vaptans differ in several ways that may affect product selection for hospitalized patients with hyponatremia (Table 1). Conivaptan is administered intravenously (i.v.) into a large vein. Infusion-site reactions are the most common adverse effects from the drug, affecting 63\% to 73\% of patients.\textsuperscript{10} The infusion site should be changed every 24 hours to minimize the risk for these reactions. A loading dose of 20 mg should be infused over 30 minutes followed by a continuous infusion of 20 mg over 24 hours for 2-4 days. If the serum sodium concentration does not rise at the desired rate, the dosage may be increased to 40 mg/day. The duration of conivaptan infusion should be limited to 4 days.

Limited data are available on the compatibility of conivaptan with other i.v. drugs. The use of conivaptan is contraindicated in patients receiving potent cytochrome P450 (CYP) 3A enzyme inhibitors (e.g., ketoconazole, itraconazole, indinavir) because conivaptan is metabolized by these enzymes and concomitant use of these drugs can increase exposure to conivaptan.\textsuperscript{10} The use of conivaptan with CYP 3A substrates (e.g., midazolam, simvastatin, amlodipine) should be avoided.

### TABLE 1. Characteristics of Vaptans\textsuperscript{7-10}

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>CONIVAPTAN</th>
<th>TOLVAPTAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors antagonized</td>
<td>V\textsubscript{1a}, V\textsubscript{2}</td>
<td>V\textsubscript{2}</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Year approved by FDA</td>
<td>2004</td>
<td>2009</td>
</tr>
<tr>
<td>FDA-approved indication</td>
<td>To raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia</td>
<td>Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium &lt;125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and SIADH</td>
</tr>
<tr>
<td>Dosage form and route of administration</td>
<td>20 mg/100 mL solution in 5% dextrose for i.v. administration</td>
<td>15-mg and 30-mg tablets for oral administration</td>
</tr>
<tr>
<td>Dosing</td>
<td>20 mg loading dose over 30 min, then 20 mg by continuous infusion over 24 hr for 2-4 days; after day 1, may increase to 40 mg/day by continuous infusion as needed to raise serum sodium</td>
<td>15 mg once daily; may increase at intervals of at least 24 hr to 30 mg once daily or a maximum of 60 mg once daily as needed to raise serum sodium</td>
</tr>
<tr>
<td>Maximum duration of therapy (days)</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Contraindicated with potent CYP 3A inhibitors Avoid with CYP 3A substrates</td>
<td>Contraindicated with potent CYP 3A inhibitors Avoid with CYP 3A inducers and moderate CYP 3A inhibitors Dosage reduction may be needed if used with P-gp inhibitors</td>
</tr>
<tr>
<td>Cautions</td>
<td>Change infusion site every 24 hr Reduce dosage by 50% in moderate hepatic impairment</td>
<td>Avoid use in patients with underlying liver disease Discontinue if liver injury suspected</td>
</tr>
</tbody>
</table>
Tolvaptan is administered orally. Health care providers should review with the patient the FDA-approved Medication Guide for tolvaptan, which contains information about the proper use of the drug to minimize safety risks. Tolvaptan therapy should be initiated using 15 mg once daily. The dosage may be increased at intervals of no less than 24 hours to 30 mg once daily or a maximum of 60 mg once daily as needed to raise the serum sodium concentration. Tolvaptan 15-60 mg/day produces aquaresis within 2-4 hours, with peak effects on serum sodium concentration and urine output noted within 4-8 hours. Dosages exceeding 60 mg/day have not been shown to be more effective for increasing serum sodium concentrations than smaller dosages. The use of tolvaptan is contraindicated in patients receiving potent CYP 3A enzyme inhibitors because tolvaptan is metabolized by these enzymes and concomitant use of these drugs can increase exposure to tolvaptan. The use of tolvaptan with CYP 3A inducers (e.g., rifampin) and moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem, verapamil) should be avoided. Dosage reduction may be needed if tolvaptan is used in patients receiving P-glycoprotein inhibitors (e.g., cyclosporine). Thirst and dry mouth were the most common adverse effects from tolvaptan in clinical trials.

Question: Can tolvaptan be crushed and given by nasogastric (NG) tube in patients unable to swallow tablets?

The results of a randomized crossover study comparing the bioavailability of tolvaptan when the tablets are crushed, suspended in water, and administered by NG tube instead of swallowed intact recently were reported. The study was conducted in 28 healthy adults who received two 15-mg doses (one as an intact tablet and the other by NG tube, not necessarily in that order) with a washout period of at least 7 days between doses. The area under the plasma concentration-time curve (i.e., bioavailability) for tolvaptan was approximately 25% lower after NG administration than after taking the intact tablets.

The investigators concluded that the NG route of administration can be used for administration of tolvaptan, although the effects on the pharmacodynamics of the drug remain to be evaluated in patients with hyponatremia receiving multiple doses.
Question: What other considerations enter into decisions to use tolvaptan in patients with heart failure?

The etiology of hyponatremia in patients with heart failure should be considered. The electrolyte disorder may resolve if underlying conditions are corrected.

Cost is a consideration because patients with heart failure have a high rate of readmission, and reimbursement from the Centers for Medicare and Medicaid Services is reduced for readmissions within 30 days after hospital discharge. Although tolvaptan is an oral therapy, it must be initiated or reinitiated in a hospital setting where the serum sodium concentration can be monitored closely. The need for hospitalization to initiate or reinitiate tolvaptan therapy and the potential economic implications of hospital readmission within 30 days after discharge are disadvantages of the long term use of the drug to treat hyponatremia in patients with heart failure.

Question: The treatment of hyponatremia in hospitalized patients is extremely complex. Unfortunately, therapy often is based on clinical judgment, and it can be inconsistent within and among hospitals because of the lack of U.S. guidelines for treatment of the disorder. What can pharmacists do to address this problem?

The use of hospital protocols, algorithms, and standardized order sets for the safe and effective treatment of hyponatremia can help ensure that the disorder is properly and consistently managed and patient outcomes are optimized. Protocols may be disease-based (i.e., facilitating therapeutic decision making for patients with a diagnosis of hyponatremia) or treatment-based, outlining the proper use of a particular intervention, such as fluid restriction, hypertonic saline, or vaptans. Algorithms can be used to stratify patients with hyponatremia based on symptoms, laboratory test results, or etiology to determine the most appropriate treatment. An example of such an algorithm used at the Cleveland Clinic is available online.26

Dr. Pepin described the protocol and standardized order set that have been developed for the use of hypertonic saline at her health system. These materials provide prompts for documenting the indications for use of hypertonic saline based on laboratory test results, symptoms, and clinical status. Calculations of the sodium deficit (i.e., requirement) and initial infusion rate are facilitated.

Expert panel recommendations for the diagnosis, evaluation, and treatment of hyponatremia based on the underlying etiology, serum sodium concentration, and severity of symptoms were published in late 2013.3 Most of these recommendations are not supported by data from randomized, double-blind, placebo-controlled trials, but the recommendations represent the consensus opinion of experts on the current best practices based on extensive clinical and research experience.3 An evidence-based clinical practice guideline on the diagnosis and treatment of hyponatremia recently was released by The European Society of Intensive Care Medicine, European Society of Endocrinology, and European Renal Association–European Dialysis and Transplant Association,17 but the guideline needs to be adapted to the local culture of practice since practices are different in Europe than in the U.S. Despite their limitations, in the absence of an evidence-based clinical practice guideline in the U.S., these two new resources provide valuable guidance for pharmacists interested in evaluating and improving the management of hyponatremia.

Pharmacists should work with an interdisciplinary team in developing hyponatremia treatment protocols, algorithms, and order sets. A physician champion should be identified to facilitate development and implementation of the materials. Other team members might include hospitalists, nephrologists, critical care specialists, cardiologists, neurologists, emergency department physicians, pharmacists, and nurses.

The hospital staff should receive education about new disease-based or therapy-based protocols to promote adherence. Protocols should be revised periodically to reflect new clinical evidence and experience in the treatment of hyponatremia.
REFERENCES


