Special Considerations in Hyponatremia Management

Hospitalized patients with hyponatremia are the focus of a series of learning opportunities planned by ASHP Advantage. The learning opportunities are designed to build on each other and illustrate ways in which the findings from disease-based medication-use evaluations (MUEs) of hyponatremia can help identify areas of patient care needing improvement.

The series began with a live symposium on the use of MUEs to improve care for patients with hyponatremia on December 9, 2014, during the 49th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California. Attendees submitted questions about unresolved issues related to the management of hyponatremia, and those frequently asked questions (FAQs) were used in developing the content of a live Ask the Experts webinar in March 2015. The faculty for the series are Joseph F. Dasta, M.S., MCCM, FCCP, and Gretchen M. Brophy, Pharm.D., BCPS, FCCP, FACC, FNCS.

The series also includes two e-newsletters. The April 2015 issue focused on real-world practices in managing hyponatremia based on a patient registry. This issue addresses special considerations in managing hyponatremia, along with feedback from participants in the live activities about how they planned to incorporate hyponatremia management strategies into practice.

Other learning opportunities in the series include the following:

- On-demand activity based on the Midyear symposium (1.5 hours of continuing pharmacy education),
- Engaging the Experts interviews with the faculty about important issues related to improving hyponatremia management, and
- New on-demand activity based on the Ask the Experts webinar (1 hour of continuing pharmacy education, available late May 2015).

For more information and to access these learning opportunities, go to the web portal at www.ashpadvantage.com/muefindings. The series is supported by an educational grant from Otsuka America Pharmaceutical, Inc.
Hyponatremia is the most common electrolyte disorder in hospitalized patients, and it often goes untreated or inadequately treated. The consequences of untreated hyponatremia are more serious in neurocritical care patients than in other hospitalized patients. Therefore, the clinical definition of moderate and severe hyponatremia often is more conservative for neurocritical care patients than for the general population of hospitalized patients (Table 1).

Disorientation, and altered mental status are associated with moderate hyponatremia, and vomiting, seizures, obtundation, coma, respiratory arrest, and death may be associated with severe hyponatremia.

The central nervous system effects of hyponatremia are the result of brain edema and swelling and increased intracranial pressure. The greater and more rapid the decline in serum sodium concentration, the greater the increase in brain swelling.

### Acute vs. Chronic Hyponatremia

Hyponatremia may be acute (i.e., developing within 48 hours) or chronic, developing more slowly. In patients with chronic hyponatremia, the brain has time to adapt to the hypotonic state, but the brain does not have sufficient time to fully adapt when hyponatremia is acute. Chronic hyponatremia often leads to brain glutamate deficiency and cerebellar dysfunction manifesting as ataxia.

Fluid restriction with a daily intake 500 mL less than the urine output to achieve a negative net fluid balance is commonly used for patients with chronic hyponatremia. Correction of the serum sodium may require several days of fluid restriction.

Using an appropriate rate of correction of hyponatremia is vital. A slow rate of correction is associated with cerebral edema but an excessively rapid rate of correction can cause osmotic demyelination syndrome (ODS), a neurologic disorder with substantial morbidity and mortality. Symptoms of ODS include dysarthria, dysphagia, oculomotor dysfunction, and quadripleasis with a “locked-in” state characterized by an inability to move other than blinking the eyelids. Other risk factors for ODS include alcoholism, cirrhosis, malnutrition, and severe burns.

Acute hyponatremia may develop after surgery, especially prostate resection and endoscopic uterine surgery, or it may be the result of polydipsia, exercise, or use of a colonoscopy bowel preparation or various drug

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### Table 1. Clinical Definitions of Hyponatremia in Hospitalized Patients

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<th>Severity Classification</th>
<th>General Hospitalized Patients</th>
<th>Neurocritical Care Patients</th>
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<tbody>
<tr>
<td>Mild (serum sodium, mEq/L)</td>
<td>131-134</td>
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<tr>
<td>Moderate (serum sodium, mEq/L)</td>
<td>120-130</td>
<td>125-130</td>
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<tr>
<td>Severe (serum sodium, mEq/L)</td>
<td>&lt; 120</td>
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therapies. These drug therapies include a wide variety of agents associated with the syndrome of inappropriate antidiuretic hormone (SIADH, Figure 1). Hyponatremia in patients with SIADH is the result of an increase in arginine vasopressin (AVP, also known as antidiuretic hormone) release, effect, or both. Diuretics also contribute to hyponatremia through their effects on sodium and water homeostasis.

In patients with drug-induced hyponatremia, the offending agent should be discontinued if the risk exceeds the benefits. Alternative therapy that does not cause hyponatremia should be used if needed. If it is not possible to discontinue the offending agent, reducing the dosage may suffice to correct hyponatremia from some medications. Fluid restriction should be used in conjunction with these strategies for patients with chronic drug-induced hyponatremia.

Figure 1. Drug Therapies Associated with SIADH

- Antidepressant agents (selective serotonin reuptake inhibitors, tricyclic antidepressants)
- Carbamazepine
- Chlorpropamide
- Clofibrate
- Cyclophosphamide
- Desmopressin (DDAVP)
- Ifosfamide
- Methamphetamine (MDMA, XTC)
- Neuroleptic agents
- Nonsteroidal anti-inflammatory agents
- Oxcarbazepine
- Oxytocin
- Thiazide diuretics
- Vincristine

SIADH = syndrome of inappropriate antidiuretic hormone

Overview of Treatment Options

Treatment options for hyponatremia include fluid restriction, sodium chloride (normal saline and hypertonic saline infusions and salt tablets), vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), demeclocycline, and mineralocorticoids (e.g., fludrocortisone). Each option has advantages and disadvantages. Fluid restriction is inexpensive but the response is limited with a slow onset, and patient nonadherence is a concern. Sodium chloride infusions provide a rapid response in symptomatic patients but require dose and rate calculations, and the infusions should not be used in patients with edema-forming disorders. Vasopressin receptor antagonists (i.e., vaptans) target excessive AVP and promote aquaresis (i.e., increased free water excretion without a substantial effect on electrolyte excretion), but they cannot be used in patients with hypovolemic states. Demeclocycline also targets excessive AVP, but the response is delayed, and the drug can cause nephrotoxicity in patients with congestive heart failure or cirrhosis.

The approach to treating hyponatremia may be based largely on symptomatology. Patients with no or minimal symptoms may be managed initially with fluid restriction, although vasopressin receptor antagonist therapy may be indicated in certain circumstances:

- Inability to tolerate or failure to respond to fluid restriction;
- Unstable gait, high fracture risk, or both;
- Very low sodium level (<125 mEq/L) with an increased risk of developing symptomatic hyponatremia;
- Need to correct serum sodium to a safer level for surgery, a procedure, or discharge from the intensive care unit (ICU) or hospital;
- Prevention of worsened hyponatremia with increased fluid administration; and
- A therapeutic trial.
Using Medication-use Evaluation Findings to Improve Patient Care

Patients with symptoms of moderate hyponatremia should receive vasopressin receptor antagonist therapy, followed by fluid restriction, if needed. Patients with symptoms of severe hyponatremia should receive hypertonic saline initially, followed by fluid restriction with or without vasopressin receptor antagonist therapy.

In a registry of 3087 patients with hyponatremia (serum sodium 130 mEq/L or less) at 225 hospitals in the United States or European Union, fluid restriction was the least effective initial monotherapy for hyponatremia. The median increase from baseline in serum sodium concentration within the first 24 hours of therapy was higher with hypertonic saline (5 mEq/L), tolvaptan (4 mEq/L), and normal saline (3 mEq/L) than fluid restriction (2 mEq/L).

In a multicenter, retrospective, observational study of 137 ICU patients with neurologic injury who were treated for hyponatremia (serum sodium <135 mEq/L), hypertonic saline was the most commonly used initial intervention (62%). In patients with a treatment response (defined as an increase from baseline in serum sodium of at least 4 mEq/L after 24 hours), the median increase from baseline in serum sodium concentration after 24 hours was greater with conivaptan (7 mEq/L), hypertonic saline (6 mEq/L), and fluid restriction (5 mEq/L) than other interventions.

Use of Vaptans

Conivaptan and tolvaptan were developed for the treatment of euvolemic and hypervolemic hyponatremia and approved by the Food and Drug Administration (FDA) in 2004 and 2009, respectively. Conivaptan antagonizes vasopressin V₁a and V₂ receptors. Tolvaptan is a selective antagonist of vasopressin V₂ receptors. The effects of both drugs in patients with hyponatremia are mediated primarily by V₂ receptor antagonism in the kidneys.

Conivaptan is administered intravenously (i.v.) as a 20-mg loading dose over 30 minutes, followed by 20-40 mg over 24 hours for 2-4 days as needed to raise the serum sodium concentration. To minimize the risk of infusion site reactions, the drug should be administered through large veins, and the infusion site should be changed every 24 hours.

Tolvaptan is administered orally. The drug should be initiated and reinitiated only in a hospital setting. The recommended initial oral dosage of tolvaptan is 15 mg once daily without regard to meals. The dosage may be increased to 30 mg once daily, followed by a maximum of 60 mg once daily as needed to raise the serum sodium concentration. Dosage increases should be made at intervals of at least 24 hours. Fluid restriction should be avoided during the first 24 hours of tolvaptan therapy. Bioavailability of tolvaptan after nasogastric administration may be less than after taking intact tablets.

As noted previously, vaptans should be used primarily to manage patients with symptoms of mild or moderate hyponatremia. Serum sodium concentrations should be monitored frequently (e.g., every 6-8 hours) during the active phase of correction with vaptan therapy (i.e., the first 24-48 hours of therapy).

Both conivaptan and tolvaptan are substrates of CYP 3A4. Use of these drugs is contraindicated in patients receiving potent CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, indinavir) because concomitant use of CYP 3A4 inhibitors can increase exposure to the vaptan. The use of conivaptan with other CYP 3A4 substrates (e.g., midazolam, simvastatin, amlodipine) and the use of tolvaptan with CYP 3A4 inducers (e.g., rifampin) and moderate CYP 3A4 inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem, verapamil) should be avoided. Because tolvaptan is also a substrate of P-glycoprotein (P-gP), tolvaptan dosage reduction may be needed if the drug is used in patients receiving P-gP inhibitors (e.g., cyclosporine).

In 2013, a safety warning was added to the FDA-approved labeling for tolvaptan because of liver enzyme elevations observed in patients with polycystic kidney disease who received the drug at higher-than-recommended doses in a clinical trial. Tolvaptan should not be used in patients with underlying liver disease, including cirrhosis.

Downloaded from www.ashpadvantage.com/muefindings
The treatment duration should be limited to 30 days to minimize the risk of liver injury, and the drug should be discontinued if symptoms of liver injury occur.

Elevated intracranial pressure (ICP) from cerebral edema is a concern in patients with severe traumatic brain injury. In theory, increasing serum sodium concentrations through the use of vaptans could provide an osmotic gradient that reduces cerebral edema and ICP. Aquaporin (AQP)-4 channels are thought to play a key role in the development of cerebral edema, and these channels may be modulated by vasopressin $V_{1a}$ receptors. $V_{1a}$ and $V_2$ receptors are expressed in the brain, and experimental models have demonstrated that vasopressin $V_{1a}$ receptor antagonism is helpful in reducing brain edema by down regulating AQP-4 channels.

Because conivaptan antagonizes both vasopressin $V_{1a}$ and $V_2$ receptors, the effect of single 20-mg i.v. bolus doses on ICP was evaluated in an open-label, randomized, controlled study of 10 normonatremic patients with severe traumatic brain injury. The drug was compared with usual care. Four hours after treatment, the serum sodium concentration was significantly higher ($p = 0.02$) and the ICP was significantly lower ($p = 0.046$) in the conivaptan group compared with the usual care group. After 48 hours, there was no significant difference between the two groups in the mean serum sodium concentration ($p = 0.71$). There were no drug-related serious adverse events in either group.

A single 20-mg i.v. bolus dose of conivaptan was given to a 22-year-old patient with hyponatremia and severe traumatic brain injury. Substantial aquaresis occurred, with a maximum effect 3-5 hours after the dose. A significant reduction in ICP was observed 4 hours after the dose (i.e., the ICP reduction was temporally associated with the maximum aquaresis), and the ICP reduction lasted throughout the 8-hour observational period after the dose. Hyponatremia was corrected within 8 hours after the dose.

Safety Considerations with Hypertonic Saline

Hypertonic saline usually is reserved for patients with severe neurologic symptoms of hyponatremia in whom the condition is acute and requires urgent intervention. Excessively rapid increases in serum sodium concentration (>12 mEq/L in a 24-hour period) should be avoided because of the risk of ODS. Therapy should be designed to provide an increase in serum sodium by approximately 0.5-1 mEq/L/hr until neurological symptoms resolve or the serum sodium exceeds 120 mEq/L. Therapy should be titrated slowly to achieve an increase in serum sodium concentration of 10-12 mEq/L in the first 24 hours and less than 18-24 mEq/L within the first 48 hours. Data from the hyponatremia registry suggest that the risk of overly rapid correction of hyponatremia is higher with the use of hypertonic saline than other therapies for hyponatremia.

Serum sodium concentrations should be checked frequently (every 2-4 hours) during treatment with hypertonic saline until values stabilize and daily after treatment is discontinued. Recurrence of hyponatremia was common in the hyponatremia registry.

Hypertonic sodium chloride 23.4% has been used to treat patients with traumatic brain injury and elevated ICP. However, the 23.4% concentration should not be used to treat hyponatremia because it can induce a hypernatremic and hyperchloremic state.

Practice Changes

An awareness of the special considerations in managing hyponatremia is essential for optimizing patient outcomes, but integrating these concepts into practice can be a challenge for pharmacists. Approximately three months after the December 2014 Midyear symposium, attendees were asked how they had changed or planned to change their practice after participating in the activity. Their responses are described here to give others ideas about how to incorporate hyponatremia management strategies into practice.
A total of 21 participants completed the survey, and the vast majority of these individuals indicated that they implemented or planned changes related to direct patient care:

- Being more vigilant about screening and evaluating hospitalized patients for hyponatremia (81% of respondents) and
- If hyponatremia is identified, assessing sodium levels during hospitalization and before discharge to ensure optimal sodium status for that individual (71% of respondents).

Changes that take institutional initiative—and hence more time (such as targeting improvements based on results of a national registry or local medication-use evaluation and developing recommendations for the safe and effective treatment of hyponatremia within the institution)—were implemented or planned by about half of the respondents.

A second group of pharmacists, this time close to 600 participants in the March 2015 Ask the Experts webinar on hyponatremia, were asked a similar question, and developing a hyponatremia protocol was the practice change most commonly mentioned (Table 2). When asked specifically about changes in patient care, participants noted that they would most likely do the following (range 47-59%):

- Identify drug-related risk factors for hyponatremia and modify as needed,
- Recognize drug-related causes of hyponatremia and discontinue the offending drug, and
- Determine appropriate hyponatremia treatment options and monitor response to therapy.

In addition, participants noted that they would assess chronicity of hyponatremia before recommending treatment, discuss hyponatremia monitoring with ICU staff, aggressively monitor hyponatremia treatment to avoid overcorrection, check the patient’s sodium level during medication reconciliation, and begin work on the hospital’s hyponatremia medication-use evaluation.

Almost 30% of participants did not foresee any barriers in implementing these changes, while 27% indicated that lack of time and resources was a potential barrier. Different approaches used by physicians for managing hyponatremia and difficulty obtaining data for medication-use evaluation were also mentioned as potential barriers.

If these practice changes pique your interest, check out the educational activities available on the initiative website (www.ashpadvantage.com/muefindings) to learn more about hyponatremia and how pharmacists can improve outcomes in hospitalized patients with this electrolyte disorder.

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<tr>
<th>Table 2. Strategies for Improving Hyponatremia Management in Hospitalsa</th>
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<td>Anticipated Practice Change</td>
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<tr>
<td>Develop a hyponatremia protocol</td>
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<tr>
<td>Increase involvement in fluid resuscitation</td>
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<tr>
<td>Screen sodium values before discharge</td>
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<tr>
<td>Conduct a hyponatremia medication-use evaluation</td>
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aBased on polling of participants in a live Ask the Experts webinar on the management of hyponatremia conducted March 26, 2015.
bSelection of more than one practice change was allowed.
Hyponatremia Management

Using Medication-use Evaluation Findings to Improve Patient Care

References


For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/muefindings. There is no charge for the activities, and ASHP membership is not required.

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Contact ASHP Advantage for assistance or questions.