

Hyponatremia Management

Using Medication-use Evaluation Findings to Improve Patient Care

Hyponatremia in the Real World

ASHP Advantage is coordinating a series of learning opportunities related to the management of hyponatremia in hospitalized patients. These opportunities are designed to build on each other and illustrate ways in which findings from disease-based medication-use evaluations (MUEs) of hyponatremia can help identify areas of patient care needing improvement. The educational activities are provided in live and on-demand formats. The series is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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 addressed in a live Ask the Experts webinar on March 26, 2015. The faculty for the series are Joseph F. Dasta, M.S., MCCM, FCCP, and Gretchen M. Brophy, Pharm.D., BCPS, FCCP, FCCM, FNCS, who are nationally recognized experts in hyponatremia and critical care.

This e-newsletter focuses on recently published findings from a hyponatremia registry that provide insight into how hyponatremia is being treated in hospitals in the United States and suggest a role for pharmacists screening hospitalized patients for untreated hyponatremia, suggesting and monitoring therapy through discharge. The next e-newsletter in this educational initiative will address special considerations in managing hyponatremia.

If you missed the Midyear symposium, it is now available as a web-based activity that is approved for 1.5 hours of continuing pharmacy education. Its on-demand format is convenient since it may be completed at any time. For more information and to access the web-based activity, go to the web portal at www.ashpadvantage.com/muefindings. Look for the web-based version of the Ask the Experts webinar in May.

Engaging the Experts

Listen to the faculty discuss important issues related to improving hyponatremia management—available at www.ashpadvantage.com/muefindings or via the ASHP Advantage Engaging the Experts podcast series.

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A Frequently Overlooked Condition

Hyponatremia is a common and potentially serious condition in hospitalized patients.¹ It is defined as a serum sodium concentration below the lower limit of the normal range, which often is 135 mEq/L, although the cutoff value varies with the laboratory and patient care setting. Mild hyponatremia (e.g., serum sodium concentration 131-135 mEq/L) often is asymptomatic but it may be associated with subtle, nonspecific symptoms, such as headache, nausea, vomiting, fatigue, confusion, anorexia, and muscle cramps.^{2,3} These symptoms along with malaise and unsteadiness are associated with moderate hyponatremia (e.g., serum sodium 120-130 mEq/L). Severe hyponatremia (e.g., serum sodium <120 mEq/L) is associated with headache, restlessness, lethargy, seizures, brainstem herniation, respiratory arrest, and death. The severity of symptoms correlates with the degree of hyponatremia. The hospital mortality rate, need for mechanical ventilation, rate of intensive care unit (ICU) admission, median length of stay, and total hospital costs are significantly higher for patients with hyponatremia than patients without the electrolyte disorder.⁴

An estimated 3.2 to 6.1 million Americans are affected by hyponatremia each year, and the electrolyte disorder is a principal or secondary diagnosis in 1 million hospitalized patients each year.⁵ The direct costs of hyponatremia amount to \$1.6 to \$3.6 billion annually in the United States.⁵

Although hyponatremia is common and potentially deadly, it often is considered benign and goes unaddressed or undertreated.^{6,7} Treatment of hyponatremia is based on symptomatology and etiology. Treatment of depletion (i.e., hypovolemic) hyponatremia is straightforward and involves fluid resuscitation. Treatment of dilutional hyponatremia is more complex. Dilutional hyponatremia may be hypervolemic and accompanied by edema in patients with heart failure, cirrhosis, or nephrotic syndrome, or it may be euvolemic in patients with syndrome of inappropriate antidiuretic hormone, hypothyroidism, or secondary adrenal insufficiency.

Treatment approaches include fluid restriction, normal saline, hypertonic saline (3% sodium chloride), loop diuretics (e.g., furosemide), demeclocycline, vasopressin receptor antagonists (i.e., vaptans, such as conivaptan and tolvaptan), and in patients with drug-induced hyponatremia, cessation of the offending agent.

Real-world Practices

A registry of patients with hyponatremia was established to generate data for analysis to identify practice patterns and shortcomings in the real-world management of hyponatremia.⁷ The results of a retrospective observational analysis of registry data representing 3087 patients from 225 hospitals in the United States and European Union were published in February 2015.

Why should pharmacists pay attention to this article and the hyponatremia registry findings? As described by Joseph Dasta, who served as the pharmacist member of the registry team and is one of the co-authors, the registry provides important insights about whether and how hyponatremia is treated during hospitalization in the United States and the relative efficacy and safety of various therapies for correcting the electrolyte disorder. Real-world practices in this large group of patients and hospitals can serve as benchmarks for comparison with practices in an institution. Shortcomings identified in the registry can be targeted with education and other strategies to improve the quality of patient care. In addition, registry parameters can serve as a foundation for hospitals interested in conducting their own hyponatremia medication-use evaluations, as discussed later in this e-newsletter.

In the registry, hyponatremia was defined as a serum sodium concentration of 130 mEq/L or less for the purposes of capturing patients likely to be receiving drug therapy. Patients with severe hyperglycemia (blood glucose >250 mg/dL) or receiving renal replacement therapy were excluded from the registry because of the high likelihood that low serum sodium values represent pseudohyponatremia in these patients.

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The most common initial management of hyponatremia in registry patients was fluid restriction (Table 1). A median of two unique therapies were used. Seventeen percent of the 3087 patients received no active therapy; half (265, or 52%) of these patients received a hyponatremia-inducing drug, but the offending drug was discontinued in only 29 (11%) patients. The use of no active therapy was less common in the patients with the most severe hyponatremia (3% of patients with serum sodium <120 mEq/L) than in those with a higher serum sodium (13% with 120-125 mEq/L and 25% with 126-130 mEq/L). Hypertonic saline, which is a high-alert drug in acute care settings, was not commonly used for initial management of hyponatremia.⁸

Most registry patients receiving active treatment experienced an increase from baseline in serum sodium concentration.⁷ A reduction from baseline by more than 2 mEq/L, however, was observed with initial therapy using fluid restriction (8%), normal saline (8%), hypertonic saline (1%), and tolvaptan (1%).

In the hyponatremia registry, therapy episode was defined as an interval during which a treatment or combination

Table 1.
Use of Initial Management Strategies
for Hyponatremia^{7,a}

Type of Therapy	Rate of Use (%)
Fluid restriction	35
No active treatment	17
Normal saline	15
Tolvaptan	5
Hypertonic saline	2
Conivaptan	<1

^aBased on a registry of 3087 patients with a baseline serum sodium concentration of 130 mEq/L or less at 225 hospitals in the United States or European Union.

of treatments was given specifically for hyponatremia without interruption.⁷ Two or more therapy episodes were associated with the hospital stay for nearly half (46%) of the registry patients, suggesting that hyponatremia often recurs after correction of serum sodium to more than 130 mEq/L.

Assessing the efficacy of individual therapies for hyponatremia is difficult since combination therapy is commonly used and these therapies changes over time. Monotherapy during the first 24 hours was the focus of the hyponatremia registry to simplify the analysis.⁷ Fluid restriction was the least effective initial monotherapy for hyponatremia (Table 2). The rate of increase in serum sodium concentration was greater with more rigorous fluid restriction (≤ 1 L/day) than with less rigorous fluid restriction (< 1 L/day).⁷ Adding fluid restriction to other therapies had little or no effect on serum sodium concentration.⁷

Table 2.
Response to Monotherapy for Hyponatremia^{7,a,b}

Type of Monotherapy	Median Increase in Serum Sodium Concentration (mEq/L) in First 24 Hr	Median Rate of Increase in Serum Sodium Concentration (mEq/L/day)
No treatment	1.0	0.4
Fluid restriction overall	2.0	1.0
Fluid restriction ≤ 1 L/day	2.0	1.2
Fluid restriction > 1 L/day	2.0	0.7
Normal saline	3.0	2.0
Hypertonic saline	5.0	3.1
Tolvaptan	4.0	3.3

^aBased on a registry of 3087 patients with a baseline serum sodium concentration of 130 mEq/L or less at 225 hospitals in the United States or European Union.

^bConivaptan data are not provided because the drug was used in only 6 patients.

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Fluid restriction can be difficult and costly to implement. Health-system pharmacists may not be aware of the order. Preparing concentrated solutions for intravenous (i.v.) drug therapy requires time and can be associated with waste. A risk of error is associated with fluid restriction if i.v. infusion pumps are not properly programmed to accommodate concentrated solutions. Nonadherence may be a problem if thirsty patients consume oral fluids. Patients in ICUs often receive substantial volumes of i.v. fluid in conjunction with drug therapy.⁹ The use of syringe pump technology might be beneficial in minimizing the volume of fluid administered to some of these patients.

Rapid correction of hyponatremia can result in brain dehydration and osmotic demyelination syndrome (ODS), a neurologic disorder that results in significant morbidity and mortality.¹ No cases of ODS were reported in the hyponatremia registry.⁷ However, overly rapid correction of hyponatremia, defined as an increase in serum sodium concentration by more than 12 mEq/L in a 24-hour period or more than 18 mEq/L in 48 hours, occurred in 7.9% of patients in the registry.⁷ The risk of overly rapid correction of hyponatremia was highest with use of hypertonic saline (incidence of 16.1%).

As shown in Table 2, in the first 24 hours, hypertonic saline was the most effective intervention for achieving sodium correction benchmarks in the registry patients, followed by tolvaptan.⁷ Tolvaptan should not be used in patients with underlying liver disease, including cirrhosis, and use of the drug should be limited to 30 days because of liver enzyme elevations observed in a clinical trial of patients with polycystic kidney disease who received higher doses of the drug than what is recommended for sodium correction.^{10,11}

At the time of hospital discharge, the serum sodium concentration was less than 135 mEq/L in 78% of registry patients and 130 mEq/L or less in 49% of patients.⁷ Thus, half of patients were discharged with hyponatremia.

Implications for Pharmacists

While the hyponatremia patient registry has several limitations, including the retrospective observational nature of the analysis, it provides valuable information about real-world practices in managing hyponatremia in hospitalized patients.

The registry findings suggest a role for pharmacists at the bedside in screening patients for untreated hyponatremia (especially drug-induced hyponatremia) and suggesting appropriate interventions, taking into consideration the relative efficacy (rate and extent of sodium increase) and safety of various therapies and patient characteristics. The pharmacist can provide education for other healthcare professionals about the consequences of untreated hyponatremia and proper use of therapies to safely correct the disorder (i.e., avoiding overly rapid sodium correction through prescribing of an appropriate drug and dosage and with frequent monitoring of serum sodium concentration). Collaboration with other members of the healthcare team to improve care for patients requiring fluid restriction may be warranted.

A need for ongoing monitoring for recurrent hyponatremia after initial correction of the serum sodium concentration is suggested by the multiple therapy episodes in the registry patients. Pharmacists can advise nursing staff and phlebotomists about the importance of obtaining blood samples at an appropriate time for measuring serum sodium concentration in patients treated for hyponatremia. Pharmacists should be alert for hyponatremia at the time of hospital discharge because of the large percentage of patients with hyponatremia at this transition of care.

Patient discharge education about the symptoms of hyponatremia and importance of taking drug therapies as prescribed and keeping appointments with the laboratory for monitoring serum sodium is another important role for the pharmacist.

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Foundation for Medication-use Evaluations

Medication-use evaluation is a tool for generating data that help identify problems associated with and opportunities for improvement in the use of drug therapies in an institution. The data can be sorted by medical or surgical service or prescriber. The hyponatremia patient registry could be used as the foundation for an MUE for hyponatremia. Because hyponatremia has multiple etiologies and the drugs used to correct hyponatremia are used for a variety of other conditions, an MUE should focus on hyponatremia as a disease state. The criteria used for the hyponatremia registry (e.g., serum sodium concentration used to define hyponatremia) could be adapted for use in an institutional MUE.

Because hyponatremia is associated with diseases and conditions treated by a wide variety of specialists, no one specialist manages the electrolyte disorder in hospitalized patients. Therefore, an interprofessional effort involving intensivists, hospitalists, cardiologists, nephrologists, endocrinologists, pharmacists, nurses, and phlebotomists is needed for a hyponatremia MUE. Pharmacists often have been the catalyst in developing protocols for disease-state management and other patient care quality improvement efforts in hospitals. Therefore, the pharmacist is well suited to serve as a champion and spearhead institutional efforts to improve the management of hyponatremia through MUEs and other quality improvement activities.

Sign Up

Sign up to be notified of updates related to this educational initiative. The second e-newsletter in this series will focus on special considerations in managing hyponatremia. Practice changes that can be used by hospital pharmacists to improve outcomes in patients with hyponatremia also will be discussed.

www.ashpadvantage.com/muefindings

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