Rational Management of Hospitalized Patients with Hyponatremia:

Application to Patient Cases

MARCH 2014 | ASHP ADVANTAGE E-NEWSLETTER

CURRENT CONSIDERATIONS IN MANAGING HYPONATREMIA IN HOSPITALIZED PATIENTS

ASHP Advantage is coordinating a series of learning opportunities related to the management of hospitalized patients with hyponatremia. These opportunities are designed to build on each other to provide practical strategies for managing this electrolyte disorder safely and effectively in various types of hospitalized patients. The series is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

The educational activities are provided in live and on-demand formats, and faculty members are nationally recognized experts in critical care and electrolyte disturbances. 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. Attendees in both live activities submitted questions about unresolved issues related to the management of hyponatremia, and these frequently asked questions (FAQs) were addressed by Initiative Chair Joseph F. Dasta, M.S., FCCM, FCCP, and faculty member, Jodie L. Pepin, Pharm.D., in a live webinar on March 4, 2014. These FAQs also serve as the basis of content explored in the two e-newsletters that are part of the educational initiative.

If you missed the January 29 webinar, it is now available as a web-based activity that is approved for one hour of continuing pharmacy education credit. 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/hyponatremiacases**

FACULTY ROUNDTABLE DISCUSSION

Visit the hyponatremia web portal to listen to a faculty roundtable discussion of important issues related to the management of hyponatremia in hospitalized patients led by Professor Joseph Dasta.

FACULTY

Joseph F. Dasta, M.S., FCCM, FCCP,
Activity Chair
Professor Emeritus
The Ohio State University College of Pharmacy
Adjunct Professor
The University of Texas College of Pharmacy
Austin, Texas

Amy L. Dzierba, Pharm.D., BCPS, FCCM
Clinical Pharmacist, Adult Critical Care
New York-Presbyterian Hospital
Lecturer
Columbia University School of Nursing
New York, New York

Jodie L. Pepin, Pharm.D.
Director of Pharmacy
Seton Medical Center Williamson
Seton Healthcare Family
Clinical Assistant Professor of Health Outcomes and Pharmacy Practice
The University of Texas College of Pharmacy
Austin, Texas

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WHY FOCUS ON HYPONATREMIA?

Hyponatremia is the most common electrolyte abnormality in hospitalized patients, affecting 15-30% of patients.[1] The prevalence of hyponatremia in intensive care units (ICUs) may be as high as 40%.[2] The condition usually is defined as a serum sodium concentration less than 135 mEq/L, although the cutoff value varies by laboratory. Symptoms correlate with the severity of hyponatremia (Table 1).

Adverse clinical and economic outcomes are linked with hyponatremia, although whether hyponatremia is a marker of disease severity or a mediator (i.e., cause) of poor outcomes has not been established (i.e., whether patients die with or because of hyponatremia is unclear).[1,2] Evaluation of billing data from large numbers of hospitalized patients with and without hyponatremia matched for other characteristics revealed that hyponatremia is an independent predictor of high morbidity, long length of stay, admission to the ICU, need for mechanical ventilation, high mortality, and high costs.[1] The relationship between adverse outcomes and hyponatremia is well established for patients with liver disease and patients with heart failure.[1] A cost-of-illness study of hyponatremia in the United States using information from databases, published literature, and an expert physician panel estimated that 3.2 to 6.1 million Americans are affected by the disorder, including 1 million persons hospitalized with a primary or secondary diagnosis of hyponatremia, at a direct cost of $1.6 to $3.6 billion annually.[5]

TABLE 1.

Symptoms Associated with Degree of Hyponatremia[3,4]

MILD (serum sodium 130-135 mEq/L)	MODERATE (serum sodium 120-130 mEq/L)	SEVERE (serum sodium <120 mEq/L)
• Asymptomatic	• Malaise	• Headache
• Headache	• Unsteadiness	• Restlessness
• Nausea	• Headache	• Lethargy
• Vomiting	• Nausea	• Seizures
• Fatigue	• Vomiting	• Brain stem herniation
• Confusion	• Fatigue	• Respiratory arrest
• Anorexia	• Confusion	• Death
• Muscle cramps	• Anorexia	
• Depressed reflexes	• Muscle cramps	

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In a retrospective cohort study of nearly 200,000 hospitalized patients, the prevalence of hyponatremia at the time of admission was 5.5%.[6] The hospital mortality rate, need for mechanical ventilation, rate of ICU admission, median length of stay, and total hospital costs were significantly higher for patients with hyponatremia than patients without the electrolyte disorder ($p < 0.001$). The incremental total hospital cost associated with hyponatremia was $2289 per patient.

Although hyponatremia is common and potentially deadly in critically ill patients, it often is considered benign and goes unaddressed.[7] Treatment often is inadequate.

This e-newsletter features frequently asked questions (FAQs) addressed by the faculty pertaining to 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. Answers to FAQs about the treatment of hyponatremia in hospitalized patients with heart failure, a patient population that can be especially challenging, and the potential role of protocols, algorithms, and standardized order sets in improving outcomes in hospitalized patients with the electrolyte disorder will be provided in the next e-newsletter.

FREQUENTLY ASKED QUESTIONS

Question: What data are available demonstrating the impact of fluctuations in serum sodium concentration on patient outcomes?

Most studies of the impact of hyponatremia on clinical and economic outcomes are based on billing data, but laboratory data were used in two large retrospective cohort studies that illustrate the impact of fluctuations in serum sodium concentrations on patient outcomes.[8,9] In one cohort study of more than 50,000 patient hospitalizations, a decline of at least 2 mEq/L in serum sodium (i.e., aggravation of hyponatremia) occurred during the first 48 hours in 1151 (5.7%) of 20,181 hospitalizations in which hyponatremia (serum sodium concentration <138 mEq/L) was present at the time of admission.[8] The odds ratio of in-hospital mortality was higher in patients with aggravation of hyponatremia (odds ratio 2.30) than in the 19,030 patients without a decline in serum sodium (odds ratio 1.46). Similarly, aggravation of hyponatremia was associated with a higher odds ratio for a prolonged length of stay (1.40 vs. 1.12 for hospitalizations without a decline in serum sodium).

In another large cohort study of dysnatremia (i.e., hyponatremia or hypernatremia) in approximately 11,000 surgical ICU patients, including 1215 (11.2%) patients with hyponatremia and 277 (2.5%) patients with hypernatremia at the time of ICU admission, the median fluctuation in serum sodium concentration during the ICU stay was 5 mEq/L.[9] The maximum fluctuation in serum sodium concentration during the ICU stay was associated with ICU and hospital mortality (i.e., mortality was higher with a large maximum fluctuation than a small maximum fluctuation). In patients who were normonatremic during the ICU stay, a fluctuation in serum sodium concentration greater than 6 mEq/L was independently associated with

hospital mortality (odds ratio 1.55). This study was the first to implicate serum sodium fluctuations as a contributor to adverse outcomes in surgical ICU patients.

Question: Why is the treatment of hyponatremia often inadequate, and what can be done to rectify the situation?

Hyponatremia is a complex disorder. The optimal treatment depends on several factors, including underlying etiology, volume status, time course of the decline in serum sodium concentration (i.e., chronicity of hyponatremia), and the presence and severity of symptoms. Much of this information can be obtained from the patient, a family member, or care giver. However, if the patient is acutely symptomatic and experiencing seizures or unconscious and no family member or care giver is available, assumptions must be made about the etiology and chronicity of the disorder so that treatment can be initiated promptly.

Hyponatremia may be classified as depletional or dilutional.[10] Depletional hyponatremia (known more commonly as hypovolemic hyponatremia) is caused by a decrease in both total body water and total body sodium, often due to excessive diuretic use, diarrhea, vomiting, burns, or trauma. This type of hyponatremia is almost always chronic and can be treated by correcting the volume deficit, which will result in diuresis and elimination of the relative water excess.

In most cases, hyponatremia is dilutional and characterized by an increase in total body water.[10] Dilutional hyponatremia may be hypervolemic and accompanied by edema if the total body sodium also is increased as is the case in patients with heart failure, cirrhosis, or nephrotic syndrome. Dietary sodium restriction and diuretic therapy are the mainstays of therapy for hypervolemic hyponatremia in the outpatient setting.

Dilutional hyponatremia may be euvolemic if the total body sodium is unchanged as is the case in patients with syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, or secondary adrenal insufficiency. Various medications and disorders (e.g., pulmonary infection, central nervous system tumors) can cause SIADH.[1] Treatment of euvolemic hyponatremia depends on the presence of underlying disease contributing to hyponatremia, the rate of onset of hyponatremia, and the presence of neurologic symptoms. Fluid restriction, hypertonic saline (i.e., 3% sodium chloride), loop diuretics, and vasopressin receptor antagonists are among the therapeutic options.[11]

Water and electrolyte balance ordinarily are regulated through negative feedback mechanisms. Plasma concentrations of arginine vasopressin (AVP, or antidiuretic hormone) rise in response to a high plasma osmolality, resulting in decreased renal water excretion, which normalizes the plasma osmolality. Conversely, plasma AVP concentrations decrease in response to a low plasma osmolality, which promotes renal water excretion and normalizes the plasma osmolality. In patients with SIADH, plasma AVP concentrations are inappropriately elevated, resulting in impaired renal water excretion, increased total body water, and hyponatremia.[12] Antagonizing vasopressin receptors in the renal collecting ducts promotes the excretion of free water and increases serum sodium concentrations in patients with hypervolemic or euvolemic hyponatremia.[13,14]

Hyponatremia may be asymptomatic or characterized by mild, nonspecific symptoms that can progress to more severe symptoms.[3,4] The severity of the symptoms

correlates with the rate of decline in serum sodium concentration (Figure 1) because although the brain adapts to subtle changes in sodium, it cannot adapt as readily to sudden changes.

A systematic approach to assessing and planning treatment for hyponatremia should be used to improve patient outcomes. Such an approach should involve first assessing the degree of symptomatology and then ascertaining the type of hyponatremia. Also important is assessing the chronicity of the hyponatremia.

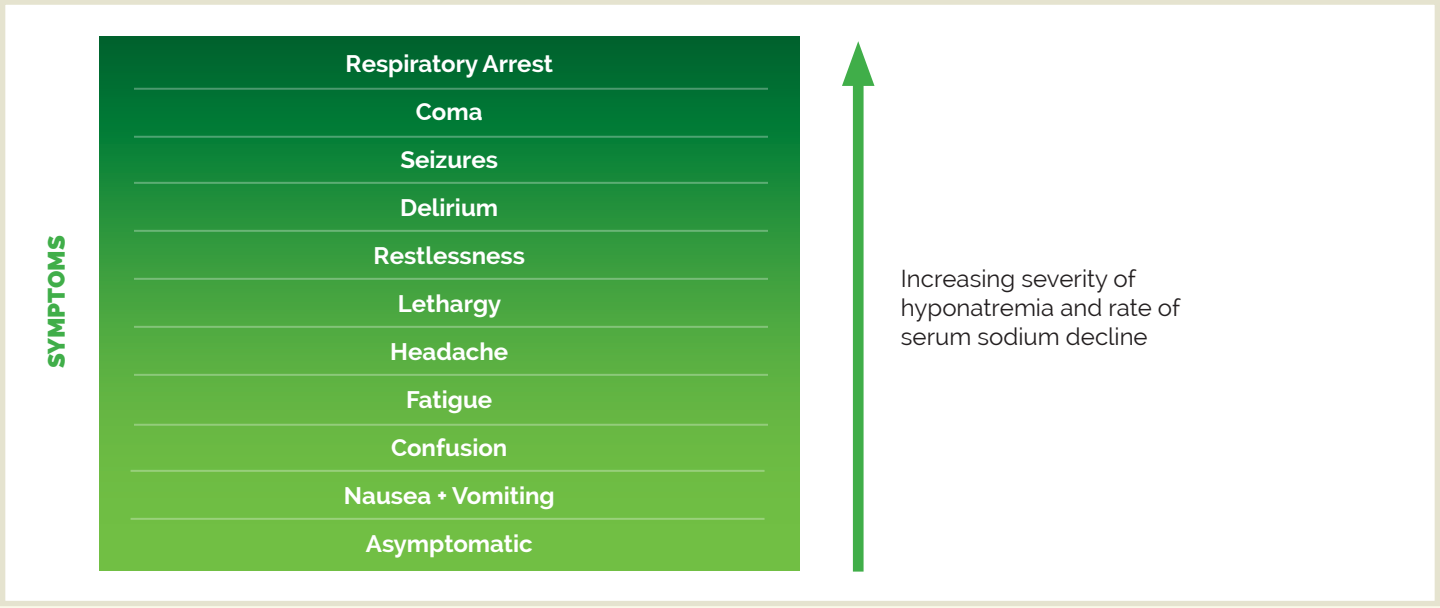
Acute hyponatremia has occurred within the past 48 hours and is characterized by cerebral edema, seizures, and a high mortality rate.[4,15] Rapid correction of acute hyponatremia reverses cerebral edema without sequelae. By contrast, chronic hyponatremia has been present for more than 48 hours and is characterized by nausea, vomiting, confusion, personality changes, neurologic dysfunction, gait disturbances, and seizures. Rapid correction of chronic hyponatremia can cause brain dehydration and osmotic demyelination syndrome (ODS), a brain demyelinating disease that results in significant morbidity and mortality. Avoiding an excessively rapid rate of correction of hyponatremia is needed to avoid ODS.

Question: Should chronically low serum sodium concentrations be treated in patients who are asymptomatic?

Patients with an incidental finding of mild chronic hyponatremia may appear to be asymptomatic, although the condition for which they sought medical attention is in part

FIGURE 1.

Correlation Between Rate of Decline in Serum Sodium and Symptom Severity[3]



the result of hyponatremia.[3,4] For example, hyponatremia may cause or contribute to falls due to alterations in gait and attention. Falls increase the risk for fractures.

In a case-control study of 122 patients with asymptomatic chronic hyponatremia seen in the medical emergency department, 26 (21%) patients were admitted for falls compared with 13 (5.3%) of 244 matched controls ($p < 0.001$).[16] The frequency of falls in patients with hyponatremia was independent of the severity of hyponatremia.

In the same case-control study, 12 patients with chronic asymptomatic hyponatremia (mean serum sodium concentration 128 mEq/L) demonstrated significant gait instability compared with 25 age-matched healthy volunteers.[16] The gait instability normalized with the correction of hyponatremia.

In a retrospective study of 1408 consecutive female patients who underwent bone mineral density measurement, including 254 women who had a prior fracture, hyponatremia was found in 8.7% of women with at least one prior fracture and 3.2% of women without a fracture ($p < 0.001$).[17] The effect of hyponatremia on fractures may be mediated by an increase in bone resorbing osteoclasts.[18]

These findings suggest that even apparently asymptomatic, mild chronic hyponatremia can cause demonstrable gait disturbances, which increase the risk for falls and fractures. Therefore, therapeutic measures that reliably increase the serum sodium concentration should be implemented in all patients with chronic hyponatremia regardless of the presence of symptoms.

Question: What challenges pose a barrier to identifying the optimal treatment of hyponatremia in hospitalized patients?

Clinical studies of treatments for hyponatremia in hospitalized patients are difficult to conduct in the real world setting because patients with this electrolyte disorder typically are complex and receive multiple therapies simultaneously. Their conditions and the therapeutic interventions used to manage them are subject to rapid change. Attributing an outcome, such as an increase in serum sodium concentration, to a specific therapy presents a challenge. The available patient data often are limited to laboratory test results and medication administration records. Drawing conclusions from data derived from multiple studies is problematic because of differences among studies in the definition of what serum sodium concentration constitutes hyponatremia. Nevertheless, observational studies provide valuable insight into the efficacy of management strategies for hyponatremia. The findings may suggest a need for educational efforts to improve the understanding of this condition by practitioners and the role that pharmacists can play in optimizing therapy.

A prospective observational hyponatremia registry has been established.[19] This registry is supported by Otsuka America Pharmaceutical, Inc. and is coordinated by a seven-member steering committee representing the specialties of cardiology, endocrinology, hepatology, nephrology, and pharmacy. Professor Dasta is the pharmacist member. Clinical and laboratory findings from patients either admitted with hyponatremia or with hyponatremia developing during hospitalization within or outside the United States are part of this first-of-its-kind registry. Data from the registry may provide insight into how various therapies are used in hospital settings.

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Through April 2012, almost 1700 patients had been enrolled in the registry, with a target enrollment of 2500 patients in the United States. Preliminary analysis of the findings revealed that 40% of patients were discharged from the hospital with a serum sodium concentration less than 130 mEq/L (i.e., hyponatremia), which may reflect problems with the use of currently available therapies for hyponatremia (e.g., failure to recognize and treat hyponatremia, improper use of currently available therapies, or lack of efficacy of currently available therapies despite attempts at optimal use of these therapies). Further insight is anticipated as additional data are collected in the registry.

Sign up to be notified of updates related to this educational initiative. The second e-newsletter in this series will focus on FAQs about use of arginine vasopressin 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 the electrolyte disorder in hospitalized patients also will be discussed.

www.ashpadvantage.com/hyponatremiacases

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

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