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HYPONATREMIA AND THE ROLE OF VASOPRESSIN

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Hyponatremia: More to the story than disordered sodium homeostasis

THE SERUM SODIUM concentration is regulated by thirst and by renal water conservation or excretion. In the kidney, two important events are necessary for normal water homeostasis:

- First, sodium reabsorption in excess of water reabsorption (urinary dilution) occurs in the thick ascending limb and distal tubules, creating hypotonicity of the tubular fluid entering the latter portion of the nephron.
- Second, the neurohormone arginine vasopressin modifies water permeability in the principal cells of the collecting duct.

Hyponatremia usually results from nonosmotic stimulation of vasopressin secretion

INSIGHTS INTO VASOPRESSIN'S ACTIONS

Our understanding of the cellular mechanisms of vasopressin has advanced since the discovery of water channels by Preston et al.[1] Vasopressin produces its effects via binding to a specific receptor (the vasopressin type 2, or V_2, receptor) on the basolateral surface of the collecting duct principal cells, initiating a sequence of events that results in the phosphorylation of the aquaporin-2 water channels. This causes translocation of the aquaporin-2–containing vesicles from the cytosol to the apical membrane of the collecting duct cell, permitting passive water movement from the tubular lumen to the interstitium along the osmotic gradient created by the countercurrent concentrating mechanism.

THE VASOPRESSIN–HYPONATREMIA CONNECTION

In the normal individual, variations in plasma osmolality (primarily due to serum sodium concentration) of as little as 1% produce significant changes in vasopressin secretion and water homeostasis, tightly maintaining serum sodium within the range of 136 to 145 mEq/L.

Hyponatremia (serum sodium < 135 mEq/L) is a common clinical disorder that usually results from the nonosmotic stimulation of vasopressin secretion. It can occur in states of normal sodium balance as well as in conditions associated with sodium depletion and excess, underscoring that disordered sodium homeostasis is not the main explanation for the hyponatremia.

GETTING A HANDLE ON HYPONATREMIA

This supplement begins with a review by Dr. Ivor Douglas in which he summarizes the clinical approach to unraveling the various causes of hyponatremia and addressing their treatment.

Two distinct hyponatremic populations

Following this overview, two special populations with hyponatremia are discussed—one very healthy and the other very sick.

Hyponatremia associated with prolonged exercise has attracted increased recognition as more and more people participate in long-distance running and other endurance sports. Though the exact mechanisms leading to exercise-associated hyponatremia are not certain, several risk factors have been identified, including inadequate conditioning prior to racing and excess fluid replacement during competition. The article here by Dr. Robert E. O'Connor discusses the observed and proposed mechanisms of exercise-associated hyponatremia and suggests preventive measures.

A second population with hyponatremia includes patients with nephrotic syndrome, severe cirrhotic liver disease, and advanced heart failure. In each of these conditions, the decrease in effective (perceived) circulating volume and the upregulation of several hormones, including angiotensin and catecholamines, cause nonosmotic stimulation of vasopressin.

Because these patients are already volume-expanded and sodium-retentive, they are typi-

cally placed on sodium-restricted diets and permitted only hypotonic fluids. The upregulation of vasopressin impairs the excretion of the hypotonic fluids they receive and initiates and sustains the hyponatremia. Vasopressin (via binding to vasopressin type 1A receptors on vascular smooth muscle and cardiac myocytes) also increases arteriolar vasoconstriction and is mitogenic and inotropic to the cardiac myocyte.

EMERGENCE OF VASOPRESSIN-TARGETED THERAPIES

Correction of hyponatremia has been difficult, and clinicians have had to settle for partial correction at best. Because effective correction of vasopressin-mediated water retention/hyponatremia has been poor, it has not been clear whether the vasopressin disorder contributes to other aspects of the morbidity associated with these disorders. The recent development of vasopressin receptor antagonists that can be administered either parenterally or orally has provided an opportunity to analyze the role of vasopressin in these disorders and to observe the benefits of treatment.

Among the subpopulations of hyponatremic patients, it is those with advanced heart failure in whom the pathophysiologic role of vasopressin and the potential of vasopressin receptor antagonists have been best studied. The supplement's third article, by Dr. Steven R. Goldsmith, details the role of increased vasopressin specifically in these patients.

The supplement concludes with a review by Dr. Joseph G. Verbalis of available clinical data on the use of vasopressin receptor antagonists to treat hyponatremic patients with severe heart failure or any of the other underlying conditions discussed above.

Advances in the management of hyponatremic disorders appear to be on the horizon. Careful clinical trials must be completed to clarify which patients with which of these disorders will be the greatest beneficiaries.

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Clinicians treating hyponatremia have had to settle for partial correction at best

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Hyponatremia: Why it matters, how it presents, how we can manage it

ABSTRACT

Hyponatremia is a common electrolyte disorder among hospitalized patients and has been associated with increased mortality. Most patients are asymptomatic, but many do present with symptoms, usually of a generalized neurologic nature. Based on medical history, physical examination (including volume-status assessment), and laboratory tests, patients can be classified as having either hypervolemic, euvolemic, or hypovolemic hyponatremia. Management depends on the speed of hyponatremia onset; its degree, duration, and symptoms; and whether there are risk factors for neurologic complications. The risks of overly rapid correction must be weighed against the benefits of treating hyponatremia. Traditional therapies have significant limitations. New agents that antagonize arginine vasopressin at the V_2 receptor or both the V_{1A} and V_2 receptors show promise for treating hypervolemic and euvolemic hyponatremia, as they induce desired free water diuresis without inducing sodium excretion.

KEY POINTS

Hyponatremia results from changes in total body water, not body sodium content. These changes are regulated primarily by thirst, the hormone arginine vasopressin, and the kidney.

The rate of decline in plasma sodium concentration, the patient's age, and the extracellular fluid volume affect the clinical presentation in patients with hyponatremia.

Prompt, controlled correction of serum sodium is indicated for acute symptomatic hyponatremia. Hypertonic saline and a loop diuretic are often given to achieve this goal.

Potentially fatal demyelination can occur with overly rapid serum sodium correction; a moderate rate of correction (< 12 mEq/L/day) minimizes this risk.

* Dr. Douglas reported that he has served as a paid consultant to and is on the speakers' bureau of Astellas Pharma US, Inc.

HYPONATREMIA is common among hospitalized patients and can lead to serious complications, yet its assessment can be a challenge and strategies for its management have traditionally been suboptimal. New therapies are emerging that promise a more targeted approach to regulating body water and sodium balance in patients with this disorder. This article reviews the incidence and clinical significance of hyponatremia, discusses patient evaluation and classification, and surveys current and emerging management approaches for the various types of hyponatremia.

DEFINITION AND EPIDEMIOLOGY

Hyponatremia represents an excess of body water relative to body sodium content and is frequently defined as a serum sodium concentration of less than 135 mEq/L.[1,2] Abnormalities of the mechanisms that regulate body water and sodium metabolism are often present in hospitalized patients. Untreated acute severe hyponatremia is associated with an increase in mortality.[3]

Hyponatremia is the most common electrolyte disorder,[1] reported to occur in up to 6% of hospitalized patients.[4] The precise incidence of hyponatremia varies depending on the conditions underlying it and the criteria used to define it.[1] When defined as a serum sodium concentration of less than 135 mEq/L, hyponatremia has been reported in 15% to 22% of hospitalized patients.[1] In studies defining it as a concentration of 130 mEq/L or less, hyponatremia has been described in hospitalized patients at incidences of 1% to 4%.[1,5] The frequency of hyponatremia varies by clinical setting as well. In an analysis of the prevalence of hyponatremia among 120,137 patients at initial presentation to health care providers, 7.2% of patients in the

community-care setting were hyponatremic compared with as many as 28.2% of patients in the acute-care hospital setting.[6]

PHYSIOLOGY OF WATER AND SODIUM BALANCE

Hyponatremia is associated with decreased serum osmolality resulting from changes in total body water, not body sodium content.[7] These changes are regulated primarily by thirst, arginine vasopressin (AVP), and the kidney.[7] A net increase in water reabsorption, however, fails to account entirely for the decrease in serum sodium concentration seen in patients with hyponatremia.[8]

What stimulates AVP release?

AVP is synthesized in the hypothalamus and transported to the pituitary, where it is stored.[7] Changes in effective arterial volume stimulate AVP release, causing a decrease in urine flow, maximal concentration of urine, and water reabsorption. The primary stimuli of AVP release are changes in plasma osmolality and changes in effective arterial volume that are sensed by the carotid baroreceptors and left atrium. Other important stimuli causing AVP release include certain medications (eg, diuretics), pulmonary infections, nausea, and mechanical ventilation.[7]

Aging increases likelihood of hyponatremia

Several changes in the mechanisms that regulate water and sodium balance occur as a normal part of the aging process, such as decreased glomerular filtration rate, decreased renal blood flow, impaired ability to dilute urine, and impaired water excretion.[1] These physiologic changes result in an increased likelihood of developing hyponatremia with increasing age.

INITIAL PATIENT EVALUATION

The initial evaluation of a patient with known or suspected hyponatremia consists of a careful medical history and physical examination, including a thorough neurologic evaluation and clinical assessment of volume status.[1] Additionally, laboratory measurements of serum electrolytes, glucose, blood urea nitrogen, creatinine, uric acid,[1] plasma osmolality, urine osmolality,[9] and urine sodium concentration may be useful.

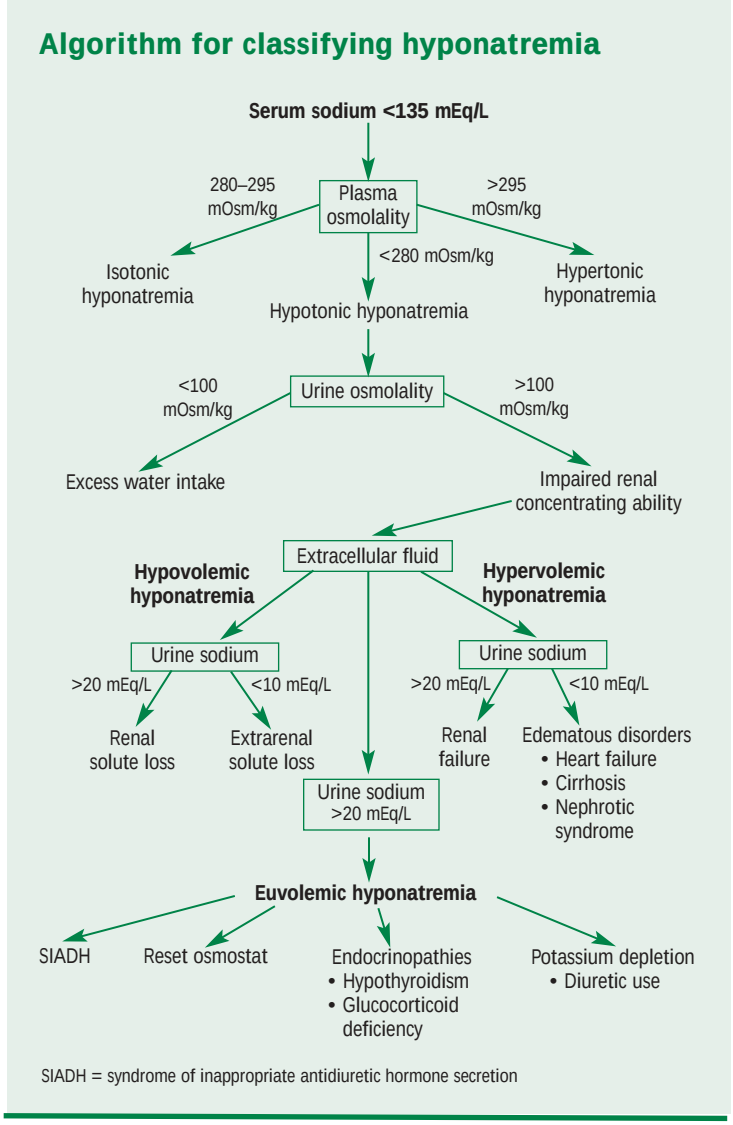

FIGURE 1. On the basis of volume status, urine osmolality, and urine sodium, patients with hypotonic hyponatremia can be categorized into one of three clinically important classes of hyponatremia: hypovolemic, euvolemic, or hypervolemic. Adapted from references 2 and 10.

Based on the initial assessment of volume status, medical history, and laboratory measurements of urine osmolality and sodium, patients with hypotonic hyponatremia can have their hyponatremia classified into one of three main categories (Figure 1):[2,10]

- Hypervolemic
- Euvolemic
- Hypovolemic.

What to exclude

Because spurious (normo-osmolar) hyponatremia is a common cause of decreased serum

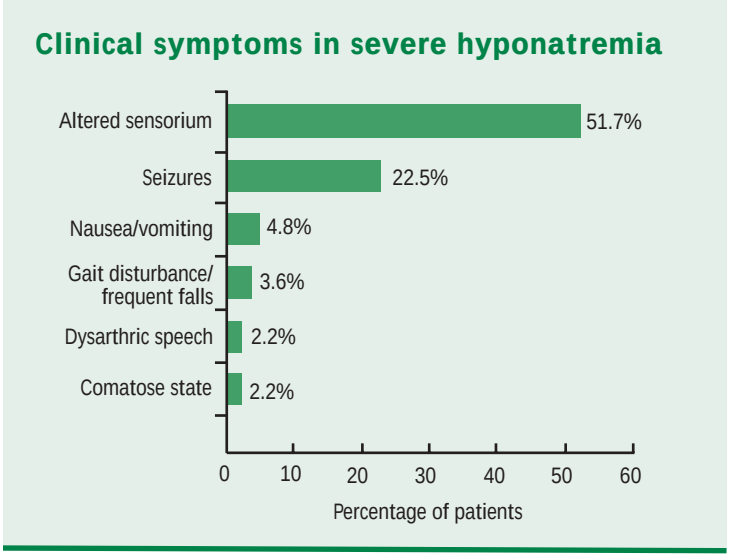

FIGURE 2. Incidences of symptoms observed in a retrospective study of 168 hospitalized patients with severe hyponatremia (serum sodium < 115 mEq/L) in a US medical center. Adapted from data in reference 14.

Accurate assessment of effective arterial volume is key to interpreting hyponatremic states

sodium levels, hypertriglyceridemia (> 1,500 mg/dL) and hyperproteinemia (> 10 g/dL) should be excluded in patients with compatible clinical syndromes, such as acute pancreatitis or myeloma, and in patients receiving total parenteral nutrition.

Clinical presentation

Although most hyponatremic patients may appear asymptomatic, severe symptomatic hyponatremia is a medical emergency that calls for immediate treatment. Signs and symptoms depend on several factors and vary by patient. The rate of decline in serum sodium concentration, the patient's age, and the volume of extracellular fluid (ECF) all affect the clinical presentation.[2]

CNS symptoms dominate

Symptoms are related largely to dysfunction of the central nervous system and are more evident when the decrease in the serum sodium concentration is large or fast.[11] However, patients also present with nonneurologic symptoms, such as fatigue, thirst, weakness, cramping, nausea, vomiting, bloating, swelling, and tightness of the hands and feet.

Most patients with a serum sodium concentration greater than 125 mEq/L or with chronic hyponatremia do not have neurologic symptoms, owing to volume adaptation by the brain.[1] Gastrointestinal symptoms, such as nausea and vomiting, are more common in patients with serum sodium levels between 125 and 130 mEq/L.[12] Acute hyponatremia (< 48 hours in duration) in a previously asymptomatic young adult can cause severe central nervous system symptoms even at serum sodium levels between 125 and 130 mEq/L.[2,13] Once the level falls below 125 mEq/L, neurologic symptoms predominate.[12] Headache, muscle cramps, reversible ataxia, psychosis, lethargy, restlessness, disorientation, apathy, anorexia, and agitation are symptoms seen in patients with serum sodium levels below 125 mEq/L.[12]

Clinical signs include abnormal sensorium, hypothermia, depressed reflexes, pseudobulbar palsy, and Cheyne-Stokes respiration.[2]

Complications can be severe

Complications of severe and rapidly developing hyponatremia include seizures, coma, brainstem herniation, respiratory arrest, permanent brain damage, and death. These complications result primarily from hyponatremia-induced cerebral edema, which is most often seen in patients following surgery or in those with primary polydipsia. Menstruating women are also at elevated risk of severe neurologic complications associated with hyponatremia.[11]

Clinically important hyponatremia is a particular challenge in patients with acute neurologic diseases such as cerebral salt-wasting syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anoxic or traumatic brain injury, or subarachnoid hemorrhage, since the presentations can overlap significantly.

Profile of symptoms and complications

A retrospective study of 168 patients with severe hyponatremia (serum sodium < 115 mEq/L) found that 89 patients (52.9%) developed one or more symptoms, the incidences of which are detailed in Figure 2.[14] The mean serum sodium level of symptomatic patients was 109 mEq/L before treatment and 120 ± 8 mEq/L after 48 hours of therapy. Twenty-eight patients (16.7%) in this cohort were considered to have chronic hyponatremia, with the remainder considered to have acute hyponatremia. The overall mortality was 20%, and

there was a trend toward increasing mortality with a slow rate of correction.

One percent of all postoperative patients are believed to develop hyponatremia, of whom approximately 15% develop symptomatic hyponatremic encephalopathy.[15]

Various comorbidities that complicate patient care have been associated with hyponatremia,[3] as detailed in Figure 3.[5]

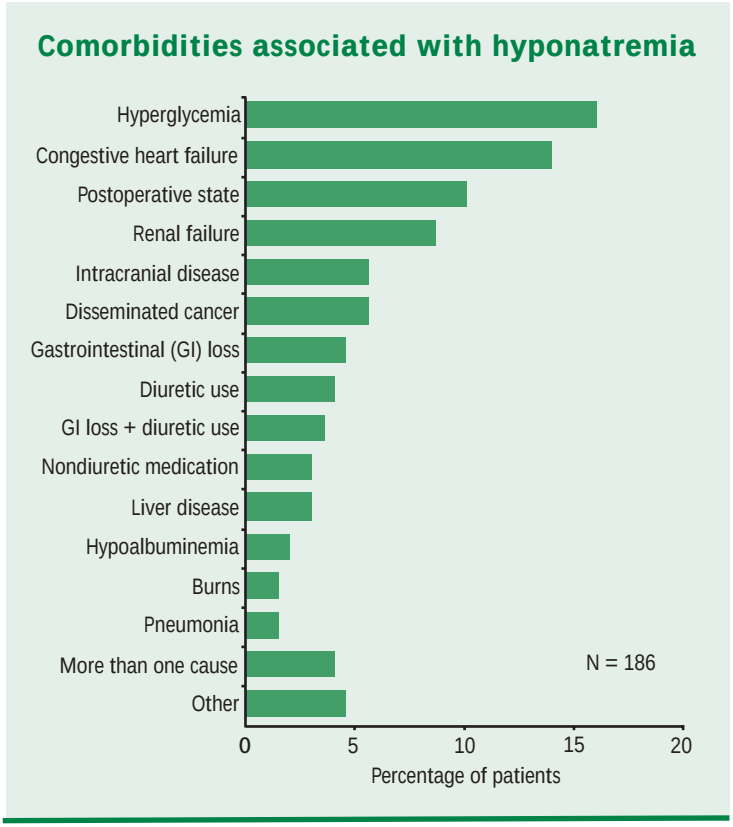

FIGURE 3. Prevalences of various comorbidities in a prospective analysis of hospitalized adults with hyponatremia at a US medical center. Adapted from data in reference 5.

CLINICALLY IMPORTANT TYPES OF HYPONATREMIA

A key to the interpretation of hyponatremic states is accurate assessment of the effective arterial volume. Baroreceptor sensing of arterial fullness tightly regulates autonomic outputs for vasomotor tone and neurohormonal production of AVP. *Hypervolemic* hyponatremia is associated with an increased ECF volume, indicative of total body sodium excess, whereas *hypovolemic* hyponatremia is associated with a reduction in ECF volume and often in effective arterial volume. By contrast, *euvolemic* hyponatremia involves AVP stimulation that is not volume-mediated.

Assessment of volume status in hyponatremic patients is essential in helping to differentiate the types of hyponatremia and determining the most appropriate treatment. Body weight, skin turgor, axillary and mucosal moistness, positional variation in blood pressure, and hemodynamic responses to volume challenge are useful indicators.

Hypervolemic hyponatremia

Hypervolemic hyponatremia is associated with impaired water excretion.[12] In patients with congestive heart failure, cirrhosis, or nephrotic syndrome, hypervolemia results from salt retention, increased AVP levels, and decreased glomerular filtration. This combination leads to water and salt retention,[1] which is the cause of the clinical finding of edema in patients with hypervolemic hyponatremia.

Total body sodium and total body water are increased in hypervolemic hyponatremia, with total body water exceeding total body sodium (Table 1).[2] This condition is detected by the presence of edema or ascites on physical examination.[1] Edema-forming states, including congestive heart failure, liver failure, and nephrotic syndrome, are comorbidities commonly associated with hypervolemic hyponatremia.[4] Despite an increased ECF volume, these disorders all have in common a decreased effective arterial blood volume or pressure, elevated plasma AVP levels leading to water retention, and concomitant hyper-reninemic hyperaldosteronism[1] with resulting sodium retention that exacerbates the dilutional state.

A typical patient with hypervolemic hyponatremia may present with complaints of dyspnea with minimal activity, orthopnea, and night-time awakening. Physical examination may reveal a lethargic, confused, cyanotic patient with nausea or vomiting, tachycardia, third heart sound, jugulovenous distension, and pitting edema in the lower extremities, highly suggestive of congestive heart failure.

Euvolemic hyponatremia

The most common form of hyponatremia in hospitalized patients is euvolemic hyponatremia.[2,4,12] AVP-mediated water retention leads to

TABLE 1

Volume status and common etiologies of major classes of hyponatremia

	HYPERVOLEMIC	EUVOLEMIC	HYPOVOLEMIC
Volume status			
Total body water	Increased	Increased	Reduced
Total body sodium	Increased	Unchanged	Reduced
Extracellular fluid	Greatly increased	Increased	Reduced
Edema	Present	Absent	Absent
Etiologies	Congestive heart failure Cirrhosis Nephrotic syndrome Acute/chronic renal failure	SIADH –Drugs (antidepressants, antipsychotics, barbiturates, nicotine, NSAIDs, morphine, vincristine) –Physical/emotional stress Glucocorticoid deficiency	Diuretic excess Mineralocorticoid deficiency Salt-losing nephritis Osmotic diuresis Ketonuria Bicarbonaturia Vomiting or diarrhea (extrarenal origin) Third-spacing (ie, burns, pancreatitis)

SIADH = syndrome of inappropriate antidiuretic hormone secretion; NSAIDs = nonsteroidal anti-inflammatory drugs
Adapted from data in references 2 and 19.

Hyponatremia in hospitalized patients is most commonly of the euvolemic form

an increase in total body water. However, patients with euvolemic hyponatremia show no indication of an increase or decrease in sodium stores.[2] In contrast to hypervolemic hyponatremia, edema is absent (Table 1), hence the term *euvolemic* hyponatremia.[2]

Although urinary sodium levels vary depending on daily fluid and salt intake, patients with euvolemia have urine sodium concentrations generally greater than 20 mEq/L.[2] Normal urine sodium levels generally range from 15 to 250 mEq/L and depend on hydration status and daily sodium intake. A high urinary sodium level indicates non–volume-mediated hyponatremia similar to that in patients with SIADH.[16]

The more common etiologies of euvolemic hyponatremia (Table 1) result from nonosmotic stimuli for AVP release or increased receptor sensitivity to circulating AVP. SIADH is the most common cause of clinically important euvolemic hypnatremia. SIADH commonly results from medications, underlying thoracic, intra-abdominal, or intracerebral infection, or ectopic secretion by neoplasms. Hypothyroidism-related hyponatremia may result from increased release of AVP or from increased renal tubular AVP sensitivity. Hypothyroidism may not be obvious in elderly patients because symptoms, such as confusion or lethargy, may be incorrectly attributed to aging.[1] Assessment of thyroid function is recommended in patients with euvolemic hyponatremia. Glucocorticoid deficiency is also associated with increased AVP release. This can result in impaired water excretion and exacerbate mineralocorticoid deficiency–mediated hypovolemic hyponatremia.[17]

Additional conditions to be considered in the differential diagnosis of euvolemic hyponatremia include secondary adrenal insufficiency, with associated low cortisol and adrenocorticotropic hormone levels, and emotional or physical stress.[2]

Euvolemic hyponatremia is commonly associated with small-cell lung carcinoma leading

to SIADH. The ectopic release of vasopressin causes a decrease in serum sodium, resulting in severe confusion and lethargy without causing edema. Regrettably, iatrogenic hyponatremia continues to be common in hospitalized patients who have a physiologic stimulus for AVP release and are also receiving significant volumes of hypo-osmolar intravenous fluids.[18]

Hypovolemic hyponatremia

Hypovolemic hyponatremia is characterized by deficits of both total body sodium and total body water, with the sodium deficit greater than the water deficit.[11] There are a number of etiologies of hypovolemic hyponatremia (Table 1).[19]

Excessive use of diuretics, specifically thiazide diuretics, is responsible for most cases of hypovolemic hyponatremia and is associated with a preponderance of neurologic symptoms disproportionate to clinical signs of hypovolemia.[20] Thiazide diuretics inhibit sodium chloride reabsorption in the distal convoluted tubule and impair urinary diluting capacity, resulting in modest volume depletion, AVP secretion, and water retention, without perturbing urinary concentration capacity.[2] A recent study by Kim et al suggests additional possible mechanisms for thiazide-associated hyponatremia.[21] These researchers showed that thiazide diuretics cause upregulation of aquaporins in animals previously treated with lithium, a drug known to induce nephrogenic diabetes insipidus and to downregulate aquaporin.

Patient age, body weight, and serum potassium level were the strongest predictors of thiazide-mediated hyponatremia in a stepwise logistic regression analysis that compared 223 patients with thiazide-associated hypovolemic hyponatremia with 216 controls.[22] Loop diuretics and other medications, such as nonsteroidal anti-inflammatory drugs, were not strongly associated.[22]

Chronic renal insufficiency, such as diabetic renal disease, is commonly associated with impaired sodium reabsorption and AVP sensitivity. Patients with medullary cystic disease, chronic interstitial nephritis, polycystic kidney disease, analgesic-induced nephropathy, partial urinary tract obstruction, or chronic glomerulonephritis may in rare cases present with hypovolemic hyponatremia secondary to salt-wasting nephropathy.[2] Other situations in which electrolyte losses and depletion of ECF can occur include diabetic glucosuria, postobstructive diuresis, and mannitol infusion therapy for intracranial hypertension without appropriate electrolyte replacement.[2]

A typical patient with hypovolemic hyponatremia is on a low-sodium diet and a thiazide diuretic for hypertension and presents with lethargy, confusion, and dizziness in the setting of a low serum sodium level. Excessive thirst, postural hypotension, and decreased skin turgor may be present, depending on fluid intake. Nonspecific signs and symptoms such as weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, and fever may also be observed. In contrast to patients with euvolemic or hypervolemic hyponatremia, those with hypovolemic hyponatremia have decreased body sodium and water. Patients with hypovolemic hyponatremia do not present with edema.

MANAGEMENT OF HYPONATREMIA

To be optimal, therapy for hyponatremia must be individualized. In all patients, the risk of hyponatremia-associated complications must be balanced against the risk of serum sodium correction.[1,3] Several important factors should be considered when deciding on treatment, including the following[1,4]:

- The rapidity of onset of hyponatremia
- The degree, duration, and symptomatology of hyponatremia
- The presence or absence of risk factors for neurologic complications.

Neurologic symptoms predominate once serum sodium falls below 125 mEq/L

Acute symptomatic hyponatremia

Acute symptomatic hyponatremia develops in less than 48 hours. Clinical manifestations are largely related to central nervous system dysfunction resulting from brain cell swelling. Patients are at particular risk for this condition during the perioperative period.[15] Once the serum sodium level falls below 125 mEq/L, neurologic symptoms predominate.[12] In acute severe and rapidly developing hyponatremia, the risk of complications of cerebral edema exceeds the risk of osmotic demyelination associated with too-rapid correction of serum sodium, so treatment should begin promptly.[1,4]

Prompt, controlled correction of the serum

sodium level is indicated for patients with acute symptomatic hyponatremia. The goal is to raise the serum sodium level by 1.5 to 2 mEq/L/hour until symptoms subside[1] or until the concentration has risen to a safer level—usually greater than 118 to 120 mEq/L, with the primary focus being to minimize the risk of seizures. Even in symptomatic patients, the sodium level should not be raised by more than 12 mEq/L in the first 24 hours and by more than 18 mEq/L in the first 48 hours, in order to avoid osmotic demyelination (central pontine myelinolysis).[23]

Infusion of hypertonic saline (3%) at a rate of 1 to 2 mL/kg/hour and addition of a loop diuretic, to enhance water excretion, are commonly used to achieve this goal.[4] Hypertonic saline may be infused at a rate of 4 to 6 mL/kg/hour if severe neurologic symptoms, particularly seizures, are present.[1] Once a patient is asymptomatic and sodium levels are greater than 118 mEq/L, correction should be slowed to no more than 8 mEq/L in 24 hours to achieve a target level of 125 mEq/L.[11] In all cases, close and frequent monitoring of serum sodium and electrolytes is mandatory until sodium levels increase and symptoms subside.[4]

Do not raise serum sodium by more than 12 mEq/L in the first 24 hours

Chronic symptomatic hyponatremia

In hyponatremia of unknown duration, or of more than 48 hours' duration, sodium correction should be managed very cautiously because of significant osmotic adaptation of the brain to prolonged hyponatremia.[2] In patients presenting with severe symptoms, treatment should be similar to that for acute symptomatic hyponatremia: hypertonic saline plus a loop diuretic. Careful monitoring is critical because of an increased risk of irreversible osmotic demyelination. Correction should be limited to no more than 10 to 12 mEq/L on the first day of treatment and less than 6 mEq/L/day thereafter.[4] In patients presenting with mild to moderate symptoms, slower correction is required, generally 0.5 mEq/L/hour. Once the desired correction is achieved, therapy may continue in the form of fluid restriction.[2]

Adequate correction of serum sodium levels, using appropriate infusion rates, involves complex calculations. Adrogué and Madias[11] have described a useful approach using formulas that allow for calculation of appropriate volume and rate of infusate for patients with or without symptoms.

Chronic asymptomatic hyponatremia

The goal in treating asymptomatic hyponatremia is to prevent a further decline in serum sodium and to maintain levels as close to normal as possible. Treatment involves a more conservative approach than for symptomatic hyponatremia. Initially, underlying causes of hyponatremia should be investigated and treated; this should include evaluation for drug-induced hyponatremia. Fluid restriction, isotonic saline, and loop diuretics may be used to treat the hyponatremia.

Euvolemic hyponatremia is the most common form of asymptomatic hyponatremia. If the underlying cause is SIADH and its etiology is unknown or cannot be effectively treated, therapy should be instituted for the hyponatremia itself.[2,4] In cases where the etiology of SIADH is known (eg, tumor), the underlying cause should be treated or removed[2] in addition to correcting the serum sodium level.

Current management options

Fluid restriction can play a role in the treatment of hypervolemic and euvolemic forms of hyponatremia. Although fluid restriction is inexpensive, it takes days for an effect to be seen. It also is associated with poor patient adherence and may prolong hospitalization.

Pharmacologic agents may be used concomitantly with fluid restriction. Demeclocycline directly inhibits AVP action at the level of the distal renal tubules and reduces urine concentration, even in the presence of increased AVP levels. The starting dose of demeclocycline ranges from 600 to 1,200 mg/day, and it may be used in patients with chronic hyponatremia.[1,2,4] However, demeclocycline is expensive, has low potency, and is rarely used because of nephrotoxicity, particularly in patients with liver cirrhosis.[2]

Lithium is also a direct competitive antagonist ofs AVP action via its induction of nephrogenic diabetes insipidus. It is rarely used, however, owing to its adverse effects.[24]

Emerging options: AVP antagonists

Traditional therapeutic options for managing AVP-induced hyponatremia are suboptimal

and have significant limitations, as outlined in Table 2.[24–26] As a result, newer agents that antagonize vasopressin receptors have been developed. These AVP antagonists, or "aquaretics," cause increased free water clearance without directly affecting tubular sodium handling. Some act at both the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors (ie, conivaptan, recently approved by the US Food and Drug Administration for treating euvolemic hyponatremia in hospitalized patients), while others act solely at the V_2 receptor (ie, the investigational agents lixivaptan, satavaptan, and tolvaptan).

Dual V_{1A}/V_2 receptor antagonism has been shown to have favorable aquaretic effects in patients presenting with hypervolemic and euvolemic hyponatremia.[27] Vasopressin receptor antagonists may also have potential therapeutic benefit in patients with cardiovascular diseases, such as congestive heart failure. Combined V_{1A}/V_2 receptor antagonism is of particular interest because V_{1A} antagonism may provide further benefit by decreasing afterload in addition to V_2-mediated aquaresis.[27] Patients with symptomatic euvolemic hyponatremia are at particular risk of inappropriate sodium correction or seizures. These patients are especially likely to benefit from aquaretic-based correction to avoid the unpredictable effects of volume restriction and saline repletion.

Complications: Risks and strategies for avoidance

Menstruating women, prepubescent children, and patients with preexisting hypoxic cerebral injury are thought to be at elevated risk for developing direct neurologic complications of cerebral swelling related to hyponatremia. Osmotic demyelination is a potentially fatal complication that may develop one to several days after aggressive treatment of hyponatremia. Hepatic failure, potassium depletion, and malnutrition are risks for this iatrogenic complication.[11] Demyelination may occur in the face of overly rapid correction of hyponatremia and causes brain cell shrinkage.[1,3] Oligodendrocytes are thought to be particularly sensitive to sudden osmotic shrinkage, resulting in rapid cellular apoptosis.[28] A moderate and appropriate rate of correction (< 12 mEq/L/day), without increasing sodium to more than 125 to 130 mEq/L,[11] will minimize the likelihood of demyelination.

TABLE 2

Traditional treatment options for hyponatremia

TREATMENT	MECHANISM	LIMITATIONS
Fluid restriction (most common)	Induces negative water balance Increases plasma osmolality and serum sodium	No direct inhibition of excess hormone No inhibition of hormone on kidneys Nonadherence
Demeclocycline	Impairs AVP action at renal tubules Induces nephrogenic diabetes insipidus Reduces urine concentration, even with increased AVP levels	Nephrotoxicity (cirrhosis patients) Hypersensitivity Drug interactions Unsafe in pregnancy
Urea	Decreases sodium excretion	Hypersensitivity Unsafe in pregnancy Azotemia Liver failure Can reduce effects of lithium Phlebitis, thrombosis
Lithium	Impairs AVP at renal tubules	Inconsistent results Lithium toxicity Anti-anabolic effects mainly in cirrhosis and congestive heart failure Unsafe in pregnancy
Diuretics (loop/thiazide)	Increase water excretion by inhibiting sodium and chloride reabsorption in loop of Henle and distal tubule	Hypersensitivity Hepatic coma Anuria Severe electrolyte depletion

AVP = arginine vasopressin

Data from references 24–26.

SUMMARY AND CONCLUSIONS

Hyponatremia is the most common electrolyte disorder in hospitalized patients. Severe pre-

sentations are associated with increased mortality. Hyponatremia must be managed on an individual basis, with great care taken to ensure safe and controlled serum sodium correction. Important factors to consider when managing patients with hyponatremia include the rapidity of hyponatremia onset; its degree, duration, and symptomatology; and risk factors associated with neurologic complications.

Traditional therapies for hyponatremia have limitations that make them suboptimal. These include the time to serum sodium correction with fluid restriction and the potential for additional electrolyte losses with diuretics. An ideal treatment for hypervolemic or euvolemic hyponatremia would provide solute free water excretion with prompt, controlled correction of serum sodium. With this goal in mind, new medications that antagonize AVP have been developed, including a dual V_{1A}/V_2 receptor antagonist and several V_2 receptor antagonists. These agents may represent a significant advance over current therapies for hypervolemic and euvolemic hyponatremia.

AVP antagonists increase free water clearance without affecting tubular sodium handling

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Exercise-induced hyponatremia: Causes, risks, prevention, and management

ABSTRACT

Exercise-induced hyponatremia is most commonly associated with prolonged exertion during sustained, high-intensity endurance activities such as marathons or triathlons. In most cases, exercise-induced hyponatremia is attributable to excess free water intake, which fails to replete the sometimes massive sodium losses that result from sweating. The risk of hyponatremia can be lowered by strategies to ensure fluid balance during exercise by maintaining the proper volume and type of fluid intake. Treatment of exercise-induced hyponatremia is based on whether the patient is volume-depleted, euvolemic, or fluid-overloaded. Because therapy must be tailored to volume status, physicians must make this determination before initiating therapy. If hyponatremia is life-threatening, hypertonic saline may be warranted to increase sodium in the extracellular fluid compartment and restore the natural balance.

KEY POINTS

Up to 10% of ultradistance athletes experience exercise-induced hyponatremia, or a post-exercise serum sodium level below 135 mEq/L, but symptoms are often present only with levels below 125 mEq/L.

Female sex and longer race-completion times appear to be associated with greater risk of exercise-induced hyponatremia.

In symptomatic hyponatremic athletes with oliguria, physicians should rule out overhydration before giving intravenous fluids.

Hypertonic saline must be administered with great caution, since overly rapid correction of hyponatremia can result in fatal complications such as central pontine myelinolysis.

*Dr. O'Connor reported that he has no financial relationships that pose a potential conflict of interest with this article.

THE DURATION and intensity of "ultradistance" exercise such as marathon running and triathlons can wreak havoc on the body if proper nutrition and fluid balance are not maintained. Exercise-induced hyponatremia, defined as a serum sodium level of less than 135 mEq/L following a high-intensity endurance activity, can occur if fluid and sodium repletion is not maintained during sustained physical exertion.[1–4]

Because exercise-induced hyponatremia is potentially life-threatening, it is important for physicians, especially those treating athletes in acute settings, to be familiar with its causes and management. This article briefly reviews the etiology, risk factors, signs, symptoms, prevention, and treatment of exercise-induced hyponatremia.

ENDURANCE SPORTS ARE GROWING

Once the domain of a select group of world-class athletes, participation in ultradistance sports such as marathons and triathlons has grown in recent years. Currently, more than 400,000 athletes run in more than 300 26.2-mile (42-km) marathons in the United States each year.[5] While elite runners can complete a marathon in less than 3 hours, recreational joggers may require 6 or more hours. Triathlons are combination events that take 8.5 to 16.5 hours to complete. For example, the New Zealand Ironman triathlon consists of a 3.8-km swim, a 180-km bicycle ride, and a 42.2-km run.[1]

HOW COMMON IS EXERCISE-INDUCED HYPONATREMIA?

Hyponatremia is the most common medical complication of ultradistance exercise and is recognized as potentially serious.[6] Exercise-induced hyponatremia was first described in 1985 by

Noakes et al,[7] who referred to it as "water intoxication." Over the years, as participation in endurance sports has risen, so has research into the possible health effects associated with these activities.[8] During the 1990s in the United States, exercise-induced hyponatremia was increasingly recognized among soldiers, runners who completed a 42-km marathon in 5 hours or more, and recreational hikers, especially those exploring the desert.[9,10]

Up to 10% of ultradistance athletes have a serum sodium level of 135 mEq/L or less after a race.[9] Studies have reported the incidence of exercise-induced hyponatremia to be even higher among triathletes—18% among those completing triathlons in New Zealand and as high as 29% among those completing the Hawaiian Ironman event.[6]

Almond et al[11] studied a cohort of marathon runners in the 2002 Boston Marathon to estimate the incidence of hyponatremia and to identify the major risk factors. Of 766 runners enrolled, 488 (64%) provided a usable blood sample at the finish line. Thirteen percent had hyponatremia (serum sodium ≤ 135 mEq/L) and 0.6% had critical hyponatremia (≤ 120 mEq/L). Univariate analyses showed that hyponatremia was associated with substantial weight gain, consumption of more than 3 L of fluids during the race, consumption of fluids every mile, a racing time of greater than 4 hours, female sex, and low body-mass index. Multivariate analysis showed that hyponatremia was associated with weight gain, a racing time of greater than 4 hours, and extremes in body mass index. These findings clearly showed that hyponatremia occurs in a substantial fraction of nonelite marathon runners and can be severe.

Symptoms often do not manifest until serum sodium is less than 125 mEq/L

While many athletes with mildly reduced serum sodium levels may not present for medical care, patients with serum sodium levels of less than 125 mEq/L often have symptoms and are more likely to seek medical care.[1]

ETIOLOGY

Two factors play key roles in the development of hyponatremia in athletes:

- Dehydration and salt depletion
- Excess fluid intake during exercise.

Dehydration and salt depletion

Dehydration results from loss of large volumes of water and salt due to sweating. Up to 1,800 mL of sweat can be lost per hour, depending on the athlete's body size, his or her exercise intensity, and the environmental humidity and temperature.[12] Typically, the sodium content of sweat ranges from 25 to 75 mEq/L. Sodium losses, however, seem to be equivalent among ultradistance athletes regardless of their sodium level at the end of a race; differences in sodium levels at the end of a race are more likely due to the tonicity and volume of beverages used for repletion.[6] Since sweat is hypotonic, if an athlete does not drink, free water loss will exceed sodium loss and dehydration will most likely result in *hyper*natremia, not hyponatremia. With excessive water intake relative to sodium replacement, the athlete will become overhydrated and have dilutional hyponatremia.[6]

Excess fluid intake

Evidence to date suggests that excess fluid intake is the most common cause of exercise-induced hyponatremia.[6] Many athletes with exercise-induced hyponatremia lose weight during exercise because their fluid replacement is less than the weight lost due to respiration, sweat, urination, and oxidative breakdown of glycogen and adipose stores.[9] These athletes are usually asymptomatic and have mild hyponatremia.[9] In contrast, symptomatic hyponatremic athletes gain weight or lose the least weight. These are the athletes who are overhydrated with free water and have the lowest serum sodium levels (Figure 1).[9,13] Hence, there is an inverse relationship between serum sodium concentration and the amount of exertional fluid loss.[9,13] There also is an inverse relationship between weight gain during a race and serum sodium concentration (Figure 2).[1,9] Most athletes with a serum sodium concentration of less than 125 mEq/L are symptomatic and either gained weight or did not lose weight during exercise.

SYMPTOMS OFTEN LIMITED TO MORE SEVERE CASES

Exercise-induced hyponatremia is often asymptomatic, particularly in patients in whom serum sodium is only mildly reduced.

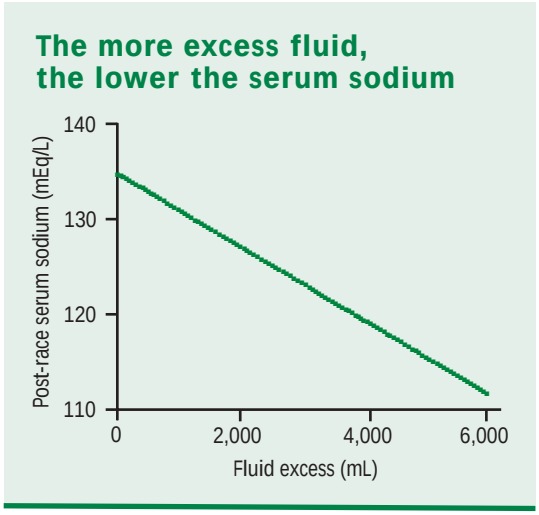

FIGURE 1. Among ultradistance athletes, the serum sodium concentration is inversely related to the fluid excess excreted during post-race recovery ($P = .02$). Reprinted, with permission, from Noakes[9] and based on data from a study of 8 marathon runners reported by Irving et al.[13]

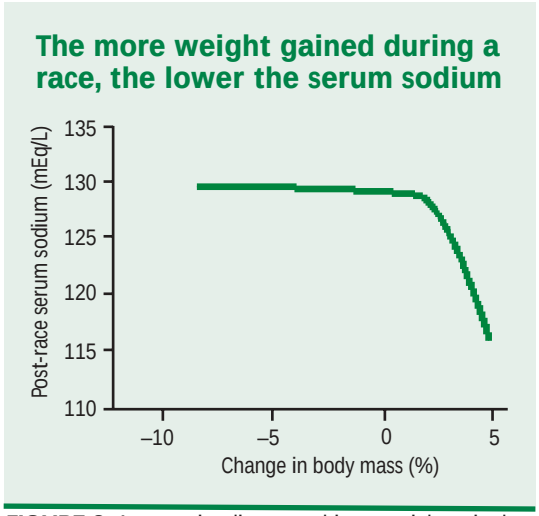

FIGURE 2. Among ultradistance athletes, weight gain during a race is inversely related to post-race serum sodium concentration. Reprinted, with permission, from Noakes[9] and based on data from a study of triathletes in the 1997 New Zealand Ironman event reported by Speedy et al.[1]

Up to 10% of ultradistance athletes have a serum sodium level of 135 mEq/L or less.[9] Those who are symptomatic usually have a level of less than 125 mEq/L.[9]

Symptoms can be mild and nonspecific

Hyponatremic athletes present with vomiting more frequently than do nonhyponatremic athletes.[4] Mild symptoms of hyponatremia, which may be nonspecific, include malaise, nausea, light-headedness, dizziness, and fatigue.[6]

...or potentially ominous

Altered mental status, confusion, headache, incoordination, seizures, and coma are ominous signs that may indicate developing cerebral edema, which is life-threatening.[6]

RISK FACTORS

Risk factors for hyponatremia among ultradistance athletes include the athlete's sex and the time it takes to finish a race.

Who needs intravenous fluids?

An observational, retrospective, case-control series based on the 2000 Houston Marathon analyzed risk factors for hyponatremia among 5,082 runners who completed the 42-km course in 5 hours 30 minutes or less.[4] Mean finishing times were longer for females (4 hours 45 minutes) than for males (4 hours 24 minutes). During the event, 237 runners were seen in the medical area and 73 of them were treated in the major medical tent. Among the 55 runners requiring intravenous (IV) fluids, serum sodium levels were as follows:

- 34 had levels greater than 135 mEq/L (nonhyponatremic control group)
- 8 had levels of 130 to 135 mEq/L
- 11 had levels of 120 to 129 mEq/L
- 2 had levels less than 120 mEq/L.

Both of the runners whose serum sodium level was less than 120 mEq/L were women. The incidence of diagnosed hyponatremia was 5.1 per 1,000 runners among women vs 3.6 per 1,000 runners among men.

This study also found that hyponatremic runners had significantly lower levels of potassium, chloride, and blood urea nitrogen compared with nonhyponatremic runners.[4]

Up to 1,800 mL of sweat can be lost per hour during exercise

Longer finishing times linked to higher risk

The same study also revealed that runners with longer finishing times were at higher risk of developing hyponatremia (Figure 3).[4] One theory to explain this is that slower runners have more opportunities to consume fluids while also having lower fluid requirements.[6]

Other proposed risk factors

Although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been the-

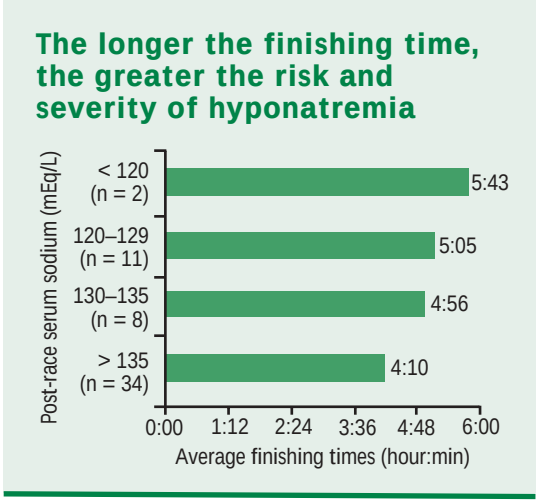

FIGURE 3. Finishing times for marathon runners according to the presence and degree of hyponatremia. The most severe cases of hyponatremia (serum sodium < 120 mEq/L) were associated with the longest average finishing time, whereas nonhyponatremic runners (serum sodium > 135 mEq/L) had the shortest average finishing time. The cross-group difference was statistically significant ($P < .001$). Based on data from the observational trial by Hew et al.[4]

Altered mental status may signal developing cerebral edema

orized to be related to development of exercise-induced hyponatremia, a clear relationship has not been established, since a similar incidence of NSAID use has been found among hyponatremic and normonatremic athletes.[4,6] The theory behind this proposed association is that NSAIDs reduce renal prostaglandin production, which consequently reduces the glomerular filtration rate, causing exercise-induced hyponatremia.[6] Of note, Almond et al[11] found no association between NSAID use and the development of hyponatremia in marathon runners.

Environmental factors may also contribute to the risk of fluid imbalance. In particular, the combination of high temperatures and high humidity may lead to excessive sweating and ineffective cooling, resulting in fluid or sodium imbalance. Hot, humid environments also drastically increase the risk of dehydration.[12]

PREVENTING HYPONATREMIA IN ATHLETES: FLUID BALANCE IS KEY

The best strategy for preventing hyponatremia is to maintain the proper volume and type of fluid intake to ensure fluid balance during exercise.

For noncompetitive athletes, fluid intake of 500 mL/hour is recommended during prolonged exercise.[6] A joint position statement from the American College of Sports Medicine, the American Dietetic Association, and Dietitians of Canada[12] addresses proper fluid balance to ensure optimal performance during exercise. Adequate fluid and food intake before, during, and after exercise can help to maintain blood glucose during exercise, maximize exercise performance, and improve recovery time.[12] Table 1 provides recommendations for optimizing fluid balance.

'Sports drinks' and sodium content of fluids

For athletes participating in intense exercise for more than 1 hour (eg, marathon runners), beverages containing carbohydrates in concentrations of 4% to 8% (ie, "sports drinks") are recommended. During exercise, consumption of sports drinks containing carbohydrates and electrolytes will provide fuel for the muscles, help maintain blood glucose and the thirst mechanism, and decrease the risk of hyponatremia.[12]

Including sodium in the fluid replacement beverage in amounts from 0.5 to 0.7 g/L is also recommended for exercise sessions lasting more than 1 hour, since sodium may drive the thirst center (however, this amount of sodium generally exceeds that found in commercial sports drinks).[12] If the fluid contains sodium, it could help avoid reduced serum sodium levels and thereby lower the risk of hyponatremia. Restricting fluid intake so that it does not surpass sweat loss can also lower the risk of hyponatremia.[12] Runners should sporadically check their body weight before and after training runs to determine their ideal rate of hydration.[11]

Education, other strategies can make a difference

In an interventional study with historical controls, Speedy et al[3] showed that educating athletes about the appropriate rate of fluid intake and limiting the availability of fluids during a triathlon reduced the percentage of athletes treated in the medical tent for hyponatremia from 22% to 3%. This study used numerous strategies to increase awareness of exercise-induced hyponatremia, including reducing the number of drink stations along the race course,

encouraging consumption of sports drinks, providing newsletters with information on appropriate fluid intake to all athletes, and having the medical director of the race hold a briefing to inform athletes of the danger of overhydration.[3]

MANAGEMENT

Acute vs chronic hyponatremia

Management of acute hyponatremia (< 48 hours in duration) differs from management of chronic hyponatremia. Compared with chronic hyponatremia, acute hyponatremia tends to be associated with more severe degrees of cerebral edema for a given level of serum sodium. The primary cause of morbidity and death is brainstem herniation and mechanical compression of vital midbrain structures. Rapid identification and correction of serum sodium is necessary in patients with severe acute hyponatremia to avert brainstem herniation and death.

In chronic hyponatremia, a slow rate of correction is desired to minimize the risk of central pontine myelinolysis.[14] In acute hyponatremia, gradual correction is preferred so as to reduce the likelihood of precipitating cerebral edema and respiratory arrest.[14]

Tailor management to volume status

Management recommendations (Table 2) generally apply to symptomatic athletes, since most asymptomatic athletes do not present for medical attention and are thus not treated.

Management of symptomatic athletes with exercise-induced hyponatremia begins with assessment of the patient's volume status, which should guide subsequent therapy. Treatment is based on whether the patient is volume-depleted, euvolemic, or fluid-overloaded. Dilutional hyponatremia due to free water overload should be sought by checking for peripheral edema before routinely administering IV fluids to symptomatic hyponatremic athletes.[6]

Indeed, if an athlete with symptomatic hyponatremia is clinically stable and has no signs or symptoms of significant cerebral or pulmonary edema, several hours of close clinical observation with regular monitoring of serum sodium is often sufficient management while awaiting spontaneous diuresis of retained fluid. In addition to patient observation until spontaneous diuresis occurs, isotonic fluids may be given.[6]

TABLE 1

Recommended fluid intake for optimizing exercise performance and safety

BEFORE EXERCISE	DURING EXERCISE	AFTER EXERCISE
Drink generous amounts of fluid in the 24 hours prior to exercise. Drink 400–600 mL (14–22 oz) of fluid 2–3 hours before exercise. An accompanying meal or snack should provide sufficient solute and nutrition to maintain hydration.	Goal is to maintain fluid balance. Drink 150–350 mL (6–12 oz) of fluid every 15–20 minutes, beginning at the start of exercise and depending on tolerance.	Drink adequate fluid to replace sweat losses. Drink at least 450–675 mL (16–24 oz) of fluid for every pound of body weight lost during exercise.

Adapted from recommendations in a joint position statement on nutrition and athletic performance from the American College of Sports Medicine, the American Dietetic Association, and Dietitians of Canada.[12]

The goal in correcting acute symptomatic hyponatremia is to increase the serum sodium concentration by 2 mEq/L/hour until symptoms resolve.[15] Athletes weighing more than 70 kg are likely to benefit from a higher rate of sodium administration due to their larger extracellular fluid volume.[9] However, hypertonic saline (3% sodium [NaCl] solution) must be administered with extreme caution, since overly rapid correction of hyponatremia may result in fatal complications such as central pontine myelinolysis. Davis et al[2] showed that 3% sodium solution given at a rate of 100 mL/hour corrected exercise-induced hyponatremia in marathon runners at a rate of 3.4 mEq/L/hour.

Severe acute hyponatremia requires rapid correction to avert brainstem herniation and death

In mildly symptomatic patients, oral rehydration with salty solutions is often the safest method of increasing the serum sodium level and improving symptoms.[6]

Two likely clinical pathways

Following exercise, a symptomatic hyponatremic athlete will generally follow one of two basic pathways. Spontaneous diuresis may occur within 1 or 2 hours after completing exercise, or the athlete may produce minimal urine for many hours following

TABLE 2

Guidance for the treatment of acute hyponatremia in athletes

Urgent treatment indicated only in symptomatic hyponatremic athlete

Determine patient's weight loss or gain

Calculate sodium deficit

Administer sodium-containing solution at a rate that will raise serum sodium no more than 1 to 2 mEq/L/hr, not to exceed 12 mEq in first 24 hours

exercise completion (oliguria). In the latter case, physicians should suspect that the patient is *over*hydrated, not dehydrated, in which case additional fluids would be unwarranted.[9]

In patients with mild symptoms, oral rehydration with salty solutions is safe and often effective

CONCLUSIONS

Prolonged exertion during exercise is commonly associated with hyponatremia. In many cases, this exercise-induced hyponatremia is due to excess fluid intake during exercise, which causes dilutional hyponatremia. The risk of hyponatremia can be lowered through strategies to ensure fluid balance during exercise by maintaining the proper volume and type of fluid intake. Appropriate treatment is based on the patient's volume status, which physicians must assess before initiating therapy. Although oliguria is often assumed to be due to dehydration, it can also be associated with decreased glomerular filtration. Current treatment for hyponatremia is often counterintuitive and dependent on volume status. Often, hypertonic saline is warranted to increase sodium in the extracellular fluid compartment and restore the natural balance.

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The role of vasopressin in congestive heart failure

ABSTRACT

Neurohormonal abnormalities contribute to the pathophysiology of congestive heart failure (CHF). Successful approaches to improving the prognosis of patients with CHF are based largely on therapeutic interruption of activated neurohormonal systems. The use of antagonists and inhibitors of the renin-angiotensin-aldosterone and sympathetic nervous systems has significantly improved clinical outcomes in CHF. Excessive secretion of arginine vasopressin (AVP) has the potential for deleterious effects on various physiologic processes in CHF. Inhibition of AVP through vasopressin receptor antagonist therapy is a potentially beneficial new therapeutic approach to CHF.

KEY POINTS

Stimulation of vasopressin type 1A (V_{1A}) receptors results in vasoconstriction and a positive inotropic effect. Stimulation of vasopressin type 2 (V_2) receptors leads to increased water retention.

Plasma AVP levels are increased or incompletely suppressed in patients with CHF.

Hyponatremia is associated with poor outcomes in CHF and may be caused or aggravated by excess AVP.

AVP antagonism, either with a combined V_{1A}/V_2 antagonist or a pure V_2 antagonist, is a logical and promising therapeutic option in acute and chronic CHF.

ALTHOUGH BY NO MEANS FULLY CLEAR, our understanding of the pathophysiology of congestive heart failure (CHF) has evolved greatly over the past 2 decades. Among the chief insights is that hemodynamic derangements do not fully explain the syndrome since hemodynamically oriented therapy is not sufficient, and is sometimes even harmful. Recent attention has focused on the role of neurohormonal imbalances as important contributors to both load-dependent and load-independent processes that may aggravate CHF.[1]

Among neurohormonal targets for therapy in CHF, arginine vasopressin (AVP) has attracted much recent interest. Indeed, it is increased AVP secretion in heart failure, and its potential to promote hyponatremia and other effects that can lead to CHF progression, that makes CHF a topic of interest for this supplement. This article reviews the role of AVP as it relates to CHF and the potential benefits of AVP antagonism as a new therapeutic option for patients with CHF.

NEUROHORMONES IN HEART FAILURE

Under normal circumstances, acute activation of neurohormonal systems helps preserve circulatory homeostasis and maintain arterial pressure. Chronic excess of these neurohormones, however, plays an important role in the development and progression of CHF. This role has been clearly established by the therapeutic success achieved with agents that are active in interfering with the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, aldosterone antagonists, and beta-blockers have all provided significant clinical benefits in patients with CHF.[2–9]

The question now is whether further intervention in CHF based on neurohormonal

* Dr. Goldsmith reported that he has received grant/research support from, is a paid consultant to, and serves on the speakers' bureau of Astellas Pharma US, Inc.

TABLE 1

Site of action and physiologic effects of AVP receptor subtypes

RECEPTOR SUBTYPE	SITE OF ACTION	PHYSIOLOGIC EFFECTS
V_{1A}	Vascular smooth muscle Cardiac myocytes	Vasoconstriction Positive inotropy/mitogen
V_{1B} (V_3)	Anterior pituitary	ACTH and beta-endorphin release
V_2	Renal collecting ducts	Free water reabsorption

ACTH = adrenocorticotropic hormone

Reprinted, with permission, from reference 14.

mechanisms would be useful. Recent studies with endothelin antagonists have not shown benefit, nor has the long-term approach of increasing natriuretic peptide signaling by combining endopeptidase inhibition with an ACE inhibitor.[10,11] A remaining candidate hormone for therapeutic targeting is AVP, which was one of the three neurohormones proposed as possible contributors to the pathophysiology of CHF in the first paper written describing the "neurohumoral axis" in CHF.[12]

Plasma AVP levels correlate with adverse outcome in CHF

PHYSIOLOGY OF AVP

Arginine vasopressin has three distinct receptor subtypes (Table 1).[13,14] From a cardiovascular perspective, the most important receptors are the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors.

V_{1A} receptors are located on vascular smooth muscle and cardiac myocytes. These are G protein–coupled receptors, which increase intracellular calcium via the inositol triphosphate pathway. This increase in intracellular calcium results in vasoconstriction and a positive inotropic effect.[15] Stimulation of the V_{1A} receptor also promotes the synthesis of contractile protein in myocytes.[16] Stimulation of the V_{1A} receptors in vascular smooth muscle could therefore increase systemic vascular resistance, increasing impedance to ventricular emptying (ie, afterload) and thereby adversely affect ventricular function in heart failure. Sustained increases in afterload also contribute to myocardial remodeling and progressive failure. Direct stimulation of the myocyte over time may have the same effect.

V_2 receptors mediate their effects via adenyl cyclase–dependent signaling in the renal collecting ducts. Activation of these receptors increases water retention, which is accomplished by upregulation of the aquaporin-2 water channels.[17] This upregulation results in an increased movement of water from the collecting ducts back into the plasma, increasing free water reabsorption, which leads to increased water retention. This effect, if sustained, may contribute to volume expansion that exacerbates diastolic wall stress in CHF, another mechanism that may contribute to ventricular remodeling and dysfunction. Depending on the balance of factors influencing water and sodium intake and excretion, V_2 receptor–mediated water retention may also contribute substantially to hyponatremia, a common condition in moderate and severe CHF.

ROLE OF AVP IN HEART FAILURE

Plasma AVP levels are increased, or at least incompletely suppressed, in patients with chronic stable CHF and acute decompensated CHF[18–23] (Figure 1). As with other neurohormones, plasma AVP levels correlate with adverse outcome in CHF and tend to be much higher in severe CHF, or soon after major insults such as myocardial infarction (MI). A cause-and-effect relationship between inappropriate AVP levels and CHF progression has not yet been proven, but if experience with the other neurohormonal systems is a guide, increased AVP is likely not just an epiphenomenon.

As discussed above, a number of mechanisms related directly to the physiologic effects of AVP could underlie pathophysiologic contributions (Figure 2). AVP could potentially contribute directly and indirectly to well-characterized load-dependent and load-independent mechanisms that may aggravate progressive ventricular remodeling and failure, as well as the expression of the clinical heart failure syndrome. Congestion, in particular, is a hallmark of decompensated or severe CHF, and the volume retention secondary to excessive AVP secretion adds to the volume retention of sodium and water caused by aldosterone and other renal mechanisms. Likewise, hyponatremia, which is associated with poor outcome in CHF, may be caused or aggravated by excessive AVP levels.

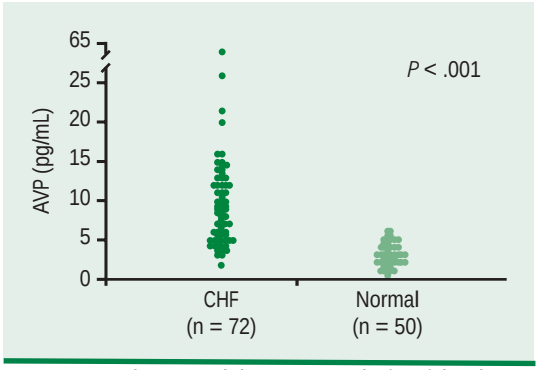

FIGURE 1. Plasma arginine vasopressin (AVP) levels, although heterogeneous, are two to three times greater in patients with mild to moderate congestive heart failure (CHF) compared with controls without cardiovascular disease. Reprinted, with permission, from reference 13.

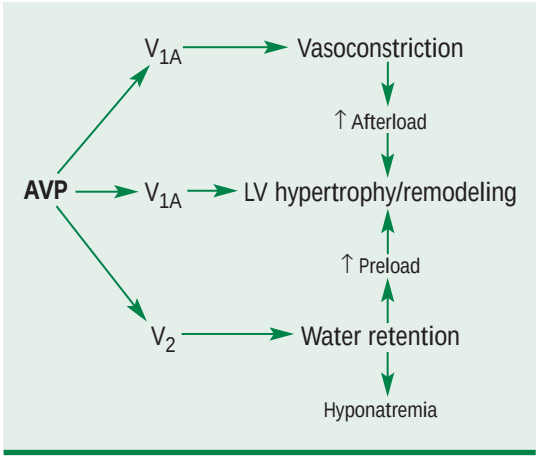

FIGURE 2. The actions of arginine vasopressin (AVP) are mediated through the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors. The consequences of V_{1A} activation are vasoconstriction, increased afterload, and left ventricular (LV) hypertrophy and remodeling. V_2 activation promotes water retention, leading to volume expansion and potentially hyponatremia.

Interfering with either or both the V_{1A} and V_2 receptors could therefore, at least theoretically, be of substantial value in chronic or acute CHF.

Ultimately, before a definitive role for AVP in chronic or acute CHF is established, we must establish not just a potential pathophysiologic role and adequate hormone levels or signaling, but evidence that interfering with hormone secretion or effect has a clinically important benefit. This process is just beginning with AVP, but preliminary experimental and clinical results are encouraging.

Experimental models

Many studies in several animal models of CHF have shown acute and moderately sustained beneficial effects of V_{1A}, V_2, and combined V_{1A} and V_2 antagonism.[24–32] A more recent study by Naitoh and colleagues[33] assessed the long-term effect of dual V_{1A} and V_2 receptor blockade either alone or in combination with an ACE inhibitor in a well-accepted animal model of post-MI remodeling. They found that blockade of V_{1A} and V_2 receptors was associated with increased free water excretion, and, when combined with an ACE inhibitor, a degree of reduction in right ventricular mass not achieved with ACE inhibition or AVP blockade alone.

These results establish an active degree of AVP signaling in this setting, and suggest that although blockade of V_{1A} and V_2 receptors alone may be of limited utility, a synergistic effect may occur when combined with an ACE inhibitor. Synergy between these two drug classes is relevant clinically in that any benefit of AVP antagonists would have to occur over a background of ACE inhibitor therapy. Other studies on the vascular effects of AVP blockade also suggest important synergies between V_{1A} blockade and interventions that interrupt the RAAS.[31,34,35]

A synergistic effect may occur with AVP antagonism and ACE inhibition

Effects in clinical CHF

Reports of the effects of AVP antagonists in clinical CHF are limited. AVP signaling, however, has been shown to be adequate to produce a hemodynamic effect in patients with CHF. Exogenous infusion of AVP produces a fall in cardiac output and an increase in systemic vascular resistance, among significant hemodynamic changes (Figure 3).[20,21,36] Following acute administration of a V_{1A} antagonist, plasma levels of vasopressin correlate inversely with the percentage change in systemic vascular resistance in patients with chronic stable CHF.[37] Additionally, acute administration of a pure V_2 antagonist has been shown to produce a marked increase in water excretion.[38,39]

No clinical experience with sustained administration of either a pure V_{1A} antagonist or a combined V_{1A}/V_2 antagonist has been reported to date. Administration of a V_2 antagonist (tolvaptan) in the setting of acute decompensated CHF is associated with superior early weight loss and a sustained reduction in body weight after up to 60 days of administration.[40]

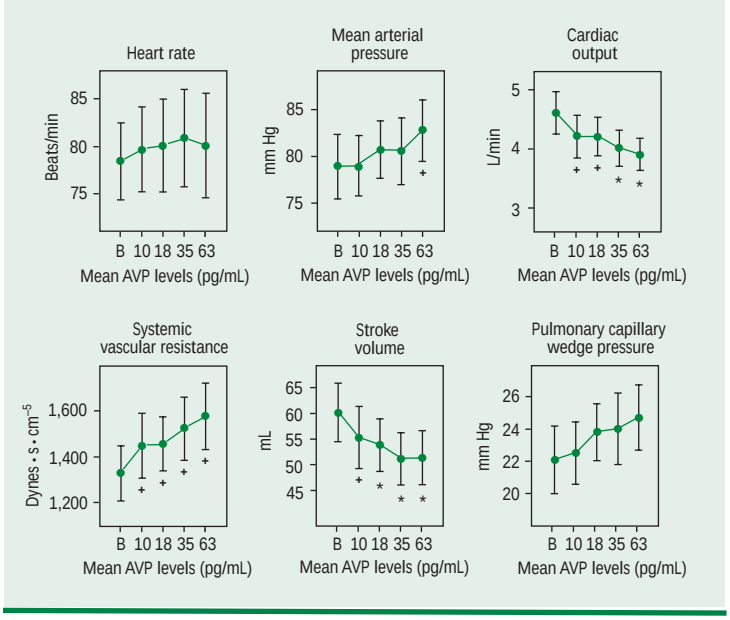

FIGURE 3. Stepwise infusion of exogenous vasopressin led to acute hemodynamic deterioration in a group of 11 patients with chronic stable congestive heart failure, including increases in heart rate, mean arterial pressure, systemic vascular resistance, and pulmonary capillary wedge pressure and decreases in cardiac output and stroke volume. AVP = arginine vasopressin; B = baseline. Reprinted, with permission, from reference 36.

Serum sodium, when low, remained corrected. This report is encouraging in that it demonstrated sustained effects of a V_2 antagonist in clinical CHF. However, there were significant tolerability issues regarding thirst, and a somewhat surprising lack of change in blood pressure despite the significant effect on body weight. Plasma AVP levels have not been reported from this study, but one may expect that they rose in the group of patients on active treatment. A vasoconstrictive effect from unopposed V_{1A} stimulation could therefore have accounted for the lack of fall in blood pressure.

The final article in this supplement reviews in detail the available clinical trials of all AVP antagonists in late-stage development, both in CHF and in other conditions associated with hyponatremia.

CONSIDERATIONS FOR DRUG DEVELOPMENT

With several AVP antagonists under active development for CHF, and potentially more on the way, several factors must be considered in future studies. How to measure efficacy is a major concern, and this decision will depend on the type of compound and the study setting. Mortality is the ultimate endpoint for testing therapies for chronic CHF, and a mortality study with tolvaptan is under way. Given the current low mortality rate in stable CHF, demonstrating a benefit of any new treatment on this endpoint may be a challenge. Hence, looking for benefits on surrogate endpoints such as ventricular remodeling may also be crucial. For both acute and chronic CHF, morbidity and cost of care are also reasonable endpoints, and here the effects of V_2 or combined antagonists may be particularly valuable given the potential benefits of these agents on congestion and hyponatremia.

For chronic CHF, the type of antagonist studied may be important. As noted before, the reasons to expect benefit from a V_{1A} antagonist are many, assuming adequate signaling is present. But a pure V_{1A} antagonist may lead to elevated AVP levels and unwanted water retention, which would not be desirable, particularly in patients with well-compensated CHF. Likewise, a pure V_2 antagonist, although useful acutely, may lead over time to unwanted V_{1A} stimulation. When AVP levels rise in response to increased osmolality in patients with normal serum sodium levels who receive a V_2 antagonist, any level of adverse endogenous AVP stimulation from the V_{1A} side is obviously enhanced. For long-term studies, therefore, it would seem most desirable to combine V_{1A} and V_2 antagonism, whereas for acute decompensated CHF, a pure V_2 antagonist may be equally useful. These are the types of issues that will need to be resolved with additional clinical studies.

CONCLUSIONS

There is now adequate theoretical justification to pursue AVP antagonism in acute and chronic CHF. AVP is a logical target both in terms of conventional hemodynamic understanding of CHF and in view of the successes of neurohormonally based therapy. Excessive AVP levels are present in clinical CHF, and acute studies with AVP antagonists in both experimental and clinical settings are encouraging. Many issues remain unresolved, however, and much work will be required in the coming years before a meaningful role for AVP in the pathophysiology of CHF can be definitively established.

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AVP receptor antagonists as aquaretics: Review and assessment of clinical data

ABSTRACT

The antidiuretic hormone arginine vasopressin (AVP) is primarily responsible for regulating osmotic and volume homeostasis of body fluids, largely through binding to vasopressin type 1A (V_{1A}) and type 2 (V_2) receptors. Increased AVP secretion leads to decreased free water excretion with resulting water retention, and can cause dilutional hyponatremia. A new class of medications known as AVP receptor antagonists induces free water diuresis without natriuresis or kaliuresis, an effect termed *aquaresis*. Numerous clinical trials show AVP antagonists to be effective at increasing free water excretion and serum sodium in patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion or edema-forming states such as congestive heart failure and cirrhosis. This article reviews clinical trial data on the AVP antagonists in late development (lixivaptan, satavaptan, and tolvaptan) and recently approved for marketing (conivaptan).

KEY POINTS

AVP receptor antagonists correct hyponatremia by blocking activation of the V_2 receptor.

Lixivaptan, satavaptan, and tolvaptan are selective for the V_2 receptor and are being developed for oral administration, whereas conivaptan is a dual V_{1A}/V_2 antagonist for intravenous administration.

All four AVP antagonists increase urine volume, reduce urine osmolality, and generally have no effect on 24-hour sodium excretion.

Clinical trials to date indicate that AVP antagonists produce a safe and predictable aquaresis, thereby raising serum sodium levels in patients with hyponatremia.

* Dr. Verbalis reported that he has received grant/research support from Yamanouchi Pharma and Astellas Pharma US, Inc, and is a paid consultant to Astellas Pharma US, Inc; Ferring Pharmaceuticals; Otsuka America Pharmaceutical; and Sanofi-Aventis.

TRADITIONAL THERAPIES for patients with hyponatremia can be effective, but they have significant limitations, as detailed by Douglas earlier in this supplement and by other authors.[1] A new class of medications that acts on the arginine vasopressin (AVP) receptor—AVP receptor antagonists—will likely become a viable alternative to these traditional therapies for hyponatremia, based on the predictability of their effect, their rapid onset of action, and the limited urinary electrolyte excretion associated with their use.[2]

This article reviews the available clinical data on the therapeutic potential of AVP receptor antagonists for the treatment of hyponatremia.

AVP AND FLUID IMBALANCES

AVP, also known as antidiuretic hormone, is a peptide hormone involved in diverse physiologic functions, including contraction of vascular smooth muscle, stimulation of liver glycogenolysis, regulation of corticotropin release, and renal antidiuresis.[3–5] These functions are mediated through the binding of AVP to specific membrane receptors in targeted cells.

Disorders of AVP secretion frequently cause imbalances of body water: deficient AVP secretion can cause hyperosmolality as a result of inadequate renal water conservation, and excess or inappropriate AVP secretion can cause hypoosmolality due to impaired renal water excretion.[6] Hypoosmolality usually manifests as hyponatremia, a very common electrolyte disorder associated with a variety of underlying conditions that are usually caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[7] In addition to SIADH, patients with edema-forming states such as congestive heart failure (CHF) and cirrhosis, as well as patients treated with diuretics, also often have elevated plasma levels of AVP and hyponatrem-

ia.[8–10] Hyponatremia has been associated with increased morbidity and mortality across the spectrum of these conditions.[11]

AVP receptor antagonists correct hyponatremia by blocking activation of the vasopressin type 2 (V_2) receptor.[2] These agents induce a free water diuresis without an accompanying natriuresis or kaliuresis; this effect has been termed *aquaresis* to differentiate it from the effect produced by traditional diuretic agents.

ROLES OF AVP RECEPTOR SUBTYPES

AVP receptors are G protein–coupled receptors and have been divided into three subtypes that mediate all known actions of AVP: V_{1A}, V_{1B}, and V_2.[3–5] The V_{1A} and V_{1B} receptors are linked to the phosphoinositol signaling pathway, with intracellular calcium acting as the second messenger, whereas the V_2 receptors are linked to the adenylate cyclase signaling pathway, with intracellular cyclic adenosine monophosphate (cAMP) acting as the second messenger.[5]

The V_{1A} receptors are responsible for multiple physiologic effects, such as vasoconstriction, glycogenolysis, and platelet aggregation.[3]

The V_{1B} receptors exist mainly in the anterior pituitary, where they mediate adrenocorticotropin release.[4]

The V_2 receptors are found primarily in the collecting ducts of the kidney and mediate antidiuresis by causing renal free water reabsorption and retention. Extrarenal V_2 receptors are also present in vascular endothelial cells, where they mediate release of coagulation factor.[12] In the kidney, circulating AVP activates the V_2 receptor in renal collecting duct cells, leading to an increase in cAMP levels via stimulation of G protein–mediated adenylate cyclase activity.[13] These events cause insertion of aquaporin-2 water channels into the apical plasma membranes of the collecting duct cells, thereby increasing water permeability of the apical plasma membranes and causing antidiuresis.[14]

PROFILE OF AVP RECEPTOR ANTAGONISTS

Several AVP receptor antagonists are under clinical investigation: conivaptan (YM-087), lixivaptan (VPA-985), satavaptan (SR-121463), and tolvaptan (OPC-41061).[2,15] Conivaptan has antagonist activity at both the V_{1A} and V_2 receptors,[16] whereas the other agents are selective V_2 receptor antagonists.[17]

TABLE 1

Profile of AVP receptor antagonists

	CONIVAPTAN (YM-087)	LIXIVAPTAN (VPA-985)	SATAVAPTAN (SR-121463)	TOLVAPTAN (OPC-41061)
Receptor(s)	V_{1A}/V_2	V_2	V_2	V_2
Admin. route	Intravenous	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Sodium excretion in 24 hr	↔	↔ at low dose ↑ at high dose	↔	↔
Company developing	Astellas Pharma US, Inc	CardioKine	Sanofi-Aventis	Otsuka America Pharmaceutical

AVP = arginine vasopressin; ↔ = no change

Adapted, with permission, from reference 17.

As outlined in Table 1, all four AVP receptor antagonists increase urine volume, decrease urine osmolality, and (except for high-dose lixivaptan) have no effect on 24-hour sodium excretion. Conivaptan is currently the only AVP receptor antagonist that is commercially available in the United States, having recently received US Food and Drug Administration (FDA) approval for the treatment of euvolemic hyponatremia in hospitalized patients. Conivaptan is available for intravenous (IV) administration, whereas the other three agents are being developed for oral administration.

AVP antagonists induce free water diuresis without natriuresis or kaliuresis—an effect called *aquaresis*

The AVP receptor antagonists have been proven effective at increasing free water excretion and serum sodium levels in multiple clinical trials.[15] The remainder of this article reviews and assesses the available clinical trial data for each individual agent, with key trial details summarized in Table 2.

CONIVAPTAN IN HYPONATREMIA

Two clinical trials have been reported on the use of conivaptan to treat hyponatremia.[18,19]

Oral conivaptan

One study was a placebo-controlled, randomized, double-blind evaluation of oral conivap-

TABLE 2

Summary of randomized clinical trials of AVP receptor antagonists

AUTHORS/ REFERENCE	TREATMENT REGIMENS	PATIENT POPULATION	EFFECT ON SERUM SODIUM*	EFFECT ON BODY WEIGHT*
Conivaptan				
Ghali et al[18]	Coni 40 mg/d po × 5 d Coni 80 mg/d po × 5 d Placebo × 4 d	74 hospitalized patients with euvolemic or hypervolemic hyponatremia	Significant increases	Not reported
Verbalis et al[15,19]	Coni 40 mg/d IV × 4 d (after 20-mg bolus) Coni 80 mg/d IV × 4 d (after 20-mg bolus) Placebo × 4 d	84 hospitalized patients with euvolemic or hypervolemic hyponatremia	Significant increases	Not reported
Lixivaptan				
Wong et al[21]	Lixi 25 mg bid po × 7 d Lixi 125 mg bid po × 7 d Lixi 250 mg bid po × 7 d Placebo × 7 d	44 hospitalized patients with stable hyponatremia and cirrhosis, CHF, or SIADH	Significant dose-dependent increases	No significant change
Gerbes et al[22]	Lixi 50 mg bid po × 7 d Lixi 100 mg bid po × 7 d Placebo × 7 d	60 hospitalized hyponatremic patients with cirrhosis	Significant dose-dependent increases	Significant decrease with higher dose
Satavaptan				
Soupart et al[23]	Sata 25 mg qd po × 5–23 d Sata 50 mg qd po × 5–23 d Placebo × 5–23 d	34 hyponatremic patients with SIADH	Dose-dependent increases	Not reported
Tolvaptan				
Gheorghiade et al[24]	Tol 30 mg qd po × 25 d Tol 45 mg qd po × 25 d Tol 60 mg qd po × 25 d Placebo × 25 d	254 patients with CHF in outpatient setting (28% with hyponatremia)	Small mean increases over baseline (vs small mean decrease for placebo)	Significant decreases
Gheorghiade et al (ACTIV in CHF)[25]	Tol 30 mg qd po × ≤60 d Tol 60 mg qd po × ≤60 d Tol 90 mg qd po × ≤60 d Placebo × ≤60 d	319 patients hospitalized with worsening CHF (21.3% with hyponatremia)	Small mean increases over baseline (vs small mean decrease for placebo)	Significant decreases
Gheorghiade et al[26]	Tol 10–60 mg/d po × 27 d Fluid restriction (1,200 mL/d) plus placebo × 27 d	28 hospitalized patients with serum sodium < 135 mEq/L	Significant increase	No change
Gross et al (SALT-2)[27]	Tol 15–60 mg qd po × 30 d Placebo × 30 d	240 patients with hyponatremia	Significant increases	Significant decrease (similar change) in all dose groups

* With AVP antagonist vs placebo (or, for reference 26, vs fluid restriction). Unless otherwise noted, effects are for all AVP antagonist doses in the study.

AEs = adverse events; AVP = arginine vasopressin; Lixi = lixivaptan; Sata = satavaptan; Tol = tolvaptan; Coni = conivaptan; CHF = congestive heart failure; GI = gastrointestinal; SIADH = syndrome of inappropriate antidiuretic hormone secretion

EFFECT ON URINE OUTPUT*	SIDE EFFECTS*
Not reported	No significant increase in reported AEs
Significant increases in effective water clearance	Local irritation at infusion site
Significant dose-dependent increases in free water clearance	Significant dehydration (especially with higher doses), worsening encephalopathy in 2 pts
Dose-dependent increases in urine volume; significant increases in free water clearance at end of study	Increased thirst sensation; rates of serious AEs similar to placebo
Reduced urine osmolality	No serious drug-related AEs
Significant dose-dependent increases in urine volume	Dry mouth, thirst, and polyuria (including urinary frequency)
Significant increases in urine volume	AEs in 85% of patients; most common were thirst, dry mouth, dizziness, nausea, hypotension, but rates not significantly different from placebo
Significant increase in urine output by last inpatient visit	No significant increase in reported AEs
Decreased urine osmolality	Increased thirst, trend to increased AVP levels

tan in hospitalized patients with euvolemic or hypervolemic hyponatremia.[18] Seventy-four patients with a baseline serum sodium between 115 and 130 mEq/L were randomized to receive conivaptan 40 mg/day (n = 24) or 80 mg/day (n = 27) or placebo (n = 23) in two divided doses for 5 days.

The mean change in serum sodium from baseline to the end of treatment was 3.4 mEq/L with placebo, 6.4 mEq/L with conivaptan 40 mg/day, and 8.2 mEq/L with conivaptan 80 mg/day (P = .002 vs placebo). The percentage of patients achieving a normal serum sodium level (≥ 135 mEq/L) or an increase of at least 6 mEq/L was 48% in the placebo group and 71% and 82% in the lower and higher conivaptan dose groups, respectively (P = .014 vs placebo). The incidence and types of adverse events were similar between the two conivaptan groups and the placebo group; the most common were headache, hypotension, nausea, constipation, and postural hypotension.[18]

Despite the efficacy of oral conivaptan in this trial, development of the oral formulation was discontinued because of significant inhibition of the cytochrome P-450 3A4 system. To minimize the possibility of drug interactions, the FDA restricted conivaptan's distribution to a parenteral form for short-term in-hospital use.

AVP antagonists increase urine volume, reduce urine osmolality, and do not affect sodium excretion

IV conivaptan

The second reported study assessed IV conivaptan using a randomized, double-blind, multicenter, placebo-controlled, parallel-group design.[19] Eighty-four adults with euvolemic or hypervolemic hyponatremia (serum sodium between 115 and 130 mEq/L) were randomized to placebo (n = 29) or conivaptan given as a 20-mg IV bolus followed by a continuous infusion of 40 mg/day (n = 29) or 80 mg/day (n = 26) for 4 days. The primary efficacy measure was the change in serum sodium from baseline over treatment duration (measured as the area under the serum sodium curve from the beginning to the end of the treatment period). Secondary measures included the change in serum sodium levels from baseline to day 4, the time from the first dose to a 4-mEq/L increase in serum sodium, the number of patients achieving serum sodium normalization or a 6-mEq/L increase, and effective water clearance (a measure of electrolyte free water excretion).

TABLE 3

Efficacy results from randomized trial of IV conivaptan for hyponatremia

END POINT	PLACEBO (n = 29)	CONIVAPTAN 40 MG/DAY (n = 29)	CONIVAPTAN 80 MG/DAY (n = 26)
Baseline mean serum sodium, mEq/L (± SD)	124.3 ± 4.9	123.3 ± 4.7	124.8 ± 3.4
Least-squares mean change in serum sodium AUC to day 4, mEq/L • hr (± SE)	12.9 ± 61.2	490.9 ± 56.8*	716.6 ± 60.5*
Least-squares mean change in serum sodium at day 4, mEq/L (± SE)	2.0 ± 0.8	6.8 ± 0.8*	9.0 ± 0.8*
Median time from first dose to 4-mEq/L rise in serum sodium, hr	NE	23.7*	23.4*
Number (%) of patients achieving ≥ 6-mEq/L increase in or normalization of serum sodium (≥135 mEq/L)	6 (20.7)	20 (69)†	23 (88.5)*
Mean change in effective water clearance from baseline to day 1, mL (± SD)	–332.3 (434.1)	1,984.0 (1,559.4)‡	1,759.4 (1,748.3)‡

* $P < .001$ vs placebo † $P < .01$ vs placebo ‡ $P < .05$ vs placebo

AUC = area under the curve; IV = intravenous; NE = not estimable; SD = standard deviation; SE = standard error

Adapted from reference 19.

Infusion of conivaptan should not exceed 4 days

As shown in Table 3, both doses of conivaptan were associated with statistically significantly greater increases, relative to placebo, in the primary end point of mean change in serum sodium over treatment duration. Both doses also were associated with significant improvements over placebo in mean change in serum sodium levels on day 4, median time to a 4-mEq/L increase in serum sodium, percentage of patients achieving serum sodium normalization or a 6-mEq/L or greater increase, and mean change in effective water clearance, a measure of aquaretic effect (see Table 3). The researchers reported that conivaptan was well tolerated over the 4-day treatment period except for frequent infusion-site reactions.[19]

Indications, dosage

Based on these and other data,[20] conivaptan has been granted FDA approval in parenteral form for the treatment of euvolemic hyponatremia in hospitalized patients; the FDA has issued an approvable letter for its use as a treatment for hypervolemic hyponatremia.

For euvolemic hyponatremia, conivaptan should be given as a 20-mg IV loading dose over 30 minutes followed by a 20-mg continuous infusion over 24 hours. Following the initial day of treatment, it is suggested that conivaptan be given for an additional 1 to 3 days as a continuous infusion of 20 mg/day (total duration of infusion not to exceed 4 days). The dose can be titrated to a 40-mg/day continuous infusion if the serum sodium level does not rise at the desired rate. Conivaptan is not indicated for the treatment of CHF at this time.[20]

LIXIVAPTAN IN HYPONATREMIA

Two randomized, multicenter studies of lixivaptan in humans have been reported.[21,22] Most patients in these trials had cirrhosis, which produces a dilutional hypervolemic hyponatremia.

The first was a placebo-controlled study of hospitalized patients with stable hyponatremia (<130 mEq/L for 3 consecutive days); of the 44 patients enrolled, 33 had cirrhosis, 6 had CHF, and 5 had SIADH.[21] The patients had a constant sodium intake and were randomized to receive one of three doses of oral lixivaptan (Table 2) or placebo twice daily for 7 days. End points included changes in net fluid balance, free water clearance, and serum osmolality.

The study found a significant increase in free water clearance with the 125-mg and 250-mg twice-daily doses of lixivaptan compared with placebo on days 3, 5, and 7 (Figure 1). The 250-mg twice-daily dose was associated with significant increases in serum sodium levels compared with placebo on day 4 ($P < .01$) and days 5 and 6 ($P < .05$). On day 7, plasma AVP levels were significantly increased with the two higher doses of lixivaptan compared with baseline, placebo, and the lowest lixivaptan dose ($P < .05$ for all comparisons). There were no significant changes in orthostatic

blood pressure, serum creatinine levels, or urinary sodium excretion in the lixivaptan groups compared with the placebo group. The 250-mg twice-daily dose was not as well tolerated and was associated with reports of excessive thirst and dehydration manifested by marked increases in serum sodium levels, often requiring one or more doses to be withheld.[21]

The second published study of lixivaptan was a double-blind trial in 60 patients with cirrhosis and dilutional hyponatremia.[22] Patients were randomized to receive 100 or 200 mg/day of oral lixivaptan or placebo for 7 days or until serum sodium was normalized. Fluid intake was restricted to 1,000 mL/day. The primary end point was normalization of serum sodium level, defined as a concentration of 136 mEq/L or greater on two separate consecutive measurements. Baseline mean serum sodium concentrations were comparable among the three treatment arms (127 to 128 mEq/L).

Serum sodium levels were normalized in 27% of patients receiving lixivaptan 100 mg/day and 50% of patients receiving 200 mg/day compared with 0 placebo recipients ($P < .05$ and $P < .001$ vs placebo, respectively). The mean time to a complete response was 5.7 days in the 100-mg dose group and 4.8 days in the 200-mg dose group. The 200-mg dose also was associated with significant reductions in urine osmolality and body weight ($P < .001$ vs placebo on both measures).[22]

Thirst sensation increased significantly in the 200-mg dose group ($P = .01$ vs baseline) but not in the 100-mg or placebo groups. Rates of serious adverse events leading to treatment discontinuation were similar among the three groups. Renal impairment (increase in serum creatinine to ≥ 200 µmol/L) was observed in two patients in each of the three groups. No patient developed neurologic abnormalities, and lixivaptan had no significant effects on blood pressure or heart rate.[22]

SATAVAPTAN IN HYPONATREMIA

Satavaptan was evaluated in 34 hyponatremic patients with SIADH in a randomized, multicenter, phase 2 clinical trial.[23] Patients received satavaptan 25 or 50 mg once daily or placebo and adhered to fluid restriction (1.5 L/day) for 5 to 23 days.

Baseline mean serum sodium levels were 125 to 127 mEq/L in the three treatment groups. Response, defined as serum sodium normalization or an increase of at least 5 mEq/L from baseline to day 5, was achieved in 13% of placebo recipients compared with 79% of patients receiving satavaptan 25 mg/day ($P = .006$ vs placebo) and 83% of patients receiving satavaptan 50 mg/day ($P = .005$ vs placebo). By day 5, mean (± SD) serum sodium levels were 130 ± 5 mEq/L in the placebo group, 136 ± 6 mEq/L in the 25-mg dose group, and 140 ± 6 mEq/L in the 50-mg dose group. In addition, urinary osmolality was reduced significantly with satavaptan, and no serious drug-related adverse events were reported.[23]

In a subsequent open-label extension of this study, satavaptan appeared to maintain its efficacy over a 12-month period without evidence of tachyphylaxis.[23] Based on these results, the authors concluded that satavaptan is an effective and safe treatment for hyponatremia in patients with SIADH.

Cirrhosis produces a dilutional hypervolemic hyponatremia

TOLVAPTAN

Heart failure trials

Much of tolvaptan's initial development has focused on CHF, and two randomized clinical studies of this agent in patients with CHF have been published.[24,25]

The first was a double-blind, placebo-controlled study of 254 patients with exacerbation of known CHF (mostly New York Heart

Lixivaptan increases free water clearance in hyponatremia

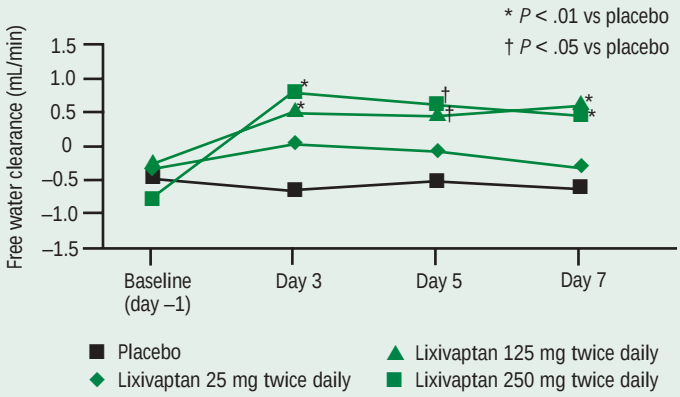

FIGURE 1. Effects of lixivaptan on free water clearance in a 7-day randomized study among 44 hospitalized patients with hyponatremia. Reprinted, with permission, from reference 21.

Tolvaptan produces enduring increases in serum sodium in heart failure patients

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Please see original source figure (figure 2) in: *Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V_2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003; 107:2690–2696.*

FIGURE 2. Effect of tolvaptan on serum sodium levels in a 25-day randomized study of 254 patients with congestive heart failure. The dose-dependent increase gradually weakened over the treatment period, but serum sodium levels remained statistically significantly greater in all tolvaptan groups than in the placebo group at all time points except for the 45-mg dose group at day 25. Reprinted, with permission, from reference 24.

Association class II and III), 28% of whom were hyponatremic (serum sodium < 136 mEq/L) at baseline.[24] Patients were randomized to one of three oral doses of tolvaptan (Table 2) or placebo for 25 days. All patients were treated in the outpatient setting, did not have their fluids restricted, and continued their existing therapies for CHF, including loop diuretics, angiotensin-converting enzyme inhibitors, digoxin, beta-blockers, hydralazine, and nitrates. The primary end point was change in body weight from baseline. Other end points were ankle edema, urine sodium excretion, urine volume, and urine osmolality.

All three doses of tolvaptan were associated with significant reductions in body weight at 24 hours after administration ($P < .001$ for all doses vs placebo). The initial reductions in body weight were maintained during the study, but no further reductions were observed after day 1. All doses of tolvaptan significantly increased urine output compared with placebo ($P < .05$) and also appeared to improve clinical signs and symptoms of CHF as assessed by ankle edema. In addition, all tolvaptan doses produced small mean increases in serum sodium levels, whereas placebo was associated with small decreases (Figure 2). Significantly greater mean net fluid losses were observed in tolvaptan recipients than in placebo recipients ($P < .05$ for each dose vs placebo). In the tolvaptan groups, patients with hyponatremia at baseline had greater increases in serum sodium during the study than did those with normal serum sodium levels at baseline.[24]

Dry mouth, thirst, and polyuria were more frequent in patients receiving tolvaptan than in those on placebo, but there was no change from baseline in heart rate, blood pressure, serum potassium levels, or renal function in any of the treatment groups.[24]

A second double-blind, multicenter, placebo-controlled, parallel-group study of tolvaptan in CHF has been published, this one in patients hospitalized for acute exacerbation of CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure [ACTIV in CHF]).[25] The study's 319 patients were randomized to receive one of three doses of oral tolvaptan (Table 2) or placebo for up to 60 days in addition to standard CHF therapy. The in-hospital end point was change in body weight at 24 hours after the first dose of study drug, and the outpatient end point was worsening CHF at 60 days after randomization. Other end points were changes in body weight, urine output, and serum electrolyte levels. Sixty-eight patients (21.3%) had hyponatremia (serum sodium < 136 mEq/L) at randomization, and they were evenly distributed among the treatment groups.

At 24 hours, all tolvaptan groups had significant reductions in body weight compared with the placebo group ($P \leq .009$ for all comparisons). Compared with placebo, all tolvaptan doses were associated with significantly higher urine volume on day 1, and this difference was maintained throughout the hospital stay. Patients in all tolvaptan groups also had small mean increases in serum sodium levels from baseline to day 1, whereas placebo recipients had a small decrease; this difference persisted throughout the hospital stay. Patients with hyponatremia at baseline who received tolvaptan had increases in serum sodium that were maintained throughout the study. Changes in body weight with tolvaptan were not associat-

ed with changes in heart rate, blood pressure, potassium level, or renal function.[25]

Although event-free survival tended to be longer with tolvaptan than with placebo,[25] additional studies, such as the ongoing Efficacy of Vasopressin Antagonism in Heart Failure (EVEREST) trial, are needed to provide more definitive data on morbidity and mortality in patients with CHF.

Hyponatremia trials

Tolvaptan also has been evaluated specifically for the treatment of hyponatremia in two reported trials.[26,27]

One was a prospective, randomized, active-control, open-label study in 28 hospitalized subjects with a serum sodium less than 135 mEq/L.[26] Patients were randomized to oral tolvaptan alone (n = 17) or fluid restriction (1,200 mL/day) plus placebo (n = 11). Tolvaptan was started at 10 mg/day and titrated to 60 mg/day as per protocol. Active treatment was continued for up to 27 days, and follow-up continued for up to 65 days.

The primary end point was normalization of serum sodium (> 135 mEq/L) or an increase in serum sodium of at least 10% from baseline. At the last inpatient visit, serum sodium had increased by 5.7 ± 3.2 mEq/L in the tolvaptan group and 1.0 ± 4.7 mEq in the fluid-restricted group (P = .0065). No significant differences in adverse events were observed between the groups. The authors concluded from this small study that tolvaptan appears to be more effective than fluid restriction at correcting hyponatremia in hospitalized subjects without an increased frequency of adverse events. This has led to larger ongoing placebo-controlled trials of tolvaptan in hyponatremic patients.

The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-2) is one such larger, placebo-controlled trial. This study, which has been presented only in preliminary form,[27] randomized 243 hyponatremic patients to receive placebo or 15 to 60 mg/day of tolvaptan in a stepwise fashion for 30 days. Similar to results of the lixivaptan trials, significantly greater increases in serum sodium levels were reported in patients receiving tolvaptan than in those on placebo. However, 25% of patients dropped out of the study, and resistance (defined as failure to achieve a serum sodium increase ≥ 5 mEq/L) occurred in 37%, 17%, and 11% of patients with cirrhosis, CHF, and SIADH, respectively.

ASSESSMENT OF AVP RECEPTOR ANTAGONISTS

Based on the results of multiple clinical trials with four different AVP receptor antagonists, it is likely that this class will become a mainstay of treatment for euvolemic hyponatremia. These agents predictably cause an aquaresis that leads to increased serum sodium in the majority of patients with hyponatremia due to SIADH, CHF, or cirrhosis. Although the initial FDA approval for conivaptan was only for euvolemic hyponatremia, increased exposure of larger numbers of patients with CHF should eventually lead to approval for hypervolemic hyponatremia as well.

The optimal use of AVP receptor antagonists has not yet been determined, but some predictions can be made with reasonable confidence.

Short-term vs chronic use

AVP antagonists often increase thirst even in hyponatremic patients

For hyponatremia in hospitalized patients who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, conivaptan will likely be the preferred agent. Phase 3 studies show that it reliably raises serum sodium over the short term, beginning as early as 1 to 2 hours after administration, and permits normalization of serum sodium in most hyponatremic patients over a 4-day treatment course. Selective orally active V_2 receptor antagonists such as lixivaptan, satavaptan, and tolvaptan correct serum sodium more slowly but will likely prove useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia.

Potential use with hypertonic saline

Despite the appeal of using a pure aquaretic agent to correct life-threatening hyponatremia, available clinical trial data are inadequate to clarify whether sufficiently rapid correction can be achieved in patients with acute, severe hyponatremia without the use of hypertonic saline. Theoretically, both treatments could be used initially, with the hypertonic saline then stopped after the serum sodium increased by several mEq/L, with the remainder of the first day's correction accomplished through aquare-

sis. The two therapies might be complementary in that the hypertonic saline infusion would cause sufficient expansion of the extracellular fluid to balance any volume depletion resulting from the aquaresis.

Fluid restriction mitigated, not eliminated

Most placebo-controlled trials of AVP receptor antagonists to treat hyponatremia have been of limited duration, generally 7 days or less. However, sufficient data from longer-term open-label studies exist to suggest that these agents will likely prove highly useful in chronic hyponatremia due to SIADH, cirrhosis, and CHF. Although the effect of AVP receptor antagonists on plasma AVP levels is variable, it bears emphasis that these agents often increase thirst even in hyponatremic patients and, unless fluids are restricted, water intake generally increases as well. For example, in the initial tolvaptan study in CHF, the serum sodium increased only during the first day despite a persistently dilute urine.[24] Thus, the use of AVP receptor antagonists will mitigate, but in many cases not eliminate, the need for fluid restriction.

Do not use AVP antagonists in cases of hypovolemic hyponatremia, to avoid possible hypotension

Safety issues

Safety issues must also be considered carefully with any new class of agents. The possibility of overcorrection has been of significant concern in all clinical studies of the AVP receptor antagonists, but osmotic demyelination has not yet been reported with any agent. Nonetheless, it is expected that these agents will need to be used judiciously if correction of the serum sodium at a rate faster than 8 to 12 mEq/L per 24 hours is to be avoided. Because all of these agents have a half-life of less than 12 hours, all will require daily or continuous dosing to maintain activity, so it will be possible to limit the serum sodium rise by stopping the drug or reducing the dosage. If necessary, hypotonic fluid can be infused to abrogate the rise in serum sodium until the aquaresis abates. These safeguards should be sufficient to protect against too-rapid correction, assuming that serum sodium levels are monitored frequently during active treatment.

A second major concern is the need to avoid AVP receptor antagonist therapy in cases of hypovolemic hyponatremia, where an aquaresis would aggravate underlying volume contraction and potentially cause hypotension. This can be avoided by careful differential diagnosis among the subtypes of hyponatremia.

The potential for serious drug interactions via interference with cytochrome P-450 3A4 metabolism of other drugs by AVP receptor antagonists must be recognized. This will likely not be of concern with short-term use of AVP receptor antagonists such as IV conivaptan, but may cause problems during long-term therapy, requiring appropriate monitoring.

Finally, whether V_2 receptor inhibition will have any adverse effect in the vascular endothelium is unknown. Bleeding complications have not been reported to date, but surveillance will be needed now that a combined V_{1A}/V_2 receptor antagonist is in general use.

CONCLUSIONS

All of the AVP receptor antagonists produce an aquaretic effect via their activity at the V_2 receptor, which improves dilutional hyponatremia. All data to date indicate that the AVP antagonists are highly effective in producing a safe and predictable aquaresis, thereby increasing serum sodium levels in hyponatremic patients. Conivaptan is the first AVP receptor antagonist to receive FDA approval, specifically for IV administration to hospitalized patients with euvolemic hyponatremia. Several investigational oral AVP receptor antagonists are in late-stage clinical trials and hold promise for long-term therapy of chronic hyponatremia.

Further studies are needed to assess the appropriate use of AVP receptor antagonists in various areas:

- For correction of symptomatic hyponatremia alone or in conjunction with hypertonic saline infusions
- To assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and length of stay in the hospital and intensive care unit
- For long-term treatment of minimally symptomatic hyponatremia in order to reduce the risks of neurocognitive dysfunction and gait instability.[28]

Despite many yet unanswered questions about their optimal use, AVP receptor antagonists will undoubtedly prove highly useful and promise to usher in a new era in the treatment of hyponatremia.

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