

Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion

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KEYWORDS

Hyponatremia;
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Osmolality;
Serum sodium concentration;
Syndrome of inappropriate antidiuretic hormone secretion;
Vasopressin receptor antagonists

Abstract

Disorders of sodium $[Na^+]$ and water metabolism are commonly encountered in the hospital setting due to the wide range of disease states that can disrupt the balanced control of water and solute intake and output. In particular, the prompt identification and appropriate management of abnormally low serum $[Na^+]$ is critical if we are to reduce the increased morbidity and mortality that accompany hyponatremia in hospitalized patients. Use of an algorithm that is based primarily on the symptomatology of hyponatremic patients, rather than the serum $[Na^+]$ or the chronicity of the hyponatremia, will help to choose the correct initial therapy in hospitalized hyponatremic patients. However, careful monitoring of serum $[Na^+]$ responses is required in all cases to adjust therapy appropriately in response to changing clinical conditions. Although this approach will enable efficacious and safe treatment of hyponatremic patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) at the present time, evolving knowledge of the consequences of chronic hyponatremia will likely alter treatment indications and guidelines in the future.

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PALABRAS CLAVE

Hiponatremia;
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Síndrome de secreción inadecuada de hormona antidiurética;
Antagonistas del receptor de la vasopresina

Manejo de la hiponatremia en pacientes con síndrome de secreción inadecuada de hormona antidiurética

Resumen

Los trastornos del metabolismo del sodio y el agua son habituales en el entorno hospitalario, debido a la amplia gama de estados de la enfermedad que pueden alterar el control equilibrado de la ingesta y salida de solutos y del agua. Concretamente, la identificación inmediata y el manejo adecuado de una concentración sérica de $[Na^+]$ anormalmente baja es crucial para reducir el aumento de la morbimortalidad que acompaña a la hiponatremia en los pacientes hospitalizados. El uso de un algoritmo que se basa principalmente en la sintomatología de los pacientes hiponatremicos, en vez de en el $[Na^+]$ sérico o la cronicidad de la hiponatremia, ayudará a elegir el tratamiento correcto inicial para los pacientes hiponatremicos hospitalizados. Sin embargo, en todos los casos, es preciso realizar una supervisión cuidadosa de la respuesta del $[Na^+]$ sérico para ajustar el tratamiento de forma adecuada, dependiendo de los cambios

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observados en las condiciones clínicas. Aunque en la actualidad este enfoque permitirá un tratamiento más eficaz y seguro de los pacientes hiponatremicos con SIADH, la evolución del conocimiento sobre las consecuencias de la hiponatremia crónica, probablemente, alterará en el futuro las indicaciones y las directrices para el tratamiento.

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Introduction

This review will address the management of hyponatremia caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in hospitalized patients and outpatients. To do so requires an understanding of the pathogenesis and diagnosis of SIADH, as well as currently available treatment options. The article will first review current knowledge of pathophysiology, diagnosis and treatment of SIADH, followed by a presentation of an algorithm for determining the most appropriate treatments for individual patients with SIADH based on their presenting symptoms.

Clinical importance of syndrome of inappropriate antidiuretic hormone secretion

Disorders of body fluids, and particularly hyponatremia, are among the most commonly encountered problems in clinical medicine, affecting up to 30% of hospitalized patients. In a study of 303,577 laboratory samples collected from 120,137 patients, the prevalence of hyponatremia (serum $[Na^+] < 135$ mmol/L) on initial presentation to a healthcare provider was 28.2% among those treated in an acute hospital care setting, 21% among those treated in an ambulatory hospital care setting, and 7.2% in community care centers¹. Numerous other studies have corroborated a high prevalence of hyponatremia in hospitalized patients², which reflects the increased vulnerability of this patient population to disruptions of body fluid homeostasis. Recognizing the many possible causes of hyponatremia in hospitalized patients and implementing appropriate treatment strategies therefore are critical steps toward optimizing care and improving outcomes in hospitalized patients with hyponatremia.

In addition to its frequency, hyponatremia is also important because it has been associated with worse clinical outcomes across the entire range of inpatient care, from the general hospital population to those treated in the intensive care unit (ICU). In a study of 4,123 patients aged 65 years or older who were admitted to a community hospital, 3.5% had clinically significant hyponatremia (serum $[Na^+] < 130$ mmol/L) at admission. Compared with non-hyponatremic patients, those with hyponatremia were twice as likely to die during their hospital stay (relative risk [RR], 1.95; $p < 0.05$)³. In another study of 2,188 patients admitted to a medical ICU over a 5-year period, 13.7% had hyponatremia. The overall rate of in-hospital mortality among all ICU patients was high at 37.7%. However, severe hyponatremia (serum $[Na^+] < 125$ mmol/L) more than doubled the risk of in-hospital mortality (RR, 2.10; $p < 0.001$)⁴. In addition to the general hospital population, in virtually every disease ever studied, the presence of

hyponatremia has been found to be an independent risk factor for increased mortality, from congestive heart failure to tuberculosis to liver failure².

Pathogenesis of hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion

Hyponatremia can be caused by one of two potential disruptions in fluid balance: *dilution* from retained water, or *depletion* from electrolyte losses in excess of water. Dilutional hyponatremias are associated with either a normal (euvolemic) or an increased (hypervolemic) extracellular fluid (ECF) volume, whereas depletion hyponatremias generally are associated with a decreased ECF volume (hypovolemic). Dilutional hyponatremia can arise from a primary defect in osmoregulation, such as the SIADH, or as a result of ECF volume expansion, as seen in conditions associated with secondary hyperaldosteronism, such as heart failure, hepatic cirrhosis, or nephrotic syndrome. Among hospitalized patients, euvolemic hyponatremia is the most common presentation of abnormally low serum $[Na^+]$. In a study of patients who developed clinically significant postoperative hyponatremia (defined as a serum $[Na^+] < 130$ mmol/L) in a large teaching hospital, only 8% were hypovolemic, whereas 42% were euvolemic and 21% were hypervolemic⁵.

Euvolemic hyponatremia results from an increase in total body water, but with normal or near-normal total body sodium. As a result, there is an absence of clinical manifestations of ECF volume expansion, such as subcutaneous edema or ascites. Euvolemic hyponatremia can accompany a wide variety of pathological processes, but the most common cause by far is SIADH. Normally, increased plasma osmolality activates osmoreceptors located in the anterior hypothalamus and stimulates the secretion of arginine vasopressin (AVP), also called antidiuretic hormone (ADH), a key neurohormone that regulates fluid homeostasis. However, in patients with euvolemic hyponatremia due to SIADH, plasma AVP levels are not suppressed despite normal or decreased plasma osmolality⁶. This can be a result of ectopic production of AVP by tumors, or stimulation of endogenous pituitary AVP secretion as a result of nonosmotic stimuli that also stimulate vasopressinergic neurons, which include hypovolemia, hypotension, angiotensin II, nausea, hypoxia, hypercarbia, hypoglycemia, stress, and physical activity. Non-suppressed AVP levels have been documented in the majority of hyponatremic patients, including those with SIADH⁷ and heart failure⁸.

SIADH can develop as the result of many different disease processes that disrupt the normal mechanisms that regulate AVP secretion, including pneumonias and other lung infections, thoracic and extrathoracic tumors, a variety of

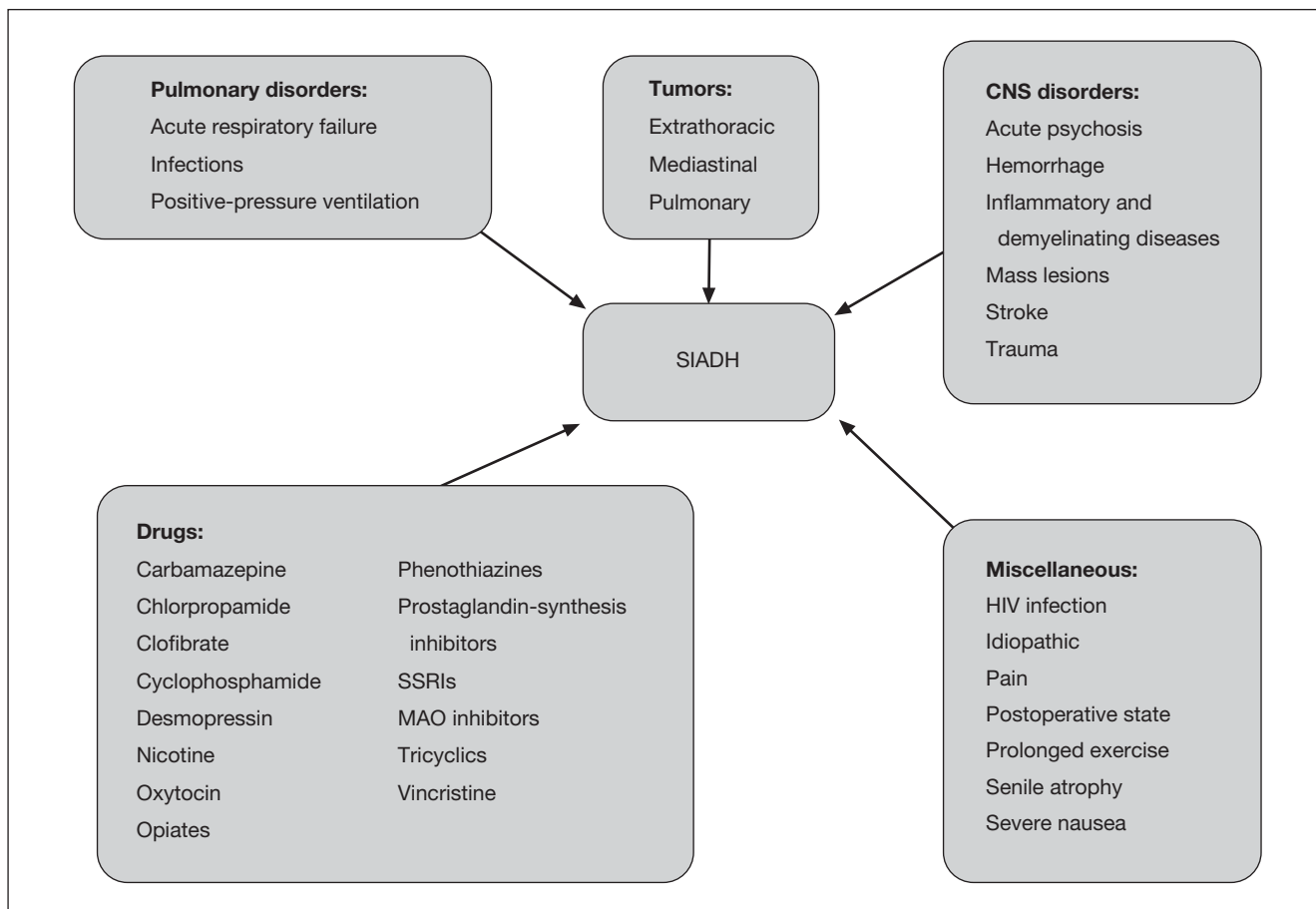


Figure 1 Etiologies of syndrome of inappropriate antidiuretic hormone secretion (SIADH). CNS: central nervous system; HIV: human immunodeficiency virus; MAO: monoamine oxidase; SIADH: syndrome of inappropriate antidiuretic hormone hypersecretion; SSRIs: selective serotonin reuptake inhibitors.

different central nervous system disorders, the postoperative state, human immunodeficiency virus (HIV), and many different drugs (fig. 1). Given the multiplicity of disorders and drugs that can cause disrupted AVP secretion, it is not surprising that hyponatremia is the most common electrolyte abnormality seen in clinical practice.

Symptomatology associated with syndrome of inappropriate antidiuretic hormone secretion

Symptoms of hyponatremia correlate both with the degree of decrease in the serum $[Na^+]$ and with the chronicity of the hyponatremia. Acute hyponatremia, defined as < 48 hrs in duration, is often associated with life-threatening clinical features such as obtundation, seizures, coma, and respiratory arrest. These symptoms can occur abruptly, sometimes with little warning⁹. In the most severe cases, death can occur as a result of cerebral edema with tentorial herniation. Hypoxia secondary to neurogenic pulmonary edema can increase the severity of brain swelling¹⁰.

In contrast, chronic hyponatremia is much less symptomatic, and the reason for the profound differences between the symptoms of acute and chronic hyponatremia is now well

understood to be due to the process of *brain volume regulation*¹¹. It is essential that this process be understood in order to understand the full spectrum of hyponatremic symptoms. As the ECF $[Na^+]$ decreases, regardless of whether because of a loss of sodium or a gain of water, there is an obligate movement of water into the brain along osmotic gradients. That water shift causes swelling of the brain, or cerebral edema. If the increased brain water reaches approximately 8% in adults, it exceeds the capacity of the skull to accommodate brain expansion, leading to tentorial herniation and death from respiratory arrest and/or ischemic brain damage. However, if the patient survives the initial hyponatremia, a very strong volume regulatory process follows consisting of loss of electrolytes and small organic molecules called osmolytes into the ECF¹². As the solute content of the brain decreases, the water content is allowed to normalize, eventually reaching a state in which brain edema is virtually absent, and as a result symptoms are markedly less than with acute hyponatremia. Although the time required for the brain to achieve a volume-regulated state varies across patients, this process is completed within 48 hours in experimental animal studies¹³, and probably follows a similar time course in humans.

Despite this powerful adaptation process, chronic hyponatremia is frequently associated with neurological symptomatology, albeit milder and more subtle in nature.

A recent report found a fairly high incidence of symptoms in 223 patients with chronic hyponatremia as a result of thiazide administration: 49% had malaise/lethargy, 47% had dizzy spells, 35% had vomiting, 17% had confusion/obtundation, 17% experienced falls, 6% had headaches, and 0.9% had seizures¹⁴. Although dizziness can potentially be attributed to a diuretic-induced hypovolemia, symptoms such as confusion, obtundation and seizures are more consistent with hyponatremic symptomatology. Because thiazide-induced hyponatremia can be readily corrected by stopping the thiazide and/or administering sodium, this represents an ideal situation in which to assess improvement in hyponatremia symptomatology with normalization of the serum $[Na^+]$; in this study, all of these symptoms improved with correction of the hyponatremia. This represents one of the best examples demonstrating reversal of the symptoms associated with chronic hyponatremia by correction of the hyponatremia, because the patients in this study did not in general have severe underlying co-morbidities that might complicate interpretation of their symptoms, as is often the case in patients with SIADH.

Requirements for making a diagnosis of syndrome of inappropriate antidiuretic hormone secretion in hospitalized patients

In patients with hypotonic hypoosmolality, ascertainment of their ECF volume status (i.e., hypovolemic, euvolemic, or hypervolemic) is an essential first step, as this will segregate patients into different treatment paradigms. For example, in patients who are truly clinically hypovolemic with a decreased ECF volume by clinical parameters, treatment would generally consist of solute repletion with sodium, generally isotonic saline infusion with or without potassium, until the sodium concentrations normalize. In patients who are hypervolemic, treatment should focus first on the underlying disease rather than addressing the serum $[Na^+]$ directly. In patients with clinical euvoolemia, the standard diagnostic pathway should be followed to confirm a diagnosis of SIADH as described below.

Assessing ECF volume status can be difficult, even for the most experienced clinicians. Physical signs such as orthostatic decreases in blood pressure and increases in pulse rate, dry mucus membranes, and skin tenting indicate hypovolemic hyponatremia, while signs such as subcutaneous edema, ascites, or anasarca indicate hypervolemic hyponatremia. Patients without any of these findings are generally considered to be euvolemic. However, in any situation these signs are only applicable if there are no other reasons to suspect an altered ECF volume. Along with a complete history and physical examination that includes a careful neurological evaluation, several laboratory tests can help to assess the etiology of the hyponatremia, once serum sodium concentrations have been shown to be below normal ($[Na^+] < 135$ mmol/L):

- *Urine osmolality.* A urine osmolality (U_{osm}) less than 100 mOsm/kg H_2O can indicate low dietary solute intake, primary polydipsia, or a reset osmostat after suppression of AVP release by increased water loading.
- *Urine sodium concentration.* The excretion of sodium, as measured by a spot urine $[Na^+]$ (U_{Na^+}), can indicate

depletional hyponatremia if the concentration is less than 30 mmol/L¹⁵. A low U_{Na^+} reflects a volume depleted state unless the patient is clinically hypervolemic, and patients with these results are more likely to respond to isotonic saline. Euvolemic patients who have a normal dietary sodium intake will generally have spot $U_{Na^+} \geq 30$ mmol/L and will not benefit from isotonic saline administration¹⁵. However, if the patient is on diuretics, the results of this test cannot always be interpreted, as a $U_{Na^+} \geq 30$ mmol/L may reflect the natriuretic effect of the diuretic and not a volume replete state.

- *Blood tests.* Additional indicators of volume status include serum blood nitrogen (BUN) and uric acid concentrations. A BUN < 10 mg/dl and uric acid < 4 mg/dl are generally consistent with a euvolemic state. Elevated BUN and uric acid levels (BUN > 20 mg/dl and uric acid > 6 mg/dl), especially if prior values are available for comparison, can also help to establish whether ineffective vascular volume status may be contributing to the pathophysiology of the hyponatremia. In certain clinical scenarios, the B-type natriuretic protein (BNP) can be helpful to support a clinical impression of congestive heart failure.

The criteria necessary for a diagnosis of SIADH remain essentially as defined by Bartter and Schwartz in 1967 (table 1)¹⁶, but several points deserve emphasis¹⁷. First,

Table 1 Criteria for the diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Essential
– Decreased effective osmolality of the extracellular fluid ($P_{osm} < 275$ mOsm/kg H_2O)
– Inappropriate urinary concentration ($U_{osm} > 100$ mOsm/kg H_2O with normal renal function) at some level of hypoosmolality
– Clinical euvoolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
– Elevated urinary sodium excretion while on a normal salt and water intake
– Absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism (Addison's disease or secondary adrenal insufficiency) and diuretic use
Supplemental
– Abnormal water load test (inability to excrete at least 90% of a 20 ml/kg water load in 4 hours and/or failure to dilute U_{osm} to < 100 mOsm/kg H_2O)
– Plasma AVP level inappropriately elevated relative to plasma osmolality
– No significant correction of serum $[Na^+]$ with volume expansion but improvement after fluid restriction

AVP: arginine vasopressin; $[Na^+]$: sodium; P_{osm} : plasma osmolality; U_{osm} : urine osmolality.

true ECF hypoosmolality must be present and hyponatremia secondary to pseudohyponatremia or hyperglycemia excluded. Second, urinary osmolality must be inappropriate for plasma hypoosmolality (P_{osm}). This does not require a $U_{osm} > P_{osm}$, but simply that the urine osmolality is greater than maximally dilute (i.e., $U_{osm} > 100$ mOsm/kg H_2O in adults). Furthermore, urine osmolality need not be inappropriately elevated at all levels of P_{osm} but simply at some level under 275 mOsm/kg H_2O , since in patients with a reset osmostat, AVP secretion can be suppressed at some level of osmolality resulting in maximal urinary dilution and free water excretion at plasma osmolalities below this level¹⁸. Although some consider a reset osmostat to be a separate disorder rather than a variant of SIADH, such cases nonetheless illustrate that some hypoosmolar patients can exhibit an appropriately dilute urine at some, though not all, plasma osmolalities. Third, clinical euvolemia must be present to diagnose SIADH, and this diagnosis cannot be made in a hypovolemic or edematous patient. Importantly, this does not mean that patients with SIADH cannot become hypovolemic for other reasons, but in such cases it is impossible to diagnose the underlying SIADH until the patient is rendered euvolemic. The fourth criterion, renal salt wasting, has probably caused the most confusion regarding SIADH. As noted above, the importance of this criterion lies in its usefulness in differentiating hypoosmolality caused by a decreased effective intravascular volume in which case renal Na^+ conservation occurs, from dilutional disorders in which urine Na^+ excretion is normal or increased due to ECF volume expansion. However, U_{Na} can also be high in renal causes of solute depletion such as diuretic use or Addison's disease, and conversely patients with SIADH can have a low U_{Na+} if they subsequently become hypovolemic or solute depleted, conditions sometimes produced by imposed salt and water restriction. Consequently, although high urinary Na^+ excretion is generally the rule in most patients with SIADH, its presence does not necessarily confirm this diagnosis, nor does its absence rule out the diagnosis. The final criterion emphasizes that SIADH remains a diagnosis of exclusion, and the absence of other potential causes of hypoosmolality must always be verified. Glucocorticoid deficiency and SIADH can be especially difficult to distinguish, since either primary or secondary hypocortisolism can cause elevated plasma AVP levels and in addition has direct renal effects to prevent maximal urinary dilution¹⁹. Therefore, no patient with chronic hyponatremia should be diagnosed as having SIADH without a thorough evaluation of adrenal function, preferably via a rapid corticotropin (ACTH) stimulation test (acute hyponatremia of obvious etiology, such as postoperatively or in association with pneumonitis, may be treated without adrenal testing as long as there are no other clinical signs or symptoms suggestive of adrenal dysfunction)²⁰.

Hyponatremia is a particularly common complication in elderly hospitalized patients, increasing in prevalence from approximately 7% in the general older population to 18-22% among elderly patients in chronic care facilities²¹. Despite the many known causes of SIADH (fig. 1), hyponatremia is often associated with idiopathic SIADH in the elderly population. In a study of 119 nursing home residents aged

60-103 years, 53% had at least one episode of hyponatremia during the previous 12 months²². Of these patients, 26% were diagnosed with idiopathic SIADH. In another study of elderly patients with hyponatremia and SIADH, 60% were diagnosed as idiopathic SIADH. Among remaining patients, the two main causes identified were pneumonia (9 cases/18%) and medications (6 cases/12%)²³. Therefore, more than half of elderly patients who present with hyponatremia due to SIADH may have an idiopathic form, with no detectable underlying treatable disease.

Selection of candidates for treatment of hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion

Correction of hyponatremia is associated with markedly improved neurological outcomes in patients with severely symptomatic hyponatremia. In a retrospective review of patients who presented with severe neurological symptoms and serum $[Na^+] < 125$ mmol/L, prompt therapy with isotonic or hypertonic saline resulted in a correction in the range of 20 mmol/L over several days and neurological recovery in almost all cases. In contrast, in patients who were treated with fluid restriction alone, there was very little correction over the study period (< 5 mmol/L over 72h), and the neurological outcomes were much worse, with most of these patients either dying or entering a persistently vegetative state²⁴. Consequently, prompt therapy to rapidly increase the serum $[Na^+]$ represents the standard-of-care for treatment of patients presenting with severe life-threatening symptoms of hyponatremia

As discussed earlier, chronic hyponatremia is much less symptomatic because of the process of brain volume regulation. Because of this adaptation process, chronic hyponatremia is arguably a condition that clinicians feel they may not need to be as concerned about, and in some publications this has been called "asymptomatic hyponatremia". However, such patients often do have neurological symptoms, even if milder and more subtle in nature, including headaches, nausea, mood disturbances, depression, difficulty concentrating, slowed reaction times, unstable gait, increased falls, confusion, and disorientation. Consequently, any patient with hyponatremia secondary to SIADH who manifests any neurological symptoms that could be related to the hyponatremia should be considered as appropriate candidates for treatment of the hyponatremia, regardless of their level of serum $[Na^+]$.

Current therapies for managing syndrome of inappropriate antidiuretic hormone secretion in hospitalized patients

Conventional management strategies for euvolemic hyponatremia range from saline infusion and fluid restriction to pharmacologic adjustment of fluid balance. Consideration of treatment options should include an evaluation of the benefits as well as the potential toxicities of any therapy (table 2). Sometimes, simply stopping treatment with an

Table 2 Therapeutic options for the management of hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion

Therapy	Targets underlying pathophysiology	Limitations
Isotonic saline		Ineffective in dilutional hyponatremias; can't be used in edema-forming disorders; no controlled safety database
Hypertonic saline		No consensus regarding appropriate infusion rates; overcorrection can cause osmotic demyelination; can't be used in edema-forming disorders; no controlled safety database
Fluid restriction		Slow to correct over many days; poorly tolerated due to thirst; can't be used effectively in patients with high AVP levels and urine osmolalities
Demeclocycline	✓	Not FDA or EMA approved for hyponatremia; slow to correct; nephrotoxic in cirrhosis and heart failure
Mineralocorticoids		Only one report in elderly patients with SIADH; no safety database; cannot be used in edema-forming disorders
Urea		Not FDA or EMA approved for hyponatremia; poor palatability
AVP receptor antagonists (vaptans)	✓	Conivaptan approved only for in-hospital use secondary to CYP3A4 inhibition; infusion-site reactions with intravenous use. Tolvaptan must be initiated and reinitiated in the hospital, as serum sodium needs to be monitored closely to avoid overly rapid correction of hyponatremia

AVP: arginine vasopressin; CYP3A4: cytochrome P450 3A4; EMA: European Medicines Agency; FDA: Food and Drug Administration; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

agent that is associated with causing hyponatremia is sufficient to reverse a low serum $[Na^+]$.

- *Isotonic saline.* The treatment of choice for depletional hyponatremia (i.e., hypovolemic hyponatremia) is isotonic saline ($[Na^+] = 154 \text{ mmol/L}$) to restore ECF volume and ensure adequate organ perfusion. This initial therapy is appropriate for patients who either have clinical signs of hypovolemia, or in whom a spot U_{Na^+} is $< 30 \text{ mmol/L}$. However, this therapy is ineffective for dilutional hyponatremias such as SIADH²⁵, and continued inappropriate administration of isotonic saline to a euvolemic patient may worsen their hyponatremia²⁶, and/or cause fluid overload.
- *Hypertonic saline.* Acute hyponatremia presenting with severe neurological symptoms is life-threatening, and should be treated promptly with hypertonic solutions, typically 3% sodium chloride (NaCl) ($[Na^+] = 513 \text{ mmol/L}$), as this represents the most reliable method to quickly raise the serum $[Na^+]$. A continuous infusion of hypertonic NaCl is usually utilized in inpatient settings. Various formulae have been suggested for calculating the initial rate of infusion of hypertonic solutions²⁷, but perhaps the simplest utilizes the following relationship:

$$\text{Patient's weight (kg)} \times \text{desired correction rate (mmol/L/h)} = \text{infusion rate of 3\% NaCl (mL/h)}$$

Depending on individual hospital policies, the administration of hypertonic solutions may require special considerations (e.g., placement in the ICU, sign-off by a consultant, etc.), which each clinician needs to be aware of in order to optimize patient care.

An alternative option for more emergent situations is administration of a 100 mL bolus of 3% NaCl, repeated X1 if no clinical improvement, which has been recommended by a consensus conference organized to develop guidelines for prevention and treatment of exercise-induced hyponatremia, an acute and potentially lethal condition²⁸. Injecting this amount of hypertonic saline intravenously raises the serum $[Na^+]$ by an average of 2-4 mmol/L, which is well below the recommended maximal daily rate of change of 10-12 mmol/24 h or 18 mmol/48 h²⁹. Because the brain can only accommodate an average increase of approximately 8% in brain volume before herniation occurs, quickly increasing the serum $[Na^+]$ by as little as 2-4 mmol/L in acute hyponatremia can effectively reduce brain swelling and intracranial pressure³⁰.

Unfortunately, until now there has been no consensus regarding appropriate infusion rates of 3% NaCl, and many physicians are hesitant to use in patients with chronic hyponatremia because it can cause an overly rapid correction of serum sodium concentrations that can lead to the osmotic demyelination syndrome (ODS)³¹. Nonetheless, this remains the treatment of choice for patients with severe neurological symptoms. The administration of hypertonic saline is generally not recommended for most patients with edema-forming disorders because it acts as a volume expander and may exacerbate volume overload.

- *Fluid restriction.* For patients with chronic hyponatremia, fluid restriction has been the most popular and most widely accepted treatment. When SIADH is present, generally fluids should be limited to 500-1,000 mL/24 h. Because fluid restriction increases the serum $[Na^+]$ by

under-replacing the excretion of fluid by the kidneys, some have advocated an initial restriction to 500 ml less than the 24-hour urine output³². When instituting a fluid restriction, it is important for the nursing staff and the patient to understand that this includes all fluids that are consumed, not just water. Generally the water content of ingested food is not included in the restriction because this is balanced by insensible water losses (perspiration, exhaled air, feces, etc.). Restricting fluid intake is effective when properly applied and managed, but serum sodium concentrations are increased only slowly (1-2 mmol/L/d) even with severe restriction²⁵. In addition, this therapy is often poorly tolerated because of an associated increase in thirst. However, it is economically favorable, and some patients do respond well to this option. Fluid restriction should not be used with hypovolemic patients, and is particularly difficult to maintain in patients with very elevated urine osmolalities secondary to high AVP levels; in general, if the sum of urine Na⁺ and K⁺ exceeds the serum [Na⁺], most patients will not respond to a fluid restriction³³, and in patients in intensive care settings who often require administration of fluids as part of their therapies.

- *Demeclocycline*. Demeclocycline, a tetracycline antibiotic, inhibits adenylyl cyclase activation after AVP binds to its V2 receptor in the kidney, and thus targets the underlying pathophysiology of SIADH. This therapy is typically used when patients find severe fluid restriction unacceptable and the underlying disorder cannot be corrected. However, demeclocycline is not approved by the United States (US) Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to treat hyponatremia, and can cause significant nephrotoxicity in patients with heart failure and cirrhosis³⁴.
- *Mineralocorticoids*. Administration of mineralocorticoids, such as fludrocortisone, has been shown to be useful in a small number of elderly patients³⁵. However, the initial studies of SIADH did not show it to be of benefit in patients with SIADH, and it carries the risk of fluid overload and hypertension. Consequently, it is rarely used to treat hyponatremia.
- *Urea*. Administration of urea has been successfully used to treat hyponatremia because it induces osmotic diuresis and augments free water excretion. Effective doses of urea for treatment of hyponatremia are 30-60 g daily in divided doses³⁶. Unfortunately, its use is limited because there is no United States Pharmacopeia (USP) formulation for urea, and it is not approved by the FDA or EMA for treatment of hyponatremia. As such, urea has not been used extensively, and there are limited data to support its long-term use. Furthermore, urea is associated with poor palatability; however, patients with feeding tubes may be excellent candidates for urea therapy since palatability is not a concern, and the use of fluid restriction may be difficult in some patients with high obligate intake of fluids as part of their nutritional and medication therapy.

Clinicians have used all of the above conventional therapies for hyponatremia over the past decades. However, conventional therapies for hyponatremia, although effective in specific circumstances, are suboptimal for many different

reasons, including variable efficacy, slow responses, intolerable side effects, and serious toxicities, as summarized in table 2. But perhaps the most striking deficiency of most conventional therapies is that with the exception of demeclocycline, these therapies do not directly target the underlying cause of most all dilutional hyponatremias, namely inappropriately elevated plasma AVP levels. A new class of pharmacological agents, vasopressin receptor antagonists, that directly block AVP-mediated receptor activation have recently been approved by the FDA and EMA for treatment of euvolemic and hypervolemic hyponatremia³⁷.

- *Arginine vasopressin receptor (AVPR) antagonists*. Conivaptan and tolvaptan are antagonists of the AVP V2 (antidiuretic) receptor and have been approved by the FDA for the treatment of euvolemic and hypervolemic hyponatremia in the United States. Tolvaptan has also recently been approved by the European Medicines Agency (EMA) for treatment of hyponatremia due to SIADH in the European Union. These agents, also known as “vaptans,” compete with AVP/ADH for binding at its site of action in the kidney, thereby blocking the antidiuresis caused by elevated AVP levels and directly attacking the underlying pathophysiology of dilutional hyponatremia. AVPR antagonists produce electrolyte free water excretion (called “aquaresis”) without significantly affecting renal sodium and potassium excretion³⁸. The overall result is a reduction in body water without natriuresis, which leads to an increase in the serum [Na⁺]. One of the major benefits of this class of drugs is that serum [Na⁺] is significantly increased within 24-48 hours^{39,40}, which is considerably faster than the effects of fluid restriction that can take many days. Also, compliance has not been shown to be a problem for vaptans, whereas this is a major problem with attempted long-term use of fluid restriction. Because only tolvaptan has been approved for use in European Union countries, only this agent will be discussed in this review.

Tolvaptan is approved for treatment of dilutional hyponatremia caused by SIADH. Because it is administered orally, it can be used for both short- and long-term treatment of hyponatremia⁴⁰. Tolvaptan treatment must be initiated in the hospital so that the rate of correction can be monitored carefully. Patients with a serum [Na⁺] < 135 mmol/L are eligible for therapy with tolvaptan as primary therapy for hyponatremia. The starting dose of tolvaptan is 15 mg on the first day, and the dose can be titrated to 30 mg and 60 mg at 24 hr intervals if the serum [Na⁺] remains < 135 mmol/L or the increase in serum [Na⁺] has been ≤ 5 mmol/L in the previous 24 hrs⁴¹. Importantly, it is critical that the serum [Na⁺] concentration is measured frequently during the active phase of correction of the hyponatremia (a minimum of every 8 hrs, but more frequently in patients with risk factors for development of osmotic demyelination, such as severely low serum [Na⁺], malnutrition, alcoholism and hypokalemia)⁴². If the correction approaches 12 mmol/L in the first 24 hrs, the drug should be stopped and the patient monitored on a fluid restriction. If the correction exceeds 12 mmol/L, consideration should be given to administering sufficient water, either orally or as intravenous D₅W (5% dextrose in water) to bring the overall correction below 12 mmol/L.

The maximum correction limit should be reduced to 8 mmol/L in patients with risk factors for development of osmotic demyelination. Common side effects include dry mouth, thirst, increased urinary frequency, dizziness, nausea and orthostatic hypotension, most of which were relatively similar between placebo and tolvaptan groups in clinical trials^{40,41}.

General principles of treatment of syndrome of inappropriate antidiuretic hormone secretion in hospitalized patients

In all severely hyponatremic patients (i.e., serum $[\text{Na}^+] < 125$ mmol/L) neurological symptomatology should be carefully assessed very early in the diagnostic evaluation to assess the severity of the hyponatremia and to determine whether the patient requires more urgent therapy. All patients undergoing treatment for hyponatremia should have frequent monitoring of serum $[\text{Na}^+]$ and ECF volume status to ensure that the serum $[\text{Na}^+]$ does not exceed the recommended levels during the active phase of correction⁴², since overly rapid correction of serum sodium can cause damage to the myelin sheath of nerve cells, resulting in central pontine myelinolysis, also called the osmotic demyelination syndrome (ODS)³¹. Active treatment should be stopped when the patient's symptoms are no longer present, a safe serum sodium concentration (usually $[\text{Na}^+] > 120$ mmol/L) has been achieved, or the rate of correction has reached 12 mmol/L within 24 hours or 18 mmol/L within 48 hours^{29,42}. Importantly, ODS has not been reported either in clinical trials or with therapeutic use of any vaptan. Because inducing increased renal fluid excretion via either a diuresis or an aquaresis can cause or worsen hypotension in patients with hypovolemic hyponatremia, vaptans are contraindicated in this patient population⁴². However, clinically significant hypotension was not observed in the tolvaptan clinical trials in euvoletic and hypervolemic hyponatremic patients. Although tolvaptan are not contraindicated with decreased renal function, it generally will not be effective if the serum creatinine is > 2.5 mg/dl.

Hyponatremia treatment guidelines for hospitalized patients with syndrome of inappropriate antidiuretic hormone secretion

Although various authors have published recommendations on the treatment of hyponatremia^{17,27,42-44}, no standardized treatment algorithms have yet been widely accepted. A synthesis of existing expert recommendations for treatment of hyponatremia is illustrated in figure 2. Importantly, this algorithm is based primarily on the symptomatology of hyponatremic patients, rather than the serum $[\text{Na}^+]$ or the chronicity of the hyponatremia, which is often difficult to ascertain. In this model, patients are divided into 3 groups based on their presenting symptoms.

– Level 1 symptoms include seizures, coma, respiratory arrest, obtundation, and vomiting, and usually imply a

more acute onset or worsening of hyponatremia requiring immediate active treatment. Therapies that will quickly raise serum sodium levels are required to reduce cerebral edema and decrease the risk of potentially fatal herniation.

- Level 2 symptoms, which are more moderate, include nausea, confusion, disorientation, and altered mental status. These symptoms may be either chronic or acute, but allow time to elaborate a more deliberate approach to treatment.
- Level 3 symptoms range from minimal symptoms such as a headache, irritability, inability to concentrate, altered mood, and depression, to a virtual absence of discernable symptoms, and indicate that the patient may have chronic or slowly evolving hyponatremia. These symptoms necessitate a cautious approach, especially when patients have underlying co-morbidities.

Patients with severe symptoms (Level 1) should be treated with hypertonic saline as first-line therapy, followed by fluid restriction with or without vasopressin receptor antagonist therapy. Patients with moderate symptoms will benefit from a more aggressive regimen of vaptan therapy or limited hypertonic saline administration, followed by fluid restriction or long-term vaptan therapy. Although moderate neurological symptoms can indicate that a patient is in an early stage of acute hyponatremia, they typically indicate a chronically hyponatremic state with sufficient brain volume adaptation to prevent marked symptomatology from cerebral edema. However, close monitoring of these patients in a hospital setting is warranted until the symptoms improve or stabilize. Patients with no or minimal symptoms should be managed initially with fluid restriction, although treatment with vaptans may be appropriate for a wide range of specific clinical conditions, foremost of which is a failure to improve the serum $[\text{Na}^+]$ despite reasonable attempts at fluid restriction (fig. 2).

Transitioning to chronic treatment of hyponatremia

Some patients will benefit from continued treatment of hyponatremia following discharge from the hospital. In many cases, this will consist of a continued fluid restriction. However, as discussed previously, long-term compliance with this therapy is poor due to the increased thirst that occurs with more severe degrees of fluid restriction. Thus, for selected patients who have responded to tolvaptan in the hospital, consideration should be given to continuing the treatment as an outpatient after discharge. In patients with established chronic hyponatremia, tolvaptan has shown to be effective at maintaining a normal $[\text{Na}^+]$ for as long as 3 years of continued daily therapy⁴⁵. However, many patients with inpatient hyponatremia will have a transient form of SIADH without need for long term therapy. In the conivaptan open-label study, approximately 70% of patients treated as an inpatient for 4 days had normal serum $[\text{Na}^+]$ concentrations 7 and 30 days after cessation of the vaptan therapy in the absence of chronic therapy for hyponatremia. Selection of which patients with inpatient hyponatremia are candidates for long-term therapy should be based on the etiology of the

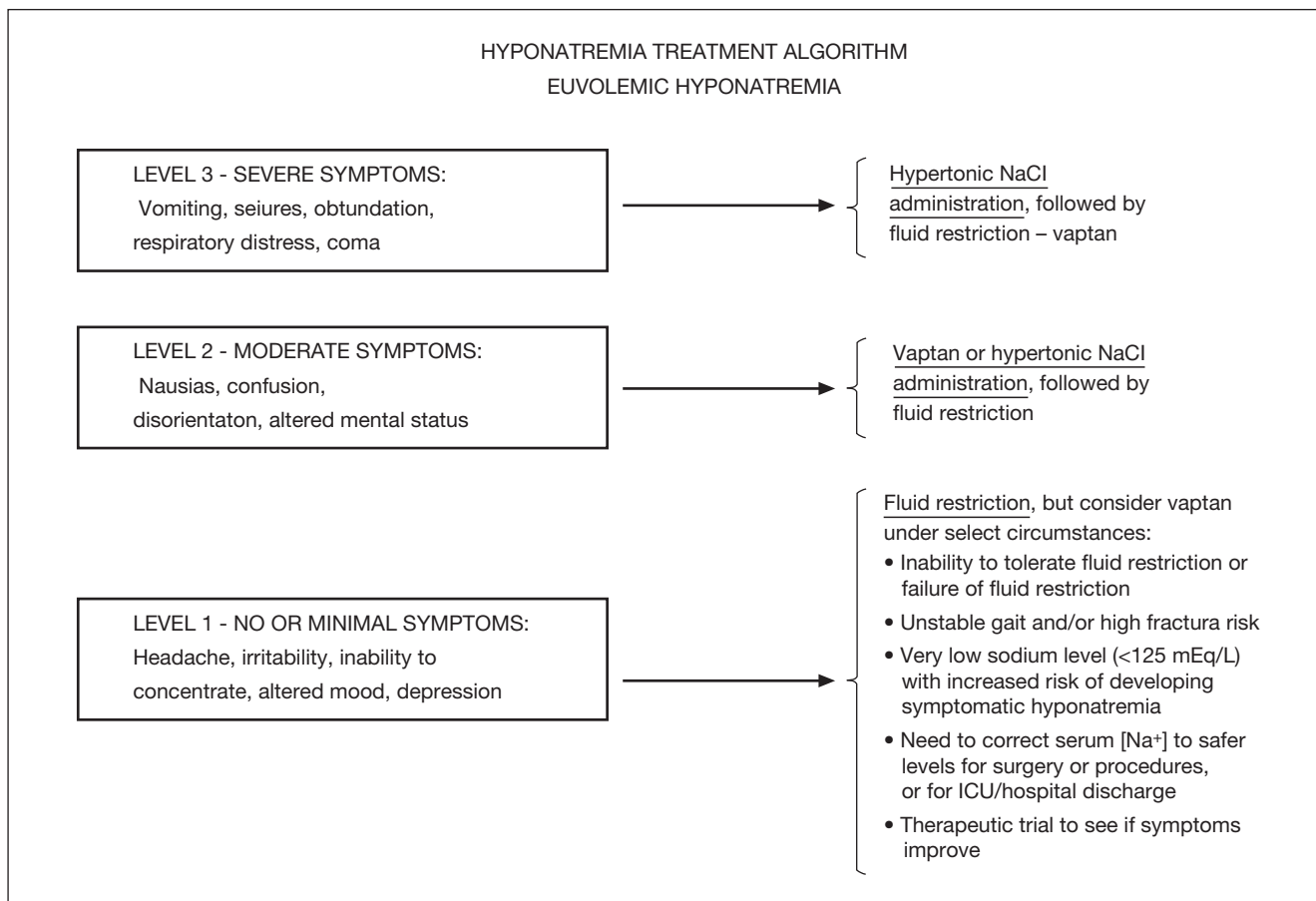


Figure 2 Algorithm for treating patients with euvolemic hyponatremia. NaCl: sodium chloride.

Table 3 Probability of need for long-term treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH) depending on underlying etiology

Etiology of SIADH	Likely duration of SIADH	Relative risk of chronic SIADH
Tumors producing AVP ectopically (small-cell lung carcinoma, head and neck carcinoma)	indefinite	1.0
Drug-induced, with continuation of offending agent (carbamazepine, SSRI)	duration of drug therapy	1.0
Subarachnoid hemorrhage	1-4 weeks	0.8
Brain tumors	indefinitely	0.8
Idiopathic (senile)	indefinitely	0.6
CVA	1-2 weeks	0.5
Respiratory failure (chronic obstructive lung disease)	dependent on response to therapy	0.5
Inflammatory brain lesions	dependent on response to therapy	0.4
HIV infection	dependent on response to therapy	0.2
Traumatic brain injury	0.5-2 years	0.2
Nausea, pain, prolonged exercise	variable depending on cause	0.1
Post-operative hyponatremia	2-3 days postoperatively	0
Drug-induced, with cessation of offending agent	duration of drug therapy	0
Pneumonia	2-5 days	0

AVP: arginine vasopressin; CVA: cardiovascular accident; HIV: human immunodeficiency virus; SIADH: syndrome of inappropriate antidiuretic hormone secretion; SSRI: selective serotonin reuptake inhibitors.

SIADH. Table 3 shows estimates of the relative probability that patients with different causes of SIADH will have persistent hyponatremia that may benefit from long-term treatment with tolvaptan following discharge from the hospital based on clinical experience. Nonetheless, for any individual patient this simply represents an estimate of the likelihood of requiring long-term therapy. In all cases, consideration should be given to a trial of stopping the drug 2-4 weeks following discharge to see if hyponatremia is still present. A reasonable period of tolvaptan cessation to evaluate the presence of continued SIADH is 7 days, since this period was sufficient for demonstration of a recurrence of hyponatremia in the tolvaptan SALT (Study of Ascending Levels of Tolvaptan) trials^{40,45}. Serum $[Na^+]$ should be monitored every 2-3 days following cessation of tolvaptan so that the drug can be resumed as quickly as possible in those patients with recurrent hyponatremia, since the longer the patient is hyponatremic the greater the risk of subsequent osmotic demyelination with overly rapid correction of the low $[Na^+]$.

Potential future indications for treatment of hyponatremia

Correction of hyponatremia improves other symptoms, such as gait stability, in patients who may be considered to be "asymptomatic" by virtue of a normal neurological exam. In one study, 16 patients with hyponatremia secondary to SIADH in the range of 124-130 mmol/L demonstrated a significant gait instability that normalized after correction of the hyponatremia to normal ranges⁴⁶. The functional significance of the gait instability was illustrated in a study of 122 Belgian patients with a variety of levels of hyponatremia, all judged to be "asymptomatic" at the time of visit to an emergency department (ED). These patients were compared with 244 age-, sex-, and disease-matched controls also presenting to the emergency department during the same time period. Researchers found that 21% of the hyponatremic patients presented to the ED because of a recent fall, compared to only 5% of the controls, resulting in an adjusted odds ratio for presenting to the ED because of a recent fall of 67 for hyponatremia ($p < 0.001$)⁴⁶. Consequently, this study clearly documented an increased incidence of falls in so-called "asymptomatic" hyponatremic patients.

The clinical significance of the gait instability and fall data was further evaluated in a study that compared 553 patients with fractures to an equal number of age- and sex-matched controls. Hyponatremia was found in 13% of the patients presenting with fractures compared to only 4% of the controls⁴⁷. Similar findings have been reported in a 364 elderly patients with large-bone fractures in New York⁴⁸ and 1,408 female patients with chronic renal failure in Ireland⁴⁹. More recently published studies have shown that hyponatremia is associated with increased bone loss in experimental animals and a significant increased odds ratio for osteoporosis of the femoral neck (OR, 2.87; $p < 0.003$) in humans over the age of 50 in the NHANES (National Health and Nutrition Examination Survey) III database⁵⁰. Thus, the true clinical significance of chronic hyponatremia may be the increased morbidity and mortality associated with falls and fractures in our elderly population.

Conflict of interests

The author declares he is a consultant to Astellas, Cardio-kinine and Otsuka Pharma, and has served on Advisory Boards for each of these companies regarding their vasopressin antagonist drug development programs.

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