Hyponatremia: basic concepts and practical approach

Hiponatremia: conceitos básicos e abordagem prática

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Abstract

Hyponatremia is the most common electrolyte imbalance in hospitalized patients. It is associated with several unfavorable endpoints such as: the need for intensive care, longer hospital stay, higher hospitalization costs, discharge to long-term care facilities, and mortality. It is still not clear if there is a direct causal relationship or if hyponatremia is simply a marker of disease severity. Nevertheless, it is quite clear that improper management of a hyponatremic patient may result in severe neurologic damage or death. This paper addresses the basic pathophysiologic concepts about hyponatremia followed by a practical approach to its diagnosis and management.

Keywords: hyponatremia, inappropriate ADH syndrome, receptors, vasopressin, liver cirrhosis, heart Failure.

Resumo

Hiponatremia é o distúrbio hidroeletrolítico mais comum em pacientes hospitalizados. A presença de hiponatremia está associada a uma série de desfechos desfavoráveis, tais como: necessidade de internamento em unidade de terapia intensiva, hospitalização prolongada e de maior custo, transferência para abrigos e mortalidade. Ainda não está claro se existe relação de causalidade direta ou se a hiponatremia é apenas um marcador de gravidade da doença de base. No entanto, sabe-se que o manejo inadequado de um paciente hiponatrêmico pode causar graves danos neurológicos ou até mesmo a morte. Neste manuscrito, os conceitos básicos sobre a fisiopatologia da hiponatremia serão revisados, seguido de uma abordagem prática sobre sua investigação e tratamento.

Palavras-chave: hiponatremia, síndrome de secreção inadequada de HAD, receptores de vasopressina, Cirrose Hepática, Insuficiência Cardíaca.

Submitted on: 02/04/2011
Accepted on: 20/04/2011

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The author declares no conflict of interest.

Case report

A sixty-year-old white female, recently diagnosed with glioblastoma multiforme and treated with temozolomide, presented to the oncologist's office complaining of drowsiness. Laboratory tests were normal, except for [Na+] = 115 meq/L (Reference: 135 to 145 meq/L). Since she had been hospitalized three times over the past two months for management of hyponatremia, her oncologist decided to request a Nephrology consult during this admission. The patient was taking escitalopram for approximately one month because the drowsiness had been interpreted as a sign of depression. She denied using diuretics or other medications. Physical examination showed no fever, blood pressure of 120/80 mmHg, heart rate of 80/bpm, no postural changes, weight 50 kg (110 lb). Clinical examination was normal, except for the

drowsiness. The patient had no edema. Laboratory studies revealed: normal blood glucose, lipid profile, total proteins and fractions, renal, adrenal and thyroid function. Urinary osmolality was 600 mOsm/L, and urinary sodium was 80 mmol/L.

Definition

Hyponatremia can be defined as a serum sodium concentration [Na+] below the inferior limit of the reference range; for most laboratories, this means [Na+] < 135 meq/L,[1] but [Na+] < 136 meq/L is commonly used as well.[2]

In a recent Canadian study with more than 53,000 patients, hyponatremia was defined as [Na+] < 138 meq/L.[3] The authors modified the reference range of serum sodium to 138 to 142 meq/L after observing that sodium levels outside this interval were associated with significantly higher in-hospital mortality rates.

Even though most authors define hyponatremia as [Na+] < 135 or 136 meq/L, the findings of this Canadian study emphasized the need for a discussion about reference values.

Epidemiology

Hyponatremia is the most common electrolyte disorder in hospitalized patients. In a study carried out in two hospitals in Boston, with approximately 100,000 adult patients, Waikar, Mount and Curhan identified hyponatremia at admission in 14.5% of the cases; when serum sodium was corrected for the glucose concentration, the frequency of hyponatremia varied between 11.8 and 12.8%, depending on which formula was used.[4] In 2010, Funk et al. analyzed approximately 150,000 patients hospitalized in 77 Intensive Care Units (ICUs) in Austria, and detected hyponatremia at admission in 17.7% of them.[5] The studies by Waikar[4] and Funk[5] used [Na+] < 135 meq/L to define hyponatremia. In the aforementioned Canadian study, which defined hyponatremia as [Na+] < 138 meq/L, the frequencies of this disorder identified at admission and acquired during hospital stay were much higher: 37.9% and 38.2%, respectively.[3]

In patients with advanced cirrhosis awaiting liver transplantation, the prevalence of hyponatremia may exceed 30%. It was demonstrated that the use of serum sodium to adjust the MELD score {MELDNa = MELD – NA – [0,025 x MELD x (140 – Na)] + 140} improves the ability to predict mortality in these patients and, consequently, the criteria for transplant allocation.[6]

Hyponatremia is associated with a series of unfavorable endpoints, such as longer hospital stay[3], need for ICU admission,[4] higher costs of hospitalization[7] and higher mortality.[3,5] The association of hyponatremia with increased mortality rates is rather consistent, whether it was acquired in the community, in the hospital or in the ICU. The association persists when analyzed in specific subgroups of diseases, such as neoplasms, congestive heart failure (CHF) and cirrhosis. More recently, hyponatremia was associated with increased mortality in chronic kidney disease patients on hemodialysis.[8]

Although the strength of these associations increases with the severity of hyponatremia, a direct cause-effect relationship cannot be established; it is also unclear if the correction of hyponatremia may reverse the described associations. In Waikar, Mount and Curhan's study, hyponatremias that resolved during hospital stay were associated with lower mortality rates than hyponatremias that persisted or were acquired during hospitalization.[4] However, the observational design of this study does not provide a definite response. Well conducted prospective studies in CHF patients showed that correction of hyponatremia with Tolvaptan, a V2 receptor antagonist, did not reduce hospital admissions for heart failure nor mortality rates due to cardiovascular diseases or other causes.[9]

Physiopathology

From the mathematics point of view, serum sodium concentration is a fraction expressed in milliequivalents of sodium per liter of water, as described in Formula 1:

$$[Na+] = \frac{\text{Milliequivalents of sodium}}{\text{liters of water}}$$

Since there is also a small participation of potassium in the determination of the serum sodium concentration, it would be more appropriate to express such concentration like this (Formula 2):

$$[Na+] = \frac{\text{Total body exchangeable (sodium + potassium) content}}{\text{Total bodywater}}$$

In certain situations, as it will be later discussed in this paper, the administration of potassium chloride to a hyponatremic patient may result in a clinically relevant increase in the serum sodium concentration.[10] This fact is recognized by the most

recent formulas for hyponatremia correction, such as Adrogué and Madias's.[2] However, to simplify, we may continue to think about the concentration of sodium as a function of total body sodium divided by total body water.

Because it is a fraction, the result may be altered by changes in the numerator (total body sodium) or in the denominator (plasma water in which the sodium is dissolved). Hence, hyponatremia may be the result of any of the situations shown in Table 1. This clarifies that, except for the hypovolemic situation, hyponatremia is caused by an increase in plasma water (denominator), and not by a reduction in total body sodium (numerator). One may notice that even in hypovolemic hyponatremia there is a relative excess of water in relation to total sodium. The conclusion is that hyponatremia should be interpreted as a disorder of water excess rather than sodium deficit.

Table 1 Combinations that may cause hyponatremia

ECF volume (volemia)	Total body sodium	Total body water
Reduced	↓↓	↓
Normal	Normal	↑
Increased	↑	↑↑

ECF: extracellular fluid.

What is the body's physiological response to a water excess?

Water excess results in dilution of serum sodium and hyponatremia. Since the serum sodium concentration is the main determining factor of serum osmolality, true hyponatremia is accompanied by hypoosmolality (Formula 3).

$$\text{Calculated serum osmolarity}$$

$$2 \times [Na^+](meq/L) + \frac{Glucose\,(mg/dL)}{18} + \frac{BUN\,(mg/dL)}{2.8}$$

In a hypothetical example, in which [Na+] = 140 meq/L, glucose = 90 mg/dL, and BUN = 14 mg/dL, the calculated serum osmolality is 290 mosm/L. In this case, the concentration of serum sodium contributes with 280 mosm/L, while the sum of glucose and BUN contributes with only 10 mosm/L.

In the presence of hypoosmolality, antidiuretic hormone secretion (ADH) is suppressed. Without ADH, collecting ducts are impermeable to water, resulting in the excretion of a great quantity of dilute urine and elimination of excess water (Table 2).

How much water can the kidneys excrete?

With adequate solute ingestion, an adult needs to excrete 600 to 900 mosm of solutes, mostly sodium, potassium and urea salts. Considering an ingestion of water capable of completely inhibiting ADH secretion,

Table 2 Water metabolism (osmoregulation) *versus* sodium metabolism (volume regulation)

	Water metabolism	Sodium metabolism
What is sensed	Osmolality	ECV
Sensors	Osmoreceptors	Baroreceptors
Effectors	Thirst, ADH	ANP, RAAS, Catecholamines, ADH
Response	Excretion or retention of water	Excretion or retention of sodium, changes in cardiac output and vascular tone
Marker	Serum sodium	Urinary sodium

1) Dysnatremias are the result of disorders of water metabolism. Water deficit causes hypernatremia and hyperosmolality. Hyperosmolality is sensed by hypothalamic osmoreceptors, leading to thirst and ADH secretion. Ingested water is conserved and water deficit is corrected. In hyponatremia, the problem is excess water; the response involves suppression of thirst and ADH secretion. Hyponatremia may be identified in situations of hypovolemia, euvolemia or hypervolemia; therefore, volume status cannot be inferred from the serum sodium concentration. 2) Disorders of volume status are the result of changes in total body sodium content. When ECV is increased (for example, due to administration of normal saline to a previously euvolemic patient), two phenomena concur to increase renal excretion of sodium and correct the excessive volume: ANP secretion in response to distension of cardiac mechanoreceptors and pressure natriuresis. With ECV reduction, baroreceptors initially trigger a vasopressor response, with catecholamine secretion. Subsequently, RAAS activation promotes renal sodium retention. Baroreceptor-induced ADH secretion causes water retention, which explains why patients with reduced ECV are prone to hyponatremia.

ADH: antidiuretic hormone; ECV: effective circulating volume; ANP: atrial natriuretic peptide; RAAS: rennin-angiotensin-aldosterone system.

urine osmolality may decrease to 50 mosm/L. An individual who needs to excrete 800 mosm of solute in urine with such a degree of dilution will do so in 16L of urine (800 ÷ 50). So, if the renal capacity to excrete water is maintained, a person would need to ingest more than 16L of water to develop hyponatremia.

But why don't the kidneys of hyponatremic patients excrete the water excess?

Non-osmotic vasopressin secretion

When vasopressin (ADH) binds to its receptors in the collecting ducts (V2), it promotes the synthesis and phosphorylation of aquaporins – these are proteins that can insert pores in the membrane of the tubular cell, making it water-permeable.[11-13] This allows the reabsorption of water towards the medullary interstium following an osmotic gradient and, consequently, the generation of a concentrated urine. ADH is typically secreted in response to water deficit and hyperosmolality (Table 2), to retain the ingested water and correct this deficit. However, there are other stimuli for its secretion. The most common is reduced effective circulating volume (ECV); in this setting, ADH secretion is mediated by underperfused baroreceptors. This is the operating factor in both hypovolemic and "hypervolemic" hyponatremia; although edematous patients have increased extra-cellular volume, the ECV is reduced and baroreceptors unloaded. Non-osmotic ADH release may also occur in response to pain and nausea, which are common symptoms in postoperative patients.[14,15] Finally, some drugs and tumors may cause inappropriate secretion of ADH (SIADH).[16] Box 1 summarizes the different stimuli involved in ADH secretion.

In daily clinical practice, serum ADH is not measured but its presence can be inferred from a simple analysis of the urine. Concentrated urine (urine density > 1005 and urine osmolality > 100 mosm/kg) suggests the presence of ADH.

Reduction in glomerular filtration rate

Patients with acute kidney injury or chronic renal disease present a global reduction in their capacity to excrete water and solutes. They may develop edema and/or hypertension if challenged with an excess of salt; similarly, they may develop hyponatremia if challenged with large amounts of hypotonic fluids.

Mutations in the V2 vasopressin receptor gene

The clinical picture is identical to that of SIADH (euvolemic hypotonic hyponatremia with concentrated urine) but ADH serum levels are undetectable. This condition, which has been termed nephrogenic syndrome of inappropriate antidiuresis, is the result of mutant V2 receptors that are constitutively active.[17]

Particular situation: low ingestion of solutes

An illustrative clinical scenario would be that of an individual who spends the day drinking beer. Beer has very low quantities of salt, potassium and proteins. Because of its glucose content, beer not only reduces hunger, but also minimizes protein catabolism. In this scenario, it is possible that this individual may produce a very low amount of solute to be excreted, for example, 250 mosm. Now, even with maximally dilute urine (urine osmolality = 50 mosm/L), the capacity to excrete free water falls to 5L (250 ÷ 50). If the ingestion of fluids surpasses 5L, the person may develop hyponatremia.

Box 1 Stimuli for ADH secretion

Osmotic ADH secretion: with dehydration, the increase in serum osmolality is detected by osmoreceptors, which inflict two responses to correct this deficit: thirst and ADH secretion so that ingested water can be retained.

Non-osmotic ADH secretion, baroreceptor stimulus: with the reduction in effective circulating volume, unloaded arterial baroreceptors activate several neurohormonal systems, aiming at the correction of volume status and maintenance of tissue perfusion. ADH secretion is a key component of this response. When a patient with ECV reduction receives hypotonic fluids, volume status is not restored, ADH remains high, the ingested water is not excreted and the patient develops hyponatremia. If isotonic fluids are use and volume status is restored, ADH levels decrease, the excess water excreted, and the serum sodium concentration returns to normal.

Non-osmotic ADH secretion, pain or nausea: these stimuli for ADH secretion are commonly found in the postoperative period. In this situation, administration of hypotonic fluids leads to hyponatremia.

Inappropriate ADH secretion (SIADH): ADH secretion occurs without a justifiable physiological stimulus (such as hyperosmolality, ECV reduction, pain, nausea). The ingestion of hypotonic fluids leads to hyponatremia.

This situation, known as beer potomania,[18,19] illustrates how the low ingestion of solutes may reduce the ability to excrete free water and facilitate the development of hyponatremia. This is a peculiar situation, since dilute urine suggests that the renal ability to excrete water is maintained. Although beer potomania (as it was originally described) is relatively rare, it is representative of common clinical situations, such as: elderly people whose eating habits are based on tea and toasts ("tea and toast" disease), and hospitalized patients submitted to low ingestion of solutes and infusions of hypotonic fluids.[20,21]

Can there be hyponatremia if the renal ability to excrete water is maintained?

If the ingestion of water is superior to the renal ability to excrete it, the person will develop hyponatremia. In such situations, urine will be dilute, indicating that kidneys are trying to excrete excess water. As aforementioned, with the normal ingestion of solutes, the individual would have to ingest more than 10L of water to develop hyponatremia. This may happen with psychiatric patients who have psychogenic polydipsia.[22,23] However, if the ingestion of water is very acute, even smaller quantities may result in hyponatremia. Santos-Soares et al. reported the case of a previously healthy 34-year-old man who was admitted to the emergency room with seizures and [Na+] = 123 meq/L after ingesting approximately 8L of water.[24] He was playing domino with friends, and they bet that whoever missed a round should drink a glass of water (around 200 mL); he ended up losing several consecutive rounds and ingested approximately 40 glasses of water in a very brief period of time.

Analogous situations would be drowning in fresh water[25] and endoscopic surgeries, like hysteroscopy,[26] uterine curettage,[27] transurethral resection of the prostate,[28,29] in which there may be rapid absorption of large amounts of water from irrigation solutions.

In these cases, after the excessive ingestion of water stops, the kidneys excrete the excess and the serum [Na+] returns to normal. However, with severe symptomatic hyponatremia, the treatment with hypertonic saline is indicated to reduce cerebral edema.

Etiology and diagnostic investigation

When faced with a hyponatremic patient, the first step should be to rule out pseudohyponatremia. In true hyponatremia, serum osmolality is always low. If the patient is hyponatremic and serum osmolality is normal or high, he is said to have pseudohyponatremia. These situations do not represent disorders of water metabolism and therapeutic measures should not be aimed at correcting the serum sodium concentration.

Pseudohyponatremia with high serum osmolality

The most common cause of hypertonic hyponatremia is hyperglycemia, but it can also occur during the administration of hyperosmolar ionic contrast. In these cases, there is water shift from the intracellular fluid (ICF) to the extracellular fluid (ECF) in an attempt to balance the osmolality between the two spaces. The water that enters the ECF dilutes the serum sodium. When hypertonicity is reversed by the correction of hyperglycemia or renal elimination of the contrast material, serum sodium concentration is normalized. The most commonly used equation to estimate corrected serum sodium concentration in a patient with hyperglycemia was developed by Katz, in 1973 (Formula 4).[30]

$$\text{Correct sodium} = \text{Measured sodium} + \left[1{,}6 \times \left(\frac{\text{glucose}-100}{100}\right)\right]$$

More recently, Hillier, Abbott and Barrett demonstrated that a correction factor of 2.4 would be more appropriate for this estimate than 1.6.[31] Also, they demonstrated that the relation between serum glucose and serum sodium concentration is not linear; for glucose values lower than 400 mg/dL, the correction factor of 2.4 worked well, but for values higher than 400 mg/dL, a correction factor of 4.0 was better.[31]

Pseudohyponatremia with normal serum osmolality

This is classically described in hyperproteinemias, (for example, multiple myeloma) and severe dyslipidemia (for example, hypertriglyceridemia), when the aqueous plasma fraction is reduced due to the excess of proteins or lipids.[32] Such phenomenon is more common when serum sodium is measured by the flame photometry technique.[33-36]

Since serum osmolality analysis is not performed in many Brazilian hospitals and laboratories (and, when it is, the result may take a while), in practice, it is very common to rule out pseudohyponatremia based on readily available clinical and laboratory data, such as serum glucose, total proteins and fractions, and lipid profile.

If a pseudohyponatremia is ruled out, the next step is to analyze volume status. Unlike plasma osmolality, there is no single laboratory data that determines the volume status of a patient. The evaluation of volume status is typically based on several aspects of the history and physical exam, as well as laboratory studies. For ICU patients, clinical evaluation of volume status is even more complex and requires the determination of measures of preload, cardiac output or tissue perfusion.[37]

Hypovolemia

History suggests low ingestion and/or excessive skin, gastrointestinal or renal losses, while physical exam shows tachycardia and/or hypotension (spontaneous or postural). Urinary sodium is low and urine osmolality is high, demonstrating an appropriate salt and water retention in response to the true hypovolemia

Hypervolemia

History and physical examination suggest an edematous syndrome, such as CHF, cirrhosis or nephrotic syndrome. Each of these syndromes has specific signs at physical examination, but edema and weight gain are common factors. Likewise, urinary sodium is low and urine osmolality is high, but here the retention of salt and water is due to the relative hypovolemia (ECV reduction).

Euvolemia

There should be an absence of history and physical examination data suggesting hypo or hypervolemia. This group includes beer potomania, psychogenic polydipsia (since the excessive ingestion of electrolyte free water does not cause hypervolemia), endocrine alterations (hypothyroidism, primary adrenal insufficiency, hypopituitarism), SIADH (Box 2), thiazide diuretics and other drugs. Many drugs cause hyponatremia because they promote SIADH, but Magaldi et al. showed that others interfere in the ability to excrete free water due to direct effects on collecting ducts.[38-41] Gain-of-function mutations in the V2 vasopressin receptor gene are rare additional causes of euvolemic hyponatremia.

Some laboratory studies are very useful in the differential diagnosis of hyponatremia. Serum osmolality must be low in true hyponatremia; if it is normal or high, there is pseudohyponatremia. Blood glucose level, lipidogram, total proteins and fractions can also be used to rule out pseudohyponatremias; their advantages in comparison to serum osmolality are: low cost, universal availability and fast results. A low urinary sodium (< 20 meq/L) suggests renal salt retention, which can be found in true hypovolemia as well as in relative hypovolemia; the latter is commonly encountered in edematous states, in which the total body volume is increased, but the ECV is reduced. Urine osmolality provides an indirect sign of the presence of circulating ADH; if there is ADH, urine osmolality is always higher than 100 mosm/L (and usually higher than 300 mosm/L). Hyponatremia with urine osmolality < 100 mosm/L suggests less common etiologies, like psychogenic polydipsia and beer potomania. Serum creatinine must be measured to evaluate renal function. When the diagnosis is

Box 2 SIADH

Main causes:

- Neoplasms: ADH is secreted in the context of a paraneoplastic syndrome.

- Lung diseases: not only lung cancer, but pneumonia,[42] and even mechanical ventilation with PEEP.

- CNS disorders: neoplasms, stroke, subarachnoid hemorrhage, brain surgery. In this scenario, it is important to consider the differential diagnosis with the cerebral salt wasting syndrome.[43,44] The only clinical difference is the volume status, which is normal in SIADH and reduced in the cerebral salt wasting syndrome. Given the difficulty in establishing a precise diagnosis of the volume status of patients subjected to brain surgery, it is clear that, in daily practice, the differentiation between these two syndromes is very difficult.[45] This, as well as the incomplete understanding of the pathogenesis of cerebral salt wasting syndrome, has led some authors to question its existence.[46,47]

- Drugs: antidepressants,[39] opioids, anticonvulsants,[48] cyclophosfamide.[49,50]

Diagnostic criteria:

- Hypotonic hyponatremia (low serum osmolality).

-Urine osmolality > 100 mosm/L (in general > 300 mosm/L). It must be fixed, that is, it should not decrease with NaCl administration.

- Urinary sodium > 40 meq/L, the patient must be euvolemic and without edema.

- Normal renal, cardiac, hepatic, thyroid and adrenal functions

- Absence of thiazide diuretic.

not clear or when the clinical picture suggests an endocrinopathy, cortisol (and, if recommended, corticotropin stimulation test), TSH and other pituitary hormones, like LH and FSH, must be checked.

The medication list must be reviewed in detail, since several common drugs (like anti-inflammatories, antidepressants, anticonvulsants and thiazide diuretics) may cause hyponatremia.

Clinical manifestations

In hyponatremia, ECF becomes hypotonic in relation to ICF, which causes water to enter the cells. Therefore, the main clinical manifestations of hyponatremia are neurological because since the skull limits the expansion of cerebral parenchyma, the cerebral edema causes intracranial hypertension.

Depending on the severity and duration of hyponatremia, symptoms may range from absent to full-blown encephalopathy, coma and seizures. These symptoms are not specific, and may be interpreted as clinical manifestations of the underlying disease. Sometimes, drowsiness may be interpreted as secondary to depression.

The velocity with which hyponatremia develops is an essential factor in determining symptomatology. For example, a moderate acute hyponatremia may be more symptomatic than a severe chronic hyponatremia. This is because in chronic hyponatremia, the neurons attempt to reduce intracellular osmolality by excreting sodium and potassium salts as well as organic osmolytes to minimize the water shift and cerebral edema.

These adaptive mechanisms should be considered during treatment. The inadvertently rapid correction of chronic hyponatremia may severely reduce neuron volume and result in brainstem demyelination, especially at the pons (pontine myelinolysis)[51]. Since neurological damage resulting from pontine myelinolysis is frequently irreversible, the best alternative is prevention.

Treatment

The proper management of hyponatremia requires the consideration of several aspects, such as the duration and severity of the disorder, the presence or absence of symptoms and etiological diagnosis.

Duration

Except when hyponatremia develops in the hospital environment (for example, in the postoperative period), it is difficult to determine the exact duration of the disorder. Since after 48 hours of hyponatremia the aforementioned adaptive mechanisms are already in place, it is wise to treat most cases slowly. The current recommendation is to increase [Na+] in < 10 meq/L in the first 24 hours (ideally 6 to 8 meq/L/d) and < 18 meq/L in the first 48 hours.[52]

Severity

Severe hyponatremia (< 115 meq/L) should be treated in the hospital setting, ideally in intensive care or step-down units, where frequent assessments of serum sodium may be performed (for example, every four hours); this close monitoring is particularly important in the first 24 hours of treatment.

Symptomatology

This is usually a function of the duration and severity of hyponatremia. Acute and severe hyponatremias are usually symptomatic and may lead to seizures (cerebral edema). In such cases, [Na+] may be increased up to 2 meq/L/hour in the first couple of hours. Afterwards, the speed of the correction must be reduced to avoid surpassing the limit of < 10 meq/L in the first 24 hours.

Etiological diagnosis

Whenever possible, it is important to remove the cause by: reversing hypovolemia, withdrawing suspicious drugs, interrupting excessive ingestion of water, replacing a deficitary hormone (hypothyroidism, suprarenal insufficiency, hypopituitarism), and optimizing the underlying disease (CHF, cirrhosis). Establishing an etiological diagnosis also helps to determine the most appropriate sodium chloride solution (normal versus hypertonic saline).

Hypovolemic hyponatremia

In general, these patients are treated with normal (0.9%) saline. By reversing the hypovolemia, normal saline removes the baroreceptor stimulus for ADH secretion. Thus, urine osmolality decreases and the relative excess of water is excreted. Hypovolemic hyponatremias tend to be mild and they usually do not dominate the patient's clinical picture. Therapy should be focused on the correction of hypovolemia because after this, sodium concentration is expected to normalize "automatically". Usually, there is no need to use formulas to calculate the amount of sodium chloride to be administered. If formulas are used, the rate and degree of correction will be underestimated because they do not take into account the electrolyte

free water diuresis that occurs in response to the reversal of hypovolemia.

A few exceptions should be considered. In severe cases of hyponatremia associated with exercise, hypertonic (3%) saline administration is indicated.[53,54] For patients with cerebral salt wasting syndrome, the use of hypertonic saline[45] might be necessary; fludrocortisone also seems to be beneficial.[55]

Hypervolemic hyponatremia

Sodium chloride administration is not recommended, hence there is no need for formulas. The correction of serum sodium depends on the optimization of the underlying disease, restriction of water ingestion (< 1,000 mL/day), and the use of furosemide to reduce urine osmolality and facilitate the excretion of excess water. Recently, a new class of drugs has been approved in the USA to treat hypervolemic hyponatremia. Vaptans are inhibitors of vasopressin receptors, which are capable of promoting electrolyte-free water diuresis (also known as aquaretics). These may be administered orally (Tolvaptan) or via intravenous route (Conivaptan, Satavaptan, Lixivaptan)[56]. These drugs increase serum sodium concentration in patients with hypervolemic hyponatremia and have been approved for clinical use in the USA; in Brazil, they are still unavailable. Studies on patients with CHF show that vaptans increase serum sodium and improve symptoms,[57] but do not reduce mortality rates.[9]

Euvolemic hyponatremia

It is important to focus on the identification and correction of the cause: replacement of thyroid hormone in hypothyroidism; replacement of mineralocorticoid (fludrocortisone) in hypopituitarism or adrenal insufficiency; discontinuation of thiazide diuretics or drugs that may be causing SIADH. If the cause of SIADH can't be removed, the treatment should focus on measures to restrain the ingestion (< 1,000 mL/day) and increase urinary excretion of free water. A few strategies are available to increase urinary excretion of free water in SIADH. In hospitalized patients, one strategy is to use hypertonic saline; the excretion of the solute overload will cause the obligatory excretion of a large amount of free water. Furosemide may be used in combination with hypertonic saline to prevent hypervolemia and to accelerate the correction of serum sodium, because this diuretic interferes with the urinary concentrating ability, thus increasing free water clearance.

Chronically, patients may be placed in a high solute diet (same rational as hypertonic saline), oral furosemide, vaptans, lithium and demeclocycline. Lythium and demeclocycline share the side effect of antagonizing the action of ADH in collecting ducts. They cause nephrogenic diabetes insipidus and increase the urinary excretion of free water. Lithium and demeclocycline are seldom used to treat SIADH due to their toxicity profile; as the specific ADH antagonists (vaptans) become available, we should no longer need to use lithium or demeclocycline for this indication.

Can we use normal saline to treat SIADH-induced hyponatremia?

Let's consider the patient presented in the beginning of this article: what would happen to [Na+] after the administration of 1 L of normal saline, which contains 308 mosm/L (Table 3)?

According to Adrogue and Madias' formula (Table 4), the administration of 1 L of normal saline would raise the serum sodium by almost 2 meq/L (Formula 5):

$$\frac{(154+0)-115}{(50\text{x}0,4)+1} = +1,86 \text{ meq/L}$$

However, in practice, the administration of normal saline does not usually increase serum sodium in patients with SIADH; it may actually worsen hyponatremia (Box 3).

For the same patient, the administration of 1 L hypertonic saline, which contains 1,026 mosm of solute, would result in an obligatory excretion of 1.7 L of urine (1,026 ÷ 600). Since these solutes were administered in only 1 L of water, there would be an effective loss of 700 mL of water, resulting

Table 3 Characteristics of the solutions used for the treatment of hyponatremia

	[Na+] meq/L	[Cl-] meq/L	Osm mosm/L
Normal saline 0.9% NaCl	154	154	308
Hypertonic saline 3.0% NaCl	513	513	1,026

The osmolality of the solution is the sum of solutes (sodium + chloride) divided by the volume of solvent (in these cases, 1 L).

Table 4 Formulas most commonly used to correct hyponatremia

Formulas	Comments
"Sodium deficit" (140 - [Na+]of the patient) x TBW	By using 140 in the formula, we will arrive at the amount of sodium needed to raise the [Na+] of the patient to 140. Usually, the goal is not to normalize [Na+], but rather to increase it by < 10 meq/L in 24 hours. Therefore, the suggestion is to use the desired [Na+] instead of 140.
Adrogue and Madias $\frac{(Na+K)\text{ of solution} - [Na+]\text{ of the patient}}{TBW + 1}$	One advantage is that it considers the [K+] of the solution. The "+ 1" in the denominator aims to adjust the patient's TBW to the liter of the solution to be administered. The result does not show the amount of sodium to be administered, but how much the concentration of serum sodium will increase for each liter of the solution to be administered.

TBW: total body water. For young men, TBW = weight (kg) x 0.6. For young women and elderly men, TBW = weight (kg) x 0.5. For elderly women, TBW = weight (kg) x 0.4.

Box 3 The desalination phenomenon caused by the administration of normal saline to a patient with SIADH

· 1 L of normal saline contains approximately 300 mosm of solutes (precisely, 308 mosm – Table 3).

· Given her urine osmolality, the patient is able to excrete 600 mosm of solutes in 1 L of urine.

· So, in order to excrete 300 mosm of solute, she will only need 0.5 L of urine. This implies retention of 0.5 L of electrolyte free water.

· End result: decrease in serum sodium concentration.

· Take home message: to increase the serum sodium concentration of a patient with SIADH, the osmolality of the administered solution must be higher than that of the patient's urine. Since urine osmolality in SIADH is usually higher than 300 mosm/L, normal saline is not a good treatment choice.

in an increase in the serum sodium concentration. According to Adrogue and Madias' formula, the magnitude of this increase would be of almost 19 meq/L (Formula 6):

$$\frac{(510+0)-115}{(50x0,4)+1} = +18,8 \text{ meq/L}$$

If the purpose is to raise [Na+] by only 8 meq/L in 24 hours, a simple rule of three can be applied: if 1,000 mL of hypertonic saline increases [Na+] by 18.8 meq/L, how many mL would be necessary to raise [Na+] by 8 meq/L? The answer is approximately 425 mL of hypertonic saline that should be infused over 24 hours at a rate of 18 mL/hour.

Using the sodium deficit formula, the calculation would be as follows (Formula 7):

(desired [Na+] - patient's [Na+]) x TBW

Therefore, the sodium deficit would be: (123 – 115) x 20 = 160 meq.

Since hypertonic saline has approximately 510 meq of sodium in 1,000 mL, a simple rule of three shows that, to administer 160 meq of sodium, 310 mL of hypertonic saline are necessary, and they should be infused over 24 hours at a rate of 13 mL/hour.

Since both formulas are imprecise and present several limitations, some authors suggest simpler approaches for the use of hypertonic saline. One strategy would be to administer 0.5 mL/kg/hour for asymptomatic patients; 1.0 to 2.0 mL/kg/hour for the symptomatic ones; and up to 2.0 to 4.0 mL/kg/hour for a brief period of time (one to two hours) for patients with seizures.[58] It is important to perform a close laboratory follow-up (every two hours, depending on the severity), and to adjust the infusion as needed to avoid surpassing the limits of increase in serum sodium concentration.

Another strategy is the administration of a 100 mL bolus (over 10 minutes) of hypertonic saline for patients with symptomatic hyponatremia.[54] This approach was initially recommended in 2005 for encephalopathy related to exercise-associated hyponatremia,[59] and was later adopted by the Second International Exercise-Associated Hyponatremia Consensus Development Conference.[53] In an article

published in 2010, the authors suggested broadening this approach for all patients with encephalopathy related to hyponatremia.[54] They defend the idea that a 100 mL bolus of hypertonic saline would rapidly increase serum sodium, but by only 1 to 2 meq/L, which would be ideal to improve cerebral edema without the risks of an exaggerated correction.[54]

In Brazil, hypertonic saline is not commercially available, so the solution has to be mixed by the nursing staff (Table 5).

Regardless of the approach, the phsyician must always be vigilant to avoid an overly rapid correction of chronic hyponatremia, to minimize the risks of pontine myelinolysis. The risk of overly rapid correction is higher when the cause of hyponatremia can be rapidly reversed. Hypovolemic patients could be taken as an example; in such cases, the correction of hypovolemia removes the baroreceptor stimulus for ADH secretion, which results in free water diuresis. This leads to a much faster rise in serum sodium than predicted by the formulas. Likewise, the withdrawal of culprit drugs or replacement of missing hormones (thyroid or mineralocorticoids) may rapidly reverse the mechanism that was causing hyponatremia and result in a disproportionate rise in serum sodium.

A recent study illustrated the risk of overly rapid correction of serum sodium with the administration of potassium chloride. Berl and Rastegar reported the case of a 59-year-old patient who presented with [Na+] = 96 meq/L and [K+] = 1.6 meq/L, secondary to the use of hydrochlorothiazide (HCTZ)[10]. To avoid the rapid correction of hyponatremia, the authors were careful to administer sodium (only 300 mL of normal saline) and focused the initial treatment on the correction of potassium, providing a total of 430 meq of KCl in the first 24 hours; HCTZ was suspended and the ingestion of water was restricted to 800 mL a day. With these measures, serum sodium increased by 17 meq/L in the first 24 hours. On the eighth day, the patient developed tetraparesis and pontine myelinolysis was later confirmed by magnetic resonance imaging (MRI). The authors emphasize that serum potassium depletion may contribute to hyponatremia, due to sodium shift from the ECF to the ICF. With potassium replacement, there is the inverse movement of sodium from ICF to ECF, which accelerates the correction of hyponatremia. Other factors that might have contributed to the overly rapid correction in this case included the withdrawal of HCTZ, reversal of hypovolemia and water restriction. The authors admitted that, after detecting a sudden rise in serum sodium, they should have immediately started the infusion of hypotonic fluids to halt the sodium correction and allow the continued administration of potassium chloride[10].

According to the literature, when an overly rapid correction is noticed, it is important to immediately stop the administration of sodium and attempt to halt the rise in serum sodium by infusing hypotonic solutions or DDAVP.

Alternately, when the risk of overly rapid correction is deemed too high, DDAVP may be given preventively (every six or eight hours), along with water restriction and administration of hypertonic saline.[60] In hypovolemic patients with severe drug-induced hyponatremia, for example, the withdrawal of drugs and the correction of hypovolemia may result in a brisk aquaresis and a much faster rise in serum sodium than predicted by the formulas. In these cases, the objective of the preventive administration of DDAVP is to avert the aquaresis, making the correction of hyponatremia with hypertonic saline more controlled and predictable, as in patients with SIADH.

Clinical scenario: comments

Even without the serum osmolality of the patient, it is possible to rule out pseudohyponatremia due to the severity of serum sodium reduction and by the normal

Table 5 Simple ways to prepare 1 L of hypertonic saline

With 1 L of solution	[Na+]meq/L of the original solution	Volume of 20% NaCl to be added	Ammount of sodium to be added (in meq)	[Na+]meq/L of the final solution
Distilled water	0	150 mL	510	510
Dextrose 5%	0	150 mL	510	510
Normal saline	154	105 mL	357	511

20% NaCl has 3.4 meq of sodium per mL.

results of blood glucose, lipid profile, total proteins and fractions. Since the patient has neither edema nor history or physical findings that suggest hypovolemia, she is believed to be euvolemic. A urinary sodium of 80 mmol/L confirms this clinical impression. The high urinary osmolality suggests the presence of ADH. Since there is no osmotic or hypovolemic justification for this ADH secretion, the diagnosis is syndrome of inappropriate secretion of ADH (SIADH). Renal, adrenal and thyroid functions must be normal to fit this diagnosis. The most likely cause for SIADH in this patient is brain tumor. The selective serotonin reuptake inhibitor (escitalopram) that she was taking may also cause SIADH, but the patient already had hyponatremia when the drug was introduced. Nevertheless, escitalopram was discontinued. The treatment with hypertonic saline was initiated aiming for a 6 meq/L rise in [Na+] in the first 24 hours. After 48 hours, [Na+] = 128 meq/L, hypertonic saline was suspended and the patient was discharged with water restriction (800 mL/day), a high solute diet and furosemide 40 mg/day. One week after discharge, [Na+] = 134 meq/L. Although vaptans were indicated, such medications are still unavailable for clinical use in Brazil (Table 6).

Table 6 Summary

	Main clinical aspects of hyponatremia		
	Hypovolemic	Euvolemic	Hypervolemic
ECF volume	Reduced	Normal	Increased
ECV	Reduced	Normal	Reduced
Urinary sodium	< 20 mEq/L	> 40 mEq/L	< 20 mEq/L
Serum ADH	Increased	Increased or reduced	Increased
Urinary osm	Incresed	Increased or reduced	Increased
Main causes	GI losses	Urinary osm. ↑	CHF
	Diarrhea	Hypothyroidism	Cirrhosis
	Vomiting	Adrenal insufficiency	Nephrotic syndrome
	Skin losses	Thiazide	AKI
	Marathon runners	Postoperative	CKD
	Renal losses	SIADH	
	Diuretics	Urinary osm.↓	
	Osmotic diuresis	Polydipsia	
	Salt-wasting nephropathy	Potomania	
	Cerebral salt wasting syndroma (CSWS)	Tea and toast	
		TURP	
		Hysterocopy	
Treatment	Minimizing losses	Hypertonic saline	Water restriction
	Normal saline in most cases	Water restriction	Furosemide
	Hypertonic saline in specific cases (marathon runners and in CSWS)	Furosemide	Vaptans
	Fludrocortisone in CSWS	Vaptans	Treating underlying disease
		Treating underlying disease	
		Discontinuation of drugs	

TURP: transurethral resection of the prostate; CHF: congestive heart failure; AKI: acute kidney injury; CKD: chronic kidney disease.

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