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Diagnosis and management of hyponatremia in acute illness

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Abstract

Purpose of review—Hyponatremia is the most common electrolyte disorder present in hospitalized patients. Acute and severe hyponatremia can cause significant morbidity and mortality. The present review discusses the epidemiology, causes, and a practical approach to the diagnosis and management of acute and chronic hyponatremia, including the appropriate use of hypertonic saline and potential future use of the new V2 vasopressin receptor antagonists in critically ill patients.

Recent findings—The increasing knowledge of aquaporin water channels and the role of vasopressin in water homeostasis have enhanced our understanding of hyponatremic disorders. Increased vasopressin secretion due to nonosmotic stimuli leads to decreased electrolyte-free water excretion with resulting water retention and hyponatremia. Vasopressin receptor antagonists induce electrolyte-free water diuresis without natriuresis and kaliuresis. Phase three trials indicate that these agents predictably reduce urine osmolality, increase electrolyte-free water excretion, and raise serum sodium concentration. They are likely to become a mainstay of treatment of euvolemic and hypervolemic hyponatremia.

Summary—The correct diagnosis and management of hyponatremia is complex and requires a systematic approach. Vasopressin receptor antagonists are potential tools in the management of hyponatremia. Further studies are needed to determine their role in the treatment of acute, severe, life-threatening hyponatremia as well as chronic hyponatremia.

Keywords

aquaretics; hyponatremia; hypoosmolality; vasopressin

Introduction

Hyponatremia is common in acutely ill patients [1,2]. Diminished plasma sodium concentration is the most common electrolyte disorder in hospitalized patients, occurring in 15–30% of such patients [3]. In general, over 50% of this hyponatremia occurs during hospitalization [2,4]. With the development of a sensitive radioimmunoassay for the antidiuretic hormone, arginine vasopressin (AVP), the pathogenesis of hyponatremia has been found to occur secondary to the nonosmotic secretion of AVP in over 95% of cases [2,5]. A new class of medications, AVP receptor antagonists, is now available, and numerous trials have shown them to be effective at increasing electrolyte-free water excretion and serum sodium concentration in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) or edema-forming states such as congestive heart failure and cirrhosis. The present article reviews the practical approach

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to the diagnosis of hyponatremia and summarizes the role of AVP receptor antagonists in the management of hyponatremia.

Role of vasopressin in hyponatremia

In normal individuals, plasma AVP secretion is regulated by osmoreceptors in the hypothalamus [5,6]. A decrease in plasma osmolality of only 1–2% with water intake normally suppresses AVP secretion and leads to urinary excretion of excess water. In contrast, the nonosmotic secretion of AVP is mediated by arterial stretch baroreceptors in response to an 8–10% decrease in arterial pressure [5]. The arterial baroreceptors are located in the carotid body, aortic arch, and afferent arteriole of the glomerulus. Although osmotic regulation of AVP is more sensitive, nonosmotic stimulation is more potent. Thus, in spite of hyponatremia and hypoosmolality, nonosmotic stimulation of AVP overrides the osmotic AVP regulation and leads to water retention and hyponatremia. In general, nonosmotic stimulation of AVP is due to decreased integrity of the arterial circulation, either secondary to a decrease in cardiac output (*CO*), systemic arterial vasodilation, or both. Decreased *CO* and arterial vasodilation are shown as clinical entities in Fig. 1a and Fig. 1b, respectively, which cause arterial underfilling and stimulate the neurohumoral axis, including the nonosmotic stimulation of AVP [7,8]. In the absence of diuretics or an osmotic diuresis, for example glucosuria, bicarbonaturia, the normal kidney will respond to arterial underfilling by increasing tubular sodium reabsorption with a decrease in fractional excretion of sodium (FENa) to less than 1.0%. A clinical search for the cause of hyponatremia relating to a decrease in *CO* or arterial vasodilation as a nonosmotic stimulus of AVP is therefore indicated. FENa remains of value in diagnosing hyponatremia even if deterioration of renal function has occurred. Specifically, if the renal dysfunction is due to renal vasoconstriction without tubular dysfunction, that is, prerenal azotemia, as may occur with a decrease in extracellular fluid volume (ECFV), for example, gastrointestinal losses, hemorrhage, or arterial underfilling with an increase in ECFV (e.g. cardiac failure and cirrhosis), the FENa should be below 1.0% in the absence of diuretic use. On the contrary, in case of acute kidney injury with tubular dysfunction or advanced chronic kidney disease, FENa may be greater than 1.0% in spite of the presence of arterial underfilling and hyponatremia [9].

Classification, causes, and diagnosis of hyponatremia

A practical approach is necessary in order to diagnose and correctly manage hyponatremia in acutely ill patients. Hyponatremia indicates a relatively greater amount of water to sodium in the plasma. This can occur with a decrease in total body sodium (hypovolemic hyponatremia), a near normal total body sodium (euvolemic hyponatremia), and an excess of total body sodium (hypervolemic hyponatremia). This diagnostic approach is summarized in Fig. 2 [10]. Total body sodium and its anion determine ECFV; therefore, total body sodium is assessed primarily by history and physical examination. Pseudohyponatremia (from marked elevation of lipids or proteins in plasma causing artifactual decrease in serum sodium concentration as a larger relative proportion of plasma is occupied by excess lipid or proteins) and translocational hyponatremia (from osmotic shift of water from intracellular fluid to extracellular fluid due to additional solutes in plasma, e.g. glucose, mannitol, and radiographic contrast agent) are two situations in which hyponatremia is not associated with relatively greater amount of water and should be ruled out before managing hyponatremia.

In hypovolemic hyponatremia, there is a deficit of both total body water and sodium, but relatively less deficit of water, thus causing hyponatremia. A history of vomiting, diarrhea, diuretic use, or hyperglycemia with glucosuria, along with increased thirst, weight loss, orthostatic hypotension and tachycardia, and dry mucous membranes, supports the diagnosis of hypovolemic hyponatremia. If the fluid and sodium losses are extrarenal, such as

gastrointestinal losses, FENa should be less than 1%. On the contrary, if the source of sodium and water losses is the kidney, for example, diuretics, glucosuria, or bicarbonaturia, then FENa will be greater than 1% [9].

In euvolemic hyponatremia, total body sodium concentration is near normal so there should be no evidence of ECFV depletion or excess, that is, no peripheral edema, ascites, pulmonary congestion, or pleural effusions. Before turning to the diagnosis of SIADH in patients with euvolemic hyponatremia, several other clinical entities need to be excluded. These include hypothyroidism (measure thyroid-stimulating hormone), hypopituitarism (measure cortisol response to adrenocorticotropic hormone), severe emotional (e.g. psychosis) or physical stress (e.g. anesthesia and surgery), and various medications that stimulate antidiuretic hormone (ADH) release. There are various pharmacological agents associated with SIADH:

1. Nicotine,
2. Chlorpropamide,
3. Tolbutamide,
4. Clofibrate,
5. Cyclophosphamide,
6. Morphine,
7. Barbiturates,
8. Vincristine,
9. Carbamazepine (Tegretol),
10. Acetaminophen,
11. NSAIDs
12. Antipsychotics,
13. Antidepressants.

In the absence of these diagnoses, SIADH can be entertained, and a search for pulmonary or central nervous system infections, vascular, or neoplastic diseases should reveal the cause in over 90% of SIADH cases. Because the urine volume in SIADH is low, for example, 500 ml/24 h, the urinary sodium concentration is generally high even when the patient is in sodium balance. For example, with a very modest daily sodium intake of 100 mmol/24 h, the urinary sodium concentration in 500 ml of daily urine would have to be 200 mmol/l of urine for the patient to remain in sodium balance. Thus, a high urine sodium concentration in SIADH should not be called ‘renal sodium wasting.’

In hypervolemic hyponatremia, total body sodium concentration and water are increased, but total body water is increased more, and thus hyponatremia occurs. When hypervolemic hyponatremia occurs with cardiac failure or cirrhosis, the patient has advanced and, therefore, readily diagnosed disease. Decreased plasma sodium concentration is a risk factor for poor survival in patients with cardiac failure and cirrhosis [11–16]. In the absence of diuretics, FENa should be below 1.0% in hyponatremic cardiac or cirrhotic patients, as the kidney is normal and responding to decreased arterial perfusion in these edematous disorders. Specifically, in case of either a successful heart or liver transplant in cardiac or hepatic failure patients, respectively, the kidneys no longer retain sodium and water. The situation in which hypervolemic hyponatremia occurs with a FENa greater than 1.0% is with acute kidney injury or chronic kidney disease, settings in which renal tubular dysfunction is present and neither water nor sodium can be optimally excreted.

Treatment of hyponatremia

The correct treatment of hyponatremia in acute illness depends first and foremost on the correct diagnosis. Unfortunately, occasionally a physician believes that all types of hyponatremia means a decrease in total body sodium concentration and therefore the treatment is isotonic saline administration. As noted in the above discussion, only hypovolemic hyponatremia is appropriately treated by volume expansion with isotonic saline (Fig. 2). Therefore, when hypovolemic hyponatremia is the suspected diagnosis, a trial of volume expansion with isotonic saline is certainly appropriate. If the diagnosis of hypovolemic hyponatremia is correct, the nonosmotic release of AVP should be suppressed, and the renal function improves with isotonic saline replacement. This corrects the hyponatremia over the next 24–48 h. It is, however, important to remember that patients with SIADH may become ECFV depleted and their FENa may be decreased to less than 1.0%. In these patients with SIADH, isotonic saline will correct the ECFV depletion, the FENa will rise, but the hyponatremia of SIADH will persist. Thus, these patients initially had a combined cause of low plasma sodium concentration, namely hypovolemic and euvolemic hyponatremia. Using the above diagnostic approach and in the absence of a reversible cause of symptomatic euvolemic or hypervolemic hyponatremia, the treatment very much depends on whether hyponatremia has developed acutely within a few hours or chronically over more than 48 h [17••,18].

Acute hyponatremia

Acute symptomatic hyponatremia can be a very serious clinical situation. In hyponatremia, the water equilibrates across the brain cell membrane and leads to cell swelling. Because maximum brain swelling is limited to 8% secondary to the rigid calvarium, acute hyponatremia can lead to severe brain swelling, herniation, and cardiopulmonary arrest. There are, however, adaptive changes that occur in the brain over time. Within the first 1–3 h, extracellular fluid moves into the cerebrospinal fluid and then into circulation. A slower process of adaptation then occurs in which brain cells extrude potassium and organic solutes, thereby decreasing intracellular osmolality and, thus, brain water. Over approximately 48 h with persistent hyponatremia, other organic osmolytes including phosphocreatine, myoinositol and amino acids such as glutamine and taurine are lost. This leads to the brain cells losing water and brain volume returning to near normal, however, at the expense of losing intracellular potassium and organic osmolytes.

In acute hyponatremia with neurological symptoms, the treatment of choice is 3% hypertonic saline at 100 ml/h. For each 100 ml of 3% hypertonic saline, the serum sodium concentration will increase by approximately 2 mmol/l. The duration of hypertonic saline treatment of acute symptomatic hyponatremia should be based on the improvement in the patient's symptoms and signs. Patients with acute hyponatremia may be lethargic, disoriented, agitated, and have anorexia and nausea [18]. Physical findings include abnormal sensorium, pathological reflexes, Cheyne-Stokes respiration, hypothermia, and seizures. In case of severe symptoms, such as seizures, obtundation, and coma, 3% sodium may be infused at 4–6 ml/kg/h. A loop diuretic, for example, furosemide, may be added to this treatment, as it may cause hypotonic urine. Urinary electrolytes, however, should be replaced to avoid ECFV depletion and electrolyte disturbances such as decreased plasma potassium, magnesium, and calcium.

There are now nonpeptide antagonists to V2 vasopressin receptors, which increase electrolyte-free water excretion and raise serum sodium concentration (Table 1) [19,20]. One of these agents, conivaptan, has been approved by the US Food and Drug Administration for 4-day intravenous use in hospital to treat euvolemic and hypervolemic hyponatremia. There are, however, insufficient results at this time to recommend the use of conivaptan to treat acute symptomatic hyponatremia. Because conivaptan is an antagonist to both V1 and V2 vasopressin receptors, there is some hesitation in using conivaptan to treat hyponatremia in cirrhosis. The theoretical basis for this hesitancy is that antagonism of splanchnic V1 receptors

could increase splanchnic flow and further elevate portal pressures and potentially cause esophageal bleeding. On the contrary, in patients with cardiac failure, V1 vasopressin receptor antagonism could theoretically decrease cardiac afterload, diminish coronary artery constriction, and block the proliferation of cardiac myocytes, which may contribute to cardiac remodeling [21,22]. There are, however, not enough data at this time to support such a beneficial effect of V1 receptor antagonism in patients with cardiac failure. Selective V2 receptor antagonists, which are orally active for chronic use, are in phase three clinical studies. Several of these agents have been shown to correct hyponatremia in patients with advanced cardiac or liver failure without complications [23]. Moreover, in the Medical Outcomes Study 12-items Short Form General Health Survey, the mental component was improved significantly after increasing plasma sodium concentration with tolvaptan, an orally active, selective V2 antagonist [24].

The above described brain adaptation, which occurs during chronic hyponatremia and protects against brain edema, can nevertheless predispose to brain injury if correction of chronic hyponatremia occurs too rapidly. This brain damage has been termed osmotic demyelination and involves the destruction of myelin sheaths that cover axons in the brainstem. Osmotic demyelination occurs in the pontine and extrapontine sites during rapid correction of chronic hyponatremia [25,26]. The most predisposed areas of brain damage with osmotic demyelination appear to be those where the reuptake of organic osmolytes is the slowest. Positive imaging findings by computed tomography or MRI of osmotic demyelination generally are not apparent until 6–10 days after the onset of clinical symptoms [27]. Studies in humans and experimental animals have lead to recommendations regarding the rate of correction of chronic hyponatremia so as to avoid osmotic demyelination. The consensus is that correction of chronic hyponatremia should be limited to less than 12 mmol in 24 h and less than 18 mmol in 48 h [17••,28]. There are high-risk patients, however, with severe malnutrition, alcoholism, or advanced liver disease in whom the rate of correction of chronic hyponatremia should be below these limits [29]. Patients with too rapid correction of chronic hyponatremia who develop osmotic demyelination syndrome demonstrate a bipolar clinical course. The patients demonstrate improved neurological symptoms initially, but one to several days later, new and progressive neurological symptoms emerge and can lead to permanent neurological deficits or even death.

Various formulae have been proposed to aid in predicting the increment in serum sodium concentration that would accompany the infusion of either isotonic saline or hypertonic saline in order to avoid over and rapid correction [30•]; the Adrogue-Madias formula is the one most widely used [31]. However, it is not clear how accurately these calculations predict correction rates in clinical use. In a recent retrospective review, the achieved serum sodium concentration exceeded the one predicted from the Adrogue-Madias formula in three of four patients whose serum sodium concentration was less than 120mEq/l at the outset; the average correction in over-correctors was 2.4 times the predicted [32•]. In another review, in every subgroup, the achieved serum sodium concentration was higher than the anticipated one from the Adrogue-Madias formula, but the difference failed to reach statistical significance because of the low number of patients in each subgroup. Nonetheless, the discrepancy achieved statistical significance in hypovolemic, primary polydipsic, and hypernatremic groups [33]. Unrecognized hypovolemia, failure to assess ongoing renal and extrarenal losses, and other reversible causes of water retention are shortcomings of this formula and pose risk for inadvertent overcorrection. Barsoum and Levine [34] proposed a formula that incorporates all of these variables, but its complexity makes it impractical for clinical use. Therefore, a close monitoring of serum sodium concentration as well as the urinary electrolyte content is an essential element in the management of patients with hyponatremia, as there is no perfect formula for predicting the rate and amount of hypertonic saline to correct, but not to overcorrect hyponatremia.

Electrolyte-free water excretion during the treatment of hyponatremia can be documented if urine sodium and urine potassium concentration is less than plasma sodium. The excess body water volume that is causing hyponatremia can be roughly calculated as follows. Total body water is 60% in men or 50% in women. Thus, for a 70 kg man, total body water is approximately 42 l. If his current serum sodium concentration is 120mmol/l and the therapeutic goal is to raise the serum sodium to 130mmol/l, then the following formula can be used:

$$\frac{120\ \text{mmol/l}}{130\ \text{mmol/l}} \times 421 = 38.81$$

Thus, the excess electrolyte-free water to be removed would be 421−38.81 = 3.21 to raise the serum sodium concentration to 130 mmol/l.

Chronic hyponatremia

Correction of chronic hyponatremia with hypertonic saline is generally only necessary if the patient is symptomatic. In asymptomatic patients with euvolemic or hypervolemic hyponatremia in which no specific intervention is available (e.g. SIADH), fluid restriction is generally the treatment of choice. The daily fluid intake must, however, be severely restricted to less than 24 h urine output and insensible losses. For example, if the hyponatremic patient has a daily urinary output of only 500 ml with average daily insensible losses of 250 ml, then fluid restriction must be less than 750 ml/day in order to cause a negative water balance and increase serum sodium concentration. There may, however, be patients with chronic hyponatremia who will not tolerate or comply with this degree of daily fluid restriction. In these patients, several approaches have been used in the past. Demeclocycline causes AVP-resistant nephrogenic diabetes insipidus and has been used to treat chronic hyponatremia by administering divided doses ranging from 600 to 1200 mg/day [35,36]. The demeclocycline doses should only be increased every 3–4 days. This tetracycline is metabolized in the liver, and nephrotoxicity has been reported in hyponatremic patients with liver disease [37] and in hyponatremic patients with congestive heart failure treated with demeclocycline [38]. An osmotic diuresis can increase solute-free water excretion and has also been used to treat chronic hyponatremia [39]. In this regard, oral urea (30 g/day) has been recommended. Palatability is, however, an issue with urea ingestion, and therefore, it should be administered in orange juice or another liquid to improve taste. Lithium has a narrow risk-benefit ratio, is inconsistent in causing nephrogenic diabetes insipidus and therefore should not be used to treat chronic hyponatremia [40]. When the orally active V2 receptor antagonists are available, they could be used to treat chronic hyponatremia, particularly in patients who do not comply with fluid restriction. In a large randomized study, tolvaptan was shown to be effective in raising serum sodium concentrations in hyponatremic patients with cardiac failure, cirrhosis, and SIADH [24]. Cessation of the drug was associated with return of the serum sodium concentrations to hyponatremic levels (<136 mmol/l). To date there have been no reports of osmotic demyelination using these aquaretic drugs; however, the rate of correcting serum sodium concentration in patients with chronic hyponatremia should follow the aforementioned guidelines.

A normal kidney's capacity to excrete electrolyte-free water ranges from 15–20 l over 24 h. Thus, unless an individual places a hose in the stomach or stands under a shower, hyponatremia due only to water intake is very rare. Therefore, patients with primary polydipsia generally have low normal serum sodium concentrations. In addition, because they are drinking more fluids, for example, 10 l/day, any process causing ECFV depletion such as vomiting, diarrhea, or treatment with diuretics is more likely to cause hyponatremia in these polydipsic patients. Although loop diuretics are more potent than thiazide diuretics, the latter are much more likely to cause hyponatremia. In one review of the literature on diuretic-induced hyponatremia, 73%

was caused by thiazide diuretics alone, 20% by thiazide diuretics in combination with antikaliuretic agents, and only 8% due to furosemide alone [41]. Because thiazides block the sodium cotransporter in the renal cortex, only urinary dilution is disturbed. In contrast, loop diuretics such as furosemide block the NaK2Cl cotransporter in the medullary loop of Henle, and therefore, both urinary concentration and diluting mechanisms are impaired. As previously mentioned, furosemide may cause hypotonic urine and is thus much less likely to cause hyponatremia. It should also be remembered that hypokalemia secondary to decreased intracellular potassium may contribute to a decrease in serum sodium concentration by causing sodium shift into cells. Thiazide-induced hyponatremia occurs most commonly in elderly women, and there is also some evidence that the predisposed women may be drinking more water than normal. One limitation of the urinary excretion of electrolyte-fee water is the amount of solute excreted. With maximal urinary dilution of 50 mmol/l and diminished daily solute intake of 200 mmol/l, only 4 l of electrolyte-free water can be excreted. This is the problem that causes hyponatremia with beer drinkers who are not eating. Beer is very hypotonic and contains little solute; therefore, these beer drinkers may develop hyponatremia with an intake of 6–10 l of beer/day. Normal solute intake is 600–800 mmol/day, thus allowing for substantial electrolytefree water excretion.

Cerebral salt wasting

One confusing diagnostic area should be briefly mentioned. This is the differential diagnosis of SIADH versus cerebral salt wasting in neurological patients. Before Schwartz *et al*. [42] described the diagnostic criteria for SIADH, many of these patients were termed cerebral salt wasters. Because many patients with SIADH have been treated with isotonic saline infusions, subsequent natriuresis may be related to the administered sodium load. The definitive diagnosis of cerebral salt wasting must involve the documentation of a decreased ECFV secondary to renal sodium losses [43•]. This ECFV depletion causing the nonosmotic secretion of AVP and enhanced thirst or hypotonic fluid administration leads to hyponatremia. These criteria have rarely been fulfilled in cases of hyponatremia claimed to be secondary to cerebral salt wasting. Nevertheless, symptomatic patients with acute hyponatremia and neurological symptoms should be treated with hypertonic saline whether the diagnosis is SIADH or cerebral salt wasting.

Exercise-associated hyponatremia

With more individuals involved in prolonged and strenuous physical exercise such as marathons, ultramarathons, and triathlons, the entity of exercise-associated hyponatremia has emerged. Risk factors for these individuals include low body mass, less well trained, race time exceeding 4 h, consumption of fluids every mile, and the use of NSAIDs [44]. The occurrence of exercise-induced hyponatremia does not seem to be due to sodium imbalance, but rather due to retention of more water. With such vigorous exercise, the nonosmotic stimulation of AVP would be expected, thereby leading to renal water retention [45,46]. When hypotonic fluid ingestion exceeds insensible loss due to sweating, the runner actually gains weight and hyponatremia occurs. The symptomatic hyponatremic runners generally have ingested amounts of hypotonic fluid, for example, water or Gatorade, in excess of 400–800 ml/h. They may develop seizures, ataxia, disturbed level of consciousness, focal neurological deficits, and even mortality can occur. In runners with these symptoms, treatment with 3% hypertonic saline should begin immediately, even before the measurements of serum sodium concentration have returned, and continued until symptoms resolve. Further treatment is generally not needed when serum sodium concentration reaches 130mmo/l.

Conclusion

The diagnosis and management of hyponatremia can be challenging in critically ill patients. A systematic approach including comprehensive history, physical examination to determine the volume status and FENa is essential to make the correct diagnosis. AVP receptor antagonists may represent a future option for the care of critically ill patients with hyponatremia associated with SIADH, cirrhosis, congestive heart failure, and the postoperative state. Further studies will be needed to assess the appropriate use of AVP antagonists for correction of symptomatic hyponatremia either alone or in conjunction with hypertonic saline infusions and for long-term treatment of minimally symptomatic hyponatremia.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 720).

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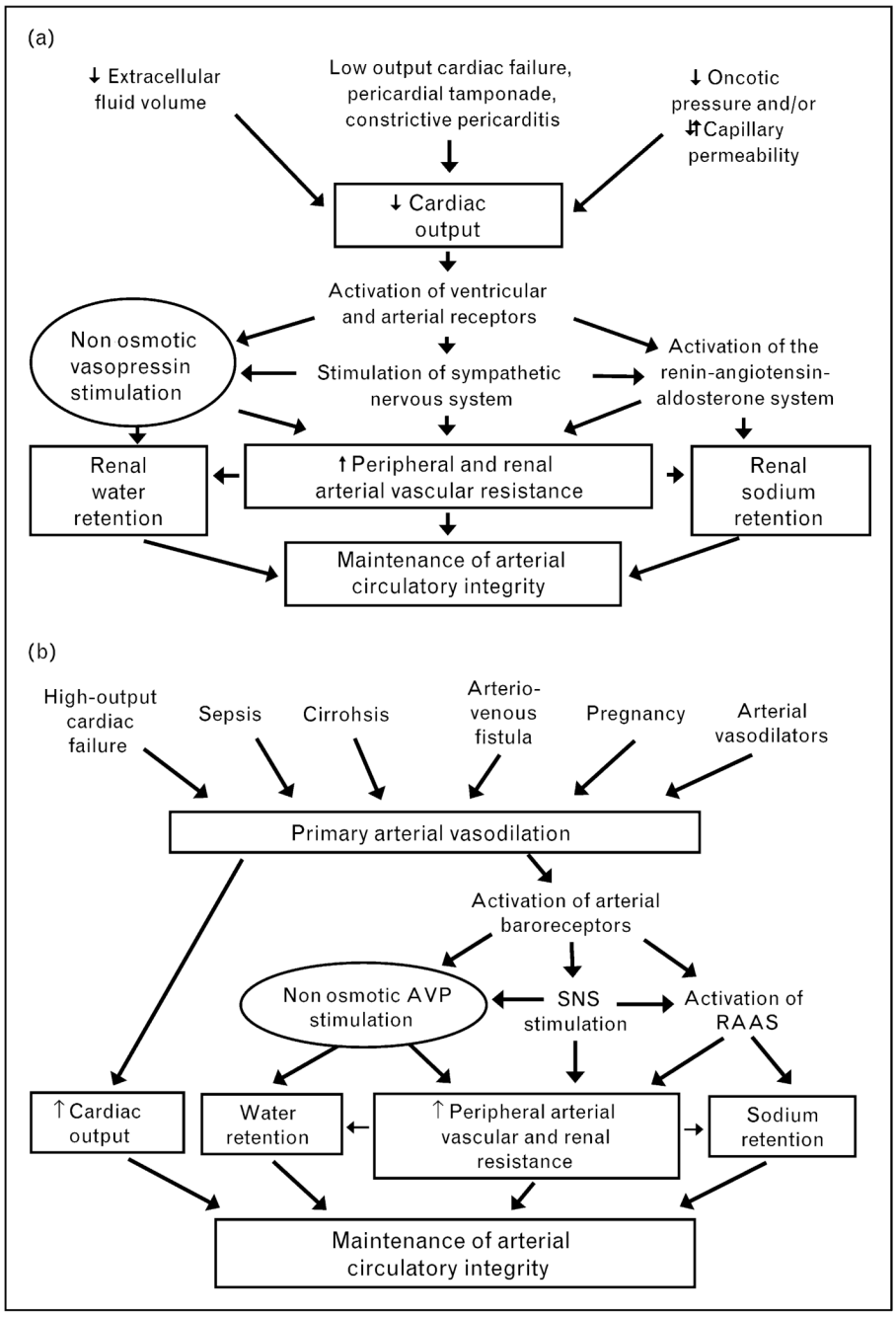

Figure 1. Nonosmotic arginine vasopressin secretion during arterial underfilling

Nonosmotic, baroreceptor-mediated release of arginine vasopressin occurs due to arterial underfilling secondary to either a decrease in cardiac output (a) or primary arterial vasodilation (b). AVP, arginine vasopressin; RAAS, rennin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Adapted with permission [7,8].

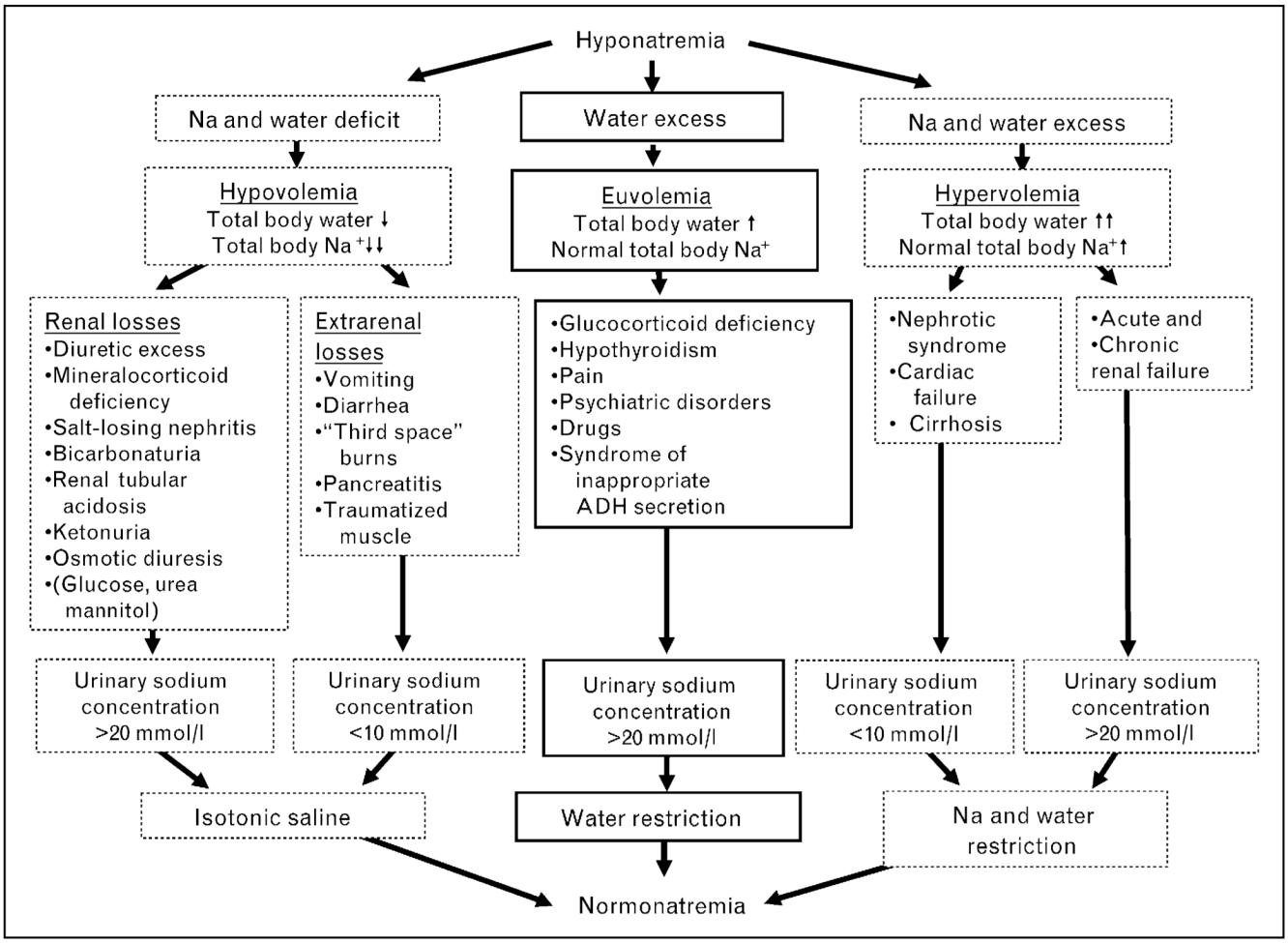

Figure 2. The schema summarizes the diagnostic and therapeutic approach for euvolemic, hypovolemic, and hypervolemic hyponatremia

ADH, antidiuretic hormone. Adapted with permission [10].

Table 1

Selected vasopressin receptor antagonists

	Company	Approval stage	Description/mode of administration	Purpose
Conivaptan (YM-087) (Vaprisol)	Astellas	Approved	Vasopressin V1 and V2 receptor antagonist; nonselective, i.v. limited to 4 days	Euvolemic hyponatremia
Mozavaptan, (OPC-31260) (Physuline)	Otsuka Pharmaceutical	Approved	Vasopressin V2 receptor antagonist; selective, orally active, nonpeptide	Paraneoplastic SIADH[a]
Satavaptan (SR-121463)	Sanofi-Synthelabo	Phase III	Vasopressin V2 receptor antagonist; selective, orally active, nonpeptide	Euvolemic and hypervolemic[b] hyponatremia
Tolvaptan (OPC-41061)	Otsuka Pharmaceutical	Phase III	Vasopressin V2 receptor antagonist; selective, orally active, nonpeptide	Euvolemic and hypervolemic hyponatremia
Lixivaptan (VPA-985)	Cardiokine	Phase III	Vasopressin V2 receptor antagonist; selective, orally active, nonpeptide	Euvolemic and hypervolemic hyponatremia

i.v., intravenous; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a] Syndrome of inappropriate antidiuretic hormone secretion – euvolemic hyponatremia.

[b] Cirrhosis and heart failure – hypervolemic hyponatremia. Adapted with permission [20].