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Hyponatremia in the Setting of Acute Heart Failure Syndrome

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Hyponatremia is usually defined as a decrease in plasma sodium to a level ≤135 mEq/L. It is the most frequent electrolyte disorder occurring in hospitalized patients.[1–3] Its actual incidence depends on the defined level of hyponatremia: 20% for natremia ≤136 mEq/L and 1% to 4% for natremia <130 mEq/L. This chapter discusses the pathophysiology, diagnosis and principles of treatment of hyponatremia, and suggests specific considerations for hyponatremia occurring in patients with heart failure.

Hyponatremia: General Considerations

Pathophysiology

Cell Volume: Osmolarities

Total body water (TBW) represents in an adult 50% to 70% of body weight, which is distributed in two compartments[4–7]:

- Intracellular fluid compartment (ICF), which represents two thirds of TBW, that is, 40% to 50% of body weight, a high concentration of potassium, and a low concentration of sodium.
- Extracellular fluid compartment (ECF), which represents the remaining third of TBW, that is, 20% to 25% of body weight. The ECF is subdivided in two other volumes: (1) plasma volume or effective volemia corresponds to water circulating in vessels, that is, about 5% of TBW with a high sodium and proteins contents; (2) the interstitial compartment equals 10% to 20% of TBW, and its ion concentration is very close to plasma volume, except for proteins, which are normally absent (Gibbs-Donan equilibrium).

The movement of water between interstitial and plasma volume depends on both hydrostatic and oncotic pressures. Water freely crosses the semipermeable cell membrane. Consequently, under steady-state conditions transcellular movements of water are passive and the concentration of particles in the ECF and the ICF is identical. Water shifts between ECF and ICF depends on the osmotic gradient between these two compartments. According to their ability for distribution among cell membrane, two types of solute particles are present:

- Ineffective or diffusive osmoles (e.g., urea, methanol, ethanol, ethylene glycol) are readily permeable to cell membranes. They do not create any osmotic gradient and consequently no movement of water between ECF and ICF.
- Effective or active osmoles are impermeable to cell membrane. Their accumulation in ICF or ECF leads to an osmotic gradient, and therefore obligates the movement of water until reaching the same osmotic forces between both compartments. In this way, an increase in ECF particle concentration such as sodium, glucose, mannitol, or glycerol is responsible for a movement of water from the ICF to the ECF, that is, intracellular dehydration.

Based on these physiologic principles, three types of plasma osmolarities are defined:

- Plasma osmolality is defined by the concentration of all solutes per kilogram of plasma water (mOsm/kg). It is measured directly by an osmometer (delta cryoscopic).
- Plasma osmolarity is defined by the concentration of all solutes per liter of plasma (mOsm/L). As sodium, glucose, and urea are the major osmotic particles of ECF, it can be easily calculated at bedside using the following formula: (Sodium × 2) + Glucose + Urea (mEq/L) = 280 to 295 mOsm/L.
- Plasma tonicity is defined by the concentration of effective osmoles alone per liter of plasma (mOsm/L). As urea is the only substantial ineffective osmole in the plasma, it is not taken into account for the calculation of plasma tonicity, which is as follow: (Sodium × 2) + Glucose (mEq/L) = 275 to 290 mOsm/L.

In most situations, plasma osmolality and osmolarity are close because 1 L of plasma contains 93% of water, the remaining 7% being constituted by proteins and lipids. Only severe hyperprotidemia or hyperlipidemia can lead to subsequent differences between plasma osmolarity and osmolality. If nonionic abnormal solutes accumulate in the plasma (methanol, ethanol, ethylene glycol, mannitol), measured plasma osmolality will largely exceed calculated plasma osmolarity, leading to a high osmolar gap (>12 mOsm/L). This parameter is clinically useful to detect the presence of such toxic substances.

Regulation of Water Balance

Water intake and excretion vary largely during the day. However, ICF and electrolytes concentrations remain unchanged thanks to an equilibrium in the water balance (Fig. 72.1). The regulation of water balance depends especially on two major mechanisms: arginine vasopressin (AVP) secretion and thirst.[4–9]

Regulation of Arginine Vasopressin Secretion

Arginine vasopressin or antidiuretic hormone (ADH) is synthesized by the supraoptic and paraventricular nuclei of hypothalamus. Osmoreceptors are stimulated by several factors (Fig. 72.2):

- Osmotic stimulus: Hypothalamic receptors are highly sensitive to changes in plasma tonicity. This is the most powerful stimulus, because only 1% of the change in plasma tonicity induces AVP release. Plasma hypertonicity stimulates the release of AVP and vice versa. When plasma tonicity range between 280 and 295 mOsm/L, the release of AVP is linearly related to the increase in plasma tonicity. At a plasma tonicity less than 280 mOsm/L, plasma AVP concentration is undetectable. Above 295 mOsm/L, despite the elevation of plasma AVP concentration, urine reaches its maximal concentration (1200 mOsm/L).
- Nonosmotic stimulus: Hypovolemia and arterial hypotension stimulate the release of AVP

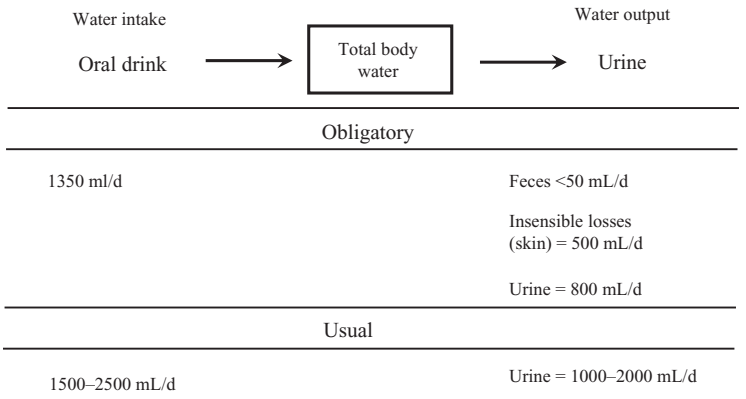

FIGURE 72.1. Water balance (standard intake of 70 g of proteins and 4 g of sodium per day).

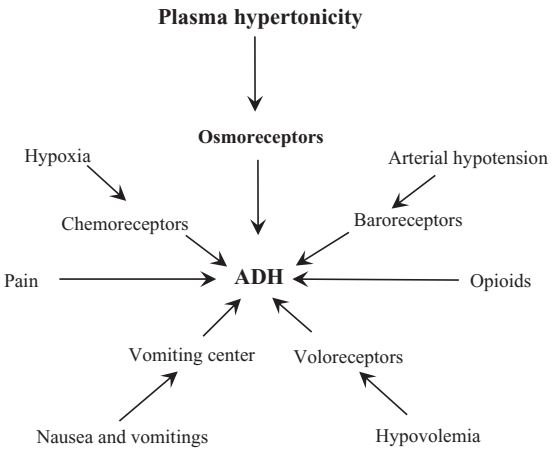

FIGURE 72.2. Major factors responsible for antidiuretic hormone (ADH) release.

via volo- and baroreceptors. Activation of these receptors is less sensitive than osmoreceptors, as they require at least a reduction of 8% to 10% of the ECF volume. The release of AVP may be activated by a variety of other stimuli: nausea and vomiting, pain, opioids, and hypoxia.

The effects of AVP result from the activation of four types of receptors: V1a, V1b (or V3), V2, and V4[5,10–14]:

- V1a receptors are located on vascular smooth muscles, myocardium, hepatocytes, and platelets. Their activation, which is cyclic adenosine monophosphate (cAMP)-mediated phosphorylation, results in vasoconstriction, glycogenolysis in the liver, and platelet aggregation. They also have a positive inotropic effect and promote myocyte hypertrophy.
- V1b receptors are found in the anterior pituitary, and they activate the release of adrenocorticotropin via a phosphoinositide pathway.
- V2 receptors are located in the collecting duct cells. They mediate renal water retention by the kidney and are predominantly responsible for the antidiuretic effect of AVP. Binding of AVP on V2 receptors activates adenylate cyclase, which stimulates cAMP, resulting finally in the release of protein kinase. This latter induces the translocation of aquaporins (water channels) from intracellular vesicles to the apical membrane, thereby allowing water retention.
- V4 receptors are present in the glial cell membranes. They contribute to the activation of aquaporin-4 water channel in the brain and could have a role in the development of brain edema.

Regulation of Thirst

Thirst is targeted by plasma hypertonicity, hypovolemia, and arterial hypotension,[4–7] and is suppressed by hypotonicity and hypervolemia. Thirst is mediated by osmoreceptors, which are located in the hypothalamus, but distinct from those responsible of AVP release. The osmotic threshold for thirst is greater than AVP (290 to 295 mOsm/L).

Cerebral Osmoregulation

Because it is contained in a rigid skull, the brain is particularly vulnerable to osmotic shift. Thus, plasma hypotonicity may be responsible for cerebral swelling and thereby for intracranial hypertension. Fortunately, the brain is not a perfect osmometer, and it is able to regulate its volume. This phenomenon, so-called cerebral osmoregulation, is mediated by modifications in the cerebral content of intracellular osmotically active particles.[15–18] Two types of such protective osmoles are involved in this mechanism:

- Inorganic osmoles are electrolytes (sodium, potassium, chloride)
- Organic osmolytes or idiogenic osmoles are essentially represented by amino acids, polyols, and triethylamines.

The efficacy of cerebral osmoregulation depends on the rapidity of the development of tonicity variation. In fact, cellular loss of electrolytes occurs in response to acute hypotonicity. It begins in the first hour by sodium extrusion and persists for 24 hours aided by potassium extrusion. The delayed response to chronic hypotonicity is characterized by a decrease in intracellular organic osmolyte content. Acute osmoregulation due to changes in electrolytes content is very rapid but not complete, so that the osmotic gradient is only attenuated and moderate changes in cerebral volume appear. In cases of chronic changes in plasma tonicity, the modifications of organic

osmolytes permit obtaining an osmotic equilibrium between ECF and ICF, and thus avoiding modifications in cerebral volume. Converse phenomenon develops in case of plasma hypertonicity. Beside the rapidity of variation in tonicity, gender may influence the efficacy of cerebral osmoregulation. Estrogen and progesterone, which inhibit the activity of NA-K–adenosine triphosphatase (ATPase), reduce the cerebral volume regulation. Thus, menstruating women have a higher risk of brain damage during hyponatremia.[18–22] Hypoxia, by the same mechanism, alters cerebral osmoregulation and must be considered a risk factor of brain injury during variations of plasma tonicity.

Classification and Treatment of Hyponatremia

Hyponatremia may be present with normal, decreased, or increased osmolality. Thus according to plasma tonicity, hyponatremia may be associated with normal ICF, intracellular dehydration, or hyperhydration.

Hyponatremia with Normal or Increased Plasma Osmolality

Both severe hyperprotidemia and hyperlipidemia may coexist with hyponatremia. As sodium is only dissolved in this aqueous phase, the sodium concentration measured per liter of plasma will be low, but normal if measured per liter of plasma water. These factitious hyponatremias are isotonic and have no effect on ICF volume.[4–7,23] Hyperglycemia creates plasma hypertonicity and thereby water shift from ICF to ECF. This movement is responsible for both ICF dehydration and a dilutional hyponatremia in ECF. In this situation, hyponatremia accompanies plasma hypertonicity.[4–7,23] Such hypertonic hyponatremia is also reported with hypertonic mannitol treatments.

Hypotonic Hyponatremia

Diagnosis and Classification

Only hypotonic hyponatremia induces intracellular hyperhydration. The first step is to evaluate the severity of the trouble, which determines the therapeutic management and the prognosis.[4–7,24] Classically, the degree of severity of hyponatremia was based on the value of sodium concentration; severe hyponatremia is defined by a plasma sodium concentration <110 to 120 mEq/L. However, more than an absolute value, severity of hyponatremia depends on the efficacy of cerebral volume regulation, that is, the rapidity of development of hyponatremia, gender, and age. Although hyponatremia is also often classified as acute or chronic, it is more clinically relevant to distinguish symptomatic from asymptomatic hyponatremia. Indeed, the severity of hyponatremic encephalopathy reflects the severity of cerebral edema, which is the result of the individual efficacy of cerebral osmoregulation. Neurologic symptoms are not specific and variable.

Sodium concentration is the primary determinant of ICF volume, whereas total body sodium content determines ECF volume. Therefore, plasma tonicity may vary independently of ECF volume, and hyponatremia may develop with a normal, increased, or decreased ECF volume. This classification is the second step in diagnosing the cause of hyponatremia (Table 72.1).

Principles of Nonspecific Treatment

Whatever the cause, the actual management of hyponatremia is based on the absence or presence and severity of neurologic symptoms. This enables deciding between a passive, slow treatment and an active, rapid one. This decision must be made because an inappropriate rate (too rapid or not rapid enough) of correction of sodium concentration may lead to the death of the patient. In cases of severe symptomatic hyponatremia, brain death resulting from cerebral edema may occur if natremia does not rapidly reach a safe level. In contrast, a rapid correction of asymptomatic hyponatremia may be responsible for severe brain damage, for example, osmotic demyelination lesions. Central pontine and extrapontine myelinolysis is the classic severe complication of a rapid correction of hyponatremia.[4,11,12,25–28] This syndrome appears after an initial improvement of the patient followed by a free period of some days. Finally, at days 4 to 7, the neurologic status of the patient worsens progressively. Manifestations are

Table 72.1. Major causes of hypotonic hyponatremia according to the variation of the extracellular fluid volume

Euvolemia	Hypervolemia	Hypovolemia
Water retention	Water and Na^+ retention	Water and Na^+ losses
Syndrome of inappropriate ADH secretion (SIADH) Potomania Endocrinologic illnesses: Adrenal insufficiency Hypothyroidism Thiazides	Natriuresis >20 mEq/L Oliguric acute renal failure Iatrogenous causes: Abundant infusions of hypotonic solutions Natriuresis <20 mEq/L Edema states: congestive heart failure, cirrhosis, nephrotic syndrome, sepsis Severe denutrition Pregnancy	Natriuresis >20 mEq/L Renal losses: Renal salt wasting Hypoaldosteronism Loop diuretics (furosemide) Cerebral salt wasting Natriuresis <20 mEq/L Gastrointestinal losses : Vomiting, diarrhea, gastrointestinal fistulas or suctioning Skin losses Burns

variable, beginning with a simple stupor, but the evolution is often severe, characterized by a pseudobulbar paralysis, dysphagia, dysarthria, quadriparesis, locked-in syndrome, or death. All of these complications must be prevented by treatment (Fig. 72.3). Symptomatic hyponatremia requires an active therapeutic intervention with hypertonic saline solution associated if necessary with the treatment of vital function. The rate of increase in sodium concentration must be rapid (4 to 5 mEq/L/h) until neurologic signs disappear, and slower in the following hours. Infusion of hypertonic saline should be discontinued when natremia achieves 130 mEq/L to avoid a rebound effect.[9,12,25–30] Intravenous furosemide may be added, but is never sufficient alone. Repeated clinical examinations and electrolytes concentration determinations are always necessary. Water restriction combined with a loop diuretic is usually sufficient to treat asymptomatic hyponatremia.

Hyponatremia During Heart Failure

Pathophysiological Mechanisms

Hyponatremia as a Consequence of Heart Failure

The pathophysiologic mechanisms of heart failure (HF) are complex. Heart failure is usually characterized by decreased cardiac output associated with impaired left ventricular function and decreased arterial pressure. These modifications lead to the compensatory activation of vasoactive neurohormonal systems including the sympa-

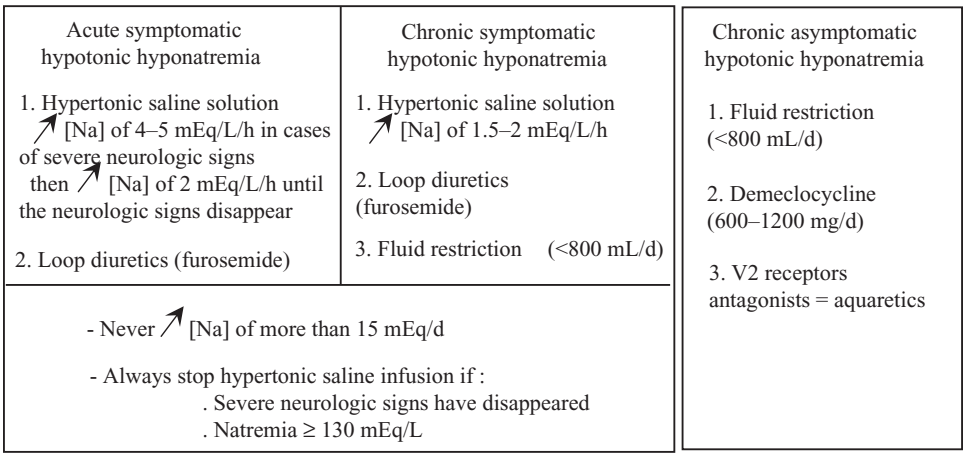

Figure 72.3. General principles of treatment of hypotonic hyponatremia according to their severity.

thetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and the AVP hormone.[30–36] All of them may initially help to maintain blood flow to vital organs. However, in both acute and chronic situations, these systems lead finally to adverse effects and to the development of a vicious circle. The activation of RAAS induces vasoconstriction, sodium and water renal retention, and AVP overproduction. In addition to these classic effects, RAAS produces inflammatory reactions (cytokines production) and remodeling processes, which aggravate myocardial hypertrophy and cell apoptosis. The nonosmotic AVP secretion during HF seems to play a major role in the pathogenesis and severity of HF.[18,34–37] Indeed, AVP aggravates the progression of HF by several mechanisms. The V1 receptor activation could induce vasoconstriction and lead to increase left ventricular afterload and cardiac remodeling. The V2 receptors stimulation could also induce volume expansion and increase cardiac preload. Plasma AVP levels are inappropriately high in both acute and chronic HF.[30–42] Moreover, AVP levels seem to be related to the severity of HF.

Hyponatremia during HF is mostly due to the excessive AVP secretion resulting from nonosmotic stimulation. AVP secretion increases from free-water absorption, leading to a hypervolemic hyponatremia.[4–7,12]

Hyponatremia as a Consequence of Diuretic Treatments

Even though they are widely prescribed, the use of diuretics in patients with HF remains debated.[43] Diuretic therapy has a large number of side effects, including worsening renal function and electrolyte disturbances.[44,45] Among them, thiazides are the most often implicated in the occurrence of hyponatremia.[45–49] Sonnenblick et al.[50] have found that diuretic-induced hyponatremia was related in 73% of cases to thiazides, but only in 6% and 1% of cases, respectively, to furosemide and spironolactone. Thiazides act by blocking sodium chloride cotransport in the distal convoluted tubule, which is the major site for diluting urine. Loop diuretics may also impair free-water clearance on the loop site, but to a lesser extent. Thiazide-induced hyponatremia usually appears 2 weeks after initiation of treatment, whereas it develops after a longer delay with furosemide. Hyponatremia occurs preferentially in women (80% of cases) and in elderly patients.[45,46,50,51] In this situation, hyponatremia may cause severe neurologic symptoms and severe brain damages. Consequently, thiazides in elderly women should be used with great caution and a close sodium level monitoring.

Hyponatremia: A Risk Factor During Heart Failure

Hyponatremia occurs approximately in 5% of patients with HF.[33] The relationship between hyponatremia and the importance of neurohormonal disturbances support the fact that hyponatremia is a marker of the severity of HF. However, several studies demonstrated that hyponatremia is an independent factor of poor prognosis in patients with HF.[52–56] Hyponatremia has been found to be a predictor of 30-day and 1-year mortality in patients hospitalized for congestive heart failure (CHF).[52] Hyponatremia is also an independent factor of readmission in hospital, and of major complications.[52–56] Klein et al.[56] have shown that hyponatremia was associated with a higher number of days hospitalized for cardiovascular causes and a twofold higher in-hospital and 60-day mortality. Interestingly, the improvement in sodium level during hospitalization was associated with an improved postdischarge mortality. Finally, hyponatremia in HF may interact with the administration of diuretics.[46]

Hyponatremia and Heart Failure: Treatment

General principles of treatment of hyponatremia are the same in HF. However, most of the conventional treatments of HF may induce or aggravate hyponatremia, and most of the treatments of hyponatremia may worsen HF. Thus, correction of hyponatremia in HF is more complicated than in other situations.

Conventional Treatments

Fluid Restriction

The restriction of water intake remains the first nonaggressive treatment of asymptomatic

hypervolemic hyponatremia.[4–7,12,25] However, its efficacy to increase natremia is limited: a fluid intake <80 mL/d increases natremia by only 1 to 2 mEq/L.[9] Thus, this therapy is not appropriate in severe symptomatic hyponatremia. Moreover, adherence to strict fluid restriction is often difficult because of the obligatory fluid infusions in hospitalized patients. Thirst and decrease in blood volume, which are aggravated by diuretics, make this therapy difficult in chronic patients too.

Hypertonic Saline Solutions

Hypertonic saline intravenous infusion remains the best treatment of severe symptomatic hyponatremia. However, beside the previous risk of osmotic demyelination, this treatment could be poorly tolerated in patients with CHF. Indeed, hypertonic saline solutions, by increasing the ECF volume, could precipitate pulmonary edema. If necessary, this therapy must be cautiously administered in association with diuretics and controlled by a strict hemodynamic monitoring. A recent randomized study conducted in 1047 patients with a refractory CHF has compared one group receiving high-dose furosemide alone with another one receiving the same dose of furosemide associated with a small infusion of hypertonic saline.[57,58] The study found that serum sodium levels were corrected only in the group receiving hypertonic saline infusion. Interestingly, the survival rate during a 4–year follow-up period was 55% and 13%, respectively, in the group treated with hypertonic saline and the group treated with furosemide alone. This result strongly supports hyponatremia as an independent risk factor in CHF.

Diuretics

Diuretic therapy represents an essential treatment of CHF. But diuretics are responsible for many electrolyte disorders, especially hyponatremia. Thiazides must be stopped in cases of acute hyponatremia. Loop diuretics, even possibly inducing hyponatremia, may be combined with hypertonic saline infusion if necessary. Other diuretics aside from thiazides do not often lead to severe hyponatremia, which is precipitated by other factors such as a prolonged sodium intake restriction, thirst, hypovolemia, and AVP secretion.

Hemofiltration and Ultrafiltration

Hemofiltration and ultrafiltration offer some substantial advantages in treating acute and chronic CHF. These techniques enable an appropriate fluid regulation, permitting obtaining large losses from the ECF while maintaining the effective circulating volume.[58–63] Because of isotonic losses, these techniques also enable correcting electrolytes disturbances in a safe way, especially hyponatremia. Several studies have confirmed the beneficial effects of hemofiltration in patients with acute HF resistant to diuretics: persistent weight loss, improvement in renal function and diuresis, and correction of hyponatremia.[58–63] If continuous hemofiltration is the most appropriate technique in acute patients, intermittent ultrafiltration could be efficient in less severe patients with CHF.

Vasopressin Antagonists

Considering the pathophysiology of CHF, vasopressin antagonists appear as theoretical appropriate molecules. Several nonpeptide vasopressin receptors antagonists, so-called vaptan, have been developed. Their action depends on their relative selectivity for the different vasopressin receptors subtypes. Blockade of the V1a receptor induces vasodilation, and decrease in systemic vascular resistance, which may improve cardiac and renal hemodynamic. To date, for pharmaceutical reasons, no clinical study has been performed with such antagonists. In contrast to salidiuretics, V2 receptor antagonists, "aquaresis," induce diuresis (positive free-water clearance) without any change in electrolytes. Moreover, by decreasing preload, they do not activate the RAAS. Unlike conventional diuretic treatments with their side effects and their limited efficacy, vasopressin antagonists seem to offer prolonged efficacy without worsening HF.[1,39]

V2 Antagonists

Tolvaptan, an oral specific and selective V2 receptor antagonist, has been studied in two large controlled trials in patients with CHF.[64–66] The first double-blind trial was conducted in 221 patients with moderate CHF. Three doses of daily tolvaptan for 25 days were compared to the usual treat-

ment.[64] A significant decrease in edema, body weight, increase in diuresis, and correction of hyponatremia were found in all patients receiving tolvaptan. These beneficial effects were observed from day 1 and persisted in the following days. No severe side effect related to tolvaptan was observed. The second trial was performed using a similar methodology, but including more severe patients presenting an acute CHF with clinical congestion and a left ventricular fraction <40%.[66] Two doses of intravenous tolvaptan were administered in addition to standard therapy for 60 days. The same beneficial effects were found and a trend toward a lower mortality was observed.

Combined V1a/V2 Antagonists

Conivaptan has been evaluated in humans by intravenous administration. Udelson et al.[67] compared the effect of two single intravenous doses of conivaptan versus placebo in 142 patients with advanced CHF. They found that conivaptan significantly reduced pulmonary wedge pressure and right atrial pressure at 3 and 6 hours after administration, without any effect on cardiac index, systemic vascular resistance, and blood pressure. Moreover, diuresis increased during the first 4 hours in a dose-dependent manner.

Association of Vasopressin Antagonists and Other Treatments

As both AVP and RAAS are involved in the pathophysiology of CHF and hyponatremia, coadministration of AVP antagonists and angiotensin-converting enzyme inhibitor could induce an effective management of vasoconstriction while treating overload and hyponatremia. An experimental randomized trial has confirmed that the administration of conivaptan alone significantly decreases body weight, whereas a combination of conivaptan and captopril decrease blood pressure, natriuretic peptide level, and ventricular mass.[68]

Gheorghiade et al.[69], in a recent randomized controlled trial, compared the efficacy of fluid restriction with or without the addition of tolvaptan to treat hyponatremia in euvolemic or hypervolemic states. A significant increase in serum sodium level was observed rapidly, 4 hours after the first dose of tolvaptan. In both groups, the increase in natremia reached a plateau at day 5, but it was higher with tolvaptan (+5.2 ± 4.5 vs. +1 ± 4.7 mEq/L, $p = .019$). Correction of hyponatremia was associated with a significant increase in urine output and positive free-water clearance, but no change in body weight.

Conclusion

Hyponatremia mostly occurs as a consequence of neurohormonal activation during CHF. High AVP levels and RAAS activation usually lead to a hypervolemic asymptomatic hyponatremia. Diuretic treatments, especially thiazides, may induce severe euvolemic or hypovolemic hyponatremia in patients at risk, such as elderly women. Rules and risks of the treatment of hyponatremia are the same whatever the cause. Hypertonic saline infusion is necessary in severe symptomatic disorder to avoid brain edema. A slow increase in serum sodium level is recommended in asymptomatic hyponatremia to prevent central nervous myelinolysis.

Hyponatremia occurring during HF represents not only a marker of severity, but also an independent factor of poor prognosis. Thus, correction of hyponatremia is widely recommended, but it represents a real challenge. Indeed, conventional treatments of HF have some limitations due to a possible worsening of hyponatremia and vice versa. The new molecules, AVP antagonists, which act as aquaretic agents, could be the most appropriate treatment in the future, and recent clinical data are promising.

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