

# The Editor's Roundtable: Pathophysiology and Management of Hyponatremia and the Role of Vasopressin Antagonists

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## Introduction

The most common clinically relevant electrolyte abnormality is hyponatremia, which is associated with increased morbidity and mortality in several disease states, including heart failure (HF).<sup>1</sup> An important decision in the management of patients with HF is whether hyponatremia should be treated and how this is most effectively and safely accom-

plished. These and other issues about hyponatremia are discussed in this Editor's Roundtable.

## Discussion

**Dr. Friedewald:** What level of hyponatremia is clinically significant?

**Dr. Gheorghiade:** For many years, hyponatremia was not considered significant unless the serum sodium (Na) was <125 mg/dl, a level that causes central nervous system (CNS) changes. In recent years, however, even "mild" hyponatremia has been recognized as an important laboratory finding for poor prognosis in patients with HF. Although "mild" hyponatremia is relatively common in patients with HF, severe hyponatremia is rare.

**Dr. Friedewald:** What serum Na level is considered "hyponatremic"?

**Dr. Gheorghiade:** "Mild" hyponatremia is defined as a serum Na of <135 mEq/L.<sup>2</sup>

**Dr. Friedewald:** Why do other low electrolyte concentrations (i.e., hypokalemia, hypocalcemia, hypomagnesemia) have significant direct effects on cardiac function, but hyponatremia does not?

**Dr. Emmett:** One possibility is that in terms of molar concentration, hyponatremia, even with an acute reduction from 140 to 120 mEq/L, is fractionally small compared to a reduction of a serum potassium from 4 to 3 mEq/L, which is a 25% drop. Na<sup>+</sup>/K<sup>+</sup>-ATPase (adenosine triphosphatase) and other Na-dependent ion transporters and pumps may not be as adversely affected by a serum Na concentration that is only modestly reduced.

**Dr. Roberts:** Does the definition of hyponatremia as a serum Na <135 mEq/L also apply to patients with HF?

**Dr. Gheorghiade:** Yes.

**Dr. Emmett:** The main issue is at what level is a low serum Na concentration clinically relevant, as opposed to the level it causes obvious symptoms.

**Dr. Gheorghiade:** The cardiovascular response to drugs differs between patients with normal serum Na compared to patients with hyponatremia. One example of clinical relevance is the response to angiotensin-converting enzyme inhibitors (ACEIs) in patients with HF, which may be altered in the presence of hyponatremia. Hyponatremic patients may develop severe hypotension in response to an ACEI. The effects of digitalis preparations may also be less predictable in the presence of hyponatremia.

**Dr. Emmett:** It is difficult to know, however, whether the differences in drug response are due to the serum Na level per se or whether the reduced serum Na is mainly a marker of the severity of the underlying heart disease. Patients with hyponatremia probably have the most severe HF, making them more sensitive to some drug effects.

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**Dr. Gheorghiade:** I agree. Hyponatremia is like anemia. It is not a diagnosis; rather, it is a manifestation of multiple, different underlying problems. Hyponatremia in very old people, or “sick-cell syndrome,” was described many years ago and may be seen with patients with HF, liver insufficiency, or inappropriate secretion of antidiuretic hormone (ADH). It may also be associated with therapy such as diuretics, ACEIs, and aldosterone-blocking agents. Once hyponatremia is diagnosed, finding the cause is of paramount importance. In addition, one should distinguish between normovolemic, hypovolemic, and hypervolemic hyponatremia.

**Dr. Friedewald:** How common is hyponatremia in HF?

**Dr. Gheorghiade:** Mild hyponatremia occurs in approximately 25% of hospitalized HF patients.

**Dr. Friedewald:** Is hyponatremia in HF related to decreased systolic left ventricular (LV) function?

**Dr. Gheorghiade:** No, it is the same in patients with preserved or reduced LV systolic function. In the last few years, we’ve learned that patients admitted with hyponatremia and HF do not normalize their serum Na during hospitalization. Therefore, they are being sent home with hyponatremia. Their clinical and hemodynamic responses are no different than normonatremic patients. In other words, the hyponatremic patient and the normonatremic patient improve during hospitalization to a similar degree. In spite of the improvement during hospitalization for the hyponatremic patient, the mortality and rehospitalization rate is much higher than patients who have a normal serum Na.

**Dr. Emmett:** In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial,<sup>3</sup> very few patients enrolled with decompensated HF had significant hyponatremia.

**Dr. Gheorghiade:** It is true that that <8% of >4,000 patients hospitalized with worsening HF and a reduced EF (ejection fraction) enrolled worldwide in the EVEREST trial had hyponatremia. This differs from registries such as OPTIMIZE (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) in the United States and European registries in which approximately 25% of patients admitted with HF have hyponatremia. The reason for this discrepancy is unclear. The role of vasopressin antagonists in patients admitted with HF and hyponatremia remains to be tested.

**Dr. Friedewald:** What is the mechanism of hyponatremia in HF?

**Dr. Gheorghiade:** In HF, as demonstrated by Dr. Gary Francis many years ago, there is increased production of vasopressin. The serum concentration of vasopressin is also correlated with the severity of HF. For unknown reasons, plasma vasopressin levels are inappropriately high in both acute and chronic HF. In HF, however, there is a nonosmotic stimulation of vasopressin secretion. In addition to causing sympathetic activation and vasoconstriction, high levels of circulating vasopressin may also cause myocardial fibrosis and hypertrophy as well as severe water retention, increased intravascular volume, and, as a consequence, dilutional hyponatremia.

**Dr. Emmett:** The fact that tolvaptan, which blocks the renal tubule effects of vasopressin, significantly raises the serum Na concentration in HF patients is good evi-

dence that high vasopressin levels are the main cause of the hyponatremia.

**Dr. Gheorghiade:** Retention of *both* Na and water occurs in HF. Thus, although the total body Na is increased, there is more excess water than Na, resulting in dilutional hyponatremia.

**Dr. Emmett:** There also are multiple other possible causes of hyponatremia in patients with HF, such as the use of thiazide diuretics and conditions that generate the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Dr. Gheorghiade:** Even trauma patients are often hyponatremic, a common finding on the orthopedic ward, especially among older patients.

**Dr. Roberts:** Is vasopressin measurable?

**Dr. Emmett:** Yes, vasopressin can be measured, and urinary aquaporin-2, which is increased by vasopressin, is also measurable.

**Dr. Roberts:** Does hyponatremia adversely affect anti-HF medications?

**Dr. Gheorghiade:** This has not been well studied. It is possible, however, that both the effects and the side effects in response to ACEIs, ARBs (angiotensin receptor blockers), aldosterone-blocking agents, and/or digoxin may be somewhat different in patients with hyponatremia when compared to normonatremic patients.

**Dr. Roberts:** Is in-hospital mortality higher in HF patients with hyponatremia?

**Dr. Gheorghiade:** It is difficult to assess in-hospital mortality from registries, because in-hospital mortality is relatively low. However, in patients presenting with relatively low blood pressure, hyponatremia has been associated with higher mortality.

**Dr. Roberts:** Is mild hyponatremia a good predictor of late mortality?

**Dr. Gheorghiade:** Yes. Patients discharged with hyponatremia, within a couple of months, have a mortality and readmission rate that is almost double compared to normonatremic patients.

**Dr. Friedewald:** What is meant by “mild” hyponatremia?

**Dr. Gheorghiade:** “Mild” hyponatremia refers to serum Na <135 to >125 mEq/L. Severe hyponatremia is serum Na <120 to 125 mEq/L. However, when using the term “severe,” we must also evaluate for other clinical manifestations. For example, if the patient is significantly symptomatic with a serum Na of 130 mEq/L, we might label this as “severe” hyponatremia.

**Dr. Friedewald:** How is serum Na used as a determinant of treatment in patients with HF?

**Dr. Gheorghiade:** Hyponatremia is 1 of the most important prognostic indicators of poor prognosis in HF. These patients should be aggressively treated with evidence-based therapies.

**Dr. Friedewald:** What are the symptoms of hyponatremia?

**Dr. Emmett:** Levels of hyponatremia serum Na in the range of 128 to 130 mEq/L, which we used to consider “asymptomatic” hyponatremia, probably does cause subtle symptoms due to cerebral edema.

**Dr. Gheorghiade:** I distinguish between acute versus chronic hyponatremia. The manifestations of acute hyponatremia are related to cerebral overhydration that usually

occur when the serum Na concentration falls below 125 mEq/L. This manifests with headache and lethargy. Seizures, coma, or even respiratory arrest may occur if the concentration falls below 110 to 115 mEq/L. Rapid correction of hyponatremia may be deleterious. Many patients with chronic moderate hyponatremia are asymptomatic. However, they may have subtle neurological findings often missed in the routine evaluation.

**Dr. Emmett:** These levels of hyponatremia generate neurologic changes that can be measured with various mental status and coordination exams, such as walking, balance, and gait. These all improve when the serum Na concentration is increased to levels >130 mEq/L. Thus, we have now raised the target desired serum Na concentration from 125 to 130 mEq/L, although there is no easy way to accomplish such an increase.

**Dr. Gheorghiad:** Patients admitted with HF and hyponatremia have signs and symptoms of congestion manifested by peripheral edema and dyspnea. Because these patients have a low osmolality, it is often difficult to mobilize fluid from the extravascular space. Vasopressin-2 antagonists that are known to increase serum osmolality and are also known to have a powerful aquaretic effect are very effective in decreasing total body water without a significant decrease in intravascular volume.

**Dr. Emmett:** The removal of water from the body caused by antagonists of vasopressin comes from both the extracellular fluid (ECF), about 1/3, and the intracellular (ICF), about 2/3. The osmolality of cell water increases symmetrically with the osmolality of the ECF. Thus, there should be no development of an osmotic gradient that will move fluid from the ICF to the ECF.

**Dr. Gheorghiad:** Hypertonic saline, however, has been shown to effectively mobilize the fluid in patients with severe HF.

**Dr. Emmett:** I refer to the action of drugs like tolvaptan, not hypertonic saline.

**Dr. Gheorghiad:** That is the point. A vasopressin-2 antagonist such as tolvaptan may not be different from hypertonic saline, with 1 important distinction: a vasopressin-2 antagonist is much safer, because it is less likely to cause intravascular fluid overload.

**Dr. Emmett:** The distribution of hypertonic saline is restricted to the ECF. This initially raises the ECF osmolality. The osmotic gradient which develops will then cause water to shift from the ICF to the ECF. I agree that this will simultaneously reduce cell fluid (i.e., cerebral edema, for example) and expand the ECF. When drugs like tolvaptan cause net water excretion, 1/3 comes from the ECF and 2/3 comes from the ICF. Both spaces shrink!

**Dr. Gheorghiad:** In cardiovascular patients, it is difficult to mobilize fluid when the serum Na is low, perhaps related to low serum osmolality.

**Dr. Emmett:** I agree, but I believe that is due to severe HF and because diuretics become less effective.

**Dr. Roberts:** Is there any particular area in the brain where edema forms secondary to hyponatremia?

**Dr. Emmett:** I do not know which areas of the brain are most susceptible. It is likely that both anatomic areas and certain cell types have variable sensitivity to hyponatremia. Differences between white and gray matter

have been described. Some areas of the brain are much more susceptible to water shifts. For example the demyelination syndrome can affect many parts of the central nervous system (CNS) but is often most severe in the pons. Certain parts of the brain may be more susceptible to water shift related to the density and specific forms of aquaporins in various CNS cells.

**Dr. Friedewald:** Is the main problem in treating HF in patients with hyponatremia due to more difficulty in causing diuresis?

**Dr. Gheorghiad:** Yes. Regardless of the mechanism, it is more difficult to mobilize fluid in patients who are hyponatremic, particularly when thiazide, loop diuretics, and aldosterone-blocking agents may further aggravate the hyponatremia.

**Dr. Friedewald:** And loop diuretics are less effective than thiazides in the presence of hyponatremia?

**Dr. Gheorghiad:** I do not know. Except for metolazone, however, thiazides do not work well in patients with a low GFR (glomerular filtration rate). Loop diuretics are therefore preferred in this setting.

**Dr. Emmett:** I agree, but we do not know all of the resistance mechanisms responsible. Also, because hyponatremia also reflects more severe HF, treatment in general is less effective.

**Dr. Gheorghiad:** Both selective and nonselective vasopressin antagonists have a significant aquaretic effect when added to loop diuretics.

**Dr. Emmett:** More water than salt is mobilized, however.

**Dr. Gheorghiad:** That is why I use the term "aquaretic" for a vasopressin antagonist, since it increases urine volume without natriuresis.

**Dr. Emmett:** Even if *no* sodium is removed, the excretion of 6 L of water contracts the ECF by 2 L.

**Dr. Roberts:** What do you do when a patient on 25 mg of hydrochlorothiazide develops hyponatremia?

**Dr. Emmett:** Thiazides are contraindicated in patients susceptible to hyponatremia, so it should be discontinued in that setting. Loop diuretics, however, *can* be used in patients with hyponatremia.

**Dr. Friedewald:** Is it correct that as many as 10% of people on a chlorothiazide diuretic will become hyponatremic?

**Dr. Emmett:** I do not know the exact number; it varies with age and gender.

**Dr. Friedewald:** This is an important point, however, since chlorothiazide diuretics are first-line agents for hypertension.

**Dr. Gheorghiad:** Yes, but most patients with HF and congestion, particularly patients with reduced renal function, respond poorly to chlorothiazide and thus require a loop diuretic.

**Dr. Roberts:** What is the effect of age and gender on the incidence of hyponatremia with chlorothiazide diuretics?

**Dr. Emmett:** Older women seem to be much more susceptible to severe, symptomatic hyponatremia when treated with thiazide diuretics. It can occur very rapidly and it is reproducible. The mechanism is not well understood but is likely due to a combination of stimulation of ADH secretion, polydipsia, and negative sodium and potassium balance. These women often *gain* weight. Potassium loss also contributes to their hyponatremia. It is an interesting

phenomenon, but it probably is not often relevant to HF treatment, because thiazide diuretics are seldom used to treat HF.

**Dr. Roberts:** Is thiazide-induced hyponatremia dose related?

**Dr. Emmett:** It is often reproducible and can occur after only 1 or 2 doses of a thiazide.

**Dr. Gheorghiade:** Among the 48,000 patients in OPTIMIZE at the time of admission for HF, 11% in the hyponatremic group were getting a thiazide, compared to 8% in patients who were not.<sup>4</sup> Thus, thiazide diuretics are more likely to be associated with hyponatremia in HF patients. However, in OPTIMIZE, >60% of patients were receiving a loop diuretic. There was not a substantial difference in the use of loop diuretics between the normonatremic and hyponatremic groups.

**Dr. Emmett:** Thiazides impair the kidney's ability to dilute urine but not its ability to concentrate urine. Loop diuretics potently decrease *both* dilution and concentration by the kidney. This fact accounts, at least in part, for the greater likelihood of thiazides than loop diuretics to cause hyponatremia.

**Dr. Roberts:** Are loop diuretics as effective as thiazide diuretics for treatment of systemic hypertension?

**Dr. Emmett:** No, thiazide diuretics are more effective. Thiazides have several unique characteristics that contribute to their better antihypertensive action, including a longer half-life and greater long-term net salt depletion.

**Dr. Friedewald:** How often should loop diuretics be given for HF?

**Dr. Gheorghiade:** Two to 3 doses per day are needed.

**Dr. Friedewald:** A large number of patients with HF have received prior treatment for hypertension. The most commonly used antihypertensive regimens include a thiazide diuretic, so this is an important issue.

**Dr. Gheorghiade:** Approximately 25% of the patients in OPTIMIZE were markedly hypertensive, but they had *reactive* hypertension and became normotensive soon after beginning HF treatment. Thus, hypertension at the time of admission for HF is usually related to a high sympathetic tone and a high LV filling pressure.

**Dr. Friedewald:** What is the etiology of the HF in patients you have studied?

**Dr. Gheorghiade:** Eighty percent have a *history* of hypertension, so hypertension commonly contributes to the development of HF. Once HF occurs, however, hypertension is no longer a target of treatment in many patients. Many patients admitted with acute heart failure syndromes (AHFS), and in particular those with preserved systolic function, have a mismatch between the increase in afterload or blood pressure and reduced diastolic function that often causes severe pulmonary congestion and even pulmonary edema. For these patients, the main targets are reduction of afterload and intravascular volume with a vasodilator and a diuretic.

**Dr. Roberts:** What about the patient with systemic hypertension who has a large myocardial infarct? The infarct eliminates the hypertension as a result of the decreased cardiac output. Does HF in them then cause reactive hypertension?

**Dr. Gheorghiade:** An outpatient with significant myocardial damage due to a large myocardial infarction and is normotensive may not increase the blood pressure during worsening HF because there is no cardiac reserve. Those patients have a worse prognosis than those who, during acute exacerbation of HF, are able to increase their blood pressure. In fact, in the OPTIMIZE database, patients admitted with so-called reactive hypertension had much lower mortality in hospital and postdischarge compared to those who are normotensive at the time of admission.

**Dr. Friedewald:** What is the difference between patients with chronic HF and HF requiring hospitalization?

**Dr. Gheorghiade:** These are 2 different entities. The patient requiring hospitalization for HF not only requires urgent therapy, but available data suggest that during the process—before, during, or soon after—there is additional cardiac and/or kidney injury. Although mortality in outpatients with chronic HF has decreased from about 17% to 4% in clinical trials over the last 15 years, the mortality and rehospitalization in patients *hospitalized* for HF have not decreased during this period. After admission for HF, the postdischarge mortality and rehospitalization can be as high as 15% and 30%, respectively, within 60 to 90 days. Most of what we know about hyponatremia in HF is in the hospitalized patient.

**Dr. Roberts:** How many of the 5 million persons in the USA with HF have the hospitalized versus the nonhospitalized type of HF?

**Dr. Gheorghiade:** In the USA, we have >1 million hospitalizations per year for HF. There is no other medical condition in which patients appear to respond to therapies through hospitalization and within 60 to 90 days of discharge have such high event rates. As I said before, it's important to realize that this high event rate has not decreased in the last 10 to 15 years, in spite of the introduction of newer therapies for chronic HF.

**Dr. Roberts:** What do you mean by "event rate"?

**Dr. Gheorghiade:** I'm talking about mortality and rehospitalization within a few months after discharge. We also need to realize the majority of patients who die do so from progressive HF. In contrast, in chronic ambulatory HF patients, the majority are dying suddenly and unexpectedly. AHFS differs from chronic HF because it requires urgent therapy, myocardial and kidney injury may occur during or soon after hospitalization, and it has a very high event rate in spite of the available therapy.

**Dr. Friedewald:** Does correction of hyponatremia in the hospitalized patient with HF cause better outcomes, or is hyponatremia merely a biomarker for poor outcomes?

**Dr. Gheorghiade:** I do not know whether correction of hyponatremia results in better outcomes. Based on retrospective data, the answer is "yes," but there are no prospective data to answer the question.

**Dr. Roberts:** Do HF patients with poor LV systolic function compared to HF in patients with preserved LV systolic function have the same frequency of hyponatremia?

**Dr. Gheorghiade:** Yes. Approximately 50% of patients admitted for HF have relatively preserved systolic function. The frequency of hyponatremia is the same in patients with preserved or reduced EF. After admission for HF, EF is no longer a predictor of prognosis since the mortality and

readmission rate is the same in patients with preserved or reduced EF. However, the mode of death and the cause of death or rehospitalization may be different.

**Dr. Roberts:** Do patients with HF secondary to idiopathic dilated cardiomyopathy have the same frequency of hyponatremia as patients with HF due to ischemic cardiomyopathy?

**Dr. Gheorghiu:** Yes. The prevalence of hyponatremia is identical. Approximately 50% to 60% of all admissions for HF occur in patients who have coronary artery disease.

**Dr. Roberts:** What percent of patients with chronic HF are never hospitalized?

**Dr. Gheorghiu:** I do not know.

**Dr. Roberts:** But it is a large number, is it not?

**Dr. Gheorghiu:** Yes, it is a very large number. However, in this group, many will die suddenly and unexpectedly. Sudden cardiac death in that population accounts for 60% of deaths.

**Dr. Roberts:** How do you define sudden cardiac death in patients with HF?

**Dr. Gheorghiu:** I define sudden cardiac death as death that is *unexpected*: death among patients who do not have severe signs and symptoms of HF before they die. In research trials, this is adjudicated by a committee.

**Dr. Friedewald:** Most patients with chronic HF are treated by primary care physicians, not cardiologists. Are there better outcomes among patients treated by cardiologists than by primary care physicians?

**Dr. Gheorghiu:** In the USA, a significant number of patients admitted for HF are seen by hospitalists or primary care physicians. Another group is being seen by general cardiologists. Approximately 5% are treated by HF specialists, who usually treat patients who are refractory to other therapies for HF. Thus, because patients treated by HF specialists are generally much sicker, it is very difficult to answer your question. However, it is clear that patients who are admitted with HF and respond very well to diuretic therapy—to the point of having no congestion at the time of discharge—have a very high postdischarge mortality and readmission in spite of “responding well” to inpatient therapy.

**Dr. Friedewald:** What are the indications for giving a vasopressin antagonist to a HF patient with hyponatremia?

**Dr. Gheorghiu:** Patients with hyponatremia are at increased risk for death. In those patients, there should be maximal use of therapies proven to improve outcomes, such as  $\beta$  blockers, ACE inhibitors, ARBs, and renin-aldosterone-angiotensin blockade and cardiac resynchronization therapy for patients with a wide QRS complex. The main reason for admission is congestion manifest by dyspnea, rales, increased jugular venous pressure, and edema. The addition of a vasopressin-2 antagonist to standard therapy can cause a modest reduction in these signs and symptoms and a significant reduction in body weight without affecting significant renal function in patients with or without hyponatremia. In addition, vasopressin-2 antagonists may improve or normalize serum Na in patients who are hyponatremic.

**Dr. Friedewald:** What signs and symptoms improve?

**Dr. Gheorghiu:** In EVEREST, the addition of once-a-day tolvaptan started after 24 to 48 hours caused a significant but modest decrease in dyspnea, reduced jugular ve-

nous pressure, and decreased pulmonary rales, without significantly affecting renal function, blood pressure, or heart rate. However, in EVEREST only 8% of patients have hyponatremia. From a theoretical point of view, those are the patients who may derive a significant benefit from this therapy.

**Dr. Emmett:** Patients with *severe* hyponatremia and HF often have significant neurologic manifestations from the hyponatremia, including cerebral edema, which can be improved by a vasopressin antagonist.

**Dr. Gheorghiu:** In such patients, however, the hyponatremia must not be corrected too rapidly.

**Dr. Emmett:** Yes. The goal should be to limit the serum Na increase to no more than about 10 mEq/L during the first day of treatment with the vasopressin antagonist.

**Dr. Gheorghiu:** I agree. Vasopressin antagonists have not been tested in patients with HF and hyponatremia. Tolvaptan and other vasopressin antagonists, such as conivaptan, are not approved for HF, whereas they are approved for hyponatremia, defined as a serum Na <125 mEq/L or in patients who have symptoms related to hyponatremia.

**Dr. Friedewald:** This is true even in HF patients with a normal serum Na?

**Dr. Emmett:** Yes.

**Dr. Friedewald:** The indication for tolvaptan reads, in part, “for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction.” Thus, I interpret “or less marked hyponatremia that is symptomatic” to mean that a patient with a serum Na of 130 mEq/L and dyspnea is a candidate, within approved labeling, for tolvaptan.

**Dr. Gheorghiu:** I agree.

**Dr. Emmett:** I also agree.

**Dr. Friedewald:** Thus, the main reason for treatment of a HF patient with a vasopressin antagonist is for temporary symptom relief. Is that correct?

**Dr. Gheorghiu:** Yes.

**Dr. Roberts:** HF patients are already on many drugs. Are there any problems in using vasopressin antagonists with other HF drugs, such as spironolactone?

**Dr. Gheorghiu:** No. There is no change in blood pressure or heart rate with vasopressin antagonists.

**Dr. Emmett:** There are 2 vasopressin antagonists available in the United States, tolvaptan and conivaptan.

**Dr. Friedewald:** Tell us about conivaptan.

**Dr. Gheorghiu:** Conivaptan is for intravenous use, and its hemodynamic effects are the same as tolvaptan, which is taken orally. Neither drug affects heart rate or cardiac output, and they both increase osmolarity and decrease the pulmonary capillary wedge pressure.

**Dr. Emmett:** Although there have been no obvious hemodynamic differences in studies so far, theoretically conivaptan should have greater arterial and venous dilating effect because it is *both* a vasopressin-1 and a vasopressin-2 antagonist.

**Dr. Roberts:** How much do vasopressin antagonists cost?

**Dr. Emmett:** They are both expensive, which is 1 reason they are not used as much as they could be.

**Dr. Friedewald:** How effective is the absorption of an oral medication such as tolvaptan by patients with HF?

**Dr. Gheorghiane:** This is an important question that has not been well studied. It appears that peripheral edema or right-sided HF does not affect absorption of tolvaptan.

**Dr. Emmett:** Tolvaptan is a small peptide that should be easily absorbed, but this has not been studied.

**Dr. Friedewald:** How does standard treatment of HF affect hyponatremia?

**Dr. Gheorghiane:** Traditional therapy in patients with HF is ineffective for hyponatremia. The patient who is hyponatremic on admission usually is still hyponatremic on discharge with standard therapy, even when the pulmonary capillary wedge pressure and cardiac output are improved.

**Dr. Friedewald:** If a good treatment response for the HF is achieved, what difference does it make if the hyponatremia persists?

**Dr. Gheorghiane:** That is the point of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) database, which showed the event rate to be double.<sup>5</sup>

**Dr. Emmett:** Why?

**Dr. Gheorghiane:** I do not know.

**Dr. Emmett:** In theory, with HF improvement, hyponatremia also should improve, but the data do not show that.

**Dr. Roberts:** How long can a patient survive with a serum Na of 125 mEq/L?

**Dr. Emmett:** Years.

**Dr. Roberts:** Does a serum Na of 120 mEq/L have a proarrhythmic effect or effect on cardiac conduction?

**Dr. Gheorghiane:** I am not aware of such effects.

**Dr. Friedewald:** When giving a vasopressin antagonist in the hospital, is the drug continued after discharge?

**Dr. Gheorghiane:** Generally, no, since there are no outcome studies that support long-term use. The current clinical benefit is primarily sign and symptom relief, mainly neurologic, during hospitalization. EVEREST data do not show cardiac benefits for continuing a vasopressor antagonist after discharge.

**Dr. Emmett:** I would consider treating a patient with hyponatremia—even modest hyponatremia—if there was significant neurological improvement, especially better gait and balance, which would lessen the chance of a fall and its consequences, such as a broken hip.

**Dr. Gheorghiane:** I agree.

**Dr. Friedewald:** Is there difficulty obtaining reimbursement for using these drugs?

**Dr. Gheorghiane:** When it is the only treatment for severe hyponatremia, which can be life threatening, there should not be. A vasopressin antagonist is an antidote for hyponatremia.

**Dr. Friedewald:** Improved outcomes in HF patients receiving vasopressin antagonists for hyponatremia, however, have not been established?

**Dr. Gheorghiane:** We do not know whether they improve outcomes because this has not been studied. Retrospective data from the ACTIV (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure) trial<sup>6</sup> suggested improved outcomes, but this remains a hypothesis to be tested.

**Dr. Roberts:** How did these drugs get approved by the Food and Drug Administration?

**Dr. Gheorghiane:** They were approved based on SALT (Study of Ascending Levels of Tolvaptan in Hyponatremia), a trial for hyponatremia due to liver problems, HF, or SIADH.<sup>7</sup>

**Dr. Friedewald:** What is the efficacy of vasopressin antagonists for treating hyponatremia?

**Dr. Gheorghiane:** These agents are extremely effective in elevating and even normalizing the serum Na in patients who are hyponatremic, based on both prospective and retrospective studies.

**Dr. Emmett:** In the presence of severe renal insufficiency, however, they are less effective and may not work at all.

**Dr. Friedewald:** Are there any contraindications for vasopressin antagonists?

**Dr. Gheorghiane:** Yes, patients who cannot freely ingest fluids for whatever reason should not receive a vasopressin antagonist, as they may develop severe hypernatremia.

**Dr. Emmett:** The main concerns regarding the use of vasopressin antagonists are raising the serum Na too rapidly and giving it to patients with reversible hyponatremia due to intra-arterial volume contraction. The true volume-contracted patient needs intravascular volume expansion with saline and not a vasopressin antagonist.

**Dr. Friedewald:** A patient admitted to the hospital with severe HF, however, may have an inadequate sense of thirst.

**Dr. Gheorghiane:** If a patient cannot drink water, then tolvaptan should not be given, due to the danger of hypernatremia.

**Dr. Emmett:** It is important to closely monitor the serum Na, especially if drinking water may be a problem.

**Dr. Friedewald:** How often do you measure the serum Na in patients receiving tolvaptan?

**Dr. Gheorghiane:** It depends on the degree of initial hyponatremia. With mild hyponatremia (i.e., 134 mEq/L), it should be measured once per day or every other day. As long as the patient is drinking water, however, I am not greatly concerned about hypernatremia. Compared to other drugs used for acute HF, they are relatively safe in terms of heart rate, blood pressure, and renal function, and the serum potassium and magnesium levels are unaffected. As for the serum Na itself, if it is normal or only slightly low, it changes little, but if it is low, it rises and even may normalize.

**Dr. Emmett:** I agree that the ability to drink water is very important, especially in the patient who is producing large volumes of urine. In the original SALT studies, 2% to 3% of patients had serum Na increases >12 mEq/L per day. This rate of increase should be prevented if possible.

**Dr. Roberts:** What is the danger of increasing the serum Na too rapidly?

**Dr. Emmett:** Permanent brain damage is at least partially due to demyelination.

**Dr. Roberts:** What is the lowest serum Na compatible with life?

**Dr. Gheorghiane:** I do not know.

**Dr. Emmett:** I have seen patients with a serum Na in the range of 90 mEq/L, but I do not know if they survived to discharge. Also, it is important to point out that what we have been discussing is *hypo*-osmolal, hypotonic hypona-

tremia. In the presence of severe hyperglycemia, however, *hyperosmolar*, hypertonic hyponatremia may be present. This type of hyponatremia is very different and has very different etiologies, pathologic implications, treatments, and prognosis.

**Dr. Friedewald:** What are the side effects of vasopressin antagonists?

**Dr. Emmett:** Side effects are generally not serious if the drug is prescribed as outlined by the manufacturer and the serum Na concentration is not increased too rapidly. When used as directed, the side effects include dry mouth, thirst, and polyuria. These can be very bothersome to patients. Some patients urinate every 15 minutes, all day and throughout the night.

**Dr. Roberts:** Prostatic enlargement could be a problem for these patients.

**Dr. Friedewald:** There are a lot of unanswered questions about vasopressin antagonists. What studies do you advocate next?

**Dr. Gheorghide:** First, we need to understand the differences between blocking vasopressin-2 receptor alone versus blocking both vasopressin-1 and vasopressin-2 receptors. Second, there need to be outcome studies when treating hyponatremia in patients with HF. Third, we should further study the effects of vasopressin blockade in both inpatients and outpatients with HF independent of their serum Na.

**Dr. Friedewald:** Although there appear to be significant benefits, at least with symptom improvement, the drug cost appears to be a major issue. Thus, outcome studies would seem to be critically important if we are going to make optimal use of these drugs.

**Dr. Gheorghide:** Definitely.

**Dr. Friedewald:** Which is too bad, because symptom relief must always be a high priority, and I am afraid we are entering an era in which that alone will not suffice. There are probably few things worse than patients' feelings that they cannot catch their breath, which tolvaptan helps, correct?

**Dr. Gheorghide:** In the EVEREST trial, standard HF therapy improves dyspnea in 65% of patients, compared to 72% when tolvaptan was added to standard therapy.

**Dr. Friedewald:** Can dyspnea improvement be regarded as an outcome?

**Dr. Gheorghide:** Dyspnea improvement is an *approval end point* by the Food and Drug Administration. It is an approvable end point when the improvement in dyspnea is substantial and the drug is very safe. It will take a large patient population to demonstrate that the drug is safe.

**Dr. Friedewald:** Is there evidence that vasopressin antagonists reduce rehospitalization?

**Dr. Gheorghide:** In EVEREST, it did not reduce rehospitalization.

**Dr. Roberts:** Does hyponatremia affect the blood pressure?

**Dr. Emmett:** It depends on the mechanism responsible for the hyponatremia. For example, when hyponatremia is due to SIADH, the ECF volume is expanded, the urine Na is high, and the blood pressure usually rises a little from baseline.

**Dr. Gheorghide:** Except for digoxin, a vasopressin antagonist is the only type of drug used in treating HF that does not lower the blood pressure, which is good in patients who are hypotensive, and many HF patients are hypotensive. Thus, vasopressin removes fluid even in patients who are hypotensive without further decreasing the blood pressure.

**Dr. Roberts:** Are there any studies of patients with chronic HF who received *only* a vasopressin-2 antagonist?

**Dr. Gheorghide:** Such a study would be difficult to do, but we do know that both diuretics and tolvaptan decrease body weight with minimal additive effect when they are combined.

**Dr. Emmett:** Another issue relates to the effect of vasopressin-2 antagonists on von Willebrand factor. This increases with the administration of desmopressin, a vasopressin-2-specific agonist. Do von Willebrand factor levels fall when tolvaptan is given?

**Dr. Gheorghide:** I do not know.

**Dr. Friedewald:** What is the effect of tolvaptan on acute myocardial infarction and stroke risk?

**Dr. Gheorghide:** In a retrospective analysis in EVEREST, acute myocardial infarctions decreased and stroke risk increased from 1% to 2%, but there was no effect on overall mortality.

**Dr. Emmett:** Conivaptan, but not tolvaptan, blocks the effects at the vasopressin-1a receptor, so with that drug there is a theoretical risk of increased variceal bleeding.

**Dr. Roberts:** Where is vasopressin made in the body?

**Dr. Emmett:** In the posterior pituitary gland. Tiny amounts also may be synthesized in other tissues, like the heart. It may have autocrine or paracrine effects locally as opposed to the endocrine effects produced by pituitary vasopressin.

**Dr. Gheorghide:** And there are probably more than 2 vasopressin receptors.

**Dr. Emmett:** Yes, there are at least 2 vasopressin-1 receptors,  $V_{1a}$  and  $V_{1b}$ , and there may be other receptors that are currently not characterized.

**Dr. Friedewald:** Where are the receptors located?

**Dr. Emmett:** The  $V_{1b}$  receptors seem to be mainly located in the brain. They are probably responsible for vasopressin related increases in adrenocorticotrophic hormone levels. The  $V_{1a}$  receptors are located mainly in vascular endothelium. The V-2 receptor is found in all tissues that are susceptible to vasopressin water transport, mainly the distal renal tubule and vascular endothelium.

**Dr. Friedewald:** Given its receptor location in the endothelium, what effect does vasopressin have on nitric oxide generation?

**Dr. Emmett:** I do not know.

**Dr. Emmett:** A potentially large market for vasopressin antagonism is comprised of patients with chronic SIADH, such as persons with neoplasms and lung disease. They often have chronically low, symptomatic serum Na concentrations. Again, cost is a major factor in the use of vasopressin antagonists in these patients.

**Dr. Gheorghide:** The same applies to patients with chronic liver disease, who might do much better if they could be rid of excess water due to cirrhosis.

**Dr. Emmett:** This could be an important perioperative treatment for liver transplantation, because anesthesiologists are reluctant to anesthetize patients with very low serum Na.

**Dr. Roberts:** Why are these 2 drugs so expensive?

**Dr. Gheorghide:** I am uncertain, but it could relate to research costs.

**Dr. Emmett:** These drugs were in the pipeline for a very long time before they came to market.

**Dr. Friedewald:** Thank you.

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