doi: 10.1111/j.1751-7133.2010.00164.x

REVIEW PAPER

Treatment Options for Hyponatremia in Heart Failure

Hyponatremia is independently associated with adverse outcomes in patients with congestive heart failure (CHF). The primary cause of hyponatremia in CHF is the inappropriate secretion of the antidiuretic hormone arginine vasopressin (AVP). The binding of AVP to V_2 receptors in the renal collecting duct promotes water retention, a process that can lead to dilutional hyponatremia as well as increased ventricular preload. Conventional treatment of hyponatremia in CHF is largely based on water restriction, which is neither effective nor well-tolerated. V_2- and dual $V_{1\alpha}/V_2$-receptor antagonists offer physiologically based treatment for dilutional hyponatremia. Clinical trials in patients with hyponatremia including those with CHF using both selective and nonselective vasopressin antagonists have demonstrated the effectiveness and safety of these agents in correcting this common electrolyte abnormality. Congest Heart Fail. *2010;16(4)(suppl 1):S15–S18.*

Steven R. Goldsmith, MD
From the Hennepin County Medical Center, Minneapolis, Minnesota, and the University of Minnesota, Minneapolis, MN

Address for correspondence:
Steven R. Goldsmith, MD, Cardiology Division, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415
E-mail: srg_hcmc@yahoo.com
Manuscript received April 13, 2010; accepted April 25, 2010

Congestive heart failure (CHF) affects an estimated 5 million people in the United States and is the leading cause of hospitalization among the elderly.[1,2] Despite advances in treatment, CHF is associated with substantial mortality and morbidity, particularly after hospitalization for worsening heart failure. In a large recent study of patients with decompensated CHF, 35% of patients either died or were readmitted within 60 days of hospitalization.[3] There are several well-characterized high-risk features for patients with acute heart failure, including renal failure, persistent congestion, and hyponatremia. Hyponatremia is likely to be due to a combination of factors in both acute and chronic CHF. Failure to deliver solute to the diluting segment of the nephron coupled with diuretic-induced compromise of the function of the loop of Henle may contribute; however, excessive secretion of the antidiuretic hormone arginine vasopressin (AVP) is the dominant factor. Studies conducted more than 2 decades ago showed that CHF patients with and without hyponatremia have inappropriately elevated plasma AVP levels.[4–7] In patients with hyponatremia, the AVP level is increased paradoxically when the plasma osmolality is low. Even after acute water loading, plasma AVP secretion is not suppressed entirely, nor is the urine maximally dilute.[8–10] Both hyponatremia and inadequately suppressed AVP secretion are more often associated with persistent or severe congestion, which is also linked to a poor outcome in patients with CHF.[11]

Hyponatremia could simply be a marker of the severity of the CHF syndrome, or it could be a contributor to morbidity and mortality. Currently, data are insufficient to distinguish these possibilities. There are, however, several reasons to suspect that hyponatremia could contribute to morbidity and mortality in CHF. The disorder may limit the use of diuretics out of fear of further lowering serum sodium and therefore contribute to suboptimal decongestion. Cognitive and motor impairments have been reported with hyponatremia in other settings,[12] which could, if present in CHF patients, adversely affect physical conditioning and exercise tolerance. Perhaps most provocatively, it is known that the brain compensates for the edema induced by acute and chronic hyponatremia by reducing concentrations of key osmolytes and cofactors involved in neural signaling; this "adaptation" presumably causes the neurologic abnormalities. There is no reason to assume that a similar process might not occur in myocytes. A potential causal relationship between hyponatremia and a poor outcome in CHF is in fact supported by a recent study in which correction of serum sodium using the drastic and potentially dangerous intervention of hypertonic saline, was, independent of other measured variables, associated with better clinical outcomes during an observation period of several months.[13] And, although based on a retrospective analysis of a relatively small subgroup, hyponatremic heart failure patients assigned to V_2 antagonist therapy in the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan (EVEREST) trial had a survival benefit (M. Gheorghiade, oral communication, June 2009).

More comprehensive study of the relationship between hyponatremia and heart failure has been hampered by the difficulty of safely and easily increasing serum sodium. In patients with hyponatremia and CHF, water restriction is neither effective nor well-tolerated since to work at all, free water intake must be restricted to less than 1 L/d. The impact of water restriction has also never been studied in clinical trials. Hypertonic

saline is not an option for treatment of hyponatremia with CHF other than in severely symptomatic cases and must be used with the utmost care, even in emergency situations. Urea or demeclocycline can be effective, but neither has been prospectively studied in hyponatremia in any setting, and their clinical utility is limited by adverse effects including renal toxicity, which makes them extremely unattractive in patients with CHF in whom preventing renal dysfunction is critically important. The simple truth is that until the advent of the V_2 and combined V_{1a}/V_2 antagonists, there have been no physiologically rational, effective, safe, and well-tolerated therapies for hyponatremia in any setting, including CHF.

AVP in CHF

The secretion of AVP from the posterior pituitary is regulated by plasma osmolality and many nonosmotic factors. In CHF, plasma AVP remains coupled to plasma osmolality, but the set point is shifted to a higher AVP concentration.[8–10] Thus, although AVP levels decline as plasma osmolality decreases, they do not fall to the expected levels but often remain elevated. This inappropriate elevation of AVP levels therefore reflects the influence of nonosmotic processes on AVP secretion, but the specifics of these mechanisms are not understood. Frequently, "ineffective arterial volume" is cited as the cause, but this phrase has no physiologic correspondent, and the various components of the baroreflex system known to control AVP in quadrupeds do not seem to be as important in monkeys and humans[14] (for obvious reasons, in that primates spend much of their time upright, and changing positions would wreak havoc with serum osmolality if AVP secretion were sensitive to small changes in central venous and arterial pressure). It is more likely that the nonosmotic stimulation of AVP in CHF arises from central stimulation as a result of up-regulated activity of the sympathetic nervous system and renin angiotensin systems, both of which may stimulate AVP centrally and both of which are activated in patients with CHF. Whatever the cause, hyponatremia in CHF clearly does represent a state of inappropriate ADH secretion (arginine vasopressin being the antidiuretic hormone), and therefore, the therapeutic goal should be either to diminish AVP secretion, not currently possible other than with ethanol, or to antagonize its effects.

AVP generates its effects through interaction with several structurally distinct receptor subtypes, each of which belongs to the G-protein–coupled 7-domain transmembrane superfamily.[15] These receptors are coupled to different secondary messenger systems and mediate different physiologic processes. Most effects of excessive AVP secretion relevant to hyponatremia are linked to signaling at the renal V_2 receptors, which are located in the renal collecting duct and are coupled to adenylate cyclase via the guanosine triphosphate–binding protein G_S.[16] When the V_2 receptors are activated, the intracellular cyclic adenosine monophosphate (cAMP) level increases, which, in turn, triggers the translocation of the aquaporin-2 water channel to the apical plasma membrane of the renal collecting duct cells, leading to increased permeability of the collecting duct membrane and thus to enhanced water reabsorption.[17] The ascending limb of the loop of Henle also contains V_2 receptors, which, when activated, mediate Na^+–K^+–Cl^- cotransport. They are also found on vascular endothelial cells, where they may induce vasodilation and contribute to homeostasis through the secretion of von Willebrand factor.[18,19]

Excessive signaling at the V_{1a} AVP receptor may produce other cardiovascular effects. V_{1a} activation is coupled to the phosphoinositol signaling pathway, thereby increasing inositol triphosphate and, subsequently, intracellular calcium levels. V_{1a} receptors are located on vascular smooth muscle cells, myocytes, platelets, and hepatocytes, where they mediate vasoconstriction, myocardial hypertrophy, platelet aggregation, and glycogenolysis.[15] Much less is known about the physiologic role of the V_{1b} receptors, located predominantly in the anterior pituitary, where they mediate corticotropin release both under stress and under normal conditions.

AVP Receptor Antagonists

Single (V_{1a} or V_2) and dual (V_{1a} and V_2) AVP receptor antagonists have been developed. The role of the V_{1b} receptor is less well defined; until recently, it was not a target for drug development. Only very limited data are currently available with selective V_{1a} antagonists in clinical CHF.[20] These data suggest that if plasma AVP is elevated, a vasodilating response to V_{1a} antagonism may occur. No long-term data are available, and there are no V_{1a} antagonists under development for the treatment of CHF.

V_2 receptor antagonism produces aquaresis—the electrolyte-sparing excretion of water—which increases free water clearance (FWC).[16] Aquaresis differs from the diuresis produced by currently available diuretics, such as furosemide, in that electrolytes (eg, sodium and potassium) are not depleted during aquaresis. As a result, V_2 receptor antagonism increases urine volume, decreases urine osmolality, and raises serum sodium without disturbing plasma potassium and magnesium levels.

The 3 AVP receptor antagonists that have been studied most extensively and are either already approved by the US Food and Drug Administration or currently undergoing further development are the V_2 receptor antagonists tolvaptan, lixivaptan, and the dual V_{1a}/V_2 receptor antagonist conivaptan.[16] These agents have been fully characterized in vitro and in vivo. Each is a potent antagonist of the targeted receptors as demonstrated in binding assays and in the expected physiologic responses observed in animal studies.[21–27] Any of the agents possessing V_2 receptor antagonist activity would be expected to be useful in treating the hyponatremia of CHF.

Vasopressin Receptor Antagonism for Hyponatremia in Patients With CHF

Randomized controlled trials of both conivaptan and tolvaptan in euvolemic

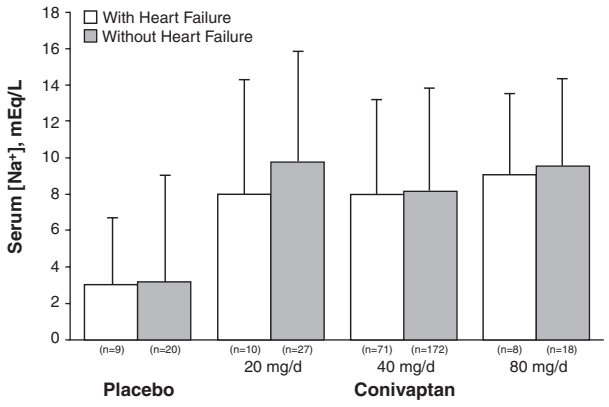

Figure. Effect of intravenous conivaptan on mean change in serum sodium ([Na+]) from baseline to end of treatment in patients with and without heart failure.

and hypervolemic hyponatremia have been published and show benefit, acutely in the case of conivaptan[28–30] and up to 30 days in the case of tolvaptan. These studies included patients both with and without CHF. The efficacy and safety of conivaptan were evaluated in three phase 3 randomized, double-blind, placebo-controlled trials.[28–30] In the first trial, patients received a 20-mg intravenous (IV) loading dose of conivaptan, followed by continuous infusion of conivaptan 40 or 80 mg/d for 4 days or placebo. In the other 2 trials, 83 and 74 patients, respectively, received oral conivaptan 40 or 80 mg/d or placebo in 2 divided doses for 5 days.[29,30] Compared with placebo, increases from baseline in serum sodium and FWC were significantly greater in patients given IV conivaptan, and treatment was well-tolerated.[28]

Data from all 3 trials were analyzed to determine the efficacy of conivaptan, specifically in patients with hyponatremia and CHF (Figure).[31] Of the 241 enrolled patients, 94 patients (39%) had CHF (placebo, n=31; conivaptan 40 mg/d, n=25; conivaptan 80 mg/d, n=28). Compared with placebo, serum sodium increased significantly from baseline after IV administration of conivaptan 40 and 80 mg/d. Similar results were observed in the patients given oral conivaptan 40 and 80 mg/d. Conivaptan was well-tolerated in patients with CHF; most adverse events were mild to moderate. In a retrospective analysis, the efficacy and safety of IV conivaptan were evaluated in hyponatremic patients, with and without underlying heart failure, from the double-blind placebo-controlled trial and one open-label trial.[32] Patients in the open-label trial received an IV loading dose of conivaptan 20 mg followed by a continuous 4-day infusion of conivaptan 20 or 40 mg/d. IV conivaptan increased serum sodium with all doses, regardless of heart failure status; however, increases in serum sodium were slower in patients with heart failure. Conivaptan was well-tolerated among patients with and without heart failure.

The data supporting the use of tolvaptan in the hyponatremia of CHF come from the SALT 1 and SALT 2 trials, which were randomized, double-blind, placebo-controlled trials in patients with hyponatremia, including patients with CHF. Tolvaptan 15 mg/d (increased to 30 or 60 mg/d based on the rate of serum sodium increase) produced significant increases from baseline in serum sodium.[33] The response was maintained to 30 days, and there was no difference in response in patients with and without CHF, who represented approximately one-third of the study population. In another trial designed to investigate the effects of tolvaptan on the treatment of acute decompensated heart failure, tolvaptan 30 mg/d also produced significant and sustained increases from baseline in serum sodium in patients with hyponatremia.[34]

Conclusions

In patients with CHF, hyponatremia is an independent predictor of poor outcome, including death. In many patients with CHF, the AVP level is elevated inappropriately and contributes to the development of hyponatremia. Until now, there have been no effective and/or well-tolerated treatments for hyponatremia, including the hyponatremia of CHF. Based on pathophysiologic and pharmacologic principles as well as the safety and efficacy data from well-conducted placebo-controlled trials, combined V_{1a}/V_2 and selective V_2 antagonists clearly are the treatments of choice when hyponatremia requires treatment in patients with CHF. Clinical research should now shift to investigating the possible pathophysiologic contribution of hyponatremia and/or inappropriate AVP secretion to outcomes in CHF. The tools are now available to conduct such studies, and the results, if hyponatremia and/or excessive AVP secretion are causally linked to poor outcomes in patients with hyponatremia and CHF, could open a potentially important new therapeutic strategy for many of the highest-risk patients with this persistently lethal syndrome.

Disclosures: *Dr. Goldsmith has served as a speaker and consultant for Otsuka Pharmaceuticals and Astellas, has received grant support from Astellas, and received an honorarium funded by Abbott Laboratories and Otsuka America Pharmaceuticals for time and expertise spent in preparation of this article.*

References

1 *Heart Disease and Stroke Statistics – 2004 Update*. Dallas, TX: American Heart Association; 2003.

2 Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med*. 2003;4(suppl 7):S21–S30.

3 Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287: 1541–1547.

4 Szatalowicz VL, Arnold PE, Chaimovitz C, et al. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med*. 1981; 305:263–266.

5 Riegger GAJ, Liebau G, Kochsiek K. Antidiuretic hormone in congestive heart failure. *Am J Med*. 1982;72:49–52.

6 Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.

7 Goldsmith SR, Francis GS, Cowley AW Jr, et al. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol*. 1983;1:1385–1390.

8 Goldsmith SR, Francis GS, Cowley AW Jr. Arginine vasopressin and the renal response to water loading in congestive heart failure. *Am J Cardiol*. 1986;58:295–299.

9 Pruszczynski W, Vahanian A, Ardaillou R. Role of antidiuretic hormone in impaired water excretion in patients with congestive heart failure. *J Clin Endocrinol Metab*. 1984; 58:599–605.

10 Bichet DG, Kortas C, Mettauer B, et al. Modulation of plasma and platelet vasopressin by cardiac function in patients with heart failure. *Kidney Int*. 1986;29:1188–1196.

11 Gheorghiade M, Gattis WA, O'connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA*. 2004;291:1963–1971.

12 Renneboog B, Musch W, Vandemergel X, et al. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119:71–78.

13 Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J*. 2003;145: 459–466.

14 Goldsmith SR. Baroreflex control of vasopressin secretion in normal humans. In: Cowley AW, Liard J-F, Ausiello DA, eds. *Vasopressin: Cellular and Integrative Functions*, New York: Raven Press; 1988;389–397.

15 Goldsmith SR. Vasopressin: a therapeutic target in congestive heart failure? *J Card Fail*. 1999;5:347–356.

16 Verbalis JG. Vasopressin V2 receptor antagonists. *J Mol Endocrinol*. 2002;29:1–9.

17 Nielsen S, Kwon TH, Christensen BM, et al. Physiology and pathophysiology of renal aquaporins. *J Am Soc Nephrol*. 1999;10: 647–663.

18 Hirsch AT, Dzau VJ, Majzoub JA, Creager MA. Vasopressin-mediated forearm vasodilation in normal humans. Evidence for a vascular vasopressin V2 receptor. *J Clin Invest*. 1989;84:418–426.

19 Kaufmann JE, Oksche A, Wollheim CB, et al. Vasopressin-induced von Willebrand factor secretion from endothelial cells involves V2 receptors and cAMP. *J Clin Invest*. 2000; 106:107–116.

20 Creager MA, Faxon DP, Cutler SS, et al. Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. *J Am Coll Cardiol*. 1986;7:758–765.

21 Yamamura Y, Nakamura S, Itoh S, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. *J Pharmacol Exp Ther*. 1998;287:860–867.

22 Chan PS, Coupet J, Park HC, et al. VPA-985, a nonpeptide orally active and selective vasopressin V2 receptor antagonist. *Adv Exp Med Biol*. 1998;449:439–443.

23 Tahara A, Tomura Y, Wada KI, et al. Pharmacological profile of YM087, a novel potent nonpeptide vasopressin V1A and V2 receptor antagonist, in vitro and in vivo. *J Pharmacol Exp Ther*. 1997;282:301–308.

24 Tomura Y, Tahara A, Tsukada J, et al. Pharmacological profile of orally administered YM087, a vasopressin antagonist, in conscious rats. *Clin Exp Pharmacol Physiol*. 1999;26:399–403.

25 Risvanis J, Naitoh M, Johnston CI, Burrell LM. In vivo and in vitro characterisation of a nonpeptide vasopressin V(1A) and V(2) receptor antagonist (YM087) in the rat. *Eur J Pharmacol*. 1999;381:23–30.

26 Yatsu T, Tomura Y, Tahara A, et al. Pharmacological profile of YM087, a novel nonpeptide dual vasopressin V1A and V2 receptor antagonist, in dogs. *Eur J Pharmacol*. 1997; 321:225–230.

27 Serradeil-Le GC. An overview of SR121463, a selective non-peptide vasopressin V(2) receptor antagonist. *Cardiovasc Drug Rev*. 2001;19:201–214.

28 Zeltser D, Rosansky S, van RH, et al. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol*. 2007;27:447–457.

29 Annane D, Decaux G, Smith N. Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvolemic or hypervolemic hyponatremia. *Am J Med Sci*. 2009;337:28–36.

30 Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab*. 2006; 91:2145–2152.

31 Ghali JK, Verbalis JG, Gross P, et al. Conivaptan, a novel arginine vasopressin antagonist, increased serum sodium concentration in patients with heart failure and euvolemic or hypervolemic hyponatremia [abstract]. *Am Coll Cardiol*. 2006; 47: 816–817.

32 Ghali JK, Yan B, McNutt B. Conivaptan, a vasopressin-receptor antagonist, for the treatment of hyponatremia in patients with and without underlying heart failure [abstract]. *Heart Fail Soc*. 2008;14(suppl 1): 236.

33 Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099–2112.

34 Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297: 1319–1331.