Vasopressin Antagonists in the Treatment of Water-Retaining Disorders

Sumit Kumar, MD, MPH, and Tomas Berl, MD†*

Summary: The tools available to physicians for the treatment of hyponatremia, the most common of electrolyte disorders, are limited by lack of effectiveness, compliance difficulties, and toxicity problems. For this reason the development of novel oral antagonists of vasopressin provide a new approach to the management of these disorders. Since vasopressin plays a central role in the pathogenesis of most hyponatremic disorders, the inhibition of binding of the hormone to its receptors is likely to provide a most reliable and reproducible response leading to increases in free water excretion. This article reviews many of the studies that have been undertaken with this new class of agents, both in hypovolemic and hypervolemic settings.
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Hyponatremia is perhaps the most commonly occurring electrolyte disorder in hospitalized patients.[1] Although mild hyponatremia (serum sodium level, 130-134 mEq/L) is very common, occurring in 15% to 20% of hospitalized patients,[2] it often is asymptomatic. More severe hyponatremia (serum sodium level, <125 mEq/L) with possibly serious consequences occurs less commonly.[3,4] The most common causes of hyponatremia are the syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia associated with extracellular volume depletion.[5] The pathophysiology of hyponatremia directs the management, but central to most approaches is water restriction. Most conventional approaches that include the use of lithium, demeclocycline, urea, and salt tablets are unsatisfactory, difficult to sustain, and have serious side effects. Recently, exploiting the known pathobiology of water transport and metabolism, several agents have been developed that serve to fill this void and provide viable and sustainable water balance.

*Department of Nephrology, Presbyterian Hospital, Dallas, TX.
†Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado at Denver and Health Sciences Center, Denver, CO.
Address reprint requests to Tomas Berl, MD, Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado at Denver and Health Sciences Center, 4200 E. Ninth Ave, Box C281, Denver, CO 80262. E-mail: Tomas.Berl@uchsc.edu
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VASOPRESSIN PHYSIOLOGY

Vasopressin's primary site of action is the principal cell of the renal collecting tubules, where the V2 receptors (V2R) predominantly are expressed, although minor expression is known in the vascular endothelium where they stimulate the release of von Willebrand factor and factor 8. The V2R is part of a broader family of G_s-protein–coupled receptors that differ in localization and action. These include the V_{1a} and V_{1b} receptors. Upon sensing hyperosmolality, the osmoreceptors bring out the release of antidiuretic hormone (vasopressin) into the blood that then couples with the V2R and activates the G_S-coupled adenylyl cyclase system, thereby increasing intracellular cyclic adenosine monophosphate. Protein kinase A gets stimulated by cyclic adenosine monophosphate, leading to the phosphorylation of preformed aquaporin-2, leading to cellular translocation of vesicular aquaporin-2 (AQP2) to the apical membrane of the principal cells, making the cells water permeable (Fig. 1).[6] The control of vasopressin is governed by both osmotic and nonosmotic stimuli, with changes in osmotic stimuli being the primary stimulus. The physiologic actions of the various vasopressin receptors are summarized in Table 1.[7]

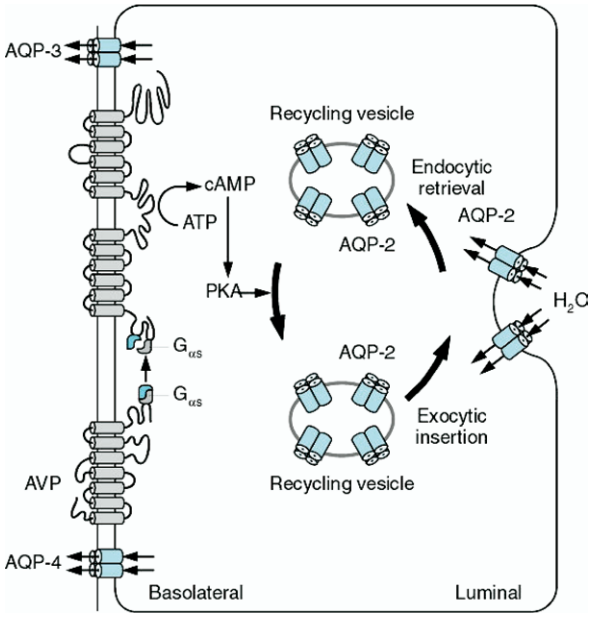

Figure 1. Cellular action of ADH. The binding of ADH with the basolateral V2 receptor in the principal cells of the renal collecting tubules affects all the events that follow. The cytoplasmic vesicles carry the water channels to the apical membrane in response to the binding, making it water permeable. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A. Reprinted with permission from Kumar and Berl.[37]

APPROACH TO THE HYPONATREMIC PATIENT

The volume status of the patient allows classification of hyponatremia into hypovolemic, euvolemic, and hypervolemic hyponatremia (Fig. 2).[8] Often patients may be volume depleted, but may have alterations in thirst perception. The measurement of urinary sodium can aid the diagnosis. A low urine Na (<20 mEq/L) may imply hypovolemia. Antidiuretic hormone (ADH) levels are increased to defend against volume contraction that leads to water retention and impaired water excretion. On the other hand, hypervolemic patients such as those with cirrhosis, congestive heart failure (CHF), and nephrotic syndrome have an excess of total body sodium, possibly even pulmonary vascular congestion, but have decreased effective arterial blood volume resulting in poor renal perfusion. These conditions are characterized inherently by avid sodium and water retention caused by increased ADH levels. Patients with euvolemia present a different paradigm in the evaluation and management of hyponatremia. Patients with the syndrome of inappropriate antidiuresis (SIAD) have variable levels of measurable ADH and excessive water intake driven by nonosmotic stimuli that together result in hyponatremia. The causes of SIAD can be divided broadly into pulmonary, central nervous system, paraneoplastic (malignancy related), and drug induced (Table 2). The diagnostic criteria for SIAD are summarized in Table 3.

THERAPEUTIC APPROACH TO HYPONATREMIA

There are no professional guidelines that outline the therapy for hyponatremia because

Table 1. Physiologic Action of the Vasopressin Receptors

Subtype	Location	Function
V1a	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy
	Platelets	Platelet aggregation
	Hepatocytes	Glyogenolysis
	Myometrium	Uterine contraction
V1b	Anterior pituitary gland	Releases ACTH, prolactin, endorphins
V2	Basolateral membrane of collecting tubule	Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis
	Vascular endothelium	Releases von Willebrand factor and factor VIII
	Vascular smooth muscle	Vasodilatation

Abbreviation: ACTH, adrenocorticotropic hormone.
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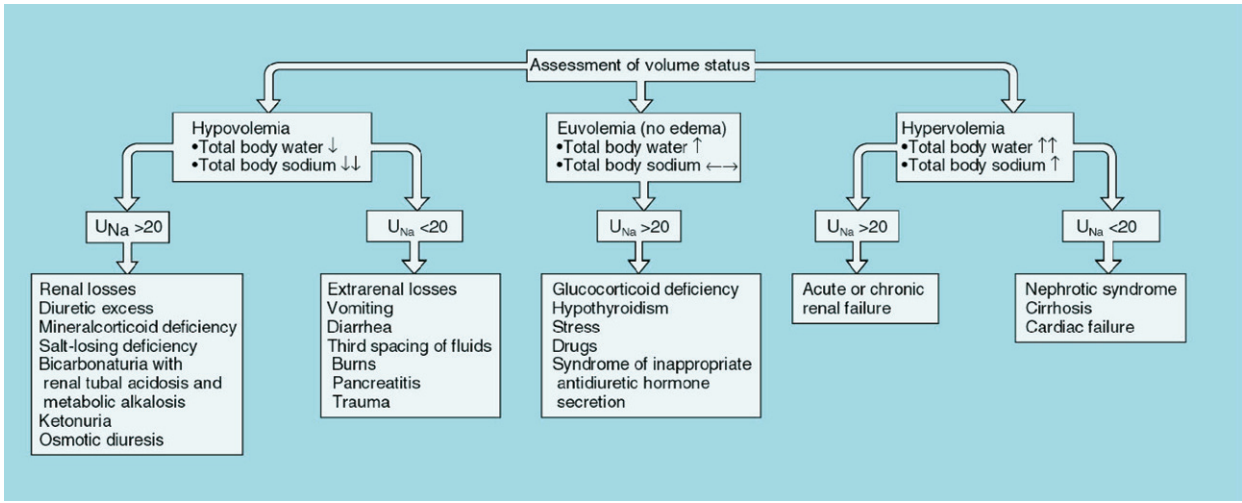

Figure 2. Classification of hyponatremia. Reprinted with permission from Kumar and Berl.[37]

there are no randomized controlled trials that compare 2 or more therapeutic options. Studies, mainly retrospective in nature, have been summarized recently.[9] On the other hand, the understanding of the pathophysiology, natural history, and end-organ complications has allowed acceptable standards of care to be developed over the past decades. The advent of new agents that specifically inhibit the vasopressin 2 receptor in the kidney hold much promise for the future. Overall, the rapidity with which hyponatremia develops dictates the aggressiveness of therapy. Most cases of hyponatremia, especially mild, respond to a correction of the underlying pathophysiology and judicious water restriction. In patients with severe hyponatremia (<125 mEq/L) and/or symptomatic patients, the use of hypertonic saline has been popularized over the years.[10] The pitfalls include compliance with water restriction, the risk for osmotic demyelination with overcorrection, and potential volume overload, among others, in patients treated with hypertonic saline.

The development of orally active nonpeptide vasopressin antagonists has revolutionized the management of hyponatremia in various clinical settings. There is currently one agent, conivaptan (a V_{1a}/V_2-receptor antagonist), available for intravenous use and 3 others in development for oral use (Table 4).

VAPTANS: PHARMACOLOGY

Conivaptan is the only combined V_{1a}/V_2 receptor whereas lixivaptan, satavaptan, and tolvaptan are specific V_2- receptor antagonists. All vaptans are orally active and all interact with the cytochrome P450 3A4 enzymes, however, conivaptan is the most potent inhibitor, limiting its use to hospitalized patients only for short durations of time.

Structurally, the agents available and in current development (Table 4) are all benzazepine or oxindole derivatives. The nonpeptide antagonists penetrate deeper into the transmembrane region of the V_2R than does native arginine vasopressin (AVP), preventing binding of the native hormone without themselves interacting with the H1 helix site that is critical for V_2R-mediated G-protein activation.[11] There is only a partial overlap in the binding sites for arginine vasopressin and the antagonists (Fig. 3). These agents displace radioactively labeled hormone from its receptor and thereby potently inhibit AVP stimulation of adenylate cyclase.[12]

EUVOLEMIC HYPONATREMIA

Hyponatremic Patients With SIADH

Early in the development, the first-generation oral vasopressin antagonist, OPC 31260, was used to treat patients with hyponatremia. In a

Table 2. Causes of SIADH

Malignant Diseases	Pulmonary Disorders	Disorders of the Central Nervous System
Carcinoma	Infections	Infection
Lung	Bacterial pneumonia	Encephalitis
Small-cell	Viral pneumonia	Meningitis
Mesothelioma	Pulmonary abscess	Brain abscess
Oropharynx	Tuberculosis	Rocky Mountain spotted fever
Gastrointestinal tract	Aspergillosis	AIDS
Stomach	Asthma	Bleeding and masses
Duodenum	Cystic fibrosis	Subdural hematoma
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage
Genitourinary tract		Cerebrovascular accident
Ureter		Brain tumors
Bladder		Head trauma
Prostate		Hydrocephalus
Endometrium		Cavemous sinus thrombosis
Endocrine thymoma		Other
Lymphomas		Multiple sclerosis
Sarcomas		Guillain–Barré syndrome
Ewing's sarcoma		Shy–Drager syndrome
		Delirium tremens
		Acute intermittent porphyria

Abbreviations: AIDS denotes the acquired immunodeficiency syndrome; SSRI, selective serotonin-reuptake inhibitor; MDMA 3,4-methylenedioxymethamphetamine.
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case series, 11 patients were treated successfully for hyponatremia secondary to SIADH.[13] Other investigators[14] treated hyponatremic patients in the setting of cirrhosis and SIADH with lixivaptan and in 6 patients achieved a correction of serum sodium from 126 (placebo group) to 133 mEq/L. Observations in this study included a decrease in urinary sodium excretion, likely as a result of volume expansion correction. Lixivaptan was used in the North American Lixivaptan study.[15] Four patients with SIADH improved their serum sodium level from 127 to 139 mEq/L. Satavaptan, a selective V_2-receptor antagonist, has been shown to increase serum sodium levels reliably in patients with SIADH.[16] Conivaptan, a V_{1a}- and V_2-receptor antagonist, orally administered, also has been shown to increase serum sodium in patients with SIADH unresponsive to water restriction.[14] On the heels of the smaller studies, the largest study to date examined the effect of tolvaptan (oral) in the randomized, double-blind, placebo-controlled Study of Ascending Levels of Tolvaptan in Hyponatremia in the United States (SALT-1) as well as multiple international sites (SALT-2) to ensure comparability.[17] Patients with euvolemic or hypervolemic hyponatremia with SIADH (44% patients) or chronic heart failure and cirrhosis were included. Subjects were randomized to receive tolvaptan or placebo in the outpatient setting, without mandated fluid restriction or changes in other drugs, including diuretics. As shown in Fig. 4, the serum sodium level was higher at all time points in both studies. Interestingly, the serum sodium level reverted to placebo levels after a 7-day follow-up period, implying that the aquaretic effect of the drug is

Table 2. Continued.

Drugs	Other Causes
Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Chlorpropramide	Idiopathic
SSRIs	Transient
Tricyclic antidepressants	Endurance exercise
Clofibrate (Atromid-S, Wyeth–Ayerst)	General anesthesia
Carbamazepine (Epitol, Lemmon, Tegretol, Ciba–Geigy)	Nausea
Vincristine (Oncovin, Lilly, Vincasar, Pharmacia and Upjohn)	Pain
Nicotine	Stress
Narcotics	
Antipsychotic drugs	
Ifosfamide (Ifex, Bristol-Myers Squibb)	
Cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pharmacia and Upjohn)	
Nonsteroidal antiinflammatory drugs	
MDMA (ecstasy)	
AVP analogues	
Desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon)	
Oxytocin (Pitocin, Parke–Davis; Syntocinon, Novartis)	
Vasopressin	

required to sustain a normal serum sodium. Health-related quality-of-life assessment by the short form (SF)-12 survey showed an improvement in the mental component.

In a double-blind, placebo-controlled trial, conivaptan was very effective in increasing the serum sodium levels in patients with euvolemic or hypervolemic hyponatremia. Herein, a placebo group was compared with 2 dose levels of 40 mg/d and 80 mg/d. The increases in serum sodium level were predictable and sustained over the study duration of 5 days.[18] Conivaptan was used in 56 patients with SIADH in another double-blind, placebo-controlled study. Thirty-five subjects received a bolus of 20 mg of intravenous conivaptan followed by either 40 mg/d or 80 mg/d by continuous infusion. All patients were treated with a 2-L water restriction. Patients treated with conivaptan had a predictable and significant ($P < .05$) increase in serum sodium level.[19]

Conivaptan is a substrate and potent inhibitor of the microsomal enzyme cytochrome P450 (CYP) 3A4, prohibiting the concomitant use of many chemotherapeutic agents, calcium channel blockers, ketoconazole, itraconazole, clarithromycin, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, benzodiazepines, ritonavir, indinavir, and immunosuppressants.[20] Thus, this drug is approved by the Food and Drug Administration for intravenous use only.

Hypervolemic States

The mechanism of hyponatremia in cirrhosis and CHF entails a decrease in the effective ar-

Table 3. Diagnostic Criteria for SIADH

Essential features
Decreased effective osmolality (<275 mOsm/kg of water)
Urinary osmolality >100 mOsm/kg of water during hypotonicity
Clinical euvolemia
No clinical signs of volume depletion of extracellular fluid
No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
No clinical signs of excessive volume of extracellular fluid
No edema or ascites
Urinary sodium >40 mmol/L with normal dietary salt intake
Normal thyroid and adrenal function
No recent use of diuretic agents
Supplemental features
Plasma uric acid <4 mg/dL
Blood urea nitrogen <10 mg/dL
Fractional sodium excretion >1%; fractional urea excretion >55%
Failure to correct hyponatremia after 0.9% saline infusion
Correction of hyponatremia through fluid restriction
Abnormal result on test of water load (<80% excretion of 20 mL of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)
Increased plasma AVP levels despite the presence of hypotonicity and clinical euvolemia

The test for water load and measurement of AVP are rarely recommended. To convert the value for blood urea nitrogen to millimoles per liter, multiply by 0.357.
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terial blood volume and intense sodium avidity sustained by the renin-angiotensin-aldosterone axis; and water retention sustained by antidiuretic hormone.[21,22]

Hyponatremic Patients With Cirrhosis

Characteristically, patients with cirrhosis and end-stage liver disease have an intense disequilibrium of several vasoactive substances that leads to vasodilatation and a decrease in the effective arterial blood volume. Sodium and water avidity results from this shift.

Decaux[23] administered Lixivaptan to 5 cirrhotic patient in a phase II trial. Lixivaptan was effective in increasing the serum sodium level to 133 ± 4.9 mEq/L from 126 ± 4.5 mEq/L over 48 hours. In a larger multicenter trial in Europe, Gerbes et al[24] reported the use of lixivaptan in 60 cirrhotic patients. At doses of 100 mg or 200 mg twice daily, serum sodium levels normalized in 27% and 50% of subjects, respectively, compared with the placebo-administered group, in whom there was no change noted in serum sodium level. Free water clearance also was enhanced in the lixivaptan-treated group. There was no difference in the incidence of side effects; and no neurologic sequelae occurred either. In the aforementioned SALT-2 trial, approximately 30% of the enrolled subjects were cirrhotic.[17] This subgroup of patients responded somewhat slower than those with SIADH. In fact, 37% of the cirrhotic patients showed resistance or unresponsiveness to the drug. Of note, conivaptan also antagonizes V_{1a} receptors (in addition to V_2 receptors), and in doing so could cause hypotension and either cause or worsen variceal bleeding. Keeping in view the mixed results of oral lixivaptan on the one hand and the response to tolvaptan on the other hand, as well as the risk with the use of conivaptan, the role of vaptans in the management of hyponatremia in cirrhotic patients remains to be clarified.

Hyponatremic Patients with CHF

Varying degrees of volume overload are commonplace in patients with congestive heart failure. Patients with advanced heart failure have

Table 4. AVP Receptor Antagonists

Parameter	Conivaptan	Lixivaptan	Satavaptan	Tolvaptan
Compound	YM-087	VPA-985	SR-121463	OPC-41061
Receptor	V1a/V2	V2	V2	V2
Route of administration	IV	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Na+ excretion over 24 hours	⇔	⇔ at low dose ↑ At high dose	⇔	⇔
Pharmaceutical company	Astellas Pharma US, Inc.	CardioKine	Sanofi-Aventis	Otsuka America Pharmaceutical, Inc.

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significant derangement of their renin-angiotensin-aldosterone axis (leading to sodium retention), as well as increased antidiuretic hormone (vasopressin) leading to water retention, which contributes to the volume overload that is commonplace in patients with CHF.[22,25] Hyponatremia is associated with higher in-hospital mortality rates related to CHF, longer hospital stays, and higher in-hospital and early postdischarge mortality rates.[26] Over the past several years, there has been a constant effort to improve outcomes in patients with CHF.[27] Vasopressin blockade has appeared as an attractive adjunct to available therapy.

Gheorghiade et al[28] designed a double-blind, placebo-controlled study to examine the effects of oral tolvaptan in 254 patients with class II or III CHF (28% of whom were hyponatremic). Patients were treated with 30 mg, 45 mg, or 60 mg tolvaptan daily for 25 days. They were maintained on furosemide, but not water restricted. All patients on the drug lost weight and maintained their weight loss for the duration of the study. Further, their serum sodium level increased by 3 mEq/L in the first 24 hours and then drifted back to baseline. Of the hyponatremic patients at baseline, 80% normalized their serum sodium level and maintained it (compared with 40% of those on placebo). The same group then examined the effect of tolvaptan for sicker, hospitalized patients with CHF.[29] A total of 319 patients with CHF with an ejection fraction of less than 40% were treated with 30 mg, 60 mg, or 90 mg of tolvaptan. The drug-treated

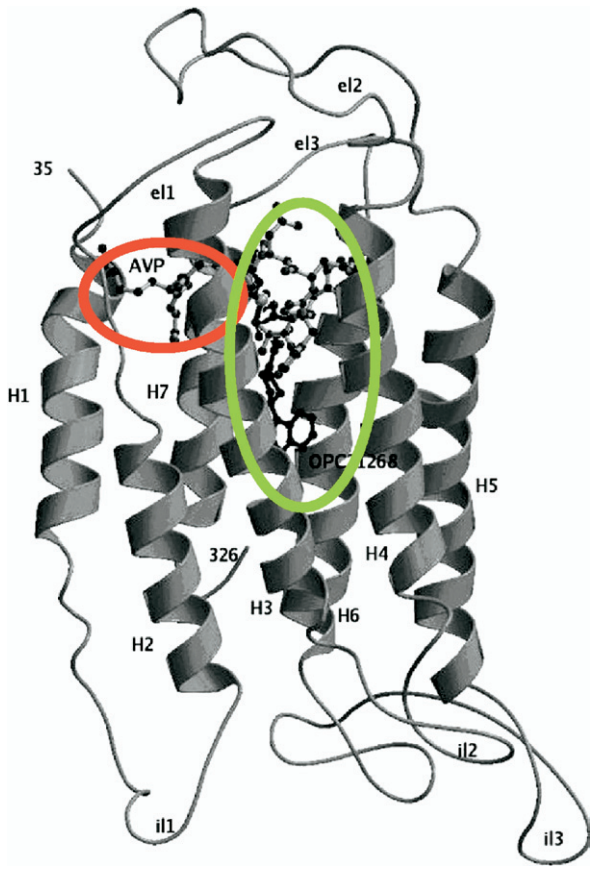

Figure 3. AVP and AVP binding sites in the V2 receptor. The V2 receptor has 7 transmembrane regions (H1-H7). AVP binds in a smaller region and is superficial. V2-receptor antagonists have more extensive, competitive, and deeper transmembrane binding. The sites are distinct and only partially overlap. Modified with permission from Macion-Dazard et al.[11]

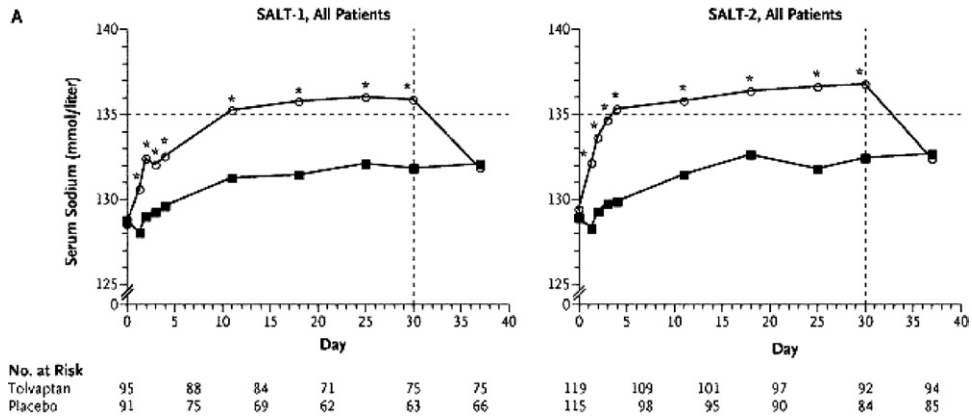

Figure 4. Effect of tolvaptan on serum sodium concentration in the SALT-1 and SALT-2 trials. ○, tolvaptan; ■, placebo; *, $P = .05$. Reprinted with permission from Schrier et al.[17]

group had a greater in-hospital weight loss than those on placebo.

These studies paved the way for a larger multicenter trial: The Efficacy of Vasopressin Antagonism in heart failure outcome Study with Tolvaptan trial.[30] The study was designed to investigate the long-term effect of tolvaptan on morbidity and mortality in patients hospitalized with worsening CHF, accompanied by signs and symptoms. Here, 4,733 patients hospitalized for CHF were randomized to either tolvaptan (30 mg/d) or placebo for a minimum of 60 days. There was no difference, either favorable or unfavorable, between the 2 study groups in all-cause mortality, cardiovascular mortality, or hospitalization related to heart failure.[30] Tolvaptan, however, significantly improved secondary end points of perceived dyspnea, measured body weight, and edema.[30,31] It must be noted, however, that in this study of tolvaptan in CHF, less than 10% of patients were hyponatremic, a subgroup that is too small for meaningful independent analysis.

Oral lixivaptan, a nonpeptide, selective V2-receptor antagonist, was used in 42 diuretic-requiring patients with mild to moderate heart failure in a randomized, double-blind, placebo-controlled, ascending single-dose study. Ascending doses of the drug were used along with varying degrees of fluid intake. Lixivaptan produced a significant and dose-related increase in urine volume over 4 hours, compared with placebo, along with significant increases in solute-free water excretion.[32]

Some of the aforementioned studies support the possible use of vasopressin-receptor antagonist as an adjunct to therapy for patients with varying degrees of CHF. Intravenous conivaptan is the only agent available at this time. With its combined V_{1a}- and V_2-receptor antagonism, conivaptan has been shown to have favorable hemodynamic effects in patients with advanced heart failure. Decreases in pulmonary capillary wedge pressure (PCWP) and right atrial pressure were accompanied by substantial increases in urine output, with no effects on systemic blood pressure, heart rate, and electrolyte levels.[33] On the other hand, oral tolvaptan has not been shown to impact left ventricular volume, but in contrast to the earlier-mentioned Efficacy of Vasopressin Antagonism in heart failure outcome Study with Tolvaptan trial, a significant favorable effect of tolvaptan was found on mortality and heart failure–related hospitalization.[34] It must be noted that in this trial the finding is, as the investigators admit, constrained by several factors because this was not a prespecified end point. The outcomes were investigator-reported rather than being adjudicated by a blinded committee.[34]

IS THE DRUG SAFE?

As a class, the vaptans interact with the microsomal enzyme cytochrome P450 (CYP) 3A4 enzyme system, although this interaction has been noted to be the highest with conivaptan, accounting for its approval only in intravenous form. The other agents, tolvaptan, lixivaptan,

and satavaptan, are in various stages of development.

Conivaptan, with its combined V_{1a}/V_2-receptor antagonism, may be at least theoretically potentially detrimental in patients with cirrhosis and portal hypertension by blocking the vasoconstrictive effects of AVP in the splanchnic circulation. Therefore, until further data and experience accrue, the use of conivaptan should be avoided in cirrhotic patients.[35]

There were a few side effects reported as common to the vaptans in all of the studies. These include thirst, dry mouth, and hypotension.[18,29,30] The administration of the vaptans should be reserved for euvolemic and hypervolemic hyponatremia only. Patients with hypovolemic hyponatremia should be managed with volume repletion and appropriate free water restriction.[9]

Osmotic demyelination from rapid correction of hyponatremia can lead to central pontine myelinolysis with devastating outcomes.[1,9,11] Although this is a theoretical concern, no case occurred in any of the studies and since conivaptan has been used clinically. A factor that possibly mitigates the rapid increase of serum sodium level is ongoing water and fluid intake. In none of the studies was water or fluid absolutely restricted. None of the patients were treated concomitantly with hypertonic saline either.

CONCLUSIONS

The advent of the vaptans represent a novel molecular approach to treat a complex and common problem in a very effective, well-tolerated, and predictable way. Conventional approaches require water restriction, which is very difficult to follow and in some circumstances is ineffective.[36] This drug class allows reasonable water intake with minimal side effects. There are many questions pertaining to long-term efficacy, possible physiologic escape mechanisms, strategies for recurrent or resistant hyponatremia, impacts on quality of life, and cost of treatment that remain unanswered.

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