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AVP receptor antagonists as aquaretics: Review and assessment of clinical data

ABSTRACT

The antidiuretic hormone arginine vasopressin (AVP) is primarily responsible for regulating osmotic and volume homeostasis of body fluids, largely through binding to vasopressin type 1A (V_{1A}) and type 2 (V_2) receptors. Increased AVP secretion leads to decreased free water excretion with resulting water retention, and can cause dilutional hyponatremia. A new class of medications known as AVP receptor antagonists induces free water diuresis without natriuresis or kaliuresis, an effect termed *aquaresis*. Numerous clinical trials show AVP antagonists to be effective at increasing free water excretion and serum sodium in patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion or edema-forming states such as congestive heart failure and cirrhosis. This article reviews clinical trial data on the AVP antagonists in late development (lixivaptan, satavaptan, and tolvaptan) and recently approved for marketing (conivaptan).

KEY POINTS

AVP receptor antagonists correct hyponatremia by blocking activation of the V_2 receptor.

Lixivaptan, satavaptan, and tolvaptan are selective for the V_2 receptor and are being developed for oral administration, whereas conivaptan is a dual V_{1A}/V_2 antagonist for intravenous administration.

All four AVP antagonists increase urine volume, reduce urine osmolality, and generally have no effect on 24-hour sodium excretion.

Clinical trials to date indicate that AVP antagonists produce a safe and predictable aquaresis, thereby raising serum sodium levels in patients with hyponatremia.

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TRADITIONAL THERAPIES for patients with hyponatremia can be effective, but they have significant limitations, as detailed by Douglas earlier in this supplement and by other authors.[1] A new class of medications that acts on the arginine vasopressin (AVP) receptor—AVP receptor antagonists—will likely become a viable alternative to these traditional therapies for hyponatremia, based on the predictability of their effect, their rapid onset of action, and the limited urinary electrolyte excretion associated with their use.[2]

This article reviews the available clinical data on the therapeutic potential of AVP receptor antagonists for the treatment of hyponatremia.

AVP AND FLUID IMBALANCES

AVP, also known as antidiuretic hormone, is a peptide hormone involved in diverse physiologic functions, including contraction of vascular smooth muscle, stimulation of liver glycogenolysis, regulation of corticotropin release, and renal antidiuresis.[3–5] These functions are mediated through the binding of AVP to specific membrane receptors in targeted cells.

Disorders of AVP secretion frequently cause imbalances of body water: deficient AVP secretion can cause hyperosmolality as a result of inadequate renal water conservation, and excess or inappropriate AVP secretion can cause hypoosmolality due to impaired renal water excretion.[6] Hypoosmolality usually manifests as hyponatremia, a very common electrolyte disorder associated with a variety of underlying conditions that are usually caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[7] In addition to SIADH, patients with edema-forming states such as congestive heart failure (CHF) and cirrhosis, as well as patients treated with diuretics, also often have elevated plasma levels of AVP and hyponatrem-

ia.[8–10] Hyponatremia has been associated with increased morbidity and mortality across the spectrum of these conditions.[11]

AVP receptor antagonists correct hyponatremia by blocking activation of the vasopressin type 2 (V_2) receptor.[2] These agents induce a free water diuresis without an accompanying natriuresis or kaliuresis; this effect has been termed *aquaresis* to differentiate it from the effect produced by traditional diuretic agents.

ROLES OF AVP RECEPTOR SUBTYPES

AVP receptors are G protein–coupled receptors and have been divided into three subtypes that mediate all known actions of AVP: V_{1A}, V_{1B}, and V_2.[3–5] The V_{1A} and V_{1B} receptors are linked to the phosphoinositol signaling pathway, with intracellular calcium acting as the second messenger, whereas the V_2 receptors are linked to the adenylate cyclase signaling pathway, with intracellular cyclic adenosine monophosphate (cAMP) acting as the second messenger.[5]

The V_{1A} receptors are responsible for multiple physiologic effects, such as vasoconstriction, glycogenolysis, and platelet aggregation.[3]

The V_{1B} receptors exist mainly in the anterior pituitary, where they mediate adrenocorticotropin release.[4]

The V_2 receptors are found primarily in the collecting ducts of the kidney and mediate antidiuresis by causing renal free water reabsorption and retention. Extrarenal V_2 receptors are also present in vascular endothelial cells, where they mediate release of coagulation factor.[12] In the kidney, circulating AVP activates the V_2 receptor in renal collecting duct cells, leading to an increase in cAMP levels via stimulation of G protein–mediated adenylate cyclase activity.[13] These events cause insertion of aquaporin-2 water channels into the apical plasma membranes of the collecting duct cells, thereby increasing water permeability of the apical plasma membranes and causing antidiuresis.[14]

PROFILE OF AVP RECEPTOR ANTAGONISTS

Several AVP receptor antagonists are under clinical investigation: conivaptan (YM-087), lixivaptan (VPA-985), satavaptan (SR-121463), and tolvaptan (OPC-41061).[2,15] Conivaptan has antagonist activity at both the V_{1A} and V_2 receptors,[16] whereas the other agents are selective V_2 receptor antagonists.[17]

TABLE 1

Profile of AVP receptor antagonists

	CONIVAPTAN (YM-087)	LIXIVAPTAN (VPA-985)	SATAVAPTAN (SR-121463)	TOLVAPTAN (OPC-41061)
Receptor(s)	V_{1A}/V_2	V_2	V_2	V_2
Admin. route	Intravenous	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Sodium excretion in 24 hr	↔	↔ at low dose ↑ at high dose	↔	↔
Company developing	Astellas Pharma US, Inc	CardioKine	Sanofi-Aventis	Otsuka America Pharmaceutical

AVP = arginine vasopressin; ↔ = no change

Adapted, with permission, from reference 17.

As outlined in Table 1, all four AVP receptor antagonists increase urine volume, decrease urine osmolality, and (except for high-dose lixivaptan) have no effect on 24-hour sodium excretion. Conivaptan is currently the only AVP receptor antagonist that is commercially available in the United States, having recently received US Food and Drug Administration (FDA) approval for the treatment of euvolemic hyponatremia in hospitalized patients. Conivaptan is available for intravenous (IV) administration, whereas the other three agents are being developed for oral administration.

AVP antagonists induce free water diuresis without natriuresis or kaliuresis—an effect called *aquaresis*

The AVP receptor antagonists have been proven effective at increasing free water excretion and serum sodium levels in multiple clinical trials.[15] The remainder of this article reviews and assesses the available clinical trial data for each individual agent, with key trial details summarized in Table 2.

CONIVAPTAN IN HYPONATREMIA

Two clinical trials have been reported on the use of conivaptan to treat hyponatremia.[18,19]

Oral conivaptan

One study was a placebo-controlled, randomized, double-blind evaluation of oral conivap-

TABLE 2

Summary of randomized clinical trials of AVP receptor antagonists

AUTHORS/ REFERENCE	TREATMENT REGIMENS	PATIENT POPULATION	EFFECT ON SERUM SODIUM*	EFFECT ON BODY WEIGHT*
Conivaptan				
Ghali et al[18]	Coni 40 mg/d po × 5 d Coni 80 mg/d po × 5 d Placebo × 4 d	74 hospitalized patients with euvolemic or hypervolemic hyponatremia	Significant increases	Not reported
Verbalis et al[15,19]	Coni 40 mg/d IV × 4 d (after 20-mg bolus) Coni 80 mg/d IV × 4 d (after 20-mg bolus) Placebo × 4 d	84 hospitalized patients with euvolemic or hypervolemic hyponatremia	Significant increases	Not reported
Lixivaptan				
Wong et al[21]	Lixi 25 mg bid po × 7 d Lixi 125 mg bid po × 7 d Lixi 250 mg bid po × 7 d Placebo × 7 d	44 hospitalized patients with stable hyponatremia and cirrhosis, CHF, or SIADH	Significant dose-dependent increases	No significant change
Gerbes et al[22]	Lixi 50 mg bid po × 7 d Lixi 100 mg bid po × 7 d Placebo × 7 d	60 hospitalized hyponatremic patients with cirrhosis	Significant dose-dependent increases	Significant decrease with higher dose
Satavaptan				
Soupart et al[23]	Sata 25 mg qd po × 5–23 d Sata 50 mg qd po × 5–23 d Placebo × 5–23 d	34 hyponatremic patients with SIADH	Dose-dependent increases	Not reported
Tolvaptan				
Gheorghiade et al[24]	Tol 30 mg qd po × 25 d Tol 45 mg qd po × 25 d Tol 60 mg qd po × 25 d Placebo × 25 d	254 patients with CHF in outpatient setting (28% with hyponatremia)	Small mean increases over baseline (vs small mean decrease for placebo)	Significant decreases
Gheorghiade et al (ACTIV in CHF)[25]	Tol 30 mg qd po × ≤60 d Tol 60 mg qd po × ≤60 d Tol 90 mg qd po × ≤60 d Placebo × ≤60 d	319 patients hospitalized with worsening CHF (21.3% with hyponatremia)	Small mean increases over baseline (vs small mean decrease for placebo)	Significant decreases
Gheorghiade et al[26]	Tol 10–60 mg/d po × 27 d Fluid restriction (1,200 mL/d) plus placebo × 27 d	28 hospitalized patients with serum sodium < 135 mEq/L	Significant increase	No change
Gross et al (SALT-2)[27]	Tol 15–60 mg qd po × 30 d Placebo × 30 d	240 patients with hyponatremia	Significant increases	Significant decrease (similar change) in all dose groups

* With AVP antagonist vs placebo (or, for reference 26, vs fluid restriction). Unless otherwise noted, effects are for all AVP antagonist doses in the study.

AEs = adverse events; AVP = arginine vasopressin; Lixi = lixivaptan; Sata = satavaptan; Tol = tolvaptan; Coni = conivaptan; CHF = congestive heart failure; GI = gastrointestinal; SIADH = syndrome of inappropriate antidiuretic hormone secretion

EFFECT ON URINE OUTPUT*	SIDE EFFECTS*
Not reported	No significant increase in reported AEs
Significant increases in effective water clearance	Local irritation at infusion site
Significant dose-dependent increases in free water clearance	Significant dehydration (especially with higher doses), worsening encephalopathy in 2 pts
Dose-dependent increases in urine volume; significant increases in free water clearance at end of study	Increased thirst sensation; rates of serious AEs similar to placebo
Reduced urine osmolality	No serious drug-related AEs
Significant dose-dependent increases in urine volume	Dry mouth, thirst, and polyuria (including urinary frequency)
Significant increases in urine volume	AEs in 85% of patients; most common were thirst, dry mouth, dizziness, nausea, hypotension, but rates not significantly different from placebo
Significant increase in urine output by last inpatient visit	No significant increase in reported AEs
Decreased urine osmolality	Increased thirst, trend to increased AVP levels

tan in hospitalized patients with euvolemic or hypervolemic hyponatremia.[18] Seventy-four patients with a baseline serum sodium between 115 and 130 mEq/L were randomized to receive conivaptan 40 mg/day (n = 24) or 80 mg/day (n = 27) or placebo (n = 23) in two divided doses for 5 days.

The mean change in serum sodium from baseline to the end of treatment was 3.4 mEq/L with placebo, 6.4 mEq/L with conivaptan 40 mg/day, and 8.2 mEq/L with conivaptan 80 mg/day (P = .002 vs placebo). The percentage of patients achieving a normal serum sodium level (≥ 135 mEq/L) or an increase of at least 6 mEq/L was 48% in the placebo group and 71% and 82% in the lower and higher conivaptan dose groups, respectively (P = .014 vs placebo). The incidence and types of adverse events were similar between the two conivaptan groups and the placebo group; the most common were headache, hypotension, nausea, constipation, and postural hypotension.[18]

Despite the efficacy of oral conivaptan in this trial, development of the oral formulation was discontinued because of significant inhibition of the cytochrome P-450 3A4 system. To minimize the possibility of drug interactions, the FDA restricted conivaptan's distribution to a parenteral form for short-term in-hospital use.

AVP antagonists increase urine volume, reduce urine osmolality, and do not affect sodium excretion

IV conivaptan

The second reported study assessed IV conivaptan using a randomized, double-blind, multicenter, placebo-controlled, parallel-group design.[19] Eighty-four adults with euvolemic or hypervolemic hyponatremia (serum sodium between 115 and 130 mEq/L) were randomized to placebo (n = 29) or conivaptan given as a 20-mg IV bolus followed by a continuous infusion of 40 mg/day (n = 29) or 80 mg/day (n = 26) for 4 days. The primary efficacy measure was the change in serum sodium from baseline over treatment duration (measured as the area under the serum sodium curve from the beginning to the end of the treatment period). Secondary measures included the change in serum sodium levels from baseline to day 4, the time from the first dose to a 4-mEq/L increase in serum sodium, the number of patients achieving serum sodium normalization or a 6-mEq/L increase, and effective water clearance (a measure of electrolyte free water excretion).

TABLE 3

Efficacy results from randomized trial of IV conivaptan for hyponatremia

END POINT	PLACEBO (n = 29)	CONIVAPTAN 40 MG/DAY (n = 29)	CONIVAPTAN 80 MG/DAY (n = 26)
Baseline mean serum sodium, mEq/L (± SD)	124.3 ± 4.9	123.3 ± 4.7	124.8 ± 3.4
Least-squares mean change in serum sodium AUC to day 4, mEq/L • hr (± SE)	12.9 ± 61.2	490.9 ± 56.8*	716.6 ± 60.5*
Least-squares mean change in serum sodium at day 4, mEq/L (± SE)	2.0 ± 0.8	6.8 ± 0.8*	9.0 ± 0.8*
Median time from first dose to 4-mEq/L rise in serum sodium, hr	NE	23.7*	23.4*
Number (%) of patients achieving ≥ 6-mEq/L increase in or normalization of serum sodium (≥135 mEq/L)	6 (20.7)	20 (69)†	23 (88.5)*
Mean change in effective water clearance from baseline to day 1, mL (± SD)	–332.3 (434.1)	1,984.0 (1,559.4)‡	1,759.4 (1,748.3)‡

* $P < .001$ vs placebo † $P < .01$ vs placebo ‡ $P < .05$ vs placebo

AUC = area under the curve; IV = intravenous; NE = not estimable; SD = standard deviation; SE = standard error

Adapted from reference 19.

Infusion of conivaptan should not exceed 4 days

As shown in Table 3, both doses of conivaptan were associated with statistically significantly greater increases, relative to placebo, in the primary end point of mean change in serum sodium over treatment duration. Both doses also were associated with significant improvements over placebo in mean change in serum sodium levels on day 4, median time to a 4-mEq/L increase in serum sodium, percentage of patients achieving serum sodium normalization or a 6-mEq/L or greater increase, and mean change in effective water clearance, a measure of aquaretic effect (see Table 3). The researchers reported that conivaptan was well tolerated over the 4-day treatment period except for frequent infusion-site reactions.[19]

Indications, dosage

Based on these and other data,[20] conivaptan has been granted FDA approval in parenteral form for the treatment of euvolemic hyponatremia in hospitalized patients; the FDA has issued an approvable letter for its use as a treatment for hypervolemic hyponatremia.

For euvolemic hyponatremia, conivaptan should be given as a 20-mg IV loading dose over 30 minutes followed by a 20-mg continuous infusion over 24 hours. Following the initial day of treatment, it is suggested that conivaptan be given for an additional 1 to 3 days as a continuous infusion of 20 mg/day (total duration of infusion not to exceed 4 days). The dose can be titrated to a 40-mg/day continuous infusion if the serum sodium level does not rise at the desired rate. Conivaptan is not indicated for the treatment of CHF at this time.[20]

LIXIVAPTAN IN HYPONATREMIA

Two randomized, multicenter studies of lixivaptan in humans have been reported.[21,22] Most patients in these trials had cirrhosis, which produces a dilutional hypervolemic hyponatremia.

The first was a placebo-controlled study of hospitalized patients with stable hyponatremia (<130 mEq/L for 3 consecutive days); of the 44 patients enrolled, 33 had cirrhosis, 6 had CHF, and 5 had SIADH.[21] The patients had a constant sodium intake and were randomized to receive one of three doses of oral lixivaptan (Table 2) or placebo twice daily for 7 days. End points included changes in net fluid balance, free water clearance, and serum osmolality.

The study found a significant increase in free water clearance with the 125-mg and 250-mg twice-daily doses of lixivaptan compared with placebo on days 3, 5, and 7 (Figure 1). The 250-mg twice-daily dose was associated with significant increases in serum sodium levels compared with placebo on day 4 ($P < .01$) and days 5 and 6 ($P < .05$). On day 7, plasma AVP levels were significantly increased with the two higher doses of lixivaptan compared with baseline, placebo, and the lowest lixivaptan dose ($P < .05$ for all comparisons). There were no significant changes in orthostatic

blood pressure, serum creatinine levels, or urinary sodium excretion in the lixivaptan groups compared with the placebo group. The 250-mg twice-daily dose was not as well tolerated and was associated with reports of excessive thirst and dehydration manifested by marked increases in serum sodium levels, often requiring one or more doses to be withheld.[21]

The second published study of lixivaptan was a double-blind trial in 60 patients with cirrhosis and dilutional hyponatremia.[22] Patients were randomized to receive 100 or 200 mg/day of oral lixivaptan or placebo for 7 days or until serum sodium was normalized. Fluid intake was restricted to 1,000 mL/day. The primary end point was normalization of serum sodium level, defined as a concentration of 136 mEq/L or greater on two separate consecutive measurements. Baseline mean serum sodium concentrations were comparable among the three treatment arms (127 to 128 mEq/L).

Serum sodium levels were normalized in 27% of patients receiving lixivaptan 100 mg/day and 50% of patients receiving 200 mg/day compared with 0 placebo recipients ($P < .05$ and $P < .001$ vs placebo, respectively). The mean time to a complete response was 5.7 days in the 100-mg dose group and 4.8 days in the 200-mg dose group. The 200-mg dose also was associated with significant reductions in urine osmolality and body weight ($P < .001$ vs placebo on both measures).[22]

Thirst sensation increased significantly in the 200-mg dose group ($P = .01$ vs baseline) but not in the 100-mg or placebo groups. Rates of serious adverse events leading to treatment discontinuation were similar among the three groups. Renal impairment (increase in serum creatinine to ≥ 200 µmol/L) was observed in two patients in each of the three groups. No patient developed neurologic abnormalities, and lixivaptan had no significant effects on blood pressure or heart rate.[22]

SATAVAPTAN IN HYPONATREMIA

Satavaptan was evaluated in 34 hyponatremic patients with SIADH in a randomized, multicenter, phase 2 clinical trial.[23] Patients received satavaptan 25 or 50 mg once daily or placebo and adhered to fluid restriction (1.5 L/day) for 5 to 23 days.

Baseline mean serum sodium levels were 125 to 127 mEq/L in the three treatment groups. Response, defined as serum sodium normalization or an increase of at least 5 mEq/L from baseline to day 5, was achieved in 13% of placebo recipients compared with 79% of patients receiving satavaptan 25 mg/day ($P = .006$ vs placebo) and 83% of patients receiving satavaptan 50 mg/day ($P = .005$ vs placebo). By day 5, mean (± SD) serum sodium levels were 130 ± 5 mEq/L in the placebo group, 136 ± 6 mEq/L in the 25-mg dose group, and 140 ± 6 mEq/L in the 50-mg dose group. In addition, urinary osmolality was reduced significantly with satavaptan, and no serious drug-related adverse events were reported.[23]

In a subsequent open-label extension of this study, satavaptan appeared to maintain its efficacy over a 12-month period without evidence of tachyphylaxis.[23] Based on these results, the authors concluded that satavaptan is an effective and safe treatment for hyponatremia in patients with SIADH.

Cirrhosis produces a dilutional hypervolemic hyponatremia

Lixivaptan increases free water clearance in hyponatremia

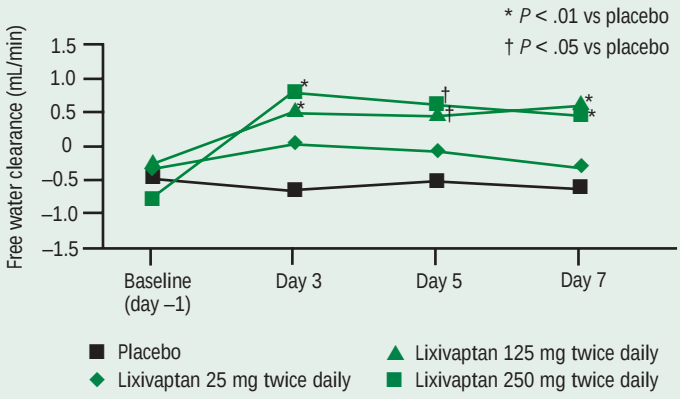

FIGURE 1. Effects of lixivaptan on free water clearance in a 7-day randomized study among 44 hospitalized patients with hyponatremia. Reprinted, with permission, from reference 21.

TOLVAPTAN

Heart failure trials

Much of tolvaptan's initial development has focused on CHF, and two randomized clinical studies of this agent in patients with CHF have been published.[24,25]

The first was a double-blind, placebo-controlled study of 254 patients with exacerbation of known CHF (mostly New York Heart

Tolvaptan produces enduring increases in serum sodium in heart failure patients

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Please see original source figure (figure 2) in: *Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V_2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003; 107:2690–2696.*

FIGURE 2. Effect of tolvaptan on serum sodium levels in a 25-day randomized study of 254 patients with congestive heart failure. The dose-dependent increase gradually weakened over the treatment period, but serum sodium levels remained statistically significantly greater in all tolvaptan groups than in the placebo group at all time points except for the 45-mg dose group at day 25. Reprinted, with permission, from reference 24.

Association class II and III), 28% of whom were hyponatremic (serum sodium < 136 mEq/L) at baseline.[24] Patients were randomized to one of three oral doses of tolvaptan (Table 2) or placebo for 25 days. All patients were treated in the outpatient setting, did not have their fluids restricted, and continued their existing therapies for CHF, including loop diuretics, angiotensin-converting enzyme inhibitors, digoxin, beta-blockers, hydralazine, and nitrates. The primary end point was change in body weight from baseline. Other end points were ankle edema, urine sodium excretion, urine volume, and urine osmolality.

All three doses of tolvaptan were associated with significant reductions in body weight at 24 hours after administration ($P < .001$ for all doses vs placebo). The initial reductions in body weight were maintained during the study, but no further reductions were observed after day 1. All doses of tolvaptan significantly increased urine output compared with placebo ($P < .05$) and also appeared to improve clinical signs and symptoms of CHF as assessed by ankle edema. In addition, all tolvaptan doses produced small mean increases in serum sodium levels, whereas placebo was associated with small decreases (Figure 2). Significantly greater mean net fluid losses were observed in tolvaptan recipients than in placebo recipients ($P < .05$ for each dose vs placebo). In the tolvaptan groups, patients with hyponatremia at baseline had greater increases in serum sodium during the study than did those with normal serum sodium levels at baseline.[24]

Dry mouth, thirst, and polyuria were more frequent in patients receiving tolvaptan than in those on placebo, but there was no change from baseline in heart rate, blood pressure, serum potassium levels, or renal function in any of the treatment groups.[24]

A second double-blind, multicenter, placebo-controlled, parallel-group study of tolvaptan in CHF has been published, this one in patients hospitalized for acute exacerbation of CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure [ACTIV in CHF]).[25] The study's 319 patients were randomized to receive one of three doses of oral tolvaptan (Table 2) or placebo for up to 60 days in addition to standard CHF therapy. The in-hospital end point was change in body weight at 24 hours after the first dose of study drug, and the outpatient end point was worsening CHF at 60 days after randomization. Other end points were changes in body weight, urine output, and serum electrolyte levels. Sixty-eight patients (21.3%) had hyponatremia (serum sodium < 136 mEq/L) at randomization, and they were evenly distributed among the treatment groups.

At 24 hours, all tolvaptan groups had significant reductions in body weight compared with the placebo group ($P \leq .009$ for all comparisons). Compared with placebo, all tolvaptan doses were associated with significantly higher urine volume on day 1, and this difference was maintained throughout the hospital stay. Patients in all tolvaptan groups also had small mean increases in serum sodium levels from baseline to day 1, whereas placebo recipients had a small decrease; this difference persisted throughout the hospital stay. Patients with hyponatremia at baseline who received tolvaptan had increases in serum sodium that were maintained throughout the study. Changes in body weight with tolvaptan were not associat-

ed with changes in heart rate, blood pressure, potassium level, or renal function.[25]

Although event-free survival tended to be longer with tolvaptan than with placebo,[25] additional studies, such as the ongoing Efficacy of Vasopressin Antagonism in Heart Failure (EVEREST) trial, are needed to provide more definitive data on morbidity and mortality in patients with CHF.

Hyponatremia trials

Tolvaptan also has been evaluated specifically for the treatment of hyponatremia in two reported trials.[26,27]

One was a prospective, randomized, active-control, open-label study in 28 hospitalized subjects with a serum sodium less than 135 mEq/L.[26] Patients were randomized to oral tolvaptan alone (n = 17) or fluid restriction (1,200 mL/day) plus placebo (n = 11). Tolvaptan was started at 10 mg/day and titrated to 60 mg/day as per protocol. Active treatment was continued for up to 27 days, and follow-up continued for up to 65 days.

The primary end point was normalization of serum sodium (> 135 mEq/L) or an increase in serum sodium of at least 10% from baseline. At the last inpatient visit, serum sodium had increased by 5.7 ± 3.2 mEq/L in the tolvaptan group and 1.0 ± 4.7 mEq in the fluid-restricted group (P = .0065). No significant differences in adverse events were observed between the groups. The authors concluded from this small study that tolvaptan appears to be more effective than fluid restriction at correcting hyponatremia in hospitalized subjects without an increased frequency of adverse events. This has led to larger ongoing placebo-controlled trials of tolvaptan in hyponatremic patients.

The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-2) is one such larger, placebo-controlled trial. This study, which has been presented only in preliminary form,[27] randomized 243 hyponatremic patients to receive placebo or 15 to 60 mg/day of tolvaptan in a stepwise fashion for 30 days. Similar to results of the lixivaptan trials, significantly greater increases in serum sodium levels were reported in patients receiving tolvaptan than in those on placebo. However, 25% of patients dropped out of the study, and resistance (defined as failure to achieve a serum sodium increase ≥ 5 mEq/L) occurred in 37%, 17%, and 11% of patients with cirrhosis, CHF, and SIADH, respectively.

ASSESSMENT OF AVP RECEPTOR ANTAGONISTS

Based on the results of multiple clinical trials with four different AVP receptor antagonists, it is likely that this class will become a mainstay of treatment for euvolemic hyponatremia. These agents predictably cause an aquaresis that leads to increased serum sodium in the majority of patients with hyponatremia due to SIADH, CHF, or cirrhosis. Although the initial FDA approval for conivaptan was only for euvolemic hyponatremia, increased exposure of larger numbers of patients with CHF should eventually lead to approval for hypervolemic hyponatremia as well.

The optimal use of AVP receptor antagonists has not yet been determined, but some predictions can be made with reasonable confidence.

Short-term vs chronic use

AVP antagonists often increase thirst even in hyponatremic patients

For hyponatremia in hospitalized patients who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, conivaptan will likely be the preferred agent. Phase 3 studies show that it reliably raises serum sodium over the short term, beginning as early as 1 to 2 hours after administration, and permits normalization of serum sodium in most hyponatremic patients over a 4-day treatment course. Selective orally active V_2 receptor antagonists such as lixivaptan, satavaptan, and tolvaptan correct serum sodium more slowly but will likely prove useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia.

Potential use with hypertonic saline

Despite the appeal of using a pure aquaretic agent to correct life-threatening hyponatremia, available clinical trial data are inadequate to clarify whether sufficiently rapid correction can be achieved in patients with acute, severe hyponatremia without the use of hypertonic saline. Theoretically, both treatments could be used initially, with the hypertonic saline then stopped after the serum sodium increased by several mEq/L, with the remainder of the first day's correction accomplished through aquare-

sis. The two therapies might be complementary in that the hypertonic saline infusion would cause sufficient expansion of the extracellular fluid to balance any volume depletion resulting from the aquaresis.

Fluid restriction mitigated, not eliminated

Most placebo-controlled trials of AVP receptor antagonists to treat hyponatremia have been of limited duration, generally 7 days or less. However, sufficient data from longer-term open-label studies exist to suggest that these agents will likely prove highly useful in chronic hyponatremia due to SIADH, cirrhosis, and CHF. Although the effect of AVP receptor antagonists on plasma AVP levels is variable, it bears emphasis that these agents often increase thirst even in hyponatremic patients and, unless fluids are restricted, water intake generally increases as well. For example, in the initial tolvaptan study in CHF, the serum sodium increased only during the first day despite a persistently dilute urine.[24] Thus, the use of AVP receptor antagonists will mitigate, but in many cases not eliminate, the need for fluid restriction.

Do not use AVP antagonists in cases of hypovolemic hyponatremia, to avoid possible hypotension

Safety issues

Safety issues must also be considered carefully with any new class of agents. The possibility of overcorrection has been of significant concern in all clinical studies of the AVP receptor antagonists, but osmotic demyelination has not yet been reported with any agent. Nonetheless, it is expected that these agents will need to be used judiciously if correction of the serum sodium at a rate faster than 8 to 12 mEq/L per 24 hours is to be avoided. Because all of these agents have a half-life of less than 12 hours, all will require daily or continuous dosing to maintain activity, so it will be possible to limit the serum sodium rise by stopping the drug or reducing the dosage. If necessary, hypotonic fluid can be infused to abrogate the rise in serum sodium until the aquaresis abates. These safeguards should be sufficient to protect against too-rapid correction, assuming that serum sodium levels are monitored frequently during active treatment.

A second major concern is the need to avoid AVP receptor antagonist therapy in cases of hypovolemic hyponatremia, where an aquaresis would aggravate underlying volume contraction and potentially cause hypotension. This can be avoided by careful differential diagnosis among the subtypes of hyponatremia.

The potential for serious drug interactions via interference with cytochrome P-450 3A4 metabolism of other drugs by AVP receptor antagonists must be recognized. This will likely not be of concern with short-term use of AVP receptor antagonists such as IV conivaptan, but may cause problems during long-term therapy, requiring appropriate monitoring.

Finally, whether V_2 receptor inhibition will have any adverse effect in the vascular endothelium is unknown. Bleeding complications have not been reported to date, but surveillance will be needed now that a combined V_{1A}/V_2 receptor antagonist is in general use.

CONCLUSIONS

All of the AVP receptor antagonists produce an aquaretic effect via their activity at the V_2 receptor, which improves dilutional hyponatremia. All data to date indicate that the AVP antagonists are highly effective in producing a safe and predictable aquaresis, thereby increasing serum sodium levels in hyponatremic patients. Conivaptan is the first AVP receptor antagonist to receive FDA approval, specifically for IV administration to hospitalized patients with euvolemic hyponatremia. Several investigational oral AVP receptor antagonists are in late-stage clinical trials and hold promise for long-term therapy of chronic hyponatremia.

Further studies are needed to assess the appropriate use of AVP receptor antagonists in various areas:

- For correction of symptomatic hyponatremia alone or in conjunction with hypertonic saline infusions
- To assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and length of stay in the hospital and intensive care unit
- For long-term treatment of minimally symptomatic hyponatremia in order to reduce the risks of neurocognitive dysfunction and gait instability.[28]

Despite many yet unanswered questions about their optimal use, AVP receptor antagonists will undoubtedly prove highly useful and promise to usher in a new era in the treatment of hyponatremia.

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