REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES
Julie R. Ingelfinger, M.D., *Editor*

Vasopressin Antagonists

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Ample evidence is available to implicate vasopressin, a small polypeptide that is synthesized in the hypothalamus and secreted from the posterior pituitary, in the pathogenesis of most hyponatremic disorders. As the most common electrolyte disorder, hyponatremia is consistently associated with increased mortality and morbidity. The treatment of hyponatremia has been plagued by a paucity of controlled studies and by a lack of reliable and safe approaches. Therefore, the regulatory approval of vasopressin antagonists represents a milestone in the field. This review summarizes the salient discoveries that culminated in the development of these drugs and focuses on what vasopressin antagonists do and do not do, side effects, emerging safety concerns, and important gaps in data. An attempt has been made to reconcile the disparate recommendations for the use of vasopressin antagonists that are available in two guidelines. The review concludes with suggestions as to how and when vasopressin antagonists should be used and for how long.

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HISTORICAL BACKGROUND

The milestones in vasopressin biology are summarized chronologically in Table 1. The observation that posterior pituitary extracts, which are rich in vasopressin, inhibit the excretion of urine[1] was made after such extracts were reported to increase blood pressure.[2,3] Decades later, Verney and Jewell[4,5] described the osmotic control of vasopressin release, Schrier et al. described the nonosmotic control,[6] and Dunn et al. studied the interaction between the two control systems.[7] Concomitantly, Schwartz et al. described patients with lung carcinoma and concentrated urine samples who had hyponatremia that was caused by inappropriate secretion of vasopressin (i.e., antidiuretic hormone), a condition that is often called the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[8] Vasopressin secretion in SIADH was confirmed by means of radioimmunoassay.[9]

Purification and amino acid sequencing of vasopressin[10] was soon followed by identification of the gene[11] and cloning of the hormone receptors.[12,13] The V_{1A} receptor, which is found in liver, smooth muscle, myocardium, brain, and platelets, and the V_{1B} receptor, which is involved in the secretion of corticotropin in the anterior pituitary, initiate cell signaling by increasing the levels of intracellular calcium. The V_2 receptor, which is located primarily in the basolateral membrane of collecting-duct cells, signals by generating cyclic AMP. Loss-of-function and gain-of-function mutations cause X-linked disorders in water balance — congenital nephrogenic diabetes insipidus and nephrogenic syndrome of inappropriate antidiuresis (NSIAD), respectively. The discovery of water channels,[14] one of which (aquaporin-2) is regulated by vasopressin,[15] completed the pathway of its cellular action. Mutations in the gene encoding aquaporin 2 (*AQP2*) cause autosomal recessive congenital nephrogenic diabetes insipidus or, more rarely, the autosomal dominant form of the disease.

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Elucidation of the amino acid sequence of vasopressin propelled research that led to the synthesis of polypeptide antagonists.[16] These agents, which were plagued by low oral bioavailability, residual agonist activity, and species heterogeneity,[17] stimulated the development of oral nonpeptide antagonists (vaptans). Mozavaptan was first described in 1992[18] and was followed by a more selective V_2-receptor antagonist, tolvaptan.[19] In 2006, mozavaptan was approved in Japan for tumor-associated SIADH. Tolvaptan and conivaptan (with the latter blocking both the V_{1A} and V_2 receptors) have garnered approval for the treatment of euvolemic and hypervolemic hyponatremia in the United States. Tolvaptan is approved in Europe by the European Medicines Agency and in Canada by Health Canada for the treatment of euvolemic hyponatremia.

MECHANISM OF ACTION

The stable expression of vasopressin receptors in cell lines has allowed for the study of their molecular mechanisms. Thibonnier et al. developed a three-dimensional model of the receptor and docked vasopressin in its binding site.[20] Using site-directed mutagenesis and affinity binding, the investigators established the site on the receptor at which antagonists are likely to disrupt binding to the V_{1A}[21] and V_2[22] receptors (Fig. 1). Vasopressin binds at a superficial site, whereas the antagonist penetrates deeply into the membrane, altering the ability of the agonist to bind to the receptor in the adjacent loop. This inhibition culminates in the prevention of the insertion of water channels into the apical membrane, which thereby inhibits the reabsorption of water and the generation of concentrated urine (Fig. 2). Cyclic AMP, which is implicated in the growth of renal cysts, fluid secretion, and cell proliferation,[23] is a target for the treatment of adult polycystic kidney disease.[24] Tolvaptan has not garnered approval for the treatment of this disorder from the Food and Drug Administration (FDA).

PHARMACOKINETICS AND PHARMACODYNAMICS OF VAPTANS

Conivaptan and tolvaptan have differing affinities for the vasopressin receptor. The inhibitory constant (Ki) for each drug is summarized in

Table 1. Landmarks in Vasopressin Biology.

Year	Landmark
1895	Discovery that the use of pituitary extracts increases blood pressure
1898	Discovery that pressor activity resides in the posterior lobe
1913	Discovery that the use of pituitary extracts decreases urine excretion
1947	Discovery that vasopressin is released under osmotic control
1952	Report on the structure and amino acid sequence of vasopressin
1957	Localization of the osmoreceptor in the anterior hypothalamus
1957	Reports of patients with presumed vasopressin-mediated hyponatremia
1970s–1980s	Synthesis of numerous polypeptide antagonists
1973–1975	Reports of nonosmotic release of vasopressin baroreceptors
1973	Development of radioimmunoassay for vasopressin
1982	Identification of gene encoding vasopressin carrier — neurophysin II — on chromosome 20
1991	Discovery of water channels
1992–1994	Cloning of human vasopressin V_1 and V_2 receptors
1992	Development of nonpeptide oral vasopressin antagonists
1994	Cloning of vasopressin-regulated water channel
2004–2008	Approval of vasopressin antagonists for treatment of hyponatremia

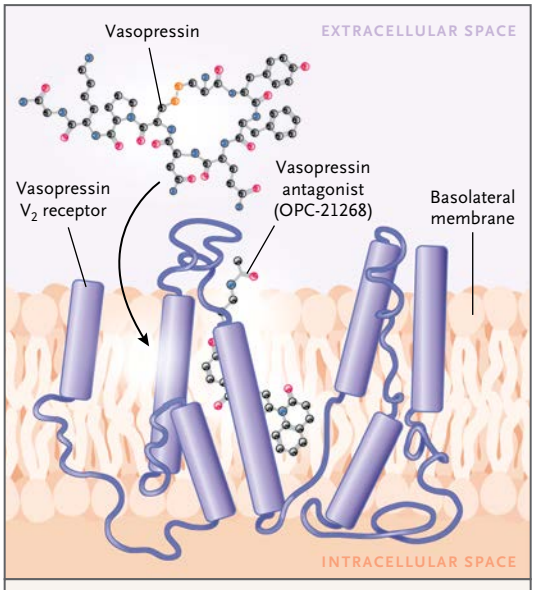

Figure 1. Binding of Vasopressin to Its Receptor and Location of Antagonist.

The tubular segments represent the seven transmembrane portions of the receptor, and the stringlike lines represent extracellular and intracellular loops. Vasopressin and its antagonist do not occupy the same locus but are in adjacent regions. Modified and adapted from Macion-Dazard et al.[22]

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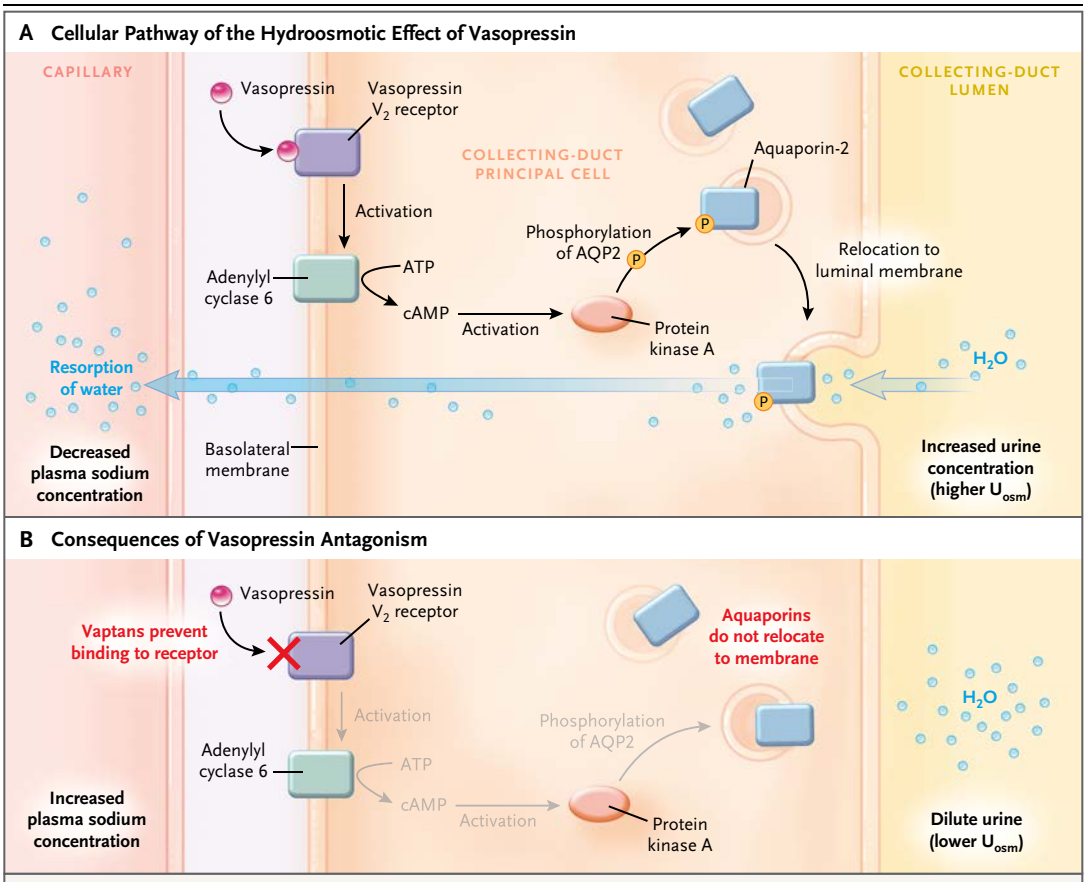

Figure 2. Cellular Effects of Vasopressin and Consequences of Vasopressin Antagonism.

Panel A shows the cellular pathway of the hydroosmotic effect of vasopressin. The binding of the hormone to the V_2 receptor on the basolateral membrane of the principal cell of the collecting duct activates adenylyl cyclase and generates cyclic AMP (cAMP) from adenosine triphosphate (ATP). In turn, cAMP activates protein kinase A, which phosphorylates aquaporin water channels (AQP2) and induces them to relocate to the luminal membrane. This promotes the reabsorption of water from tubular fluid to blood, rendering the tubular fluid more concentrated (increased osmolality). Panel B shows the consequences of vasopressin antagonism. In the presence of a vasopressin antagonist, the signaling pathway that is described in Panel A is not activated. As a consequence, the water permeability of the cell remains high and water is not reabsorbed, causing the excretion of dilute urine (decreased osmolality) and thereby increasing the level of sodium in the blood compartment.

Table 2. Conivaptan is twice as potent as tolvaptan as an inhibitor of the V_1 receptor, but tolvaptan is 2.5 times as potent an inhibitor of the V_2 receptor.[25,26] The relative inhibition of the two receptors (V_2:V_1 selectivity ratio) is much greater with tolvaptan (by a factor of 29) than with conivaptan (by a factor of 5.7). Thus, conivaptan is a nonselective vasopressin inhibitor, whereas tolvaptan is a more selective V_2 inhibitor.

Table 2 summarizes the similar pharmacokinetics of the two drugs.[27] Each of the drugs has a half-life that ranges from 6 to 10 hours and has activity that peaks several hours after administration. The two drugs are highly protein-bound and are metabolized by the hepatic cytochrome P-450 isoenzyme CYP3A4 system, resulting in minimal (<5%) urinary excretion. Conivaptan is a potent inhibitor of this enzyme; concern for drug interactions has limited its use to a 4-day intravenous course, which makes it suitable for patients who are limited to this route of administration.

The two drugs share a number of pharmacodynamic properties. Both increase urine flow and the excretion of electrolyte-free water, without substantial changes in sodium or potassium excretion, leading to their designation as aquaretic agents. Neither drug is effective in patients with advanced chronic kidney disease (stage 4 or 5).

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Table 2. Inhibitory Constants and Pharmacokinetics of Two Vasopressin Antagonists.

Variable	Conivaptan	Tolvaptan
Inhibitory constant of vasopressin antagonist*		
V_1 receptor — nM	6.3	12.3
V_2 receptor — nM	1.1	0.4
V_2:V_1 selectivity ratio	5.7	29.0
Pharmacokinetics of vasopressin antagonists†		
Dose	Intravenous administration, 40 mg daily for 4 days	Oral administration, 15 to 60 mg daily
Half-life — hr	6–10	6–8
Time to maximum aquaresis after administration — hr	2	2
Protein binding — %	95–99	99
Oral bioavailability — %	40–50	40–50
Primary metabolism	CYP3A4	CYP3A4
Urinary excretion — %	<1	<5

* Data are adapted from Tahara et al.[25] and Yamamura et al.[26] The inhibitory constant (Ki) is the inhibitor level that produces half the maximal rate, so a smaller Ki value indicates a more potent inhibitor.
† Data are adapted from Costello-Boerrigter et al.[27]

WHAT VASOPRESSIN ANTAGONISTS DO

In phase 3 trials, treatment with vasopressin antagonists consistently increased plasma sodium levels. Intravenous conivaptan (at a dose of 40 mg per day) increased plasma sodium levels by a mean of 6.3 mmol per liter.[28] Likewise, in the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT 1 and 2), tolvaptan (at an oral dose of 30 mg per day) increased the level by a mean of 3.6 mmol per liter at 4 days and by 4.4 mmol per liter at 30 days.[29] In a meta-analysis of 15 randomized, controlled trials involving 1619 patients, tolvaptan increased the mean plasma sodium level by 5.27 mmol per liter (95% confidence interval [CI], 4.27 to 6.26) on days 3 to 7.[30] In another meta-analysis of 11 randomized, controlled trials involving 1094 patients, vaptans increased the mean plasma sodium level by 5.7 mmol per liter (95% CI, 4.1 to 7.4).[31]

In an analysis of 20 randomized, controlled trials involving 2900 patients,[32] the European Clinical Practice Guideline group, which consists of members of three medical societies with an interest in hyponatremia, found that the use of vasopressin antagonists led to a mean increase in the plasma sodium level of 4.30 mmol per liter (95% CI, 3.51 to 4.95) above that in the placebo group at 3 to 7 days. The increase persisted at 7 months, in agreement with a study reporting persistent efficacy for up to 4 years.[33] In a hyponatremia registry of more than 3000 patients, vasopressin antagonists increased the plasma sodium level by a median of 4.0 mmol per liter.[34] The majority of patients in these trials had mild-to-moderate hyponatremia (sodium level, >125 mmol per liter) and were asymptomatic or had mild symptoms. Thus, the efficacy of vasopressin antagonists in increasing the plasma sodium level is unquestionable.

WHAT VASOPRESSIN ANTAGONISTS DO NOT DO

Dependence on the excretion of free water makes the response to vasopressin antagonists too slow to benefit patients with hyponatremia who have severe cerebral symptoms. Such patients require a prompt decrease in the volume of brain water, which is best achieved with hypertonic saline.[35] At 8 hours, the use of tolvaptan was associated with a small increase in the sodium level in the SALT trials. At 12 hours, only half of patients

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receiving conivaptan had an increase of more than 4 mmol per liter in the plasma sodium level.[36] Therefore, the vasopressin antagonists appear to have no role to play in the treatment of patients with hyponatremia who have severe central nervous system symptoms, in whom cerebral edema increases the risk of tentorial herniation. Similarly, patients with hypovolemic hyponatremia require volume repletion to halt nonosmotic release of vasopressin.[35] Furthermore, V_{1A}-receptor antagonists can cause hypotension in such patients.

COMPARATOR STUDIES

Few studies comparing vasopressin antagonists with alternative treatments for hyponatremia are available. In a small, 1-year crossover study involving 12 patients, increases in plasma sodium levels were similar among patients receiving tolvaptan and those receiving urea.[37] (The drawbacks of urea treatment are discussed later.) In a retrospective study of patients with similar sodium levels at baseline, there was no significant difference in sodium levels between 15 patients receiving conivaptan and 34 receiving hypertonic saline at various times or at 24 hours.[38] In the registry study, in which fluid restriction was the comparator, the relative likelihood of correction of the plasma sodium level by more than 5 mmol per liter was most significant for patients receiving tolvaptan (2.55; 95% CI, 1.82 to 3.57), was less significant for hypertonic saline (1.60; 95% CI, 1.16 to 2.20), and was not significant for isotonic saline.[34] The registry study did not provide for randomization according to covariates that can affect responses to therapy, including the baseline plasma sodium level, age, and use of concomitant medications. These shortcomings notwithstanding, hypertonic saline and vasopressin antagonists are the most predictable methods for increasing plasma sodium levels. Studies that directly compare vasopressin antagonists with demeclocycline (an antibiotic that is used off-label for the treatment of hyponatremia) and with water restriction would be of interest.

ADVERSE EVENTS

Polyuria, urinary frequency, thirst and mouth dryness,[29] and constipation[31] are more common among patients receiving tolvaptan than among those receiving placebo. In the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST), there were more adverse events among the 232 patients with hyponatremia who were receiving placebo than among the 242 patients who were receiving tolvaptan; in the latter group, only thirst and nausea were more common.[39] In a study of adult polycystic kidney disease involving 1445 patients, elevations in hepatic enzymes were more frequent in the group receiving tolvaptan (at doses four times those that are administered for the treatment of hyponatremia) than in the control groups.[26] In 2 patients in that trial, the drug was withdrawn because of liver injury; such withdrawal resulted the resolution of the liver disorder. The FDA recommends limiting the use of tolvaptan to 30 days and specifically states that the drug should not be used in patients with liver disease.[40] This suggestion may not apply to patients with end-stage liver disease who are awaiting liver transplantation, since hyponatremia increases the risk of osmotic demyelination after transplantation.[41]

Excessive correction of hyponatremia enhances the risk of the osmotic demyelination syndrome. The risk ratio for overcorrection[34] and for hypernatremia[31] is higher among patients receiving vasopressin antagonists than among those receiving placebo. In the SALT trials, a rate of 0.5 mmol of sodium per hour was exceeded in 4 of 223 patients receiving tolvaptan, and the plasma sodium level rose above 146 mmol per liter in a similar number of patients,[29] although the osmotic demyelination syndrome did not develop in any of the patients. In the Safety and Sodium Assessment of Long-term Tolvaptan with Hyponatremia (SALTWATER) study, 18 of 111 patients in the tolvaptan group had a plasma sodium level of more than 145 mmol per liter at least once.[33] The osmotic demyelination syndrome was not diagnosed in any of these patients or in any of the patients with hyponatremia in EVEREST.[42] In the context of a review, a case of osmotic demyelination was reported in a patient receiving tolvaptan, in whom the plasma sodium level rose by 45 mmol to 167 mmol per liter.[43] Another review article describes the osmotic demyelination syndrome in 2 additional patients who were receiving tolvaptan along with a 3% solution of sodium chloride.[44] The manufacturer of tolvaptan (Otsuka America Pharmaceutical) issued a letter expressing concern in light of neurologic

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sequelae in patients treated with tolvaptan "where the correction of serum sodium was exceeded."[45] It is unclear whether any of these patients had the osmotic demyelination syndrome, and there have been no communications to the reporting website of the Medicines and Healthcare Products Regulatory Agency in the United Kingdom (https://mhra.gov.uk/yellowcard). Despite the rarity of the osmotic demyelination syndrome, the plasma sodium level should be frequently monitored, and the need for action to prevent overcorrection cannot be overstated. To this end, the combination of hypertonic saline and a vasopressin antagonist should be avoided.

RESISTANCE TO VASOPRESSIN ANTAGONISTS

Approximately 15% of patients with hyponatremia do not have a response to vasopressin antagonists.[46] This lack of response is seen in patients in whom urine is not diluted and electrolyte-free water is not excreted.

HIGH CIRCULATING VASOPRESSIN LEVELS

Most patients with euvolemic and hypervolemic hyponatremia have vasopressin levels that range from 1 to 10 pg per milliliter, levels that are within the normal range but are inappropriately elevated in the hypotonic state.[9] Since the vaptans appear to be competitive antagonists,[18,47] it is possible that patients with very high hormone levels may not have a response to standard doses.

VASOPRESSIN-INDEPENDENT DILUTING DEFECT

Among patients with cirrhosis in the SALT trials[29] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and in the SALTWATER trials[33] and among those with hypervolemia in a meta-analysis,[31] the increase in the plasma sodium level was more modest than among those with euvolemic hyponatremia. In addition, a lower percentage of these patients achieved a sodium level of more than 135 mmol per liter. The difference in response was probably due to vasopressin-independent impaired urinary dilution as a result of a reduced glomerular filtration rate, enhanced reabsorption of proximal tubular fluid, or both. This combination of factors resulted in decreased delivery of tubular fluid to the cortical thick segment of the ascending limb of Henle's loop, where it is rendered hypotonic; the tubular fluid is then delivered distally to vasopressin-responsive nephron segments, where the hypotonicity is dissipated.[48] These disturbances are prevalent among patients with advanced heart failure and particularly among those with cirrhosis.

EXCESSIVE WATER INTAKE

If water intake exceeds or is equal to the amount that is excreted, the plasma sodium level will not increase. In such cases, patients may have persistent hyponatremia despite the dilution of urine. In patients with SIADH, such a response may be caused by a "reset osmostat," in which an increase in the plasma sodium level causes the secretion of vasopressin and stimulates thirst but does so at a lower-than-normal plasma sodium level.

NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS

An activating mutation in the V_2 receptor causes hyponatremia associated with NSIAD,[49] a condition that has been reported in adults who have a resistance to vaptans.[50] However, in a recent study, investigators found that a mutation in the vasopressin receptor may be uncommon in the 10% of patients with SIADH who have no measurable hormone levels.[51]

VASOPRESSIN ANTAGONISTS IN PRACTICE GUIDELINES

Despite the paucity of data, panels have put forth recommendations for the treatment of hyponatremia.[52] Of the available guidelines, two have garnered the most attention. The first set of guidelines was prepared by an expert panel that was supported by the manufacturer of tolvaptan[53]; the second set, the European Clinical Practice Guideline, was developed by members of three medical societies with an interest in hyponatremia without support from the pharmaceutical industry.[32] However, the committee did not exclude persons who had potential conflicts of interest but, rather, insisted that such conflicts be declared. The two panels agree that limited data are available for treatment with demeclocycline, loop diuretics, and urea. However, they have divergent recommendations regarding the use of vasopressin antagonists (Table 3). The European guidelines do not recommend the use of vasopressin antagonists in

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Table 3. Recommendations for the Use of Vaptans in the Treatment of Hyponatremia.

Hyponatremia Classification	Expert Panel Recommendation*	European Clinical Practice Guideline†
Hypovolemic hyponatremia	Vaptan is not a treatment option.	Vaptan is not a treatment option.
Euvolemic hyponatremia		
Asymptomatic	Vaptan is a treatment option.	Vaptan is not a treatment option.
Moderate-to-severe central nervous system symptoms	Vaptan is not a treatment option.	Vaptan is not a treatment option.
Hypervolemic hyponatremia		
Asymptomatic	Vaptan is a treatment option, except in patients with liver disease.	Vaptan is not a treatment option.
Moderate-to-severe central nervous system symptoms	Vaptan is not a treatment option.	Vaptan is not a treatment option.

* Data are adapted from Verbalis et al.[53]
† Data are adapted from Spasovski et al.[32] These guidelines were developed by members of three medical societies: the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association–European Dialysis and Transplant Association.

patients with euvolemia who have SIADH and recommend against their use in patients with heart failure, in whom the need for water restriction and the wider use of urea are recommended. In contrast, the expert panel recommends that vasopressin antagonists be used in patients with SIADH when water restriction fails and states that vasopressin antagonists are "a viable option along with loop diuretics" in patients with heart failure. Such discrepancies may be explained by differences in drug availability and exposure and by different methods of analyzing and interpreting the data.[54]

There are cogent arguments on both sides of the debate over the use of vasopressin antagonists. The European panelists express concern regarding the neurologic consequences of overcorrection, the risk of hepatotoxicity, and the lack of data supporting a survival benefit. Their meta-analysis of six trials of vasopressin antagonists including mortality (involving 733 patients) showed no significant difference between patients receiving a vasopressin antagonist and those receiving placebo (odds ratio for death in the vasopressin group, 0.67; 95% CI, 0.38 to 1.18).[32] In a phase 2 study involving patients with congestive heart failure who had an increased plasma sodium level, there was a 50% decrease in mortality 60 days after discharge.[55] Nonetheless, in EVEREST, there was no survival benefit for the use of vasopressin antagonists,[42] although the event rate in the subgroup with hyponatremia was too small for a reliable analysis. It also has not been established whether vasopressin antagonists decrease the length of hospitalization. In EVEREST, patients with hyponatremia had a longer hospital course than those with normonatremia; patients in the tolvaptan group had a lower mean length of stay, but the difference was not significant.[56] In the SALT trials, patients with euvolemia (sodium level, <130 mmol per liter) who were included in a retrospective subgroup analysis had a significant decrease in the length of hospital stay.[57] Finally, the high cost of vasopressin antagonists (which ranges from $300 to $350 per 30-mg tablet) represents another barrier to the use of these drugs.

The recommendations of the expert panel also have merit, particularly since none of the alternative approaches have been subjected to the rigors of a regulatory process requiring randomized, controlled trials nor have they received the approval of any regulatory agency. Each of the alternative approaches lacks survival data, and each has limited efficacy or unacceptable side effects. Water restriction, while financially attractive, is frequently associated with low compliance and is ineffective when urinary osmolality is greater than 500 mOsm per kilogram of body weight or the ratio of urinary to plasma electrolytes (sodium plus potassium levels) is greater than 1.[58] These measures also predict the failure of treatment to increase the plasma sodium level with isotonic sodium chloride (0.9% solution).[59,60] Urea is distasteful and unavailable in a standard formulation for human consumption.

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WHEN AND HOW TO USE VASOPRESSIN ANTAGONISTS

SHORT-TERM USE

Several therapeutic options are available to hospitalized patients who have euvolemia or hypervolemia with mild or moderate symptoms attributable to hyponatremia, particularly if the plasma sodium level is more than 125 mmol per liter.[61] Among such patients, vasopressin antagonists, while not indicated for those with severe neurologic symptoms, are simplest and safest to use. (A detailed case is described in the Supplementary Appendix.) After administration of the drug, the plasma sodium level should be monitored every 4 hours. When an increase of 6 to 8 mmol per liter is achieved, water intake (orally or intravenously as a 5% dextrose solution) is initiated to match urine output, which prevents the plasma sodium level from rising excessively and minimizes the risk of demyelination.

LONG-TERM USE

In patients with irreversible euvolemic hyponatremia (<130 mmol per liter) who have a gait disturbance or a history of falls[62,63] and who do not have a response to or are not compliant with water restriction, in my opinion the risk–benefit balance favors the use of tolvaptan. Treatment is initiated at a daily dose of 15 mg, and the plasma sodium level is monitored for 24 hours. The dose can be increased to 30 and 60 mg per day if the plasma sodium level does not rise by 5 mmol per liter, or above 135 mmol per liter, within approximately 1 week. Thereafter, monthly determinations suffice. Water restriction is not advisable, since thirst and water intake help to prevent undesirable increases in the plasma sodium level. Liver enzymes should be monitored if the drug is used beyond the FDA-recommended duration of 30 days; the drug should be discontinued if liver enzymes are elevated to three times the upper limit of their normal level. In patients with decompensated heart failure, the drug acutely improves congestion and dyspnea but is an adjunct to a natriuretic agent in the relief of fluid retention. The long-term effect of such treatment has not been determined.

The care of patients with hyponatremia carries a substantial financial burden.[64] It would be desirable if vasopressin antagonists were priced so as to mitigate rather than add to this burden. During the next decade, it would be highly desirable to establish whether the use of vasopressin antagonists has an effect on the length of hospitalization and rehospitalization and to examine the effect on morbidity and quality of life. Such data could expand the use of an effective drug with an acceptable side-effect profile and help to answer the lingering question as to whether hyponatremia plays a pathogenic role or is simply an "innocent bystander" (i.e., a marker of more severe underlying disease).[65]

CONCLUSION

The advent of the use of vasopressin antagonists has provided physicians with a new means of increasing the plasma sodium level in patients with hyponatremia. These agents appear to offer substantial advantages over previously available therapies that have been shown to have limited efficacy, an unacceptable side-effect profile, or both. To ascertain whether such increases in the plasma sodium level have an effect on mortality and morbidity associated with hyponatremia is a challenge for the next decade.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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REFERENCES

1. Von de Velden V. Die Nierenwirkung von hypophyseuxtrakten beim menschen. Herl kiln Wochnschr 1913;1:2083-6. (In German.)
2. Oliver G, Schäfer EA. On the physiological action of extracts of pituitary body and certain other glandular organs. J Physiol 1895;18:277-9.
3. Howell WH. The physiological effects of extracts of the hypophysis cerebri and infundibular body. J Exp Med 1898;3:245-58.
4. Verney EB. The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond B Biol Sci 1947;135:25-106.
5. Jewell PA, Verney EB. An experimental attempt to determine the site of neurohypophyseal osmorereceptors in the dog. Phil Trans Roy Soc 1957;240:197-324.
6. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol 1979;236:F321-F332.
7. Dunn FL, Brennan TJ, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin

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secretion in the rat. J Clin Invest 1973;52:3212-9.
8. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1957;23:529-42.
9. Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982;72:339-53.
10. Turner RA, Pierce JG, du Vigneaud V. The purification and the amino acid content of vasopressin preparations. J Biol Chem 1951;191:21-8.
11. Schmale H, Richter D. Single base deletion in the vasopressin gene is the cause of diabetes insipidus in Brattleboro rats. Nature 1984;308:705-9.
12. Thibonnier M, Auzan C, Madhun Z, Wilkins P, Berti-Mattera L, Clauser E. Molecular cloning, sequencing, and functional expression of a cDNA encoding the human V1a vasopressin receptor. J Biol Chem 1994;269:3304-10.
13. Birnbaumer M, Seibold A, Gilbert S, et al. Molecular cloning of the receptor for human antidiuretic hormone. Nature 1992;357:333-5.
14. Agre P. The aquaporin water channels. Proc Am Thorac Soc 2006;3:5-13.
15. Fushimi K, Uchida S, Hara Y, Hirata Y, Marumo F, Sasaki S. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. Nature 1993;361:549-52.
16. Manning M, Sawyer WH. Discovery, development, and some uses of vasopressin and oxytocin antagonists. J Lab Clin Med 1989;114:617-32.
17. Stassen FL, Bryan W, Gross M, et al. Critical differences between species in the in vivo and in vitro renal responses to antidiuretic hormone antagonists. Prog Brain Res 1983;60:395-403.
18. Yamamura Y, Ogawa H, Yamashita H, et al. Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V2 receptor antagonist. Br J Pharmacol 1992;105:787-91.
19. Ohnishi A, Orita Y, Okahara R, et al. Potent aquaretic agent: a novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. J Clin Invest 1993;92:2653-9.
20. Thibonnier M, Coles P, Conarty DM, Plesnicher CL, Shoham M. A molecular model of agonist and nonpeptide antagonist binding to the human V(1) vascular vasopressin receptor. J Pharmacol Exp Ther 2000;294:195-203.
21. Thibonnier M, Coles P, Thibonnier A, Shoham M. The basic and clinical pharmacology of nonpeptide vasopressin receptor antagonists. Annu Rev Pharmacol Toxicol 2001;41:175-202.
22. Macion-Dazard R, Callahan N, Xu Z, Wu N, Thibonnier M, Shoham M. Mapping the binding site of six nonpeptide antagonists to the human V2-renal vasopressin receptor. J Pharmacol Exp Ther 2006;316:564-71.
23. Pinto CS, Reif GA, Nivens E, White C, Wallace DP. Calmodulin-sensitive adenylyl cyclases mediate AVP-dependent cAMP production and Cl– secretion by human autosomal dominant polycystic kidney cells. Am J Physiol Renal Physiol 2012;303:F1412-F1424.
24. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407-18.
25. Tahara A, Saito M, Sugimoto T, et al. Pharmacological characterization of YM087, a potent, nonpeptide human vasopressin V1A and V2 receptor antagonist. Naunyn Schmiedebergs Arch Pharmacol 1998;357:63-9.
26. 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;287:860-7.
27. Costello-Boerrigter LC, Boerrigter G, Burnett JC Jr. Pharmacology of vasopressin antagonists. Heart Fail Rev 2009;14:75-82.
28. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol 2007;27:447-57.
29. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-112.
30. Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L, Gafter U. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. Am J Kidney Dis 2010;56:325-37.
31. Jaber BL, Almarzouqi L, Borgi L, Seabra VF, Balk EM, Madias NE. Short-term efficacy and safety of vasopressin receptor antagonists for treatment of hyponatremia. Am J Med 2010;124(10):977.e1-977.e9.
32. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 2014;29:Suppl 2:i1-i39.
33. Berl T, Quittnat-Pelletier F, Verbalis JG, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 2010;21:705-12.
34. Greenberg A, Verbalis J, Amin A, et al. Hyponatremia: current treatment practice and outcomes report of the hyponatremia registry: an observational multicenter international study. Kidney Int 2015 February 11.
35. Thurman J, Berl T. Therapy of dysnatremic disorders. In: Wilcox C, ed. Therapy in nephrology and hypertension. 3rd ed. Philadelphia: Saunders, 2008:337-52.
36. Velez JC, Dopson SJ, Sanders DS, Delay TA, Arthur JM. Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience. Nephrol Dial Transplant 2010;25:1524-31.
37. Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. Clin J Am Soc Nephrol 2012;7:742-7.
38. Dominguez M, Perez JA, Patel CB. Efficacy of 3% saline vs. conivaptan in achieving hyponatremia treatment goals. Methodist Debakey Cardiovasc J 2013;9:49-53.
39. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail 2013;19:390-7.
40. Food and Drug Administration. FDA safety communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death, 2013 (http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm).
41. Yun BC, Kim WR, Benson JT, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology 2009;49:1610-5.
42. 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;297:1319-31.
43. Malhotra I, Gopinath S, Janga KC, et al. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. Case Rep Endocrinol 2014;2014:807054.
44. Lehrich RW, Ortiz-Melo DI, Patel MB, Greenberg A. Role of vaptans in the management of hyponatremia. Am J Kidney Dis 2013;62:364-76.
45. Di Benedetto G, See M. Direct Healthcare Professional Communication on the risk of increases in serum sodium with tolvaptan (Samsca) which are too rapid, March 26, 2012 (http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con146921.pdf).
46. Decaux G. V2-antagonists for the treatment of hyponatraemia. Nephrol Dial Transplant 2007;22:1853-5.
47. Serradeil-Le Gal C, Lacour C, Valette G, et al. Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. J Clin Invest 1996;98:2729-38.
48. Gottschalk CW, Mylle M. Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. Am J Physiol 1959;196:927-36.

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49. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med 2005;352:1884-90.
50. Decaux G, Vandergheynst F, Bouko Y, Parma J, Vassart G, Vilain C. Nephrogenic syndrome of inappropriate antidiuresis in adults: high phenotypic variability in men and women from a large pedigree. J Am Soc Nephrol 2007;18:606-12.
51. Fenske WK, Christ-Crain M, Hörning A, et al. A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. J Am Soc Nephrol 2014;25:2376-83.
52. Nagler EV, Vanmassenhove J, van der Veer SN, et al. Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. BMC Med 2014;12:1.
53. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126:Suppl 1:S1-S42.
54. Verbalis JG, Grossman A, Höybye C, Runkle I. Review and analysis of differing regulatory indications and expert panel guidelines for the treatment of hyponatremia. Curr Med Res Opin 2014;30:1201-7.
55. 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;291:1963-71.
56. Cyr PL, Slawsky KA, Olchanski N, et al. Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. Am J Health Syst Pharm 2004;68:328-3.
57. Verbalis JG, Adler S, Schrier RW, et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol 2011;164:725-32.
58. Furst H, Hallows KR, Post J, et al. The urine/plasma electrolyte ratio: a predictive guide to water restriction. Am J Med Sci 2000;319:240-4.
59. Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. Ann Intern Med 1997;126:20-5.
60. Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. QJM 1998;91:749-53.
61. Jovanovich AJ, Berl T. Where vaptans do and do not fit in the treatment of hyponatremia. Kidney Int 2013;83:563-7.
62. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 2006;119(1):71.e1-71.e8.
63. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM 2008;101:583-8.
64. Shea AM, Hammill BG, Curtis LH, Szczech LA, Schulman KA. Medical costs of abnormal serum sodium levels. J Am Soc Nephrol 2008;19:764-70.
65. Hoorn EJ, Zietse R. Hyponatremia and mortality: how innocent is the bystander? Clin J Am Soc Nephrol 2011;6:951-3.

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