Vaptans for the treatment of hyponatremia

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Abstract | The vaptans constitute a new class of pharmaceuticals developed for the treatment of the hypervolemic and euvolemic forms of hyponatremia. These agents are nonpeptide vasopressin antagonists that interfere with the antidiuretic effect of the hormone by competitively binding to V_2 receptors in the kidney. This blockade results in water diuresis (aquaresis) that, if not offset by increased fluid intake, reduces body water content and raises plasma sodium levels. Probably as a result of this rise in plasma sodium, thirst and plasma vasopressin concentration increase, potentionally limiting the effects of the vasopressin antagonists. Nonetheless, vaptans are particularly useful to treat hypervolemic hyponatremia associated with severe congestive heart failure or chronic liver failure, as the only other treatments currently available, such as fluid restriction and diuretics, are slow-acting and minimally effective. Vaptans are also useful for treating euvolemic hyponatremia associated with the syndrome of inappropriate antidiuretic hormone (SIADH), at least when it is chronic and/or minimally symptomatic. However, because their effects vary unpredictably from patient to patient, vaptans are less useful than hypertonic saline infusion in cases of acute, severe and symptomatic hyponatremia. Vaptan therapy is absolutely contraindicated in hypovolemic hyponatremia (in which total body water is reduced) and is ineffective in the vasopressin-independent form of inappropriate antidiuresis caused by constitutive activating mutations of V_2 receptors.

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Introduction

Over the past 20 years, the development of nonpeptide, vasopressin V_2 receptor antagonists for the treatment of hyponatremia has virtually exploded. This new class of pharmaceuticals, known collectively as vaptans, selectively antagonizes the antidiuretic effect of vasopressin by competitively binding to V_2 receptors in the kidney. This blockade increases water excretion without loss of electrolytes (aquaresis) and, unless compensated for by an increase in fluid intake, reduces total body water content and raises plasma sodium concentration.

This Review summarizes the data on the pharmacology and clinical effects of the five different vaptans most widely studied in healthy individuals and patients with hyponatremia. It will also direct attention to certain unexplained characteristics of these drugs that may affect the use of vaptans in individual patients and offer recommendations on the use of vaptans versus the more traditional methods of treating the various types of hyponatremia. However, no attempt will be made to compare the relative therapeutic efficacy or safety of different vaptans, because the studies published to date vary too much in design, patient selection and data analysis to permit reliable conclusions. Instead, emphasis will be given to other variables, such as fluid intake and the underlying pathophysiology that may influence efficacy.

Osmoregulation

In healthy adults, plasma osmolarity and its principal determinant, the concentration of sodium and its anions, are normally maintained within a narrow range

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Key points

- Vaptans are nonpeptide agents that antagonize the antidiuretic effect of vasopressin by competing with it for binding to V_2 receptors in the kidney
- Vaptans increase solute-free water excretion, reduce body water content and raise the plasma sodium level by reducing urine concentration, unless the aquaresis is offset by increased fluid intake
- The vaptan-induced rise in plasma sodium often stimulates thirst and/or vasopressin secretion, which, in turn, may feed back to increase fluid intake and/or overcome blockade of the V_2 receptor
- In conjunction with modest restriction of fluid intake, vaptans have proven safe and effective in treating chronic hypervolemic and euvolemic hyponatremia
- The use of vaptans to treat acute, symptomatic forms of hyponatremia is still debatable, because their effects on plasma sodium vary unpredictably from patient to patient
- Vaptan therapy is contraindicated in hypovolemic hyponatremia, a disorder associated with decreased total body water and sodium levels, and is ineffective in a form of inappropriate antidiuresis that is independent of vasopressin

at 275–295 mosmol/l and 135–145 mmol/l, respectively. This constancy is achieved by rapidly raising or lowering total body water to compensate for changes in sodium intake and water output owing to obligatory, insensible (evaporation from skin and lungs) and urinary loss of water. These adjustments in body water content are made by overlapping hypothalamic osmostats that regulate thirst and secretion of the antidiuretic hormone arginine vasopressin (Figure 1).[1] Each osmostat functions like a threshold or set-point regulator, with that for thirst set slightly higher than that for vasopressin secretion (Figure 2). This arrangement maintains basal plasma osmolarity, that is sodium and its anions, between the two thresholds and ensures that thirst and water intake are not stimulated until plasma sodium concentrations rise above the level at which the water-conserving effect of vasopressin is maximal.

Hyponatremia

Classification and pathophysiology

Hypotonic hyponatremia is a heterogenous disorder that results from several fundamentally different types of sodium and water imbalance. It differs from the hyponatremia caused by hyperglycemia in that plasma osmolarity as well as plasma sodium are low and is caused by a combination of impaired water excretion and excessive water intake that result in a relative excess of body water. The abnormalities in water intake and excretion can have different causes and be associated with different disturbances in sodium balance. Thus, hypotonic hyponatremia is divided into three types depending on whether extracellular fluid volume and sodium are increased (hypervolemic), decreased (hypovolemic) or relatively normal (euvolemic) (Table 1).[2]

Hypervolemic hyponatremia

Hypervolemic hyponatremia is due to excessive retention of water and sodium, usually as a result of congestive heart failure or cirrhosis. These disorders are believed to cause a decrease in 'effective' blood volume or filling pressure that decreases glomerular filtration; increases reabsorption of sodium and water in the proximal tubule;[3] decreases delivery of filtrate to distal diluting sites; increases plasma renin activity and aldosterone; and stimulates thirst and/or vasopressin release, probably by lowering the set of

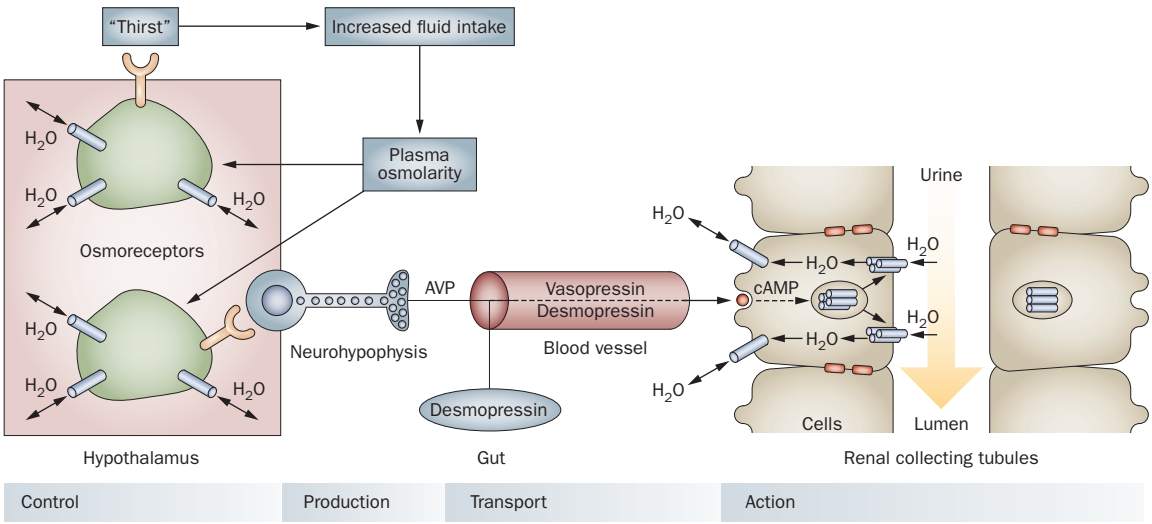

Figure 1 | Principal elements of the osmoregulatory system. Vasopressin reduces urine output and raises urine concentration (osmolarity) by increasing the reabsorption of solute-free water in collecting tubules of the kidney.[45] This antidiuretic effect is mediated via the V_2 receptor that acts via adenyl cyclase to insert preformed aquaporin 2 water channels into the luminal surface of the cell,[46] thereby permitting solute-free water to diffuse passively from the lumen and through the cell along the osmotic pressure gradient created by the hypertonic renal medulla. In the absence of V_2 receptor stimulation, dilute filtrate passes unmodified through the collecting ducts to be excreted as urine with an osmolarity <90 mosmol/l and a flow rate as high as 900 ml/h. As output of this magnitude can compensate for all but the most pathologically excessive rates of water intake, the threshold or set point of the vasopressin osmostat effectively determines the lowest level to which plasma osmolarity and sodium can be depressed, provided glomerular filtration and solute excretion are normal. Abbreviations: AVP, arginine vasopressin; cAMP, cyclic AMP.

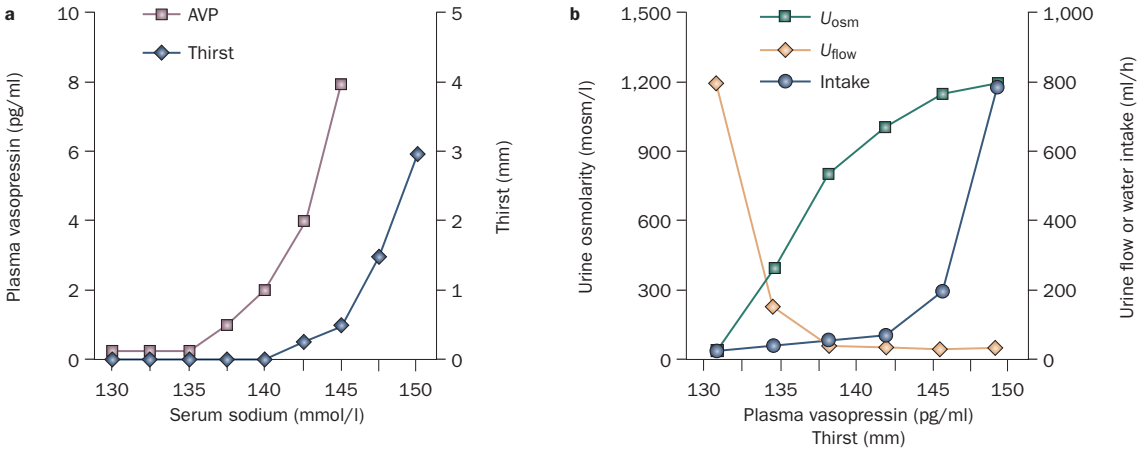

Figure 2 | Osmoregulation of water balance in healthy adults. **a** | Relation of plasma vasopressin and thirst to plasma sodium concentration. **b** | Relation of urine osmolarity (U_{osm}), urine flow (U_{flow}) to plasma vasopressin and of water intake to thirst. Based on data in Robertson, G. L. *et al.*[25] and Zerbe, R. L. *et al.*[26]. Abbreviation: AVP, arginine vasopressin.

the osmostat for vasopressin[4] and possibly thirst. The net effect is a greater increase in body water than in sodium resulting in hyponatremia and generalized edema, as well as other signs of volume expansion.

Hypovolemic hyponatremia

Hypovolemic hyponatremia is caused by excessive loss of water and electrolytes from the gastrointestinal tract or kidneys, usually as a result of severe diarrhea or abuse of diuretic drugs. The resultant hypovolemia decreases glomerular filtration; increases readsorption of salt and water in the proximal nephron; decreases delivery of filtrate to distal diluting segments; and increases plasma renin activity and aldosterone secretion. Less often, hypovolemic hyponatremia can result from primary hypoaldosteronism or Addison disease (primary adrenal insufficiency), in which case plasma aldosterone concentration is inappropriately low. In either scenario, hypovolemia also stimulates thirst and/or vasopressin secretion by lowering the threshold of the osmostats.[5] The resultant increase in water intake and delay in water excretion partially corrects the water deficiency but does not correct the sodium deficiency, which results in hyponatremia and persistent signs of extracellular volume depletion.

Euvolemic hyponatremia

Euvolemic hyponatremia is caused by a primary defect in urinary dilution which, if combined with excessive water intake, expands and dilutes body fluids. If large enough, the expansion of body fluids also suppresses plasma renin activity and aldosterone levels and triggers natriuresis (urinary excretion of sodium). This phenomenon worsens the hyponatremia but also reduces extracellular volume, thereby eliminating overt signs of hypervolemia. The defect in urine dilution is usually owing to an abnormality in the osmoregulation of vasopressin. Sometimes this abnormality is secondary to interference by a recognized and correctable nonosmotic stimulus, such as nausea, a drug or secondary adrenal insufficiency.[6] However, more often it results from ectopic vasopressin secretion (from a tumor) or eutopic vasopressin secretion (from the neurohypophysis) in the absence of any detectable or readily correctable stimulus. This disorder is commonly referred to as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and can be caused by several different abnormalities in osmoregulation.[2]

The most frequent abnormality appears to be a down-regulation of the osmostat. The cause is unknown but may be abnormal input from the baroregulatory system. The other variants manifest either as large erratic fluctuations in plasma vasopressin levels (type A) or as a constant slow leak of the hormone (type B) and are unaffected by changes in plasma sodium levels. Infrequently, the inappropriate antidiuresis seems to be vasopressin-independent. This disorder manifests as impaired urinary dilution without any demonstrable abnormality in plasma vasopressin levels.[2] In some patients, the inappropriate antidiuresis is the result of a constitutive activating mutation of the V_2 receptor[7] that can affect heterozygous women as well as hemizygous men.[8] The cause of the excessive water intake in patients with euvolemic hyponatremia also varies, as it may be owing to an associated abnormality in the osmoregulation of thirst but can also be psychogenic or iatrogenic (for example, caused by intravenous administration of fluids).

Differential diagnosis

The type of hyponatremia can be determined from the clinical history as well as standard physical and laboratory signs of volume status (Table 1).[9] Hypervolemic hyponatremia occurs in patients with severe congestive heart failure or cirrhosis. It presents with physical signs of cardiac failure or ascites, as well as generalized edema and laboratory abnormalities consistent with decreased renal perfusion (for example, pre-renal azotemia).

Hypovolemic hyponatremia typically occurs in patients with a history or other evidence of severe diarrhea, diuretic abuse or Addison disease. In addition, it is associated with physical and/or laboratory signs of severe extracellular volume depletion, such as postural hypotension, tachycardia and pre-renal azotemia. Hypokalemia may also be present, unless the cause is

Table 1 | Differential diagnosis of hyponatremia

Characteristics	Hypervolemic*		Hypovolemic*			Euvolemic (SIADH)*			Euvolemic (SIAD)‡	
	CHF	Cirrhosis	Diarrhea	Diuretic abuse	Primary adrenal failure	Nausea	Secondary adrenal failure	Other§	Nephrogenic	Idiopathic
Edema	Yes	Yes	No	No	No	No	No	No	No	No
Blood pressure	Variable	Variable	Low‖	Low	Low	Variable	Low	Normal	Normal	Normal
BUN	High	Variable	High	High	High	Variable	Variable	Low	Low	Low
Serum potassium	Low	Low	Low	Low	High	Variable	Normal	Normal	Normal	Normal
PRA	High	High	High	High	High	Normal	Variable	Low	Low	Low
Aldosterone	High	High	High	High	Low	Variable	Normal	Normal	Normal	Normal
Cortisol	Normal	Normal	Normal	Normal	Low	Variable	Low	Normal	Normal	Normal
Vasopressin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
V_2 receptor mutation	No	No	No	No	No	No	No	No	Yes	No

*Partially or completely vasopressin-dependent. ‡Vasopressin-independent. §Other common causes refers to the many different illnesses or drugs thought to cause SIADH by unknown or uncertain mechanisms. ‖It is virtually impossible to put specific numbers on lab results associated with the different types of hyponatremia, because firstly, the reference ranges for tests vary from lab to lab and are always (or always should be) shown on the report alongside the patient values, making it easy to conclude if it is high, low or within normal limits; and secondly, the magnitude of the lab abnormality (high or low) varies markedly from patient to patient depending on the severity or duration of each type of hyponatremia. Abbreviations: BUN, blood urea nitrogen; CHF, congestive heart failure; PRA, plasma renin activity.

hypoaldosteronism or Addison disease, in which case serum potassium concentration is usually high.

Euvolemic hyponatremia occurs in many different clinical settings, for example, stroke, pneumonia or malignancy; however, this type of hyponatremia can also be idiopathic.[9] Diagnosis is largely made on the basis of exclusion, as edema or overt physical signs of extracellular volume expansion or contraction are not present, although blood levels of urea nitrogen and uric acid are often low presumably owing to slight volume expansion. The vasopressin-dependent forms of euvolemic hyponatremia are subdivided by the presence or absence of known, correctable stimuli, such as emesis or secondary adrenal insufficiency. Measurement of plasma vasopressin levels is of no diagnostic value except to differentiate SIADH from the syndrome of inappropriate antidiuresis (SIAD). In the latter, a thorough family history and analysis of the V_2 receptor gene may be informative.

In some cases, other indicators may also be useful for the differential diagnosis, at least in retrospect (Table 1). Plasma renin activity is usually high in hypervolemic and hypovolemic hyponatremia but low in euvolemic hyponatremia, unless the latter is caused by secondary adrenal insufficiency. If adrenal insufficiency is suspected on clinical grounds (for example, hypovolemic hyponatremia with hyperkalemia or euvolemic hyponatremia with hypoglycemia), before starting emergency glucocorticoid therapy, plasma should be collected to measure cortisol levels that aid in later confirmation or exclusion of the diagnosis. In theory, the measurement of urinary sodium excretion rate (mmol per unit time) should also be useful in the differential diagnosis of hyponatremia. In practice, however, this analysis is tedious and usually not worthwhile, as it varies considerably depending on other factors, including the developmental phase of the syndrome. The concentration of sodium in urine (mmol/l) is not meaningful for differential diagnosis, because it is largely a function of the level of antidiuresis.

Traditional treatments and management

The treatment of hyponatremia varies depending on the type, duration, severity and clinical effects (Table 2). Symptoms, which range from headache and mild confusion to coma and convulsions, usually occur if the hyponatremia develops rapidly over 24–48 h and/or is severe (plasma sodium <125 mosmol/l). These symptoms are attributable to increased intracranial pressure caused by an osmotically driven shift of water into brain cells.[10] However, brain swelling and resultant symptoms usually diminish after a few days even if hyponatremia persists, presumably because an as yet undetermined intracellular solute is inactivated (excreted or taken up into larger molecules), which allows water to diffuse back to the extracellular space. At this stage, when symptoms are minimal, hyponatremia should be corrected slowly, because rapid correction risks serious brain injury by osmotic demyelinization.[11] The rate of correction required to avoid this risk is uncertain but is generally thought to be <12 mmol/l in 24 h. However, if the hyponatremia is symptomatic and of relatively short duration (24–48 h), it should be corrected promptly, as the risks of delay, such as convulsions, coma and death from herniation of the brain, may be greater than the risk of osmotic demyelinization. In most cases, correction of hyponatremia eliminates the symptoms in a few hours, although complete recovery from coma or a seizure may take 1 day or longer.

Hypervolemic hyponatremia should be treated by reduction of body water, not by increasing the amount of body sodium. Restricting fluid intake to 500 ml per day less than the urinary output is effective, but also very slow (the rate of rise in plasma sodium levels rarely exceeds 1–3 mmol/l per day) and difficult to maintain, particularly on an ambulatory basis. No absolute level of fluid intake will reduce body water to the same extent in all patients because their size and rate of urine output varies depending on the level of antidiuresis and solute intake. Estimates of urine output may not

Table 2 | Therapy for hyponatremia

Therapy	Total change		Rate	Hypervolemic (Cause of Na^+ and H_2O gain)		Hypovolemic (Cause of water electrolyte loss)			Euvolemic (Vasopressin-dependent)			Euvolemic (Vasopressin-independent)	
	Na^+	H_2O		CHF	CLF	Renal	GI	Adrenal	Emetic	Adrenal	SIADH	V2R	?
Fluid restriction	↔	↓	Slow	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Isotonic saline	↑	↑	Slow	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3% saline	↑	↑	Fast	No	No	Yes	Yes	Maybe	Maybe	Maybe	Yes	Yes	Yes
Fludrocortisone	↑	↔	Slow	No	No	No	No	Yes	No	No	Yes*	Yes*	Yes*
Demeclocycline	↔	↓	Slow	No	No	No	No	No	No	No	Yes*	?*	?*
Urea	↓	↓↓	Slow	No	No	No	No	No	No	No	Yes*	Yes*	Yes*
Cortisol	↔	↓	Slow	No	No	No	No	Yes	No	Yes	No	No	No
Antiemetic	↔	↓	Slow	No	No	No	No	No	Yes	No	No	No	No
Vaptan	↔	↓	Fast	Yes	Yes	No	No	No	Maybe	No	Yes*	No	?

*Hyponatremia is chronic or asymptomatic. Abbreviations: ↑, increased; ↓, decreased; ↓↓, severely decreased; ↔, unchanged; ?, unknown; CHF, congestive heart failure; CLF, chronic liver failure with cirrhosis; GI, gastrointestinal; NA^+, sodium; SIADH, syndrome of inappropriate antidiuretic hormone; V2R, activating mutation of vasopressin V2 receptor.

be completely accurate but are usually more reliable than changes in body weight for adjusting restriction to individual requirements. If the hyponatremia is severe and symptomatic, complete restriction (except for ice chips if thirst is extreme) should be started before the rate of urine output is estimated. The loop diuretic furosemide increases water as well as sodium excretion, but the improvement in plasma sodium is limited and often accompanied by hypokalemia. The tetracycline antibiotic demeclocycline, which slowly increases water excretion by causing reversible nephrogenic diabetes insipidus, is contraindicated in patients with congestive heart failure and cirrhosis given the risk of nephrotoxicity. Thus, conventional ways of treating hypervolemic hyponatremia are not optimum, and a better way of promoting water excretion is needed in this condition.

Hypovolemic hyponatremia should be treated by increasing total body water and sodium, not by decreasing the amount of body water. Usually, it should be corrected promptly, as it is often acute and symptomatic and also presents risks to hemodynamic function. The easiest way is by intravenous infusion of normal (0.9%) or hypertonic (3.0%) saline. Irrespective of the saline used, the resultant increase in plasma sodium levels should be monitored closely (about every 2–4 h) and controlled by adjusting the infusion rate, because water diuresis can develop, thereby accelerating the rate of rise in plasma sodium levels, even before the hypovolemia is fully corrected.

Euvolemic hyponatremia can be treated by decreasing body water content, increasing total body sodium or both. If this type of hyponatremia is caused by protracted nausea or secondary adrenal insufficiency, prescription of an antiemetic or of cortisol is usually sufficient to inhibit vasopressin secretion, increase water excretion and raise plasma sodium levels to normal. In acute symptomatic SIADH or SIAD, the hyponatremia can be corrected promptly and predictably via restriction of fluid intake and infusion of hypertonic saline (at a rate of about 0.05 ml/kg body weight/min). This infusion replenishes the sodium deficiency and reduces body water levels by producing a natriuretic solute diuresis. The effect on plasma sodium concentration should be monitored closely, and the rate of infusion adjusted as necessary to a rate that promptly relieves symptoms without the risk of osmotic demyelinization. The 'safe' rate is controversial and probably depends to some extent on other variables, but a prudent target at present is approximately 2 mmol/l over 4 h. However, if the hyponatremia is chronic and/or minimally symptomatic, this rate can and probably should be more gradual (somewhere between 1–2 mmol/l over 4 h). Treatments such as salt tablets, fludrocortisone, urea or democlocycline are usually effective but can also have undesirable adverse effects, such as hypokalemia, hypertension, unpleasant taste, azotemia and photosensitivity. Because of several marked adverse effects, such as goiter and hypercalcemia, lithium is no longer recommended for the treatment of hyponatremia. Therefore, a simple, safe way of increasing water excretion to raise plasma sodium concentration would also be useful in SIADH and SIAD.

Vaptans

Several different vaptans (mozavaptan, conivaptan, tolvaptan, satavaptan, lixivaptan and RWJ351647) have been developed and evaluated in humans.[12–24] All of these drugs are competitive antagonists of vasopressin receptors without detectable agonist activity. However, their specificity for the various vasopressin receptors differs slightly. Conivaptan binds similarly to V_{1a} and V_2 receptors, whereas the other vaptans are relatively specific for V_2 receptors; however, vasopressin does not seem to exert any important physiologic or pathophysiologic effects via the V_1 receptors. The only exception may be that the extremely high plasma vasopressin levels produced by nausea (or infusion of large doses of vasopressin) may cause some cutaneous vasoconstriction that is responsible for the pallor that occurs in these settings.

All vaptans can be taken orally, although conivaptan can also be administered intravenously. Data on their

pharmacokinetic and pharmacodynamic properties are limited, but these agents seem to differ only slightly in terms of bioavailability, time to peak plasma concentration, peak urinary effect and clearance half-times after oral administration. However, interindividual variation in these properties is large. In addition, all of them are substrates and inhibitors of cytochrome P450 3A4 (CYP3A4) and should not be used with other drugs known to be metabolized by this system, such as ketoconazole, clarithromycin and ritonavir. Two vaptans —intravenous conivaptan and oral tolvaptan—have been approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia in hospitalized patients.

Effects in healthy individuals

The effect of vaptans on water balance is exemplified by a study in normally hydrated healthy adults.[15] Less than 1 h after an oral dose of conivaptan, mean urine osmolarity fell by 50% and mean urine flow nearly doubled. These changes were maximum at 2 h, then returned to baseline over the next 6–12 h. The increase in urine output was caused solely by aquaresis, as urinary solute excretion did not increase. The lack of effect on solute excretion seems to be characteristic of all vaptans and contrasts with that of diuretics or natriuretics, such as furosemide, which also increase excretion of sodium and other electrolytes.[13]

The vaptan-induced aquaresis reduced total body water content by an average of about 1.5 l in the first 6 h, because the mean cumulative urine output was about 2.4 l, when total fluid intake was restricted to 900 ml (150 ml/h) during the same period. As a result of the reduction in body water, plasma osmolarity rose by an average of about 7 mosmol/l. This rise varied considerably from patient to patient, as indicated by the SD of about 5 mosmol/l. The increase in plasma osmolarity, in turn, stimulated thirst and a rise in plasma vasopressin concentration. Both are physiologically appropriate responses to the decrease in body water and rise in plasma sodium levels and are not unique to conivaptan or healthy adults. These effects also occur in healthy adults treated with mozavaptan[12–14] and in patients with hyponatremia treated with other vaptans (see below).

The increase of thirst and vasopressin secretion during vaptan therapy may not be inconsequential, as these responses could 'feed back' to reduce or limit efficacy. The rise in vasopressin levels could diminish or shorten the aquaretic effect of the vaptan by enabling the hormone to compete more effectively for binding sites at V_2 receptors. If so, it could also amplify interindividual differences in aquaretic effect, as the vasopressin response to osmotic stimulation also varies greatly from person to person,[25] apparently on the basis of genotype.[26] This interference could contribute to the relatively large interindividual differences in the rise of plasma sodium concentration in healthy adults after administration of mozavaptan[13,14] or conivaptan.[15] By increasing fluid intake, thirst could also offset the effects of aquaresis on body water content and plasma osmolarity. The importance of this variable is shown by another study in which fluid intake was restricted for only 2 h after administration of five different doses of tolvaptan (60–240 mg) to healthy study participants.[18] Here, mean 24 h urine output increased in proportion to the dose but did not correlate with the rise in plasma sodium levels or the change in water intake. However, individual changes in plasma sodium concentration did correlate well with net changes in water balance, calculated as the difference between 24 h fluid intake and urine output. Thus, water intake is an important codeterminant of the change in plasma sodium concentration with vaptan therapy.

Effects in hypervolemic hyponatremia

Congestive heart failure

Six placebo-controlled clinical trials of vaptan therapy included patients with congestive heart failure or cirrhosis, as well as individuals with euvolemic hyponatremia.[27–32] All of these studies found that vaptans produced variable increases in urine output and plasma sodium levels in the group as a whole, and some noted a modest improvement in mental status or signs and symptoms of congestive heart failure. However, no improvement in long-term mortality or rehospitalization rates was demonstrated. Apart from symptoms of thirst and polyuria, as well as occasional asthenia and constipation, no drug-related adverse events were noted, even though the rise in serum sodium levels in a few patients exceeded the limit recommended to avoid the risk of osmotic demyelization. However, none of these studies separated the findings in patients with hypervolemic hyponatremia from those with other types of hyponatremia. Thus, they do not permit conclusions about possible differences in efficacy or safety that result from differences in the pathophysiology of impaired water excretion.

Four other reports focused exclusively on patients with congestive heart failure.[33–36] These studies were concerned primarily with the effect of vaptans on hemodynamic function and included few patients with hyponatremia. Nevertheless, they provide useful information about the effects of vaptans on water balance and plasma sodium levels in congestive cardiac failure. One study compared the effects of placebo and three different doses of tolvaptan for up to 23 days in 254 patients.[33] The study participants were allowed to drink *ad libitum* and remain on their usual treatments, including furosemide. On the first day of tolvaptan therapy, a dose-dependent fall in 24 h urine osmolarity and a rise in urine output occurred. However, thirst and fluid intake also increased, so the calculated decreases in water balance and body weight were modest, and mean plasma sodium levels rose by only about 2.5–3.5 mmol/l in the three treated groups. These changes were associated with a reduction in pedal edema but no improvement in the patients' quality-of-life scores. The mean increase in plasma sodium concentration after the first dose of tolvaptan in a subset of 20 patients with hyponatremia was slightly larger (5 mmol/l) than in the group as a whole[33] and was similar to that observed in healthy adults given the same doses of tolvaptan and allowed to drink *ad libitum*.[18] These small differences

may not be clinically significant and cannot be explained easily, but might reflect differences in drug absorption or clearance, thirst, fluid intake and/or plasma vasopressin concentration in the various conditions.

When tolvaptan therapy was extended for 25 days in normonatremic patients with congestive heart failure, the initial changes in mean urine osmolarity, body weight and plasma sodium levels declined slowly in the group as a whole.[33] The reason for this decline is uncertain, as it was not observed in the subset of hyponatremic patients with congestive heart failure.[33] This difference suggests the long-term decrease in efficacy in the normonatremic group was caused by larger increases in thirst, fluid intake and/or vasopressin secretion that probably resulted from the higher absolute basal levels of plasma sodium in the normonatremic than the hyponatremic group. Apart from thirst, no drug-related adverse events were observed, even though the initial rise in plasma sodium level in a few patients exceeded the recommended, safe limit.

A second study evaluated the acute effects of five different doses (10–400 mg) of lixivaptan in patients with New York Heart Association class III congestive heart failure and normal or low serum sodium levels.[34] This study found that, compared with placebo, doses of lixivaptan >10 mg produced variable increases in urine flow and free water clearance, 2–4 h after treatment. At higher doses (150–400 mg), the increased water excretion was associated with a statistically significant rise in levels of serum sodium (of unspecified magnitude) and plasma vasopressin. The effect on hyponatremic symptoms, if any, was not reported. No serious adverse events were linked specifically to the treatment.

Two additional studies were concerned mainly with the effects of tolvaptan on cardiac function and survival in patients with congestive heart failure. In one study,[35] 45 of 68 hospitalized patients with hyponatremia increased their plasma sodium by at least 2 mmol/l during treatment with 30 mg, 60 mg or 90 mg doses of tolvaptan. These patients also had a lower mortality rate (11%) 60 days after discharge than did patients whose hyponatremia did not improve (22%). This finding suggests that correction of hyponatremia in congestive failure improves the poor outcome with which it is otherwise associated. In the other study,[36] treatment with 30 mg daily of tolvaptan for 60 days raised plasma sodium levels and improved some secondary measures of cardiac function in patients with acute heart failure and normal or low plasma sodium concentration but did not effect mortality or morbidity compared with placebo. Thus, the major benefits of vaptan therapy seem to be limited to patients with hyponatremia.

Cirrhosis

Several placebo-controlled trials of tolvaptan or lixivaptan therapy have included patients with cirrhosis, as well as other types of hypervolemic or euvolemic hyponatremia.[30–32] Over treatment periods that ranged from 4 to 25 days, investigators found that vaptans produced variable but statistically significant increases in mean urine output, free water clearance and serum sodium levels with no drug-related adverse events or symptoms other than thirst. However, the findings in patients with cirrhosis were not reported separately, making it impossible to determine if they respond similarly to those with congestive cardiac failure or euvolemic hyponatremia.

Four studies have focused exclusively on the effects of vaptans in patients with cirrhosis. One study compared the aquaretic effects of a single oral dose of mozavaptan and a fixed rate of fluid intake over 24 h in six healthy adults and eight patients with cirrhosis, most of whom were normonatremic.[37] The results showed that a single 30 mg dose rapidly reduced urine osmolarity and increased urine volume in both groups in the first 2 h after treatment, but the changes in patients with cirrhosis were smaller than those in healthy individuals. This finding is unexplained but is consistent with the concept that impaired water excretion in cirrhosis is due partly to a vasopressin-independent mechanism, such as decreased distal delivery of filtrate. Interestingly, this study also found that plasma vasopressin more than doubled in both groups, even though little or no increase in plasma sodium levels occurred, presumably because water intake was only moderately restricted and fractional sodium excretion rose slightly in healthy individuals. This finding raises the possibility that the vaptan stimulates release of vasopressin by a nonosmotic mechanism. The effect on thirst was not mentioned in this report.

Another study,[23] compared the pharmacokinetics and pharmacodynamics of five different doses (25 mg, 50 mg, 100 mg, 200 mg and 300 mg) of oral lixivaptan in patients who had cirrhosis and ascites, but who were mostly normonatremic. Fluid intake was prohibited for the first 4 h after treatment but was unrestricted thereafter. The results showed that lixivaptan produced a rapid, dose-dependent fall in urine osmolarity and a rise in urine output and free water clearance that peaked at about 2 h, then declined gradually to baseline over the next 22 h. At the highest dose, total 24 h urine output averaged 4.6 l, but it also varied greatly from patient to patient, ranging from 1.2–12.2 l daily. Spontaneous fluid intake also increased, but it was generally less than urine output. Thus, water balance was negative and plasma sodium levels rose by (mean ± SD) 1.2 ± 1.0 mmol/l, 2.7 ± 1.5 mmol/l, 4.0 ± 2.6 mmol/l, 4.3 ± 3.2 mmol/l and 5.0 ± 3.0 mmol/l after 12 h in each of the five dose groups. Plasma vasopressin levels also rose twofold to threefold after administration of the highest vaptan dose. The increases in plasma sodium concentration were slightly smaller in magnitude and similar in variability to those produced by the highest dose of tolvaptan in patients with congestive heart failure, most of whom were also normonatremic.[33] Individual variations of a similar magnitude were also observed in a trial of intravenous conivaptan in patients with hyponatremia caused by cirrhosis.[38] In this case, the variation probably did not result from individual differences in bioavailability but possibly from variations in vaptan clearance rates, fluid intake or plasma vasopressin, none of which were reported.

A third trial in patients with cirrhosis sheds light on the issue of efficacy during repeat dosing.[39] Researchers

enrolled 110 participants with cirrhosis and hyponatremia (mean baseline plasma sodium 127 ± 5 mmol/l) treated with fluid restriction (1.5 l per day) plus placebo or three fixed doses of satavaptan (5.0 mg, 12.5 mg or 25.0 mg once daily) for up to 14 days. On the first day, satavaptan reduced body weight and increased plasma sodium levels by an average of 3–5 mmol/l, changes similar to those produced by lixivaptan in normonatremic patients with cirrhosis and by tolvaptan in normonatremic patients with congestive cardiac failure. Over the next 4 days of treatment, however, these changes persisted or increased slightly to the point that the mean increments (± SD) in plasma sodium were 4.5 ± 3.5 mmol/l, 4.5 ± 4.8 mmol/l and 6.6 ± 4.3 mmol/l in the three groups treated with satavaptan. As indicated by the SD scores, individual variations were as large as in other trials. In fact, only 54–64% of patients normalized plasma sodium concentrations or increased them by >5 mmol/l, and two patients (2.3%) developed hypernatremia, albeit without neurologic sequelae. No drug-related adverse events, other than increased thirst which was dose-related, occurred.

Over an additional 9 days of treatment, the effects of satavaptan on sodium levels were largely maintained and the aquaretic effect was still evident. This result in hyponatremic patients with cirrhosis differs from the gradual attenuation observed during tolvaptan therapy of normonatremic patients with congestive heart failure; however, this finding is similar to the continued effect of tolvaptan on plasma sodium concentration in hyponatremic patients with congestive heart failure.[33] Thus, the effect on plasma sodium levels seems to be of longer duration in hyponatremic than normonatremic patients possibly because of the resultant differences in absolute levels of osmotic stimulation of thirst, fluid intake and/or vasopressin secretion produced by treatment. In cirrhosis, the duration of vaptan action could also be longer owing to decreased hepatic clearance. The pharmacokinetics of lixivaptan in normonatremic cirrhosis have been reported,[23] but only for a 24 h period, and comparative data from healthy adults or hyponatremic patients with cirrhosis are not available.

Effects in euvolemic hyponatremia

Syndrome of inappropriate antidiuresis

Patients who fulfilled the criteria for euvolemic hyponatremia were included with others who had hypervolemic hyponatremia in five placebo-controlled trials of vaptan therapy.[27–32] However, the results were pooled and reported without distinction as to the type of hyponatremia. Two other trials[40,41] focused exclusively on patients with euvolemic hyponatremia. The patients were categorized as having SIADH, but the proportion of individuals who may have had other vasopressin-dependent or vasopressin-independent causes of inappropriate antidiuresis cannot be determined from the data provided.

In one study of 56 patients with euvolemic hyponatremia (mean baseline plasma sodium approximately 125 mmol/l),[38] the combination of moderate fluid restriction (<2 l daily) and intravenous conivaptan (40 mg or 80 mg per day) raised serum sodium levels by an average of about 3 mmol/l and 5 mmol/l, respectively, in the first 12 h and by about 6–7 mmol/l after 24 h. This effect was accompanied by a marked increase in free water clearance. Over the next 24–72 h, however, continued infusion of conivaptan produced little or no further increase in plasma sodium concentration and free water clearance declined almost to baseline. Both of these effects were characterized by relatively large interindividual variations. As estimated from the SEM and numbers of patients in each group, the mean (± SD) increases in free water clearance in the first 24 h of therapy with the two doses of conivaptan were approximately 950 (± 1,870) ml and 2,000 (± 2,300) ml, respectively, whereas the increases in plasma sodium after 48 h were 5.7 ± 4 mmol/l and 6.4 ± 4 mmol/l, respectively—a variability similar to that observed during treatment of hypervolemic hyponatremia with a vaptan. However, none of the patients developed hypernatremia or increased plasma sodium concentration faster than the recommended rate. The effects on thirst and plasma vasopressin levels were not reported, but the measurements of fluid intake indicate it increased quite variably in response to conivaptan therapy, at least at the highest dose. The effect on other symptoms was not reported, but an increased incidence of drug-related adverse events, mostly phlebitis at the infusion site, occurred.

The reason(s) for the large individual variations in plasma sodium response in this study of SIADH are no clearer than those observed in the hypervolemic forms of hyponatremia. Differences in fluid intake could have played a part, as some patients may have exceeded the intended restriction of less than 2 l per day. The marked variations in water excretion could also have contributed, but the relative importance of these possibilities cannot be evaluated because the relationship between the three variables was not reported. The cause(s) of the marked differences in aquaretic effect is (are) equally unclear; it cannot be attributed to individual differences in drug bioavailability, as conivaptan was given intravenously. Differences in the rate of drug clearance could play some part, although large individual differences were observed even on the first day of treatment, and patients with renal insufficiency or inhibitors of CYP3A4 were excluded. A more probable explanation for the variability in aquaresis may be uneven interference with the efficacy of the vaptan due to large individual differences in plasma vasopressin concentration. Vasopressin levels were not reported in the study but have been known to vary greatly from patient to patient with SIADH both before and during treatment of hyponatremia[2]. Moreover, if many of the patients had the common type of SIADH that results in downregulation of the osmostat, the rise in plasma sodium levels could have produced an increase in plasma vasopressin concentration sufficient to counteract the antagonism of the vaptan, resulting in the observed decline in aquaresis after the first 24 h of treatment.

The apparent failure of the antagonist to increase urine output and/or plasma sodium levels in a few patients with euvolemic hyponatremia may signify that their inappropriate antidiuresis is vasopressin-independent[2]

and, therefore, unaffected by a vaptan. Further study tracking and relating individual differences in plasma vasopressin, drug levels and free water clearance during vaptan therapy may reveal the cause of the variability and suggest ways to reduce it.

The effects of oral satavaptan[41] in euvolemic hyponatremia attributed to SIADH were similar but not identical to those of intravenous conivaptan. When combined with fluid restriction (1.5 l per day), both 25 mg and 50 mg of satavaptan produced increases in free water clearance and plasma sodium on day 1 that exceeded the changes in the placebo-treated group and were as large as those produced by 40 mg and 80 mg of intravenous conivaptan. However, in contrast to conivaptan therapy, mean plasma sodium levels continued to rise gradually, and the aquaresis decreased only slightly during the next 72 h of satavaptan treatment. These variations may be attributed partly to the different routes of administration (intravenous versus oral) and/or rates of clearance of the two vaptans. However, they could also reflect smaller increases in plasma vasopressin levels in the satavaptan study. In patients on the highest satavaptan dose, the rise in plasma vasopressin concentration was highly variable but modest overall (2.6 ± 6.7 pg/ml), even though the concomitant increase in plasma sodium level averaged nearly 16 mmol/l.[41] This disparity could signify that a relatively high proportion of the patients in this group had the type A or type B osmoregulatory defect.[2] The persistent efficacy of satavaptan was also evident in an open label follow-up trial of 23 days to 12 months which minimized or prevented recurrence of hyponatremia in most study participants.[41]

That the effects of oral satavaptan on urine output and plasma sodium varied from patient to patient as much, or more, as the effects of intravenous conivaptan should also be noted. About 20% of patients treated with satavaptan had little or no increase in plasma sodium concentration, whereas about 10% had increases greater than 12 mmol/l in the first 24 h. Two patients with sodium level increases progressed to mild hypernatremia with symptoms of nausea, vomiting and confusion, which resolved without sequelae. As in the other studies, the effect of the variable rise in sodium on other symptoms was not described, and the reason for this difference is not completely evident. In two patients, the lack of sodium increase was attributed to surreptitious drinking, as it was associated with a large aquaresis. In others, however, the variable rise in sodium may have been largely based on differences in aquaretic effect, given that the former were found to correlate with large interindividual variations in plasma levels of satavaptan.

Notably, the average increase in plasma sodium concentration produced by conivaptan and satavaptan in patients with SIADH seems slightly larger than that produced in the hypervolemic forms of hyponatremia. This finding could be the result of differences in experimental design or the V_2 binding affinity of different vaptans. However, it could also reflect differences in the cause(s) of the impaired water excretion, because, in patients with hypervolemic hyponatremia, this phenomenon is due not only to vasopressin action but also to decreased delivery of filtrate to the distal nephron, a vasopressin-independent defect. This issue might be clarified by separately analyzing and then comparing the data obtained from the different groups studied in the large 'mixed' trials.

Psychogenic polydipsia.
The hyponatremia that occurs in some patients with psychogenic polydipsia seems to be caused by a subtle change in vasopressin secretion and/or action that impairs the ability to rapidly excrete the huge volumes of water ingested.[42] A placebo-controlled trial of tolvaptan therapy without fluid restriction in patients with mild hyponatremia and impaired urinary dilution shows that this vaptan promptly increased plasma sodium by about 7 mmol/l and maintained it at this level for the duration of treatment (30 days).[43] This result confirms that excess water retention is the result of a subtle defect in the suppression of vasopressin secretion and reveals another potentially important clinical use for the vaptans.

Nephrogenic syndrome of inappropriate antidiuresis
The vasopressin-independent form of inappropriate antidiuresis caused by an activating mutation of the V_2 receptor is not affected by tolvaptan or satavaptan.[44] It would be worthwhile to determine how often this defect occurs and whether other forms of inappropriate antidiuresis that appear to be vasopressin-independent (SIAD) are also refractory to vaptans.

Adverse effects

The safety profile of the vaptans is good with no consistent adverse effects other than thirst. However, intravenous conivaptan can cause inflammation at infusion sites and tolvaptan has been associated with an increased incidence of gastrointestinal bleeding in patients with liver disease and should be used with caution and only if absolutely necessary in patients with this condition.

Occasionally, vaptans have been observed to raise plasma sodium levels faster or higher than is recommended to avoid osmotic demyelinization, but this potential complication was not observed in any trial reported to date. Nevertheless, concern over this effect has led some clinicians to advise against the use of fluid restriction with vaptan therapy, at least during the first 24 h, even though thirst is a common adverse effect and increased fluid intake may offset much of the desired effect on plasma sodium levels. In any case, the effects on plasma sodium concentration should be monitored closely during treatment and used to guide adjustments to fluid intake and continued dosing.

Conclusions

The nonpeptide vasopressin antagonists known collectively as vaptans are a valuable new tool for the management of certain types of hyponatremia, as they produce a pure water diuresis that can reduce total body water levels and increase the concentration of sodium in plasma and extracellular fluid. Independent of the administration route, their aquaretic effects begin quickly, peak within

a few hours and generally subside within 12–24 h. The rise in plasma sodium parallels the aquaresis and is probably facilitated or enhanced by concurrent restriction of fluid intake. However, individual variations in aquaresis and plasma sodium response to these drugs are relatively large. The cause of the variation is uncertain but may involve differences in bioavailability and clearance of the vaptan, as well as offsetting effects of increased thirst and vasopressin secretion. For unknown reasons, the effects of the vaptan on plasma sodium levels and/or urine output sometimes decline when treatment is continued beyond 24–72 h; however, this attenuation seems to occur mostly, if not solely, when basal plasma sodium concentration is normal. This phenomenon apparently does not limit the utility of vaptans for long-term treatment of patients with hyponatremia.

Vaptans are most valuable for the treatment of hypervolemic hyponatremia, as the individual variability in therapeutic effect is of less immediate concern, and correction of the hyponatremia may have additional benefits for long-term survival. Vaptans are also useful in patients with subacute or chronic forms of SIADH, including patients with psychogenic polydipsia. However, the role of vaptans in treating acute, symptomatic or severe forms of hyponatremia in SIADH is less certain because intravenous infusion of hypertonic (3%) saline is just as safe and cheaper, and the effects are more predictable and easier to control. Vaptans should not be used to treat patients with hypovolemic hyponatremia, as these individuals have a large deficit in water and sodium that compromises hemodynamic stability and renal function. Vaptans are also not necessary and should not be used to treat the type of euvolemic hyponatremia caused by emetic stimuli or secondary adrenal insufficiency, and they are ineffective in the vasopressin-independent form of SIAD caused by an activating mutation of the V_2 receptor and possibly other mechanisms. Future studies should include the causes of the unpredictable variability in efficacy with particular attention to the role of endogenous vasopressin and vasopressin-independent mechanisms of antidiuresis.

Review criteria

A search for original articles published between 1990 and 2010 was performed in MEDLINE and PubMed. The search terms used were “vaptan” and “hyponatremia”. All articles identified were English-language, full-text papers. The author also searched the reference lists of identified articles and other reviews for further papers.

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