Review Article

Vasopressin receptor antagonists and their role in clinical medicine

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ABSTRACT

Hyponatremia is the most common electrolyte abnormality in hospitalized patients. Its treatment is based not only on extracellular fluid volume status of patients but also on its pathogenetic mechanisms. Conventional treatment of hyponatremia like fluid restriction, which is useful in euvolemic and hypervolemic hyponatremia, has very poor patient compliance over long term. Vasopressin receptor antagonists (Vaptans) are a new group of nonpeptide drugs which have been used in various clinical conditions with limited success. Whereas conivaptan is to be administered intravenously, the other vaptans like tolvaptan, lixivaptan, and satavaptan are effective as oral medication. They produce aquaresis by their action on vasopressin type 2 (V2R) receptors in the collecting duct and thus increase solute free water excretion. Vaptans are being used as an alternative to fluid restriction in euvolemic and hypervolemic hyponatremic patients. Efficacy of vaptans is now well accepted for management of correction of hyponatremia over a short period. However, its efficacy in improving the long-term morbidity and mortality in patients with chronic hyponatremia due to cirrhosis and heart failure is yet to be established. Vaptans have not become the mainstay treatment of hyponatremia yet.

Key words: Aquaporins, hyponatremia, vaptans, vasopressin, vasopressin antagonists

Introduction

Hyponatremia defined as serum sodium < 135 mmol / l is one of the most common electrolyte abnormality observed in clinical practice. It is reported in 15 – 30% of hospitalized patients and is a significant contributor to morbidity and mortality especially in cases with acute severe hyponatremia.[1] Gill and colleagues have reported a three fold increase in mortality in patients admitted with serum sodium of < 125 mmol/l as compared to normonatremic controls[2] it is particularly common in elderly persons, patients on thiazide diuretics, respiratory infections and neurosurgical cases. Most of the patients with mild hyponatremia are asymptomatic but the symptoms depend upon the rapidity with which it develops. In contrast to hypernatremia which always indicate hyper tonicity of plasma, hyponatremia can be associated with high, normal or low tonicity. Its etiology is multifactorial and is associated with normal, expanded or depleted intra vascular volume. It normally results when normal renal diluting mechanism is disturbed. It can result from diminished glomerular filtration rate (GFR) with increase in proximal tubular fluid and sodium absorption with resultant decrease delivery of sodium to the diluting segments of nephron. In some cases hyponatremia results from a defect in Na^+ / Cl^- transport out of the impermeable thick ascending loop of Henle and distal convoluted tubule. In majority of cases hyponatremia results from continuous stimulation and secretion of vasopressin by non osmotic stimuli despite presence of serum hypoosmolality. Proper evaluation for the underlying cause of hyponatremia is essential for its management. Fluid restriction and infusion of 3 % NaCl solution is the mainstay of treatment in the management of euvolemic and hypervolemic hyponatremia. Over the last decade vasopressin receptor antagonists (Vaptans) are being increasingly used in clinical practice with promising results especially in acute cases.

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Physiology of Water Balance

Water constitutes about 50–55% and 60–70% of the body weight in a healthy female and male, respectively. Of the total fluids, two third resides inside the cell [intracellular fluid (ICF)] and one third is extracellular fluid (ECF).[3] The extracellular compartment is further divided into intravascular (plasma) and extravascular (interstitium, lymph, connective tissue, bone, etc.) [Table 1].

An excess of interstitial fluid constitutes edema. Presence of pitting edema, especially generalized edema, always signifies excess of ECF, particularly in the interstitial compartment, but in some of these situations, the intravascular volume may be decreased, normal, or increased. The electrolyte composition of the ECF and ICF differs markedly. Whereas sodium is the predominant cation in the ECF, potassium is most abundant in the intracellular compartment. The anions in the extracellular compartment are mainly chloride and bicarbonate. The solute or particle concentration of a fluid is known as its osmolality and is expressed as mOsm/kg of water. This can be measured by an osmometer utilizing the freezing point of the sample. It can also be calculated by serum biochemical value using the formula: Plasma osmolality = 2 × serum sodium (mmol/l) + BUN (mg/dl)/2.8 + blood sugar (mg/dl)/18.

Since most of the cell membranes are freely permeable to water to achieve osmotic equilibrium (ECF osmoles equals ICF osmoles), any change in osmolality of one compartment affects the volume and osmolality of the other. In normal circumstances, plasma osmolality is clearly related to plasma sodium concentration, and in health, the osmolality is maintained within a very narrow range of 285 ± 5 mOsm/kg by balancing daily water intake and excretion.

The intake of water is controlled by thirst, mediated by an increase in effective plasma osmolality sensed by receptors located in supraoptic nuclei of hypothalamus, which in turn regulates the release of arginine vasopressin (AVP), formally known as antidiuretic hormone (ADH). In normal healthy adult, a rise in plasma osmolality of even 1–2% above basal level produces thirst that promotes water intake and normalization of osmolality. The average osmotic threshold of thirst is approximately 290–295 mOsm/kg, but varies among individuals. In most of the cases, the water intake is more than the physiological requirement. Apart from the osmotic stimuli, decrease in effective circulatory volume [e.g. congestive cardiac failure (CCF), cirrhosis, and gastrointestinal losses] through baroreceptors located in carotid sinus and aortic arch leads to an increase in the circulating AVP levels [Table 2]. Other stimuli like nausea, postoperative pain, and pregnancy also lead to the release of AVP. In situations of low effective arterial blood volume, the stimulus from these receptors overrides the effect of hypo tonicity on the release of AVP. Substances like glucose and urea, which easily cross the cell membrane, do not change the osmolality, but hypertonic saline and mannitol which stay in the vascular space act as osmotic stimuli to decrease the cell volume which stimulates AVP release.[3]

Table 1: Distribution of fluid in various compartments of the body

Compartment	Amount of body weight (%)	Volume (litres)
Total body fluid	60	42
Intracellular fluid	40	28
Extracellular fluid	20	14
Interstitial fluid	Two-third of ECF	9.4
Plasma	One-third of ECF	4.6
Venous	85 of plasma	
Arterial	15 of plasma	

Water Excretion

Water excretion is regulated by various physiological factors of which the principal determinant is AVP. Other than AVP, medullary hyper tonicity plays a very important role in mediating the action of AVP for water absorption. Factors which decide medullary hyper tonicity are countercurrent multiplication and exchange system, typical solute and water permeability of descending and ascending vasa recta, respectively, its arrangement around loop of Henle and collecting duct, different permeability of water in two limbs of loop of Henle, urea and ammonia recycling, and nutritional status of a person. In fact, it is the high concentration of sodium and urea which is mainly responsible for medullary hyper tonicity. In the absence of medullary hyper tonicity, action of AVP will not result in water absorption even if other mediators of water absorption like aquaporins 2, 3, and 4 (discussed below) are intact. This is because the driving force for water absorption

Table 2: Regulation of vasopressin secretion

Osmotic stimuli	Effect on AVP secretion
Changes in serum osmolality	Increase or decrease depending on changes in osmolality
Nonosmotic stimuli	
Hemodynamic changes associated with low effective arterial blood volume	Increase
Act of drinking especially cooler fluids	Decrease
Nausea	Increase
Hypoglycemia	Increase
Renin angiotensin system (AgII)	Increase
Hypoxia and hypercapnia	Increase

AVP: Arginine vasopressin

from tubular lumen to medullary interstitium is lost. This is illustrated in beer protomaniac in which patients are unable to excrete solute free water because of low medullary osmolarity as a result of protein malnutrition state leading to low urea concentration in medullary interstitium.

Physiology of Vasopressin

Earlier known as ADH, AVP is a peptide hormone containing nine amino acids. It is synthesized in the cell bodies of magnocellular neurons located in supraoptic nucleus in hypothalamus. Secretion of ADH occurs in response to various osmotic and non osmotic stimuli[3] and is regulated by cell volume of osmoreceptor cells located near supraoptic nuclei in anterior hypothalamus.

AVP binds to three types of receptors. The V1 receptors (old name V1a) located in vascular smooth muscles, platelets, and hepatocytes through G protein coupled phosphorylation cause vasoconstriction, myocardial contractility, platelet aggregation, glycogenolysis, and uterine contraction. The V3 receptors (old name V1b) also act by G protein coupled phosphorylation to cause adrenocorticotropic hormone (ACTH) release from the anterior pituitary. The main receptor for maintaining water balance is the V2 receptor (V2R) primarily located in the collecting duct, which leads to increase in the water permeability through cellular water transporter aquaporin 2 (AQP2).[4] Aquaporins are the principal channels through which water is absorbed. They were first characterized by Peter Agre for which he was awarded the Nobel prize in 2003.[5] There are various types of aquaporins[5-7] which are distributed in various parts of the body [Table 3] including the entire length of renal tubules [Figure 1].

The first member (AQP1) is located in the apical and basolateral regions of proximal tubular epithelial cells and descending limb of loop of Henle, which is responsible for the high permeability of these segments to water. AQP1 is naturally expressed in these segments and is not controlled by AVP. AQP2 is found in the apical membrane of the cortical collecting duct and its action is controlled by the AVP. In response to the release of AVP, there is a rapid increase in water permeability of the collecting duct. AVP binds to V2R located on the basolateral membrane and activates G protein, and through its action *on adenylate cyclase*, it activates protein kinase A (PKA) by increasing the concentration of cAMP. This in turn results in insertion of phosphorylated AQP2 from sub apical vesicles into the luminal membrane of the collecting duct [Figure 2]. Increase in the number of AQP2 channels results in increasing the water permeability of the collecting duct epithelium. Intracellular calcium ions also take part in regulating the relocation of AQP2 from intracellular space to luminal cell membrane of the principal cell of collecting duct. After water absorption gets over, AQP2 molecule is internalized and comes inside the cell till it gets shifted to the apical surface again by further stimulation by vasopressin–PKA–cAMP pathway. Absorbed water is extruded from the cell through the mediation of other aquaporins, i.e. AQP3 and AQP4, located on the basolateral cell membrane.[4] In addition, AQP3 is permeable to urea and allows the passage of urea into the interstitium. Aquaporin is also present in the hypothalamus and is responsible for the release of AVP.[6]

Hyponatremia

Patients with hyponatremia have varied clinical presentations and this depends upon the rapidity with which there is reduction in the serum sodium concentration. Patients with acute reduction are more symptomatic than those in whom the hyponatremia develops over a period of time. Approach to a patient with hyponatremia is based on

Table 3: Aquaporins and their distribution

Aquaporin	Localization	Subcellular distribution	Extrarenal localization
AQP1	Proximal tubules, descending thin limbs of Henle, outer medullary descending vasa recta	Apical and basolateral plasma membrane	Erythrocytes, ciliary and lens epithelium, choroid plexus, pulmonary vascular endothelium
AQP2	Principal cells of the collecting duct	Apical plasma membrane and subapical vesicles	Epididymis
AQP3	Principal cells of the collecting duct	Basolateral plasma membrane	Conjunctiva, pulmonary airway epithelia, colonic epithelia, keratinocytes, erythrocytes
AQP4	Principal cells of the collecting duct	Basolateral plasma membrane	Astroglia, ependyma, retinal glia, muscle fiber cells, keratinocytes, pulmonary airway epithelia, stomach parietal cells
AQP6	Intercalated cells of the collecting duct	Intracellular vesicles	Cerebellum, synaptic vesicles
AQP7	S3 segment of proximal tubules	Apical plasma membrane	Adipose tissue, testis, skeletal muscle, heart, brain, intestine
AQP11	Proximal tubule	Endoplasmic reticulum	Testes, thymus, liver, intestine

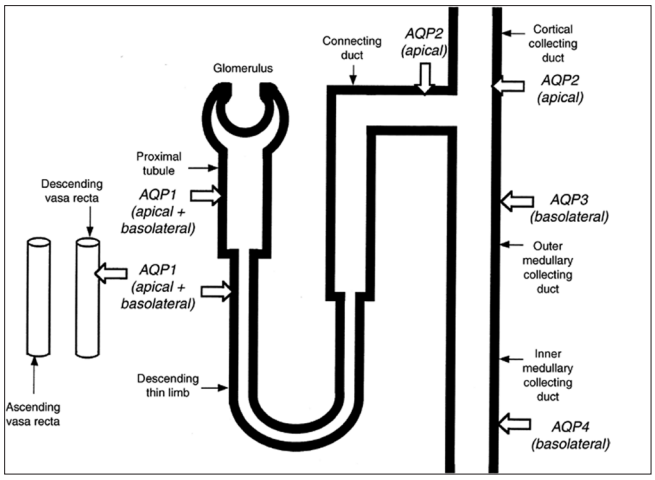

Figure 1: Aquaporins and their distribution along the renal tubules: Aquaporin 1 is located in the apical and basolateral regions of proximal tubular epithelial cells and descending limb of loop of Henle and functions independently of ADH. AQP2 is distributed along the apical membrane of the cortical collecting duct and is ADH dependent. AQP3 and AQP4 are located on the basolateral cell membrane and it allows the passage of urea into the interstitium

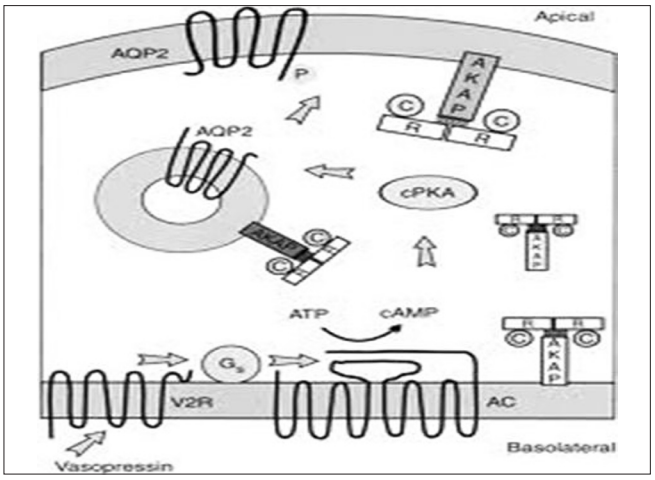

Figure 2: Action of vasopressin on principal cells of the collecting duct: AVP binds to V2R located on the basolateral membrane and activates G protein, and through its action on adenylate cyclase, it activates protein kinase A (PKA) by increasing the concentration of cAMP. This in turn results in insertion of phosphorylated AQP2 from subapical vesicles into the luminal membrane of the collecting duct which results in increasing the water permeability of the collecting duct epithelium

extracellular fluid volume (ECV) status of the individual.[8] Management depends upon whether the patient is hypovolaemic ,euvolemic or has expanded ECV. [Table 4].

Mechanism of hyponatremia and high antidiuretic hormone in syndrome of inappropriate antidiuretic hormone hypersecretion, heart failure and cirrhosis

a. **SIADH:** In normal condition, with fall in serum osmolality below its set point, plasma AVP levels get suppressed and aquaresis results. But in syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), AVP release is not fully suppressed despite hypo tonicity. With adequate water intake, high concentration of AVP produces antidiuresis and with that hyponatremia, plasma hypoosmolality, and a small degree of water expansion which decreases plasma renin and aldosterone in the presence of high AVP. Diagnosis of SIADH is based on the presence of euvolemic hyponatremia and in appropriate urine concentration (>100 mOsm/kg) and normal adrenal and thyroid functions [Table 5].
b. **Congestive Cardiac failure:** It is the impaired cardiac function with high after load which leads to non osmotic release of AVP which is responsible for water retention in spite of the hypo tonicity of plasma in patients with CCF. Bichet *et al.*[9] showed that after load reduction improved cardiac performance and led to enhanced water excretion and improved suppressibility of plasma vasopressin in the 17 patients with elevated plasma vasopressin concentrations, in spite of hypo-osmolality and hyponatremia. Under ordinary circumstances, release of AVP gets suppressed due to high-pressure

Table 4: Approach to a patient with hyponatremia

	Clinical characteristics	Urine Na <30 mmol/l	Urine Na >30 mmol/l
Hypovolemia	Tachycardia Postural hypotension Dry skin Reduced skin turgor Raised blood urea and renin	Vomiting Diarrhea Burns Heat exposure	Diuretics Addison's disease CSWS Salt losing nephropathy
Euvolemia	Blood urea normal or slightly decreased	Hypothyroid Any cause + hypotonic fluid	SIADH ACTH deficiency
Hypervolemia	Peripheral, sacral, pulmonary edema Ascites Raised JVP or CVP	Nephrotic syndrome Cardiac failure Liver failure	Renal failure Cardiac failure + diuretics

CSWS: Cerebral salt wasting syndrome, JVP: Jugular venous pressure, CVP: Central venous pressure (Adapted from ref. 8), ACTH: Adrenocorticotropic hormone, SIADH: Syndrome of inappropriate antidiuretic hormone hypersecretion

Table 5: Criteria for the diagnosis of syndrome of inappropriate antidiuretic hormone hypersecretion

Essential criteria
- Plasma sodium <135 mmol/l
- Urine osmolality >100 mOsm/kg
- True plasma hypo-osmolality (<275 mOsm/kg H_2O)
- Urine osmolality >100 mOsm/kg
- Urine sodium >30 mmol/l
- Patient clinically euvolemic; no edema, ascites, or signs of hypovolemia
- Normal salt intake
- Exclusion of glucocorticoid deficiency

Additional criteria
- Unable to excrete >80% of a water load (20 ml/kg) in 4 hours and/or failure to achieve urine osmolality <100 mOsm/kg H_2O
- No significant increase in serum sodium after volume expansion, but improvement with fluid restriction

baroreceptors in the ventricles, carotid sinuses, and aortic arch, acting through vagal afferents.[10] Arterial under distension and baroreceptors unloading in CCF, inhibits this vagal tone and hence AVP levels are elevated in patients with CCF. Other reasons for hyponatremia in CCF are impaired maximum water excretory capacity by tubules due to impaired delivery of solute to the diluting site because of enhanced renin angiotensin axis, elevated nor epinephrine, and diminished glomerular filtration rate [Figure 3].

c. **Cirrhosis of liver**: In cirrhosis, there is decrease in effective circulating arterial volume because of systemic (especially splanchnic circulation) vasodilatation as a result of release of nitric oxide and vasodilatory prostaglandins [Figure 3]. Nitric oxide production may be stimulated by absorbed endotoxin from the gastrointestinal tract and decreased reticuloendothelial cell function in cirrhosis.[10] Like CCF, there is impaired maximal water excretory capacity by tubules due to impaired delivery of solute to the diluting site or a diminished glomerular filtration rate. Patients with cirrhosis and ascites or edema can be classified according to whether they are able to excrete a standardized water load. Along with water retention, "nonexcretors" have worse liver disease, more sodium retention, ascitis, higher AVP, renin, and aldosterone levels than "excretors" who handle a water load normally.[11] These data suggest that non osmotic release of AVP is principally responsible for the abnormal water retention of cirrhosis.

Thus, patients with hyponatremia caused by SIADH, CCF, and cirrhosis are all potential targets for treatment with V2R antagonists.

Treatment of hyponatremia

There are a number of conventional therapies which are helpful in hyponatremic cases and their use is based mainly on cause and rapidity of onset of hyponatremia.

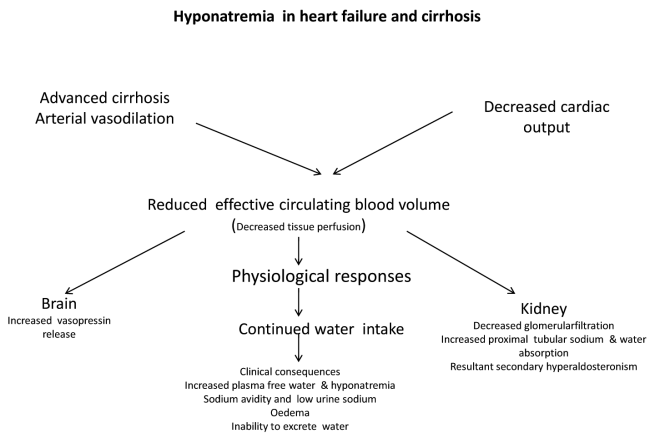

Figure 3: Mechanism of hyponatremia in heart failure and cirrhosis

In general, treatment of hyponatremia is based on the mechanism that produces it and the rate of development, i.e. acuteness. The other factor which decides its treatment is ECV status of the patient. Although sometimes difficult at bedside to categorize hyponatremic patient according to the ECV status, especially in case of SIADH and cerebral salt or renal salt wasting disorder, in most instances, it is helpful. So, for hypovolemic hyponatremia, restoration of blood volume with intravenous saline is most useful. Drugs which are known to produce hyponatremia like diuretics, especially thiazide, should be discontinued.

a. **Hypovolemia**: The main aim of management is to correct the depleted intravascular volume to restore the immediate fluid deficit, followed by maintenance of the restored ECF volume in the presence of ongoing losses. Treatment of the underlying cause should be taken up whenever possible. The treatment of the underlying illness, for example, corticosteroid in Addison's disease, is also important. In these clinical situations, isotonic saline (154 mmol / l NaCl) is helpful in restoring the volume. In certain cases of hypovolemic hyponatremia, choice of fluid depends on acuteness as well as severity of hyponatremia. In patients with neurological symptoms due to acute hyponatremia prompt treatment with hypertonic (3%NaCl, 513 mmol / l) solution can be used. The aim is to correct sodium by not more than 10-12 mmol / l in 24 hours. Hypertonic saline can be given as slow continuous infusion (0.05 ml/kg) with frequent monitoring of serum sodium and volume status of the individual. In some acute cases where initial correction is required, rapid infusion of 3 % NaCl solution may increase the serum sodium by 3-4 mmol / l.

b. **In hypovolemic hyponatremia** due to cerebral salt wasting (CSW, now known as salt wasting hyponatremia), proper hydration with normal saline should be maintained. Although it is not easy to differentiate CSW from SIADH because of almost similar clinical and biochemical findings other than increased fractional excretion of phosphate and low effective blood volume (EBV) in CSW, it will be inappropriate if proper clinical decision is not taken at initiation of therapy. For example, the clinical condition of SIADH patient will deteriorate further if fluid therapy is not restricted because EBV here is either normal or high due to inappropriate level of AVP. In comparison to SIADH, in CSW, fluid supplementation is necessary.

c. **Euvolemic and hypervolemic hyponatremia**: Therapy with isotonic saline is ineffective in this clinical setting and in fact continuous infusion may worsen hyponatremia and cause fluid overload[8] Intake of fluid should be restricted as there is disproportionate rise in

total body water in comparison to total body sodium level. Administration of loop diuretics with NaCl helps in enhancing the electrolyte free water excretion (aquaresis) Thiazide diuretics are not effective in this setting.[3]

d. **Demeclocycline**: It is a tetracycline antibiotic which inhibits adenylyl cyclase activation. Hence, it decreases the concentration of c-AMP after AVP binds to its V2R in the kidney and that makes it one of the treatment modalities for SIADH patients who find fluid restriction unacceptable and the underlying disorder cannot be corrected. It is given in a dose of 150–300 mg PO three or four times a day. The effect of the demeclocycline manifests in 7–14 days and is due to production of a reversible form of nephrogenic diabetes insipidus (DI). Potential side effects include photo toxicity and azotemia.
e. **Fludrocortisone**: The effect of fludrocortisone requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements. Fludrocortisone may induce hypertension, sometimes leading to discontinuation of the treatment.
f. **Vasopressin receptor antagonists (synonyms: aquaretics, vaptans**): It was in 1985 when *Kinter et al.* demonstrated for the first time that the administration of SK and F1019, a potent V1and V2 antagonist in rat caused increased urine volume and decreased urine osmolality and they coined the term aquaretic agents (water diuretic) to distinguish their pharmacological and therapeutic utility from saluretic agents.[12] Saito *et al.* in 1997 studied the effects of non-peptide OPC-31260 in 11 patients with SIADH and it was established that this drug produces dose-dependent increase in both urine volume and free water clearance.[13] Aquaretics are a new class of drugs used for treatment of euvolemic and hypervolemic hyponatremia. They are also being tried to retard growth of cysts in polycystic kidney disease (PKD) and other disorders.

Mechanism of action

By blocking V2R in kidney, V2R antagonist prevents recruitment of AQP2 water channels to luminal cell membrane in collecting duct and so promotes electrolyte free water excretion and hence are known as *aquaretics*.[14,15] There are few more receptors of vaptans other than V2R like V1 and V3 receptors (previously known as V1A and V1B) by which it mediates its other action [Table 6]. Aquaretics have few advantages over diuretics[14] [Table 7].

The vaptans can be classified into two broad categories [Table 8].

A. Selective vaptans (acting on V2R): Lixivaptan (VPA 985), Tolvaptan (OPC 41061), SR121463, PC31260, and RWJ351647. The most important are mozavaptan, lixivaptan, satavaptan, and tolvaptan, all of which are selective V2 antagonists and are administered through the oral route.[16]
B. Nonselective vaptans (acting on V1A and V2R): Conivaptan (VPA 985)

Uses of vasopressin receptor (V2R) antagonists

1. **Hyponatremia**: These drugs have been used in hyponatremia associated with euvolemic (SIADH) and hypervolemic (CCF and cirrhosis of liver) states. Plasma AVP levels have been found to be high in hyponatremic patients with edematous disorders like CCF and cirrhosis of liver. High levels of AVP lead to up regulation of AQP2 water channels in kidney epithelial principal cells. This has been demonstrated by a study showing that lixivaptan reduced urinary AQP2 excretion in a dose-dependent manner. Vaptans are contraindicated in hypovolemic hyponatremia because of hypotension resulting from aquaresis by vaptans.[14] Although they are not contraindicated in patients with decreased renal function, these agents generally will not

Table 6: Vasopressin receptor location and functions

Subtype (older name)	Newer name	Signaling pathways	Location	Function
V1A	V1	G-protein coupled, phosphatidylinositol/calcium	Vascular smooth muscle Platelet Hepatocytes Myometrium	Vasoconstriction, myocardial hypertrophy, platelet aggregation, glycogenolysis, uterine contraction
V1B	V3	G-protein coupled, phosphatidylinositol/calcium	Anterior pituitary gland	Releases ACTH, prolactin, endorphins
V2	V2	Adenylyl cyclase/cAMP	Basolateral membrane of collecting duct, vascular endothelium and vascular smooth muscle cell	Insertion of AQP-2 water channels into apical membrane, induction of AQP-2 synthesis, releases von Willebrand factor and factor VIII Vasodilatation

ACTH: Adrenocorticotropic hormone

Table 7: Aquaretics and diuretics

Effects	Aquaretics	Diuretics
Free water excretion	More	Less
Serum potassium	No change	Decrease
Serum osmolality	No change	Decrease
RBF	No change	Decrease
GFR	No change	Decrease
Precipitate orthostatic hypotension	No	Yes
Activation of norepinephrine, plasma rennin	No	Yes
Increase BUN and serum creatinine	No	Yes

Table 8: Classification of vaptans

Type	Name
Selective (acting on V2R)	Mozavaptan Lixivaptan Satavaptan Tolvaptan
Non-selective (acting on V1A and V2R)	Conivaptan

be effective if the serum creatinine level is more than 2.5 mg/dl.[14] V2-R antagonists do not begin to increase diuresis before 1–2 hours.

a. **SIADH**: This is one example of euvolemic hyponatremia in which serum AVP level is high despite hypo tonicity. Both tolvaptan and conivaptan are approved for the treatment of hyponatremia due to SIADH. Conivaptan is an orally effective non selective ADH receptor antagonist which has affinity for both V1A and V2R subtypes. Intravenous administration of conivaptan produces aquaresis and decreases urine osmolality[17] As conivaptan has to be given intravenously it is useful in hospitalized hyponatremic patients of SIADH. Michael *et al.*,[18] in their study have shown that conivaptan hydrochloride 20 mg, administered once or twice daily via 30-minute IV infusion, significantly increased serum sodium concentration over 48 hours in patients with euvolemic or hypervolemic hyponatremia when compared with placebo. Common adverse events were similar to those seen with continuous conivaptan infusions. Kalra *et al.*[19] observed that intravenous conivaptan regimens with or without a loading dose had similar safety, tolerability, and efficacy in patients with euvolemic or hypervolemic hyponatremia. The pre-mixed formulation used with a loading dose may be associated with an increased frequency of overly rapid increase in serum sodium concentration compared with the other regimens studied. Tolvaptan is an orally effective agent which has specific action on V2 receptors. It has been approved by FDA for long term use. Several published trials have established the efficacy of oral tolvaptan in treatment of euvolemic and hypervolemic hyponatremia[20] *S*tudy of *A*scending *L*evels of *T*olvaptan in hyponatremia 1 and 2 (SALT-1 and -2)[21] has shown the efficacy of tolvaptan in hyponatremic patients.

b. **CCF and cirrhosis of liver**: Both tolvaptan and conivaptan are approved for the treatment of hyponatremia due to CCF and cirrhosis of liver. Among patients with CCF, conivaptan increases serum sodium concentration via blockade of V2R and diminishes after load via blockade of V1A receptors. Although safety and efficacy of conivaptan for the treatment of CCF have not been well defined, it may be useful in heart failure (HF) patients with hyponatremia. Like conivaptan, oral agent tolvaptan also raises serum sodium concentration in patients with HF and efficacy of tolvaptan has been shown in SALT-1 and -2 trials.[21] At present, there is no study demonstrating the benefits of vaptans for long-term survival and improved symptoms associated with treated hyponatremia.[22] Efficacy of vasopressin antagonist in heart failure outcome study with tolvaptan (EVEREST) outcome[23] trial showed greater improvement of congestion with tolvaptan than with placebo. There was no difference in mortality in treated and untreated patients. Review of the various trials show that V2 R antagonist have helped in improving serum sodium in hospitalized patients and during short term follow up.[20]

Vaptans in polycystic kidney disease

Because of *in vitro* evidence suggesting that increased cAMP level plays an important role in cystogenesis in PKD, vaptans have been evaluated in animal models of autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) because they decrease renal epithelial cell intracellular cAMP levels. OPC-31260 and tolvaptan decrease cAMP levels, inhibit cystogenesis, and prevent renal enlargement and dysfunction in three different murine models.[24] The AVP V2R antagonists OPC-31260 and tolvaptan inhibit the development of PKD in cpk mice and in three animal orthologs to human autosomal recessive PKD (PCK rat), autosomal dominant PKD (Pkd2/WS25 mice), and nephronophthisis (pcy mouse). PCK rats that are homozygous for an AVP mutation and lack circulating vasopressin are markedly protected.

Both tolvaptan and OPC-31260 inhibitmitogen-activated protein kinase (MAPK) signaling which may mediate the proliferative response to cAMP in the kidney. The *T*olvaptan *E*fficacy and safety in *M*anagement of *P*KD

and Outcome (TEMPO) trial is now an ongoing phase III trial for determining the effect of tolvaptan in patients with PKD with normal renal functions.[23] The results are still awaited.

Congenital X-linked nephrogenic DI

Most patients have defect in intracellular folding of V2 vasopressin receptor and that is responsible for defect in transfer of V2R to the cell surface where the receptors will respond to circulating vasopressin have been used in *in vitro* systems for rescuing mutant V2 receptors to promote proper folding and maturation. This resulted in the expression of functional cell surface V2 receptors. This suggests that such a therapeutic approach may be effective in these patients.[25-27]

Vaptans in other diseases

Preliminary studies with this drug class have shown potential for treatment of glaucoma, Menière's disease, cerebral vasospasm in subarachnoid hemorrhage, brain edema, Cushing syndrome, and small cell lung carcinoma.[28]

Relcovaptan is a selective V1a-receptor antagonist, which has shown initial positive results in the treatment of Raynaud's disease, dysmenorrhea, and tocolysis.[27]

SSR-149415 is a selective V1b-receptor antagonist. It has been shown to block stress-induced increase of plasma adrenocorticotropic hormone and exerted anti-anxiety or antidepressant-like effects in mouse models. A phase II trial is underway with this agent for the treatment of depression and anxiety. **SSR-149415** could have beneficial effects in the treatment of psychiatric disorders.[28]

Current indications for vaptans

A large number of trials have been conducted, both randomized control trial and open label observation studies,[29] which are given in Table 9. It is observed that vaptans have been extensively studied and have good therapeutic benefits in patients with euvolemic and hypervolemic hyponatremia, especially for enhancing free water excretion and correction of electrolyte abnormality in short term. Of the various vaptans, conivaptan and tolvaptan are approved for clinical use in USA and Europe.

Tolvaptan is administered at an initial oral dose of 15 mg once daily; after at least 24 hours, dose may be increased to 30 mg once daily to a maximum of 60 mg once daily titrating at 24-hour intervals to the desired serum sodium concentration. Conivaptan is to be administered intravenously and hence used only in hospitalized patients. IV: Loading dose – 20 mg infused over 30 minutes, then continuous infusion of 20 mg over 24 hours (0.83 mg/hour); it may be increased to a maximum dose of 40 mg over 24 hours (1.7 mg/hour) depending upon serum sodium levels. Total duration of therapy should not exceed 4 days.

Table 9: Overview of different studies on the use of vaptans in hyponatremic states

Study	End point	Number and kind of patients included; duration of study	Study design	Main results
Vasopressin blockade with tolvaptan in chronic heart failure	Short-term effects of tolvaptan in chronic heart failure	N = 254, with normo and hyponatremia; 25 days	RCT	Tolvaptan decreased the body weight by 0.84 kg and improved hyponatremia
Tolvaptan in patients hospitalized with worsening heart failure	Short term and intermediate effects of tolvaptan	N = 310, with normo and hyponatremia; 60 days	RCT	At 24 hours, body weight decreased by 1.4 kg versus placebo. At 60 days, no difference in worsening heart failure
Tolvaptan for hyponatremia	Improvement of hyponatremia with tolvaptan	N = 448, with hyponatremia; 30 days	RCT	Tolvaptan was effective in increasing the serum sodium on days 4 and 30
EVEREST clinical status trials	Short-term effects of tolvaptan on congestion of heart failure	N = 4133, with normo and hyponatremia; 7 days	RCT	Greater improvement of congestion with tolvaptan than with placebo. More weight loss on day 7 with tolvaptan (_ 3.3 kg) than with placebo (_2.7 kg)
EVEREST outcome trial	All-cause mortality in cardiac failure receiving tolvaptan	N = 4133, with normo and hyponatremia; 9.8 months	RCT	Mortality in treated and untreated patients was comparable
Effects of satavaptan on ascites and serum sodium in cirrhosis with hyponatremia	Effects on ascites and hyponatremia in cirrhosis	N = 110, with hyponatremia; 14 days	RCT	Satavaptan improved hyponatremia and the control of ascites
SALTWATER	Safety and efficacy of tolvaptan during long-term treatment	N = 111, with hyponatremia; 1.5 years	Open-label observation	Normonatremia was maintained throughout. Only one patient developed hypernatremia

Adapted from ref[29]

Future of vaptans in clinical medicine

Although vaptans have shown that they improve biochemical value of serum sodium levels in comparison to placebo in conditions like euvolemic and hypervolemic hyponatremia in SALT-1 and -2 trial, this biochemical improvement has not translated into long-term improved mortality and morbidity benefit as shown by tolvaptan in EVEREST trial in HF patients. This trial showed greater improvement of congestion with tolvaptan than with placebo, but there was no difference in mortality in treated and untreated patients during follow-up. Moreover, this drug has to be used continuously to produce its consistent effect; otherwise, effects of improving sodium levels will be lost if the drug is discontinued. Its usefulness in preventing cyst growth in PKD and congenital X-linked nephrogenic DI is still under clinical trial.

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