Review

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 11:1-8, 2013
http://dx.doi.org/10.5049/EBP.2013.11.1.1

The Role of V2 Receptor Antagonists in the Treatment of Hyponatremia

Biff F. Palmer, M.D.

Department of Internal Medicine University of Texas Southwestern Medical Center

Received: Feb 12, 2013
Accepted: Feb 18, 2013
Corresponding Author: Biff F. Palmer, M.D.
Department of Internal Medicine University of Texas Southwestern Medical Center 5323 Harry Hines Blvd. Dallas, Texas 75390
Tel: +1-214-648-7848, FAX: +1-214-648-2071
E-mail: biff.palmer@utsouthwestern.edu

Introduction

Under normal circumstances, there is a balance between water intake and water excretion such that plasma osmolality and the serum sodium (Na^+) concentration remain relatively constant. The principal mechanism responsible for prevention of hyponatremia and hyposmolality is renal water excretion. In all hyponatremic patients, water intake exceeds renal water excretion.

Excretion of water by the kidney is dependent on three factors. First, there must be adequate delivery of filtrate to the tip of the loop of Henle. Second, solute absorption in the ascending limb and the distal nephron must be preserved so that the tubular fluid will be diluted. Lastly, arginine vasopressin (AVP) levels must be low in the plasma. Of these three requirements for water excretion, the one which is most important in the genesis of hyponatremia is the failure to maximally suppress AVP levels. Given the central role of AVP in limiting renal water excretion, AVP receptor antagonists represent a physiologic and rational method to increase renal water excretion.

AVP in Regulation of Plasma Osmolality

AVP is synthesized in the supraoptic and paraventricular nucleus of the hypothalamus and then stored in the neurohypophysis. The release of AVP is exquisitely sensitive to changes in plasma osmolality. AVP is not detectable in the plasma at an osmolality below approximately 280 mOsm/kg but increases in a nearly linear fashion beginning with as little as a 2-3% increase in osmolality above this value. The extreme sensitivity of this system allows for plasma osmolality to be maintained within a narrow range.

A second major determinant of AVP release is the effective arterial blood volume. While AVP levels are very sensitive to plasma osmolality, small changes of <10% in blood pressure or blood volume have no effect on AVP levels. However, once decreases in volume or pressure exceed this value, baroreceptor-mediated signals provide persistent stimuli for AVP secretion. Baroreceptor-mediated AVP release will continue even when plasma osmolality falls below 280 mOsm/kg. Teleologically, this sys-

tem can be viewed as an emergency mechanism to defend blood pressure. Thus, small decreases in blood volume and blood pressure will cause the body to retain NaCl which will raise osmolality and lead to water retention. However, if NaCl is not available and if blood pressure and volume are becoming dangerously low (down 10%), the body behaves as if defense of blood pressure is more important than defense of osmolality, and AVP is secreted. The specific compartment whose volume is sensed in order to determine AVP secretion in this setting is the effective arterial volume. This overriding effect of volume explains the persistence of high AVP levels in hyponatremic patients with conditions such as heart failure and cirrhosis.

Other stimuli for the release of AVP include pain, nausea, and hypoxia. Inappropriate release of AVP can occur with a variety of central nervous system and pulmonary diseases as well as with drugs, particularly those that act within the central nervous system[2]. Certain tumors can synthesize and release AVP.

AVP exerts its effects on cells through three receptors. The V_{1A} receptor is expressed in a variety of tissues but is primarily found on vascular smooth muscle cells. Stimulation of this receptor results in vasoconstriction, platelet aggregation, inotropic stimulation and myocardial protein synthesis. The V_{1B} receptor is expressed in cells of the anterior pituitary and throughout the brain. Stimulation of this receptor results in release of adrenocorticotropin stimulating hormone (ACTH). Stimulation of the V_{1A} and V_{1B} receptors activate phospholipase C leading to increases in inositol trisphosphate and diacylglycerol with secondary increases in cell calcium and activation of protein kinase C.

The V_2 receptor is found on the basolateral surface of the renal collecting duct and vascular endothelium where it mediates the antidiuretic effects of AVP and stimulates the release of von Willebrand factor respectively. Unlike the V_{1A} and V_{1B} receptors, binding of AVP to the V_2 receptor activates the G_S-coupled adenyl cyclase system causing increased intracellular levels of cAMP. In the kidney, generation of cAMP stimulates protein kinase A which then phosphorylates preformed aquaporin-2 water channels causing trafficking and insertion of the channels into the luminal membrane of the tubular cells[3]. The insertion of the aquaporin-2 protein renders the collecting duct selectively permeable to water, which is then reabsorbed from the tubular lumen into the blood driven by the osmotic driving force of the hypertonic interstitium. In the absence of AVP, aquaporin membrane insertion and apical membrane water permeability are dramatically reduced.

Physiologic Rationale for Use of AVP Antagonists

AVP antagonists block the V_2 receptor located on the basolateral surface of the collecting duct thereby antagonizing the ability of AVP to cause insertion of the aquaporin-2 water channels into the luminal membrane. The increase in urine output is similar in quantity to diuretics but differs in content. V_2 receptor antagonists increase water excretion with little to no change in urinary electrolytes. As a result, lowering of the serum K^+ level, metabolic alkalosis, and increases in the serum creatinine and blood urea nitrogen concentration are avoided in contrast to diuretics such as furosemide and hydrochlorothiazide. In addition, orthostatic hypotension and activation of neurohumoral effectors such as angiotensin II, circulating catecholamines, and aldosterone are not features of V_2 receptor blockade. These differences have lead to V_2 receptor antagonists being characterized as "aquaretic" agents so as to distinguish them from diuretics.

The physiologic rationale for use of V_2 receptor antagonists is best exemplified by considering the relationship between the serum Na^+ concentration and the total body content of Na^+, K^+, and water approximated by the equation:

$$\text{Plasma } Na^+ \text{ concentration} \approx (\text{Total body } Na^+ + \text{Total body } K^+) / \text{Total body water}$$

According to this equation, increasing the plasma Na^+ concentration can be achieved through the administration of salt. This approach is clearly the treatment of choice in patients who are total body salt depleted. By contrast, in euvolemic and particularly in hypervolemic patients, such a strategy can cause potential worsening of the underlying disorder as in edematous patients with congestive heart failure or cirrhosis. In these patients selectively reducing the denominator is the preferable strategy to raise the plasma Na^+ concentration. The aquaretic properties of the V_2 receptor antagonists are well suited for this purpose.

The first specific V_2 receptor antagonists synthesized were peptide analogues of AVP. This approach was later abandoned due to agonist effects noted upon chronic administration. Development of nonpeptide antagonists capable of interacting with the receptor so as to prevent binding of native AVP without themselves stimulating the receptor are now in various stages of clinical development[4]. Tolvaptan, satavaptan and lixivaptan are selective for the V_2 receptor and are administered orally. Conivaptan is an intravenous agent with blocking effects on both the V_2 and V_{1A} receptor. These drugs (the vaptans) have been shown to be effective in increasing the serum Na^+ concentration in patients with modest asymptomatic hyponatremia. They can be considered in patients with euvolemic and hypervolemic (dilutional) hyponatremia but should not be used in patients with hypovolemic hyponatremia.

Clinical Use of AVP Antagonists

Conivaptan (an intravenous V_{1a}-V_2 receptor antagonist) is approved by the Food and Drug Administration for euvolemic and hypervolemic hyponatremia. The effectiveness of the drug was demonstrated in a randomized placebo controlled trial of 84 hospitalized patients with euvolemic or hypervolemic hyponatremia in which the serum Na^+ ranged from 115 to <130 mEq/L[5]. The patients were given a 20 mg loading dose followed by a continuous infusion of either 40 or 80 mg daily for 4 days. Conivaptan significantly raised the serum Na^+ concentration by 6.3 and 9.4 in the 40 and 80 mg/d arms respectively as compared to 0.8 mEq/L in the placebo group.

Conivaptan is also active as an oral formulation but its distribution has been restricted to parenteral use for short-term (4 days maximum) in-hospital administration only. This restriction is due to potent inhibitory effects of the drug on the hepatic cytochrome P_{450} 3A4 enzyme system and the potential for untoward drug interactions. The inhibitory effects of other members of this class on the CYP3A4 system are more limited, allowing for oral formulations to be used in a clinical setting.

Tolvaptan is the only other AVP antagonist currently approved by the Food and Drug Administration. Unlike conivaptan, tolvaptan is an oral agent with effects confined to the V_2 receptor. The drug is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia.

The efficacy of tolvaptan was evaluated in two simultaneously conducted multicenter, randomized, double blind

Table 1. Location and function of AVP receptor subtypes

Subtype	Location	Function
V_{1A}	Vascular smooth muscle to include splanchnic bed	Vasoconstriction
V_{1B}	Anterior pituitary	Release of adrenocorticotropin stimulating hormone (ACTH)
V_2	Basolateral surface of renal collecting duct, vascular endothelium, vascular smooth muscle	Insertion of aquaporin channel into luminal membrane, release of von Willebrand factor, vasodilation

AVP: arginine vasopressin

trials called Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT 1 and SALT 2)[6]. The two studies together randomized 225 patients with euvolemic or hypervolemic hyponatremia to outpatient treatment with the study drug for 30 days and 223 patients to placebo. Patients with a serum Na^+ of <120 mEq/L in association with neurologic impairment were excluded from the trial. Serum Na^+ increased more in the tolvaptan group than in the placebo during the first 4 days (3.62 vs 0.25 mEq/l). After 30 days of therapy serum Na^+ concentrations were 6.22 higher in the tolvaptan group compared with 1.66 mEq/L in the placebo group. When tolvaptan was discontinued at study end, the serum Na^+ fell over a seven day period to a value similar to that in the placebo treated patients. Four patients (1.8%) exceeded the study goal of limiting correction of the hyponatremia to <12 mEq/L in the first 24 hours of treatment, but none of these patients developed adverse clinical sequelae.

As previously mentioned conivaptan and tolvaptan are indicated for the treatment of hyponatremia in the setting of euvolemia or hypervolemia. These drugs should not be used in hypovolemic states since the increase in renal water excretion can potentially predispose to worsening hemodynamics in the setting of volume depletion. To be sure, any volume of water removed from the body is principally derived from the intracellular compartment (two thirds) and would not be expected to affect blood pressure to a major extent. However, one twelfth of any water volume loss is derived from the circulating compartment and could potentially aggravate a borderline low blood pressure in the setting of volume depletion.

This concern is particularly true for conivaptan and its blocking effects on the V_{1a} receptor. AVP can cause peripheral vasoconstriction by stimulating the V1a receptor on the peripheral vasculature[7]. However, circulating concentrations observed in euvolemic and hypervolemic conditions are not typically of a magnitude to elicit this effect thus explaining the lack of clinically significant hypotension in clinical trials. By contrast, AVP may reach a high enough concentration and play a contributory role in the maintenance of blood pressure under conditions of significant depletion of extracellular fluid volume (hemorrhage) or in states of generalized vasodilation such as sepsis or advanced cirrhosis. In these settings blockade of the V_{1a} receptor may result in significant hypotension.

Another theoretical concern of blocking the V_{1a} receptor with conivaptan is the potential to cause further sequestration of fluid in the splanchnic vascular bed and theoretically increase the risk of hepatorenal syndrome[8]. The importance of splanchnic vasodilation in the genesis of renal hypoperfusion has been indirectly illustrated by the response to ornipressin, an analog of AVP that is a preferential splanchnic vasoconstrictor. The administration of ornipressin to patients with advanced cirrhosis leads to correction of many of the systemic and renal hemodynamic abnormalities that are present. These include an elevation in mean arterial pressure, reductions in plasma renin activity and norepinephrine concentration, and increases in renal blood flow, glomerular filtration rate, and urinary sodium excretion and volume. V1a

Table 2. AVP receptor antagonists currently approved by Food and Drug Administration (FDA)

Parameter	Tolvaptan	Conivaptan
Trade name	Samsca	Vaprisol
Administration	Oral	Intravenous
Dose	15-60 mg daily	20 mg loading dose followed by 20-40 mg continuous infusion
Receptor	V_2	V_{1A} and V_2
Protein binding	99%	98.5%
Half life	6-8 hours	3-8 hours
Metabolism	Hepatic (CYP3A4)	Hepatic (CYP3A4)
Elimination	Feces	Feces

AVP: arginine vasopressin

receptor blockade has the potential to increase the degree of arterial vasodilation in the splanchnic arteriolar bed. Increasing degrees of splanchnic vasodilation contribute to a fall in mean arterial pressure and unloading of baroreceptors in the central circulation. As a result, central afferent sensors signal the activation of neurohumoral effectors which in turn decrease perfusion of other organs, particularly the kidney.

AVP Antagonists in Severe Symptomatic Hyponatremia

Symptoms of hyponatremia include nausea and malaise, which can be followed by headache, lethargy, muscle cramps, restlessness, confusion and disorientation[9]. Life threatening symptoms are those of impending brain herniation and include seizures, decreased levels consciousness, and obtundation. Hypertonic saline remains the treatment of choice in those patients who are clinically determined to be severely symptomatic[10]. Vaptan therapy does result in a brisk and relatively prolonged water diuresis. Indeed, in the first 6 hours following the parenteral administration of conivaptan there is a several mEq/L increase in the serum Na^+ concentration[5]. Whether this time course of correction is sufficient to abort fatal hyponatremic encephalopathy is simply not known. Such patients to date have been excluded from clinical studies since randomization in a placebo controlled trial would be clearly unethical in such subjects, and not using hypertonic saline might also be considered unsafe.

Although not well studied, one could co-administer conivaptan along with hypertonic saline and anticipate a more rapid initial rise in the serum Na^+. Once stabilized, the hypertonic saline could be discontinued and the remainder of correction be accomplished by use of the receptor antagonist alone. This strategy would help to minimize the likelihood of volume overload due to the use of hypertonic saline but would require frequent monitoring of the serum Na^+ to ensure the rate of correction was within accepted guidelines.

AVP Antagonists in Patients with Mild to Moderate Symptoms of Hyponatremia

Hospitalized patients with mild to moderate symptoms of hyponatremia can be considered ideal candidates for the use of V_2 receptor antagonists. Both conivaptan and tolvaptan can be expected to increase the serum Na^+ concentration to a greater extent and more predictably than fluid restriction alone. The superiority of these drugs would be particularly evident in those who require ongoing fluid administration for any number of reasons such as parenteral administration of antibiotics or proton pump inhibitors[11].

In hyponatremic patients with decompensated heart failure there may be changes in mental status in which it is difficult to separate out the contribution of hyponatremia from the decrease in cerebral perfusion. Vaptan therapy offers a predictable way to improve the serum Na^+ contribution over an acceptable period of time thereby removing one of the variables. Even if hyponatremia is not the direct cause of symptoms, it may lower the threshold for mental status changes resulting from poor cerebral perfusion. A similar argument for vaptan therapy can be made in hyponatremic patients with cirrhosis. In this population mental status changes can be due to the hyponatremia, the underlying liver disease, or both. If no improvement occurred following the correction of the hyponatremia, therapy could then be focused on the underlying liver disease. In fact, in any delirious patient with hyponatremia, correction of the underlying electrolyte disorder can help to clarify the degree to which the hyponatremia is exacerbating the altered mental status.

There are no head to head studies comparing conivaptan and tolvaptan in patients with mild to moderate symptoms of hyponatremia. Presumably both drugs would work with similar efficacy. Conivaptan therapy can be complicated by phlebitis when administered through a peripheral vein due to the irritative effects of polypropylene glycol which serves as a diluent for the drug[12]. For this

reason the drug is often given through a central vein. The theoretical risk of conivaptan's V_{1a} receptor blocking effects in patients with cirrhosis has already been discussed. Tolvaptan is given orally starting at 15 mg daily. Depending on the response the dose can be increased to 30 mg and ultimately to 60 mg daily. Few patients in the SALT 1 and 2 trials required the 60 mg dose.

Measurement of the urine osmolality may be useful in predicting how responsive a patient will be to the administration of a vaptan. In this regard, urine osmolality can be thought as a biomarker of the effect of AVP on the renal collecting duct[13]. The higher the urine osmolality, presumably the higher the serum AVP level or the greater the effect of AVP is on the tubule. By contrast, those with a lower urine osmolality presumably have less AVP effect on the tubule and therefore will manifest a less robust response to a V_2 receptor blocker.

There are circumstances unique to the hospitalized patient where one may consider use of a V_2 receptor antagonist. Consider a patient admitted with pneumonia complicated by hyponatremia (Na^+=128 mEq/L) due to SIADH who is treated with intravenous antibiotics, stabilized, and is now being considered for discharge. Despite fluid restriction the serum Na^+ concentration is currently 126 mEq/L and the admitting physician is reluctant to discharge the patient for fear the Na^+ may fall further and result in symptomatic hyponatremia. The hospital discharge is postponed and fluid restriction is intensified. Two days later the serum Na^+concentration has risen to 131 mEq/L and the patient is discharged. While one can question the wisdom of postponing the original planned discharge based on the lab value alone, this type of scenario is common in clinical practice. Fluid restriction is poorly tolerated, difficult to enforce, and often unpredictable in response. The administration of a single dose of a V_2 receptor antagonist is a reliable way to increase the serum Na^+ concentration over a 24 hour period and in this case could have potentially shortened the hospital stay.

Consider another patient admitted with a hip fracture that is found to have a serum Na^+ concentration of 126 mEq/L attributed to ongoing use of an antidepressant agent. The patient is otherwise medically stable but the anesthesiologist is unwilling to accept the patient for surgery until the serum Na^+ is at least >130 mEq/L. Fluid restriction is prescribed and only 2-3 days later has the serum Na^+ reached a value of 131 mEq/L. Once again, administration of a vaptan would have almost certainly increased the Na^+ concentration to the desired threshold over a 24 hour period, allowing the patient to undergo the surgical procedure without experiencing the undue delay.

In each of these scenarios short term use of a vaptan would provide for a more rapid and predictable increase in the serum Na^+ concentration and potentially decrease the length of hospital stay in comparison to fluid restriction alone. In addition to being less predictable and often poorly tolerated, fluid restriction is often ineffective due to the obligatory fluid administration hospitalized patients require for other therapies or nutrition.

Demeclocycline and lithium have been used to antagonize the effects of AVP on the tubule but these drugs take several days before any demonstrable increase in renal water excretion is seen. Demeclocycline antagonizes the effect of AVP through nephrotoxic effects on the tubular cell whereas vaptan's are competitive inhibitors of the V_2 receptor and are not associated with nephrotoxicity. Lithium interferes in the intracellular signaling pathways by which AVP causes insertion of water channels into the apical membrane. The doses required to illicit an increase in renal water excretion are near those which can result in lithium levels sufficient to cause neurotoxicity. The primary side effect of vaptan therapy are those one would predict from inducing an aquaretic effect and include thirst, increased urinary frequency, and increased urinary volume.

The decision to use a vaptan on a more prolonged basis is made on a case by case basis. When the underlying

cause of increased AVP is deemed to be chronic and irreversible then therapy can be extended into the outpatient setting. Consideration for more chronic therapy would be appropriate for patients with SIADH due to underlying cancer, or those with severe chronic congestive heart failure or advanced cirrhosis. An open-label trial demonstrated continued efficacy of tolvaptan to maintain serum sodium level >135 mEq/L in most treated patients for up to 4 years[14]. Because the secretion of vasopressin is sometimes transient, it would be reasonable to periodically stop the drug to determine whether it is still required.

If the cause of the increased AVP is transient, then one to two doses of a vaptan while in the hospital may be all that is required. Transient causes of increased AVP would include drug related causes, acute pneumonia, hypoxia associated with respiratory failure, and acute decompensated heart failure. Once again vaptan therapy should not be used when the cause of increased AVP is due to total body salt depletion.

AVP Antagonists in Asymptomatic Hyponatremic Patients

One remaining question concerning the use of vaptan therapy is whether they are helpful in hyponatremic patients who are asymptomatic. There are several observations which raise the possibility that patients deemed to be otherwise asymptomatic do in fact have subtle abnormalities attributable to the low Na^+ concentration and therefore could benefit if the hyponatremia was corrected. First, some patients with a serum Na^+ in the range of 120-129 mEq/L have subtle neurologic changes that improve when the serum Na^+ concentration is increased[15]. These include scores on tests of mental and social functioning. In the SALT 1 and 2 trials a general health survey filled out by the patients showed tolvaptan therapy was associated with improvements in the mental health component of the instrument assessing parameters such as vitality, social functioning, emotionally limited accomplishments, calmness, and sadness[6]. Response time and number of errors in response to various stimuli are increased while patients are hyponatremic suggesting hyponatremia is associated with reversible impairment in attention. It is certainly reasonable to speculate that correction of hyponatremia in an elderly patient with SIADH might improve that individual's quality of life by allowing them to better enjoy any number of activities such as reading or completing a cross word puzzle. The presence of concomitant neuropsychiatric disturbance (delirium and dementia in particular) may also be relevant, since even mild hyponatremia may increase vulnerability to further alterations in mental status in patients who are impaired at baseline.

Second, asymptomatic hyponatremic patients exhibit subtle disturbances in gait that improve following correction of the serum Na^+ concentration[14,15]. In this regard, case control studies have shown an association between hyponatremia and risk of falls and fractures particularly in the elderly population [16,17]. Chronic hyponatremia has been shown to cause a reduction in bone mass in an experimental model of SIADH and hyponatremia is associated with osteoporosis in cross-sectional human data[18]. Fall-related injury is associated with substantial adverse psychological and physical outcomes and is a cause of both death and disability in this population. It would be of considerable socioeconomic benefit if treatment of asymptomatic hyponatremia were able to reduce the risk of this complication.

Lastly, hyponatremia is associated with increased morbidity and mortality but generally the low Na^+ concentration is merely thought to be marker of the severity of the underlying disease and not a direct contributor to the adverse outcome [19,20]. For example in decompensated heart failure there is an inverse relationship between the degree of hyponatremia and the extent of neurohormonal activation. Adverse effects resulting from persistent activation of the renin-angiotensin-aldosterone system and sym-

pathetic nerve activity are thought to be the mechanism underlying the increase in mortality in hyponatremic patients with heart failure. Nevertheless, it has been suggested that hyponatremia itself, the associated hypotonicity, and/or elevated levels of AVP might exert adverse effects on the cardiovascular system or other organ systems and therefore play a contributory role in patient morbidity and mortality. While it remains speculative as to whether correction of the hyponatremia per se will improve patient outcomes, the V_2 receptor antagonists offer an opportunity to test this uncertainty in patients with euvolemic and hypervolemic hyponatremia.

References

1. Palmer BF, Alpern RJ: Integrated response to abnormalities in tonicity. In: Seldin DW, Giebisch G, eds. Clinical Disturbances of Water Metabolism. New York, New York: Raven Press Ltd; 273-295, 1993
2. Palmer BF, Gates JR, Lader M: Causes and management of hyponatremia. Ann Pharmacotherapy 37:1694-1702, 2003
3. Nedvetsky P, Tamma G, Beulshausen S, Valenti G, Rosenthal W, Klussmann E: Regulation of aquaporin-2 trafficking. Handb Exp Pharmacol 190:133-157, 2009
4. Chen S, Jalandhara N, Batlle D: Evaluation and management of hyponatremia: an emerging role for vasopressin receptor antagonists. Nature Clin Practice Nephrol 3:82-95, 2007
5. Zeltser D, Rosansky S, va Rensburg H, Verbalis J, Smith N: Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol 27:447-57, 2007
6. Schrier R, Gross P, Gheorghiade M, Berl T, Verbalis J, et al.: Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 355: 2099-2112, 2006
7. Koshimizu T, Nasa Y, Tanoue A, et al.: V1a vasopressin receptors maintain normal blood pressure by regulating circulating blood volume and baroreflex sensitivity. Proc Natl Acad Sci 103:7807-7812, 2006
8. Palmer B: Pathogenesis of ascites and renal salt retention in cirrhosis. J Invest Med 47:183-202, 1999
9. Adrogue H, Madias N: Hyponatremia. N Engl J Med 342: 1581-1589, 2000
10. Sterns R, Nigwekar S, Hix J: The treatment of hyponatremia. Semin Nephrol 29:282-299, 2009
11. Palmer BF: Hyponatremia in the intensive care unit. Semin Nephrol 29:257-270, 2009
12. Ghali J, Farah J, Daifallah S, Zabalawi H, Zmily H: Conivaptan and its role in the treatment of hyponatremia. Drug Design Develop Therap 3:253-268, 2009
13. Verbalis J: Vaptans for the treatment of hyponatremia: How who when and why. Neph Self Assess Prog (Neph SAP) 6:199-209, 2007
14. Berl T, Quinttnat-Pelletier F, Verbails J, Schrier RW, Bichet Dg, Ouyang J, et al.: Saltwater investigoators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 21:705-712, 2010
15. Decaux G: The syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Semin Nephrol 29(3):239-256, 2009
16. Kengne F, Andres C, Sattar L, Melot C, Decaux C: Mild hyponatremia and risk of fracture in the ambulatory elderly. Q J Med 101:583-588, 2008
17. Kinsella S, Moran S, Sullivan M, Molloy M, Eustace J: Hyponatremia Independent of Osteoporosis is Associated with Fracture Occurrence. Clin J Am Soc Nephrol 5: 275-280, 2010
18. Verbalis J, Barsony J, Sugimura Y, et al.: Hyponatremia-Induced Osteoporosis. J Bone Miner Res 999:1-37, 2009
19. Wald R, Jaber B, Price L, Upadhyay A, Madias, N: Impact of Hospital-Associated Hyponatremia on Selected Outcomes. Arch Intern Med 170(3):294-302, 2010
20. Waikar S, Mount D, Curhan G, et al.: Mortality after Hospitalization with Mild, Moderate, and Severe Hyponatremia. Am J Med 122:857-865, 2009