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THE USE OF VASOPRESSIN RECEPTOR ANTAGONISTS IN HYPONATREMIA

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ABSTRACT
Hyponatremia is one of the most common electrolyte disorder seen in hospitalized patients which is independently associated with increased mortality and in some series with increased length of hospital stay. Hyponatremia is also recognized as a poor prognostic indicator in certain subgroup of patients. The current available modalities used in treating euvolemic and hypervolemic hyponatremia are at times ineffective and unable to address the underlying pathophysiology of ADH excess. Vasopressin also known as Anti Diuretic hormone acting throughV2 receptor is the primary physiologic determinant of the rate of free water excretion. This class of drugs holds a physiologic advantage over the current and commonly used agents in treating hyponatremia.In the last decade, knowledge of vasopressin receptors has increased significantly.Multiple vasopressin receptor antagonists have been developed with differences in their specificity to V2:V1 receptors. These agents have applications in conditions of hypervolemic and euvolemic hyponatremia such as syndrome of inappropriate antidiuretic hormone secretion, congestive heart failure, cirrhosis and perhaps in brain edema following traumatic brain injury. Although V2 receptor antagonist may have clear proven role in correcting hyponatremia in certain condition, its use continues to remain limited. Various factors but mainly its lack of association with decrease in mortalityand high cost has prevented its widespread use.

Keywords
Hyponatremia, vasopressin antagonists,vaptans, congestive heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone secretion

INTRODUCTION

Hyponatremiais defined as plasma sodium concentration below 135 meq/L. It is the most common electrolyte abnormality seen in hospitalized patients affecting up to 30% of patients in some series [1]. The risk of death during hospitalization is increased by more than 50% in patients admitted with hyponatremia compared with normonatremia [2]. Most of the current treatment modalities such as fluid restriction, hypertonic saline, loop diuretic etcremains difficult to maintain and at times ineffective. The use of vasopressin antagonist has shown a promise for the treatment of hyponatremia in the last decade. The goal of this review is to discuss about vasopressin use in hyponatremia, the current available agents and its role in treating euvolemic or hypervolemic hyponatremia.

HYPONATREMIA AND ITS CLINICAL IMPLICATIONS

Hyponatremia is a very commonly encountered electrolyte disorder in hospitalized patient and it is a predictor of mortality in the general population independent of age, gender, and comorbid conditions[3].

The clinical consequences of hyponatremia are varied. The rate of decline of serum sodium concentration and the magnitude of decrease determines the presentation of the patient. Serum sodium of 125 mEq/L or less, developing acutely is a medical emergency. Symptoms pertaining to dysfunction of the neurological system tend to dominate the clinical picture. Initially headache, lethargy, ataxia, psychosis, disorientation, apathy and agitation are seen. This can progress to seizures, coma, brainstem herniation, respiratory arrest and death.

Hyponatremia is well recognized as a poor prognostic indicator in certain sub group of patient population such as in patients with CHF [4]. Recent retrospective studies have also shown it to be associated with increased mortality in cancer patients [5]. Anotherobservational studyconductedbetween January 2010 and December 2012 in a tertiary hospital palliative care unit looked at the association of hyponatremia in cancer patients. Hyponatremia was defined as serum sodium<136 mEq/L. Patient where classified into three groups; eunatremia (sodium 136–145 mEq/L), mild to moderatehyponatremia (sodium 126–135 mEq/L), and severehyponatremia (sodium ≤125 mEq/L). Univariate and multivariateCox regression analyses were performed to determinefactors affecting survival time. Of the 576 patients, hyponatremia was present in367 individuals (63.7). It was associated with increased length of hospital stay and higher mortality rate in cancer patients [6].

Hyponatremia is also relatively common and serious complication in patients with various neurosurgical pathology especially ones with cerebral edema[7]. A retrospective study was conducted analyzing 39479 cases of patients operated on at the Burdenko Neurosurgical Institute from 2008 to 2014. A total of 785 hyponatremic patients with sodium level lower than 130 mmol/L (2% of all operated patients) were identified. In adults, hyponatremia most frequently occurred after resection of craniopharyngiomas (11%) and as a result of Acute cerebrovascular accident 22%). Mortality in patients with hyponatremia was 14.3%, which was tenfold higher compared to the rest of the population of patients withoutbhyponatremia who were operated on during the same period [8].

So far traditional methods have included combined use of a loop diuretic and unloading therapy with an angiotensin converting enzyme (ACE) inhibitor for hypervolemic hyponatremia.The diuretics increases water delivery to the collecting tubule and the ACE inhibitor diminishes water reabsorption in the collecting tubules by reversing the excessive release of ADH via increase in cardiac output. Treatment for euvolemic hyponatremia has consisted of water restriction and antagonizing the effects of anti-diuretic hormone (ADH) by loop diuretics, demeclocycline or lithium. In the setting of severe hyponatremia, hypertonic saline is used to raise serum sodium concentration [9]. These methods can help

correct hyponatremia but it does not correct the underlying pathophysiology of excess vasopressin secretion.

Vasopressin receptor antagonists (V2R) have important clinical application in hypervolemic and euvolemic hyponatremia. In states with high vasopressin plasma levels including patients with the syndrome of inappropriate antidiuretic hormone secretion, liver cirrhosis with ascites and edema, and severe heart failure (hypervolemic hyponatremia) vaptans have shown to effectively improve hyponatremia [10,11,12].Additionally, some agents also have effects of antagonizing the V1 receptor, which can thereby improve systemic vascular resistance and cardiac output [13].

PHYSIOLOGY OF VASOPRESSIN

Vasopressin also known as antidiuretic hormone (ADH) is a polypeptide synthesized in the supraoptic and paraventricular nuclei in the hypothalamus [14]. Vasopressin release is stimulated primarily by hyperosmolarity and by effective circulating volume depletion [15]. After release, vasopressin exerts its effects by acting on three subtypes of receptors; V1A, V1B (V3) and V2. V1A receptor is found in liver, smooth muscle, myocardium, brain and platelet. V1B (V3) receptor is expressed by cells of the anterior pituitary involved in the secretion of corticotropin [16]. V2 receptors are expressed on the basolateral membrane of the renal collecting tubule. It signals generation of cyclic AMP [16]. Activation of adenylyl cyclase via V2 receptor initiates a sequence of events via which protein kinase A is activated leading to preformed cytoplamic vesicles containing AQP-2 channels to fuse with the luminal membrane allowing water to be absorbed down the favorable osmotic gradient [16].

VASOPRESSIN RECEPTOR ANTAGONIST

Vaptans are nonpeptide vasopressin receptor antagonists that act by inhibiting the action of vasopressin on its receptors.Various classes of drugs are available which have varying V1,V2 selectivity. Vaptans binding to the V2 receptor results in a conformation change of the V2receptor that will not allow its interaction with the G-binding protein. As a consequence, activation of adenylyl cyclase,generation of cyclic-AMP, and insertion of AQP2 water channels in the luminal membrane of the principal cells of the collecting duct will not take place. [17]

The following section below discusses the recent available V2R antagonists in the treatment of hypervolemic and euvolemic hyponatremia.

Conivaptan

Conivaptan is a nonpeptide vasopressin antagonist which has V2:V1 receptor specificity of 10:1 which can be used by both the oral and intravenous routes [18]. The efficacy and safety of conivaptan was evaluated in a randomized controlled trial in patients with euvolemic or hypervolemichyponatremia by Annane et al. 83 patients with serum sodium <130 mEq/L were randomly assigned to placebo or conivaptan by mouth. Patients given conivaptan demonstrated a serum sodium of <1 mEq/L or greater above baseline significantly faster than those given placebo ($p<0.001$) and maintained that increase for a greater total time ($p=0.0001$). The percentage of patients who obtained an increase from baseline in serum sodium of 6 mEq/L or greater or normal serum sodium was also significantly higher among patients given conivaptan than those given placebo ($p<0.001$). Conivaptan was well tolerated, the most frequent adverse events were urinary tract infection, anemia, pyrexia, cardiac failure, hypotension and hypokalemia [19].

In 2009, Wright et al also assessed the safety and efficacy of conivaptan in the treatment of euvolemic hyponatremia. All the subjects were neurologically critically ill and half had failed conventional therapy of hyponatremia. End points evaluated included time to serum sodium increase of > or = 6 mEq/L, incidence of rapid overcorrection of sodium i.e an increase of >12 mEq/L in 24 hours, infusion site reactions or other adverse events and whether sodium levels decreased after discontinuation of conivaptan. Of the 22 subjects, 86% had an increase of

serum sodium to goal. The average time to goal was 13.1 hours and no subject experienced rapid over correction. One patient experienced hypotension and one complained of thirst. Five patients had an infusion site reaction. The authors concluded that conivaptan was safe and effective in a neurocritical setting, including for patients who had failed conventional treatment for hyponatremia [20].

In 2013, Paul E.Marik performed a retrospective review of medical records of 32 hyponatremic patient with SIADH admitted to neurosurgical ICU and received a single 20 mg bolus of conivaptan between January and December 201.Each patient's natremic response over 48 hours was determined. The primary end point was an increase in serum sodium level of4 mEq/L or greater over the first 24 hours. The mean ± SD baseline serum sodium level was 129.8 ± 3.4 mEq/L, which increased to 133.1 ± 3.2mEq/L at 6 hours after administration of the bolus dose of conivaptan. The serum sodium level at 24 hours was 134.2 ± 3.2 mEq/L, indicating a 24-hour natremic response of 4.3 ± 2.6 mEq/L (range 1-13 mEq/L) from baseline ($p<0.001$). Eighteen patients (56%) met the primary end point. No adverse effects or injection-site reactions were noted. The patients who failed to reach the primary end point were treated with repeat doses of conivaptan plus other agents.Authors concluded a single dose of 20 mg as an initial primary treatment of SIADH. 24 hours natremic response should then dictate whether additional dose of conivaptan or other therapeutic intervention are required [14].

Tolvaptan

Tolvaptan is an oral nonpeptide vasopressin antagonist. In cloned human receptors, it has a V2:V1 receptor selectivity of 29:1 [15]. It has been extensively studied in animal and human clinical trials. The SALT-1 and SALT-2 trial assessed the efficacy of tolvaptan in patients with euvolemic or hypervolemic hyponatremia. The patient population included those with CHF, liver cirrhosis and SIADH. In two multicenter randomized double blind placebo controlled trials 448 patients with serum sodium of <135 mEq/L were assigned to either placebo or to tolvaptan. The two primary end points for all patients were the change in the average daily area under the curve for the serum sodium concentration from baseline to day 4 and the change from baseline to day 30. Serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 days and after the full 30 days of therapy ($p<0.001$). Additionally, a planned analysis showed significant improvement on the mental component of the Medical Outcomes Study 12-Item Short Form General Health Survey in the tolvaptan group at day 30. After discontinuation of tolvaptan there was recurrence of hyponatremia. Side effects of tolvaptan included increased thirst, dry mouth and increased urination [16].

The effects of tolvaptanin patients with heart failure were also investigated in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial. In this study, 4133 patients hospitalized with heart failure, were randomized to tolvaptan or placebo. The primary end points were all cause mortality and cardiovascular death or hospitalization for heart failure. Serum sodium level at day 7 or discharge in patients with a baseline serum sodium <134 mEq/L was included as a secondary end point. Tolvaptan did prove effective in raising serum sodium in patients with hyponatremia. However, it had no effect on long-term mortality or heart failure-related morbidity [17].

In 2014 a randomized double-blind placebo-controlled trialto study theeffect of tolvaptan on non-acute, hyponatremic SIADH Chinese patients was conducted. Hyponatremic SIADH patients received placebo (N = 18) or tolvaptan (N = 19) at an initial dose of 15 mg/day with further titration to 30 mg/day and 60 mg/day based on serum sodium concentrations. Primary endpoint was the change of the serum sodium from baseline to days 4 and 7. Analysis of covariance (ANCOVA) was used for statistical analysis.At day 4, average daily changes in serum sodium levels from baseline was

1.9 ± 2.9 mmol/L (1.9 ± 2.9 mEq/L) in the placebo group and 8.1 ± 3.6 mmol/L (8.1 ± 3.6 mEq/L) in the tolvaptan group; at day 7, the values were 2.5 ± 3.9 mmol/L (2.5 ± 3.9 mEq/L) and 8.6 ± 3.9 mmol/L (8.6 ± 3.9 mEq/L) for the placebo and tolvaptan groups (ANCOVA, $P < 0.001$). At days 4 and 7, daily urine output and proportions of patients with normalized serum sodium were significantly superior in the tolvaptan group. The most common adverse events occurring in the tolvaptan group were dry mouth and thirst. Tolvaptan demonstrated superiority to placebo in the treatment of Chinese SIADH patients with hyponatremia by elevating serum sodium concentration with acceptable safety profile [12].

(SMILE Study) Samsca Post-Marketing surveillance in heart failure compared the effectiveness and safety profile in patients aged ≥ 80 years with heart failure accompanied by congestive symptoms with those in patients < 80 years (U-80). The results showed that the effectiveness of tolvaptan in the aged patients was similar to that in U-80 patients. In the safety profile, the incidence rate of thirst was lower in the aged patients than that in U-80 patients (9.6% versus 11.6%, $P = 0.0023$). Furthermore, the incidence of hypernatremia, defined as ≥ 150 mEq/L in aged patients, was comparable with that in U-80 patients (2.9% versus 3.6%, respectively, $P = 0.3657$). Based on these findings, tolvaptan was felt to have similar effectiveness and safety profiles in aged patients compared with U-80 patients. The study also recommended that a higher starting dose of tolvaptan was markedly associated with the occurrence of hypernatremia exclusively in the aged population; therefore, the recommendation was tolvaptan should be started at lower doses in aged patients[18].

Lixivaptan

Lixivaptan is a nonpeptide, benzodiazepine derivative, oral V2 receptor antagonist. It has a V2:V1receptor selectivity of 100:1 [19]. Abraham et al examined the effects of lixivaptan in 42 diuretic requiring patients with mild to moderate heart failure in a randomized double-blind placebo-controlled study. Lixivaptan produced a dose related increase in urine volume ($p<0.01$) accompanied by significant increases in solute-free water excretion and increasein serum sodium concentration. The medication was well tolerated. There were no serious adverse events reported [20].

Wong et al also studied the use of lixivaptan in the setting of CHF, liver cirrhosis and SIADH. 44 patients (33 with cirrhosis, 6 with CHF and 5 with SIADH) were studied on a constant sodium intake with three different doses of lixivaptan or placebo. Lixivaptan produced a significant aquaretic response compared to placebo, with significant dose related increases in free water clearance ($p<0.05$) and serum sodium ($p<0.05$) without significant changes in orthostatic blood pressure or serum creatinine levels. The authors concluded that lixivaptan appeared safe and effective in correcting hyponatremia in conditions associated with water retention. Higher doses could produce dehydration and require close monitoring [21].

Satavaptan

Satavaptan is a highly selective V2 receptor antagonist with a V2:V1binding affinity of 112:1. It is an orally active nonpeptide with a long half life of 14 to 17 hours [22]. The short term and long term effects of the drug in SIADH were investigated by Soupart et al. In the first part of this randomized double-blind study, 34 patients were treated with satavaptan versus placebo for up to 5 days. This was followed by 23 days of open label treatment. The number of responders was significantly higher in the satavaptan groups than placebo. The median time to reach response in serum sodium levels was also significantly lower in the active drug groups. No drug related serious adverse events were recorded. In the second part of the study, 18 patients underwent an open label extension. 15 patients achieved 6 months and 10 patients achieved 12 months of treatment. The serum sodium response was maintained during this time with good tolerance. No adverse events related to satavaptan werenoted [23].

Gines et al studied the effects of satavaptan on serum sodium and ascites management in hyponatremic patients with liver cirrhosis. A total of 148 patients with cirrhosis, ascites and hyponatremia were included in a multi-center double-blind randomized controlled study of 14 days comparing three fixed doses of satavaptan versus placebo.

Satavaptan treatment was associated with reduction in body weight and ascites. There was also improvement in serum sodium in all satavaptan groups compared to placebo ($p<0.01$). Thirst was more common in the satavaptan groups compared to placebo, whereas the frequency of other adverse events was similar among groups [24].

Another study done by Wong F et.al in 2012 looked at 1200 patients included in three randomized double-blind studies comparing satavaptan with placebo in uncomplicated ascites (study 1: n=463 patients) and difficult-to-treat ascites, with and without concomitant diuretic treatment (studies 2 and 3: n=497 and n=240 patients, respectively). The result of this study though showedsatavaptan was not more effective than placebo in control of ascites in any of the populations studied as estimated by the primary efficacy endpoints: worsening of ascites (study 1) and the cumulative number of large-volume paracentesis during 12 weeks (studies 2 and 3). Nevertheless, some of the secondary efficacy endpoints related to the treatment of ascites was met in the three studies, suggesting a slight advantage of satavaptan over placebo in delaying ascites formation.Satavaptan was more effective than placebo in improving the serum sodium concentration in patients with hyponatremia [25].

Mozavaptan

Mozavaptan is the first orally active V2 receptor antagonist investigated in humans. Even though in animal models mozavaptan is a highly selective V2 receptor antagonist, in humans the V2:V1 selectivity is only 8:1, which has therefore limited its clinical application [26]. Saito et al studied the effectiveness of mozavaptan in a clinical trial of patients with SIADH. 11 patients were studied overduration of three days. Mean serum sodium level was 123 mEq/L at baseline. When mozavaptan was given intravenously, it caused a significant increase in serum sodium level by 3 mEq/L.The effects of the drug lasted for 4 hours when given intravenously. The drug also increased the 4-hour urine volume independent of any increase in urinary solute excretion though patients remained clinically stable with no change in mean blood pressure and heart rate, before and after administration of the drug [27].

ADVERSE EVENTS

Dalh E et al. did a meta-analysis on the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in patients with cirrhosis with ascites or hyponatremia. Twelve trials with a total of 2266 patients were included.Random effects meta-analyses found no clear differences between vaptans and control groups regarding mortality (RR = 1.06, 95% CI = 0.90-1.26, I(2) = 0%), variceal bleeding,

hepaticencephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, or renal failure. The same analysis did show increased serum sodium levels and reductions in weight. [28]

Excessive correction of hyponatremia increases the risks of osmotic demyelination syndrome. The risk for overcorrection i.e hypernatremia is higher among patients receiving vaptans. Short term studies have shown hypernatremia resulting from vaptans use due to the negative fluid balance. Rebound hyponatremia may also occur after withdrawal of vaptans due to a compensatory rise in plasma AVP level. This upregulated AVP may increase retention of water, thus offsetting the therapeutic benefit and resulting in potential neurological sequelae. [29]

SALTWATER was a multicenter, open-label extension of the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2). Out of 23 patients with reports of hyponatremia, 11 experienced their episodes during the treatment period (three during interruptions in tolvaptan therapy) and 13 during the posttreatment period.Other common adverse

events assessed by the investigator as being potentially related to tolvaptan use were pollakiuria (11 patients); thirst (10 patients); fatigue (six patients); dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral edema, and acute renal failure.Hypernatremia (>145 mmol/L) occurred in 12 patients but led to drug withdrawal in only one and was readily reversible in all others. The percentage of patients who reached and maintained normonatremia was 57%, which again was comparable to the experience in the placebo-controlled trials.[30]

DISCUSSION

Vasopressin receptor antagonists hold a physiological advantage in the management of hypervolemic and euvolemic hyponatremia. The short term clinicaltrial data on this group of drugs has been encouraging so far.

Mozavaptan is approved in Japan for treatment of paraneoplastic SIADH. Conivaptan and Tolvaptans are FDA approved for treatment of euvolemic and hypervolemichyponatremia in US and also likewise in Europe.

Data pertaining salvaptan hadinitially been encouraging (24).The study done by Gine et al showed use of salvaptan along with low dose diuretic resulted in moderate reduction in ascites and significant decrease in body weight compared to placebo.Also seen in the study was the solute free water excretion and modest improvement in hyponatremia. But a meta-analysis done by E Dahl et.al [28] showed vaptans have a small beneficial effect on hyponatremia and ascites, but do not affect mortality, complications to cirrhosis or renal failure. The data does not support the routine use of vaptans in cirrhosis.Tolvaptans use of more than 30 days has been associated with elevation of liver enzymes.FDA has issued a warning that the drug has to be discontinued if liver enzymes are elevated three times the normal range. The SALT-2trial has also shown that as much as 37% of the patients with cirrhosis were resistant to the drug [15].

Vaptans have an advantage over loop diuretic in treating hypervolemic hyponatremia as the effects of electrolyte depletion and RAAS activationseen with loop diuretics is absent.The promising role of vaptans in heart failure was refuted with the EVEREST trial. The trial showed no effect on long-term mortality or CHF-related morbidity observed in 4133 patients randomized to tolvaptan or placebo, including a subgroup analysis of the patients with hyponatremia [31]. But workers in the field believe that agents with a more mixed V1/V2 antagonist profile should be used to study the survival benefit in CHF [32]. The scientific argument is that this will prevent the unopposed action of vasopressin at its V1 receptor site, which is associated with potential adverse consequences such as vasoconstriction and myocardial hypertrophy negating the benefits of V2 receptor blockade.

The clinical trial data on V2 receptor antagonists applies to chronic hyponatremia as well. In patients with chronic hyponatremia who have not responded to or are not compliant with water restriction, vaptans if used carefully with close measurement of sodium level may have a role. Saltwater trial an open-label extension of (SALT-1 and SALT-2)followed 111 patients with hyponatremia who received oral tolvaptan for a mean follow-up of 701 days. The study concluded prolonged administration of tolvaptan maintains increased serum sodium with an acceptable margin of safety. Whether this will result in decreased hospitalizations or translate into an increase in long-term survival remains unanswered.[30]

An additional application of these agents may be in situation of acutesevere hyponatremia.Given the greater ease in titrating the correction rate of hyponatremia with vaptans than with hypertonic saline, and absence of risk of pulmonary edema with vaptans versus hypertonic saline one would think its role should be more widespread. So far, this issue has not been addressed. Clinical trials have excluded this population as patients could not ethically be randomly assigned to a placebo group. Therefore, at this point, V2 receptors cannot be recommended as treatment for acute hyponatremia until firm data is available [34].

The combined use of Vaptans with hypertonic saline has also not yet been assessed.

Last but not the least, remains the cost of V2 receptor antagonists. At present, these drugs remain expensive to use.The estimated cost of the 20 mg maintenance dose of conivaptan is $450 per day.Tolvaptan is priced at around $300 for a 15 mg or 30 mg tablet. The prices of these drugs would have to be lowered significantly for them to be used on a widespread basis.

CONCLUSION

Hyponatremia remains an important clinical condition to treat. Vasopressin receptor antagonists have shown promise in treating this condition, whether in the setting of euvolemia such as SIADH, or hypervolemia as in liver cirrhosis and CHF. They have clearly shown short term benefits in correcting serum sodium levels and a better side effect profile compared to the currently available agents. However, the challenge remains in ascertaining the association of vaptans with long term survival benefit and decreased hospitalization.Its emerging role in treating hyponatremia in patients with cancer and cerebral edema also requires further studies. The cost of the drug continues to remain a barrier. Untilthese issues remain unaddressed, the future success of this category of drug remains undecided.

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