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BMH Medical Journal 2015;2(4):106-109 **Brief Review**

Vaptans

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There are three receptors for vasopressin (Antidiuretic Hormone) - the V1a, V1b, and V2 receptors. The V2 receptors primarily mediate the antidiuretic response, while V1a and V1b receptors primarily cause vasoconstriction and adrenocorticotropic hormone (ACTH) release, respectively.

V2 receptor antagonists, collectively known as Vaptans, competitively block the binding of vasopressin to V2 receptors, which are located on renal collecting duct cells. This prevents Vasopressin-mediated activation of these receptors. These class of agents cause selective water diuresis (aquaresis), and does not cause sodium and potassium loss. These agents by causing aquaresis, helps to raise serum sodium levels.

History of vasopressin receptor antagonists starts by 1991, when a non peptide vasopressin receptor type 1 antagonist was developed [1]. Vaptans are non peptide vasopressin receptor antagonists.

There are several trials addressing at the use of Vaptans in euvolemic hyponatremia. All the available Vaptans have been used in various trials and have shown increase in serum sodium levels. Vaptans have been found useful in pareneoplastic syndrome of inappropriate ant diuretic hormone (SIADH) also.

In hypervolemic hyponatremia response to Vaptans are different in different etiologies. Primarily it is used in two groups: Hypervolemic due to congestive heart failure (CHF) and Cirrhosis. Several trials addressed the response to Vaptans in CHF, showed beneficial effect in elevating serum sodium levels and decreasing fluid overload.

In cirrhosis liver, non vasopressin mediated mechanisms also lead to fluid retention, hence the effectiveness of Vaptans are not great. Nevertheless trials appeared to confer a slight advantage in delaying ascites formation and increased serum sodium in patients with hyponatremia more effectively than placebo.

Vaptans treatment can be considered a valuable option in: 1) hyponatremic patients with moderate symptoms (eg, confusion, disorientation, nausea, unsteady gait), as an alternative to hypertonic saline infusion; or 2) patients with mild symptoms (eg, mild neurocognitive alterations, depression) or asymptomatic, if fluid restriction fails or is not tolerated [2].

Vaptans are available in oral and intravenous preparations. Tolvaptan, Mozavaptan, Satavaptan, and Lixivaptan are selective for the V2 receptor, while an intravenous agent, Conivaptan, blocks both the V2 and V1a receptors.

Two approved and marketed Vaptans are Conivaptan (intravenous) and tolvpatan.

Tolvaptan

Tolvaptan was approved by FDA in May 2009. Efficacy of Tolvaptan was shown in 2 Randomized placebo controlled, multicenter studies (SALT 1 & SALT 2). Together in these 2 studies, about 450 patients with hyponatremia (mean serum sodium 129 meq/L) caused by the SIADH (190 patients), heart failure, or cirrhosis were included. Compared with placebo, tolvaptan significantly increased the serum sodium concentration at day 4 (134 to 135 meq/L versus 130 meq/L) and day 30 (136 versus 131 meq/L). In SALT studies in patients with Serum Sodium Less than 130 had statistically significant improvement in mental scores, however clinical improvement was minimal [3]. In SALTWATER an open-label extension study, 111 patients were treated with Tolvaptan for a mean follow-up of almost two years. The mean serum sodium was maintained at more than 135 meq/L compared to 131 meq/L at baseline [4]. The major adverse effects were symptoms related to volume depletion.

Another use of tolvaptan is to delay the progression of kidney enlargement in autosomal dominant polycystic kidney disease (ADPKD). Two major studies have shown that patients with ADPKD and a total kidney volume 750 mL or above with relatively preserved renal function (eg, estimated creatinine clearance 60 mL/minute or more) had lower increase in kidney volume and less annual decline of GFR [5,6]. In the same study more than 2.5-fold increase in liver enzymes was more common among patients who received Tolvaptan compared with placebo. Based upon these data, the US FDA issued safety warnings, recommended that liver function tests be promptly performed among patients who report symptoms that suggest liver injury (eg, fatigue, anorexia, right upper quadrant discomfort, dark urine, jaundice); that Tolvaptan should not be used in any patient for longer than 30 days; and that Tolvaptan should not be used at all in patients with liver disease (including cirrhosis) because it may potentially lead to liver failure or death.

Another potential major complication of Tolvaptan is that there may be overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury.

Dosage: Initial, 15 mg once daily; after at least 24 hours, may increase to 30 mg once daily to a maximum of 60 mg once daily titrating at 24-hour intervals to desired serum sodium concentration. No dosage adjustment is required in patients with creatinine clearance > 10ml/min, and not advised to use if creatinine clearance < 10 ml/min. Avoid use in patients with underlying liver disease. Dosage reduction to be done with concomitant use with CYP3A inhibitors.

Conivaptan

Conivaptan was approved by FDA in December 2005. As Conivaptan is available in intravenous preparation, it is only useful in the treatment of SIADH in patients who are hospitalized. Conivaptan is rapid in action (action starts as early as one to two hours) and help in rapid initial rise in serum sodium [7]. However it is not shown that early correction of serum sodium reduced hospital stay. Its use is recommended in mild, moderate and severe hyponatremia along with other modalities of treatment. As described in Tolvaptan, it may also cause over correction of serum sodium and permanent neurological damage.

Dosage Intravenous: 20 mg infused over 30 minutes as a loading dose, followed by a continuous infusion of 20 mg over 24 hours for 2-4 days; may increase to a maximum dose of 40 mg over 24 hours if serum sodium not rising sufficiently; total duration of therapy not to exceed 4 days. No

dose reduction is needed if creatinine clearance > 30ml/min and not to use if it is < 30ml/min. No dose modification is required in mild hepatic impairment and requires dose reduction with moderate liver dysfunction. It is not recommended to use in severe liver dysfunction. Dose reduction to be done with concomitant use of with CYP3A inhibitors.

Lixivaptan

Lixivaptan is an oral vaptan studied in two major studies. In HARMONY study, 206 patients with or without symptoms were randomly assigned to receive lixivaptan (25 to 100 mg/day) or placebo for 24 weeks. The serum sodium after seven days of therapy (the primary endpoint) was significantly higher with lixivaptan (135 versus 133 meq/L) and remained significantly higher throughout the remainder of the study [8].

In the inpatient trial (LIBRA study), 106 hyponatremic patients (mean serum sodium 127 meq/L) with or without symptoms were randomly assigned to lixivaptan (25 to 100 mg/day) or placebo and followed for 30 days]. The serum sodium at seven days (the primary outcome) was significantly higher in the lixivaptan group (135 versus 131 meq/L). No effect on cognitive function was observed [9]. Discontinuation rate in these studies were high due to adverse reactions.

Satavaptan

Satavpatan also has several trials done in euvolemic and hypervolemic hyponatremia and has shown improvement in serum sodium levels.

Conclusion

Vaptans are useful class of drugs in treating patients with euvolemic and hypervolemic hyponatremia. It has to be used in right indications and for required duration. Careful monitoring is required to avoid rapid correction of serum sodium and for adverse effects.

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