Tolvaptan for Euvolemic and Hypervolemic Hyponatremia: A Narrative Review

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ABSTRACT

Hyponatremia is an electrolyte imbalance disorder commonly found in clinical practice. Hyponatremia is associated with significant mortality and morbidity. Tolvaptan is an orally administered V2 receptor antagonist drug capable of aquaresis without excreting electrolytes, thus increasing plasma sodium concentration. Results from clinical trials showed tolvaptan to be a relatively safe and effective treatment in euvolemia and hypervolemia hyponatremia.

Keywords: Electrolyte imbalance, hyponatremia, tolvaptan.

ABSTRAK

Hiponatremia adalah gangguan keseimbangan elektrolit yang umum dijumpai dalam praktik klinis. Hiponatremia dikaitkan dengan mortalitas dan morbiditas signifikan. *Tolvaptan* merupakan obat golongan antagonis reseptor V2 dengan rute pemberian oral yang memiliki efek *aquaresis* tanpa efek ekskresi elektrolit, sehingga dapat meningkatkan konsentrasi natrium plasma. Hasil uji klinis menunjukkan *tolvaptan* dapat menjadi salah satu pilihan pengobatan yang relatif aman dan efektif. **Terence Judian, Samuel Alexsander. *Tolvaptan* untuk Hiponatremia Euvolemik dan Hipervolemik: Tinjauan Ulang Naratif.**

Kata Kunci: Gangguan elektrolit, hiponatremia, *tolvaptan*.

Introduction

Hyponatremia, or low sodium level, is a common electrolyte imbalance found in hospital settings, consisting of up to 15%–30% of hospitalized inpatients. Hyponatremia is a condition in which sodium serum falls below 135 mEq/L and can result in significant mortality and morbidity if left untreated. Sodium is the predominant extracellular cation, which consists of 88% of extracellular fluid osmolality. A decrease in sodium level thus leads to water entry into the cells by osmosis.[1] Patients with chronic hyponatremia are commonly asymptomatic or show mild symptoms. However, severe acute hyponatremia can potentially cause severe complications such as brain herniation and seizures; thus, understanding treatment options is crucial.[2]

The current option for the treatment of hyponatremia is limited. Normal saline is administered in patients with hypovolemic hyponatremia,[3] whereas fluid restriction is the main initial treatment in patients with euvolemic and hypervolemic hyponatremia. However, treatment with fluid restriction can be challenging due to the constant need for patient supervision, resulting in poor compliance.[4,5] Moreover, long-term fluid restriction with water consumption under 800 mL/day is to a large extent difficult to maintain and can lead to a reduced quality of life.[6]

Tolvaptan is an orally administered vasopressin V2 receptor antagonist drug that can block vasopressin hormone, thus inducing water diuresis. Tolvaptan acts on the renal tubular cells, selectively avoids electrolyte excretion, and inhibits the reabsorption of water.[7] Tolvaptan has been named "aquaretic" in contrast to normal diuretics, which excrete electrolytes in urine.[8] Hence, tolvaptan excretes water without any effect on sodium and potassium.[9] Guidelines from the European Journal of Endocrinology have not recommended the use of vasopressin antagonists in daily practice due to the risk of overly rapid correction of sodium serum and hepatotoxicity.[10] However, several clinical trial results from Warren, *et al,* and Wang, *et al*, showed the efficacy and safety of tolvaptan in raising sodium serum without major adverse effects.[5,11]

Although tolvaptan has been used in numerous clinical hospital settings, on account of the lack of recommendation and research on the efficacy and safety of patients with euvolemia and hypervolemia hyponatremia, the implementation remains unclear. Thus, this review aims to help identify the potential use of tolvaptan in euvolemia and hypervolemia hyponatremia patients, focusing on the efficacy and safety.

Sodium, Water, and Mechanism of Antidiuretic Hormone

Sodium is the primary cation in the extracellular fluid. Sodium with associated anions accounts for almost 90% of extracellular fluid osmolality.

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Water moves via osmosis from lower to higher solute concentrations to stabilize ECF and ICF concentrations. The balance of sodium depends on the amount of sodium absorbed through the GI tract and the amount excreted through skin, feces, and urine. An important component of sodium balance is the excretion of sodium dependent on kidney function. Even though a part of sodium is excreted through skin and feces, the majority of sodium is excreted via the kidney. One of the major hormones necessary to maintain osmolality balance is the antidiuretic hormone.[12,13]

Antidiuretic hormone, or vasopressin, is a small peptide hormone that is synthesized in the hypothalamus. Vasopressin is majorly responsible for the homeostasis of plasma osmolality by maintaining body fluid balance.[14] Vasopressin is released into the circulation mainly when central osmoreceptors in the hypothalamus detect an increase in plasma osmolality above 295 mOsm/kg, such as dehydration. This effect causes an increase in water reabsorption in the thick ascending limb and collecting duct.[15] Vasopressin has three receptors, which are the V1a receptors, V1b receptors, and V2 receptors. V2 receptors are located in the collecting duct and the thick ascending limb of the principal cells.[14] Vasopressin acts on the V2 receptors, thus promoting the insertion of Aquaporin-2 vesicles in the luminal membrane of cells in the collecting duct, thus causing an increase in water reabsorption.[2,14]

Hyponatremia

Hyponatremia is defined as a plasma sodium concentration below 135 mEq. Symptoms of hyponatremia typically manifest due to low hypotonicity, hence cellular edema. Symptoms range from mild to severe and life-threatening.[10] Acute hyponatremia typically manifests as neurologic symptoms due to cerebral edema in onset under 48 hours.[16] However, hyponatremia that persists for more than 48 hours is typically classified as chronic hyponatremia. Chronic hyponatremia results from water entry due to efflux or organic osmolyte and typically manifests as gait disturbances, disorientation, and dysarthria. Chronic hyponatremia can be asymptomatic due to osmotic adaptation; hence, reduce edema over an extended period. Hyponatremia is divided according to volume status and history into hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia.[2,13]

Hypovolemic Hyponatremia

Patients with hypovolemic hyponatremia typically have signs of fluid depletion in addition to a deficit in serum sodium but relatively more sodium losses. The etiology of hypovolemic hyponatremia may be divided into renal causes and non-renal causes. A urine sodium level of more than 30 mEq/L is consistent with renal sodium loss, such as diuretic use, mineralocorticoid deficiency, and cerebral salt wasting. However, a urine sodium level of more than 30 mEq/L designates a non-renal etiology, such as burns, pancreatitis, excessive vomiting, and diarrhea.[2,16] The first choice treatment for hypovolemic hyponatremia is isotonic saline infusion (NaCl 0.9%). The recommended correction rate should not exceed 8-12mmol/L/day in the first 24 hour.[17]

Euvolemic Hyponatremia

Euvolemic hyponatremia involves an excess amount of body water in addition to normal or reduced total body sodium. The etiology of euvolemic hyponatremia includes hypothyroidism, glucocorticoid deficiency, and the syndrome of inappropriate antidiuresis, with SIAD being the most common. SIAD occurs when antidiuresis activity persists despite low serum tonicity. Continuous stimulation of V2 receptors in the collecting tubules causes an increase in aquaporin insertion, thus increasing the reabsorption of water in the context of sustained water ingestion. Moreover, the expansion of extracellular fluid inhibits aldosterone, causing whole-body sodium depletion with water retention. SIAD can be caused by a variety of underlying causes.[18] The main causes include malignancy, a pulmonary disorder, central nervous system pathology, and medications.[13] Treatment of euvolemic hyponatremia generally begins with fluid restriction and correcting the underlying etiology. The patient should be limited to 500 mL/day of fluid intake with no salt or protein intake restriction.[19] An alternative treatment includes an aquaresis, such as V2 receptor antagonists, the vaptans.[20] Vaptans are capable of raising sodium concentration by inducing free-water diuresis.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia involves an excess of sodium accompanied by an even greater excess of water. Patients with hypervolemic hyponatremia typically have signs of fluid overload, such as congestive heart failure, cirrhosis, nephrotic syndrome, and renal failure. These conditions can cause a decrease in cardiac output and systemic arterial underfilling. Thus, resulting in beta-adrenergic stimulation and non-osmotic release of vasopressin. Sodium urine level in hypervolemic hyponatremia is typically low.[2,13]

Administration of NaCl 3% in hypervolemic hyponatremia is typically contraindicated. Fluid restriction and loop diuretics are usually the keystone treatment of hypervolemic hyponatremia treatment. However, fluid restrictions are generally ineffective; pharmacologic treatment using Vaptans is gradually becoming an alternative.

Tolvaptan

Vaptans are a class of drugs that can block the binding of vasopressin hormones to V2 receptors in the collecting duct and distal convoluted tubule, hence inducing water diuresis. Tolvaptan is an orally selective V2 receptor antagonist used for the treatment of dilutional hyponatremia. Tolvaptan is capable of binding to V2 receptor 1.8 times with greater affinity compared to ADH. Tolvaptan is effective for correcting sodium levels but is limited for treating euvolemic/hypervolemic hyponatremia only. Therefore, it is important for clinicians to assess the patient's volume status before initiating tolvaptan therapy. Tolvaptan is eliminated via nonrenal routes and thus is not recommended for patients with hepatic impairment.[3,9,19]

Safety and Efficacy of Tolvaptan

The benefit and safety of tolvaptan have been proven in several clinical trials. A trial conducted by Wang, *et al*, investigated the impact of Tolvaptan on the 6-month survival of cirrhotic patients with hyponatremia. Results showed an increase in sodium level with a 7-day follow-up ($p < 0.01$), and no side effects were detected.[5] Hence, the study concluded tolvaptan can improve short-term survival in patients with cirrhotic hyponatremia. In addition, a randomized controlled trial by Verbalis, *et al,* conducted a study to investigate the neurocognitive effect of Tolvaptan in chronic asymptomatic euvolemic and hypervolemic hyponatremia. Results from the trial revealed a greater increase of sodium in

the tolvaptan group compared to the placebo group (p <0.001).[21] However, there was no improvement in neurocognitive scores.

Dosage

The standard starting dose of Tolvaptan is 15 mg on the first day. It is necessary to monitor sodium serum every 6 hours or more frequently during the active phase of hyponatremia correction. Dosage can be titrated to 30-60 mg at 24-hour intervals if sodium serum is still insufficient. The maximum dosage is 60 mg/day.[17,22] On the contrary, a nonrandomized open-label trial from Castello, *et al*, compared the safety and efficacy of the standard dose of 15 mg against a lower dose of 7.5 mg in patients with moderate-severe euvolemic and hypervolemic hyponatremia in the emergency department. The study revealed that Tolvaptan can raise sodium levels with a low dose of 7.5 mg. However, the correction rate is lower compared to the standard dose of 15 mg (12 vs. 6 mEq/L/24 hours, p = 0.025).[20] Nevertheless, the 15 mg dose showed a risk of overcorrections of more than 12 mEq/24 hours in 41.7% of patients. Thus, Castello, *et al,* conclude that Tolvaptan dosage of 7.5 mg is a safe and effective alternative in euvolemic and hypervolemic hyponatremia.[20] Another clinical trial conducted by Bondanelli, *et al,* conducted a retrospective study that tested the efficacy and safety of low-dose tolvaptan under 15 mg/day for 6 months. Sodium concentration using the 7.5 mg dose significantly increased in the 3-day follow-up but was lower than the 15 mg dose (p<0.01). In addition, the trial revealed that low-dose tolvaptan was associated with no incidence of osmotic demyelination syndrome and no liver toxicity.[23] However, the slight limitation is the unblinded and non-randomization design; therefore, more studies are needed to safely conclude the effective dosage.

Clinical Use, Indications, and Contraindications

Tolvaptan is generally used in patients with hyponatremia without volume depletion.[9] The two most common etiologies of hypervolemic and euvolemic hyponatremia are heart failure and syndrome of inappropriate antidiuretic hormone (SIADH).[24] Tolvaptan is not recommended for the treatment of hypovolemic hyponatremia.[17] The FDA has also contraindicated the usage of tolvaptan in patients with underlying liver disease and renal failure, in particular if glomerular filtration rate is <50 mL/min.[17]

Precautions

Tolvaptan is generally quite well tolerated with mild side effects. The most common side effects are headaches, nausea, and increased urinary frequency. SALT1[25] and SALT2 trial[25] showed that overcorrection of sodium levels rarely rs. Precaution towards monitoring sodium levels should be taken when taking tolvaptan, and active therapy should be stopped if the rate of correction exceeds 8–12 mmol/L in the first 24 hours.[17] Tolvaptan should not be used for longer than 30 days.[9] There are also several reported cases of liver injury due to Tolvaptan consumption.[17] Thus, ALT and AST levels should be measured before initiating treatment. Inhibitors of CYP3A4 drugs can raise levels of tolvaptan, and combinations should be avoided.[9,17]

Tolvaptan vs. Other Treatment Modalities

Tolvaptan is a relatively new method for the treatment of hypervolemic and euvolemic hyponatremia. The mainstay method of euvolemic hyponatremia, such as SIADH, is fluid restriction.[11] Fluid restriction is the standard initial treatment for euvolemic hyponatremia, stated by international guidelines with a target negative balance of 500 mL/day to be clinically effective.[26] Despite being the initial first-line treatment, there have been questions about the lack of efficacy of the fluid restriction method. Martin-Grace, *et al,*[26] stated that an observational study from the hyponatremia registry study[27] reported that fluid restriction only achieved an elevation of plasma sodium of 2 mmol/L in the first day, which was statistically stagnant compared to no treatment. On the other hand, trials such as SALT1 and SALT2 reported that tolvaptan was very effective in the treatment of SIADH and hypervolemic hyponatremia. Tolvaptan can excrete water-free electrolyte without exacerbating hyponatremia. Patients consuming tolvaptan were more likely to achieve a normal sodium level. Classic diuretics such as furosemide and spironolactone are frequently used in water retention; however, they can potentially worsen hyponatremia in certain populations, such as cirrhotic patients.[5,11,26]

Recommendation

The UK Kidney Association recommends that tolvaptan may be used for patients over 18 years with autosomal polycystic kidney ney disease.[28] Another guideline from Japan recommends that tolvaptan may be used for diuretic-resistant heart failure.[29]

Conclusion

Tolvaptan is proven to be effective for the treatment of euvolemic and hypervolemic hyponatremia. It is also relatively safe with minimal adverse effects. Further studies are needed to establish an evidence-based guideline regarding the usage of vasopressin antagonists in the treatment of dilutional hyponatremia.

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Conflict of Interest

There is no conflict of interest in this study

AUTHOR CONTRIBUTION

The author fully contributes from the process of data analysis from literature to the preparation of reports in the form of manuscripts ready for publication.

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