Tolvaptan

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Abstract

Hyponatremia is a common and often under-recogonised clinical problem in oncologic practice. The recogonition of the cause of hyponatremia and initiation of appropriate and timely intervention can prevent morbidity and improve treatment tolerance. This drug review aims at discussing the currently approved oral vaptanagent Tolvaptan. Vaptans including Tolvaptan act as "aquaretic" agents cousing excretion of water while retaining the sodium. Administration of this agent for prescribed periods result in improvement of serum sodium levels. The drug can be used in many clinical situations resulting in hyponatremia including congestive heart failure, cirrhosis and syndrome of inappropriate ADH secretion (SIADH) including SIADH related to malignancies.

Key words: Hyponatremia, tolvaptan, syndrome of inappropriate anti-diuretic hormone, paraneoplastic syndrome

Introduction

Hyponatremia is a common and difficult problem encountered in oncology practice. The necessity to recognize the presence of hyponatremia and identify the cause is often underestimated.[1] Clinical studies show that moderate chronic and otherwise asymptomatic hyponatremia between 120 meq/L to 129 meq/L in elderly patients can result in increased incidence of falls which may be the result of subtle and unrecognized neurological deficits.[2] This underlines the importance of recognition and treatment of hyponatremia in cancer patients. Hyponatremia is mostly associated with low serum osmolality. Hyponatremia associated with low serum osmolality may be classified according to volume status (hypovolemic, euvolemic or hypervolemic) or according to the level of circulating anti diuretic hormone (ADH, arginine vasopressin).

ADH action is mediated via three receptors V1a, V1b and V2. The V1a receptors are mainly seen in the heart and blood vessels and V1b receptors are confined to the anterior pituitary where they play a role in adrenocorticotrophin hormone release. The V2 receptors are located in the collecting tubules in the kidney and increase the re-absorption of water from the urine. Excessive ADH secretion results in increased water re-absorption resulting in an increase in the total body water with consequent high urine osmolality and lower plasma serum sodium level. most common cause of hyponatremia in malignancy is primary increase in ADH level without hypovolemia and is called syndrome of inappropriate anti-diuretic hormone secretion (SIADH) Administration of isotonic saline in patients with SIADH does not result in normalization of sodium levels. Although an initial rise in sodium concentration is seen with administration of hypertonic saline in SIADH, this is followed by excretion of administered sodium with retention of water. The appropriate initial management of SIADH therefore is the restriction of water to 500-1000 mL/day. The addition of a loop diuretic may be beneficial in patients with high urine to serum ratio of Sodium as these agents inhibit re-absorption of sodium and chloride in the thick ascending limb of the loop of henle which in turns induces a state of ADH resistance and increases water diuresis. The underlying cause of SIADH must be identified and appropriate treatment for the condition initiated.[1]

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/2278-330X.136811

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The blockade of ADH activity by vasopressin receptor antagonists (VRA) offer a therapeutic strategy to counter the effect of ADH and have been evaluated in clinical trials since early 1990s. The non-peptide VRAs are called vaptans and many of the agents are also active orally. This group of dugs include selective V2 receptor blockers-tolvapatan, mozavaptan, satavaptan, lixivaptan, V1a selective blocker-relcovaptan, V1b selective blocker-nelivaptan and unselected V1a/V2 blocker-conivaptan. Tolvaptan is an orally active agent which has been evaluated in hyponatremia and autosomal dominant adult polycystic kidney disease.[3,4]

Tolvaptan: Chemistry

Tolvaptan is a non-peptide orally active VRA. The empirical formula is C26H25ClN2O3. Molecular weight is 448.94. Tolvaptan is (±)-4'-([7-chloro-2,3,4,5-tetrahydro -5-hydroxy-1H-1-benzazepin-1-yl] carbonyl)-otolu-m-toluidide.

Tolvaptan: Mechanism of Action

Tolvaptan binds to V2 receptor with 1.8 times greater affinity than ADH. The drug is a selective V2 receptor antagonist and shows 30 times more avidity for V2 receptor than V1 receptors. Tolvaptan antagonises the effect of ADH which results in excretion of water-aquaresis; without any effect on sodium and potassium excretion which is in contrast to traditional diuretics. The drug is highly plasma protein bound (99%). About 40% of tolvaptan is bioavailable and the terminal half-life is about 12 h.[5,6]

Tolvaptan: Metabolism and Elimination

Tolvaptan is almost entirely eliminated by non-renal routes. The drug is handled almost entirely by the CYP3A. There is no known interaction with food. *In vitro* studies reveal inhibition of p-glycoprotein by tolvaptan. The peak plasma concentration is achieved within 2-4 h of drug administration. The onset of drug action also occurs in about 2-4 h, but the peak aquaretic action and elevation of sodium level occurs between 4-8 h after the drug administration.[5,6]

Tolvaptan: Clinical Trials

Tolvaptan: Trials evaluating the efficacy in hyponatremia

Tolvaptan has been evaluated in hyponatremia associated with congestive heart failure, cirrhosis of the liver and SIADH in two major trials-*Studies of Ascending Levels of Tolvaptan* (SALT-1 and SALT-2).[7] The pooled analysis of these two trials indicate improvements in serum sodium levels with the agent. However serum sodium levels reverted to hyponatremic status in theses patients one week after drug discontinuation. The patients on these trials were further randomized and evaluated for prolonged treatment (804 days) with Tolvaptan. The prolonged use was associated with normalization of serum sodium in 60% patients.

Tolvaptan was discontinued in 61 patients of which 30 patients discontinued due to adverse events including death. Pertaining to SALT and SALTWATER studies.[8,9]

Tolvaptan in the treatment of SIADH and hyponatremia has been compared to supportive care combined with fluid restriction and loop diuretics especially frusemide. Randomized phase III data for efficacy over other agent like the other vaptans or demeclocycline is lacking. This is mainly because most of the other agents produce only transient effects and are not approved in this indication.

The evaluation of tolvaptan in patients with congestive heart failure-EVEREST[10,11] efficacy of vasopressin antagonist in heart failure outcome study with tolvaptan[10,11] and acute and chronic therapeutic impact of vasopressin antagonist in congestive heart failure did not demonstrate a survival benefit in these patients with tolvaptan. In addition, tolvaptan has been evaluated in multiple Phase III trials in heart failure and these studies showed normalization of serum sodium which did not translate into an improved clinical outcomes.[12,13]

Tolvaptan has also been evaluated in autosomal dominant polycystic kidney disease in the TEMPO trial.[14] This was one of the largest trials evaluating tolvaptan. The endpoint of this study was delaying progression of polycystic kidney disease. Although the trial met its primary endpoint, the authors also reported elevation of transaminases to more than 3 times the normal in three patients in the tolvaptan group. The incidence of liver toxicity coupled with the need for long-term use and the lack of longer follow-up has led to US Food Drug Administration (FDA) warning limiting the use of tolvaptan to a maximum of 30 days and withdrawal of approval for autosomal dominant adult polycystic kidney disease.

Tolvaptan: Indications

The vaptans have mainly been evaluated in all forms of hyponatremia not associated with volume depletion. Though this class of agents have been evaluated in autosomal dominant adult polycystic kidney disease, they are not recommended for routine use in this group at the present time. Furthermore, the FDA restricts the use of tolvaptan to a maximum of 30 days. The restriction for use beyond 30 days is mainly due to the increased incidence of liver enzyme elevations and probability of liver toxicity with prolonged use. The FDA approved indications now include Moderate hyponatremia (<125 meq/L) without hypovolemia and Lesser degrees of hyponatremia not responding to fluid restriction.

Tolvaptan: Dose

The starting dose is 15 mg/day which may be escalated to 30 mg/day after 24 h and to a maximum of 60 mg/day if optimal response is not achieved with lower doses. Escalation beyond 60 mg does not significantly increase the plasma drug concentration and may be associated with higher rates of liver toxicity.

Tolvaptan: Cautions and contraindications

Tolvaptan is contraindicated in:

- Hypovolemic states associated with hyponatremia, anuria and in patients with impaired ability to perceive/report thirst
- CYP3A4 inhibitors: Patients who are concurrently on strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin)
- Long-term use in autosomal dominant adult polycystic kidney disease
- Hypertonic saline: Concurrently with hypertonic saline
- Anuria: Contraindicated in anuric patients. There is no data regarding the use in patients with creatinine clearance <10 ml/min.

Cautions

- Liver dysfunction: The use of tolvapatan in patients with impaired liver function including cirrhosis requires careful monitoring of transaminases and withdrawal of the drug at the evidence of worsening of liver parameters
- Serum sodium should be monitored and too rapid correction of sodium must be avoided as it can result in osmotic demyelination
- Teratogenicity: Tolvaptan is teratogenic in high doses in rabbits and mice. The use in pregnant women should be decided based upon the risk benefit ratio of the clinical benefit to risk of fetal damage
- Lactation: There is no data available on secretion of drug in breast milk and it is recommended to avoided in lactating women
- CYP3A4 drug use: Tolvapatan is mainly handled by the CYP3A4 and drugs inducing/inhibiting the enzyme should be used with caution.

Tolvaptan: Adverse effects

The clinical trials which evaluated tolvapatan for longer durations (>30 days) have shown hepatic toxicity to be a rare, but potentially lethal side effect of the drug.[7-14] Use in patients with impaired hepatic function including cirrhotic patients may result in potentially fatal acute hepatitis. Increased thirst has been reported in many subjects and this may offset the aquaretic effect of the drug. In addition, polyuria and pollakiuria may be seen in many patients. Tolvaptan is fairly well-tolerated with nausea, dry mouth, pollakiuria and polydipsia being the most common adverse events. Hypotension has been reported in the Cardiac Failure trial, but the rates of hypotension in patients on tolvaptan were similar to that seen in the control arm and likely to be related to underlying cardiac disease/concurrent diuretics.

Conclusion

Hyponatremia remains a commonly encountered and often overlooked cause of morbidity in clinical practice in general and in oncology patients. Even mild levels of hyponatremia may be associated with subtle neurological deficits which in turn may lead to falls or other potentially fatal complications.[1,2] Furthermore low sodium levels in cancer patients may be related to increased fatigue, myalgia and lead to an impaired quality of life. Tolvaptan is an important therapeutic option in such patients. The identification of hyponatremia and initiating early appropriate treatment will enable cancer patients to have an improvement in quality of life parameters and may prevent potentially lethal outcomes.[15]

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How to cite this article: Rangarajan B, Binoy V, Hingmire SS, Noronha V. Tolvaptan. South Asian J Cancer 2014;3:182-4.

Source of Support: Nil. **Conflict of Interest:** None declared.

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