SAFETY AND EFFICACY OF TOLVAPTAN IN PATIENTS WITH HYponATREMIA-A REVIEW


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ABSTRACT
Hyponatremia is the most common electrolyte disorder which increases the morbidity and mortality in hospitalized patients and its management is incompletely established in clinical practice due to diversity in underlying disease states and varying pathophysiology. Tolvaptan is the first orally active, specific V2 receptor antagonist to be approved by FDA for treatment of hypervolemic and euvolemic hyponatremia under brand name Samsca. As the part of the study, ‘evaluation of safety and efficacy of tolvaptan in patients with hyponatremia’ a review on tolvaptan in the treatment of hyponatremia was conducted. Tolvaptan has significant evidence that it improves serum sodium concentration by increasing the electrolyte-free water clearance, thereby facilitating its application in the treatment of euvolemic and hypervolemic hyponatremia. The drug was found highly effective in the treatment of hyponatremic associated with cardiac failure and in syndrome of inappropriate anti-diuretic hormone. Tolvaptan also proved to maintain increased serum sodium concentration by prolonged therapy in patients with chronic hyponatremia at a modest safety margin.

Keywords: FDA, hyponatremia, electrolyte.

INTRODUCTION
Hyponatremia is an electrolyte disorder in which serum sodium level is less than 135mmol/l. [1] It is one of the most common disorder associated with heart failure, SIADH (Syndrome of inappropriate Antidiuretic Hormone), Neurologic disorders, Cirrhosis etc. [2, 3] Incidence of Hyponatremia in clinical practice was reported as 15-30%. [1] Hyponatremia can be classified as hypervolemic hyponatremia, euvolemic hyponatremia and hypovolemic...
hyponatremia based on fluid level. The cause of hyponatremia varies in each patient depending upon underlying disease, comorbidities, medications etc. Severe hyponatremia increases the mortality and morbidity risks. [4, 5] Care should be taken during the treatment of hyponatremia because under correction leads to cerebral dysfunction and sudden rapid increase in sodium levels can lead to Rhabdomyolysis and seizure which contribute to the risk of severe morbidity while treatment. [6]

Arginine vasopressin (AVP) is a neuropeptide hormone synthesized in the supraoptic nuclei and para-ventricular nuclei of hypothalamus and stored in the posterior pituitary. The fine control of serum sodium levels and serum osmolality is achieved by the controlled release of arginine vasopressin which is strongly influenced by the small changes (as little as 1%) in plasma osmolality detected by osmoreceptors in the hypothalamus. [7] Changes in the intra-arterial plasma volume sensed by the baroreceptors in the carotid artery, aortic arch and left atrium also regulates the secretion of arginine vasopressin. In heart failure, liver cirrhosis, SIADH, surgical stress an unfavorably increased levels of arginine vasopressin were seen. [8] The increased secretion of arginine vasopressin, the antidiuretic hormone is associated with hyponatremia. Increased vasopressin levels causes enhanced synthesis and transport of aquaporin channels leading to increased water reabsorption while urinary sodium excretion continues. [9] Hence vasopressin antagonists, also known as aquaretics have applications in the treatment of hyponatremia which can reduce the expression of aquaporin channels which consequently lowers the loss of sodium ions from the body. [10]

Tolvaptan was the first orally administered nonpeptide vasopressin2 (V2) receptor antagonist to be licensed for use in man and chemical name of the drug is N-(4-{{(5R)-7-chloro-5-hydroxy-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl}carbonyl}-3-methyl)-2-methylbenzamide with empirical formula C_{26}H_{25}ClN_{2}O_{3} and the molecular weight was found to be 448.941. [11, 12, 13] Chemical structure of tolvaptan
APPROVAL

FDA approved tolvaptan on May 19th, 2009 under the brand name Samsca by Otsuka pharmaceuticals. [13] CDSCO approved tolvaptan tablets of 15mg and 30mg for the treatment of clinically significant hypervolemic and euvoicmic hyponatreemia (serum sodium <125mEq/L or less marked hyponatreemia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, SIADH and cirrhosis on September 06th, 2012. [14] Later, on April 30th, 2013 FDA determined that tolvaptan should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially leading to liver transplant or death. [13,15] The study was carried out in 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) as double-blind, three year, placebo controlled trial and its open-label extension trial, a significant increase in serum alanine aminotransferase was observed in 3 patients treated with tolvaptan, along with a concomitant clinically significant increase in serum total bilirubin. In trials the drug was administered in doses of 90mg in the morning and 30mg in the afternoon (maximum daily dose) was higher than the maximum daily dose 60mg approved for the treatment of hyponatreemia. During the first 18 months of therapy most of the liver enzyme abnormalities were observed and all the three patients were improved following the discontinuation of treatment. These 3 cases leaded to the assessment that tolvaptan has either probably or highly likely potential to cause irreversible and potentially fatal liver injury by an external panel of liver experts. [15]

MECHANISM OF ACTION

Tolvaptan is an aquaretic drug which reduces the expression of aquaporin channels as the drug is a vasopressin receptor antagonist which blocks AVP from binding V2 receptors in the distal nephron. Hence the drug leads to an increase in free water clearance, decrease urine osmolality, also cause an increase in serum sodium concentration. This makes tolvaptan very effective in raising serum sodium levels in euvoicmic and hypervolemic patients with hyponatreemia. In humans, metabolites of tolvaptan do not appear to have relevant pharmacological activity at clinical concentrations. [13]

The affinity of tolvaptan towards the V2 receptor is 1.8 fold greater than the native arginine vasopressin and twenty nine times greater selectivity towards V2 receptors than V1a receptors. [11,16] Tolvaptan is known to have little or weak interaction with V1b receptors and the metabolites of the drug have no proven activity on V2 receptors. Plasma
concentrations of native vasopressin may increase to an average between 2 to 9 pg/ml with tolvaptan administration. [11, 13]

PHARMACOKINETICS
At least 40 % of tolvaptan is absorbed after its oral administration. Tolvaptan was not found to have any food interaction and reaches peak concentration within 2 to 4 hours following oral administration. [11,13] The drug is highly protein bound (99 %) with 12 hours of terminal phase half-life. About 2 to 4 hours after oral administration the onset of aquareisis (free water diuresis) and elevation in serum sodium concentration were observed. Peak effect of the drug for aquareisis and increase in serum sodium concentration occurs within 4 to 8 hours of oral administration. The peak effect increases gradually in higher doses up to 60mg beyond which the drug do not exhibit any increase in peak effect. An average of 60% of the peak serum sodium concentration is maintained even at 24 hours after drug administration. Metabolism of tolvaptan occurs in liver and is mainly mediated by CYP450 isoenzyme. Elimination is mainly non-renal with less than 1% of active drug excreted unchanged through urine. For doses between 15 to 60mg tolvaptan shows linear pharmacokinetics. Increased volume of distribution and decreased clearance were observed in moderate to severe hepatic impairment and congestive cardiac failure. Patients with creatinine clearance < 10 mL / min (chronic kidney disease) and patients who are under dialysis were not studied. [11, 13, 16, 17]

STUDIES ON TOLVAPTAN
Study of Ascending Levels of tolvaptan (SALT-1 and -2) evaluated tolvaptan in two identical multicenter, randomized, double-blinded, placebo-controlled studies participating 448 patients with euvolemic or hypervolemic hyponatremia. In patient group treated with tolvaptan the serum sodium concentrations were significantly higher within eight hours after the first administration of tolvaptan than in the placebo group for both the total patient population and for subgroups categorized to degree of hyponatremia at baseline. A significant number of patients attained normal serum sodium level by day 30 under tolvaptan treatment than the placebo treated patients. In both studies urine output was greater in patient group treated with tolvaptan. Thirst and dry mouth were the most common adverse events observed for tolvaptan during the study which is due to the consequence of increased free water clearance. Dizziness, hypotension, acute renal failure, sepsis and ascites were the other
adverse events observed during the study. A decrease in serum sodium levels were observed after discontinuation of tolvaptan treatment. [13, 18]

The Safety and Sodium Assessment of Long term Tolvaptan With hyponatremia (SALTWATER) study evaluated the long term use of tolvaptan in chronic hyponatremia including 111 patients with hyponatremia who received oral tolvaptan for a mean follow up of 701 days. Rapid correction of serum sodium observed in five patients and increased serum sodium concentration was maintained in patients with chronic hyponatremia by prolonged tolvaptan therapy with a modest safety margin. Hypernatremia occurred in one patient. Thirst, dry mouth, pollakiuria and polyuria were the most common adverse events observed during the study. [13, 19]

The effects of tolvaptan in patients hospitalized with heart failure were assessed in The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trials. 4,133 patients were randomized to receive tolvaptan at a dose of 30mg/day or placebo with a mean follow up period of 9.9 months. Tolvaptan treated group showed a rapid improvement of signs and symptoms without serious adverse events. But there was no difference in overall quality of life scores between groups and therefore tolvaptan could not be initial standard therapy in heart failure patients due to evidence observed from EVEREST trials. [20, 21, 22]

Joseph G Verbalis et al analyzed a subgroup of 448 patients with SIADH to evaluate the efficacy and safety of tolvaptan in this group. Improvement in serum sodium was significantly greater in tolvaptan treated group than in placebo group over the first 4 days of therapy as well as the entire 30 day study, with minimal effects of increased thirst, dry mouth, and urination. 5.9% patients had overly rapid correction of hyponatremia. [23]

Vasopressin V2 receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia done by Gheorghiade et al is a randomized study in which tolvaptan alone versus fluid restriction plus placebo in 28 hospitalized patients with serum sodium concentration less than 135mEq/L. Normalization of serum sodium occurred in 50% of patients by day 4 when treated with tolvaptan and by day 8 on fluid restriction. [24]
DOSE & METHOD OF ADMINISTRATION

Tolvaptan should be administered orally with an initial dose of 15mg per day which may be gradually increased up to 60mg per day as tolerated overviewing serum sodium concentration and volume status of the subject. [11, 13] Further dose greater than 60mg per day neither increase aquareasis nor serum sodium concentration. Tolvaptan therapy should be initiated and re-initiated only in hospital setting. [13] Dose titration should be done while monitoring necessary parameters of the patient to achieve desired serum sodium concentration and also to prevent too rapid increase in serum sodium level to avoid cerebral sequel. The treatment of hyponatremia is linked with the underlying disease and its treatment. If desired serum sodium level is not achieved other treatment options should be chosen either in place of or in addition to tolvaptan. If appropriate increase in serum sodium level is observed in the subject, the underlying disease, serum sodium level, volume status should be monitored at regular intervals to assess the need of further treatment. Tolvaptan treatment can be continued until underlying disease is adequately treated or hyponatremia is corrected without any recurrent incidences.

Tolvaptan should be swallowed with a glass of water without chewing. The drug should be given preferably in morning without regard to foods but, should avoid concomitant intake of grapefruit juice. [11, 13]

Dose adjustment of tolvaptan is not required in patients with mild to moderate renal impairment. The safety and efficacy of the drug has not been established in patients with severe renal failure and it is contraindicated in anuric patients. [15] Dose adjustment is not required in elderly patients. Tolvaptan is not recommended in pediatric age group. [13]

There is no reported case of overdose. But prolonged free water clearance is anticipated; hence adequate fluid intake must be maintained. Clinical trials in healthy volunteers demonstrated that single doses up to 480 mg and multiple doses up to 300 mg per day for 5 days have been well tolerated. In rats and dogs oral median lethal dose (LD₅₀) was >2000 mg/kg. No mortality was observed in single oral doses up to 2000 mg/kg (maximum feasible dose) in rats and dogs. But, in mice a single oral dose of 2000 mg/kg was lethal and the symptoms of toxicity observed in mice were locomotor activity, staggering gait, tremor and hypothermia. [11, 13]
Tolvaptan is contraindicated in hypersensitivity to tolvaptan, volume depletion, anuria, hypovolemic hyponatremia, hypernatremia, patients who cannot perceive thirst, underlying liver disease, pregnancy (Studies have shown reproductive toxicity in animals. No adequate data for use in pregnant women.), breast feeding (studies in rats have shown excretion of tolvaptan in breast milk). [11, 13]

In fluid restricted patients extra caution should be taken while administering tolvaptan that the patient does not become overly dehydrated. In patients with partial obstruction of urinary flow there is a high risk of developing acute retention. Patients with very low baseline serum sodium concentrations may have an increased risk of rapid correction of serum sodium (≥ 12 mmol/l/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriplegia, seizures, coma, death. Patients should be closely monitored more frequently for serum sodium concentration and volume status. Patients with Diabetes mellitus may present pseudohyponatremia due to elevated glucose concentration. Such conditions should be excluded before and during tolvaptan therapy. Patients having inadequately controlled type II Diabetes should be managed cautiously. Tolvaptan may cause hypoglycemia. As tolvaptan may occasionally cause dizziness, asthenia or syncope it is better to avoid driving vehicles or using machines. [11, 13, 15]

INTERACTIONS OF TOLVAPTAN
Tolvaptan is CYP3A4 substrate which has no effect on the plasma concentrations of some other CYP3A4 substrates like warfarin, amiodarone etc. Strong CYP3A4 inhibitors increase plasma concentration of tolvaptan up to five fold. Caution should be taken while co administering CYP3A4 inhibitors like ketoconazole, macrolide antibiotics, diltiazem etc. with tolvaptan. When tolvaptan is administered along with grapefruit juice, 1.8 fold increases in the absorption of Tolvaptan was observed. [13] Hence patients should avoid ingesting grapefruit juice while under Tolvaptan therapy. CYP3A4 inducers such as rifampicin, barbiturates etc. decreases plasma concentration of tolvaptan up to 87%, hence caution should be exercised. [11]

ADVERSE REACTIONS
Adverse reaction profile of tolvaptan is based on clinical trial data base which consisted 3294 patients treated with tolvaptan and it was consistent with the pharmacology of the active substance. Frequencies are categorized in to very common ≥1/10, common ≥1/100 to <1/10
and uncommon ≥1/1000 to <1/100. The most commonly reported as well as pharmacologically predictable adverse reactions include thirst, dry mouth and pollakiuria occurring in approximately 18%, 9% and 6% of patients. [11] Common adverse drug reactions observed were polydipsia, hyperkalemia, dehydration, hyperglycemia, decreased appetite, orthostatic hypotension, nausea, constipation, dry mouth, ecchymosis, polyuria, thirst, asthenia, pyrexia, increased blood creatinine, rapid correction of hyponatremia sometimes leading to neurological symptoms. Uncommon adverse reactions included dysgeusia, pruritic rash. [11, 13]

Undesirable effects observed in clinical trials while investigating for other indications were hypernatremia, hypoglycemia, hyperuricaemia, syncope, dizziness, headache, malaise, and diarrhea. [11]

CONCLUSION
Tolvaptan significantly proved to improve serum sodium concentration in patients with mild as well as marked euvoletic or hypervolemic hyponatremia. The drug was able to maintain raised serum sodium concentration while prolonged therapy in patients with chronic hyponatremia at a modest margin of safety. Tolvaptan is contraindicated in patients with underlying liver disease due to risk of liver injury and the drug should be initiated and reinitiated only in a hospital setting which can also help in the dose titration based on the changes in serum sodium concentration.

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