Research Article

A Study on Safety and Efficacy of Tolvaptan in Hyponatremic Patients with Urinary Sodium Loss

Remya Reghu*[1], Sai keerthana PC[1], Aparna R Das[1], Neethu C.M[1], Tiny Joseph[1], Arun Kumar K[2], Ajith Venugopal[2], Sreekrishnan TP[3], Gireesh Kumar KP[4]

[1*]Lecturer, Dept of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, Kochi, Kerala.

[1]Pharm D students, Dept of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, Kochi, Kerala.

[4]HOD, Department of Emergency Medicine, AIMS Health Sciences Campus, Amrita Vishwa Vidyapeetham, Kochi, Kerala.

[2]MD Resident, [3]Assistant Professor, Dept of Emergency Medicine, Amrita Vishwa Vidyapeetham, Kochi, Kerala.

***Corresponding author's E-mail:** remyareghu@aims.amrita.edu

Accepted on: 22-03-2016; **Finalized on:** 30-04-2016.

ABSTRACT

The aim of the study was to find out drug related problems with a special focus on ADRs during Tolvaptan administration and also to assess the change in serum (Na+) levels, improvement in physical and mental functioning of patients before and after Tolvaptan administration. A total of 74 patients prescribed with Tolvaptan were selected during the study period and their data relevant to the study was collected which includes urine sodium, serum sodium, serum osmolarity, urine osmolarity, liver function test, renal function test, was collected. 12 –item short-form (SF-12) General Health Survey Questions and Glasgow coma scale were used for mental and physical functioning assessment after drug entry. Adverse event that occurred includes Thirst (21 patients), Dry mouth (7 patients), and Hyperkalemia (7 patients) and all events was confirmed using Naranjo probability ADR scale in which causality for majority of adverse event was probable (5-9). Out of 74, 15 patients who were admitted directly to the intensive care unit (ICU), 14 patients (93.3%) were shifted within 3days of treatment with Tolvaptan to the ward and remaining one was shifted on day 5. The primary efficacy outcome in the study was change in average serum sodium concentration baseline to day 3, 5, and 7. The patient on Tolvaptan exhibited a highly significant improvement in serum sodium from base line to 7th day. The effect of Tolvaptan on SF12 General Health Survey was examined and a remarkable increase in Physical Component Score (PCS) and Mental Component Score (MCS) was found after treatment. The vasopressin receptor antagonist, Tolvaptan was superior in raising and maintaining serum sodium (Na+) in patients with hyponatremia with minimal side effects and can be safely administered without any major concerns at a dose of 15mg OD for 7 days.

Keywords: Tolvaptan; Safety; Efficacy; Hyponatremia; Sodium.

INTRODUCTION

Hyponatremia is one of the most common electrolyte aberrations in clinical practice.[1] Management of hyponatremia is imperative since severe hyponatremia can cause substantial morbidity and mortality and is notably higher in patients with underlying disease conditions like congestive heart failure, cirrhosis, neurological diseases etc[2,3]. Tolvaptan, a vasopressin receptor antagonist (VRAs or "vaptans") directly target stimulated arginine vasopressin (AVP) receptors in the collecting duct of the kidney. The drug was approved by FDA on May 2009. In view of worrisome adverse effects of Tolvaptan seen in clinical trials, including elevated liver enzyme levels, the high cost (Rs 223.09/for 7days) Tolvaptan is under used in clinical practice[4]. FDA has determined that the drug 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 hepatic failure. The present work was designed to study safety and efficacy of Tolvaptan in hyponatremic patients with urinary sodium loss with a special focus on drug related problem and to assess the change in serum (Na+) levels, improvement in physical and mental functioning of patients before and after Tolvaptan administration[5]. On these perspectives, the study was focussed on how Tolvaptan can be used effectively in hyponatremic patients to provide symptomatic relief with minimal adverse events and reduce the length of hospital stay. Lastly, statistical tests were used to examine the various relationships between the study parameters[6].

MATERIALS AND METHODS

The study was conducted in the Department of Emergency medicine, Amrita institute of medical sciences, a 1200 bedded tertiary care referral hospital in Kochi. The study is a prospective non experimental (observational) study.

The study was approved by the Institutional Ethical Committee. The patients were selected based on the following inclusion and exclusion criteria.

Inclusion criteria

1) Hyponatremia in euvolemic or hypervolemic state, defined as serum sodium less than 135meq/L prior to randomisation.

2) Urine sodium loss greater than 20 mg/dl.

Exclusion criteria

1) Women who are pregnant and breast feeding.

2) Acute and transient hyponatremia associated with head trauma or Postoperative state.

3) Hypersensitivity to Tolvaptan.

4) Anuric patients/hypovolemic hyponatremia.

Sample size

Sample size for the study was determined using the formula n>Z2PQ/d2 as per biostatistician.

The minimum sample size worked out for the study is 74.

Data collection tools

1) Data collection form

Patients data relevant to the study was collected from electronic medical record data base via Amrita Hospital Information System (AHIS) and also by direct interview of the patients using a data collection form. The data collection form includes patients demographic details like age, gender, risk factors of hyponatremia, past medication history of Tolvaptan, co morbidities and various management patterns adopted for hyponatremia, and any drug related problems occurred during treatment. Details regarding urine sodium, serum sodium, serum osmolarity, urine osmolarity was collected from Department of Biochemistry and Emergency medicine. Apart from these parameters laboratory investigation reports like renal function test, liver function test were also assessed.

2) 12 –item short-form (SF-12) General health survey questions

12–item short-form (SF-12) General health survey for mental and physical functioning assessment. SF-12 is a generic measure and does not target a specific age or specific disease group. It has been developed to provide a shorter, a yet valid alternative of SF-36. The SF 12 is weighed and summed to provide easily interpretable scale for physical and mental health[7,8,9].

3) Naranjo scale for causality assessment of ADRs.

The scale was used to standardise assessment of causality for all adverse drug reactions. The ADR probability scale consist of 10 questions that are answered as either Yes, No, or don't know. Different point values (-1, 0, +1 or +2) are assigned to each answer. Total score ranges from -4 to +13, the reaction was considered as Definite (if the score is 9 or higher), Probable (if 5 to 8), Possible (if 1 to 4) and Doubtful (if 0 or less)[10].

4) Glasgow coma scale (GCS)

Glasgow coma scale is the most common scoring system used to describe the level of consciousness in patients. Basically it is used to help gauge the severity of acute brain injury. Gcs measures following functions eye opening, verbal and motor functions[11,12,13].

Assessment of efficacy

Patients sodium levels were evaluated at base line, thereafter on days 3, 5 and 7. Efficacy assessment includes change in base line serum sodium level to days 3,5,and 7, change in body weight if edema present, change from base line scores in Glasgow Coma Scale(GCS), change from base line score on Physical Component Summary(PCS) and Mental Component Summary(MCS)of the medical outcomes study 12-item short –form (SF-12) General health survey.

Assessment of safety

Safety was assessed by observing the drug related problems especially ADRs, laboratory values and vital signs. The causality of adverse drug reactions were evaluated using Naranjo ADR probability scale.

Statistical analysis

The collected data were compiled using Microsoft Word, Microsoft Excel and were presented in graphical format using pie charts, histograms, bar diagrams etc. Calculation of mean±SD were done using statistical calculators.

Because there was no placebo or drug comparator, all statistical comparisons were made with base line changes. The significance of the results were done using paired t-test.

RESULTS

This study comprised of data from 74 patients with hyponatremia who were admitted in Emergency medicine department of a teritiary care teaching hospital during the year 2014-2015.

About 46 patients out of 74 were under the age group of 61 to 80 years, 14 patients under 40-60 years and 12 patients under >80 years. The mean age was found to be 66.3±12.4 years.

In this study we found out that male patients were predominant (59.4%) than females (40.5%)

Table 1: Patients admitted with edema

Edema	No. of Patients (n=74)	Percentage (%)
Present	17	22.9
Absent	57	77.02

Table 1 represents the No. of patient's admitted with edema and figure 1 represents change in body weight of patients admitted with edema. 14 (82%) of them had a significant weight loss which indicates edema was resolving and for 2 patients (12%) there was weight gain and for 1 patient (6%) there was no significant change in weight.

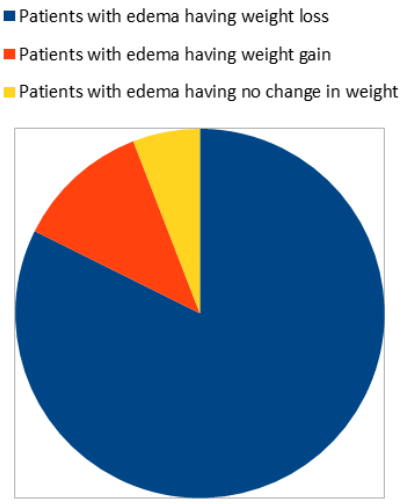

Figure 1: Change in body weight of patient admitted with edema

The patients were categorized according to their sodium levels as Mild hyponatremia (135-130meq/l), Moderate hyponatremia (130-125 meq/l) and Severe hyponatremia (<125meq/l).

In this study 72% patients had severe hyponatremia during the initiation of therapy (Table 2).

Table 2: Classification of Hyponatremia

Hyponatremia	No. of Patients (n=74)	Percentage (%)
Mild (135-130meq/l)	1	1
Moderate (130-125meq/l)	20	27
Severe (<125meq/l)	53	72

In the present study, co-morbid condition was found in 65 patients. 16 patients (22%) were suffering from single co morbid condition, 18 patients (24%) had 2 co morbid conditions, 23 had 3 co-morbidities (31%) and 16 (22%) patients were suffering from more than three co morbid condition. Majority of patients (31%) were suffering from 3 co morbid condition.

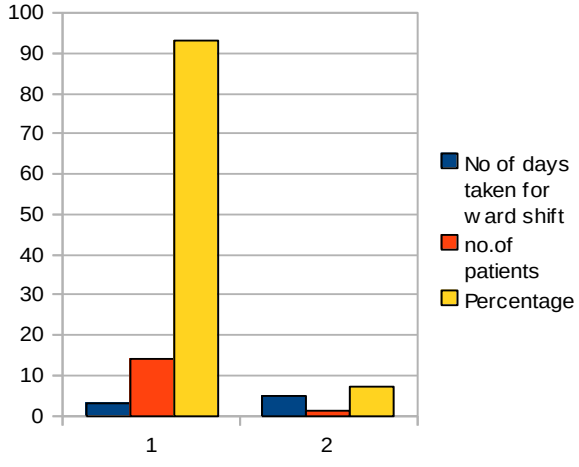

Figure 2: No. of days taken for ward shift

During study period out of 74, 15 patients were admitted directly to the Intensive Care Unit (ICU). In this, 14 patients (93%) were shifted within 3 days of treatment with Tolvaptan to the ward and remaining one was shifted on day 5 (Figure 2).

Mean hospital stay of patients was found to be 12 days which also showed the safety and efficacy of the same. Length of hospital stay (LOS) was not an outcome measure in most of the other studies but in this we have included it as one[14] Table 3 represents the number of days of hospitalization.

Table 3: No. of days of Hospitalisation

No.of days	No of Patients(n=74)	Percentage(%)
≤7	21	28.3
8-14	31	42
15-21	16	22
22-28	3	4.0
>28	3	4.0

Various treatment modalities were adopted for hyponatremia. As per the present study, 54 patients were treated with Tolvaptan alone (72.9%), 15 patients with Tolvaptan and 3% normal saline (20.2%), and 4 with Tolvaptan and added salt (5.55%) for hyponatremia. From this we could understand mean sodium level was higher for those patients who were treated with Tolvaptan and added salts. During the follow up time of Tolvaptan 35 of 74 patients experienced an adverse event. Adverse event that occurred includes Thirst (21 patients), Dry mouth (7 patients), Hyperkalemia(7 patients). In this study the most common adverse drug reaction observed was Thirst (60%). (figure 3)

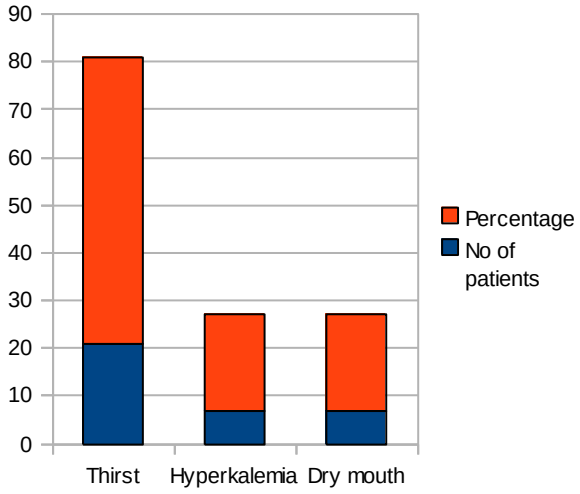

Figure 3: Adverse drug reactions

Figure 4 depicts mean sodium level after Tolvaptan administration on day 1 mean sodium level was found to be 121+6.8, on day 3 it was 125+ 5.9, on day 5 was 128+5.1 and on day 7 was 131.4+4.9. This indicated that there is an increase in mean sodium level after the drug

administration from baseline. P value was <0.001 which showed that the result was significant.

Patient's self assessed health status was determined at baseline and day 7 using SF 12 General Health Survey. In this study there is a positive increase in Physical Component Score (PCS) and Mental Component Score (MCS) in SF12 of patients from day 3 to day 7 (Table 3) during treatment.

The mean MCS score on day 3 was 46.9±5.7 and that on 7th day was found to be 47.2. The mean PCS score on day 3 was 35.6± 7.2 and that on day 7 it was found to be 41±6.7. Change from baseline for MCS was 0.3± 0.1 and for PCS was 5.4±0.5.

The P value for PCS is 0.001 hence the result was significant and P value for MCS was found to be 0.06 which showed that the result was not significant.

Table 3: SF12 Assessment

Days	Mean MCS	P value for MCS	Mean PCS	P value for PCS
3	46.9±5.7	0.06	35.6±7.2	0.001
7	47.2±5.8		41±6.7	

The Glasgow Coma Scale used for assessing level of consciousness was done on day 1, 3, 5 and 7 and compared the GCS score of the first day with seventh day which showed a positive improvement in eye opening, verbal and motor response by the patient after drug entry. On the 7th day of GCS assessment it was found that majority of patients were under mild classification which showed an improvement in their eye, verbal, and motor responses from day 1 to day 7.

DISCUSSION

In our study we prospectively evaluated the safety and efficacy of Tolvaptan in hospitalized patients with hyponatremia. Sample size calculated for the study was not less than 74. The study extended over a period of approximately 8 months. Majority of patients in this study comes under the age group 61-80 years with a mean age of 66.3±12.4 years and also the male patients were predominant than females.

Hyponatremia can also occur as a result of co morbid conditions. Co morbidity has been shown to intensify health care utilization and to increase medical care costs for patients[15]. In the present study, co-morbid condition was found in 65 patients. Majority of patients were observed to be suffering from at least 3 co morbid conditions of which hypertension was the most common.

Treatment with diuretics for hypertension can also lead to hyponatremia[1,17,18].

Most of our patients had severe hyponatremia during the initiation of Tolvaptan. Mean dosage of Tolvaptan was 15mg/day[16].

All 74 patients were analyzed for safety and efficacy. Mean follow-up time on Tolvaptan therapy was 7 days. During this time 35 of 74 patients experienced an adverse event. Adverse event that occurred include thirst (21 patients), dry mouth (7 patients), hyperkalemia (7 patients). Most common adverse event assessed potentially related to Tolvaptan use was thirst (21 patients) and all the adverse events was confirmed using Naranjo Probability ADR Scale in which causality for majority of adverse event was probable (5-9). Thirst may be associated with increased aquaresis which leads to dehydration and will stimulate the thirst centre[11,19].

Treatment with Tolvaptan is associated with an acute reduction of extracellular fluid volume which could result in increased serum potassium. Serum potassium level should be monitored after initiation of Tolvaptan treatment in patient with a serum potassium greater than 5 meq/Litre as well as those who are receiving drugs known to increase the level of the same[13-16]. No consistent and clinically meaningful changes were observed in serum chemistries (other than serum sodium, ser potassium) during study.

Out of the 74 patients treated with Tolvaptan the correction time of sodium over the 48 hours was found to be 3.82 meq/L. The continued concern of all treatment used to correct hyponatremia has the potential to cause osmotic demeylination with rapid correction of hyponatremia[17]. Multiple clinical studies have provided guidances on the correction rates that increase the risk of adverse outcomes. This study shows that no patients treated with Tolvaptan exceeded the limits (the correction rate should not be exceeded 12 mmol/litre over 24 hrs and 18 mmols/litre over 48 hours). Inappropriate elevation of arginine vasopressin, plays a key role in mediating water retention, electrolyte imbalance[20].

Tolvaptan was effective most likely because of its impact on fluid balance. Consistent with its mechanism of action, it influenced the primary end point mainly by reducing body weight and maintaining serum sodium[18,19].

The primary efficacy outcome in the study was change in average serum sodium concentration baseline to day 3, 5, and 7. The patient on Tolvaptan exhibited a highly significant improvement in serum sodium from base line (120.7+6.78), 3rd day (124.6+5.98), 5th day (128.1+5.18) and 7th day (131.4+4.59).

In addition to an increase in serum sodium, the effect of Tolvaptan on SF12 General Health Survey was examined and there was a markable increase in Physical Component Score (PCS) and Mental Component Score (MCS) was found after treatment. Glasgow Coma Scale used for

assessing level of consciousness also showed improvement in eye opening, motor and verbal responses during the treatment. Decrease in body weight was approximately 0.21kg for patients who were having edema at time of treatment with Tolvaptan.

CONCLUSION

Many of the therapies that are available to treat euvolemic and hypervolemic hyponatremic disorders are fraught with adverse effect and/or limited effectiveness, the advent of orally active inhibitors of the vasopressin 2 receptor represent a welcome addition to other therapies. The vasopressin V2 receptor antagonist Tolvaptan was superior in raising and maintaining serum sodium (Na+) in patients with hyponatremia[20]. Tolvaptan was generally well tolerated, having minimal side effects consistent with its physiological activity and could be safely titrated to achieve the desired rate and degree of serum sodium (Na+) levels avoiding overly rapid correction. Clinical benefits of Tolvaptan therapy include decreased length of hospital stay and improved self reported physical and mental functions. Accordingly, the study indicated that Tolvaptan can be safely administered without any major concerns at a dose of 15mg/day for 7 days in hyponatremic patients.

REFERENCES

1. Hyponatremia: Get the facts on symptoms and treatment, 2015. (Accessed on may 3, 2015, at http://www. medicinenet.com/hyponatremia/article.html)
2. Overview of treatment of hyponatremia in adults, 2015.(Accessed on April6, 2015, at http:// www.uptodate.com/contents/overview of treatment of hyponatremia in adults.)
3. Hyponatremia: Practice essentials, background, pathophysiology, 2015. (Accessed on April 24, 2015, at http.//emedicine.medscape.com/article/242166-overview)
4. Med calc.serumosmolarity calculator, 2000. (Acessed on may 2015 on http//www.medcalc.com/osmol.html)
5. Biswas M, Davies J .Hyponatremia in clinical practice. Postgrad Med J 2007; 83: 373-378.
6. Martinez Marco J. Hyponatremia: classification and differential diagnosis. Endocrinol Nutr, 57, 2010, 4-16.
7. Serum and renal osmolality, 2015 (Accessed on May 16, 2015, at http://www.rnceus.com/renal/renal osmo.html.
8. Rose BD. New approach to disturbances in the plasma sodium concentration. AM J, 81, 1986, 1033-40.
9. Kumar S, Beri T The sodium Lancet, 352, 1998, 220-8.
10. Overview of hyponatremia, 2014 (Accessed on may 30, 2015, at http://emedicine.medscape.com/article /2088250-overview
11. Rose BD. Hypo osmolal state: clinical physiology of acid–base on the electrolyte disorders. 5th ed. Newyork:McGraw Hill, 2001, 696-745.
12. Mange K, Matsuura D, Cizman B, Language guiding therapy: the case of dehydration versus volume depletion. Ann Intern Med 127, 1997, 848-53.
13. Weisberg LS. Pseudohyponatremia: a reappraisal. Am J Med, 89, 1989, 315-8.
14. Allan B wolfson, Marx A John, Hockberger S Robert. Rosen's emergency medicine: concepts and clinical practice, 7th edition Philadelphia:Mosby/Elsevier 627-628.
15. George Lackerman, Walker H.K, Hall WD Clinical methods: The history, physical and laboratory examinations, 3rd edition. Boston: Butterworths 879-883.
16. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. SeminNephronl, 29, 2009, 282-99.
17. Kerns E, Patel S, Cohen DM. Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia. ClinNephrol, 382, 2014, 97.
18. Verbalis JG, Goldsmith SR, Greenberg A. Hyponatremia treatment guidelines: expert panel recommendations. AM J Med, 120, 2007, S1-21.
19. Shimizu K. Aquarectic effects of the non peptide V2 antagonist OPC-31260 in hydropenic humans. Kidney Int, 48, 1995, 220-6.
20. Matsuhisa A, Tanijuchi N, Koshio H. A non peptide arginine vasopressin antagonist for both V1 A and V2 receptors: synthesis and pharmacological properties of 4-(1,4,5,6-tetrahydroimidazo(4,5-d)benzoazepine-6-carbony)benzanlin derivatives and '-(5,6-dihydro 4 H-thiazola(5,4- d)benzoazetine-6 carbonyl)benzanilide derivatives. ChemPharm Bull Tokyo, 48, 2000, 21-31.

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