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

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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 osmolality, urine osmolality, 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 (S-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. 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. 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. 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 hyponatreic 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. On these perspectives, the study was focussed on how Tolvaptan can be used effectively in hyponatreic 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.

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

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).

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.

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 tertiary 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

<table>
<thead>
<tr>
<th>Edema</th>
<th>No. of Patients (n=74)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>17</td>
<td>22.9</td>
</tr>
<tr>
<td>Absent</td>
<td>57</td>
<td>77.02</td>
</tr>
</tbody>
</table>

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

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

Table 2: Classification of Hyponatremia

<table>
<thead>
<tr>
<th>Hyponatremia</th>
<th>No. of Patients (n=74)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (135-130 meq/l)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (130-125 meq/l)</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Severe (&lt;125 meq/l)</td>
<td>53</td>
<td>72</td>
</tr>
</tbody>
</table>

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.

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. Table 3 represents the number of days of hospitalization.

Table 3: No. of days of Hospitalisation

<table>
<thead>
<tr>
<th>No. of days</th>
<th>No of Patients (n=74)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>21</td>
<td>28.3</td>
</tr>
<tr>
<td>8-14</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>15-21</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>22-28</td>
<td>3</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt;28</td>
<td>3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

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)
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.

Table 3: SF12 Assessment

<table>
<thead>
<tr>
<th>Days</th>
<th>Mean MCS</th>
<th>P value for MCS</th>
<th>Mean PCS</th>
<th>P value for PCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>46.9±5.7</td>
<td>0.06</td>
<td>35.6±7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>7</td>
<td>47.2±5.8</td>
<td></td>
<td>41±6.7</td>
<td></td>
</tr>
</tbody>
</table>

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. 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.

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

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 aquareasis which leads to dehydration and will stimulate the thirst centre.

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. No consistent and clinically meaningful changes were observed in serum chemistries (other than serum sodium, 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 dememyllation with rapid correction of hyponatremia. Multiple clinical studies have provided guidelines 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.

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.

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. 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 se

REFERENCES


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