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Original Article

Adverse Drug Reaction Profile of Tolvaptan in Patients with Hyponatremia in a Tertiary Care Centre: A Prospective Observational Study

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ABSTRACT

Objectives
Primary objective

1) To find out the adverse drug reaction profile of Tolvaptan in hyponatremic patients.

Secondary objectives

2) To find out the effect of Tolvaptan on urine output in these patients.

Methods & materials: This prospective observational study was conducted in the Department of Internal Medicine, involving thirty consecutive patients, both sexes, ≥ 18 years, with hyponatremia, prescribed 15mg Tolvaptan once daily. On day 1 and day 4, adverse effects and urine output were recorded Causality of ADR was determined using Naranjos Algorithm.. The data was analyzed using SPSS version 27. Quantitative variables were expressed as mean and standard deviation and qualitative variables as proportion with 95% confidence interval. Change in Serum sodium levels and Urine output was analyzed using Paired 't' test.

Results: Thirst, dry mouth, fatigue, vomiting and hypernatremia were the adverse effects observed. Mean increase in urine output was 976.67±472.29 ml ($p<0.001$) by day 4.

Conclusion: Tolvaptan has caused only mild adverse effects and produced significant increase in urine output in patients with hyponatremia.

Keywords*: Tolvaptan; Hyponatremia; Urine output; Adverse effects.*

INTRODUCTION

Tolvaptan is a non-peptide vasopressin V_2-receptor antagonist which suppresses the water reabsorption by inhibiting the V2 receptors in the renal collecting duct. There by it promotes diuresis without significant electrolyte loss. Tolvaptan is used in clinically significant hypervolemic and euvolemic hyponatremia including conditions such as heart failure, cirrhosis and syndrome of inappropriate antidiuretic hormone secretion (SIADH). [1,2]. Tolvaptan is approved for the treatment of autosomal dominant polycystic kidney disease (ADPKD) in the United States and Japan, as it reduces the growth and size of renal cysts, by inhibiting the action of vasopressin in the kidneys thereby slowing the progression of renal function deterioration.[3] Widespread use of tolvaptan in clinical settings inevitably presents some adverse effects. Common side effects including thirst, dehydration, increased urine output, hypernatremia, and potential hepatotoxicity. [4] In 2013, a safety alert was issued by FDA indicating that tolvaptan carries a risk of serious and potentially fatal liver injury.[1]

The rationale behind conducting this study is therefore to obtain a reliable data regarding the safety of Tolvaptan in hyponatremic patients so as to ensure better patient care and thereby improve their quality of life as hyponatremia is aprevalent in clinical practice and tolvaptan is being widely used in the treatment of hyponatremia in our setting.

METHODS & MATERIALS

Study design

This was a prospective observational study carried out for a duration of 18 months in the Department of Internal Medicine.

Study population
A total of 30 patients were recruited. Consecutive patients admitted in Department of Internal Medicine, GMC, Thiruvananthapuram with hyponatremia, satisfying the inclusion and exclusion criteria and initiated on Tolvaptan during the study period were included in the study, until the sample size was met.

Inclusion criteria:
- Patients of both sexes, 18 years and above, admitted with hyponatremia, due to any etiology, initiated on Tolvaptan 15mg once daily and willing to give informed consent.

Exclusion criteria:
- Patients with psychogenic polydipsia, liver diseases, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency, or iatrogenic hyponatremia.
- Patients on hypertonic saline.
- Patients whose doses of diuretics are changed during the study period.

Study procedure
The study was initiated after obtaining approval from the Institutional ethics committee and was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines. In our setting, patients with serum sodium levels <135mEq/L, who are symptomatic, are treated with Tolvaptan 15mg once daily initially. If the desired response (an increase in S.Na of more than 4mEq/L in 24 hours) is not seen, then the dose would be escalated to 30 mg, 45mg and 60 mg at every 24 hours interval by the treating clinician. But in this study, only those patients on 15mg once daily Tolvaptan were included. On day 1 and day 4, patients were asked for any adverse effects like thirst, dry mouth, headache, vomiting, fatigue, etc and serum sodium levels, values of renal function and liver function tests were noted from the case sheet at basal level (before initiating Tolvaptan) and at day 4 of therapy, in the case record form. Naranjo algorithm was used to determine the causality of the adverse drug reactions noted. Urine output was also noted down from the case sheet at basal level and at day 4 of therapy.

Statistical analysis
Data was entered in the Excel sheet. Qualitative variables were expressed as proportion with 95 percentage confidence interval. Quantitative variables were expressed as mean and standard deviation. Analysis of data was done using SPSS version 25.0. Change in urine output was analyzed using Paired 't' test.

RESULTS
I)Demographic details
The mean age of the study population was 66.27 ± 8.38 years. Analysis of gender distribution in this study showed that out of 30 patients, 18 were females (60%) and 12 were males (40%). (Figure1)

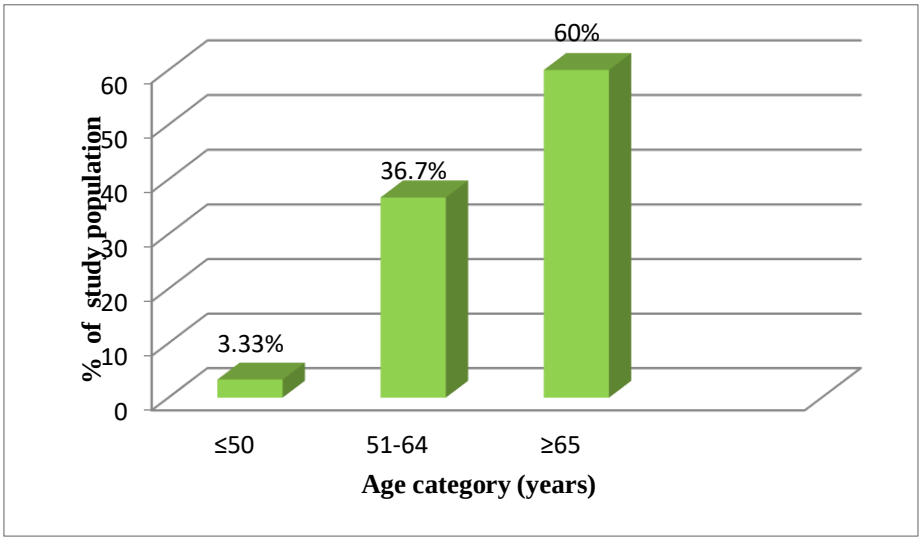

Figure 1: Age distribution of the study population

II)Primary diagnosis
By analyzing the data on primary diagnosis of the patients included in this study, following observations were made as recorded in Table1.

Among 'others' recorded in Table 1 (6 patients), one patient had hypoglycemic encephalopathy, one had exacerbation of COPD (chronic obstructive pulmonary disease) and 4 others were having varying degrees of hyponatremia with other comorbidities.

Table 1: Distribution of study population based on primary diagnosis

Diagnosis	Male	Female	Total (n=30)	Percentage of study population
CAD	2	3	5	16.7
CVA	3	3	6	20
CHF	1	3	4	13.3
Tropical fever	0	3	3	10
COVID	2	1	3	10
SIADH	3	0	3	10
Others	1	5	6	20

III) Adverse effects

Thirst, dry mouth, fatigue, hypernatremia, and vomiting were the adverse effects observed in this study (Figure 2). The drug was discontinued in patient with hypernatremia (in this patient baseline serum sodium was 124mEq/L and 146mEq/L on day 4). There were no patients with derangement in the liver function test and renal function test. There were no reports of any serious adverse events. Causality of each adverse reaction observed was determined using Naranjo algorithm. (Table 2)

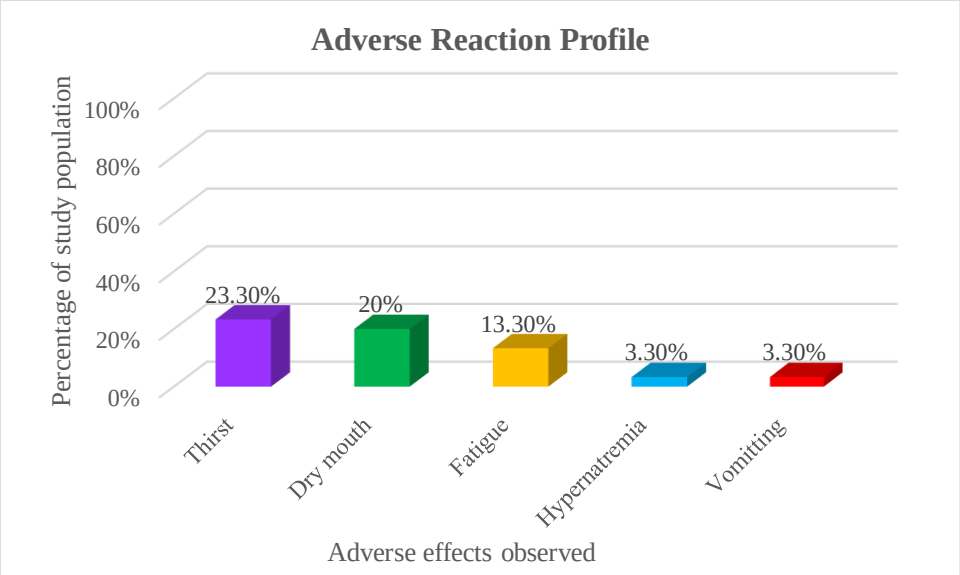

Figure 2: Adverse drug reaction profile

Table 2: Causality of adverse effects observed

Adverse reaction	% of study population (No. of patients) N=30		
	Probable	**Possible**	**Doubtful**
Thirst	20 (6)	3.3 (1)	-
Dry mouth	16.7 (5)	3.3 (1)	-
Fatigue	-	3.3 (1)	10 (3)
Vomiting	-	3.3 (1)	-
Hypernatremia	3.3(1)	-	-

IV) Urine output in study population

In the study population, the mean urine output at baseline (before tolvaptan) was 1256.67± 364.77ml and on day 4 was 2233.33± 495.03ml. (Figure 3) There was a mean increase of 976.67± 472.29 ml by day 4 and this increase in urine output was statistically significant ($p<0.001$).

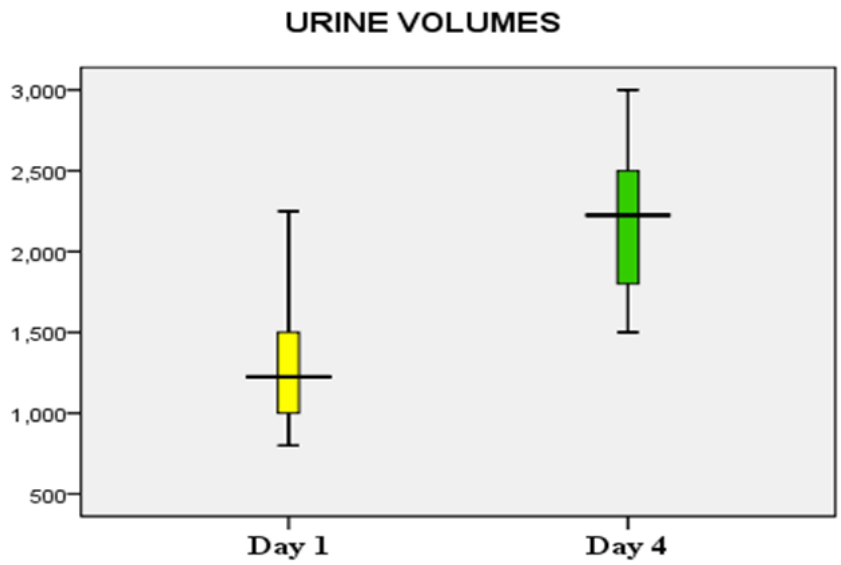

Figure 3: Mean Urine output in study population on day one and day four

DISCUSSION

Tolvaptan is a commonly used drug in the treatment of hyponatremia due to various etiologies. A retrospective study done in patients with heart failure reported that tolvaptan rapidly increased the urine output , improved the hyponatremia and alleviated the congestive symptoms and overall tolerability was good with common side effects including dry mouth and thirst, and rare incidence rate of hypernatremia.[5]In a study by Verbalis et al, adverse effects were thirst in 17.6% , dry mouth in 15.7% , fatigue in 9.8% and vomiting in 2%, along with other adverse events like pollakiuria, headache, nausea, peripheral edema , diarrhea and constipation over a 30 day period.[6] In a study conducted in Korea the adverse effects seen with Tolvaptan therapy were dry mouth (45%), thirst (26%), pollakiuria (18%) and overcorrection (13%).[7]In our study, by analyzing the adverse drug reaction profile of the study population we observed that thirst and dry mouth were the most common adverse effects. Thirst was seen in 23.3%, dry mouth in 20%, fatigue in 13.3% hypernatremia in 3.3%, and vomiting in 3.3%. In our study we have also assessed the causality of the above mentioned adverse reactions using Naranjos algorithm. Of the most common adverse reactions reported in this study- thirst (23.3%)- the causality was 'probable' in 20% and dry mouth (20%) –the causality was 'probable' in 16.7%.

In a meta-analysis, tolvaptan therapy has shown an improvement in 24 hour urine output with a mean difference of about 987.64 ml. [8]A study conducted by Komiya et al, in a group of 21 patients with CHF and CKD, average urine volume at baseline was 975ml which got increased to 1426 ml after 1 week of Tolvaptan treatment.[9]In another study by Umbrello et al , he observed an increase in urine output by 1.5 litres in patients on Tolvaptan with low urine sodium, indicating free water diuresis.[10] In our study, there was a mean increase of 976.67 ± 472.29 ml in urine output by day 4, which was statistically significant ($p<0.001$).

CONCLUSION

This was a prospective observational study done to find out the adverse drug reaction profile of tolvaptan conducted in the department of Internal Medicine. In this study, we observed the occurrence of adverse reactions like thirst, dry mouth, fatigue, hypernatremia and vomiting. These finding suggests healthcare professionals should exercise caution while prescribing tolvaptan and patients should be made aware of these adverse reactions. Further studies should be conducted in larger population for a longer duration to ensure the long term safety of the drug.

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