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Therapeutic Efficacy and Safety Profile of Tolvaptan Administered In Hyponatremia Patients

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ABSTRACT

Hyponatremia is an electrolyte disturbance in which the sodium ion concentration in the serum is lower than normal. Sodium is the dominant extracellular cation (positive ion) and cannot freely cross from the interstitial space through the cell membrane, into the cell. Its homeostasis (stability of concentration) inside the cell is vital to the normal function of any cell. Normal serum sodium levels are between 135 and 145 mEq/L. Hyponatremia is defined as a serum level of less than 135 mEq/L and is considered severe when the serum level is below 125 mEq/L. In the vast majority of cases, Hyponatremia occurs as a result of excess body water diluting the serum sodium (salt level in the blood). Hyponatremia is often a complication of other medical illnesses in which excess water accumulates in the body at a higher rate than can be excreted (for example in congestive heart failure, syndrome of inappropriate antidiuretic hormone, SIADH, or polydipsia). Sometimes it may be a result of over hydration (drinking too much water). Lack of sodium (salt) is very rarely the cause of Hyponatremia, although it can promote Hyponatremia indirectly. In particular, sodium loss can lead to a state of volume depletion (loss of blood volume in the body), with volume depletion serving as a signal for the release of ADH (anti-diuretic hormone). As a result of ADH-stimulated water retention (too much water in the body), blood sodium becomes diluted and Hyponatremia results.

Keywords: Tolvaptan, Hyponatremia, Syndrome of insufficient anti diuretic hormone (SIADH), euvolemic Hyponatremia.

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INTRODUCTION

Hyponatremia, the most common electrolyte derangement occurring in hospitalized patients, is usually classified as hypovolemic, euvolemic, or hypervolemic. The secretion of arginine vasopressin appears to be of central importance in the decline of serum sodium concentrations in all these conditions. Hyponatremia is reported to be associated with increased morbidity and mortality among patients with heart, liver, or neurologic disease. Even mild chronic hyponatremia has been associated with subtle neurologic defects, manifested as impairments in balance and attention that can increase the incidence of falls. These deficits may be reversed with the correction of the hyponatremia¹

Tolvaptan, a novel, orally active, selective, nonpeptide antagonist that blocks arginine vasopressin from binding to V₂ receptors of the distal nephron, induces the excretion of electrolyte-free water without changing the Verbalis JK.et.al¹total level of electrolyte excretion. In patients with heart failure, tolvaptan appears to decrease body weight and edema and increase serum sodium concentrations without adversely affecting serum electrolyte levels, vital signs, or renal function.

Volume overload and hyponatremia cause significant morbidity and may lead to increased mortality in patients with the syndrome of inappropriate antidiuretic hormone (SIADH), congestive heart failure, and liver cirrhosis. Elevated levels of arginine vasopressin (AVP or antidiuretic hormone) contribute to this state of total body water excess and hyponatremia. Diuretics and free water restriction have historically been used to combat this condition but have unwanted side effects including electrolyte imbalances, arrhythmias, and renal failure. Vasopressin receptor antagonists directly target stimulated AVP receptors in the collecting duct of the kidney, down-regulating aquaporin insertion and free water absorption. Tolvaptan, an oral V₂-receptor specific antagonist, has been very effective and safe in outpatient trials in treating hyponatremia and volume overload. Prevalence of Hyponatremia in India is 28.9 % (Medscape - 907841) generally higher in summer. VAPTANS: These are the most preferred class of drugs especially for Hyponatremia.

Tolvaptan, is a selective, competitive vasopressin receptor 2 antagonist used to treat Hyponatremia (low blood sodium levels) associated with chronic kidney disease, congestive heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH). It shows great promise but because of the requirement for hospitalization for initiation or reintroduction and the expense of the drug, its use at this time is limited new class of drugs, AVP

receptor antagonists, designed specifically to promote aquaresis (electrolyte-sparing excretion of free water), and also has been evaluated in clinical trials for the treatment of hyponatremia. Being a new drug, Tolvaptan has shown significant results according to studies conducted internationally and there are rare studies in India. Therefore, studying the therapeutic efficacy of Tolvaptan will be further useful to determine the response of Hyponatremic patients in our study site even helps in finding any new adverse reaction which were not previously reported. and contribute to better therapeutic treatment and minimal side effects,² Further enhance and explore about newly introduced drug Tolvaptan and assess the safety profile of the drug.

MATERIALS AND METHOD:

Patient selection:

All male and female patients newly diagnosed for Hypervolemic, euvolemic Hyponatremia. Patients from all age groups above 18 years are included. Ability to understand and the willing to sign a written informed consent document at the screening visit before any protocol specific procedures are performed.

Inclusion Criteria-

- All male and female patients newly diagnosed for Hypervolemic, euvolemic Hyponatremia
- Patients from all age groups above 18 years are included.

Ability to understand and the willing to sign a written informed consent document at the screening visit before any protocol specific procedures are performed.

Exclusion Criteria:-

Patients who are not already treating with Tolvaptan. Patients with hypovolemic hyponatremia. Patients diagnosed other than Hyponatremia.

Designing a data collection form:

A data collection form was designed to collect the patient's data including patient's personal details (name, age, sex, height, weight, address, marital status and occupation) family history, past medical history, complications and lifestyle modifications.

Collection of data:

The required information was collected from the case sheets of individual patients in designed data collection form. KIMS foundation and research center ethics committee approval was obtained. Patient details were collected through self designed data collection form, by patient interview, by prescriptions or medication chart, patient data collection include

- Patient's demographics details.

- Co-morbid conditions.
- Post medical and medication history.
- Habituations and addictions.
- Present medication.
- Patient compliance.

Efficacy and safety evaluation

- The study was conducted according to the declaration of Helsinki (as amended in 1996) and Good Clinical Practice Guideline.
- Ethical committee approval has been obtained from independent ethical the institution where the study is being performed.
- Written informed consent was obtained from all the patients before enrollment into the study.
- Patients visit to the clinical centre were scheduled at screening.
- Primary efficacy criteria were, change in sodium level from baseline after starting the treatment with Tolvaptan.
- Body weight checked at screening and base line.
- Sodium levels were checked daily maximum till patients discharged from hospital.
- Safety and efficacy were evaluated by incidence of adverse event reported by the patients.
- To ensure the quality and consistency, determinations of sodium were made in our study site which is a research institute.
- Sodium levels were measured by potentiometer.

Sample size:

As the drug is used in limited group of hyponatremic patients a limited sample of 31 patients admitted to study centre were taken into consideration is rare .there were 31 patients available from our study center⁴.

Statistical analysis:

The demographic data were analyzed descriptively for comparability using “paired T-Test”. Were computed of electrolyte value for 10 to 15 days for follow up all the combinations and statistical significance was obtained. Descriptive statistics were computed the electrolyte values for 10 days follow were recorded. All safety and efficacy variables were assessed descriptively. Because there was no placebo or drug comparator, all statistical comparisons were with baseline values, with changes evaluated in the context of the patient's underlying clinical condition.

Protocol development and data analyses were undertaken by the investigators³.

RESULTS AND DISCUSSION:

All values of sodium levels monitored for 10 days were collected and computed statistically through paired T test method. Table 1 shows the minimum and maximum sodium values of patients shows a significant increase gradually from day 1 to day 10 with mean and standard deviation, Table 2 shows the paired sample statistics that it comparative value with day 1 and other consecutive days along with standard error mean and Table 3 describes paired differences with 95% of confidence interval of difference. Figure 1 sodium level comparisons between day 1 and other days increase and achieving normal range of sodium value , figure 2 mean sodium levels over study period (10 days) and figure 3 mean sodium level increment between one day and other study days.

Table 1 – Standard Deviation

	N	Minimum	Maximum	Mean	Std. Deviation
day1	31	89	128	109.87	12.588
day2	31	92	129	112.55	12.567
day3	31	95	129	114.13	12.863
day4	31	98	133	116.10	12.867
day5	31	101	137	118.39	13.096
day6	29	98	138	122.14	13.054
day7	27	100	140	124.78	12.261
day8	18	108	142	125.39	11.309
day9	10	106	139	125.40	10.627
day10	8	102	138	126.00	12.917
Valid N (list wise)					

Table 2 Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	day1	109.87	31	12.588	2.261
	day2	112.55	31	12.567	2.257
Pair 2	day1	109.87	31	12.588	2.261
	day3	114.13	31	12.863	2.310
Pair 3	day1	109.87	31	12.588	2.261
	day4	116.10	31	12.867	2.311
Pair 4	day1	109.87	31	12.588	2.261
	day5	118.39	31	13.096	2.352
Pair 5	day1	109.97	29	12.718	2.362
	day6	122.14	29	13.054	2.424
Pair 6	day1	109.04	27	12.678	2.440
	day7	124.78	27	12.261	2.360
Pair 7	day1	106.11	18	12.165	2.867

	day8	125.39	18	11.309	2.666
Pair 8	day1	99.80	10	4.614	1.459
	day9	125.40	10	10.627	3.361
Pair 9	day1	99.75	8	5.230	1.849
	day10	126.00	8	12.917	4.567

Table 3 – Paired differences

		Paired Differences					t	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	day1 - day2	-2.677	1.922	.345	-3.382	-1.973	-7.758	30	.000
Pair 2	day1 - day3	-4.258	2.955	.531	-5.342	-3.174	-8.023	30	.000
Pair 3	day1 - day4	-6.226	3.393	.609	-7.470	-4.981	-10.216	30	.000
Pair 4	day1 - day5	-8.516	7.150	1.284	-11.139	-5.893	-6.631	30	.000
Pair 5	day1 - day6	-12.172	5.862	1.089	-14.402	-9.943	-11.182	28	.000
Pair 6	day1 - day7	-15.741	6.797	1.308	-18.430	-13.052	-12.033	26	.000
Pair 7	day1 - day8	-19.278	8.028	1.892	-23.270	-15.286	-10.188	17	.000
Pair 8	day1 - day9	-25.600	9.430	2.982	-32.346	-18.854	-8.584	9	.000
Pair 9	day1 - day10	-26.250	11.107	3.927	-35.535	-16.965	-6.685	7	.000

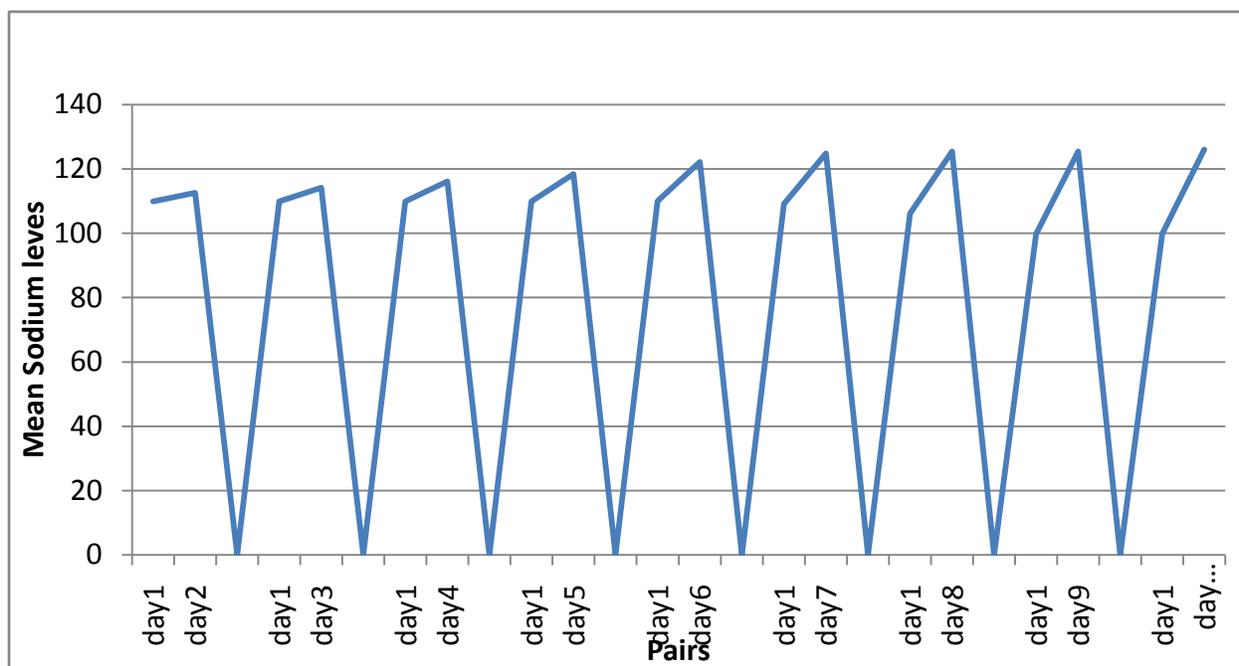


Figure 1 Mean sodium level Comparisons between day 1 vs other study days

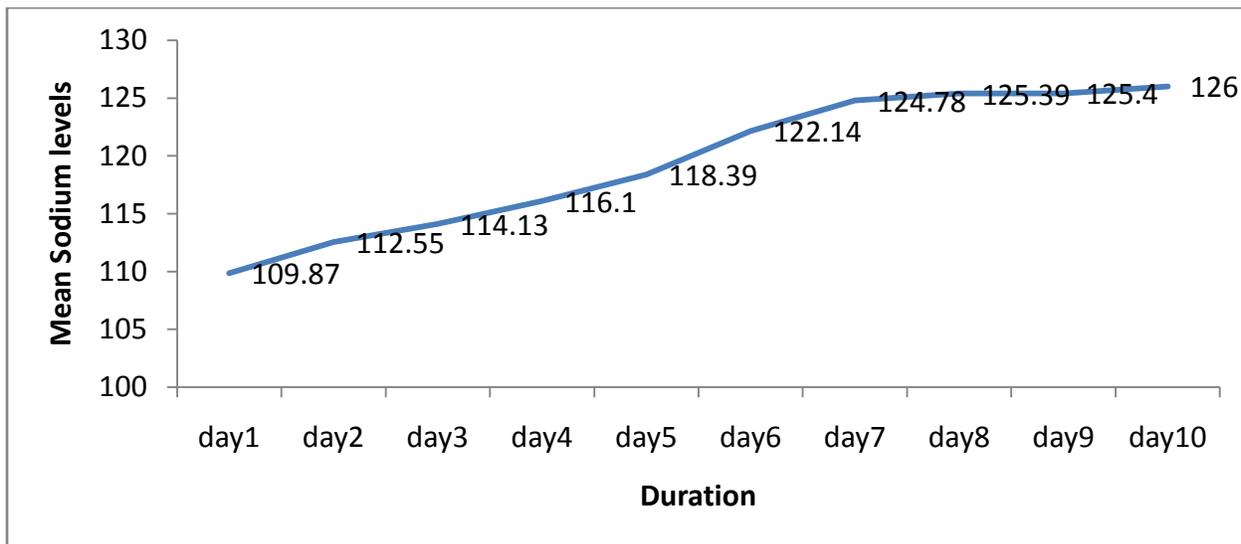


Figure 2 Mean Sodium level over the study period (10 days)

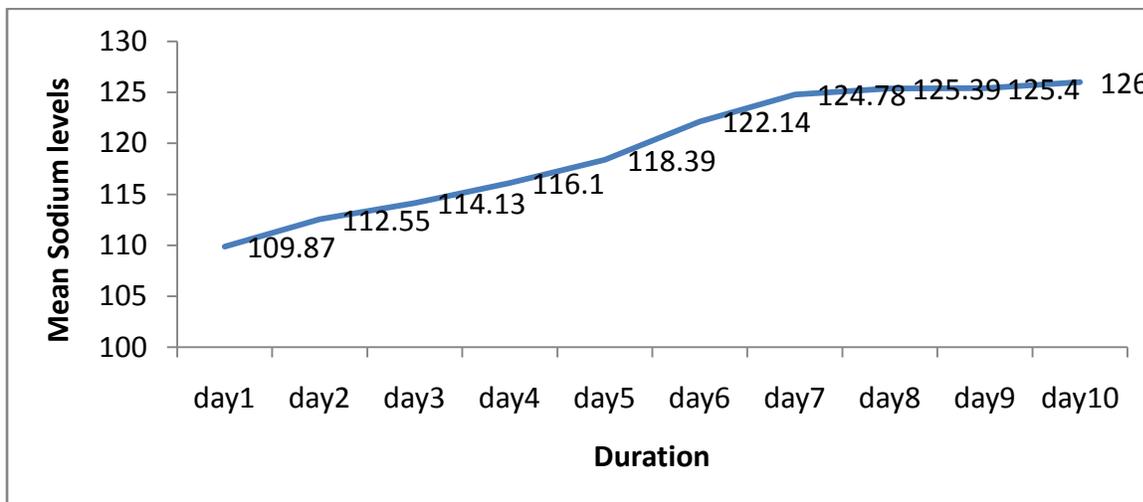


Figure 3 Mean Sodium level over the study period (10 days)

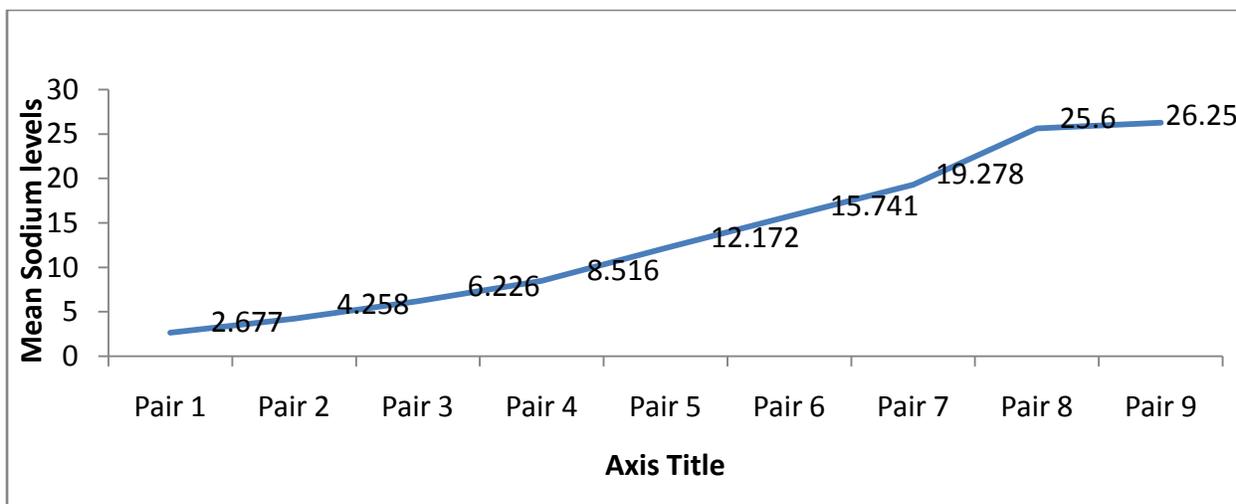


Figure 4 Mean Sodium level increments between day 1 and other study days

CONCLUSION

The present study shows that Tolvaptan provides a significant effect of control of serum sodium levels by bringing about the sodium values to normal range (67.7%) which show the drug is efficient in normalizing serum sodium levels. Low incidence of side effects in the present study established the safety profile of the drug in short term period. However in our study Tolvaptan is not administered more than 10 days which did not show any serious adverse effects. Further elucidation of the side effects longer period of observation and more number of patients need to be studied⁵.

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