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Long-term low-dose tolvaptan treatment in hospitalized male patients aged >90 years with hyponatremia

Report on safety and effectiveness

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Abstract

The retrospective study aimed at investigating the safety and clinical efficacy of long-term application of tolvaptan in patients >90 years old with hyponatremia. Although tolvaptan has been used to treat hyponatremia, the effect of its long-term use in elderly patients was unknown.

Seven patients over 90 with isovolumic or hypervolemic hyponatremia admitted to the PLA Navy General Hospital between October 2011 and October 2013 were enrolled. The patients' serum sodium levels <135 mmol/L persisted for more than 3 months, and oral treatment with tolvaptan lasted for more than 12 months. Tolvaptan dose started from 7.5 mg once daily, with maximum dose no more than 30 mg daily. Clinical and laboratory data of the patients before and after treatment were compared.

Serum sodium and chlorine levels increased significantly in the 1st 3 days after treatment ($P < .05$). All patients' serum sodium levels were above 135 mmol/L 1 month after treatment, and sustained through 1 year after treatment, without extra sodium supplementation. No serious complications were observed.

The result indicated a significant improvement in the serum sodium levels and no serious adverse effects after long-term use in very elderly patients.

Abbreviations: ADH = antidiuretic hormone, ALT = alanine aminotransferase.

Keywords: efficacy, hyponatremia, safety, tolvaptan, very elderly

1. Introduction

Hyponatremia is the most common electrolyte disorder in hospitalized patients. Owing to the deterioration in physiological functions of various organs among elderly patients, the long-term use of diuretics is associated with a high risk of hyponatremia.[1] Epidemiological data show that the incidence of hyponatremia in hospitalized elderly patients is about 25%, which is 2.5 times the level in young patients.[2,3] Recent studies showed that even mild or asymptomatic hyponatremia is associated with prolonged hospitalization, worsened primary disease, and increased mortality.[4,5] However, the management of hyponatremia is extremely challenging with complications such as congestive heart failure, and evidence suggests that it is often poorly managed, especially in older patients.

Tolvaptan is a novel selective antagonist of vasopressin V2 receptor (V2R) that can increase serum sodium concentration in patients with hyponatremia in a short period (≤30 days). Currently, it is mainly used for treating the syndrome of inappropriate antidiuretic hormone (ADH) secretion, heart failure with diuretic resistance.[6–8] However, reports on the safety and efficacy of long-term treatment with tolvaptan were limited. Long-term treatment with tolvaptan in patients aged >90 years have not been reported.

Elderly patients require drugs with high safety margins, as they have multiple underlying diseases and reduced function of multiple organs. Thus, this study collected clinical data of 7 very elderly patients admitted to the PLA Navy General Hospital between October 2011 and October 2013, and compared the changes in their general condition and clinical indicators after long-term low-dose oral treatment with tolvaptan. It is presumed that this information will better characterize the safety and efficacy of tolvaptan in very elderly patients.

2. Material and methods

2.1. Patients

This was a retrospective study. The inclusion criteria were as follows: age >90 years; isovolumic or hypervolemic hyponatremia, sodium levels <135 mmol/L persisting for more than 3 months; oral treatment with tolvaptan (Samsca, Zhejiang Otsuka Pharmaceutical, Tokyo, Japan) for >12 months; and tolvaptan dose starting from 7.5 mg once daily not exceeding the maximum

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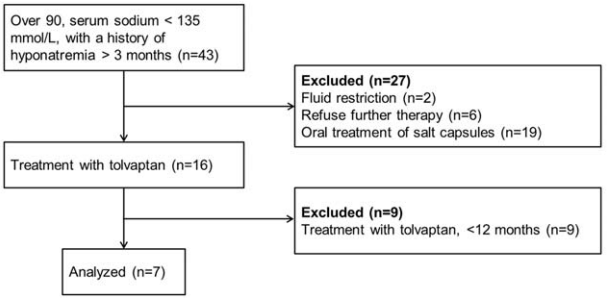

Figure 1. Flowchart of the enrollment process.

dose of 30 mg once daily. The exclusion criteria were as follows: discontinuation of tolvaptan medication or a medication interval >2 weeks; severe hepatic dysfunction before treatment; and uremia renal failure, oliguria, or anuria that required hemodialysis. Clinical data before the treatment were collected, including information on clinical symptoms, age, sex, cause of hyponatremia, and improvement in symptoms after the treatment. The protocol was approved by the PLA Navy General Hospital Ethics Review Board, and informed consent was waived.

2.2. Treatment

All patients aged >90 years with a clear diagnosis of chronic hyponatremia were required to limit fluid intake (<1.5 L/d) and increase sodium intake. For the patients who poorly responded or adhered to these treatments, tolvaptan was orally administered at a minimum dosage of 7.5 mg/d. The dosage might be adjusted by physician according to serum sodium level, with a maximum dosage of 30 mg/d. Fluid intake was not limited for the patients during treatment periods. No extra sodium supplements were given aside from normal diets. The patients routinely took other types of drugs. Furosemide might be prescribed for the patients who were indicated for diuretics.

2.3. Measurement

Information on serum sodium levels before oral treatment with tolvaptan and in the 1st 3 days, 1 month, 6 months, and 12 months after treatment, as well as blood pressure, heart rate, early morning fasting weight, and laboratory test results (including potassium, creatinine, serum urea nitrogen, uric acid, alanine aminotransferase [ALT]) were collected.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, IL). Differences between variables before and after treatment were analyzed by analysis of variance and post hoc analysis. Data were expressed as mean ± standard deviation (SD), if the variables were normally distributed. If the variables were not normally distributed, the data were expressed as median (range). $P < .05$ indicated statistical significance.

3. Results

3.1. Clinical characteristics of the patients

Between October 2011 and October 2013, 43 patients aged ≥90 years were diagnosed with chronic hyponatremia and a traditional treatment of fluid limitation (<1.5 L/d) and high sodium intake was applied. They had no previous history of taking tolvaptan. As is shown in Fig. 1, 27 patients were excluded from the study because of good effects from conventional treatment or refusing further therapy. About 16 patients who either failed the fluid restriction or not benefited from the conventional method, was given oral tolvaptan. Nine cases taking out of the research based on the following reasons. There are 3 deaths, including 1 case died of pneumonia (after 4 months of treatment), 2 cases died of cerebral apoplexy (3 months and 5 months, respectively). 3 cases were unable to adhere to the treatment because of the expensive price (after 2-3 months of treatment). 3 cases discontinued taking the medication after hyponatremia was cured. About 7 patients with treatment duration >12 months and complete data were included in the analysis (Table 1). All of these patients were men aged 94 to 99 years (mean ± SD, 96.7 ± 1.6 years), with a mean admission weight of 66.17 ± 9.59 kg. On concomitant medication use (Table 2), 2 patients received long-term oral furosemide (10–20 mg/d), and 1 patient received long-term spirolactone (10 mg/d) to relieve heart failure symptoms.

3.2. Serum sodium and serum chloride level

Before treatment, the average level of serum sodium and serum chloride were 126.6 ± 4.3 and 99 ± 3.85 mmol/L, respectively. In the 1st 3 days after treatment they rose to 139 ± 4.47 and 103 ± 4.85 mmol/L, respectively. The increasing was significant compared with the prior treatment ($P < .001$). After treatment for 1 month, 6 months, and 1 year, all the patients' serum sodium levels were kept within normal range (Fig. 2, Table 3).

Table 1

Clinical features of patients.

Patient	Gender	Age, year	Duration, year	Hyponatremia	Initial dose	Maintenance dose	Cause	Comorbidities
1	Male	99	4	Mild	7.5 mg/d	7.5 mg/d	CHF	Hypertension, DM, CRF, CHF
2	Male	96	8	Mild	7.5 mg/d	7.5 mg/d	SIADH	Hypertension, CRF, COPD, CHF
3	Male	94	3	Mild	7.5 mg/d	7.5 mg/d	SIADH	COPD, AF, CHF, pleural effusion
4	Male	98	3	Moderate	7.5 mg/d	15 mg/d	SIADH	Hypertension, COPD, AF, CHF
5	Male	97	3	Moderate	7.5 mg/d	15 mg/d	SIADH	Hypertension, COPD, CHF
6	Male	96	1	Mild	7.5 mg/d	7.5 mg every other day	CHF	CRF, CHF
7	Male	97	10	Moderate	7.5 mg/d	30 mg/d	CRF	Hypertension, CRF, stroke, COPD

AF = atrial fibrillation, CHF = chronic heart failure, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, DM = diabetes mellitus, SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Table 2

Long-term combinational medications in the 7 cases.

Drug	Case	Usage rate
β-blockers	4/7	57.1%
Calciumion antagonist	5/7	71.4%
Furosemide	2/7	28.6
Spirolactone	1/7	14.3%
ARB/ACEI	2/7	28.6%
Antiplatelet/anticoagulant drugs	5/7	71.4%
Statins	7/7	100%
Insulin	1/7	14.3%

ARB = angiotensin receptor blocker; ACEI = angiotensin-converting enzyme inhibitor.

3.3. Other outcomes

Body weight (Table 3): compared with pretreatment levels, weights at 1 month and 6 months after treatment decreased by 1.86 ± 1.14 kg ($P = .001$) and 1.17 ± 1.18 kg ($P = .027$), respectively. After 1 year of treatment, the patients' weights slightly decreased from their pretreatment values ($P = .143$).

3.4. Adverse effects

Adverse events were recorded for all 16 patients receiving tolvaptan therapy. Two patients complained of thirst in the 1st 3 days after treatment with tolvaptan, and 1 showed increased frequency of urination (mild). After long-term treatment, these symptoms persisted and the patients expressed tolerance. One patient showed serum sodium over 145 mmol/L following 1-week treatment with tolvaptan 7.5 mg/d, and the sodium level remained in normal range after reducing the dosage to 7.5 mg every other day. One patient had uric acid increased to 40 μmol/L after 3 days of therapy, but the uric acid did not continue to increase after that. The pre and posttreatment heart rate, systolic blood pressure, and were not significantly different among the patients (Table 3). No changes were observed in pre and posttreatment potassium levels. One month after treatment, the serum urea nitrogen level increased relative to its pretreatment level ($P = .093$), whereas no progressive increase was observed 1 year after treatment. Serum creatinine levels before treatment and after 3 days, 1 month, 3 months, and 1 year of treatment did not differ ($P = .079$). Similarly, the serum levels of blood uric ALT were not altered significantly ($P = .113$). The aforementioned results are shown in Table 3. No drug-induced adverse reactions, including tachycardia, low blood pressure, nausea, vomiting, and pruritus, were observed.

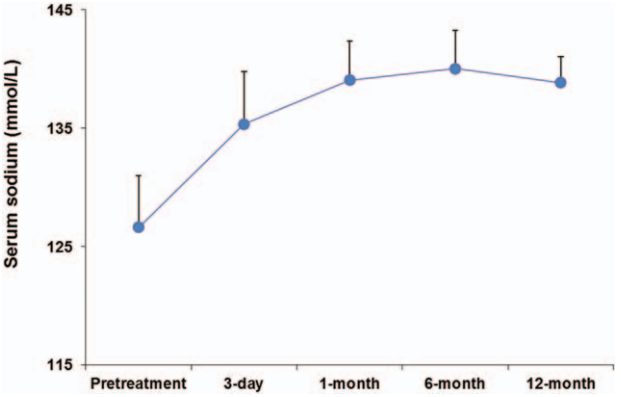

Figure 2. Evaluation of the effects of tolvaptan treatment. Changes in the serum sodium levels were measured during treatment. Values are expressed as mean ± SD. SD = standard deviation.

3.5. Follow-up

We followed up the 7 patients who received tolvaptan therapy for over 12 months for a maximum period of 2 years. One patient died of biliary tract infection caused by cholelithiasis. One patient received long-term mechanical ventilation because of heart failure and chronic obstructive pulmonary disease (COPD). No other newly occurred adverse events were reported.

4. Discussion

Elderly patients with isovolumic or hypervolemic chronic hyponatremia poorly tolerated and responded to fluid limitation. Considering the toxicity and adverse events of other drugs, sodium supplements have been widely used in routine clinical practice. Sodium chloride tablets are frequently prescribed to elderly patients, but they commonly do not show desirable effects because of the failure of eliminating causes. Tolvaptan is a selective antagonist of V2R that can bind to the V2 receptors in the distal renal tube, thereby preventing the action of ADH and

Table 3

Outcomes of patients.

Treatment group/index	Pretreatment	3 days	1 month	6 months	12 months	F	P
Na, mmol/L	126.63 ± 4.36	135.34 ± 4.47**	139.06 ± 3.31**	140.04 ± 3.24**	138.84 ± 2.20**	16.32	0
Cl, mmol/L	93.33 ± 3.85	99 ± 4.63**	103.04 ± 2.82**	102.59 ± 2.71**	102.71 ± 2.49**	10.425	0
K, mmol/L	4.30 ± 0.12	4.33 ± 0.19	4.36 ± 0.15	4.34 ± 0.19	4.41 ± 0.19	0.399	0.808
Creatinine, μmol/L	134.51 ± 73.45	130.97 ± 69.57	126.2 ± 65.51	132.93 ± 68.41	143.34 ± 72.33	0.057	0.994
BUN, mmol/L	7.73 ± 3.33	8.27 ± 3.54	8.73 ± 3.13	8.54 ± 3.90	8.81 ± 3.46	0.111	0.978
Uric acid, μmol/L	243.71 ± 82.38	259.86 ± 68.41	264.57 ± 85.72	251.15 ± 60.47	250.57 ± 59.3	0.092	0.984
ALT, U/L	10.69 ± 4.34	10.6 ± 3.45	10.9 ± 2.78	11.8 ± 3.99	10.76 ± 3.77	0.122	0.974
Heart rate, bpm	67.71 ± 4.03	67 ± 3.83	68 ± 6.56	67.6 ± 4.50	68.86 ± 5.27	0.133	0.969
SBP, mm Hg	129.29 ± 21.68	125 ± 20.70	131.43 ± 22.49	125.14 ± 20.46	130.86 ± 19.35	0.152	0.961
DBP, mm Hg	67 ± 7.02	65.71 ± 6.78	64.43 ± 6.19	64.71 ± 5.88	65 ± 4.86	0.193	0.94
Weight loss, kg	0	1.01 ± 0.72	1.86 ± 1.14**	1.17 ± 1.18*	0.86 ± 1.10	4.778	0.04

ALT = alanine aminotransferase, BNP = B-type natriuretic peptide, bpm = beats per minute, BUN = serum urea nitrogen, DBP = diastolic blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, SBP = systolic blood pressure.

* Data were presented as $P < .05$ compared with pretreatment group.

** Data were presented as $P < .001$compared with pretreatment group.

reducing water reabsorption via renal tubular transport. However, at the same time, it does not change the hemodynamic in the kidney and not increase the excretion of urinary sodium and potassium. Tolvaptan can reduce fluid retention and improve sodium levels. Therefore, it is an effective new drug for improving fluid retention without causing electrolyte imbalance.[9–11] Studies showed that tolvaptan can be used for treating hyponatremia, heart failure, diuretic resistance, and refractory ascites caused by liver cirrhosis.[8,12,13] However, studies on the long-term application of tolvaptan in very elderly patients (aged >90 years) have not been reported thus far.

Therefore, this study selected very elderly patients (aged >90 years) to evaluate the safety and efficacy of long-term application of low-dose tolvaptan by reviewing the patients' general condition and various laboratory parameters. Studies on the efficacy of tolvaptan showed that the serum sodium and chloride levels normalized after 3 days of treatment. After 1 year of treatment, the serum sodium and chloride levels normalized, with serum potassium levels unaffected. These results are consistent with those of the Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER) study,[12] indicating that tolvaptan presents good therapeutic effects on hyponatremia. There was slight weight loss after treatment because of the diuretic effects of tovalptan, but no changes in heart rate and blood pressure.

For evaluating the safety of long-term use of tolvaptan, low-dose tolvaptan (7.5 mg) was selected at the initial stage. The routine testing of the electrolyte levels was conducted to adjust the tolvaptan doses according to the serum electrolyte levels. The most commonly reported adverse events were thirst and frequent urination, both of which were resolved during successive treatments. One patient experienced hypernatremia which was subsequently resolved by dose reduction. One patient showed mild elevation of serum uric acid. In addition, serious adverse reactions were not observed, unlike in other reports.[14,15] During treatment for 1 year, the serum levels of potassium, urea nitrogen, creatinine, ALT, and uric acid remained unchanged. Those results show a low-dose tolvaptan is safety in very old patients for long-term treatment. There were 3 cases who not used tolvaptan for long-term treatment to the price reason excluded from our study. So the drug price may also effect the medication compliance during long-term treatment. Four patients died during tolvaptan treatments. One of them with COPD died of pneumonia. One died of biliary tract infections. Two of them died of cerebral hemorrhage caused by falling and subarachnoid rehemorrhage, respectively. The death cause was mainly related with underlying disease. No direct association with tolvaptan treatment was confirmed during the study. And the relationship between tolvaptan and infection/cerebral hemorrhage requires further study.

In view of comorbidities in elderly patients, the interaction between tolvaptan and other drugs was inevitable. Tolvaptan is metabolized via cytochrome P450 3A4 enzyme.[16] The combination of its inhibitors and inducers, which was not used in this study, may affect curative effect and increase the incidence of adverse events. We found that when tolvaptan was coadministered with furosemide, the cumulative urine volume remained close to tolvaptan alone, but the urinary excretion rate and duration of effect for each drug was different when administered alone and in combination. Similar facts were observed in a previous research.[17] However, additional research is still needed to determine the exact potential drug–drug interactions.

The limitations of this study were as follows: it was a retrospective study, without strict control for other confounding factors, and there was no equally ill cohort treated with placebo; the number of cases was limited, and all patients were men, because they were recruited from retired veterans, which could not represent the overall elderly population; and the patients were all treated in hospitalized environment, with routine monitoring of electrolytes, which did not give answer of the safety of long-term use of tolvaptan at home; and combinations of multiple drugs in the present study may affect the accuracy in the evaluation of the efficacy and safety of tolvaptan. Nevertheless, this study was unique as it is the 1st report to our knowledge of safety and efficacy of long term (>1 year) use of tolvaptan in very elderly patients.

In conclusion, this was a novel report about the outcomes of patients aged >90 years with hyponatremia after long-term tolvaptan treatment. The result indicated a significant improvement in the serum sodium levels, and no serious adverse effects were observed. A prospective study with a larger sample size is warranted.

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