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Research Article

Tolvaptan in the Treatment of the Syndrome of Inappropriate Anti-Diuretic Hormone in Cancer Patients

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Abstract

Objectives: This study aimed to reveal the therapeutic efficacy and side effects of tolvaptan use in patients with hypotonic euvolemic hyponatremia caused by syndrome of inappropriate anti-diuretic hormone (SIADH) in our oncology clinic. Herein is presented the first real-life data on the use of tolvaptan in hyponatremia observed in cancer patients in Turkey to the researchers' knowledge.

Methods: Clinically euvolemic patients who had serum osmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg, urine sodium concentration >40 mmol/L and were diagnosed with SIADH, were scanned via electronic data. In treatment, tolvaptan 15 mg/day was administered for 3 days.

Results: Hypotonic euvolemic hyponatremia due to SIADH was diagnosed in 24 patients (16 males, 8 females) who followed up for malignancy. The median sodium value of the patients before tolvaptan treatment was 121.5 mEq/L. The median sodium concentrations in the 3 days of treatment were 126.0 mEq/L, 132.0 mEq/L and 137.0 mEq/L, respectively. In 6 patients, adverse effects were observed; none of them stopped or paused treatment, however. Only 2 patients were discharged, while the other patients died.

Conclusion: The use of tolvaptan in the treatment of SIADH-induced hypotonic euvolemic hyponatremia provided an effective correction in serum sodium concentration, and improved the symptoms associated with hyponatremia.

Keywords: Cancer patients, hypotonic euvolemic hyponatremia, syndrome of inappropriate anti-diuretic hormone, tolvaptan

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Hyponatremia is one of the most frequently encountered electrolyte disorders in clinical practice. Serum sodium concentration between 130–135 mEq/L is defined as mild hyponatremia, between 125–130 mEq/L as moderate hyponatremia and <125 mEq/L as severe hyponatremia.[1] If hyponatremia has developed within 48 hours, it is defined as acute hyponatremia. If known hyponatremia has been present for more than 48 hours, it is defined as chronic hyponatremia. Clinical symptoms may vary from mild to severe, depending on the hyponatremia's development rate. If hyponatremia develops in less than 48 hours, brain oedema occurs more frequently; hence, it takes approximately 48 hours for the brain to adapt to the hypotonic environment. In acute hyponatremia, there is a risk of brain oedema due to low extracellular osmolality, leading to water shifting into the cell. Additionally, in the treatment of hyponatremia, if the serum sodium concentration is corrected very quickly, osmotic demyelination syndrome may occur due to the disruption of the myelin sheath.[2]

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Among all cancer types, hyponatremia is most commonly related to lung cancer. Hyponatremia occurs in 11–15% of patients with lung cancer, and one of its most crucial causes in patients is syndrome of inappropriate anti-diuretic hormone (SIADH).[3] In the literature, Schwartz et al.[4] first described hyponatremia due to anti-diuretic hormone (ADH) release in 2 patients with lung cancer. In clinical practice, hyponatremia is evaluated according to serum osmolality as hypotonic, isotonic and hypertonic.[5] Isotonic serum osmolarity (280–295 mOsm/kg) indicates the presence of pseudo-hyponatremia, which exists in patients with hyperglobulinemia and hypertriglyceridemia.[6] Hypertonic hyponatremia (>295 mOsm/kg) may be due to hyperglycaemia, mannitol, glycerol or intravenous immunoglobulin administration. Hypotonic hyponatremia (<280 mOsm/kg) is divided into three groups: hypervolemic, euvolemic and hypovolemic hyponatremia. SIADH-induced hyponatremia presents as hypotonic euvolemic hyponatremia.[7] Drugs administered to cancer patients, such as cyclophosphamide, vincristine, vinblastine, opioid analgesics and antidepressants (tricyclic antidepressant and selective serotonin reuptake inhibitor), may cause SIADH.[2] Hyponatremia is a significant cause of morbidity and mortality in cancer patients unless therapy management is adequate.[8] Several reports have shown that the presence of SIADH is associated with central nervous system (CNS) metastases, inadequate response to chemotherapy and advanced cancer stage.[9] The ADH V2 receptor blocker, tolvaptan, is one of the favoured agents in SIADH-induced hyponatremia, which is present in clinically symptomatic patients with serum sodium concentrations <125 mEq/L, despite the fluid restriction.

The present study aimed to reveal the therapeutic efficacy and side effects of tolvaptan use in patients with SIADH-related hypotonic euvolemic hyponatremia in the oncology clinic of Uludag University. Herein is presented the first real-world data on the use of tolvaptan in the treatment of hyponatremia observed in cancer patients in Turkey to the researchers' knowledge.

Table 1. Patients´ demographic and clinical features

Characteristic	n
Gender	
Male	16
Female	8
Age, median (min-max)	60.0 (22.0–80.0)
Hyponatremia development	
Inpatient	14
Outpatient	10
Hyponatremia history	
First hyponatremia episode	18
History of hospitalization for hyponatremia	6
Diagnosis	
Small cell lung carcinoma	10
Lung adenocarcinoma	3
Renal cell carcinoma	2
Ovarian carcinoma	2
Malignant melanoma	1
Neuroendocrine tumour	1
Neuroectodermal tumour	1
Ewing's sarcoma	1
Angiosarcoma	1
Gastric adenocarcinoma	1
Oesophageal adenocarcinoma	1
Hyponatremia symptoms	
Confusion	5
Headache	4
Dizziness	3
Weakness	3
Gait abnormalities	3
Nausea	2
Speech impairment	2
Difficulty of swallowing	2
Reasons for hospitalization other than hyponatremia	
Pneumonia	9
Need for supportive care	6
Pleural effusion	4
Gait abnormalities	3
Urinary tract infection	1
Haematuria	1

Methods

In this study, patients who developed hyponatremia during a follow-up appointment in the Medical Oncology Clinic at Bursa Uludag University Faculty of Medicine in 2017-2018 were retrospectively reviewed. Clinically euvolemic patients with diagnosed SIADH who had serum osmolality of <275 mOsm/kg, urine osmolality of >100 mOsm/kg and urine sodium concentration of >40 mmol/L were included in the study by scanning their electronic data. Patients who had a history of diuretic agent use and laboratory abnormalities in adrenal, thyroid, pituitary, kidney and liver function tests were excluded. Treatment consisted of administering tolvaptan 15 mg/day for 3 days. If needed, dose escalation was planned. Serum sodium concentration was monitored on a daily basis, before and during the tolvaptan therapy.

Statistical Analysis

Continuous variables were expressed in median (minimum-maximum) values; categorical variables were expressed by frequency and corresponding percentage values. The data were statistically processed with the IBM SPSS version 22 software.

Table 2. Patients' laboratory findings before and after treatment

	Parameters	Median	(Min–Max)
At diagnosis	BUN (mg/dL)	18.5	(8.0–32.0)
	Creatinine (mg/dL)	0.6	(0.3–4.7)
	AST (IU/L)	22.5	(10.0–42.0)
	ALT (IU/L)	24.0	(6.0–38.0)
	Total bilirubin (mg/dL)	0.90	(0.24–1.20)
	Uric acid (mg/dL)	3.15	(1.00–5.30)
	Plasma osmolality (mOsm/kg)	256	(239–260)
	Urine Na (mmol/L)	68	(44–98)
	Urine osmolality (mOsm/kg)	394	(143–570)
Sodium in mEq/L	At diagnosis	121.5	(113.0–123.0)
	1st day of treatment	126.0	(121.0–129.0)
	2nd day of treatment	132.0	(128.0–136.0)
	3rd day of treatment	137.0	(135.0–141.0)

BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Results

Hypotonic euvolemic hyponatremia due to SIADH was diagnosed in 24 patients (16 males, 8 females) following up for malignancy. Their median age was 60.0 (22.0–80.0) years. Of the patients, 10 followed up for small-cell lung cancer and 3 for lung adenocarcinoma; others are shown in Table 1. When the causes of hospitalization other than hyponatremia were analysed, 9 patients were hospitalized with pneumonia, 6 with functional impairment, 4 with pleural effusion, 3 with abnormal gait, 1 with an urinary tract infection and 1 with haematuria (Table 1). In total, 22 patients had metastatic disease and were receiving palliative care. In 14 patients, hyponatremia developed during hospitalization, and in 10 patients it developed out of hospital. Of the patients, 18 had hyponatremia for the first time, while 6 had multiple hospitalizations due to hyponatremia. Of the patients with multiple hospitalizations, 5 followed up for small cell lung carcinoma, and 1 for renal cell carcinoma. At the time of hyponatremia diagnosis, confusion, headache, weakness and dizziness were the most commonly observed symptoms in the patients (Table 1). The patients' laboratory values are shown in Table 2. The median patient sodium value before tolvaptan treatment was 121.5 mEq/L. All patients received tolvaptan at a dose of 15 mg/day for 3 days. Since the serum sodium levels of all patients increased more than 5 mmol/L per day, none of the patients needed dose adjustments. Therefore, the tolvaptan dosage was continued at 15 mg/day. The median sodium concentrations during the 3 days of treatment were 126.0 mEq/L, 132.0 mEq/L and 137.0 mEq/L, respectively (Table 2). As the patients' serum sodium levels increased with the treatment, symptom improvement was observed. When side effects were evaluated, 2 patients had increased hepatic enzymes, 2 had xerostomia and 2 had nausea. No adverse effects were observed that forced the tolvaptan treatment to stop. The patients' median hospitalization time was 17 (4–127) days. Only 2 patients were discharged, as the others died. All the patients died because of cancer progression.

Discussion

SIADH, as a paraneoplastic syndrome in patients with cancer, is seen more frequently in patients with a high tumour burden, lower treatment response and high morbidity. Several reports have shown that in this patient group, hyponatremia may be a prognostic factor for overall survival. Therefore, it is crucial to determine the causes of hyponatremia and give patients optimal treatment.[10] Inadequate hyponatremia treatment is associated with reduced survival, prolonged hospitalization and increased hospital costs.[11] Despite the fluid restriction and isotonic and hypertonic fluid replacement, serum sodium concentration may not increase in the treatment of hypotonic euvolemic hyponatremia due to SIADH in cancer patients. In SALT-1 (Study of Ascending Levels of Tolvaptan in Hyponatremia) and SALT-2 work-up subgroup analyses, researchers reported the efficacy of the ADH-V2 receptor blocker, tolvaptan, against a placebo in the treatment of cancer patients with SIADH-induced hyponatremia.[12] Salahudeen et al.[13] revealed tolvaptan efficacy in a study designed to compare tolvaptan against placebos in hospitalized hyponatraemic cancer patients. Volker et al.[14] investigated the effectiveness of tolvaptan in 358 cancer patients, thereby having the highest number of patients in such a study. Statistically significant treatment effects were observed 8 hours after

once-daily tolvaptan administration. Tolvaptan efficiency was observed in serum sodium concentration 24 hours after the drug's administration.[12]

The improvement of clinical symptoms associated with hyponatremia was observed after tolvaptan use. Peñas et al.[15] found improvement in symptoms associated with hyponatremia in patients at hospital day-care units.

Tolvaptan has a half-life of 6–8 hours and approximately binds to plasma proteins with a 98% reversibly rate and is metabolized extensively by the liver. Less than 1% of the intact active substance is excreted unchanged in the urine. Severe liver injury may occur due to tolvaptan. Liver enzymes and bilirubin values should be evaluated before and after treatment. If liver enzymes and bilirubin levels are doubled or more, tests should be repeated within 48–72 hours. If the serum levels increase more than three times, tolvaptan treatment should be stopped. It should also not be administered to patients with liver disease, including cirrhosis. Renal dose adjustment is not necessary for hypervolemic and euvolemic hyponatraemic patients with creatinine clearance higher than 10 mL/min. Tolvaptan treatment is not recommended for patients with creatine clearance less than 10 mL/min. The initial tolvaptan dose is 15 mg. However, if the increase in serum sodium concentration in the 24-hour interval is less than 5 mmol/L, and the serum sodium concentration remains less than 135 mEq/L, the dose can be increased to 30 mg or 60 mg, though the maximum recommended dose is 60 mg/day.[16] To prevent water loss, water restriction should be avoided during the treatment.[17]

The adverse effects of tolvaptan include dry mouth, thirst, pollakiuria, dizziness, nausea, orthostatic hypotension, hypoglycaemia, hyperuricemia, syncope, headache, weakness and diarrhea. Rare side effects include hypernatremia and polyuria.[18] In this study, no dose-limiting adverse effects were recorded. Increased hepatic enzymes, xerostomia and nausea, however, were the main side effects detected.

Conclusion

In the treatment of SIADH-induced hypotonic euvolemic hyponatremia, 3-day tolvaptan use provided an effective correction in serum sodium concentration. In palliative units, tolvaptan can be useful in the rapid recovery of resistant SIADH-related hyponatremia symptoms. The adverse events were manageable. Although the hyponatremia itself was resolved, the patients' hospitalization continued due to other cancer complications, and mortality was still high because of the tumour burden in the clinical course.

Disclosures

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Ethics Committee Approval: The study was in accordance with the ethical standards of the with the 1964 Declaration of Helsinki and approved by the clinical research ethics committee of Bursa Uludag University Faculty of Medicine (Approval number: 2019-8/27). Since retrospective planning, patient informed consent was not required.

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