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Tolvaptan for the management of SIADH: Lessons learned in titration of dose

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Abstract

Objective—To report a case of a patient with idiopathic SIADH who developed a profound aquaresis with symptomatic extracellular fluid depletion after initiation of therapy with tolvaptan and was later successfully treated with smaller doses of compounded tolvaptan to prevent rapid correction of serum sodium.

Methods—Case report and review of the literature.

Results—A 51-year-old female was diagnosed with SIADH during admission for elective surgery resulting in multiple complications. The patient failed multiple therapies including fluid restriction, salt tablets and demeclocycline. She was admitted to the hospital for initiation of therapy with tolvaptan. After a 15-mg dose of tolvaptan tolvaptan, the patient had rapid increase in urine output and symptomatic hypotension. Sodium levels corrected rapidly overnight from 126 mEq/L to 139 mEq/L. A lower dose of tolvaptan resulted in similar symptoms and sodium correction. Due to continuing symptoms of hyponatremia including headaches, nausea, vomiting, and paresthesias after re-initiation of fluid restriction and salt tablets, tolvaptan was compounded to continue to titrate at lower doses. Patient was then admitted and tolvaptan was initiated at a dose of 1.5 mg with no significant improvement of sodium levels. Tolvaptan was titrated to 3 mg which resulted in correction of sodium to 129 mEq/L with no associated symptoms of hypovolemia.

Conclusions—Tolvaptan should be initiated in an inpatient setting with close monitoring of serum sodium levels. In patients who are not able to tolerate recommended dosages, consideration should be given to use of a compounded formulation to further titrate to lower doses.

Introduction

Hyponatremia is one of the most common electrolyte abnormalities found in clinical practice (1). Hyponatremia, defined as serum sodium of < 130 mEq/L, has been estimated to occur in 2.5 to 6.2% of patients admitted to the hospital and in 4.4% of patients in the post operative period (2). The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is one of the most frequently encountered causes of hyponatremia (3). Studies have shown that severe hyponatremia (serum sodium <125 mEq/L) is associated with significant morbidity and mortality (4). Conventional therapies for patients with chronic

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hyponatremia include fluid restriction, salt tablets, diuretics, lithium and demeclocycline. However, these options are limited by efficacy and adverse effects. More recently the Food and Drug Administration (FDA) approved the use of vasopressin receptor antagonists for the treatment of euvolemic and hypervolemic hyponatremia.

Case Presentation

A 51-year-old female was referred for management of refractory hyponatremia secondary to SIADH. The patient was previously healthy until approximately 1 year prior to presentation, when she underwent elective hysterectomy complicated by perforated bowel. She had a prolonged hospital course of 56 days, which was complicated by necrotizing abdominal wall fasciitis, sepsis, and hyponatremia. During the hospital stay her sodium decreased to 107 mEq/L (reference range, 135 to 145 mEq/L), with no response to administration of normal saline. Initial evaluation demonstrated elevated urine osmolality of 564 mOsm/kg (reference range, 0 to 1200 mOsm/kg) and urine sodium of 124 mEq/L, consistent with SIADH. Further evaluation included normal morning cortisol, thyroid function, albumin and renal function. At the time of discharge she was managed with fluid restriction and salt tablets. Treatment was not effective due to continued symptoms of hyponatremia including headaches, nausea, vomiting and paresthesias of arms and legs and inability to reach normal sodium levels.

The patient was then referred to endocrinology for further evaluation, which included an extensive workup for a etiology of SIADH, including computed tomography of the chest and brain and pituitary magnetic resonance imaging. The tests failed to reveal an etiology for SIADH. Other than salt tablets, patient was not receiving any medications. Plasma arginine vasopressin (AVP) levels were found to be 1.2 pg/mL (reference range, 0 to 4.7 pg/mL). She was admitted to our institution for a water loading test to rule out reset osmostat as an etiology of her hyponatremia. The patient received 20 ml of water per kg of body weight (1.1 L total). After 4 hrs she only excreted 21% of the water load and urinary osmolality at the end of the test was 589 mOsm/kg (Table 1). At the time of discharge, she was started on demeclocycline. With the initiation of demeclocycline her serum sodium normalized to 137 mEq/L, but she developed a photosensitivity rash and medication had to be discontinued.

After the patient failed several treatment options for SIADH, the plan was to initiate therapy with tolvaptan. She was admitted to the hospital for monitoring and dose titration. Her admission sodium was 126 mEq/L (Table 2), and she then received a dose of 15-mg tolvaptan. Almost immediately, the patient noted a significant increase in urinary output (0.8L/h) associated symptoms including confusion and orthostasis. She was treated with a bolus of 500 ml of normal saline and instructed to increase her oral fluid intake in response to thirst. Over a period of 8 hours, her sodium increased to 139 mEq/L. Overnight, her recorded urine output was 6.5 L and her sodium level increased to 142 mEq/L (Table 2). After her sodium level decreased slowly to less than 140 mEq/L, she was redosed with 7.5-mg tolvaptan. Following 2 trials of the lower dose of tolvaptan, the patient experienced brisk diuresis associated with symptoms of orthostasis, as she patient was not able to keep up oral intake to match urine output. She was discharged without the medication with plans to continue fluid restriction and salt tablets with close monitoring of sodium.

Despite aggressive fluid restriction and the salt tablets, the patient continued to have symptoms of hyponatremia including headache and paresthesias. She was readmitted to the hospital with a sodium of 114 mEq/L. The decision was then made to compound tolvaptan. She was started on a low dose of 1.5-mg tolvaptan in the inpatient setting. After the dose she again noted diuresis, but was able to drink enough water to remain euvolemic. However, serum sodium did not improve (Table 2). The next day she then received a 3-mg dose of tolvaptan, which resulted in an increase in sodium to 129 mEq/L. She was able to tolerate

the level of diuresis and did not complain of symptoms of hypovolemia such as dizziness and light-headedness when standing. She was discharged home on 3-mg tolvaptan daily.

The patient has followed up closely with the endocrinology department. With better control of sodium, she has been able to return to work and symptoms related to hyponatremia have improved. The dose of tolvaptan has continued to be titrated on an outpatient basis for the last year based on serum sodium values. She is currently receiving 4.5-mg tolvaptan daily.

Discussion

AVP is released by the posterior pituitary in response to increasing serum osmolality. Activation of V_2 receptors increases water permeability in the renal collecting duct resulting in passive reabsorption of water (1). Various disorders including SIADH, heart failure, and cirrhosis have been associated with increased AVP secretion, leading to water retention or inadequate water excretion and resultant hyponatremia (5). Since the 1990s, a number of vasopressin antagonists have been developed. In 2005, the FDA approved the use of intravenous conivaptan, a V_{1A} and V_2 vasopressin receptor antagonist, for the treatment of euvoletic and hypervolemic hyponatremia. Further interest in this class of drugs led to the development of tolvaptan, which was approved by the FDA in 2009 as an oral alternative. Tolvaptan selectively inhibits the binding of AVP to the V_2 receptor and has been shown to have 1.8 greater affinity for the receptor than that of AVP (1). Binding to the V_2 receptor induces excretion of electrolyte-free water without altering the electrolyte excretion.

Two multi-center, randomized, double-blind, placebo-controlled trials, have evaluated the efficacy of tolvaptan in patients with euvoletic or hypervolemic hyponatremia (6). Patients were randomized to tolvaptan at an initial dose of 15 mg per day or placebo. The tolvaptan dose was then titrated to 30 mg and then to 60 mg on the basis of serum sodium concentration. Results of the study demonstrated a significant increase in the mean serum sodium concentration after 4 days of therapy and at the end of the 30 days of treatment in the tolvaptan group. This effect disappeared after the discontinuation of the drug (6).

In patients with chronic hyponatremia, rapid correction of serum sodium can lead to neurologic sequelae, including osmotic demyelination. One of the concerns of use of tolvaptan is the risk of rapid correction of sodium. Tolerability data has been derived in part from large studies conducted on this drug, including the SALT-1 (6), SALT-2 (6) and EVEREST (7,8) trials, from a total of 2,295 patients who received the therapy. The most common reported side effects in the tolvaptan group of these trials included thirst and dry mouth. In the SALT-1 and -2 trials (6), 26 serious adverse effects were reported which were potentially related to the study treatment. Of those adverse effects, 11 occurred in 8 patients treated with tolvaptan and included dehydration with hypotension or dizziness, syncope, acute renal failure, ascites, increased serum sodium and increased serum creatinine. Eight patients from the tolvaptan group and 8 placebo recipients withdrew from the study because of adverse effects thought to be related to the treatment. One patient in the tolvaptan group discontinued the study secondary to hyponatremia. In the SALT-1 and -2 trials, 4 of the 223 patients in the tolvaptan group exceeded the desirable rates of serum correction (>0.5 mEq/L per hour), and 4 patients were reported to surpass the set maximum tolerable serum sodium concentration of 146 mEq/L on tolvaptan therapy (6). Long-term tolerability data from the EVEREST outcome trial showed that over a 2-year period hyponatremia was reported in 1.7% of patients treated with tolvaptan compared with 0.5% in the placebo group (7). No cases of osmotic demyelination were reported in the trials. Due to concerns about adverse effects and titration phase for the therapy, the FDA issued a "black box warning" indicating that therapy with tolvaptan should be initiated in a hospital setting with close monitoring of serum sodium.

Our patient was admitted to the hospital for close monitoring prior to initiation of tolvaptan. After the first 15-mg dose, she experienced the most common side effects of therapy including increased thirst and dry mouth. The most concerning adverse effects included rapid increase in urination with greater than 0.5L of urine during the first hour after ingesting tolvaptan, and symptomatic hypotension requiring administration of intravenous normal saline with rapid correction of sodium. Despite decreasing the dose to 7.5 mg, she continued to have significant diuresis causing hypovolemia. This case is unique and does not represent the typical response of patients to recommended doses of tolvaptan. Due to limited options available, a trial with compounded tolvaptan was initiated at lower doses and she currently has been able to maintain adequate sodium concentrations at a dose of 4.5 mg daily.

Conclusion

SIADH is a common disorder encountered in clinical practice. Treatment options are limited and patients can experience symptoms which can alter their quality of life. Our case illustrates a patient with vigorous response to 15-mg tolvaptan that resulted in rapid correction of sodium. For patients who experience a brisk response to the recommended dose of tolvaptan, consideration should be given to administer the medication at lower dosages.

Abbreviations

SIADH	syndrome of inappropriate antidiuretic hormone
AVP	Arginine Vasopressin
FDA	Food and Drug Administration

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Table 1

Water Loading Test Results of the Study Patient

Time	Serum sodium (mEq/L)	Urine sodium (mEq/L)	Serum osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)
7:00 AM	124	104	265	567
9:30 AM	120	--	--	592
11:00 AM	119	--	--	513
1:00 PM	118	140	245	589

Table 2

Results of Varying Doses of Tolvaptan on Sodium Levels in Study Patient

Tolvaptan dose (mg)	Pretreatment serum sodium (mEq/L)	Posttreatment serum sodium (mEq/L)	Delta sodium value (mEq/L)	12-hour fluid intake (L/12h)	12-hour urinary output (L/12h)
15	126	142	16	4.2	6.5
7.5	137	144	7	3.9	5.1
3	123	129	6	2.5	4.1
1.5	126	123	-3	3.1	3.5