Tolvaptan Use to Treat SIADH in a Child

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Hyponatremia is one of the most common electrolyte abnormalities encountered in the clinical setting in hospitalized patients. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the leading cause of hyponatremia in most of these cases. While fluid restriction, hypertonic saline infusion, diuretics, and the treatment of underlying conditions constitute the first line of treatment of SIADH, in refractory cases, and especially for pediatric patients, there seems not to be any other choice for treatment. Tolvaptan, although its use in pediatric patients is still very limited, might be an attractive treatment option for correction of hyponatremia due to SIADH. Here we present a pediatric case of SIADH that was resistant to treatment with fluid restriction and hypertonic saline infusion and was treated successfully with tolvaptan. Tolvaptan could be a good, safe, and effective treatment option in pediatric SIADH cases that are resistant to treatment. However, the dosage should be titrated carefully.

ABBREVIATIONS ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone, AVP, arginine vasopressin; AVPR2, arginine vasopressin receptor 2; Na, sodium; NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion

KEYWORDS case report; child; hyponatremia; pediatric; SIADH; tolvaptan; treatment

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Introduction

Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical settings. In hospitalized patients, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the leading cause of hyponatremia in most cases. SIADH is a rare entity in the pediatric age group and data about the treatment of refractory cases are quite limited. The aim of this case report is to emphasize that tolvaptan could be a good, safe, and effective treatment option in pediatric SIADH cases that are resistant to treatment.

SIADH is characterized by euvoletic hyponatremia occurring owing to increased antidiuretic actions of arginine vasopressin (AVP).¹ Increased concentrations of antidiuretic hormone (ADH) lead to activation of V2 receptors located in the renal tubules, which mediates the concentration of urine, with relative water excess in plasma leading to hyponatremia.² While serum osmolality plays an important role in the stimulation of AVP release, various non-osmotic stimuli or conditions such as pain, drugs, tumors, cranial surgery, and many others may cause AVP release. Sometimes the exact etiology cannot be detected and this is known as idiopathic SIADH.^{3,4}

General principles in the management of SIADH include fluid restriction, diuretics, hypertonic saline infusions when needed, and the treatment of underlying conditions if possible. Oral urea, demeclocycline, and vaptans are other effective treatment options suggested in the literature.⁵

Vaptans are V2 receptor antagonists recently approved by the US Food and Drug Administration for managing euvoletic and hypervolemic hyponatremia in adults. Vaptans are competitive antagonists of V2 receptors. While conivaptan can only be used intravenously, it is possible to use oral forms of tolvaptan. Although there are well-designed randomized controlled studies dealing with the effectiveness of tolvaptan, data about its pediatric usage are quite limited.⁶ Here we report a case of SIADH in an adolescent patient who was resistant to fluid restriction, infusion of hypertonic saline solution, and diuretics but responded to tolvaptan. The patient's clinical situation and laboratory values were corrected safely with tolvaptan without any side effects. However, the dosage of the drug must be monitored carefully because of the lack of data about the dosage in pediatric patients.

Case

A 16-year-old female was admitted to our clinic with complaints of headache and nausea. Her physical examination and medical history were unremarkable. Her body weight was 53 kg (25th–50th percentiles) and height was 159 cm (25th–50th percentiles). Laboratory evaluation revealed hyponatremia, hypochloremia, and hypouricemia with normal findings for renal function tests, electrolytes, and blood gas analyses. Serum osmolality was decreased, while urine osmolality was increased. The results of the first laboratory evaluation are given in the Table. Urinary sodium concentration

Table. Patient's Laboratory Values at Admission, After Tolvaptan Treatment, and Last Visit

Laboratory Values	Admission	After Tolvaptan	Last Visit	Normal Laboratory Values
Urea, mg/dL	9	25	30	11–39
Serum creatinine, mg/dL	0.51	0.6	0.5	0.5–1.2
Na, mEq/L	110	142	140	136–146
K, mEq/L	4.36	4	3.8	3.5–5.2
Cl, mEq/L	89	100	102	102–112
Uric acid, mg/dL	1.4	3	3.5	2.6–6
Ca, mg/dL	9.1	8.8	9	8.4–10.2
P, mg/dL	4	4.5	5	4–7
Plasma osmolality, mOsm/kg	276	–	–	275–295
Urine osmolality, mOsm/kg	565	–	–	50–1200
ACTH, pg/mL	5.16	–	–	0–46
Cortisol, mcg/dL	10.6	–	–	6.7–22
Renin, ng/dL	22.45	–	–	3.18–32.61
Aldosterone, ng/dL	82.93	–	–	48–272
ADH, pg/mL	8.3	–	–	<13
FeNa, %	1.9	–	–	<1
Urine Na, mEq/L	173	–	–	<20
24-hr urine uric acid excretion rate, mg/1.73 m ² /24 hr	834	–	–	145–520

ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; Ca, serum calcium; Cl, serum chloride; K, serum potassium; Na, serum sodium; P, serum phosphorus

was increased to 173 mEq/L, while serum sodium concentration was 110 mEq/L. Fractional sodium excretion was 1.9% as it was expected to be higher than 0.5% to 1% in a patient with hyponatremia for the diagnosis of SIADH. The 24-hour urinary excretion rate of uric acid was increased. The possibility of cerebral salt wasting was not considered because the clinical picture was more in keeping with SIADH, as she did not have any signs of dehydration and her weight and urine output were normal. Serum ADH concentration during hyponatremia was also found to be decreased (Table). Clinical and laboratory findings such as euvolemic hyponatremia, decreased blood uric acid concentration, and serum hypo-osmolality with increased urine osmolality led us to the diagnosis of SIADH.

Extensive investigation regarding the etiology of SIADH was inconclusive and the patient was finally diagnosed with idiopathic SIADH. Thyroid function test results were normal, as were serum concentrations of adrenocorticotrophic hormone (ACTH), cortisol, renin, and aldosterone. The small-dose ACTH stimulation test revealed normal response. Other factors such as drugs, intracranial pathologies, tumors, or adrenal pathologies are commonly encountered in the etiology of SIADH. However, there was no sign of meningitis or meningoencephalitis in our patient. Her chest X-ray and abdominal ultrasonography findings were normal. Magnetic resonance imaging of the brain and hypophy-

sis was normal, excluding any intracranial pathologies such as tumors or inflammatory or infiltrative lesions.

The patient was treated with 100 mL (approximately 2 mL/kg) bolus of hypertonic saline twice. Fluid intake was restricted by approximately 70% and continued with a fluid that contained sodium at about 250 mEq/L. Later on, the sodium concentration of the fluid was titrated according to the serum sodium concentration of the patient. She initially responded to this treatment, and her serum sodium concentration increased to 125 mEq/L. However, during follow-up, it was not possible to stop or even to decrease the amount of saline infusion. Even minimal increase in the fluid rate or decrease in sodium concentration caused hyponatremia (to the lowest value of 108 mEq/L) with clinical symptoms (e.g., headache and irritability).

Thus, tolvaptan (Samsca, Abdi İbrahim-Otsuka Ltd, Istanbul, Turkey) was started in the second week at a dose of 0.28 mg/kg once a day (15 mg/day is the recommended adult dose) and titrated down, in a stepwise manner, to 0.14 mg/kg with “alternate-day” dosing based on fluid requirements and serum sodium concentrations (Figure). Serum Na concentration increased gradually with tolvaptan. The administration of tolvaptan in our patient had particularly profound effects on urinary output during the first 24 hours, as expected. Urine output increased up to 9 mL/kg/hr and close monitoring in an intensive care setting was

Figure. Serum sodium values during tolvaptan treatment.

required. During the first 24 hours of treatment, frequent measurements of Na concentration, once every 4 hours, and adjustment of fluid intake hourly as well as urinary output were needed to avoid a rapid increase in serum Na concentration. Fluid restriction was stopped and the patient was encouraged to increase fluid intake to avoid rapid increase in serum sodium concentration. On the second day of treatment, the dose of tolvaptan was titrated (decreased to 0.14 mg/kg/day) because of the rapid increase in Na concentration. Urine output was approximately 5 mL/kg/hr on the second day of treatment. During follow-up, the serum Na concentration allowed us to administer the drug at a dose of 0.14 mg/kg on alternate days. Tolvaptan treatment was continued for 2 weeks with alternate-day dose treatment and stopped gradually. The serum Na concentration was within normal limits for approximately 4 months after the cessation of tolvaptan. However, the patient was then admitted to our clinic with another attack of hyponatremia (Na = 127 mEq/L), which was milder and might have only been noticed because of the family's awareness of the symptoms of hyponatremia. Because of the recurrence of SIADH, gain-of-function mutations in the *AVPR2* gene were investigated, but no mutation was detected in whole-exon analysis. She had another course of tolvaptan treatment at a dose of 0.14 mg/kg on alternate days, based on the experience of the first attack, and for a shorter duration (10 days), with no side effects. The serum sodium concentration reached 142 mEq/L within 24 hours and remained within the normal limits for 6 months of follow-up.

Discussion

SIADH is a clinical syndrome characterized by excessive water retention with subsequent dilutional hyponatremia. In the literature, there are distinct types of SIADH, which are defined according to the AVP secretion pattern.⁷ Causes of SIADH may vary among patients. Pulmonary and mediastinal tumors, inflammatory and tumoral intracranial lesions, cranial surgeries, drugs, and pulmonary diseases could be the cause of SIADH in addition to miscellaneous and idiopathic cases.⁴

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD), due to a constitutive activation of the mutant V2 receptor, typically presents with clinical and biological features suggesting inappropriate ADH secretion with severe hyponatremia and high urine osmolality but a low plasma arginine vasopressin concentration.⁸ For our patient, genetic analyses for NSIAD were negative, and the exact etiology of SIADH in our case remains unknown.

Current treatment options for SIADH are limited and often not effective. In most cases of asymptomatic hyponatremia as a consequence of SIADH, treatment is limited to fluid restriction. However, as our case demonstrates, fluid restriction is not effective alone and discontinuation of fluid restriction is not always possible. Other treatment options in the management of SIADH are diuretics, hypertonic saline, oral urea, demeclocycline, and vasopressin receptor antagonists.⁵

There are different types of vaptans used via intra-

venous or oral routes. The best-known vaptans are conivaptan (intravenous) and tolvaptan (oral).⁹ Because the vaptans are ADH receptor antagonists, they are logical treatment options, as they specifically target the causative mechanism of the hyponatremia due to SIADH.

In the literature, there are reports dealing with vaptans in the treatment of ascites due to cirrhosis, edema management in congestive heart failure, and hyponatremia caused by SIADH. However, there are limited data on the utilization of vaptans in children.

In 2 multicenter, randomized, double-blind, placebo-controlled trials (the SALT study), the efficacy of tolvaptan was evaluated in adults with euvolemic or hypervolemic hyponatremia. Patients were randomly assigned an oral placebo (223 patients) or oral tolvaptan (225 patients) at a dose of 15 mg daily.¹⁰ According to the results of the SALT study, serum Na concentration significantly increased in the tolvaptan group compared to the placebo group. A remarkable improvement was observed in the clinical condition of patients with mild or marked hyponatremia who received tolvaptan. Side effects associated with tolvaptan included increased thirst, dry mouth, and increased urination. We did not observe any of these side effects in our patient. However, in our case we needed to decrease the dosage and switch to alternate-day treatment to avoid rapid increment in Na concentration.

Recently, in a systematic review dealing with known interventions for the treatment of chronic non-hypovolemic hypotonic hyponatremia and a meta-analysis of the vaptans, Bhandari et al¹¹ showed that vaptans are evidence-based effective treatment options to increase serum sodium concentrations in patients with hypovolemic hyponatremia.

Reports regarding the use of vaptans in pediatrics are scarce and are mostly limited to case reports. Marx-Berger et al¹² reported data on 2 infants with persistent hyponatremia in the first month of life that eventually led to SIADH diagnoses. Initial salt supplementation in 1 patient resulted in severe hypertension and this was treated with 4 antihypertensive drugs. Tolvaptan was commenced at 2 and 4 months of age, respectively, and was associated with normalization of plasma sodium values and blood pressure. The dosage of tolvaptan was 3.75 mg/day for both infants.¹² The authors reported that hyponatremia was corrected in 24 hours and transient hypernatremia was observed in 1 patient, which was corrected by a dose reduction. In our patient, hyponatremia was corrected in approximately 48 hours without experiencing hypernatremia, possibly because of the small dose that we used.

Shimizu et al¹³ used tolvaptan to treat massive edema of a young female diagnosed with steroid-dependent idiopathic nephrotic syndrome. The patient received tolvaptan for 7 days without any change in her serum Na concentration. An increase in urine Na excretion

was observed and the edema subsided.

Willemssen et al¹⁴ reported the case of an 11-year-old male who developed severe SIADH after the diagnosis of intracranial B-cell lymphoma. His sodium concentrations dropped to 118 mEq/L despite 70% fluid restriction. For chemotherapy, he required hyperhydration, which posed a challenge because of the severe hyponatremia. Tolvaptan, which was started with a dose of 0.14 mg/kg once a day and titrated up to 0.28 mg/kg twice a day, gradually increased the sodium concentrations and allowed liberalization of fluid intake and hyperhydration. Similarly, a 13-year-old male with extensively metastasized anaplastic large-cell lymphoma developed hyponatremia due to SIADH. SIADH management in this case was complicated when fluid restriction was not safely attainable because of the chemotherapeutics. Conivaptan played a significant role in this situation by allowing the provision of a large amount of intravenous fluid prior to and during induction chemotherapy.¹⁵

Vaptans could potentially cause harm, such as osmotic demyelination syndrome when the sodium increases too rapidly. A recent clinical practice guideline limited their use to patients with symptomatic hyponatremia as a consequence of SIADH.¹⁶ As illustrated by our case, there may, however, be situations in which fluid restriction is not enough to correct hyponatremia and cessation of hypertonic saline is not possible. The administration of tolvaptan in our case had profound effects on urinary output and we needed to closely monitor the sodium and fluid balance. Our recommendation, in order to avoid osmotic demyelination syndrome, is to start tolvaptan at 0.14 mg/kg and then increase the dose if the clinical response is not as expected, up to 0.28 mg/kg (the maximum dose is 15 mg). Close monitoring of oral fluid intake and urine output, as well as Na concentration, is also recommended to avoid any complications. As the Na concentration starts to increase at the expected rate, further decrement of the dose or continuation with an alternate-day schedule should also be considered.

Hyponatremia was corrected safely in 48 hours and it was possible to reach a steady state of sodium concentration within the normal limits with a small dose of tolvaptan. Cessation of intravenous treatment, discontinuation of strict fluid restriction, and continuation of treatment with a drug used orally have improved the patient's quality of life. Tzoulis et al¹⁷ also described their experiences with tolvaptan in a case series of adult patients and highlighted the noteworthy risk of overly rapid sodium correction, which seemed to be greater in patients with lower-starting sodium concentrations.

In conclusion, tolvaptan is a safe treatment and it should be emphasized that tolvaptan could be an effective treatment option for refractory cases with careful monitoring of the fluid and electrolyte status of the patient. However, randomized controlled trials for

tolvaptan treatment in children diagnosed with SIADH are needed for the determination of indications, safety, prognosis, and dosage recommendations for pediatric patients.

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