



The Treatment of Acute Hyponatremia with Tolvaptan

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Abstract

What is Known and Objective: Acute hyponatremia occurs when serum sodium declines to <135 mEq/L within a 48-hour period. Tolvaptan, a vasopressin receptor antagonist, causes aquaresis without increased sodium loss.

Details of the Case: A 77 year-old male, with a history of glioblastoma, presented with a five-day history of weakness. Serum sodium on admission was 115 mEq/L, and normal saline was started. The following morning serum sodium was 114 mEq/L. Tolvaptan 15mg was given. By hospital day 3, the serum sodium increased to 124 mEq/L following titrated tolvaptan doses.

What is New and Conclusion: Based on these results, tolvaptan may have a role in the treatment of acute hyponatremia.

Keywords: tolvaptan, hyponatremia, acute hyponatremia

WHAT IS KNOWN AND OBJECTIVE

One of the most common electrolyte abnormalities present in the hospital setting is, hyponatremia (sodium levels <135 mEq/L).^{1,2} Hyponatremia result from the kidney's inability to excrete a water load or excess water intake it commonly reflects the amounts of water to sodium in the plasma rather than a sodium deficiency. This abnormality can affect individuals chronically or acutely. Some risk factors include those taking medications such as diuretics, anti-depressant, antiepileptics, antipsychotics, and opioid analgesics.^{2,3,4} Certain disease states including syndrome of inappropriate antidiuretic hormone (SIADH), malignancies, kidney disorders, heart failure, cirrhosis, and uncommonly endocrine disorders serves as risk factors for developing chronic hyponatremia. In contrast risk factors for developing acute hyponatremia include hospitalizations and older age with other risk factors including severe burns, nausea, vomiting, and diarrhea.^{1,2,3,5} Acute hyponatremia present as a rapid decrease in sodium levels in less than 48 hours. This acute reduction in sodium can lead to cerebral. Neurologic events associated with acute hyponatremia may include nausea, vomiting, malaise, headaches, seizures, impaired mental status, coma or death.² In contrast, chronic hyponatremia is characterized by a gradual drop in sodium levels (> 48 hours) with serum sodium concentrations are usually above 120 mEq/L.² Traditional approaches to manage hyponatremia include fluid restriction, saline infusions, and diuretics.

Vaptans, which include tolvaptan and conivaptan, are non-peptide arginine vasopressin receptor antagonists. This medication class was introduced in 2005 as an alternative to traditional therapy.⁶ Tolvaptan is an oral agent indicated for chronic treatment of hyponatremia, while conivaptan is an intravenous agent indicated for acute treatment of hyponatremia. Tolvaptan has affinity for V2 and V1a in a 29:1 ratio, while conivaptan has affinity in a 1:10 ratio.⁷ Action on the V2 receptor is responsible for the antidiuretic properties of these agents. V2 receptors cause free water resorption through insertion of aquaporin-2 channels into apical membranes and induction of aquaporin-2 synthesis. The greater selectivity of tolvaptan for the V2 receptors contributes to its clinical efficacy and supports our hypothesis that tolvaptan may be effective for treatment of acute hyponatremia.⁶ Tolvaptan, like many options for the correction of hyponatremia, carries the risk of osmotic

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demyelination from too rapid correction of low sodium levels. To minimize this risk, tolvaptan should only be initiated in the inpatient setting under close monitoring and slowly titrated to the patient's goal dose.⁷ Because tolvaptan reduces extracellular volume, serum potassium may be increased. Electrolytes should be closely monitored throughout therapy and caution is advised in patients with a serum potassium above 5mEq/L or in those on medications that may concomitantly increase serum potassium levels.⁷ Due to volume loss, patients may also experience dehydration or hypovolemia and should be monitored accordingly. Patients should also be monitored for dry mouth, decreased appetite, constipation, itching, and hyperglycemia.⁷ Hepatotoxicity has been reported in patients receiving tolvaptan for chronic hyponatremia, with an average onset of three months after tolvaptan initiation. This may be less of a risk with tolvaptan in the management of acute hyponatremia as therapy should stop after the resolution of hyponatremia. Nonetheless, in all cases, liver function tests should be monitored and the duration of tolvaptan therapy should not exceed thirty days to avoid any liver injury.⁷

DETAILS OF THE CASE

A 77-year-old Caucasian male presented to the emergency department with a five-day history of worsening generalized weakness progressing to a non-ambulatory state. During this period, home blood pressure readings had been persistently in the hypotensive range. The patient had a past medical history of a recent myocardial infarction, coronary artery disease with placement of three stents, atrial fibrillation, diabetes mellitus type II, hypertension and hyperlipidemia. Three months prior to admission, the patient received a diagnosis of brain cancer when tumors were visualized in the left temporal and parietal lobes on magnetic resonance imaging (MRI). The imaging findings were most consistent with glioblastoma. He was determined to be a poor surgical candidate and tissue biopsy for histological diagnosis was not completed. The onset his weakness corresponded with the completion of his first six-week course of treatment with fractionated external beam radiation and temozolomide 75 mg/m² daily. The patient's baseline mental status had declined since the cancer diagnosis, with intermittent loss of time orientation and occasional word-finding difficulty. Per accompanying family members, the patient was not acutely altered from this new baseline at presentation. He did not report any further symptomatic complaints.

The patient's medication regimen included digoxin 125 µg daily, amiodarone 400 mg twice daily, isosorbide dinitrate 10 mg twice daily, apixaban 5 mg twice daily, clopidogrel 75 mg daily, dexamethasone 125 mg daily, levetiracetam 500 mg twice daily, atorvastatin 40 mg daily, furosemide 40 mg daily, lansoprazole 30 mg daily, ondansetron 8 mg every eight hours, and metformin 500 mg twice daily. At the time of presentation, the patient was found to be hypotensive at 90/53 mmHg and afebrile. All other vital signs were within normal limits. Initial labs showed leukopenia with a white blood cell count of $0.3 \times 10^3/\mu\text{L}$ and severe hyponatremia with a serum sodium of 114 mEq/L. Additional abnormalities included an elevated blood glucose at 240 mg/dL, serum chloride of 83 mmol/L, serum calcium of 7.9 mmol/L, total protein of 5.0 g/dL, albumin of 2.7 g/dL, hemoglobin 12.2 g/dL, hematocrit of 35.2% and platelets of $112 \times 10^3/\mu\text{L}$. Other lab values, to include thyroid studies, were found to be within normal limits.

Blood cultures were drawn and a 1000 mL bolus of intravenous normal saline was given intravenously. He was then admitted to the inpatient service on neutropenic precautions, started on intravenous normal saline at 125 mL/hr and all home medications were continued. Urine osmolality and urine random sodium were ordered and found to be 451 mOsm/kg and 114 mmol/L, respectively.

Given these values, the patient's history of an intracranial tumor, euvolemic appearance on physical exam and a calculated serum osmolality of 246 mOsm/kg, the most likely etiologies of the presenting hyponatremia were determined to be Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and cerebral salt wasting. The patient's generalized weakness was thought to be secondary to the metabolic abnormalities in addition to the recent chemotherapy and radiation treatment.

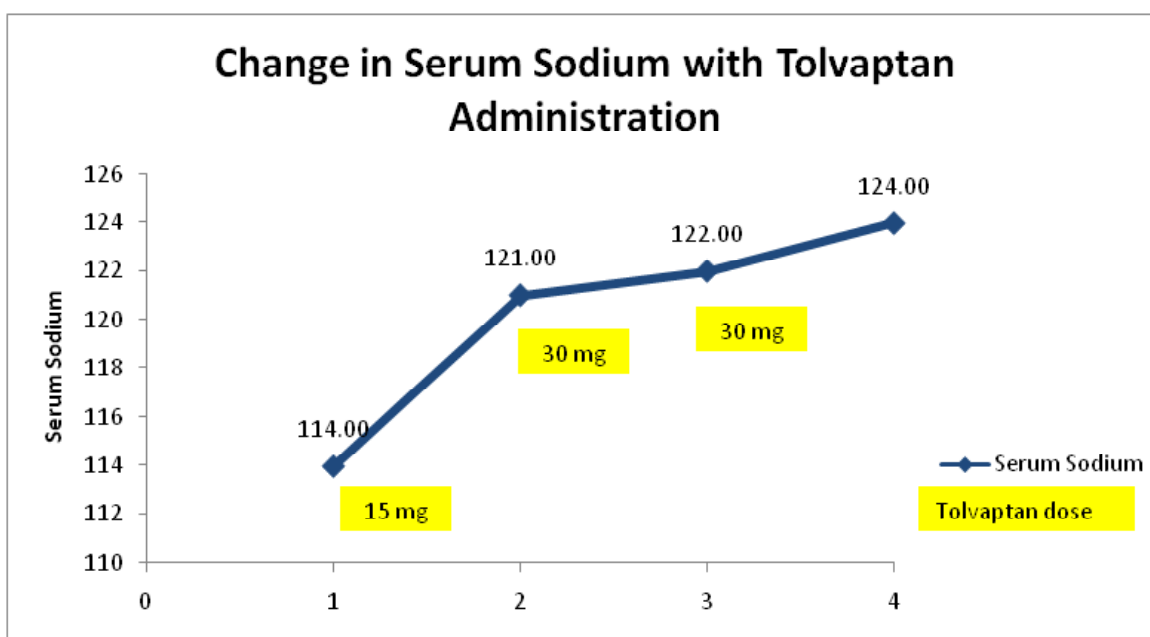
On the next day, hospital day 1, the patient's clinical picture remained stable. His vital signs were within normal limits with an improvement of blood pressure to 109/68 mmHg. Laboratory values for the day showed persistence of the leukopenia and hyponatremia at $0.2 \times 10^3/\text{L}$ and 115 mEq/L, respectively. A brain MRI was

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ordered to compare the intracranial masses with the previous study and revealed reduction in tumor size. A chest X-ray showed bibasilar segmental atelectasis more pronounced on the left, raising suspicion for a left lower lobar pneumonia. Given the leukopenia and imaging findings, the patient was started on filgastrim 480 µg subcutaneous daily and intravenous piperacillin/tazobactam 3.375 mg every eight hours. Given the lack of improvement in the serum sodium level, the patient's home furosemide was discontinued and a 1000 mL daily fluid restriction was initiated. A 20 mg dose of intravenous conivaptan was ordered. Subsequently, it was discovered that conivaptan was not presently available at the facility. As an alternative, oral tolvaptan 15 mg was ordered and administered.

On hospital day 2, the patient's sodium was measured and improved to 121 mEq/L. The patient reported feeling better and regained the ability to stand for short periods. Blood pressure improved further to 125/82 mmHg. An additional dose of 30 mg oral tolvaptan was given. The morning of hospital day 3, the patient's metabolic profile showed improvements in sodium levels with an increase 122 mEq/L. At this same time, the patient's clinical picture began to decline. He developed a temperature of 100.6° F, had a regression in blood pressure to 91/56 mmHg and developed a waxing and waning mental status with loss of orientation. His oxygen requirement increased to four liters in order to maintain oxygen saturation and blood pressure reached a nadir of 68/48 mmHg. Despite this deterioration, daily sodium levels showed continued improvement 124 mEq/L and additional tolvaptan doses were not administered. His clinical deterioration was contributed to the glioblastoma. The patient's family decided to pursue comfort care measures and the patient passed away later that day.

Timeline	Serum Sodium Value (mEq/L)	Treatment Given
On Admission	114 mEq/L	
Hospital Day 1: 1055		Tolvaptan 15 mg
Hospital Day 1: 1950	121 mEq/L	
Hospital Day 2: 1013		Tolvaptan 30 mg
Hospital Day 2: 1453	122 mEq/L	
Hospital Day 3: 0636	124 mEq/L	



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WHAT IS NEW AND CONCLUSION

This is only the second documented case of tolvaptan use for acute hyponatremia. A case published in 2013 reported the use of tolvaptan 15 mg in a 93 year-old female with hypervolemic hyponatremia and acute oliguria. In contrast, our patient experienced hypovolemic hyponatremia. To our knowledge, this is the first published report of the use of tolvaptan for the management of hypovolemic acute hyponatremia. In both cases, these patients experienced a safe rise in serum sodium of 7-9 mEq/L within 24 hours with neurologic improvement and received a second tolvaptan dose. The previous case showed a return to baseline by hospital day 4.⁶

One unique feature of our patient was comorbid glioblastoma. Both the clinical presentation of the tumor and anti-tumor therapy may be involved in the pathogenesis of hyponatremia associated with malignancies. Specifically, malignancies of the brain may lead to excessive sodium loss resulting from cerebral salt wasting. In patients with malignancies, hyponatremia is a serious comorbidity due to its particularly harmful effects on the patient's overall condition. Current available literature supports the hypothesis that hyponatremia is a negative prognostic factor in cancer patients.^{5,8} The patient did pass away during the hospitalization, but the clinical deterioration was contributed to the malignancy and a potential sepsis, but not thought to be related to the hyponatremia. The family made the decision to transition to comfort care measures and therefore pursuit and management of the patient's fever, hypotension, and other symptoms were not undertaken. Had the family wished to continue curative care for the patient, the medical team had planned to administer additional doses of tolvaptan and anticipated continued improvement and resolution of the hyponatremia.

Tolvaptan has an onset of action of two to four hours after administration. At 24 hours after administration, 60% of peak serum sodium elevation is retained, and its half-life elimination is approximately 12 hours. These factors, contribute to our hypothesis that tolvaptan could be efficacious in the acute treatment of hyponatremia.⁹ The SALT-1 and SALT-2 trials assessed the efficacy of tolvaptan. If sufficient correction of hyponatremia did not occur with 15 mg/day, then the study drug could be increased to 30 mg and again to a maximum of 60 mg/day. Responses to each dose of tolvaptan is patient specific. The decision to increase the dose and the rate of titration should be done to maintain a safe rise in serum sodium that does not exceed more than 12 mEq/L in any twenty-four hour period.⁷This titration is required to reduce the risk of osmotic demyelination.⁷Our patient received an appropriate dosing regimen of tolvaptan therapy in accordance with these trials.¹⁰

Our patient's two major risk factors for hyponatremia were his home medication levetiracetam and his malignancy. Hyponatremia is an uncommon adverse event associated with levetiracetam therapy that occurs in less than one percent of patients who take this medication. Despite this risk, we decided not to discontinue his levetiracetam, as this had been a long-term medication and likely not a cause of an acute hyponatremia incident.¹¹

The improvement in the serum sodium in our patient suggests that tolvaptan may represent an option for oral therapy in the treatment of acute hyponatremia. Clinical studies are needed to confirm its safety and efficacy in this setting.

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REFERENCES

1. Aditya S, Rattan A. (2012) Vaptans: A new option in the management of hyponatremia. *Int J Appl Basic Med Res*, 2, 77-83.
2. Chessman K, Matzke GR. (2014) Disorders of Sodium and Water Homeostasis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A pathophysiologic approach*. 9th edition. New York: McGraw-Hill Medical. 745-761.

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3. Goh KP. (2004) Management of hyponatremia. *Am Fam Physician*, 69, 2387-94.
4. Schrier RW, Bansal S. (2008) Diagnosis and management of hyponatremia in acute illness. *Curr Opin Crit Care*, 14, 627-34.
5. Castillo JJ, Vincent M, Justice E. (2012) Diagnosis and management of hyponatremia in cancer patients. *Oncologist*, 17, 756-65.
6. Decaux G, Soupart A, Vassart G. (2008) Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet*, 9624,1624-32.
7. Otsuka America Pharmaceutical Inc. (2009) *Samsca®* (Tolvaptan). MD, United States: US Physicians Prescribing Information.
8. Gopinath S, Janga KC, Greenberg S, Sharma SK. (2013) Tolvaptan in the treatment of acute hyponatremia associated with acute kidney injury. *Case Rep Nephrol*, 2013, 801575.
9. Adrogué HJ, Madias NE. (2000) Hyponatremia. *N Engl J Med*, 42, 1581-9.
10. Onitilo AA, Kio E, Doi SA. (2007) Tumor-related hyponatremia. *Clin Med Res*, 4, 228-37.
11. UCB, Inc. (2009) *Keppra®* (Levetiracetam). Smyrna, GA, United States: US Physicians Prescribing Information.

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