Vasopressin Receptor Antagonist Use in a Neurologic Rehabilitation Center

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Abstract

Background/Objective: To report successful use of a modified protocol of vasopressin receptor antagonist for effective and safe treatment of hyponatremia in a complexly ill patient in the neurorehabilitation setting.

Design: Case report.

Participants/Methods: A 57-year-old man with tetraparesis and protracted hyponatremia resistant to standard therapies.

Results: This patient's rehabilitation from epidural abscess-induced tetraplegia was complicated by symptomatic hyponatremia. The pathophysiology was multifactorial. The course was prolonged, and several therapeutic endeavors failed. Intravenous infusions of vasopressin receptor antagonist induced and maintained eunatremia. The pace of the patient's recovery improved, and he was discharged with substantial neurologic recovery. No central nervous system toxicities of the treatments were observed.

Conclusion: Intravenous vasopressin receptor antagonist is an effective and safe treatment for hyponatremia in the rehabilitation setting if the dosage and monitoring protocols are modified in accordance with the physiology of the patient with spinal cord injury.

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Key Words: Hyponatremia; Vasopressin antagonist; Tetraparesis; Conivaptan; Spinal cord injuries; Tetraplegia

INTRODUCTION

Hyponatremia identifies patients at higher mortality risk and is a common complication in hospitalized patients including those in rehabilitation facilities (1,2). Importantly, both the hypo-osmolar hyponatremic state and its overzealous therapy can cause grave neurologic injury, compounding (and sometimes obscured by) the original neurologic diagnosis (3).

Conivaptan (Vaprisol®) antagonizes both the vasopressin Ia and II receptors, the former regulating vascular tone and the latter renal water conservation (4). The antagonism at the Ia receptor can exacerbate orthostatic hypotension. Blockade of the vasopressin II receptor can cause excessive water diuresis accompanied by rapid increases in serum sodium, resulting in osmotic brain injury including central pontine myelinolysis. Finally, cytochrome p450 3A4 inhibitors elevate conivaptan levels

(5). Drugs metabolized through this cytochrome system are not infrequently used in critical care and rehabilitation medicine. Examples include cimetidine, fluoxetine, protease inhibitors, ketoconazole, itraconazole, macrolide antibiotics (exclusive of azithromycin), amiodarone, simvastatin, digoxin, amlodipine, and even grapefruit juice.

Currently there are clinical trials for 3 orally administered vaptans (lixivaptan, tolvaptan, satavaptan), but only conivaptan (Vaprisol®) is FDA approved for hyponatremia therapy. It is available only in an intravenous formulation and requires a relatively large bore intravenous line. It is not indicated for the treatment of hypovolemic hyponatremia, a diagnosis often difficult to exclude in the neurologically impaired patient. Therefore, all efforts should be taken to assure intravascular volume repletion. This may entail a trial of enteral or intravenous normal saline, cognizant that the hyponatremia of volume depletion will generally improve after normal saline, but the hyponatremia of the syndrome of inappropriate antidiuretic hormone (SIADH) may abruptly worsen. SIADH is a form of euvolemic hyponatremia for which Vaprisol® (conivaptan) is indicated.

The alternative chronic therapies for hyponatremia have major limitations. Loop diuretics cause electrolyte disturbances and worsen hypotension. Lithium is often

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Figure 1. Plasma sodium concentrations (mEq/L) during the course of hospitalization. An arrow ($\downarrow$) represents the days that 20 mg Vaprisol® was administered intravenously.

contraindicated because of its neurologic side effects. Demeclocycline is potentially hepatotoxic and may induce *Clostridium difficile* colitis. When administering demeclocycline, feedings and many essential medications must be delayed by hours, substantially complicating the patient's nutritional and nursing care. We present a case of a euvoletic hyponatremic patient successfully treated with intravenous Vaprisol®.

CASE PRESENTATION

This study received approval from the Research Task Force Committee and the Privacy Board of Craig Hospital (Englewood, CO). Our illustrative patient is a 57-year-old left-handed man who experienced neck pain and weakness just before falling. After 24 hours, the patient was found by neighbors and was sent to the emergency room, from which he was admitted to the hospital with the diagnoses of tetraplegia, bilateral pneumonia, rhabdomyolysis, and acute renal injury. In the acute care hospital, he was found to have a cervical epidural abscess extending from C3 to L1. He was treated with steroids and antibiotics and underwent a cervical laminectomy and abscess drainage. The abscess contents grew oxacillin-sensitive *Staphylococcus aureus*. His hospital course included bouts of sepsis and recurrent encephalopathy. The patient was transferred to Craig Hospital for rehabilitation, where he was found to have symptomatic and persistent hyponatremia. Of pertinence was the patient's history of alcohol abuse, resulting in hepatic cirrhosis with portosystemic shunting. He had a history of angioedema from tetracyclines and was unable to comply with fluid restriction. Bumetanide caused hypo-

kalemia and hypotension. Lithium induced intolerable fatigue and malaise. After excluding adrenal insufficiency, hypothyroidism, recurrent renal failure, removing offending medications, and assuring the patient was euvoletic, we elected to treat with intravenous conivaptan (Vaprisol®). Initially, conivaptan was used per critical care protocols, but, given the patient's need to resume physical therapy and given the chronicity, the conivaptan protocol was altered. He received a 20-mg intravenous bolus to initiate the course of therapy. This was followed by short, daily intravenous infusions of 20 mg of conivaptan in the morning before his physical therapy for a total of 13 doses.

The patient's plasma sodium concentrations are shown in Figure 1. The patient showed worsening cognition with confusion and agitation correlating with a precipitous drop in serum sodium from 134 to 126 mEq/L over 24 to 48 hours. This state was superimposed on the aforementioned encephalopathy purportedly caused by alcoholism and episodes of hypoxia. Nephrology consultation was requested. Interviewed staff attested to the patient's increased fluid intake and refusal to abide by fluid restrictions as the proximate cause of the hyponatremia. Earlier stability of the serum sodium correlated with the patient's physical inability to access water. Additionally pertinent was evidence of hepatic cirrhosis with its attendant abrogation of free water excretion (6). No significant hypotension occurred during physical therapy. There were no electrolyte imbalances, and there was no worsening of his neurologic status and no injection site reactions during the therapeutic course.

DISCUSSION

Recent therapies for hyponatremia have evolved in the acute care setting, leaving a dearth of guidelines for their use in the rehabilitation facilities. New treatments include a novel pharmacologic class of drugs called “vaptans.” These are selective vasopressin-receptor antagonists, which induce an aquaresis—ie, a predominant water diuresis, which is appropriate therapy for euvolemic or hypervolemic hyponatremia.

In this patient, the acute onset symptomatic hyponatremia was assessed as euvolemic and was treated with conivaptan per the critical care and manufacturer’s protocol, which specifies a 20-mg intravenous bolus over 30 minutes, followed by a 20-mg infusion over 24 hours. Our goal was to correct the new neurologic signs while limiting the total increment in serum sodium to <10 to 12 mEq/L in 24 hours. These are established precautions in an attempt to obviate the development of pontine and extrapontine myelinolysis. The rate of rise of the serum sodium over the next day (day 16; Figure 1) was in excess of the most current recommendations for hyponatremia correction (6). Therefore, the serum sodium level was allowed to drop quickly to the mildly hyponatremic range, and the conivaptan protocol used for subsequent dosing was decreased to the 20-mg bolus only. This regimen stabilized the serum sodium level from days 20 to 70. The frequency of conivaptan dosing was guided by multiple factors including observations of patient’s intake exceeding fluid limits, additional fluids administered as intravenous medications, and activities or medications that impair water excretion. Point in time assessment of free water excretion was approximated by the value of:

$$1 - \frac{[\text{Na}]_{\text{urine}} + [\text{K}]_{\text{urine}}}{[\text{Na}]_{\text{plasma}}}$$

wherein a negative result indicates free water retention and progressively positive results indicate improving free water clearance (7). An attempt was made to preempt episodes of acute symptomatic hyponatremia.

Fluid restriction, a treatment fundamental for most forms of hyponatremia, is notoriously difficult to enforce in patients with traumatic brain injury or stroke. Brain injury-related disinhibition, impulsivity, and altered thirst prompt patients to drink excessively. Often draconian tactics—incompatible with humanistic rehabilitative efforts—are needed to prevent excessive imbibition.

Altering the paradigm for vaptan therapy in neurorehabilitation is appropriate when considering the particularities of the pathophysiology of hyponatremia in this patient population. Unlike patients in the critical care unit, patients in neurorehabilitation are often sitting upright in a power wheelchair. The change in position and its attendant decrease in systemic blood pressure and consequent reduction in renal perfusion markedly lower renal free water clearance. The mechanisms for this effect include non-vasopressin-related factors. In this

patient, maximal urinary dilution and free water clearance were additionally impaired by hepatic cirrhosis. Conivaptan can be given in the morning, as the patient assumes the sitting position, with minimal risk of excessive diuresis, which could otherwise result in dangerous increments in plasma sodium.

Of importance with any novel therapy are the singular advantages, the cost, and the cost effectiveness. This patient showed intolerances or frank contraindications to most of the treatments for hyponatremia. The conivaptan infusions were well tolerated and increased urine output sufficiently to liberalize the fluid allowance. This resulted in a marked decrement in the need for restraints and constant observation. The patient’s agitation dissipated, and he required fewer sedatives and psychotropic agents. The patient became more compliant and was able to resume rehabilitative therapy. These issues must also be considered in any overall cost assessment. This notwithstanding, conivaptan is expensive. The pharmacy cost for 13 doses was \$7,852.74. This also needs to be compared with alternative therapies. Thirteen doses of 3% saline (250 mL/bag) was \$1,800.27 and 2.5 months of demeclocycline at 300 mg, 3 times per day (contraindicated in this patient) was \$1,368. If conivaptan resulted in avoiding complications that prolong hospital stay, offsetting cost savings would accrue.

CONCLUSION

As with any novel medication, the primary physician, consultant, and pharmacy staff must work diligently with nursing staff to evolve and implement guidelines that detail the indications and contraindications, techniques of administration, potential side effects, and safety issues. In this case, intravenous vasopressin receptor antagonist therapy was an effective and safe option for the treatment of hyponatremia in the rehabilitation setting.

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