CLINICAL VIGNETTE

Trimethoprim-Sulfamethoxazole: A Contributor to Symptomatic Hyponatremia

Sarintha Bell, RN and Adam Cavallero, MD

Case Presentation

An 81-year old Caucasian female presented to her primary care physician's office complaining of nausea, decreased appetite, and weight loss. She denied any associated fever, chills, abdominal pain, or changes in bowel movements. She had right total knee arthroplasty 3 weeks prior. The surgeon suspected postoperative wound infection and prescribed post-op cephalexin. Due to continued wound erythema and discharge, the antimicrobial therapy was changed to oral trimethoprim-sulfamethoxazole (160/800 mg) twice a day about a week before her visit.

Vital signs included elevated blood pressure of 154/80, with normal temperature, respiratory rate and pulse. Physical examination was only notable for slightly decreased skin turgor. Abdomen was non-distended, without guarding or tenderness. Preop labs were unremarkable. X-rays showed proper alignment without hardware complications.

Multiple labs were obtained in the office. Basic metabolic panel returned showing markedly decreased sodium of 122 mmol/L, and mildly decreased chloride of 84 mmol/L. Lipase and hepatic function were normal. Complete blood count revealed a mild leukocytosis with white blood cell count of 10,000 uL. Platelets were also elevated at 515,000 uL and she was mildly anemic with hemoglobin of 10.1 g/dL and a hematocrit of 30.3%.

Because of the severe hyponatremia the patient was contacted and sent to the ED for further evaluation. She was initially treated with parenteral normal saline and admitted and fluid restricted to less than 800 ml per day and started on oral sodium chloride tablets 1 g twice a day. Her hydrochlorothiazide was held and continues on benazepril 10 mg daily. She was discharged to complete her 10-day course of oral sulfamethoxazole/trimethoprim.

The patient deteriorated after hospital discharge and was re-evaluated in the office five days later. She continued with poor appetite and weight loss, now accompanied by somnolence and decreased mental acuity. She returned to the emergency room where she was again found to be hyponatremic, with a serum sodium of 125 mmol/L. Occult paraneoplastic malignancy was evaluated with a negative CT of the chest and brain. The patient was was restarted on fluid restriction of less than 1200 mL per day, and given a liberal salt diet. Her thiazide diuretic and trimethoprim-sulfamethoxazole were held. She improved back to her baseline status and was discharged home. The patient was suspected to have a multifactorial etiology of symptomatic hypotonic hyponatremia, secondary to hydrochlorothiazide and from SIADH from her postoperative status, exacerbated by nausea associated with trimethoprim-sulfamethoxazole.

Discussion

Hyponatremia is defined as serum sodium concentration less than 135 mEq/L. Hyponatremia is categorized based on volume status, as hypovolemic, euvolemic, or hypervolemic.[1] Symptoms of hyponatremia, are related to cerebral edema and include headache, lethargy, confusion, dizziness, nausea, vomiting, and muscle cramps. If untreated, severe hyponatremia may lead to seizures, coma, brainstem herniation, and death.[2] The diagnostic approach to hyponatremia requires evaluation of serum osmolality, as well as urine sodium levels which confirmed with volume status determine the classification.[3]

Treatment of hyponatremia includes correction of the underlying cause. Sodium should be replaced gradually either intravenously or orally. Too rapid sodium repletion increases risks for Osmotic Demyelination Syndrome, and irreversible neurological injury. Fluids should be carefully replaced with isotonic fluids in hypovolemic hyponatremia, or restricted in euvolemic and hypervolemic hyponatremia.[3]

This patient's unexpected hyponatremia was likely due to multiple factors including postoperative status, and diuretic use, which can contribute to hypovolemic sodium loss. Additionally, severe hyponatremia is an adverse effect of trimethoprim-sulfamethoxazole, which was likely a major contributor.

Hyponatremia associated with trimethoprim-sulfamethoxazole has been reported in multiple case reports.[4-6] The precise mechanism is not definitively established. However, it appears that trimethoprim-sulfamethoxazole may trigger SIADH and increased natriuresis.[5] It is hypothesized that this effect may be due to the fact that trimethoprim has a structural similarity to potassium sparing diuretics.[6] Signs and symptoms of hyponatremia may become apparent within the first several days of initiating therapy. Potential risk factors for trimethoprim-sulfamethoxazole induced hyponatremia include advanced age, high dose therapy, concurrent use of medications known to cause hyponatremia,[4] and HIV infection.[6]

Broader awareness of this uncommon, but serious adverse effect is needed. Prescribers should monitor patients who are undergoing treatment with longer courses of trimethoprim-sulfamethoxazole, and possibly consider alternative treatment for those with increased risk for severe hyponatremia.

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