Severe hyponatremia due to trimethoprim-sulfamethoxazole-induced SIADH

Creticus Marak1, Matthew Nunley2, Achuta Kumar Guddati3, Prashant Kaushik4, Mark Bannon2 and Adrita Ashraf2

Abstract
Hyponatremia, a serum sodium level of <135 mEq/L, is the most common electrolyte abnormality occurring in 5%–35% of hospitalized patients. It is a predictor of increased morbidity and mortality. Diuretics, psychotropic, and antiepileptic drugs are commonly implicated in drug-induced hyponatremia. Trimethoprim-sulfamethoxazole and spironolactone are two commonly prescribed drugs; unfortunately, most providers are unfamiliar with these two drugs causing hyponatremia. Simultaneous use of trimethoprim-sulfamethoxazole and spironolactone can cause serious drug interactions that increase the risk of hyponatremia, hyperkalemia, and overall mortality. Despite recommendations to avoid using these two drugs concurrently, many healthcare providers continue to prescribe them together. We report a case of an elderly female with severe hyponatremia caused by trimethoprim-sulfamethoxazole superimposed on a chronic but stable mild hyponatremia.

Keywords
Trimethoprim-sulfamethoxazole, spironolactone, amiloride, sodium channels, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), natriuresis

Date received: 25 May 2022; accepted: 27 September 2022

Introduction
Nowadays, polypharmacy is common, especially among the elderly. A wide range of prescribed and over-the-counter medications can cause hyponatremia. A well-established but underappreciated cause of hyponatremia is trimethoprim-sulfamethoxazole (TMP-SMX). Trimethoprim (TMP) is structurally similar to amiloride and acts on the same epithelial sodium channels (eNAC) in the distal nephron, causing natriuresis and hyponatremia. It is also possible to develop a syndrome of inappropriate antidiuretic hormone secretion (SIADH) while taking TMP.

TMP-SMX is a commonly prescribed antimicrobial known to cause moderate to severe hyponatremia. TMP works by blocking amiloride-sensitive sodium channels in the distal convoluted tubules and collecting ducts.1 Usually, hyponatremia begins between days 3 and 101 and resolves within 3 weeks after stopping the drug. Similarly to amiloride, TMP can cause hyperkalemia and hyponatremia.1,2

Hyponatremia occurs in approximately 72% of patients receiving high doses of intravenous (IV) TMP-SMX.3 Hyponatremia can, however, be caused by low prophylactic doses.4 High IV TMP-SMX doses can cause salt-losing nephropathy characterized by hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis.5 SIADH is more likely to occur with lower doses of oral TMP-SMX (once or twice daily dosing) than with the higher doses typically used for treating pneumocystis jiroveci pneumonia (PJP).6,7 Dilutional hyponatremia may also occur with high doses of IV TMP-SMX. In cases of moderate to severe PJP pneumonia, the recommended dose of TMP is 15–20 mg/kg/day for 21 days. TMP-SMX is usually diluted in 5% Dextrose water when administered intravenously. According to the maximum permissible dilution of TMP at 80 mg per 75 mL of 5%
Dextrose, an average 70kg patient can easily receive up to 1000 mL of free water per day. By applying Edelman’s equation, we expect the serum sodium to decrease by at least 2–3 mEq/L/day.

Case presentation

A pleasant 80-year-old female with hypertension, atrial fibrillation, hypothyroidism, chronic low back pain, and chronic hyponatremia presented to our hospital with nausea, fatigue, and generalized weakness for 3 days. She reported taking salt tablets periodically for chronic hyponatremia. Previously, her serum sodium levels ranged between 128 and 133 mEq/L; a month ago, her sodium level was 129 mEq/L (reference range: 135–145 mEq/L). Two days before hospitalization, she completed 3 days of outpatient treatment for urinary tract infection (UTI) using oral TMP-SMX (160/800 mg, 1 tablet twice daily). Her home medications included spironolactone 25 mg once daily, gabapentin 200 mg twice daily, amiodarone 200 mg once daily, aspirin 81 mg once daily, losartan 50 mg once daily, levomethoroxine 25 µg once daily, apixaban 5 mg twice daily, and hydrocortone/acetaminophen four times daily as needed. She denied headaches, syncope, paresthesia, seizures, abdominal pain, vomiting, constipation, or diarrhea. A detailed review of her other systems was unremarkable. On examination, her blood pressure (BP) was 188/80, heart rate (HR) 80/min, respiratory rate (RR) 16/min, SpO2 95% on room air (RA), and temperature 36.8°C. She was awake, alert, oriented, and seated comfortably in bed. Her oral mucosa was moist; she had no focal neurological deficits; her breath sounds were clear with no crepitation or wheezes; her heart sounds were regular with no murmur; her abdomen was soft with normoactive bowel sounds, and her extremities were warm and perfused without edema. Her routine blood test showed sodium of 111 mEq/L (reference range: 135–145), serum osmolality 230 mOsm/kg (reference range: 275–295), potassium 5.1 mEq/L (reference range: 3.5–5), chloride 77 mEq/L (reference range: 96–106), bicarbonate 18 mEq/L (baseline 24 mEq/L, reference range: 21–32), anion gap 16 (reference range: 8–12), BUN 14 mg/dL (baseline 12–14 mg/dL, reference range: 8–23), creatinine 1.0 mg/dL (baseline 1–1.10 mg/dL, reference range: 0.2–0.7), glucose 127 mg/dL (reference range: 70–115), calcium 9.7 mg/dL (reference range: 8.6–10.2), albumin 4.1 gm/dL (reference range: 3.5–5.2), random cortisol 22 µg/dL (reference range: 5–20), TSH 14.5 uIU/mL (reference range: 0.34–4.8), and uric acid 2.4 mg/dL (reference range: 3.4–7). Her urine studies revealed sodium of 99 mEq/L and urine osmolality of 354 mOsm/kg.

An initial working diagnosis was hyponatremia caused by TMP-SMX-induced natriuresis. She was started on IV normal saline (0.9% NS) with close monitoring of her serum sodium. Her serum sodium initially increased to 116 mEq/L; however, after receiving close to 2.5 L, it decreased to 112 mEq/L. At this point, we limited her 24-h oral fluid intake to 1000 mL and started her on sodium chloride tablets, 1 gm four times daily. Fluid restriction and salt supplements gradually improved her symptoms and sodium level. She was discharged on the fifth hospital day with restricted fluid intake (1000 mL daily), oral sodium chloride tablets, 1 gm four times daily, and close outpatient follow-up. At discharge, her serum sodium was 128 mEq/L, potassium 4.4 mEq/L, bicarbonate 23 mEq/L, BUN 15 mg/dL, creatinine 0.9 mg/dL with a normal anion gap of 11. Her diagnosis was hyponatremia due to TMP-SMX-induced SIADH.

Discussion

Our patient presented with severe hyponatremia. She was euvoletic, and her blood tests (sodium, serum osmolality, renal function, uric acid, TSH, cortisol) and urine tests (urine sodium and osmolality) indicated SIADH. Because of previous reports of hyponatremia caused by TMP-SMX's diuretic effect and the possibility of enhanced natriuretic effect due to drug interactions between TMP-SMX and spironolactone, we initially started her on IV 0.9% NS. Even though her sodium level initially increased, it eventually decreased after she received adequate amounts of normal saline. It is not uncommon for patients with SIADH to experience a biphasic response to IV 0.9% NS. In light of this, we put her on fluid restriction and salt tablets, which improved her sodium levels. The patient’s blood and urine tests and her response to fluid restriction and salt tablets support the diagnosis of SIADH.

Hyponatremia caused by TMP-SMX has previously been attributed to either the natriuretic effect or SIADH. Several previously reported cases of TMP-SMX-induced hyponatremia thought to be due to its natriuretic effect received high doses of the drug. Some, maybe a couple, of the reported cases cited SIADH as the cause of hyponatremia; these patients received much lower doses of oral TMP-SMX. Based on the previously published studies, we speculate that higher IV and oral doses of TMP-SMX may cause natriuresis more frequently than lower oral doses and vice versa. Our patient received a lower dose of TMP-SMX (160/800), 1 tablet twice daily for 3 days.

Spironolactone causes hyponatremia quite frequently, with an incidence comparable to chlorthalidone, a commonly prescribed diuretic. Patients who develop hyponatremia while taking spironolactone take 25 mg or less a day. Typically, hyponatremia develops around the 40th day with a sodium level of around 130 mEq/L. People with chronic kidney disease and older White people are more likely to suffer from hyponatremia. Spironolactone was probably responsible for our patients’ chronic hyponatremia.

This patient had other conditions known to cause hyponatremia, including hypothyroidism and her prescription drugs (losartan, gabapentin, amiodarone, hydrocortone). When hypothyroid patients develop hyponatremia, they usually suffer from severe symptoms or have myxedema. Although
our patient’s TSH level was elevated, she was asymptomatic, suggesting hypothyroidism was not the cause of her severe hyponatremia. She has been on her prescription medicines for years, and with no recent dose changes to her medications, it is unlikely that these medications were responsible for her severe hyponatremia.

The combination of TMP-SMX and spironolactone increases the risk of hyperkalemia, hyponatremia, and sudden death.14,15 Hyperkalemia has been reported to occur in up to 10% of patients taking TMP-SMX and spironolactone concurrently.16 TMP-SMX was probably the cause of the hyponatremia in our patient, based on Naranjo’s probability scale.16 Providers need to consider drug interactions between TMP-SMX and spironolactone since both drugs are readily available and routinely prescribed.

**Conclusion**

Depending on the dose and route of administration, TMP-SMX may cause hyponatremia by different mechanisms (diuretic effect, SIADH, and dilutional). This case will add to the growing body of literature regarding TMP-SMX-induced SIADH. Although TMP-SMX causes hyponatremia, most healthcare providers do not know about this condition due to underreporting and lack of longitudinal studies. Healthcare providers should avoid the use of TMP-SMX and spironolactone together.

**Acknowledgements**

With great pleasure, we extend our thanks to the ICU nursing staff at Northeastern Health System for taking good care of this patient.

**Author contributions**

Creticus Marak: Principal author, wrote the manuscript.

Matthew Nunley: Reviewed literature and collected data.

Achuta Kumar Guddati: Reviewed and edited the manuscript.

Prashant Kaushik: Reviewed and edited the manuscript.

Mark Bannon: Managed the patient, reviewed literature, and collected data.

Adrita Ashraf: Managed the patient, reviewed literature, and collected data.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethical approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed consent**

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

**ORCID iD**

Creticus Marak https://orcid.org/0000-0003-3666-3001

**References**

1. Lei H, Liu X, Zeng J, et al. Analysis of the clinical characteristics of hyponatremia induced by trimethoprim/sulfamethoxazole. *Pharmacology* 2022; 107(7–8): 351–358.

2. Choi MJ, Fernandez PC, Patnaik A, et al. Brief report: trimethoprim-induced hyperkalemia in a patient with AIDS. *N Engl J Med* 1993; 328(10): 703–706.

3. Tarssanen L, Huikko M and Rossi M. Amiloride-induced hyponatremia. *Acta Med Scand* 1980; 208(6): 491–494.

4. Babayev R, Terner S, Chandra S, et al. Trimethoprim-associated hyponatremia. *Am J Kidney Dis* 2013; 62(6): 1188–1192.

5. Nawaz Z, Amala CS and Oyibo SO. Syndrome of inappropriate antidiuretic hormone secretion and trimethoprim-related hyponatremia following transurethral bladder wall biopsy. *Cureus* 2021; 13(8): e17454.

6. Takubo M, Tanaka S, Kushimoto M, et al. Hyponatremia associated with prophylactic low-dose trimethoprim during systemic corticosteroid therapy for AQP4-positive optic neuritis in a diabetic patient. *Antibiotics* 2020; 9(4): 201.

7. Ghali MGZ and Kim MJ. Trimethoprim-sulfamethoxazole-induced hyponatremia in an elderly lady with Achromobacter xylosoxidans pneumonia: case report and insights into mechanisms. *Medicine* 2020; 99(33): e20746.

8. Velasco MJ. Severe symptomatic hyponatremia induced by trimethoprim-sulfamethoxazole. *J Med Case 1923*; 5(5): 283–284.

9. Handler J. Well tolerated spironolactone-related hyponatremia. *J Clin Hypertens* 2008; 10(4): 317–321.

10. Das S, Bandypadhyay S, Ramasamy A, et al. A case of losartan-induced severe hyponatremia. *J Pharmacol Pharmacother* 2015; 6(4): 219–221.

11. Falhammar H, Lindh JD, Calissendorff J, et al. Differences in associations of antiepileptic drugs and hospitalization due to hyponatremia: a population-based case-control study. *Siezure* 2018; 59: 28–33.

12. Patel GP and Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002; 22(5): 649–651.

13. Liamsis G, Filipatodos TD, Lontios A, et al. Management of endocrine disease: hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. *Eur J Endocrinol* 2017; 176(1): R15–R20.

14. Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. *BMJ* 2011; 343: d5228.

15. Antoniou T, Hollands S, Macdonald EM, et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. *CMAJ* 2015; 187(4): E138–E143.

16. Naranjo CA, Bustu U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2): 239–245.