

Hyponatremia Associated With Standard-Dose Trimethoprim-Sulfamethoxazole Use in an Immunocompetent Patient

Ahad Azeem, MD; Nida Majeed, MD; Samreen Khuwaja, MD

ABSTRACT

Introduction: Trimethoprim-sulfamethoxazole (TMP-SMX) use in immunocompromised patients can cause dose-dependent electrolyte irregularities including hyponatremia, hyperkalemia, and metabolic acidosis. We report a case of isolated hyponatremia caused by low-dose TMP-SMX use in an immunocompetent patient that mimicked the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Case Presentation: A 72-year-old woman was admitted to the hospital for acute onset of weakness and ambulatory dysfunction after starting TMP-SMX (160 mg/800 mg). She was found hyponatremic (sodium level, 125 mmol/L, down from 141 mmol/L prior to medication initiation). After ruling out diuretics use, and adrenal and thyroid dysfunction, we started her on intravenous saline infusion to manage her TMP-SMX-induced hyponatremia, and her symptoms resolved.

Discussion: Electrolyte problems in immunocompromised patients treated for opportunistic infections with high-dose TMP-SMX (≥ 8 mg/kg/d TMP) are well-documented. However, the effects in immunocompetent patients are uncommon when standard dose (< 8 mg/kg/d TMP) is used.

Conclusions: TMP-SMX blocks the aldosterone-mediated sodium reabsorption in the collecting ducts, and the trimethoprim component itself is structurally similar to potassium-sparing diuretics, which block sodium uptake at the distal nephron—both of which can cause hyponatremia.

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality seen in hospitalized patients and is usually caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH).¹ However, it is important to differentiate the etiology from other possible causes.

• • •

Author Affiliations: Creighton University, Omaha, Nebraska (Azeem); Boys Town National Research Hospital, Omaha, Nebraska (Majeed); Christus Saint Elizabeth, Beaumont, Texas (Khuwaja).

Corresponding Author: Ahad Azeem, MD, 7500 Mercy Rd, Omaha, NE 68124; phone 443.537.0078; email drahadazeem@gmail.com.

Trimethoprim-sulfamethoxazole (TMP-SMX) is used to treat various kinds of upper respiratory, pulmonary, gastrointestinal, and genitourinary infections. High-dose TMP-SMX use in treating opportunistic infections in immunocompromised patients can cause dose-dependent electrolyte irregularities, including hyponatremia, hyperkalemia, and metabolic acidosis.^{2,3} We report a case of isolated hyponatremia caused by TMP-SMX use in an immunocompetent patient that mimicked SIADH. Despite using standard dose and having a normal renal function, our patient developed a volume-depleted state requiring sodium and water supplementation.

CASE PRESENTATION

A 72-year-old woman with a past medical history of chronic thrombocytopenia and hyperlipidemia presented with acute onset

of resting tremors and weakness complicated by 2 days of ambulatory dysfunction. She was assessed in the emergency department (ED) 4 days prior to admission secondary to the development of a right finger abscess requiring local incision and drainage. On discharge from the ED, she was prescribed a 7-day course of TMP-SMX (160 mg/800 mg). On initial examination, her body temperature was 98.6°F, pulse was 94 beats/minute, blood pressure was 133/75 mmHg, and respiratory rate 16 breaths/min with a room air oxygen of 97%. Physical exam revealed an alert, thin, elderly patient with an unsteady gait.

Her metabolic panel showed a serum sodium level of 125 mmol/L (reference range, 135-145 mmol/L), and creatinine of 0.93 mg/dL (reference range, 0.50-1.30 mg/dL), along with

other laboratory results as mentioned in the Table. The metabolic panel revealed normal serum aldosterone, uric acid, and thyroid function tests and ruled out adrenal abnormalities. One month earlier, her serum sodium level was 141 mmol/L. Urine studies performed on admission are shown in the Table.

After the collection of urine and serum studies, empiric treatment with intravenous saline infusion was initiated for volume resuscitation. TMP-SMX was discontinued as a possible causative agent for the patient's clinical symptoms and hyponatremia. Her metabolic panel was monitored for the next 48 hours, and her serum sodium levels gradually improved to 137 mmol/L in 2 days—the time of discharge. The patient recovered well, and her gait improved with the resolution of hyponatremia. She was discharged to the outpatient setting. During her primary care visit 5 days later, serum sodium was 142 mmol/L. She was advised against future exposure to TMP-SMX to prevent similar complications.

DISCUSSION

Trimethoprim-sulfamethoxazole (TMP-SMX) is used to treat various kinds of upper respiratory, pulmonary, gastrointestinal, and genitourinary infections. It is a combination of 2 antibiotics that produce a bactericidal effect by blocking the biosynthesis of proteins.⁴ While the exact mechanism of action is unknown, TMP-SMX is known to block aldosterone-mediated sodium reabsorption in the collecting ducts of the kidney. The trimethoprim component is structurally like potassium-sparing diuretics, which block sodium uptake at the distal nephron and, in combination with the inactivated aldosterone-mediated process, can cause hyponatremia.⁵ Various studies have shown electrolyte problems in immunocompromised patients treated for *Pneumocystis jiroveci* pneumonia when high-dose TMP-SMX (≥ 8 mg/kg/d TMP) is used.⁶ As TMP-SMX is excreted in the urine, underlying renal dysfunction, coadministration of nephrotoxic chemotherapy, and older age predispose the patient to skin and gastrointestinal adverse effects in addition to electrolyte abnormalities.^{3,7} However, similar effects in immunocompetent patients lacking underlying comorbidities with standard dose TMP-SMX (< 8 mg/kg/d TMP) are not well-known, which was the case in our patient.⁵ Coadministration of sodium-lowering medications, such as ciprofloxacin, selective-serotonin reuptake inhibitors, thiazide diuretics, antipsychotics, antiepileptics, and angiotensin-converting enzyme inhibitors, can cause life-threatening hyponatremia, particularly in older adults with compromised kidney functions.^{5,7}

Hyponatremia is defined as serum sodium levels < 135 mmol/L and is associated with an increased mortality risk during hospitalization.^{5,8} While it is a common electrolyte abnormality, it is challenging to identify the etiology, because volume status assessment is based on the findings of a subjective clinical examination.¹ In hospitalized patients, the most frequent cause of hyponatremia is

Table. Clinical Laboratory Results

Variable	Reference Range	Hospital Day 1	Hospital Day 2	Hospital Day 3
Serum Studies				
Sodium (mmol/liter)	135–145	125 ^a	131 ^a	137
Potassium (mmol/liter)	3.5–5.3	4.3	4.0	
Chloride (mmol/liter)	96–108	92 ^a	110 ^b	
Bicarbonates (mmol/liter)	22–31	21 ^a	20 ^a	
Creatinine (mg/dL)	0.50–1.30	0.93	0.74	
Glucose (mg/dL)	77–99	101 ^b	95	
eGFR (mL/min/1.73 m ²)	≥ 90	91	86 ^a	
Aldosterone (ng/dL)	< 39.2		3.0	
Uric acid (mg/dL)	2.6–7.2		6.2	
Cortisol (μ g/dL)	6.0–18.4		12.1	
TSH (μ U/mL)	0.34–4.82	3.27		
Osmolality (osm/kg)	275–300	275		
Urine Studies				
Protein, UA (mg/dL)	Negative	1+		
Osmolality, urine (osm/kg)	50–1200	269		
Sodium, urine (mmol/L)	40–220	67		
Creatinine, urine (mg/dL)	30–125	15 ^a		

Abbreviations: eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone; UA, urine analysis.

^aThe value in this patient was below normal range.

^bThe value in this patient was above normal range.

SIADH triggered by symptoms (eg, nausea, pain), medications, and conditions (eg, AIDS and cardiovascular, pulmonary, or central nervous system diseases).^{1,6} High-dose TMP-SMX (≥ 8 mg/kg/d TMP) use with reduced kidney function can cause hyponatremia, along with hyperkalemia and metabolic acidosis—key differentiating factors from SIADH, as both conditions are associated with urine sodium levels > 40 mmol/L and elevated urine osmolality (> 100 mOsm/kg).^{6,7} Renal salt wasting secondary to TMP-SMX use usually leads to a water-depleted state, unlike SIADH, and requires sodium supplementations, intravenous saline infusion, and potassium restriction as prophylaxis and treatment.^{1,6,7}

Our patient developed symptomatic hyponatremia within 4 days of starting low-dose TMP-SMX (< 8 mg/kg/d TMP). Abnormal thyroid, adrenal, and renal functions can be associated with hyponatremia but were ruled out in this case (Table). Her urine and serum studies mimicked SIADH, but her chest x-ray and computed tomography scan of the head did not show any abnormality, infection, or malignancy, which may have been a possible cause. Based on high clinical suspicion and the patient's recent TMP-SMX use and hypovolemic state, a saline infusion was started. Her symptoms and serum sodium level improved, and SIADH was ruled out.

CONCLUSIONS

While SIADH is the most common cause of hyponatremia in hospitalized patients, it should be differentiated from other pos-

sible etiologies, such as adrenal and thyroid dysfunction. TMP-SMX blocks the aldosterone-mediated sodium reabsorption in the collecting ducts, and the trimethoprim component itself is structurally similar to potassium-sparing diuretics that block sodium uptake at the distal nephron—both of which can cause hyponatremia. Unlike SIADH, TMP-SMX-induced hyponatremia requires sodium supplementation rather than free water restriction.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Babayev R, Terner S, Chandra S, Radhakrishnan J, Mohan S. Trimethoprim-associated hyponatremia. *Am J Kidney Dis.* 2013;62(6):1188-1192. doi:10.1053/j.ajkd.2013.06.007
2. Lee JS, Owshalimpur D, Schofield C. Trimethoprim/sulfamethoxazole induced multiorgan dysfunction. *BMJ Case Rep.* 2012;2012:bcr2012007460. doi:10.1136/bcr-2012-007460
3. Memoli E, Faré PB, Camozzi P, et al. Trimethoprim-associated electrolyte and acid-base abnormalities. *Minerva Med.* 2021;112(4):500-505. doi:10.23736/S0026-4806.20.06660-4
4. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ.* 2011;183(16):1851-1858. doi:10.1503/cmaj.111152
5. Huntsberry AM, Linnebur SA, Vejar M. Hyponatremia after initiation and rechallenge with trimethoprim-sulfamethoxazole in an older adult. *Clin Interv Aging.* 2015;10:1091-1096. doi:10.2147/CIA.S82823
6. Tsapepas D, Chiles M, Babayev R, et al. Incidence of hyponatremia with high-dose trimethoprim-sulfamethoxazole exposure. *Am J Med.* 2016;129(12):1322-1328. doi:10.1016/j.amjmed.2016.07.012
7. Mori H, Kuroda Y, Imamura S, et al. Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. *Intern Med.* 2003;42(8):665-669. doi:10.2169/internalmedicine.42.665
8. Dineen R, Thompson CJ, Sherlock M. Hyponatraemia - presentations and management. *Clin Med (Lond).* 2017;17(3):263-269. doi:10.7861/clinmedicine.17-3-263

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2022 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

Visit www.wmjonline.org to learn more.