Severe hyponatremia due to trimethoprim-sulfamethoxazole: a case report

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Background: Hyponatremia, a prevalent electrolyte imbalance with varying degrees of severity, can lead to mild to severe complications. Trimethoprim-sulfamethoxazole (TMP-SMX) and spironolactone are two frequently administered medications; regrettably, most healthcare professionals are not aware that these medications might cause hyponatremia. Concurrently, the two drugs have a high chance of medication interactions that raise the risk of hyponatremia, hyperkalemia, and death overall. TMP-SMX is implicated in causing hyponatremia through diverse mechanisms, such as inhibiting the renal tubular epithelial enzyme carbonic anhydrase. Structurally akin to the potassium-sparing diuretic amiloride, TMP-SMX is linked to hyperkalemia and hyponatremia by obstructing epithelial sodium channels in the distal nephron. Moreover, TMP-SMX may enhance antidiuretic hormone (ADH) release, exacerbating the imbalance.

Case Description: This is a case of a 76-year-old man with a medical history including hypertension, type II diabetes, coronary artery disease, and dyslipidemia. This case highlights an elderly patient treated with TMP-SMX for a soft tissue wound infection, which resulted in severe hyponatremia.

Conclusions: Timely identification and careful monitoring of TMP-SMX-induced hyponatremia enabled the correction of sodium levels without severe complications. Thus, this report underscores the importance of vigilant monitoring and prompt identification of hyponatremia in patients undergoing TMP-SMX treatment. Further research is warranted due to limited data on the precise mechanisms of TMP-SMX-induced hyponatremia.

Keywords: Hyponatremia; trimethoprim-sulfamethoxazole (TMP-SMX); syndrome of inappropriate antidiuretic hormone secretion (SIADH); electrolyte imbalance; case report

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Introduction

Hyponatremia is characterized by serum sodium levels below 135 mmol/L. The causes of hyponatremia vary greatly and are often undetectable due to misleading symptoms (1). Common symptoms may include nausea, anorexia, and malaise, with far more severe symptoms, such as headaches, drowsiness, irritability, and cramping in the muscles in severe hyponatremia. Moreover, convulsions, paralysis, and coma are typically exacerbated by the increase in intracranial pressure caused by cerebral edema (2). Routine medical practice globally uses a common combination of antibiotics known as trimethoprim-sulfamethoxazole (TMP-SMX). However, syndrome of inappropriate antidiuretic hormone secretion (SIADH)-induced hyponatremia develops post-TMP-SMX use, and there is an evident gap in knowledge on this side effect (3,4). TMP-SMX also has the potential to cause both hyperkalemia and hyponatremia, similar to amiloride (5,6). Drug-induced hyponatremia is currently not higher on the list of potential causes of hyponatremia; this is especially true for TMP-SMX-induced hyponatremia. The causes of hyponatremia are usually associated with the development of SIADH.

However, evidence shows that cases that involved high-dose TMP-SMX administration resulted in hyponatremia (6). Previous research has shown that TMP-SMX oral administration is less likely to cause SIADH (7,8). One study in the USA has explained that the risk of hyponatremia was much higher in intravenous administration, and lower oral doses produced the opposite effect (9). Some research elucidates that 72% of patients administered high-dose TMP-SMX resulted in hyponatremia (10). Similarly, this is not only true for high doses, but cases with lower doses of TMP-SMX have also been increasingly associated with hyponatremia (11). Interestingly, the elderly demographic and comorbidities seem to have a higher risk of hyponatremia (12,13). Therefore, administering normal saline and discontinuing TMP-SMX resolved the hyponatremia in this case study. Hence, we present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-175/rc), which aims to shed light on the less explored causes of hyponatremia to benefit future research and treatment.

Highlight box

Key findings

- After receiving trimethoprim-sulfamethoxazole (TMP-SMX) treatment for a soft tissue wound infection, a 76-year-old male patient presented with acute hyponatremia.
- The restoration of sodium levels without significant difficulties was made possible by the prompt identification and close monitoring of TMP-SMX-induced hyponatremia.
- The drug TMP-SMX was found to be the cause of hyponatremia when its usage was stopped because sodium levels gradually returned to normal.

What is known and what is new?

- TMP-SMX is known to impair renal salt processing, which can lead to hyponatremia, especially in elderly patients.
- This case study emphasizes the severity of hyponatremia that can result from TMP-SMX in older patients, underscoring the importance of close observation and care in this group.

What is the implication, and what should change now?

- Medical professionals should regularly check salt levels in patients, especially those who are old, as there is a danger of severe hyponatremia when using TMP-SMX.
- Constant observation and early detection of hyponatremia in patients receiving TMP-SMX therapy.
- In high-risk individuals, think about using different antibiotics, or when TMP-SMX is recommended, conduct routine electrolyte testing.

Case presentation

A 76-year-old man with a medical history including hypertension, type II diabetes, coronary artery disease, dyslipidemia, benign prostatic hyperplasia, chronic myeloproliferative disease, and osteoarthritis presented to the emergency department (ED) experiencing fatigue, nausea, and vomiting for 1 week. These symptoms arose after completing a 3-day course of TMP-SMX 800/160 mg twice daily for a soft tissue wound infection on his left leg following a fall. He had a history of recurrent falls for 3 months prior, with collateral information suggesting progressive confusion and decreased oral intake. His multiple falls were attributed to weakness following spine surgery 3 years ago, leading to injuries in his left arm and leg. He described his legs as “giving out” while walking, without any loss of consciousness or seizure-like symptoms. Despite these falls, his baseline cognitive and functional status remains good, although he now requires assistance with walking. He denied fever, weight loss, chest pain, shortness of breath, bowel changes, abdominal pain, urinary symptoms, or neurological deficits. On physical examination, he exhibited reduced jugular venous pressure, moist mucous membranes, non-tachypneic nor respiratory distress, normal sensory, and motor function, and trace non-pitting edema in the lower extremities. He also showed

Table 1 Patient's full laboratory findings at the time of hospital admission

Lab parameters	Result	Reference range
Hemoglobin (g/L)	168	135–180
Total protein (g/L)	67	66–87
Serum creatinine (μmol/L)	69.9	64–115
Na (mmol/L)	119	136–145
K (mmol/L)	4.7	3.5–5.1
Cl (mmol/L)	86	98–107
eGFR (mL/min/1.73 m^2)	>60	–
Urea (mmol/L)	6.7	2.5–7.5

Na, sodium; K, potassium; Cl, chloride; eGFR, estimated glomerular filtration rate.

Table 2 Urine output

Date	Time	Urine output (mL)
7/1/2024	14:00	700
7/1/2024	10:00	600
6/1/2024	10:00	700
6/1/2024	4:00	1,200
4/1/2024	18:00	500
4/1/2024	13:00	590
3/1/2024	18:00	700
3/1/2024	4:00	800
2/1/2024	18:00	600
2/1/2024	10:00	500
2/1/2024	4:00	1,100
1/1/2024	10:00	350
28/12/2023	10:00	300
28/12/2023	6:00	100
27/12/2023	21:00	900
27/12/2023	18:00	400

soft and las, with no evidence of tenderness, guarding, or rigidity on the abdomen.

Upon admission, the patient showed an electrolyte imbalance deduced from the underwhelming levels of hypochloremia (Cl 86 mmol/L) and hyponatremia (Na 119 mmol/L). However, he showed normal creatinine, hemoglobin, potassium, and total potassium levels. The below-normal sodium level was a critical discovery that required more investigation and further attention (see *Table 1*). In the ED, his vital signs showed a temperature of 36.4 ℃, a respiratory rate of 24 breaths/minute, oxygen saturation (SpO_2) of 94% on room air, a heart rate of 73 bpm, and a blood pressure of 138/77 mmHg. He appeared disoriented with intact time orientation. His Glasgow Coma Scale score was 14/15, with normal neurological examination except for generalized debilitation. Lower limb examination was remarkable for the left lower limb mid-shaft superficial soft tissue wound with no signs of infection. Laboratory findings revealed sodium 119 mmol/L (range, 136–145 mmol/L), serum osmolarity 245 mOsm/kg (range, 275–300 mOsm/kg), and other electrolytes and renal function within normal limits. Urine chemistry showed random 160 mmol/L sodium, urine output ranged from 100 to 1,200 mL, and high urine osmolality of 490 mOsm/kg with an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m^2, indicating 60% kidney function (*Tables 1,2*). Thyroid function tests and morning cortisol levels were normal. He was admitted with a provisional diagnosis of hyponatremia due to SIADH secondary to TMP-SMX.

He received a 1,000-mL intravenous bolus of sodium chloride 0.9% administered by the ED staff. Subsequent serum sodium levels remained constant at 119 mmol/L after 6 hours. Due to suspicion of hyponatremia stemming from SIADH upon admission (day 0), fluid intake was restricted to <1 L/day as advised by Nephrology, with sodium levels closely monitored. On the first day of admission, despite continued drowsiness and no new neurological symptoms, fluid intake remained restricted to <1 L/day, with serum sodium monitored twice daily, showing a 116 mmol/L reading. By the second day of admission, serum sodium levels dropped to 114 mmol/L with no change in neurological status.

Following consultation with nephrology, a 100-mL intravenous bolus of sodium chloride 3% (hypertonic saline) was administered with desmopressin 2 mcg every 6 hours for 24 hours, alongside continued fluid restriction <1 L/day. Six hours after hypertonic saline administration, serum sodium levels improved to 117 mmol/L. On the third day of admission, there was no change in clinical condition, with serum sodium levels ranging from 116 to 117 mmol/L on fluid restriction <1 L/day and desmopressin. However, by the fourth day of admission, serum sodium levels declined again to 114 mmol/L with persistent drowsiness, though no new neurological symptoms appeared. Following a

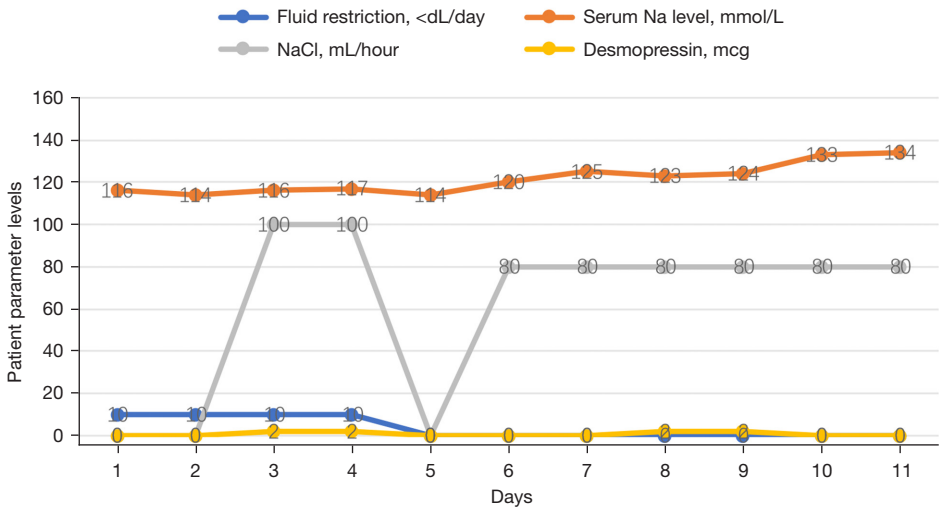

Figure 1 Serum Na level visa vis fluid restriction, NaCl, and desmopressin administration. Na, sodium; NaCl, sodium chloride.

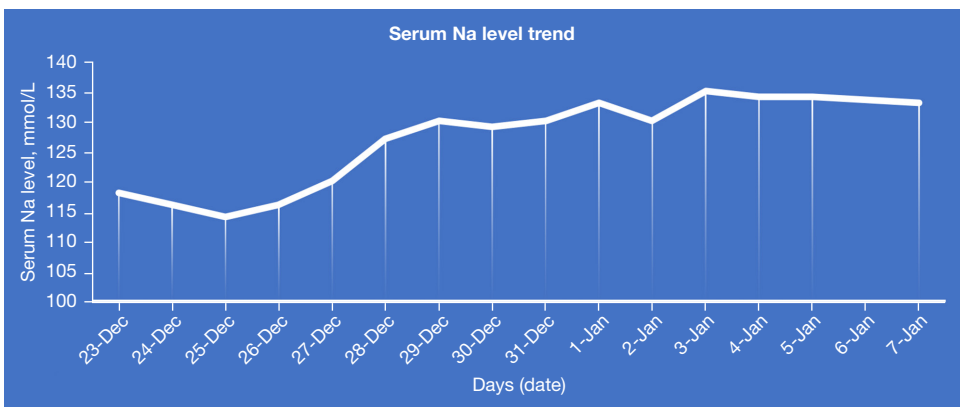

Figure 2 Serum Na level trend for the patient over the period under study. Na, sodium.

nephrology consultation, the lack of response was noted, and fluid restriction was discontinued. Maintenance fluid of sodium chloride 0.9% at a rate of 80 mL/hour (1 mL/kg) was initiated. Serum sodium levels increased to 120 and 125 mmol/L four and 6 hours after starting the maintenance fluid, prompting its discontinuation. Desmopressin 2 mcg was administered, and follow-up serum sodium levels 6 hours later ranged from 123 to 124 mmol/L. From the fifth day of admission onward, the patient resumed maintenance fluid at the same rate for 5–6 days, gradually improving serum sodium levels to 133–134 mmol/L and improving mental status to baseline upon discharge (*Figures 1*,*2*).

In addition to desmopressin 2 mcg, the patient received other concurrent medications for aforementioned comorbid conditions, which unfortunately had a contributing role in causing or worsening hyponatremia. Desmopressin can increase water retention, leading to iatrogenic hyponatremia if fluid intake is not appropriately restricted (14). He received amlodipine 5 mg daily and omeprazole 20 mg, commonly associated with hyponatremia as calcium blocker in the kidney's sodium handling and a proton pump inhibitor through a mechanism similar to SIADH, respectively (15,16). Although their direct contribution to hyponatremia is unclear, some administered drugs, such as levothyroxine, metoprolol atorvastatin, aspirin, and insulin aspart, can indirectly alter electrolyte balance.

The patient received a comprehensive evaluation for repeated falls while in the hospital. Magnetic resonance imaging (MRI) neuroimaging revealed an interval progression of moderate global parenchymal atrophy with

chronic microangiopathic changes. Despite thorough investigation, no definitive cardiac or neurological reasons were identified for the falls. Following discharge, the patient's awareness notably improved and returned to its usual state, with a serum sodium level of 133 mmol/L. He was scheduled for further comprehensive assessment of dementia at the neurocognitive clinic post-discharge.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

Hyponatremia is an electrolyte imbalance that occurs due to several factors and exhibits symptoms ranging from mild to severe fatal complications (17). SIADH is a rare but deadly complication that causes a fluid imbalance resulting in hyponatremia due to excessive secretion of antidiuretic hormone (ADH) (18). In this case study, an elderly gentleman treated at our facility for a soft tissue wound infection with TMP-SMX developed severe hyponatremia. He exhibited symptoms such as confusion, nausea, vomiting, and fatigue, which align with previous case studies done on TMP-SMX-induced hyponatremia (19,20). The immediate administration of intravenous saline in this patient corrected the sodium imbalance and highlighted the importance of fluid management in TMP-SMX-induced hyponatremia (21). The initial provisional diagnosis was TMP-SMX-induced SIADH; however, the lack of response to fluid restriction alone diminished the likelihood of SIADH, suggesting instead the diuretic effect of Bactrim as the final diagnosis.

Several clinical indicators come into play in distinguishing between hyponatremia due to SIADH and that which results from TMP-SMX's diuretic action. Clarifying this distinction is crucial since hyponatremia attributed to TMP-SMX is commonly mistaken for SIADH, which likely leads to underdiagnosis in many cases (11). TMP-SMX-induced hyponatremia has two main mechanisms of action: SIAD and trimethoprim's diuretic action. According to a study by Vuong *et al.*, the diuretic-like action of intravenous TMP-SMX is more distinct compared to when it is administered orally at higher dosages (22). This phenomenon can be explained by the similar functioning of trimethoprim components to that of potassium-sparing diuretics, which essentially block the renal tubes by inhibiting the sodium channels in the distal nephron (23). As a result of this action, sodium excretion is increased as its reabsorption is minimized, potentially causing hyponatremia.

On the other hand, TMP-SMX can elevate kidney sensitization and increase the secretion of ADH-inducing SIADH, resulting in high water retention and dilutional hyponatremia (9,24). Typically, hyponatremia development occurs quickly in the first few days after the treatment begins. Contrary, hyponatremia associated with SIADH is characteristically associated with high levels of urine sodium, osmolality, and a relatively normal operation of the renal function (25). This does not, however, change the possibility that TMP-SMX can also cause SIADH-related hyponatremia (11). That being said, it is vital to note that both disorders typically exhibit low serum sodium levels, underscoring the significance of conducting urine electrolytes and osmolality testing as a critical first step in differentiating the two causes (26).

Discontinuing the administration of medicine is essential in scenarios where TMP-SMX induces SIADH. This is crucial in rectifying the sodium imbalance because continuing to take it will worsen hyponatremia (9). Similarly, discontinuing TMP-SMX is vital in managing TMP-SMX-induced hyponatremia (21). Hence, diagnosing TMP-SMX-induced hyponatremia is a complex process with several careful considerations and clinical manifestations. It is also important to note that the initial saline infusion did not raise the sodium level in our patient, which may have been caused by the intravenous fluid and desmopressin being administered concomitantly. By raising ADH activity, desmopressin encourages water retention. This dilutes serum sodium and negates the effects of the saline infusion (14,24). Nevertheless, with subsequent intravenous saline infusion, the sodium was ultimately corrected.

Furthermore, the patient was carefully monitored and managed appropriately to correct the serum sodium levels. Identifying hyponatremia promptly and the withdrawal of TMP-SMX are essential for controlling it, as the condition may become resistant to conventional fluid management if the medication is not discontinued (11,21). To enhance patient outcomes and enable targeted management, it is imperative to differentiate between these reasons. In our case, the persistence of hyponatremia for more than 3 days despite the discontinuation of TMP-SMX suggests a multifactorial etiology. While TMP-SMX (Bactrim)

contributed to the initial development of hyponatremia through its diuretic effect, the prolonged course is likely due to additional factors. These include decreased solute intake, which impairs free water excretion, and the administration of desmopressin and other concurrent medications known to cause water retention and exacerbate hyponatremia, as discussed earlier. Together, these factors help explain why the hyponatremia persisted beyond the half-life of TMP-SMX, complicating its resolution.

Therefore, TMP-SMX-induced hyponatremia is challenging to diagnose, particularly in patients with several comorbidities and concurrent medications, as the case study highlights. It underscores the significance of keeping a high index of suspicion when patients, especially the elderly, arrive with unexplained hyponatremia. This demonstrates the necessity for physicians to thoroughly assess medication histories and take uncommon drug-induced causes into account to enhance early identification and management techniques.

Conclusions

TMP-SMX-induced hyponatremia is a rare but severe complication that requires attention. Currently, there is an existing gap in precise knowledge regarding TMP-SMX hyponatremia. This case highlights the importance of recognizing TMP-SMX-induced hyponatremia and prompts clinicians to monitor sodium levels when treating with TMP-SMX. Furthermore, early recognition of TMP-SMX-induced hyponatremia may result in appropriate management of sodium levels and favorable outcomes.

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Footnote

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