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Case Report

Life-Threatening Hyperkalemia following Low-Dose Trimethoprim-Sulfamethoxazole: A Case Report

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Cardiac arrest · Hyperkalemia · Sulfamethoxazole · Trimethoprim

Abstract
Hyperkalemia is a known adverse effect of trimethoprim-sulfamethoxazole, usually occurring at high doses. However, fatal hyperkalemia at low doses has rarely been reported. We present the case of an 80-year-old Japanese woman who experienced a cardiac arrest due to severe hyperkalemia after starting low-dose trimethoprim-sulfamethoxazole. This case suggests that trimethoprim-sulfamethoxazole can cause severe hyperkalemia and sudden death, even at low doses. When trimethoprim-sulfamethoxazole is administered, even at low doses, periodic monitoring of electrolyte levels is necessary, with the interval depending on concomitant medications and renal function.

Introduction

Trimethoprim/sulfamethoxazole (TMP/SMX) is an antimicrobial agent used worldwide for the treatment and prophylaxis of *Pneumocystis* pneumonia (PCP), urinary tract infections, and other infections. Its antimicrobial action is brought about by TMP and SMX inhibiting deoxyribonucleic acid synthesis [1, 2]. The most common side effects are rash and gastrointestinal symptoms, with hyperkalemia being a serious side effect.

Multiple cases of fatal hyperkalemia caused by high-dose TMP/SMX, such as those used to treat PCP, have been reported and several cases have been reported of hyperkalemia at

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conventional doses, such as those used in common infectious diseases [3–7]. However, few cases caused by low-dose TMP/SMX have been reported [8]. We report a case of cardiac arrest due to severe hyperkalemia that developed after starting low-dose TMP/SMX. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000530450).

Case Presentation

An 80-year-old Japanese woman weighing 48 kg, with a body surface area of 1.394 m^2, was admitted to our hospital for a suspected brain tumor. She had a history of gastric ulcer and heart failure (HF). On admission, she was receiving azosemide, spironolactone, bisoprolol, atorvastatin, and vonoprazan. After admission, she was diagnosed with non-small cell lung cancer and a metastatic brain tumor. Echocardiography showed diffuse hypokinesis and left ventricular enlargement with a reduced left ventricular ejection fraction of 21%. The patient's clinical course is shown in Figure 1. Laboratory data on admission were as follows: sodium, 141 mEq/L; potassium, 3.9 mEq/L; chloride, 106 mEq/L; blood urea nitrogen, 27.4 mg/dL; creatinine, 0.92 mg/dL (Table 1). On day 7, prednisolone and levetiracetam were initiated to prevent cerebral edema and seizures, respectively. On day 14, low-dose TMP/SMX (80 mg/400 mg/day) was initiated for PCP prophylaxis, and radiation therapy was used to treat the patient's brain metastases. On day 15, her serum potassium level was elevated to 5.4 mEq/L, but her creatinine level remained stable. Her dietary intake did not change and she did not receive any infusions. On day 21, she experienced a sudden cardiac arrest requiring immediate cardiopulmonary resuscitation. The initial electrocardiogram showed ventricular tachycardia; hence, she was defibrillated until the return of spontaneous circulation was achieved. Laboratory findings at the time of cardiac arrest were as follows: blood urea nitrogen, 100.2 mg/dL; creatinine, 1.78 mg/dL; potassium, 7.4 mEq/L; sodium, 123 mEq/L; pH, 7.28; PCO_2, 26.7 mm Hg; HCO_3, 12.2 mmol/L. Echocardiographic findings were unchanged, with no dilatation of the inferior vena cava, and no pulmonary congestion was observed on chest radiography. A 12-lead electrocardiogram performed after resuscitation was unchanged from that on admission, and echocardiography and medical history did not reveal any sign of ischemic heart disease. Hyperkalemia was suspected as the cause of cardiac arrest; therefore, 10 mL of 8.5% calcium gluconate, 40 mL of 8.4% sodium bicarbonate, 20 mL of 50% glucose solution, and 4 units of human insulin were administered slowly intravenously. The patient was immediately admitted to the intensive care unit and 90 min after the cardiac arrest, arterial blood gas analysis showed potassium 5.3 mEq/L, sodium 124 mEq/L, pH 7.43, PCO_2 32.4 mm Hg, HCO_3 21.2 mmol/L. Urinalysis revealed urinary sodium 95 mmol/L, potassium 32.8 mmol/L, and chloride 97 mmol/L. Proteinuria was absent, urinary creatinine was 10 mg/dL, fractional excretion of sodium 13.6%, fractional excretion of potassium 110.2%, transtubular potassium gradient 6.3. TMP/SMX and spironolactone were discontinued because of the hyperkalemia. On day 22, the patient's serum potassium and sodium levels had improved to 5.3 mEq/L and 130 mEq/L, respectively, and she was discharged from the intensive care unit. On day 49, she was transferred to another hospital for palliative care.

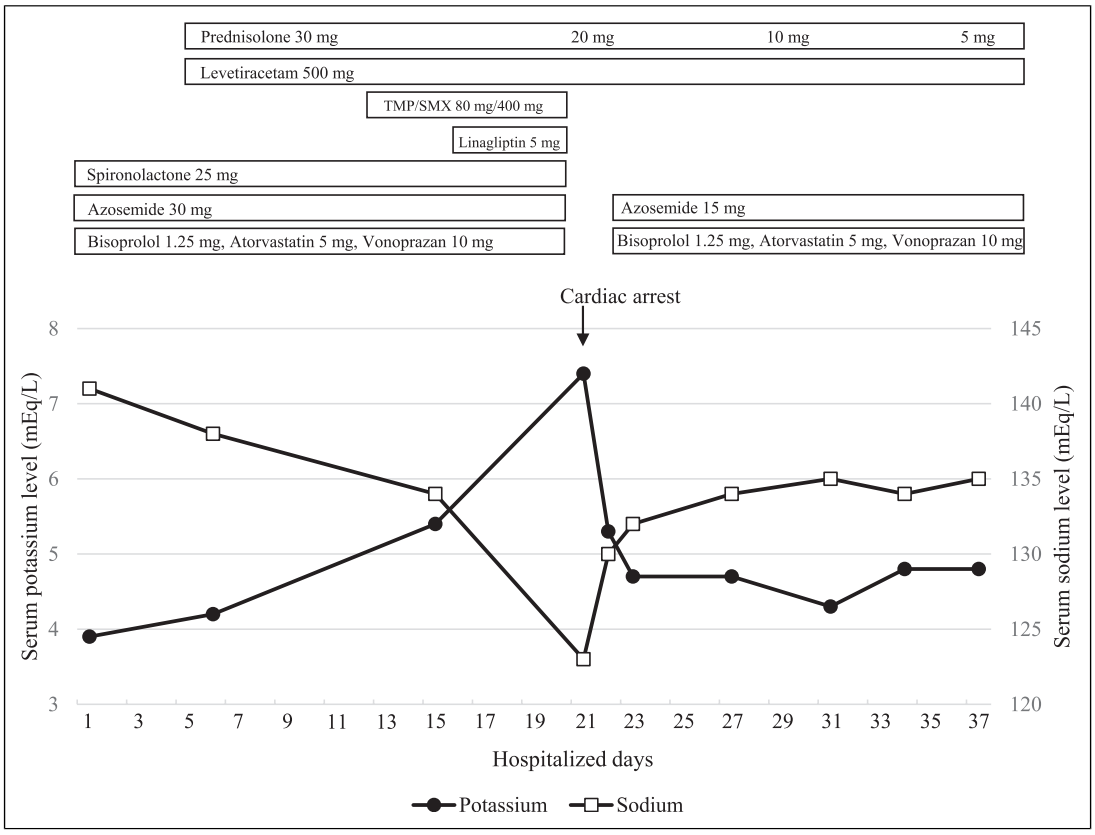

Fig. 1. Treatments administered in the hospitalization course and changes in serum potassium and serum sodium levels. TMP/SMX, trimethoprim-sulfamethoxazole.

Discussion

Hyperkalemia is a common electrolyte abnormality in clinical practice and has been reported to occur in 1–10% of hospitalized patients [9]. It is also more frequent in patients with chronic kidney disease, diabetes, HF, and certain medications such as renin-angiotensin-aldosterone system (RAAS) inhibitors and nonsteroidal anti-inflammatory drugs [10–12].

TMP/SMX is also known to cause hyperkalemia. The mechanism is as follows: TMP acts like the potassium-sparing diuretic amiloride and blocks epithelial sodium channels (ENaC) in the distal nephron, reducing transepithelial voltage and inhibiting potassium secretion [13]. Recent reviews have reported that TMP/SMX-induced hyperkalemia is dose-dependent, potentiated by RAAS inhibitors and other agents, and impaired renal function also increases the propensity for hyperkalemia. However, severe hyperkalemia with serum potassium levels exceeding 6 mEq/L is rare, occurring in only 0.2% of patients [14]. In this case, the acute onset of hyperkalemia after TMP/SMX was initiated, suggests that the hyperkalemia was probably triggered by TMP/SMX, despite the low dosage. The following factors could explain why low-dose TMP/SMX caused life-threatening hyperkalemia:

The first factor is the concomitant use of spironolactone. Spironolactone, a mineralocorticoid receptor antagonist, is widely used because it improves the prognosis of patients with HF and reduced left ventricular ejection fraction [15], but it can cause hyperkalemia. Concomitant use of spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers with TMP/SMX is associated with an increased risk of hospitalization and sudden death due to hyperkalemia in older adult patients [16–19].

Table 1. Laboratory findings after the sudden cardiac arrest

Parameters	Values								Units	Reference range
	Day 1	Day 6	Day 15	Day 21[a]	Day 22	Day 23	Day 27	Day 31		
Aspartate aminotransferase	17	18	25	26	29	26	24	24	U/L	13–30
Alanine aminotransferase	8	8	27	25	26	21	22	26	U/L	7–23
Alkaline phosphatase	202	217	216	256	NM	NM	172	215	U/L	106–322
Lactate dehydrogenase	199	208	195	342	285	258	257	288	U/L	124–222
Gamma-glutamyl transpeptidase	17	15	21	30	NM	NM	25	29	U/L	9–32
Creatine kinase	70	61	NM	39	59	41	33	34	U/L	41–153
Total bilirubin	0.4	0.5	0.5	0.7	1.2	1.3	0.4	0.5	mg/dL	0.4–1.5
Total protein	6.6	NM	6.5	6.4	6.1	5.1	4.8	NM	g/dL	6.6–8.1
Albumin	3.7	3.6	NM	3.6	3	2.6	2.6	NM	g/dL	4.1–5.1
Sodium	141	138	134	123	130	132	134	135	mEq/L	138–145
Potassium	3.9	4.2	5.4	7.4	5.3	4.7	4.7	4.3	mEq/L	3.6–4.8
Chloride	106	103	99	93	97	103	102	102	mEq/L	101–108
Phosphorus	NM	4.4	NM	8.6	5	4.5	2	2.6	mg/dL	2.7–4.6
Calcium	NM	9.3	NM	9.3	8.1	7.6	8.1	8.3	mg/dL	8.8–10.1
Blood urea nitrogen	27.4	34.7	41.9	100.2	81.5	52.1	29.3	30.6	mg/dL	8–20
Creatinine	0.92	0.94	0.91	1.78	1.35	0.92	0.64	0.64	mg/dL	0.46–0.79
Estimated glomerular filtration rate	45	44	45	22	29	45	66	66	mL/min/1.73 m^2	
Uric acid	NM	6.9	NM	10.6	NM	NM	3.7	4.3	mg/dL	2.6–5.5
C-reactive protein	0.1	NM	0.01	0.01	NM	NM	0.19	0.72	mg/dL	0–0.14
Glucose	116	147	131	241	NM	NM	211	161	mg/dL	73–109
White blood cells	4,300	6,260	10,000	19,240	19,500	11,400	8,870	8,280	/μL	3,300–8,600

(Continued on following page)

Table 1. (continued)

Parameters	Values								Units	Reference range
	Day 1	Day 6	Day 15	Day 21[a]	Day 22	Day 23	Day 27	Day 31		
Red blood cells	3.31	3.24	3.68	4.39	3.97	3.36	3.02	3.07	$\times 10^6/\mu L$	3.86–4.92
Hemoglobin	9.6	10	10.8	13.5	11.8	10	9.2	9.3	g/dL	11.6–14.8
Hematocrit	30.2	29.7	33.6	40.8	36.7	31	28.1	28.5	%	35.1–44.4
Platelets	197,000	217,000	223,000	230,000	178,000	143,000	136,000	149,000	/μL	158,000–348,000

NM, not measured.

[a]Cardiac arrest occurred on day 21, and laboratory values were recorded immediately after the cardiac arrest.

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A study found that renal failure with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use was a risk factor for low-dose TMP/SMX-induced hyperkalemia [20], but concomitant use of potassium-sparing diuretics was not. This may be because only 6 of the 186 eligible patients were concomitantly treated with potassium-sparing diuretics. Although there are insufficient data to support the effect of spironolactone on low-dose TMP/SMX-induced hyperkalemia, considering previous reports [16, 17], an effect of spironolactone on hyperkalemia is possible in this case. Further investigation of the interaction between low-dose TMP/SMX and spironolactone is warranted.

The second factor is renal failure with dehydration. The patient was taking azosemide, a loop diuretic, before starting TMP/SMX. However, her electrolyte balance was maintained. This is because ENaC reabsorption in the renal collecting duct counteracts the increased sodium excretion caused by loop diuretics [21]. However, the patient's serum sodium levels decreased after TMP/SMX was initiated. Hyponatremia due to TMP/SMX is more common at higher doses [22], reportedly occurring in 72.3% of patients at doses of TMP ≥8 mg/kg/day [23] but can also occur at lower doses [24]. TMP/SMX may have inhibited ENaC-mediated sodium reabsorption in the collecting ducts and disrupted the compensatory effect of loop diuretic-induced sodium excretion. This may have increased sodium excretion and the diuretic effects, and gradual progression of dehydration may have induced renal dysfunction with abnormal electrolyte levels. Concomitant use of loop diuretics increases the risk of acute kidney injury in patients receiving TMP/SMX [25]. As the combination of diuretics and TMP/SMX can induce hypovolemia, it may be clinically important to monitor physical findings such as body weight, thirst, and changes in vital signs, to detect adverse effects [26].

Third, the dosage of TMP/SMX may not have been a low dose for this patient. TMP/SMX was initiated at the recommended dose for PCP prophylaxis (80 mg/400 mg/day) [27]. Both TMP and SMX are primarily renally eliminated drugs, with half-lives of 11 and 9 h, respectively, but in severe renal failure the elimination half-life of both drugs can increase to 45–60 h [28]. Therefore, 50% dose reduction is generally recommended for patients with creatinine clearance of 15–30 mL/min. The patient's eGFR was reported as 45 mL/min/1.73 m^2, but, considering her body surface area, her actual eGFR was 36.3 mL/min, and the creatinine clearance calculated by the Cockcroft-Gault equation [29] was 37 mL/min, which is close to the value at which dose reduction of TMP/SMX should be considered.

Thrice weekly TMP/SMX is thought to be as effective as once-daily administration [27] for PCP prophylaxis, and if such a reduced regimen had been chosen, severe hyperkalemia could have been avoided. As it has been reported that electrolyte imbalances occur 7 days after initiating TMP/SMX [30], electrolytes should be checked within a week and a decision should be made whether to reduce the dosage.

Finally, tumor lysis syndrome (TLS) should also be considered, as the patient had undergone corticosteroid treatment and radiotherapy. However, the transtubular potassium gradient did not show a trend toward potassium overload, although fractional excretion of potassium was overestimated, and it could not be determined whether there was excess potassium supply due to TLS. Although hyperkalemia due to TLS cannot be ruled out, considering the rarity of TLS in patients with solid tumors [31] and the clinical course of the disease, TMP/SMX is most likely to have been the trigger.

In conclusion, TMP/SMX, even at low doses, can cause severe hyperkalemia, which can lead to sudden death. Therefore, treatment with low-dose TMP/SMX should be accompanied by periodic monitoring of electrolytes, with the frequency depending on renal function and the concomitant medications administered.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This case report was approved by the Institutional Ethics Committee of Niigata City General Hospital (No. 21-080).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.K. conceived the work, drafted the manuscript, and takes responsibility for the entire paper. N.S., Y.I., and Y.H. supervised this study. N.S., Y.I., K.M., H.T., and Y.H. contributed substantially to its revision. All authors have read and approved the final manuscript.

Data Availability Statement

The data used in this case report will not be shared because of the risk of identifying the individual. Further inquiries can be directed to the corresponding author.

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