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Hypoprothrombinemia During Cefmetazole Treatment: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Yuichiro Haba
ABCDEF 2 Hikaru Akizuki
ADEF 2 Naoyuki Hashiguchi
ADEF 1 Toshio Naito

1 Department of General Medicine, Juntendo University School of Medicine, Tokyo, Japan
2 Department of Emergency and Disaster Medicine, Juntendo University School of Medicine, Tokyo, Japan

Corresponding Author: Yuichiro Haba, e-mail: yhaba@juntendo.ac.jp
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Patient: Female, 76-year-old
Final Diagnosis: Drug induced hypoprothrombinemia
Symptoms: Abdominal pain • fever • loss of appetite
Medication: —
Clinical Procedure: Blood tests • CT scan
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Cefmetazole (CMZ), containing an *N*-methyl-tetrazole-thiol (NMTT) side chain, is a therapeutic option for diverticulitis in Japan. Cephems containing an NMTT, a methyl-thiadiazol, and a thiadiazolethiol side chain are known to induce coagulation disorders.

Case Report: A 76-year-old woman developed hypoprothrombinemia after receiving oral levofloxacin (LVFX) 250 mg q24h for 2 days followed by intravenous CMZ 2 g q8h for sigmoid diverticulitis. On day 5 of CMZ administration (after 12 doses in total), black stool was observed. On the following day (after 14 doses), prothrombin time (PT) prolongation was noted; PT and international normalized ratio (INR) were 37.1 s and 2.47, respectively. We diagnosed the patient with hypoprothrombinemia because of vitamin K deficiency caused by markedly elevated protein levels induced by vitamin K absence or antagonist-II on day 6 of CMZ administration. Intravenous vitamin K administration and CMZ cessation rapidly restored PT and led to the disappearance of black stool.

Conclusions: The causes of vitamin K deficiency were considered to be an impaired vitamin K cycle due to CMZ and decreased vitamin K intake because of malnutrition. These findings are consistent with CMZ's reported adverse effects. Decreased vitamin K production due to alterations in the gut bacterial flora by LVFX and CMZ was also postulated as a cause. If a bleeding tendency is noted during diverticulitis treatment with NMTT-containing cephems, switching to intravenous quinolones or carbapenems is recommended. It remains unclear how this reaction can be avoided; however, prudent monitoring of bleeding signs and PT-INR is recommended.

Keywords: Cefmetazole • Hypoprothrombinemias • Malnutrition • Vitamin K

Abbreviations: **CMZ** – cefmetazole; **NMTT** – *N*-methyl-tetrazole-thiol; **LVFX** – levofloxacin; **PT** – prothrombin time; **APTT** – activated partial thromboplastin time; **INR** – international normalized ratio; **DIC** – disseminated intravascular coagulation; **PIVKA-II** – protein induced by vitamin K absence or antagonist-II

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936712

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Background

In Japan, cefmetazole (CMZ) is a good option for the treatment of patients with intra-abdominal infections because it is a cephamycin with activity against a multitude of gram-negative bacteria such as *Escherichia coli* and *Bacteroides* species [1]. Antibiotic use has been known to be associated with a bleeding tendency, and it was first reported by Haden in 1957 [2]; in the 1970s and 80s, cephems were highlighted as hypoprothrombinemia-inducing antibiotics [3,4]. Cephems containing an *N*-methyl-tetrazole-thiol (NMTT) side chain, such as cefamandole, cefotetan, moxalactam, cefoperazone, and CMZ, are known to cause coagulation disorders by inhibiting vitamin K epoxide reductase complex subunit 1 [3,5]. Cefazolin, which contains a methyl-thiadiazol (MTD) side chain, and ceftezole, which contains a thiadiazolethiol (TDT) side chain, can also cause coagulopathy via similar effects on vitamin K epoxide reductase as NMTT-containing cephems [3,6]. According to Yasuoka et al [7], the incidence rate of any disturbance in the coagulation tests between patients who used cephems with an NMTT group and those who used cephems without an NMTT group was 22% and 10%, respectively. Furthermore, only the former group showed abnormalities in protein induced by vitamin K absence or antagonist (PIVKA)-II, with an incidence rate of 11% [7]. Here, we report a case of hypoprothrombinemia after the use of CMZ for the treatment of diverticulitis.

Case report

A 76-year-old woman with a history of asthma but living in good health accidentally fell and developed a bruise on her right cheek, for which she was brought to the emergency room. On arrival at the hospital, she reported lower left abdominal pain. Furthermore, she had a fever of 38.9°C, blood pressure of 148/82 mmHg, heart rate of 80 beats/min, and respiratory rate of 20 breaths/min. She had no conjunctival anemia, heart murmur, or rales; soft and flat abdomen; normal bowel sounds; spontaneous pain and tenderness in the localized left lower quadrant but no rebound tenderness; and skinned right cheek and right knee. Plain computed tomography revealed inflammation around diverticula in the sigmoid colon (**Figure 1**). She was administered intravenous acetaminophen 1000 mg and sent home because the diverticulitis was assessed to be less severe and was prescribed oral LVFX 250 mg every 24 h, which was a considering dosage for her renal function. She was instructed to fast; she had already been exhibiting a loss of appetite for 2 weeks. Two days later, the patient revisited the emergency room with a concern of exacerbation of the lower left abdominal pain. She looked weaker and had a body temperature of 37.7°C, blood pressure of 106/60 mmHg, heart rate of 76 beats/min, and respiratory rate of 14 breaths/min. Her body weight and height were 62.6 kg and 144.5 cm, respectively. An examination revealed localized tenderness in the lower left quadrant but no evidence of any peritoneal signs. Oral LVFX was discontinued, and intravenous CMZ was started at a high dose of 2 g every 8 h, despite her renal impairment, for the management of exacerbated diverticulitis. Laboratory findings on the first visit and on admission are shown in **Table 1**. On day 4 of CMZ administration (the fourth hospital day), she had hypoprothrombinemia; prothrombin time (PT)-international normalized ratio (INR) was prolonged to 1.40. Watery stools were observed only on the fourth hospital day. Even with no use of antithrombotic or non-steroidal anti-inflammatory drugs, muddy black stool was observed on the fifth hospital day (after the 12th administration of CMZ). The patient also had mild stomachache. We started intravenous famotidine 20 mg every 12 h, but did not perform upper endoscopy because the symptom was mild and hemoglobin and blood urea nitrogen levels showed no changes from the time of admission. She was frailer, as evidenced by her weight loss of 1.4 kg. On the sixth hospital day (after the 14th administration of CMZ), her PT and PT-INR further increased to 37.1 s and 2.47, respectively, while her activated partial thromboplastin time (APTT) was 38.5 s (reference range in our hospital: 20.0-38.0 s), but her platelet count was 37.4×10^4/μL (reference range in our hospital: 15.3-34.6×10^4/μL) (**Table 1, Figure 2**). Based on the elevation of PIVKA-II level (27 802 mAU/mL: reference range in our hospital: 0-40 mAU/mL) on day 6 of CMZ administration, a diagnosis of vitamin K deficiency was made. Her renal function on the sixth hospital day did not worsen (**Table 1**). Therefore, vitamin K 20 mg every 12 h was promptly initiated intravenously, and CMZ was discontinued. On the seventh hospital day, PT-INR recovered to 1.10; furthermore, the black stool spontaneously disappeared. As the fever and abdominal pain subsided, the patient was discharged on the eighth hospital day.

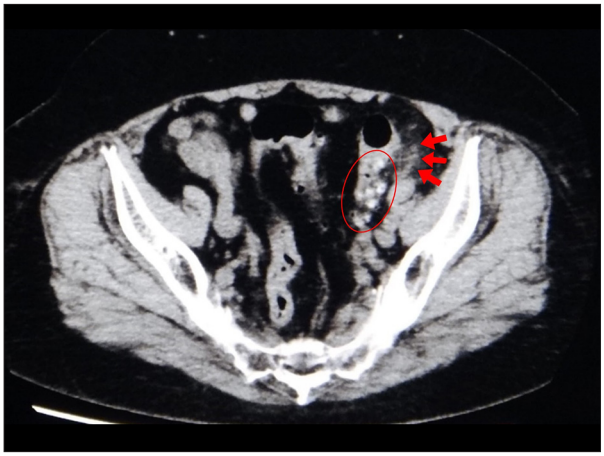

Figure 1. Plain computed tomography findings on the first visit. The scan shows inflammation around diverticula in the sigmoid colon. The diverticula are circled and its inflammation is indicated with arrows.

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Table 1. Laboratory findings on the first visit, on admission, and on the 6th hospital day.

	First visit	Admission	6th hospital day	Reference range in our hospital
WBC (/μL)	12 700	18 800	6200	3600-8900
Hb (g/dL)	11.6	11.4	11.5	11.1-15.2
PLT×10⁴ (/μL)	28.0	13.1	37.4	15.3-34.6
T-Bil (mg/dL)	0.48	0.71	0.28	0.40-1.20
AST (U/L)	17	17	18	5-37
ALT (U/L)	14	15	15	6-43
ALP (U/L)	–	143	130	110-348
γ-GT (U/L)	10	10	11	0-75
LD (U/L)	219	161	173	119-221
UN (mg/dL)	20	16	12	9-21
Cr (mg/dL)	0.90	0.96	0.70	0.50-0.80
Ccr (mL/min)	52.5	49.2	66.0	
CRP (mg/dL)	0.61	15.17	1.16	0-0.29
APTT (s)	–	31.3	38.5	20.0-38.0
PT (s)	–	13.0	37.1	13.8
PT-INR	–	0.95	2.46	0.90-1.10

Ccr – creatinine clearance

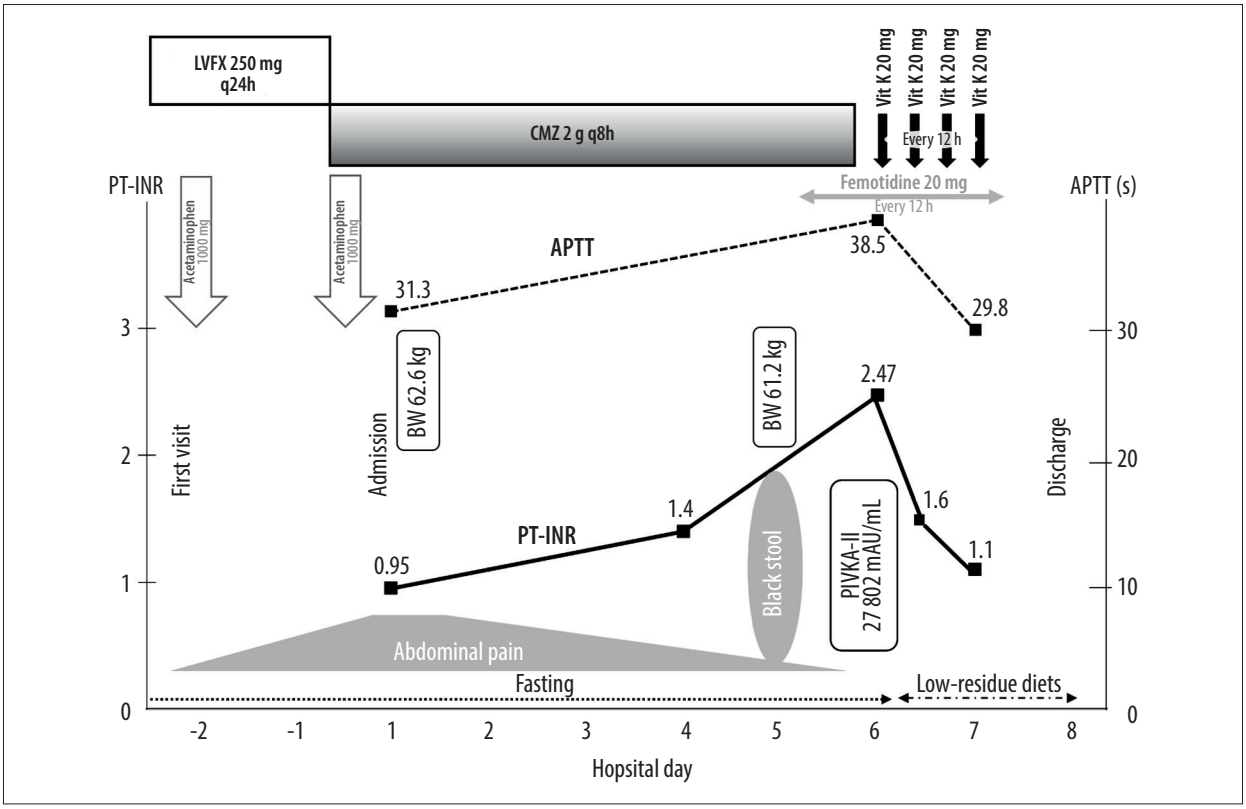

Figure 2. Clinical course and coagulation tests. APTT – activated partial thromboplastin time; PT-INR – prothrombin time-international normalized ratio; LVFX – levofloxacin; CMZ – cefmetazole; Vit K – vitamin K; PIVKA-II – protein induced by vitamin K absence or antagonist-II; BW – body weight.

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Table 2. Summary of the previous reported cases of CMZ-induced hypoprothrombinemia on MEDLINE.

Year	Country	Age	Sex	Purpose of use of CMZ	PT(s) [control (s)]
1984	JPN	86	F	Pneumonia	>45 [NA]
1984	JPN	70	F	Sepsis	22.9 [NA]
1984	JPN	81	F	Urinary tract infection, bronchitis	36.9 [NA]
1984	JPN	71	F	Prophylaxis for blood access construction surgery	>45 [11-13]
1984	JPN	72	F	NA	87.1 [11-13]
1989	US	57	M	Appendicitis and appendectomy	17 [11]
1997	US	63	M	Prophylaxis for leg amputation	91.2 [11.5]
2017	JPN	93	F	Urinary tract infection	NA
2019	JPN	84	M	Urinary tract infection	NA
2020	JPN	70	M	Prophylaxis for laparoscopic rectal cancer surgery	NA
2022	JPN	76	F	Diverticulitis	37.1 [13.8]

Year	PT-INR	Dose of CMZ	Duration from the start of CMZ to the onset of the events (days)	Bleeding	Reference
1984	NA	2-4 g/day	5	Melena	[4]
1984	NA	2 g/day	15	Melena	
1984	NA	3 g/day	20	Hematemesis	
1984	NA	2 g/day	4	Melena, Bleeding on lips, Purpura on extremities	[18]
1984	NA	4 g/day	10	Melena	
1989	NA	2 g q8h	4.5	Epistaxis	[13]
1997	8.3	1 g q24h	4	No	[19]
2017	2.51	1 g q12h	7	Melena	[20]
2019	>7.5	1 g q12h	14	Alveolar bleeding	[8]
2020	3.33	2 g/day	4	Intraperitoneal bleeding	[9]
2022	2.46	2 g q8h	4	Melena	Our study

CMZ – cefmetazole; JPN – Japan; US – United States; PT – prothrombin time; INR – international normalized ratio; NA – not available.

Discussion

In the present case, disseminated intravascular coagulation (DIC) and hepatobiliary disease were considered among the causes of hypoprothrombinemia. DIC was ruled out because there were no changes in platelet count and fibrinogen or D-dimer levels. Hepatobiliary disease was also ruled out because the imaging examinations and hepatobiliary enzyme test showed no abnormalities. As the PIVKA-II level was markedly high, vitamin K deficiency was considered the cause of hypoprothrombinemia; this finding was consistent with that reported previously [8,9]. This assumption was supported by the success of vitamin K replacement therapy. Vitamin K is involved in the activation of coagulation factors II, VII, IX, and X, and causes both PT and APTT prolongation. However, most cases are limited to PT prolongation, as in the present case. This is because the deficiency of factor VII, which has the shortest half-life (3-6 h), precedes it [10]. The factors that cause vitamin K deficiency include the following, with multiple factors often being involved: impaired vitamin K cycle, decreased vitamin K intake, altered gut flora,

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Table 3. Naranjo scale of adverse drug reaction probability. Underlining is applied for our study.

Questionnaire	Yes	No	Do not know or not done
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the drug was given?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
4. Did the adverse reaction reappear upon readministering the drug?	+2	-1	0
5. Were there other possible causes for the reaction?	-1	+2	0
6. Did the adverse reaction reappear upon administration of placebo?	-1	+1	0
7. Was the drug detected in the blood or other fluids in toxic concentrations?	+1	0	0
8. Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1	0	0
9. Did the patient have a similar reaction to the drug or a related agent in the past?	+1	0	0
10. Was the adverse event confirmed by any other objective evidence?	+1	0	0
Total score in our study		7	
≥9: definite adverse drug reaction 5-8: probable adverse drug reaction 1-4: possible adverse drug reaction 0: doubtful adverse drug reaction			

defective vitamin K absorption due to impaired bile flow or malabsorption syndromes, and chronic kidney diseases [11,12].

Administration of cephems with an NMTT group can cause coagulation disorders associated with an impaired vitamin K cycle, similar to the effects of warfarin [5]. The incidence rate of coagulation disorders associated with CMZ was reported to be 5.7% among patients treated with CMZ for intra-abdominal infections [13]. Chen et al reported that the use of CMZ increased the risk of bleeding events by 2.8-fold, which is a conspicuous increase associated with NMTT-containing cephems, along with a 4.5-fold increase associated with cefoperazone [14]. Although vitamin K deficiency does not easily occur in healthy individuals on a normal diet, it can easily occur in undernourished patients. Fasting affects coagulation factors in some cephem users [15], and bleeding events among users of NMTT-containing cephems increased 1.4-fold under malnutrition conditions compared with those among other antibiotic users [14]. In the present case, the patient had a 21-day fasting period or an insignificant intake and was undernourished, as indicated by the loss of her body weight. Furthermore, her vitamin K stores may have finally been depleted. Coagulation disorders due to LVFX are rare. Mor et al described acquired hemophilia in which factor VIII was reduced by oral LVFX therapy [16]. Our patient was previously treated with oral LVFX; however, APTT prolongation was not observed, suggesting that factor VIII was intact. Gut flora remains an issue [17]. It is not clear whether our administration of broad-spectrum antibiotics, 2-day treatment with LVFX, or 4-day treatment with CMZ disturbed the gut flora because no stool cultures were performed before and after treatment. In short, the causes of hypoprothrombinemia in the present case were an impaired vitamin K cycle and decreased vitamin K intake, with altered gut flora being considered as a potential cause.

Ten cases of CMZ-induced hypoprothrombinemia are accessible on MEDLINE, and they have been summarized in **Table 2** [4,8,9,13,18-20]. In these 10 cases, the average patient age was 74.7 (range: 57-93) years and the maximum PT and INR were 87.1 s [18] and 8.3 [19], respectively. The average duration from the start of CMZ treatment to the onset of events was 8.7 (range: 4-20) days. The dominant site of bleeding was the upper gastrointestinal tract, which is similar to a previous report regarding warfarin-associated bleeding [21]. These findings reported previously suggest that CMZ has the ability to cause gastrointestinal bleeding and can enhance the validity of our finding; that is, gastrointestinal bleeding is an adverse effect of CMZ. In our case, the Naranjo scale for adverse drug reaction score [22] was 7 points, indicating that the adverse reaction was probably attributable to CMZ (**Table 3**).

If a bleeding tendency is noted during the treatment of diverticulitis with NMTT-containing cephems and is not completely cured, we recommend switching to the following antibiotics

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as alternatives: intravenous quinolones such as ciprofloxacin or carbapenems such as imipenem and meropenem [23]. Piperacillin/tazobactam is suitable for diverticulitis management [23]; however, they should be avoided because hypoprothrombinemia has been noted in 6% of individuals who were administered piperacillin/tazobactam [24]. How to avoid this adverse effect in the clinical settings remains controversial. Breen et al recommended 2 approaches: administering prophylactic vitamin K and monitoring PT-INR daily or every other day [19].

Conclusions

Fortunately, bleeding was noticed at an early stage and CMZ administration was stopped in the present case. Although black stool was observed, rapid action, including checking the PT-INR, avoided serious bleeding events. Clinicians should recognize coagulation disorders as adverse effects of antibiotics and should carefully monitor bleeding signs and coagulation test results, while distinguishing DIC when administering NMTT-, MTD-, and TDT-containing cephems to frail patients who are likely to have an alteration of the gut flora owing to factors such as malnutrition and past use of broad-spectrum antibiotics.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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