A suspicious case of cefmetazole-induced hypoprothrombinemia

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Abstract
Cefmetazole occasionally prolongs the prothrombin time. The mechanism is considered to be because of (i) inhibition of vitamin K metabolism, (ii) a lack of vitamin K, and (iii) low vitamin K stores. We report the death of a 93-year-old woman who was administered cefmetazole and exhibited a prolonged prothrombin time. When using cefmetazole in elderly patients, PT-INR should be monitored every few days.

Keywords
cefmetazole, hypoprothrombinemia

1 INTRODUCTION
Cefmetazole is frequently used in Japan. This antibiotic is commonly used for intra-abdominal infections, PID, and surgical prophylaxis because of its activity against aerobic gram-negative rods and anaerobic bacteria. Furthermore, in Japan, cefmetazole is an option to refrain from using carbapenem in treating noncomplicated urinary tract infection caused by ESBL-producing Enterobacteriaceae. Although adverse effects, such as hypoprothrombinemia and disulfiram-like reactions, have been described, the physician would not be able to sufficiently recognize these effects.

2 CASE REPORT
A totally dependent 93-year-old woman who lived in a nursing home was admitted to our hospital because of a 2 week history of appetite loss and a 1 day history of fever and unconsciousness. She was administered 1 g ceftriaxone intravenously only once before admission. Her medical history included dementia, hypertension, and tuberculosis, and medication included benidipine, sulpiride, azosemide, trihexyphenidyl hydrochloride, memantine, etizolam, and yokukansan, an Asian herbal medicine.

On physical examination, she appeared ill. Her blood pressure was 137/70 mm Hg, pulse rate 106 beats per minute and a regular, respiratory rate 28 per minute, and body temperature 37.6°C, and consciousness level was assessed as 10 on the Japan Coma Scale. Her oral cavity and skin were dry. Her cardiorespiratory examinations were normal. There was no evidence of CVA knocking pain. Initial laboratory tests revealed blood urea nitrogen of 116.4 mg/dL, creatinine of 2.88 mg/dL, and sodium of 159 mEq/L. Coagulation screen tests were normal (PT-INR 1.07 and activated partial thromboplastin time 25.7 seconds). Urinalysis revealed pyuria; gram-negative rods were observed on Gram staining. Computed tomography and ultrasonography revealed no abscess or ureteral obstruction. She was administered 1 g cefmetazole every 12 hours and fluid repletion under a diagnosis of acute simple pyelonephritis and acute prerenal kidney injury. Although she was afebrile and both her consciousness and laboratory data gradually improved, she was unable to eat or drink. Dehydration was resolved on the sixth hospital day. On the seventh hospital day, she developed melena. On the eighth hospital day, she developed cardiopulmonary arrest. Although she was resuscitated, there was no neurological improvement, and she died on the 11th hospital day. Her PT-INR was prolonged at 2.51, but APTT and platelet count were within normal range at 38.2 seconds and 15.4×10^4 μ/L, respectively, on the eighth hospital day.

3 DISCUSSION
In our presented case, oral intake decreased 2 weeks before admission, and the patient was not able to ingest food for 8 days after consciousness level was assessed as 10 on the Japan Coma Scale. Her oral cavity and skin were dry. Her cardiorespiratory examinations were normal. There was no evidence of CVA knocking pain. Initial laboratory tests revealed blood urea nitrogen of 116.4 mg/dL, creatinine of 2.88 mg/dL, and sodium of 159 mEq/L. Coagulation screen tests were normal (PT-INR 1.07 and activated partial thromboplastin time 25.7 seconds). Urinalysis revealed pyuria; gram-negative rods were observed on Gram staining. Computed tomography and ultrasonography revealed no abscess or ureteral obstruction. She was administered 1 g cefmetazole every 12 hours and fluid repletion under a diagnosis of acute simple pyelonephritis and acute prerenal kidney injury. Although she was afebrile and both her consciousness and laboratory data gradually improved, she was unable to eat or drink. Dehydration was resolved on the sixth hospital day. On the seventh hospital day, she developed melena. On the eighth hospital day, she developed cardiopulmonary arrest. Although she was resuscitated, there was no neurological improvement, and she died on the 11th hospital day. Her PT-INR was prolonged at 2.51, but APTT and platelet count were within normal range at 38.2 seconds and 15.4×10^4 μ/L, respectively, on the eighth hospital day.
admission. Vitamin B was supplemented, but not vitamin K. The combination of melena, prolonged PT, normal APTT, and normal platelet count indicates either the use of warfarin or vitamin K deficiency. Thus, the cause of the cardiac arrest was thought to be a possible hemorrhagic shock because of the vitamin K deficiency induced by cefmetazole-induced hypoprothrombinemia. We could not conclude hemorrhagic shock because of hypoprothrombinemia as the cause of death because PT did not prolong much, and autopsy or autopsy imaging was not performed, which is a limitation of this study.

Antibiotic-induced hypoprothrombinemia can develop by three mechanisms: (i) inhibition of vitamin K metabolism, (ii) a lack of vitamin K, and (iii) low vitamin K stores.2

The first mechanism is the inhibition of vitamin K metabolism in the liver. Vitamin K is obtained from digestive food and intestinal bacterial flora and activates a clotting factor in the liver. Vitamin K is recycled by this metabolism cycle. Warfarin prolongs prothrombin time by inhibiting vitamin K reductase and vitamin K epoxide reductase in the vitamin K metabolism cycles. Cephalosporins, which include the N-methylthiotetrazole side chain (e.g., cefmetazole, cefotetan, cefamandole, cefoperazone, and moxalactam) or the 2-methyl-1,3,4-thiadiazole-5-thiol side chain (e.g., cefazolin), also inhibit vitamin K epoxide reductase.

The second mechanism is the lack of vitamin K. The supply of vitamin K from the gastrointestinal tract is decreased after ingestion of antibiotics because antibiotics suppress the intestinal bacterial flora, and bacterial infection often results in limited food intake.

The third mechanism is the low vitamin K stores of such patients. The risk factor for antibiotic-induced hypoprothrombinemia is vitamin K deficiency because of elderly patient, malnutrition, renal disease, and liver disease. Patients who were administered cefmetazole are usually forced to restrict their food intake because this antibiotic is frequently used for intra-abdominal infections. Therefore, when cefmetazole is administered to elderly patients, it is considered as an antibiotic that tends to lead to hypoprothrombinemia.

Cefmetazole-induced hypoprothrombinemia is considered uncommon. One of 118,138 patients was reported to have developed hypoprothrombinemia through cefmetazole treatment; this was assessed by a postmarketing surveillance study in Japan.3 There are three English articles and two Japanese articles assessing adult cases, and only 11 cases, including our case, have been described in total (Table 1). The average time of nine cases, except two not described in detail, from initiation of antibiotic therapy to diagnosing hypoprothrombinemia or bleeding was 8.1 days (range, 2-20 days). In contrast, the average time was reported to be 5.7 days (range, 2-15 days) when the cephalosporins were used in 17 cases.4 Eight of the nine cases were recognized as hypoprothrombinemia with bleeding; almost all cases survived after being administered vitamin K supplements. Furthermore, hypoprothrombinemia is preventable by vitamin K prophylaxis if administered once or three times weekly.5 Thus, cefmetazole-induced hypoprothrombinemia without bleeding may be underdiagnosed.

### Table 1

Summary table of cases of cefmetazole-induced hypoprothrombinemia

| Ref. | Year | Country | Age | Gender | Underlying disease | Duration of antibiotic (days) | Poor food intake (days) | PT (s) [control PT] | Bleeding | Outcome |
|------|------|---------|-----|--------|-------------------|-----------------------------|------------------------|---------------------|----------|---------|
| 1 a  | 1989 | US      | 57  | M      | Appendectomy      | 8                           | 17 s [11]              | NA                  | NA       | Survival |
| 2    | 1997 | US      | 63  | M      | Appendectomy      | 6                           | 12.4 s [11.5]          | NA                  | NA       | Survival |
| 3    | 1989 | JPN     | 57  | M      | Appendectomy      | 4                           | 8                      | 17 s [11]           | NA       | Survival |
| 4    | 1994 | JPN     | 86  | F      | Pneumonia         | 6                           | 11                     | 27                  | 42%      | Survival |
| 5    | 1994 | JPN     | 70  | F      | Sepsis            | 5                           | 15                     | 9                   | 42%      | Survival |
| 6    | 2002 | JPN     | 81  | F      | UTI               | 9                           | 20                     | 36.9 s [NA]         | NA       | Survival |
| 7    | 1994 | JPN     | 71  | F      | UTI               | 2                           | 10                     | NA                  | NA       | Survival |
| 8    | 1998 | JPN     | 72  | F      | UTI               | 4                           | 10                     | NA                  | NA       | Survival |
| 9    | 1998 | JPN     | 72  | F      | UTI               | 7                           | 21                     | 21%                 | NA       | Death   |

ESRD, end-stage renal disease; UTI, urinary tract infection; AKI, acute kidney injury; NA, not available.

Two of three cases in Ref. 4 were not described in detail.
4 | CONCLUSIONS

The adverse drug reactions should be avoided, but cannot cope when we do not know it. We should know that cefmetazole may induce hypoprothrombinemia and should monitor PT-INR every few days when cefmetazole is used in elderly patients.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. Doi A, Shimada T, Harada S, Iwata K, Kamiya T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis. 2013;17:e159–63. doi: 10.1016/j.ijid.2012.09.010.
2. Shevchuk YM, Conly JM. Antibiotic-associated hypoprothrombinemia: a review of prospective studies, 1966-1988. Rev Infect Dis. 1990;12:1109–26.
3. Saito A. Cefmetazole postmarketing surveillance in Japan. J Antimicrob Chemother. 1989;23(Suppl D):131–9.
4. Nichols RL, Wikler MA, McDevitt JT, Lentnek AL, Hosutt JA. Coagulopathy associated with extended-spectrum cephalosporins in patients with serious infections. Antimicrob Agents Chemother. 1987;31:281–5.
5. Holloway WJ, Winslow DL, Reingardt JF. Cefmetazole treatment of intra-abdominal infection. J Antimicrob Chemother. 1989;23(Suppl D):47–54.
6. Breen GA, St Peter WL. Hypoprothrombinemia associated with cefmetazole. Ann Pharmacother. 1997;31:180–4.
7. Shimada K, Matsuda T, Inamatsu T, Urayama K. Bleeding secondary to vitamin K deficiency in patients receiving parenteral cepheid antibiotics. J Antimicrob Chemother. 1984;14(Suppl B):325–30.
8. Sakamoto S, Takao Y, Ueshima E, Yamamoto F, Maekawa N. A suspicious case of massive hemorrhaging from an epidural puncture aperture resulting from coagulopathy caused by vitamin K deficiency associated with fasting and antibiotics. J Japan Soc Pain Clin. 2012;19:519–22. (in Japanese).
9. Kijima Y, Ozawa K, Nakayama I, Shoji T, Sasaoka T. A clinical study of blood coagulopathy in renal failure. Tousekikaisi. 1984;17:165–71. (in Japanese).

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