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CASE REPORT

# Fatal Vitamin K-Dependent Coagulopathy Associated with Cefoperazone/Sulbactam: A Case Report

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**Abstract**
This case report describes a suspected and fatal adverse reaction involving vitamin K-dependent coagulopathy that might be associated with cefoperazone/sulbactam (CPZ/SAM), a combined antimicrobial formulation. We reported a patient diagnosed with acute cerebral infarction and secondary pulmonary infection who was treated with an intravenous infusion of CPZ/SAM at 3 g twice daily. After receiving treatment with CPZ/SAM, the patient developed a fatal adverse reaction of CPZ-induced hemorrhage. The Naranjo assessment score in this report was 5, suggesting that the patient's coagulation function disorder was potentially associated with the use of CPZ/SAM. To prevent vitamin K-dependent coagulopathy caused by CPZ/SAM, it is suggested to avoid cephalosporins in patients with a high risk of bleeding unless the need for cephalosporins is compelling.

**Key Points**

Cefoperazone/sulbactam might induce coagulation function disorder

Clinicians should be aware of the risks and preventable adverse events while prescribing cefoperazone/sulbactam in patients with a high risk of bleeding

## Introduction

Vitamin K-dependent coagulation factors include II, VII, IX, and X. Vitamin K deficiency or utilization disorders may affect the γ-carboxylation of glutamate, and thus, the γ-carboxyglutamyl glutamic acid residue in these coagulation factors could not form [1, 2]. Vitamin K-dependent coagulopathy is characterized by decreased activity of coagulation factors and coagulation dysfunction. Insufficient intake of vitamin K, poor absorption of the gastrointestinal tract, and decreased production from gut bacteria could lead to vitamin K deficiency, which in turn results in vitamin K-dependent coagulation dysfunction.

Cefoperazone/sulbactam (CPZ/SAM, Sulperazon; Pfizer Inc., Shanghai, China) is a combined formulation of a third-generation cephalosporin and a β-lactamase inhibitor, which is mostly administered to treat severe bacterial infections in China [3]. Cefoperazone/sulbactam has low nephrotoxicity and high safety, but a long-term high-dose use may lead to vitamin K-dependent coagulation dysfunction in patients. The potential mechanism of coagulation dysfunction resulting from CPZ/SAM might be as follows: (1) affects the intestinal synthesis of vitamin $K_2$, and (2) interferes with the carboxylation of vitamin K-dependent clotting factors because CPZ might inhibit vitamin K oxide reductase and reduce the availability of vitamin K, although the evidence is not conclusive. Thus, CPZ was thought to reduce the synthesis of vitamin K-dependent factors, such as II, VII, IX, and X [4, 5]. In this report, we present a case of hemorrhage development after treatment with CPZ/SAM.

## Case Report

A 79-year-old man with acute cerebral infarction was admitted to the hospital. A cerebral computed tomography scan indicated that there was an infarction and no bleeding. He had a history of hypertension and chronic obstructive pulmonary disease. The results of a routine blood examination,

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coagulation function examination, and biochemical examination were normal at the time of admission (Figs. 1, 2). He underwent thrombolytic therapy with alteplase immediately after admission. The vital signs of the patient were normal after thrombolysis. On day 2 after admission, he exhibited dysphagia. Thus, a gastric tube was inserted to improve his nutritional status. Clopidogrel hydrogen sulfate tablets (75 mg once daily) were given that day.

On day 3 after admission, he developed a temperature of 38 °C and a physical examination showed there were wheezes and crackles in the lung. Laboratory test results revealed elevations of white blood cells and neutrophils, suggesting a lung infection. The examination results of coagulation function remained normal. Then, the patient was treated with CPZ/SAM (3 g twice daily, intravenous infusion) and ambroxol hydrochloride (12 mL once daily, intravenous infusion). One day later, he developed an extensive cerebral infarction accompanied by cerebral hemorrhage and palsy. Therefore, clopidogrel hydrogen sulfate tablets were discontinued immediately and a mannitol injection was administered that day. However, CPZ/SAM was still administered for anti-infection. On day 12 after admission, he complained of bloody diarrhea with low blood pressure. A computed tomography scan showed that the area of cerebral hemorrhage had increased.

On day 14 after admission, scattered bleeding from the lip and gum was reported. The routine blood examination showed a high percentage of white blood cells and neutrophils and low levels of red blood cells and hemoglobin. The results of a coagulation function examination revealed a prolongation of the prothrombin time (> 180 s) and activated partial thromboplastin time (87.2 s) and a decrease in coagulation factor II (10.7%), VII (2.6%), IX (19.1%), and X (13%). The value of coagulation factor V was 103.9%,

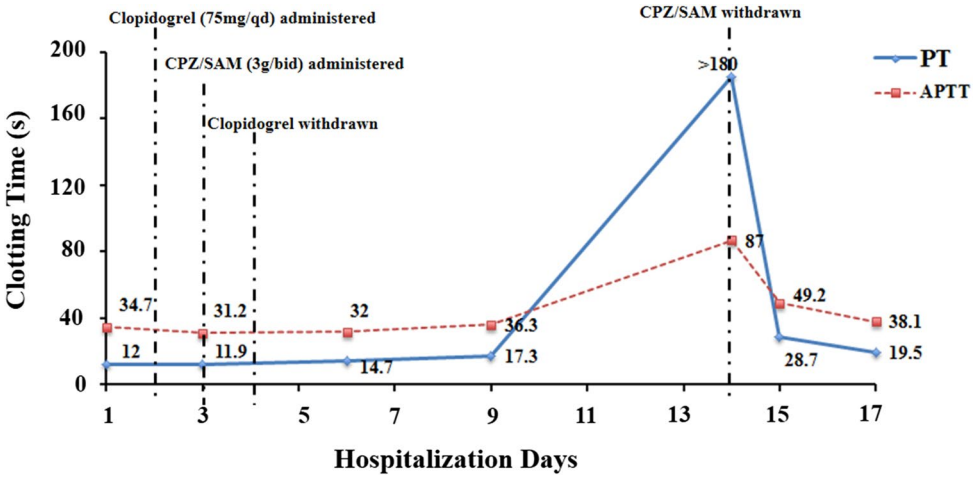


**Fig. 1** Changes in coagulation functional parameters with time after admission. *APTT* activated partial thromboplastin time, *bid* twice daily, *CPZ* cefoperazone, *PT* prothrombin time, *qd* once daily, *s* seconds, *SAM* sulbactam

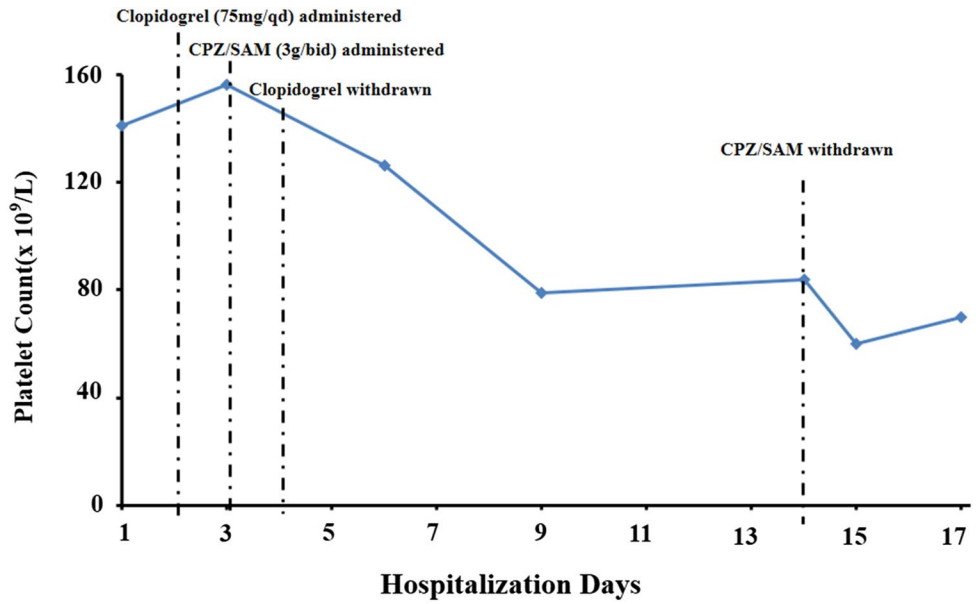


**Fig. 2** Changes in platelet count with time after admission. *bid* twice daily, *CPZ* cefoperazone, *qd* once daily, *SAM* sulbactam

which indicated that the hepatic synthetic function was normal. Thus, fresh plasma, prothrombin complex, and vitamin $K_1$ supplementation were administered to improve coagulation function. Moreover, CPZ/SAM was discontinued. Laboratory tests revealed that the values of albumin, glutamate transaminase, creatinine, lactate dehydrogenase, creatine kinase, and creatine kinase isozyme were 19.4 g/L, 139 IU/L, 632 μmol/L, 932 IU/L, 4246 IU/L, and 74 IU/L, respectively. In the following 1–3 days, a computed tomography scan showed that the area of cerebral hemorrhage had extended. On day 17 after admission, he showed a decrease in heart rate, blood pressure, and oxygen saturation. Blood gas analysis revealed that type I respiratory failure and metabolic acidosis had developed. He died after a resuscitation attempt failed. A Naranjo assessment score of 5 was obtained, indicating a probable relationship between the patient's coagulation function disorder and his use of the suspect drug.

## Discussion

Cefoperazone/sulbactam has the characteristics of low renal function toxicity and high safety and is widely used in China. However, long-term high-dose use of CPZ/SAM may cause vitamin K deficiency, which may subsequently decrease the vitamin K-dependent coagulation factors and lead to coagulopathy. Several cases of hemorrhage induced by CPZ were reported previously [6–10]. A recent study by Katukuri et al. suggested that the use of CPZ could be prevented by vitamin K supplementation and monitoring coagulation function [11].

In this report, the patient had normal coagulation function and no history of a blood system disease or liver disease before the use of CPZ/SAM. Approximately 10 days after the drug was administered, digestive tract and oral mucosal hemorrhage began to appear accompanied by cerebral hemorrhage. The results of a coagulation function examination indicated that activated partial thromboplastin time and prothrombin time increased and that coagulation factors II, VII, IX, and X were significantly reduced after the use of CPZ/SAM. Moreover, the patient's coagulation function was normal before and after thrombolytic therapy, which could exclude the presence of thrombolytic and pathological anticoagulant substances. After discontinuation of CPZ/SAM and treatment with vitamin K, the prothrombin time and activated partial thromboplastin time were close to normal, which suggested that CPZ/SAM caused the coagulopathy.

For patients using CPZ/SAM short term, the risk of bleeding may be low [12]. However, patients with serious diseases, such as gastrointestinal dysfunction and renal failure, are susceptible to bleeding when using CPZ/SAM. Moreover, the potential drug–drug interaction should not be ignored. Cefoperazone/sulbactam was used together with clopidogrel in this case for 1 day. Thus, the influence of antiplatelet aggregation agents on the occurrence/seriousness of vitamin K-dependent coagulopathy should not be excluded.

## Conclusion

In this report, we present a case of CPZ/SAM-induced vitamin K-dependent coagulopathy. After admission, the patient developed gastrointestinal dysfunction, renal failure, and electrolyte imbalance. Gastrointestinal insufficiency might affect the production of vitamin K and renal failure might affect the excretion of CPZ/SAM, which in turn increased the deficiency of the coagulation factors. Although the pathogenesis of CPZ/SAM-induced vitamin K-dependent coagulopathy remains unclear and the incidence is extremely low, for patients with a high risk of bleeding, it is strongly suggested to avoid cephalosporins unless the need for cephalosporins is compelling. Moreover, further investigations are needed to explore this safety issue of CPZ/SAM in high-risk patients.

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### Compliance with Ethical Standards

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**Conflict of Interest** Huan-rong Hu has no conflicts of interest that are directly relevant to the content of this case report.

**Consent to Participate** Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent may be requested for review from the author.



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