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CASE REPORT

A Rare Case of Cefoperazone/Sulbactam-Induced Significant Prolongation of INR

Ying Yu, Qing Wang

Medical Laboratory Department of Shaoxing People's Hospital, Yuecheng District, Shaoxing City, Zhejiang Province, China

SUMMARY

Background: **Cefoperazone/sulbactam (CPZ/SAM) is a first-line antibacterial drug in clinical practice.**
Methods: **This article reports a case of extreme elevation of INR due to the use of CPZ/SAM four days. After drug withdrawal and administration of fresh frozen plasma, the coagulation function returned to normal.**
Results: **The INR results were extremely elevated, which is believed to be caused by taking CPZ/SAM.**
Conclusions: **When patients take CPZ/SAM anti-infection therapy, the patient's coagulation function should be closely monitored for the prevention of the occurrence of adverse reactions.**
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Correspondence:
Qing Wang
Medical Laboratory Department of
Shaoxing People's Hospital
Yuecheng District, Shaoxing City
Zhejiang Province, 312000
China
Phone: +86 13957591985
Email: nancy2023123@163.com

KEYWORDS

cefoperazone/sulbactam, INR, coagulopathy, adverse reaction

INTRODUCTION

Cefoperazone/sulbactam (CPZ/SAM) is a compound preparation composed of the third-generation cephalosporin cefoperazone and the β-lactamase inhibitor sulbactam. It is particularly effective against extensively drug-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, etc. [1]. With the increasing clinical use, reports of CPZ/SAM causing abnormal coagulation function have gradually increased. The main manifestations are prolonged prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT), and in severe cases, bleeding phenomena such as hematochezia and hematuria may even occur [2]. This article analyzes a case of significant prolongation of INR caused by CPZ/SAM.

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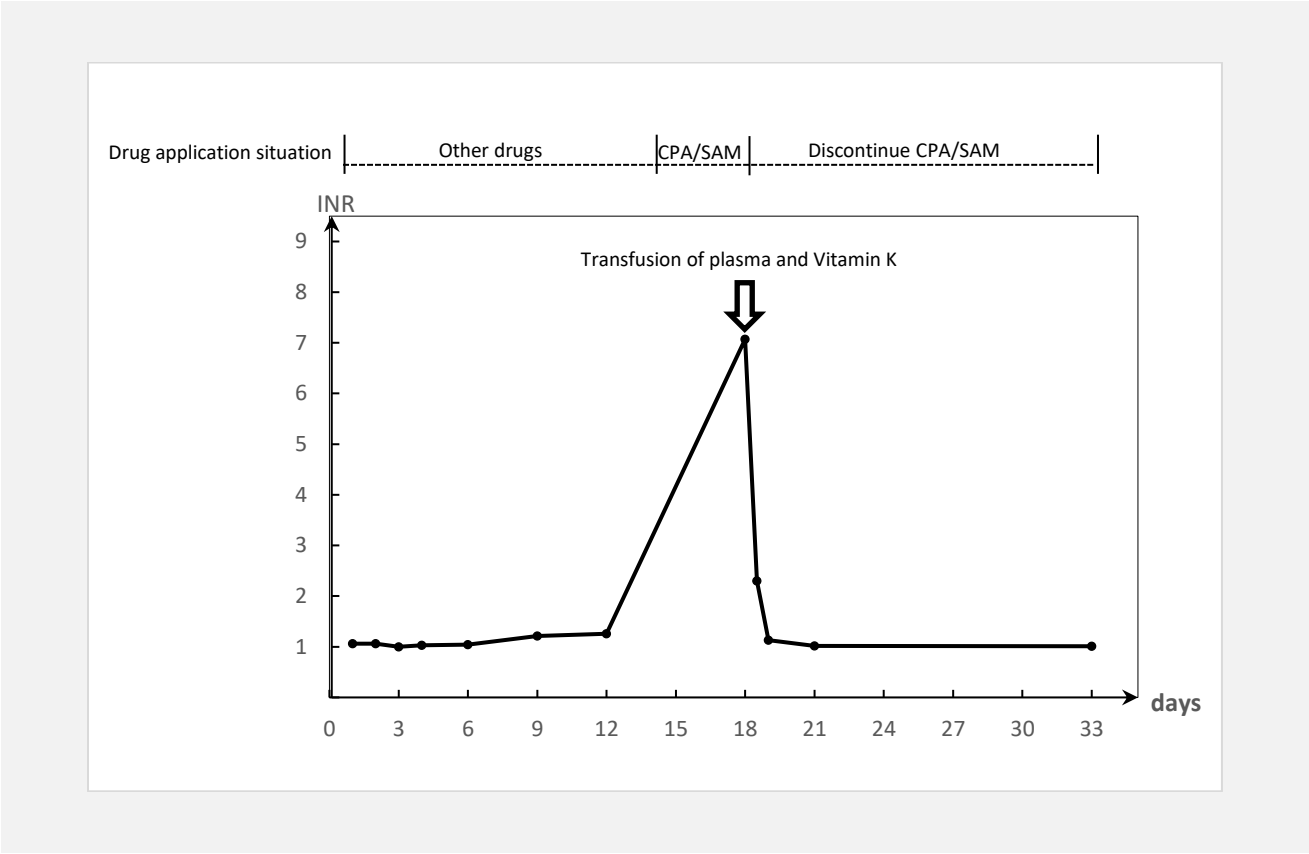

Figure 1. Line graph showing the changes in INR values.

The vertical axis represents INR values, and the horizontal axis represents the time of admission. Day 0 is defined as March 5th.

CASE REPORT

The patient (female, 92 years old) was hospitalized on March 6, 2025, because of colonic space-occupying lesion with intestinal obstruction lasting 1 day. Upon admission, blood tests were conducted: coagulation function: PT: 12.2 second, INR: 1.06; platelets: 241 x 10^9 g/L. Renal function: Urea: 5.14 mmol/L, Creatinine: 71.2 μmol/L, Estimated Glomerular Filtration Rate: 63.8↓. The patient has multiple underlying diseases, including hypertension, coronary artery disease, old myocardial infarction, and chronic renal failure with azotemia. There was no history of drug allergy. Considering that the patient had colon malignancy, a right hemicolectomy was performed on March 7th. After the operation, imipenem and cefmetazole were administered successively for anti-infection treatment. On March 19th, due to the presence of exudate at the surgical site, the anti-infection drugs were changed to CPZ/SAM 3.0 g q12 hour intravenous drip. Multiple re-examinations after admission showed no obvious abnormalities in the coagulation profile.

On March 23rd (4 days after the administration of CPZ/SAM), the coagulation function was examined and it was found that the INR was significantly prolonged: PT: 76.8s ↑↑, INR: 7.07 ↑↑, APTT: 38.8s ↑. Platelet count: 157 x 10^9 g/L. The following two aspects of possible false elevation of the results were excluded. On the one hand, after plasma extraction, using ultracentrifugation the supernatant was taken for retesting and showed no significant difference, preventing extremely small particle substances from causing non-specific interference to the specimens. On the other hand, the result of the coagulation function was tested again, after replacing the anticoagulant with EDTA, and resulted in PT: 98.4s ↑, INR: 9.13 ↑. The INR value remains at a relatively high level, which can rule out the interference from anticoagulants [3]. Therefore, we consider the result to be reliable.

Considering that the abnormal coagulation function was caused by the drug, CPZ/SAM was discontinued, vitamin K was administered intramuscularly, and 260 mL fresh frozen plasma was transfused. On the next day, the coagulation function had returned to normal levels: PT: 11.7s, INR: 1.02. Subsequent monitoring of the coagulation function did not reveal any abnormality. The patient was hospitalized for 20 days, and a total of 12 coagulation function tests were conducted during this

period. Figure 1 shows the changes in INR values during hospitalization and during outpatient follow-up visits after discharge, totaling 12 times.

DISCUSSION

This article presents a case of an elderly female patient with poor physical condition. INR was increased significantly after 4 days of CPZ/SAM anti-infection treatment. Considering the reasons for the elevation of INR in this patient related to CPZ/SAM are as follows: 1. The use of CPZ/SAM is associated with the elevation of INR in the patient, and there is a good temporal correlation. 2. After discontinuation of CPZ/SAM, INR did not increase. 3. By referring to the drug instructions, adverse reactions suggest that the risk of developing coagulation disorders is a common occurrence with a probability ranging from 1% to 10%. 4. The acute coagulation dysfunction in the patient cannot be explained by disease factors.

The detailed mechanism by which CPZ/SAM causes significant prolongation of INR is currently unclear. After searching relevant literature, the first hypothesis is that the structure of CPZ contains a N-methylthio tetrazole (NMTT) group as a side chain, which is similar in structure to glutamate and competes with vitamin K for binding to γ-glutamyl carboxylase in liver microsomes, resulting in a disorder in the synthesis of dependent vitamin K coagulation factors and the production of a large amount of inactive vitamin K deficiency-induced proteins [4]. The second hypothesis is that CPZ is mainly excreted through the biliary tract, inhibiting the intestinal flora that synthesize vitamin K, which can also cause vitamin K deficiency [5]. Vitamin K promotes the synthesis of coagulation factors II, VII, IX, and X, converting prothrombin into thrombin, and accelerating blood coagulation [6]. Therefore, when there is a deficiency of vitamin K in the body, the main manifestation is dysfunction of the extrinsic coagulation pathway, with prolonged INR coagulation time.

The risk factors for adverse reactions of coagulation dysfunction caused by CPZ/SAM mainly include: large dosage of medication (> 6 g/day), long medication course (> 5 days), advanced age, liver and kidney dysfunction, and history of gastrointestinal diseases, etc. Patients with high-risk factors should make a rational choice of medication after weighing the pros and cons. During the medication process, the coagulation function of patients should be closely monitored, and the bleeding risk should be evaluated in time. When abnormal coagulation indicators occur, the medication should be immediately stopped and the antibacterial drugs should be replaced. For patients with bleeding tendency, intramuscular injection of vitamin K can be given, and fresh frozen plasma transfusion can be used to supplement coagulation factors when necessary [7]. For critically ill patients, the thromboelastogram can be provided to the clinical doctor for feedback, providing specific coagulation kinetic indicators of the patient, so as to better determine the cause of bleeding [8].

As a laboratory staff member, when the coagulation indicators of patients show abnormalities, one should fully understand the patient's medication history and actively communicate with the clinical department to understand the patient's condition. This article proposes preventive measures for possible coagulation dysfunction caused by CPZ/SAM, providing a reference for rational clinical medication.

Declaration of Interest:

We declare that the content of this article was produced during our work and there is no conflict of interest involved. The article I submitted is entirely original and contains no instances of plagiarism or improper citation. I am fully aware that the copyright of the submitted articles belongs to this journal, and the journal has the right to reproduce, disseminate and digitally store the relevant articles.

There is no conflict of interest among all the authors.

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