

Case report

Cefoperazone-Sulbactam Induced Coagulopathy: A Lesson in Pharmacokinetics

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ABSTRACT

Cefoperazone-sulbactam is a widely used antibiotic, but clinicians must remain vigilant about potential side effects. We describe an elderly lady on immunosuppressive therapy admitted with suspected sepsis. She was empirically started on cefoperazone-sulbactam. The International normalized ratio (INR) progressively increased over the next few days. Cefoperazone-sulbactam-induced coagulopathy was suspected. INR normalized after antibiotic discontinuation and vitamin K supplementation. Several factors predispose to cefoperazone sulbactam-induced coagulopathy. Some factors include poor dietary vitamin K intake and intestinal bacterial interference with vitamin K synthesis in broad-spectrum antibiotic therapy. The serum half-life of cefoperazone is increased 2–4 fold in patients with hepatic disease and biliary obstruction. A total daily dosage above 4 g should not be necessary in such patients. Higher dosages in such situations increase the risk of toxicity. Cefoperazone therapy may prolong INR. Monitoring INR is indicated when high doses are used or when there is liver disease/biliary obstruction, renal impairment, or both.

KEYWORDS: Cefoperazone-sulbactam; Coagulation derangement; Pharmacokinetics; Hepatic dysfunction; Renal dysfunction

INTRODUCTION

Cefoperazone-sulbactam is a frequently used antibiotic. While its potential side effects, including coagulation abnormalities, are well known, the pharmacokinetic factors influencing the therapeutic and adverse effects of the drug are less well understood. This case report underscores the impact of cefoperazone-sulbactam on the coagulation profile, with a discussion of the drug's pharmacokinetics.

CASE REPORT

We present a case of a 61-year-old female with a known history of rheumatoid arthritis, secondary Sjogren's

syndrome, and interstitial lung disease. She had been on a regimen of hydroxychloroquine, methotrexate, nintedanib, and prednisolone for the past two years. Unfortunately, exact details of her medications over the two years weren't available apart from a summary at discharge, but methotrexate and nintedanib had been stopped two weeks back. The patient was referred from another hospital with complaints of anasarca over three months, painful skin lesions over two months, recent onset fever, vomiting, reduced food intake for two weeks, and decreased urine output for a week. The patient was conscious, oriented, mildly lethargic, and sick-looking on examination. The vital signs were

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stable. Physical findings included pitting anasarca with bilateral infra-axillary fine crepitations. Multiple erythematous annular lesions were noted on the trunk, with blistering in the center extending to the edge, giving a targetoid appearance. The skin over some of the lesions had denuded entirely, leaving raw areas. The clinical and biopsy findings suggest subacute cutaneous lupus erythematosus (SCLE). Laboratory investigations revealed an elevated total white cell count of 22,460/ μ L with neutrophilic predominance, anemia (7.4 g/dL), and thrombocytopenia (60,000/ μ L). Serum creatinine was mildly elevated, with nephrotic range proteinuria. Liver function tests showed elevated total bilirubin along with severe hypoalbuminemia. Erythrocyte sedimentation rate and C-reactive proteins were significantly elevated, and procalcitonin was 1.05. Serial renal and liver parameters are shown in Table 1.

Table 1: Renal and liver parameters during and after administration of cefoperazone sulbactam in our patient.

Day of cefoperazone-sulbactam administration	Serum Urea (mg/dl)	Serum Creatinine (mg/dl)	Total Bilirubin/Direct Bilirubin (mg/dl)	Aspartate aminotransferase / Alanine aminotransferase (IU/L)	Serum Total Protein / Albumin (g/dL)	Alkaline phosphatase (IU/L)
DAY-1	37	1.22	1.91/1.13	76/22	4.59/1.2	173
DAY-2	38	1.3	3.2/2.3	93/25	4.7/1.6	
DAY-3	40	1.3				
DAY-4	43	1.34	2.8/1.96	98/28	4.67/1.94	179
DAY-6 DISCONTINUED	51	1.28	1.71/1.07	124/38	4.26/1.61	529
DAY-7	60	1.31				
DAY-8	62	1.31				
DAY-9	62	1.28	2.92/2.03	129/30	4.74/1.69	728
DAY-10	71	1.4				

A diagnosis of sepsis with possible systemic lupus erythematosus (SLE) was made. She was empirically started on cefoperazone-sulbactam (8g cefoperazone and 4g sulbactam per day in 4 divided doses). A

creatinine clearance of 54 ml/min was calculated, for which dose adjustment is not required. A high dose of cefoperazone was administered, given the immunosuppressed state of the patient and the possibility of relatively resistant organisms. Investigations at admission had shown a normal international normalized ratio (INR) with an elevated d-dimer and severe thrombocytopenia. The patient gradually improved clinically, but an isolated increase in INR values was noted over the next few days. Worsening disseminated intravascular coagulation (DIC) was considered, but stable d-dimer, stable platelets, and improving general condition argue against it. Prior methotrexate use could explain thrombocytopenia but would not explain worsening INR. Methotrexate had been stopped two weeks earlier, and we did not measure levels. We stopped cefoperazone-sulbactam on day 6. Injection of vitamin K was also started. INR quickly normalized over the next three days. (Table 2).

Table 2: Coagulation profile of our patient showing derangement and recovery.

Day of cefoperazone-sulbactam administration	PT (seconds)	INR	aPTT (seconds)	D-Dimer (mg/L)	Fibrinogen (mg/dL)	Platelets (per microL)
DAY-1	12.8	1.17	39.5	5.502	212	60000
DAY-2						45000
DAY-3						42000
DAY-4	22.7	2.06	43.2	5.114	193	45000
DAY-5	29.9	2.72	44.2		325	41000
DAY-6 DISCONTINUED						47000
DAY-7						55000
DAY-8						47000
DAY-9	12	1.08	30.3	5.219		28000
DAY-10						45000

Elevated d-dimer and thrombocytopenia persisted, probably secondary to ongoing SLE disease activity and sepsis.

DISCUSSION

Our patient had received a cefoperazone dose of 8 grams per day. In patients with liver disease or biliary obstruction, doses above 4 grams should not be necessary.¹ Such a high dose was started given the likelihood of infection with resistant pathogens, but the hepatic dysfunction with concurrent renal dysfunction wasn't considered. In addition, the serum albumin was only 1.2g/dL. Cefoperazone is a highly protein-bound drug, and hypoalbuminemia will significantly increase the plasma levels of the free drug. An inverse relation between serum albumin and INR has been well documented in patients receiving cefoperazone.^{2,3} This was also not factored in when deciding the dose. With co-existing renal and hepatic dysfunction, the dose should not have exceeded 1-2 grams unless plasma concentrations are monitored, which was not done in this case. Also, our patient had received broad-spectrum antibiotics before admission at our hospital; broad-spectrum antibiotics interfere with the intestinal bacterial flora that synthesizes vitamin K. She also had a history of poor nutrition with likely reduced intake of vitamin K-containing foods. Although the above two factors were present, they were unlikely to cause a vitamin K deficiency and a prolonged INR by themselves. The derangement occurred only after cefoperazone administration. Causality assessment per the WHO-UMC system suggested "probable" causality with a reasonable time relationship of an adverse event to drug intake and clinically reasonable response to the withdrawal of drug with other causes for the adverse event not being completely ruled out.⁴

Cefoperazone-sulbactam is known for its broad-spectrum activity and beta-lactamase stability. Cefoperazone-sulbactam exhibits specific pharmacokinetic features. Approximately 25% of cefoperazone and 84% of sulbactam are excreted through the kidneys, while cefoperazone is extensively excreted in bile.⁵ The usual adult daily dose of cefoperazone is 2 to 4 grams per day, administered in equally divided doses every 12 hours.¹ In severe infections or infections caused by less sensitive organisms, the daily dose and frequency may increase. Patients have been successfully treated with a daily dosage of 6–12 grams divided into 2, 3, or 4 administrations ranging from 1.5 to 4 grams per dose.¹ Sulbactam's usual dose is 2 to 4 grams daily, with doses up to 12 grams daily used in *Acinetobacter* infections.¹ Peak bile concentrations significantly exceed serum concentrations; maximum concentration is reached between one and three hours after administration and can reach up to 100 times higher. Cefoperazone is extensively excreted in bile. The

serum half-life of cefoperazone is increased 2–4 fold in patients with hepatic disease and biliary obstruction.¹ Generally, a total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored. Mild transient elevations in liver enzymes are observed in 5-10% of patients receiving cefoperazone sulbactam, as seen with other antibiotics secreted through bile.¹

In patients with both hepatic dysfunction and significant renal disease, cefoperazone dosage should not exceed 1–2 g daily without closely monitoring serum concentrations.¹ No new liver or renal dysfunction onset is known due to cefoperazone sulbactam.⁶

Because renal excretion is not the main route of elimination of cefoperazone, patients with renal failure without liver disease require no adjustment in dosage when usual doses are administered. When high doses are used, drug concentrations in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly. In patients with renal impairment, the dose of sulbactam should be reduced, but the dose of cefoperazone should not be reduced unless there is co-existing liver disease; otherwise, it would lead to therapeutic failure. The daily sulbactam dose should not exceed 2 g for creatinine clearance (CrCl) 15 - 30 mL/min and 1 g for CrCl <15 mL/min.¹ Table 3 depicts the dosage adjustment of cefoperazone sulbactam in renal impairment.

A study highlighted that 25.8% of patients administered cefoperazone-sulbactam experienced coagulation profile derangements, notably occurring between days 3 and 12 of drug use.⁷ The N-methylthiotetrazolium side chain in cefoperazone inhibits vitamin K 2,3 epoxide reductase, impacting the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X), leading to coagulation dysfunction.⁸ The COOH group on the 7th carbon atom's substituent interferes with platelet aggregation, contributing to bleeding tendencies. Additionally, cefoperazone's inefficient metabolism and biliary excretion into the intestines inhibit normal flora and vitamin K synthesis, resulting in reduced prothrombin levels and prolonged INR, prothrombin time (PT), and activated partial thromboplastin time (aPTT).⁹ aPTT prolongation is secondary to factor X deficiency affecting the common pathway.

Several factors contribute to coagulation dysfunction, including concentration and duration of the antibiotic,⁶ sepsis severity,^{6,10} and APACHE II scores.¹¹

Table 3: Dosage adjustment of cefoperazone sulbactam in renal impairment for varying intended doses of cefoperazone.

Creatinine clearance	Desired CPZ dose	Maximal SBT per day	Using 1:1 ratio product	Using 2:1 ratio product
CrCl 15 to 30	2 g per day	2 g	CPZ-SBT 2g Q12H	
	4 g per day	2 g	CPZ-SBT 2g Q12H with plain CPZ 1g Q12H	CPZ-SBT 3g Q12H
	6 g per day	2 g	CPZ-SBT 2g Q12H with plain CPZ 2g Q12H	CPZ-SBT 3g Q12H with plain CPZ 1g Q12H
	8 g per day	2 g	CPZ-SBT 2g Q12H with plain CPZ 3g Q12H	CPZ-SBT 3g Q12H with plain CPZ 2g Q12H
	2 g per day	1 g	CPZ-SBT 1g Q12H with plain CPZ 0.5g Q12H	CPZ-SBT 1.5 g Q12H
CrCl < 15	4 g per day	1 g	CPZ-SBT 1g Q12H with plain CPZ 1.5g Q12H	CPZ-SBT 1.5g Q12H with plain CPZ 1g Q12H
	6 g per day	1 g	CPZ-SBT 1g Q12H with plain CPZ 2.5g Q12H	CPZ-SBT 1.5g Q12H with plain CPZ 2g Q12H

Hypoalbuminemia is an important factor, as in our case. 90% of cefoperazone is protein-bound, and the unbound part of the drug contributes to therapeutic effects as well as adverse events.³ A study of 65 patients showed an inverse relation between serum albumin levels and INR in patients receiving cefoperazone.² Elderly and critically ill patients have decreased liver microsomal activity, causing reduced drug metabolism. They also have poor nutritional status and intestinal flora dysfunction, putting them at risk for vitamin K deficiency.^{5,12} The patient's primary disease, most commonly infections, is also found to be a risk factor.¹¹ Platelet functional defects are likely linked to endothelial dysfunction and increased inflammatory reaction, potentially increasing the risk of abnormalities in coagulation.¹³ Malabsorption states, alcoholism, and patients on prolonged hyper-alimentation regimens (administered intravenously or via a nasogastric tube) are other potential risk factors.

Sulbactam's contribution to coagulation dysfunction is unclear, and the mechanism is not well-established. Interestingly, other N-methylthiotetrazolium-containing antibiotics did not induce coagulation profile derangements. Moreover, the risk of bleeding with cefoperazone-tazobactam is reportedly lower than with cefoperazone-sulbactam.¹⁴

Careful attention to the dosing of each of the components of cefoperazone-sulbactam is necessary to optimize efficacy and avoid toxicity. This case underscores the importance of considering pharmacokinetic factors, particularly in patients with impaired liver or renal dysfunction.

CONCLUSION

Cefoperazone sulbactam therapy may prolong INR. Monitoring INR is indicated when high doses are used or when there is liver disease/biliary obstruction, renal impairment, or both. Hypoalbuminemia will increase free drug levels and predispose to toxicity. Ideally, cefoperazone levels should be measured in the above circumstances. Monitor coagulation closely, especially in the initial days and in the event of prolonged administration. Vitamin K supplementation should be given to prevent bleeding complications in case of any derangement.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS STATEMENT INCLUDING PATIENT CONSENT

Not applicable

AUTHORS' CONTRIBUTIONS

SS: Data collection, review of literature, analysis, writing the draft

VM: Conceptualization, validation, supervision

DM: Data collection, resources, editing the manuscript

JS: Editing the manuscript, validation

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted

content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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