CASE REPORT

JIACM 2025; 26 (1-2): 73-76

Cefoperazone induced Coagulopathy in a Patient with Community-Acquired Pneumonia

Ravi K, Nagaraja Kamath**, Rishika Das***, Aditya Chandrashekar****

Abstract

Cephalosporin antibiotics, such as Cefoperazone, are widely used to treat sepsis and other bacterial infections. Although generally considered safe, rare cases of drug-induced coagulopathy have been reported. We present the case of a 31-year-old man with no prior co-morbidities who developed coagulopathy following the initiation of cefoperazone.

The patient presented with fever, cough, shortness of breath, and severe hypoxaemia. Chest X-ray revealed homogenous opacity in the middle zone of right lung field. He was diagnosed with Community-acquired pneumonia (CAP) and Cefoperazone-sulbactam was initiated. Within four days of starting the antibiotic, the patient developed hematuria and ecchymoses with a progressive increase in PT/INR values, leading to a presumptive diagnosis of drug-induced coagulopathy. Cefoperazone was discontinued, and Vitamin K therapy was initiated, resulting in symptom resolution and PT/INR values normalisation within two days.

This case underscores the importance of closely monitoring coagulation parameters in patients receiving Cefoperazone, especially those with hepatic or renal dysfunction.

Key words: Coagulopathy, cefoperazone, pneumonia.

Introduction

Cefoperazone is a third-generation cephalosporin antibiotic used to treat various bacterial infections, including septicaemia. It is generally well tolerated; however, in rare instances, it may lead to drug-induced coagulopathy. Cefoperazone contains an N-methyl-thio-tetrazole (NMTT) side chain, which inhibits vitamin K epoxide reductase. This inhibition disrupts the gamma-carboxylation of glutamic acid, resulting in a deficiency of vitamin K-dependent clotting factors (II, VII, IX, and X)[1,2]. Consequently the risk of hypoprothrombinaemia and bleeding is raised. This report highlights a case of drug-induced coagulopathy associated with cefoperazone, emphasizing the importance of prompt identification and management of this adverse effect. Additionally, we aimed to explore the underlying mechanisms that contribute to this phenomenon.

Case presentation

A 31-year-old man presented to our hospital with a 10-day history of fever, productive cough, and progressively worsening shortness of breath. He had no history of abdominal pain, chest pain, or hematuria, was an occasional smoker, and had an unremarkable medical history without known co-morbidities.

On examination, the patient was alert and oriented but exhibited severe hypoxaemia (oxygen saturation at 70% on room air), fever of 101° F, tachycardia, and tachypnoea. Respiratory auscultation revealed bilateral crepitations and rhonchi. Arterial blood gas analysis indicated persistent hypoxaemia (pH 7.31, PaO_2 44 mmHg, $PaCO_2$ 28 mmHg). A chest X-ray demonstrated a well defined homogenous opacity in the middle zone of right lung field with multiple patchy nodular opacities in the right mid- and lower zones, leading to a provisional diagnosis of Community-acquired pneumonia (CAP) (Fig. 1). Laboratory investigations revealed leukocytosis (WBC 33,670 cells/cumm), markedly elevated erythrocyte sedimentation rate (ESR 65 mm/hr), and high procalcitonin levels (43.2 ng/mL). Hepatic function tests indicated elevated AST (139 IU/L) and ALT (134 IU/L), while renal function tests showed increased serum creatinine levels (1.61 mg/dL). Baseline coagulation studies were within normal limits (PT/INR: 12/1.1). High-resolution computed tomography (HRCT) of the thorax revealed centrilobular nodules and tree-in-bud opacities with patchy consolidation in the right middle lobe. The patient was subsequently diagnosed with Sepsis secondary to Community-acquired pneumonia and Type I Respiratory failure, necessitating admission to the intensive care unit

Professor and Unit Head, **Junior Resident, ***Medical Student, Department of General Medicine, Bangalore Medical College and Research Institute, Fort, Krishna Rajendra Road, City Market, Bengaluru - 560 002, Karnataka.

Corresponding Author: Dr Nagaraja Kamath, Junior Resident, Department of General Medicine, Bangalore Medical College and Research Institute, Fort, Krishna Rajendra Road, City Market, Bengaluru- 560002, Karnataka. Tel: 8762957560, E-mail: nagaraj.kamath1998@gmail.com.

(ICU) and mechanical ventilation. Blood and sputum cultures were collected, and empirical therapy with Cefoperazone-sulbactam (3 g twice daily, IV) and Clarithromycin (500 mg twice daily, IV) was initiated, per institutional antibiotic protocols.

The sputum culture revealed the growth of *Klebsiella pneumoniae*. The organism was found to be sensitive to Cefoperazone-sulbactam, Clarithromycin, Meropenem, Tigecycline, Gentamicin, and Amikacin but resistant to Amoxicillin, Trimethoprim/sulfamethoxazole, and Levofloxacin. Based on the antimicrobial susceptibility reports, the patient was continued on Cefoperazone-sulbactam and Clarithromycin. On day 4 of hospitalisation, the patient developed hematuria and ecchymotic patches on his extremities. Repeat coagulation studies revealed elevated Prothrombin time (PT) and International Normalised Ratio (INR) levels, with normal activated partial thromboplastin time (APTT), raising concerns regarding coagulopathy. We initially suspected Disseminated intravascular coagulation (DIC), prompting the continuation of Cefoperazone-sulbactam and Clarithromycin therapy. However, further evaluation revealed normal fibrinogen levels (322 mg/dL), fibrinogen degradation products (<10 mcg/mL), and D-dimer (260 ng/mL), effectively ruling out DIC. A declining trend in serum procalcitonin levels (Day 5: 32.4 ng/mL, Day 8: 24.8 ng/mL) and negative antinuclear antibody (ANA) testing excluded autoimmune aetiologies. Improvement in liver function tests was noted, suggesting preserved hepatic synthetic function. Vitamin K1 supplementation was administered to address the coagulation abnormalities. Given the patient's clinical deterioration and laboratory findings, and with DIC ruled out, we hypothesized that the observed coagulopathy was linked to drug therapy. A review of the side effect profile for the medications revealed a rare association between coagulopathy and Cefoperazone. A Naranjo Adverse Drug Reaction assessment yielded a score of 6, indicating a probable relationship between Cefoperazone and the observed coagulopathy. Consequently, on day 8, Cefoperazone-sulbactam was discontinued and replaced with Meropenem (1 g IV three times a day). Additionally, Clarithromycin was halted on day 7. Over the next four days following the discontinuation of Cefoperazone, the patient's prothrombin time (PT) and international normalised ratio (INR) levels normalised, further supporting the diagnosis of drug-induced coagulopathy (Fig. 2).

The patient was gradually weaned off the ventilator and extubated on day 12 of hospitalisation. By day 14, the patient's renal function had improved, white blood cell counts returned to normal, the coagulation profile stabilised, and the patient was transferred to the ward, ultimately leading to a full recovery.

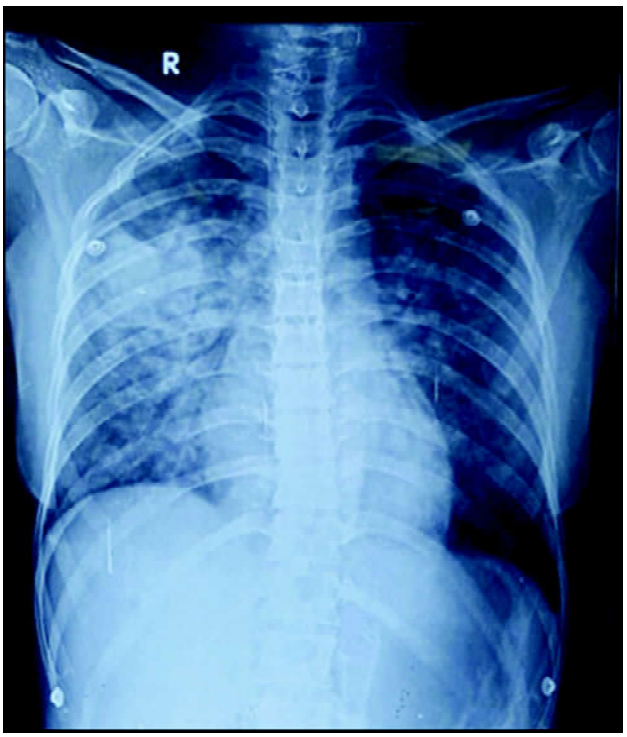

Fig. 1: *Chest X-ray demonstrating well defined homogenous radiopacity in the middle zone of right lung fields with multiple patchy nodular opacities in the right mid and lower zones.*

Discussion

Cefoperazone, a widely used third-generation Cephalosporin, is often combined with Sulbactam, a beta-lactamase inhibitor, for enhanced efficacy. Despite its safety, Cefoperazone has been associated with haemorrhagic complications, particularly in patients receiving prolonged high-dose therapy[3-6]. Several mechanisms have been

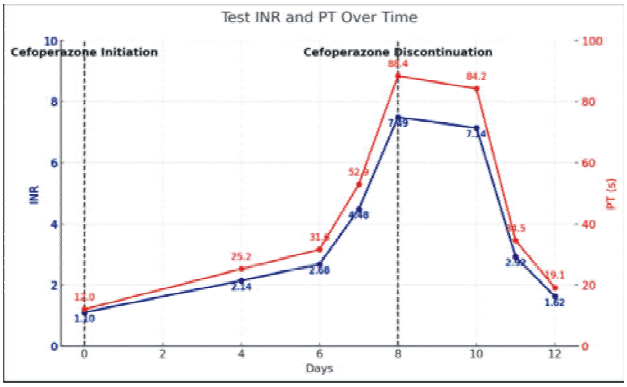

Fig. 2: *Temporal trends of prothrombin time (PT) and international normalised ratio (INR) levels. The INR values are represented on the primary y-axis (left, in blue), while the PT values are displayed on the secondary y-axis (right, in red). The figure shows an initial spike in PT levels on day 4, followed by a gradual decline, leading to normalisation by day 12.*

proposed for these complications (Fig. 3). The primary mechanisms include the inhibition of Vitamin K epoxide reductase by the NMTT side chain, which prevents the gamma-carboxylation of Vitamin K-dependent clotting factors and the suppression of Vitamin K-producing bacteria in the intestines[7].

Similar effects have been observed with other NMTT-containing cephalosporins, such as Cefamandole, Cefoperazone, Cefotetan, Cefmetazole, and Moxalactam[1,8,9]. Chen *et al,* reported that Cefoperazone and Cefmetazole, which contain NMTT-side chains, are associated with a 4.5-fold and 2.8-fold higher risk of bleeding events, respectively, with a dose-dependent response[7]. In a study by Shao *et al*, Cefoperazone/sulbactam-induced coagulation dysfunction occurred in 24.39% of 200 patients. The incidence typically occurred 2 - 19 days after starting 9.0 g/day of Cefoperazone[10].

Other contributing factors may include hepatic and renal impairment. Cochet *et al*, suggested that hypo-albuminaemia may reduce the extrarenal clearance of Cefoperazone[11]. This implies that patients with low albumin levels might be particularly susceptible to coagulation disturbances and hypoprothrombinaemia.Serum albumin levels and INR have been found to be inversely correlated in intensive care unit patients on Cefoperazone, which aligns with our case findings, where significant hepatic dysfunction and hypoalbuminaemia likely contributed to coagulopathy[12].

In patients with hepatic impairment and renal dysfunction, the dosage of Cefoperazone should not exceed 1 - 2 g/day without close monitoring of coagulation parameters[12]. Our case emphasizes the need for vigilance in high-risk patients, including those with hepatic dysfunction, hypoalbuminaemia, or high-dose Cefoperazone therapy.

This case highlights a young man with Sepsis-induced multiple organ dysfunction syndrome (MODS) due to severe pneumonia who developed coagulopathy after receiving Cefoperazone-sulbactam. Despite ongoing treatment, PT and INR abnormalities emerged, raising concerns of coagulopathy. Differentiating between DIC and drug-induced coagulopathy was crucial. Negative DIC markers, such as normal fibrinogen and FDP levels and

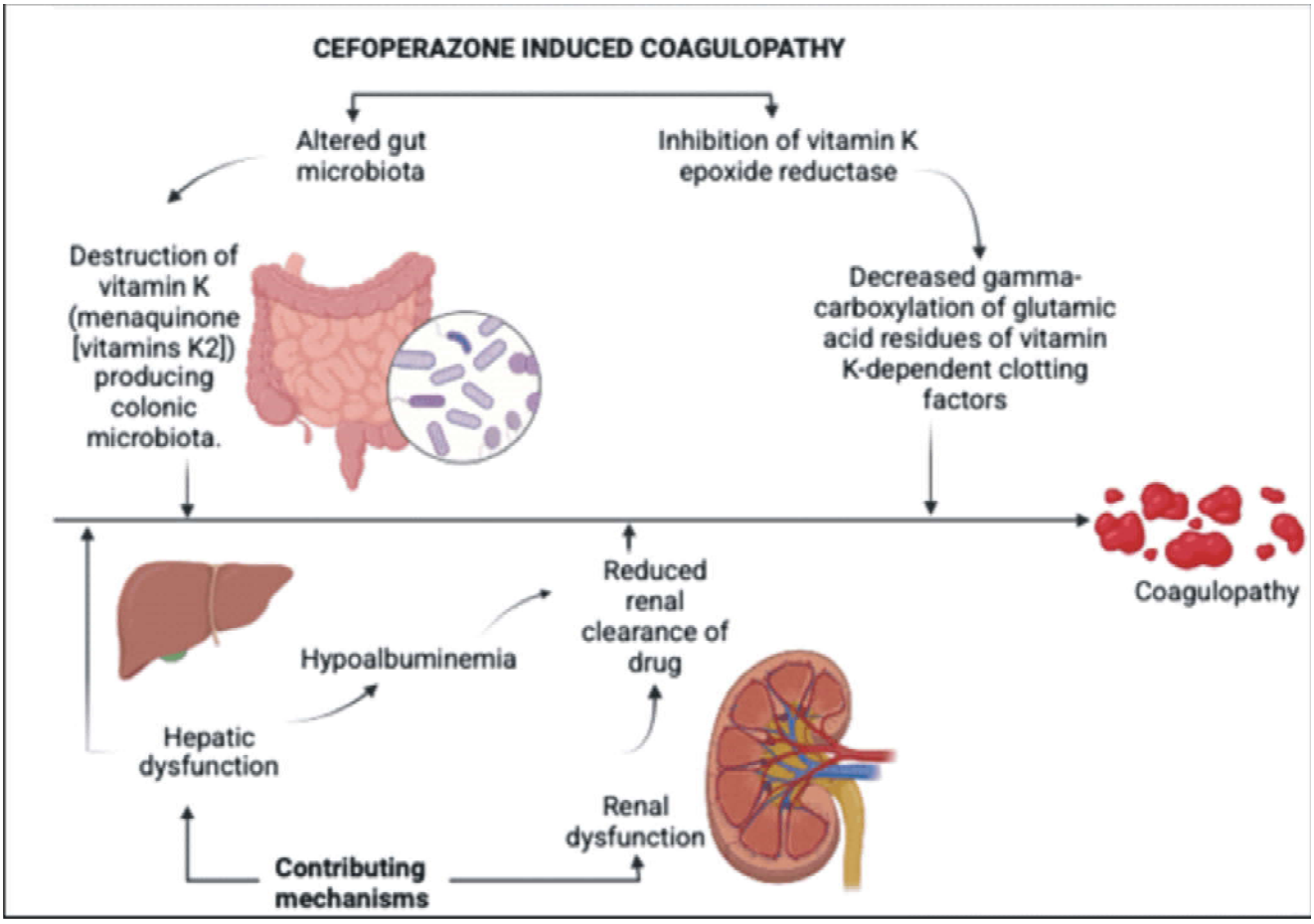

Fig. 3: *Diagram illustrating the possible mechanisms for Cefoperazone-induced coagulopathy.*

stable D-dimer levels, alongside negative autoimmune screening, helped rule-out DIC and autoimmune causes[13]. The coagulation profile was normal before antibiotic initiation, but it deteriorated after cefoperazone exposure and improved rapidly upon discontinuation. The patient's recovery after substituting Meropenem provided further evidence that drug-induced coagulopathy was the underlying cause of their condition.

Conclusion

Cefoperazone-induced coagulopathy is a rare but serious adverse effect, particularly in patients with hepatic dysfunction or hypoalbuminaemia. Early recognition, prompt cessation of the offending drug, and Vitamin K supplementation are essential for management[9,11]. Clinicians should maintain a high index of suspicion for drug-induced coagulopathy in critically ill patients receiving Cefoperazone and monitor coagulation parameters closely to prevent life-threatening bleeding complications. Early identification and discontinuation of the suspected drug can lead to a full recovery of coagulation function, as demonstrated in this case.

References

1. Lipsky JJ. N-methyl-thio-tetrazole inhibition of the gamma carboxylation of glutamic acid: possible mechanism for antibiotic-associated hypoprothrombinaemia. *Lancet* 1983; 2 (8343): 192-3.
2. Creedon KA, Suttie JW. Effect of N-methyl-thiotetrazole on vitamin K epoxide reductase. *Thromb Res* 1986; 44 (2): 147-53.
3. Mueller RJ, Green D, Phair JP. Hypoprothrombinaemia associated with cefoperazone therapy. *South Med J* 1987; 80 (11): 1360-2.
4. Hu H-R. Fatal vitamin K-dependent coagulopathy associated with cefoperazone/sulbactam: A case report. *Drug Saf Case Rep* 2019; 6 (1): 6.
5. Alitalo R, Ruutu M, Valtonen V. Hypoprothrombinaemia and bleeding during administration of cefamandole and cefoperazone. Report of three cases. *Ann Clin Res* 1985; 17 (3): 116-9.
6. Ozen IO, Moralioolu S, Karabulut R. Cefoperazone induced gastro-intestinal haemorrhage. A case report. *Acta Chir Belg* 2008; 108 (6): 777-8.
7. Chen L-J, Hsiao F-Y, Shen L-J. Use of hypoprothrombinaemia-inducing cephalosporins and the risk of haemorrhagic events: A nationwide nested case-control study. *PLoS One* 2016; 11 (7): e0158407.
8. Barza M, Furie B, Brown AE, Furie BC. Defects in vitamin K-dependent carboxylation associated with moxalactam treatment. *J Infect Dis* 1986; 153 (6): 1166-9.
9. Park GH, Kim S, Kim MS. The association between cephalosporin and hypoprothrombinaemia: A systematic review and meta-analysis. *Int J Environ Res Public Health* 2019; 16 (20): 3937.
10. Shao X, Ren Y, Xie N. Effect of cefoperazone/sulbactam on blood coagulation function in infected emergency department patients and the necessity of vitamin K1 (VK1) preventive intervention: A single-center, retrospective analysis. *Med Sci Monit* 2023; 29: e939203.
11. Cochet B, Belaieff J, Allaz AF. Decreased extrarenal clearance of cefoperazone in hepatocellular diseases. *Br J Clin Pharmacol* 1981; 11 (4): 389-90.
12. Gudivada KK, Krishna B, Sampath S. Cefoperazone-induced coagulopathy in Critically Ill Patients Admitted to Intensive Care Unit. *Indian J Crit Care Med* 2023; 27 (3): 183-9.
13. Liang Y, Xie S-B, Wu C-H. Coagulation cascade and complement system in systemic lupus erythematosus. *Oncotarget* 2018; 9 (19): 14862-81.