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Adverse Drug Reaction Reporting of Beta-Lactam Antibiotics: A Focus on Cefoperazone-Sulbactam

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Abstract: *Adverse drug reactions (ADRs) present a significant challenge in clinical practice, particularly with β-lactam antibiotics. Cefoperazone-Sulbactam, a widely used β-lactam/β-lactamase inhibitor combination for treating resistant infections, carries a risk of serious ADRs. This observational study at Manipal Hospital, Baner, evaluated the incidence, characteristics, and causality of ADRs associated with Injection Cefoperazone-Sulbactam. Using patient case reports and Naranjo's Algorithm, a case of a 35-year-old female who developed an anaphylactic reaction—marked by respiratory distress, coughing, and drowsiness—was documented. Management involved administration of adrenaline, corticosteroids, antihistamines, and nebulization, leading to resolution of symptoms. These findings highlight the importance of vigilant monitoring and prompt management when using Cefoperazone-Sulbactam, despite its clinical efficacy against multidrug-resistant organisms. Careful assessment of patient history and preparedness for adverse events are essential for optimizing outcomes. This study adds to the evidence supporting cautious use of β-lactam/β-lactamase inhibitor therapies in routine medical practice.*

Keywords: Cefoperazone-Sulbactam, Adverse drug reaction, Inj. Kipinex Forte, Naranjo'sAlgorithm**,** B-Lactam.

I. INTRODUCTION

Adverse drug reactions (ADRs) are unintended and harmful effects caused by medications. A detailed medication history can help prescribers assess a patient's past experiences with drug treatments, particularly in recognizing previous ADRs that could prevent the use of the same drug again[1,2]. An adverse drug reaction (ADR) is recognized as a notable harmful response arising from the use of a medical product. When an adverse effect results from an excessive manifestation of the intended therapeutic action, it is considered part of an ADR. On the other hand, side effects are typically linked to a drug's therapeutic properties and can have both positive and negative impacts[3,4,5].

HISTORY

Since 2012, the definition has expanded to include reactions resulting from errors, misuse, or abuse, as well as suspected adverse reactions to unlicensed medicines or those used off-label. This is in addition to reactions occurring from the authorized use of a medicinal product at normal doses[2].Groundbreaking studies in the late 20th and early 21st centuries in the USA and the UK showed that adverse drug reactions (ADRs) are commonly observed in clinical practice[6,7]. Some medications have been strongly linked to adverse drug reactions (ADRs), especially fatal ones. Fatal ADRs often result from haemorrhage, commonly caused by the combined use of an antithrombotic or anticoagulant with a nonsteroidal anti-inflammatory drug (NSAID)[8].

Classification of Adverse Drug Reaction

Adverse drug reactions are frequently classified as 'type A' and 'type B' reactions. An extended version of this classification system is shown here:

Type A Reactions: Type A adverse drug reactions (ADRs) are often dose-dependent, resulting from an intensified therapeutic effect of the drug. These reactions are influenced by pharmacokinetic and pharmacodynamic factors, with genetic variations affecting drug metabolism and elimination being key contributors to their occurrence[9]. Additionally, liver diseases have been found to cause pharmacokinetic changes, leading to alterations in drug distribution and metabolism, which can result in adverse drug reactions (ADRs)[10]. The pharmacodynamic factors contributing to Type

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A reactions include liver disease, imbalances in fluid and electrolytes, changes in drug sensitivity, and prolonged drug effects[11].

Type B adverse drug reactions: Type B (bizarre) reactions are unexpected and uncommon drug responses that do not align with the drug's known pharmacological effects. These reactions often emerge only after a drug is widely used. They are rare, unpredictable, and sometimes linked to genetic factors, with unknown mechanisms. Unlike dose-dependent effects, Type B reactions can be severe or even life-threatening. Examples include anaphylaxis from penicillin, antibiotic-induced skin rashes, halothane-induced hepatitis, chloramphenicol-associated aplastic anaemia, and neuroleptic malignant syndrome triggered by certain anesthetics and antipsychotics[12].

Type C adverse reactions: These are associated with both serious and common effects that significantly impact public health due to chronic drug toxicity. These reactions result from long-term drug use and develop gradually over time, often due to cumulative toxic effects. Examples include analgesic-induced kidney damage (analgesic nephropathy) and extrapyramidal symptoms. Type C reactions can also involve long-term drug effects such as adaptive physiological changes and withdrawal symptoms[10]. Type C adverse reactions are chronic and linked to prolonged drug use. An example is iatrogenic hyperadrenocorticism, which can develop from long-term use of prednisolone or other corticosteroids. Additionally, research has highlighted the body's adaptation upon stopping the drug, often referred to as abstinence syndrome[13].

Type D adverse reaction: Type D (delayed) reactions appear some time after taking a medication, making them harder to identify due to their timing. For instance, leucopoenia may develop as late as six weeks after a dose of lomustine. Adverse drug reactions (ADRs) can also emerge even after stopping treatment, such as corneal opacities from thioridazine, ophthalmopathy from chloroquine, or pulmonary and peritoneal fibrosis caused by methysergide[14].

Type E adverse reaction: Type E reactions, also known as "end-of-use" reactions, occur when a medication is discontinued. For instance, stopping benzodiazepines may lead to symptoms like insomnia, anxiety, and perceptual disturbances. These withdrawal reactions are common with depressant drugs, such as experiencing hypertension and restlessness after stopping opioids or seizures following alcohol or benzodiazepine withdrawal. Additionally, certain medications can cause immediate effects when first taken, such as low blood pressure (hypotension) triggered by alpha-blockers like prazosin or ACE inhibitors[14].

Type F adverse reaction: These reactions result from ineffective treatment, which was previously not included in analyses based on the WHO definition. An example is the development of accelerated hypertension due to inadequate control of blood pressure[12].

AIM & OBJECTIVE

AIM

The aim of this study is to systematically evaluate and analyse the incidence, nature, and severity of adverse drug reactions (ADRs) associated with the use of Injection Cefoperazone + Sulbactam in patients attending Manipal Hospital, Baner.

OBJECTIVE

- To identify the occurrence of adverse drug reactions (ADRs) related to Injection Cefoperazone + Sulbactam.
- To describe the type, nature, and pattern of ADRs observed following administration of the drug.
- To assess the causality of the reported ADRs using Naranjo's Algorithm.
- To evaluate the patient demographics (age, gender) and clinical conditions associated with ADR development.
- To contribute to the existing knowledge regarding the safety profile of Cefoperazone + Sulbactam for improved clinical decision-making.

II. MATERIALS AND METHODS

STUDY TITLE

Evaluation of Adverse Drug Reactions Due to INJ. Cefoperazone + Sulbactam.

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STUDY LOCATION & DURATION

The present study was conducted at Manipal Hospital, Baner, during the period of **01Nov 2024 to 20Nov 2024**.

STUDY DESIGN

Case report observational study.

SOURCE OF STUDY

Population: OPD patients visiting Manipal Hospital, Baner.

Inclusion Criteria:

Patient's name, age, and gender.

Drug prescribed.

Exclusion Criteria:

Incomplete patient information.

CASE STUDY

Patient Observations

Dosage of the prescribed drug.

Dosage form.

Route of administration.

DATA COLLECTION

Data on reported ADRs will be evaluated to identify the pattern of ADRs concerning:

Patient demographics.

Disease profile.

Nature of reactions.

Characteristics of the drugs involved.

Outcomes of the reactions.

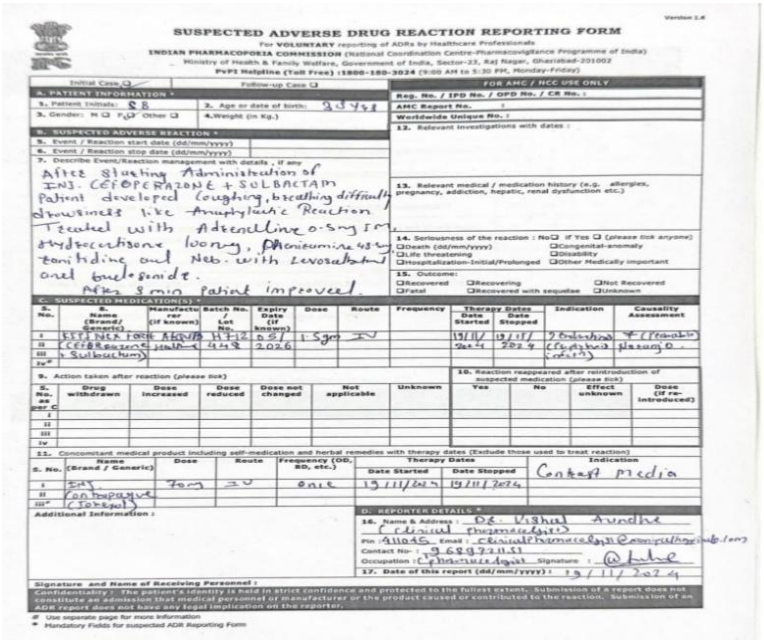
CRITERIA FOR IDENTIFYING ADRs

ADRs identified by physicians will be documented and included in the study.

ANALYSIS OF ADRs

Description and classification of ADRs reported.

Causality assessment of ADRs using **Naranjo's Algorithm** to determine the degree of association between the adverse reaction and the drug.


SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

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CASE STUDY

PATIENT INFORMATION

Patient Initials: SB
Age: 35 yrs
Sex: Female
Hospital/Clinic: Manipal Hospital, Baner, Pune

A. SUSPECTED ADVERSE DRUG REACTION DETAILS

Drug: Inj. Kipinex Forte 1.5 mg
Batch No.: H712448
Dose: 1.5 g
Route: Intravenous (IV)
Expiry Date: 05/2026
Frequency: Once
Therapy Dates:
Date Started: 19/11/2024
Date Stopped: 19/11/2024
Indication: Coughing, breathing difficulty, drowsiness.

B. CONCOMITANT MEDICATION DETAILS

Drug: Iohexol
Route: IV
BD Dose: 70 mg
Therapy Dates:
Date Started: 19/11/2024
Date Stopped: 19/11/2024
Indication: Contrast media

ADVERSE DRUG REACTION

After administration of INJ. Cefoperazone + Sulbactam, the patient developed coughing, breathing difficulty, and drowsiness, indicative of an anaphylactic reaction.

Treatment Administered:

Adrenaline 0.5 mg IM
Hydrocortisone 100 mg
Pheniramine 45 mg
Ranitidine
Nebulization with Levosalbutamol and Budesonide

TAKEN AFTER REACTION

Inj. Iohexol was administered to prevent allergic reaction.
Reaction reappeared after reintroduction of suspected medication: **No**

REPORTER DETAILS

Name: Dr. Vishal Aundhe
Address: Clinical Pharmacologist, Manipal Hospitals.
Contact: 9689721151
Occupation: Clinical Pharmacologist
Date of Report: 19/11/2024

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Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	a
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			TOTAL SCORE:	7

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin

SUSPECTED DRUG AND ITS PHARMACOLOGY

Class of Drug: Antimicrobial agent

Brand Name: Inj. Kipinex Forte

Dose and Strength: Injection - 1.5g

Manufacturer: Aristo Pharmaceuticals Pvt. Ltd.

Mechanism of action:

The appropriate combination of cefoperazone + sulbactam may be effective against bacteria with a basal or moderate level of AmpC β-lactamase expression. However, the potential antagonistic interaction between these two antibiotics must be considered. Higher concentrations of sulbactam can induce chromosomal β-lactamase production in hyperinducibleAmpC-producing bacteria, potentially reducing the efficacy of the treatment (Rizvi et al., 2009). This suggests that simply increasing the sulbactam dose may not always enhance antibacterial activity. Given the growing challenge of multidrug-resistant Gram-negative bacteria, it is essential to determine whether adjusting the cefoperazone-sulbactam ratio could serve as a viable therapeutic strategy. This review examines existing literature to address this question, as well as explores the characterization, pharmacodynamic targets, and in-vitro antimicrobial effects of cefoperazone/sulbactam on Gram-negative bacteria with various β-lactamases.[15]Cefoperazone, like other beta-lactam antibiotics, targets specific penicillin-binding proteins (PBPs) within the bacterial cell wall. By binding to these proteins, it disrupts the final stages of cell wall synthesis, ultimately leading to bacterial cell death. This process is facilitated by autolytic enzymes, such as autolysins, which break down the bacterial cell wall and cause lysis.[16]

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Composition:
Cefoperazone Sodium 1000 mg
Sulbactam Sodium 500 mg
(Usually available as 1.5 g vial)
Pharmacokinetics:[17,18,19,20.]
Plasma Concentration (Cmax)
After IV administration of **Kipinex Forte** (1.5 g dose):
Cefoperazone peak plasma concentration:170–180 mcg/mL (within 30 minutes).
Sulbactam peak plasma concentration:45–70 mcg/mL.
Volume of Distribution (Vd) Vd: 0.15–0.18 L/kg.
Therapeutic Dose
Adults:
1.5 g to 3 g every 12 hours (IV infusion).
Typical: **1.5 g IV every 12 hours**.
Severe infections: Up to 6–8 g/day may be used cautiously (adjusted based on severity).
Higher Dose Effects
Bleeding tendencies (hypoprothrombinaemia): Cefoperazone inhibits Vitamin K pathways.
Electrolyte disturbances: due to the sodium content.
Seizures (rare): at extremely high doses, especially with renal impairment.
Hepatic dysfunction risk: if underlying liver issues exist.
Monitoring of PT/INR (prothrombin time) is recommended at higher doses.
Systemic Clearance (Cl)
Cefoperazone:5–6 mL/min/kg, primarily hepatic.
Sulbactam:7–9 mL/min/kg, primarily renal.
Half-Life (t½)
Cefoperazone: 1.7–2.0 hours.
Sulbactam: 0.9–1.6 hours.
Excretion
Cefoperazone:70–80% via bile, ~20–30% via urine.
Sulbactam:75% via urine (unchanged).

General Dosing Information[21,22]
The recommended standard adult dose of Cefoperazone + Sulbactam (Kipinex Forte) is 1.5 g (one vial) administered intravenously every 12 hours. In cases of moderate to severe infections, the dose may be adjusted to between 1.5 g and 3.0 g intravenously every 12 hours, depending on the severity of the infection and patient response. The total daily dose typically falls within the range of 3 g to 6 g per day, divided into two equal doses given every 12 hours to maintain effective plasma concentrations. For patients with very severe infections, such as sepsis or hospital-acquired pneumonia, the dosage may be increased up to a maximum of 6 g per day, carefully monitored under clinical supervision to ensure efficacy while minimizing the risk of adverse effects.

Table NO.1: Adult Dose Regimen

Clinical Condition	Dose	Frequency	Route
Mild to Moderate Infections	1.5 g (Cefoperazone + Sulbactam)	Every 12 hours (BID)	IV injection/infusion
Severe Infections	3.0 g (Cefoperazone + Sulbactam)	Every 12 hours (BID)	IV infusion

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Life-threatening Infections	Up to 6.0 g/day (divided doses)	Every 8–12 hours	IV infusion

Pediatric Dose: Thegeneral pediatric dose range is 40–80 mg/kg/day, based on the total amount of cefoperazone and sulbactam combined. The dose is divided every 12 hours. In severe pediatric infections, the dose can be increased up to160mg/kg/day, divided every 12 hours.

Table 2: Pediatric Dose Regimen

Age Group	Dose	Frequency	Route
Infants (>2 months) to Children	40–80 mg/kg/day (total of both drugs)	Divided every 12 hours	IV infusion
Severe Infections	Up to 160 mg/kg/day (total)	Divided every 8–12 hours	IV infusion
Neonates (<2 months)	20–40 mg/kg/dose (careful titration)	Every 12–24 hours	IV infusion

Route and Method of Administration

Intravenous (IV) slow injection: Over 3–5 minutes.

Intravenous (IV) infusion: Over 15–30 minutes diluted in compatible IV fluids (like 0.9% Normal Saline or 5% Dextrose).

Symptoms/ side effect of Overdose for Cefoperazone + Sulbactam (Kipinex Forte)[23,24,25]

An overdose of Cefoperazone + Sulbactam can lead to various serious symptoms mainly due to high plasma concentrations of β-lactam antibiotics.

Central Nervous System (CNS):

Seizures
Dizziness
Headache
Confusion

Gastrointestinal System:

Nausea
Vomiting
Diarrhea
Abdominal pain

Hematologic System:

Thrombocytopenia
Leukopenia
Prolonged bleeding time

Liver Function:

Elevated liver enzymes (AST, ALT)
Jaundice

Hypersensitivity:

Rash
Pruritus
Anaphylactoid reactions (especially if previously sensitized)

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Adverse Reactions of Cefoperazone + Sulbactam (Kipinex Forte)[23,24,25,26]

System Affected	Adverse Reactions
Central Nervous System (CNS)	Seizures, Dizziness, Headache, Confusion
Gastrointestinal System	Nausea, Vomiting, Diarrhoea, Abdominal Pain
Hematologic System	Thrombocytopenia, Leukopenia, Prolonged Bleeding Time
Liver Function	Elevated Liver Enzymes (AST, ALT), Jaundice
Hypersensitivity	Rash, Pruritus, Anaphylactoid Reactions

Table 3: Adverse Reactions of Cefoperazone + Sulbactam (Kipinex Forte)

Contraindications of Cefoperazone + Sulbactam Combination[25,27,28]

The Cefoperazone + Sulbactam combination (like Kipinex Forte) is contraindicated in the following conditions:

Hypersensitivity to β-lactam antibiotics

Contraindicated in patients with known allergy to penicillin's, cephalosporins, sulbactam, or any β-lactam antibiotics. Cross-reactivity between penicillin's and cephalosporins can cause serious allergic reactions.

History of Severe Anaphylactic Reaction

Patients who have had severe anaphylaxis after β-lactam antibiotics must not receive this combination.

Neonates with Hyperbilirubinemia (especially premature infants)

Cefoperazone may displace bilirubin from albumin binding sites and cause kernicterus.

Severe Hepatic Dysfunction

Use is contraindicated or requires extreme caution, because cefoperazone is mainly eliminated by bile; impaired liver function can lead to accumulation and toxicity.

Bleeding Disorders

Cefoperazone can cause hypoprothrombinemia (low prothrombin levels) and bleeding risk, especially in patients with vitamin K deficiency or bleeding disorders. Extreme caution or avoidance is recommended.

Patients with Renal and Hepatic Dysfunction Together

Simultaneous impairment in kidney and liver function can significantly delay drug clearance, leading to toxicity.

Drug Interactions of Cefoperazone + Sulbactam

Alcohol (Ethanol)[29]

Cefoperazone can cause a disulfiram-like reaction, characterized by flushing, sweating, headache, and tachycardia, when taken with alcohol, due to the inhibition of aldehyde dehydrogenase.

2. Oral Anticoagulants (e.g., Warfarin)[27]

The use of cefoperazone can increase the risk of bleeding because it may inhibit the synthesis of vitamin K–dependent clotting factors.

3. Aminoglycosides (e.g., Gentamicin)[28]

The combination of sulbactam/cefoperazone can lead to additive nephrotoxicity, especially at high doses, because both drugs are individually nephrotoxic and their combined use increases the burden on the kidneys.

4. Loop Diuretics (e.g., Furosemide)[29]

The use of loop diuretics together with sulbactam/cefoperazone can increase the risk of nephrotoxicity because loop diuretics impair renal function, and when combined with nephrotoxic antibiotics, the risk to the kidneys becomes additive.

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5. Other β-lactam Antibiotics[31]

The interaction between sulbactam/cefoperazone and other antibiotics can produce either synergistic or antagonistic effects, depending on the susceptibility of the infecting organism.

Uses of Cefoperazone + Sulbactam Combination (e.g., Kipinex Forte)[23,25,27,28,31,32,33,34]

The Cefoperazone + Sulbactam combination is widely used to treat moderate to severe bacterial infections, particularly those caused by β-lactamase-producing organisms. The main uses are:

Respiratory Tract Infections: Treatment of community-acquired and hospital-acquired pneumonia, bronchitis, and lung abscesses.

Urinary Tract Infections (UTIs): For complicated and uncomplicated infections like pyelonephritis, cystitis.

Intra-Abdominal Infections: Peritonitis, intra-abdominal abscess, cholangitis, and cholecystitis.

Skin and Soft Tissue Infections: Cellulitis, wound infections, diabetic foot infections.

Gynecological Infections: Pelvic inflammatory disease, endometritis, and postpartum infections.

Septicemia (Bloodstream Infections): Especially effective in β-lactamase-producing Gram-negative bacteria.

Bone and Joint Infections: Osteomyelitis and septic arthritis.

Meningitis (in selected cases): Used off-label when sensitive organisms are identified.

Surgical Prophylaxis: To prevent postoperative infections, especially in abdominal and pelvic surgeries.

Why this Combination?

Cefoperazone is a third-generation cephalosporin effective against Gram-negative bacteria.

Sulbactam inhibits β-lactamase enzymes that would otherwise degrade cefoperazone, extending its spectrum to resistant bacteria.

II. RESULT

In a clinical observational study conducted at Manipal Hospital, Baner, the adverse drug reactions (ADRs) associated with Injection Cefoperazone + Sulbactam were evaluated. A 35-year-old female patient developed coughing, breathing difficulty, and drowsiness indicative of an anaphylactic reaction after intravenous administration of Kipinex Forte (Cefoperazone 1000 mg + Sulbactam 500 mg). Immediate treatment with adrenaline, hydrocortisone, pheniramine, and nebulization successfully resolved the symptoms.

III. DISCUSSION

The current study offers a crucial examination of the adverse drug reaction (ADR) potential associated with the administration of Cefoperazone-Sulbactam, a β-lactam/β-lactamase inhibitor combination that is frequently employed to treat multidrug-resistant infections. The reported case of an anaphylactic event in a 35-year-old female following intravenous administration of Inj. Kipinex Forte highlights the potential severity and unpredictability of ADRs even in widely used antibiotics.

Cefoperazone, a third-generation cephalosporin, in combination with sulbactam, is pharmacologically designed to overcome β-lactamase-mediated resistance. However, this advantage does not eliminate the inherent risks of hypersensitivity reactions. Type B adverse reactions, such as the one described in this case, are rare, non-dose-dependent, and typically occur in patients without prior allergic history, making them difficult to predict. The patient's rapid onset of symptoms—including respiratory difficulty and drowsiness—is consistent with immunoglobulin E (IgE)-mediated hypersensitivity responses, emphasizing the necessity for immediate clinical readiness to address such events.

Although ADRs with this combination are uncommon, the role of cefoperazone in inducing hypoprothrombinemia and sulbactam's potential to provoke β-lactamase overexpression are well-documented concerns. Furthermore, hepatic and renal pathways play a central role in drug elimination. Cefoperazone is primarily excreted through the biliary system, whereas sulbactam undergoes renal clearance. As such, patients with compromised liver or kidney function may be at heightened risk for drug accumulation and toxicity, necessitating dosage adjustments and rigorous monitoring.

The use of Naranjo's Algorithm allowed for a structured assessment of causality in this case, supporting a probable relationship between the drug and the observed reaction. However, the concurrent administration of Iohexol—a contrast agent known to carry allergic risk—adds complexity to the interpretation. While the temporal association strongly

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implicates Cefoperazone-Sulbactam as the causative agent, the potential for synergistic hypersensitivity cannot be fully excluded.

In broader clinical practice, the reliance on broad-spectrum agents such as Cefoperazone-Sulbactam, especially in tertiary care centers, is increasing. This trend is accompanied by a growing need for robust pharmacovigilance systems to detect, document, and analyze adverse effects. This study, albeit limited to a single case, emphasizes the value of case-based surveillance in identifying rare but serious ADRs. It also reinforces the importance of pre-treatment screening for drug allergies and the availability of emergency treatment protocols during intravenous drug administration.

The findings contribute to existing literature by adding a clinically documented anaphylactic event to the body of evidence supporting cautious administration of this drug combination. Future investigations should aim at multicenter data collection with larger sample sizes to elucidate risk factors and incidence rates more comprehensively. Additionally, genetic predisposition studies may be beneficial in identifying individuals at increased risk of Type B reactions.

Ultimately, while Cefoperazone-Sulbactam remains a cornerstone in the management of resistant bacterial infections, this study affirms that its administration must be guided by careful patient evaluation, risk-benefit analysis, and readiness for adverse event management.

IV. CONCLUSION

The observational case report study conducted at Manipal Hospital, Baner, systematically captured and evaluated adverse drug reactions (ADRs) associated with Injection Cefoperazone + Sulbactam. Through well-defined inclusion and exclusion criteria, real-world patient data were gathered and analyzed, focusing on demographic details, drug dosage, administration routes, and clinical outcomes. Utilizing Naranjo's Algorithm for causality assessment, the methodology enabled a structured evaluation of the ADRs observed, particularly an anaphylactic response in a 35-year-old female patient. The detailed documentation and causality analysis underscore the importance of vigilant pharmacovigilance in routine clinical settings. This methodologically sound approach reinforces the necessity for ongoing monitoring of antibiotic safety profiles, especially for β-lactam/β-lactamase inhibitor combinations in high-risk or sensitized individuals.so, further investigation is needed.

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