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Case Report

Pharmacology Section

A Rare Case of Sequential Hypersensitivity Reactions to Cefuroxime and Vancomycin in the Perioperative Setting: A Pharmacovigilance Perspective

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ABSTRACT

Surgical antibiotic prophylaxis commonly involves beta-lactams and vancomycin. Adverse Drug Reactions (ADRs) to these agents are known, but sequential hypersensitivity to both in the same patient is extremely rare. A 35-year-old male scheduled for Anterior Cruciate Ligament (ACL) reconstruction surgery was administered intravenous (i.v.) cefuroxime. Within minutes, the patient developed a localised urticarial rash over the right forearm, which resolved promptly with i.v. corticosteroids. Given this hypersensitivity, vancomycin was chosen as an alternative for surgical prophylaxis given as slow i.v. infusion along with vancomycin-impregnated beads placed locally at the surgical site. While the test dose of vancomycin was uneventful, the full dose led to a rapid onset of generalised erythema, urticaria, facial oedema, breathlessness, and hypotension. A diagnosis of Red Man Syndrome (RMS) was made. We hypothesise that the local placement of vancomycin-impregnated beads may have contributed to the severity of RMS, although evidence is limited. This unique case underscores a rare instance of dual Hypersensitivity Reactions (HSR) to two unrelated antibiotics cefuroxime and vancomycin and to the best of our knowledge, previously unreported in such rapid succession. Literature suggests no significant cross-reactivity between these agents and the occurrence of sequential ADRs in this patient is likely coincidental. Both WHO-Uppsala Monitoring Centre (UMC) and Naranjo's ADR Probability Scale suggested a 'Probable' causal relationship for each ADR. Timely ADR reporting and AMC-led causality assessment are crucial for enhancing drug safety, optimising future antibiotic use, and promoting a culture of clinical vigilance and institutional learning.

Keywords: Adverse drug reaction, Causality assessment, Cefuroxime hypersensitivity, Red man syndrome, Surgical prophylaxis

CASE REPORT

A 35-year-old male sustained an ACL tear in his left knee following a road traffic accident. He was clinically stable with normal vital and haemodynamic parameters and no evidence of head trauma, fractures, or other major injuries. X-ray of the left knee was unremarkable, while Magnetic Resonance Imaging (MRI) confirmed a complete ACL tear. After discussing treatment options, the patient consented to undergo left arthroscopic ACL reconstruction. The preoperative antibiotics were planned as per standard surgical prophylaxis guidelines. The patient's past medical history and family history were unremarkable, with no prior history of drug allergies, chronic illnesses, or hereditary conditions.

On the day of surgery, spinal anaesthesia with injection bupivacaine 0.5% was administered along with pre-anaesthetic medications. The i.v. cefuroxime 1.5 g was administered at 9:45 AM after confirming no past history of allergy to cefuroxime. Within minutes of administration, the patient developed an erythematous rash over the right forearm, without any associated systemic symptoms such as dyspnoea, or hypotension. His vital signs remained stable. Prompt treatment with i.v. hydrocortisone 100 mg and i.v. dexamethasone 1 mg, led to rapid resolution of the rash within five minutes. Given the mild nature of the reaction and the patient's stability, the surgical plan was continued.

As the patient developed an immediate HSR to cefuroxime, i.v. vancomycin was chosen as a substitute. At 11:00 AM, a test dose of vancomycin (approximately 100 mg diluted in 100 mL normal saline) was administered slowly over 20 minutes under close haemodynamic monitoring. The test dose was uneventful, with no signs of hypersensitivity or infusion-related reaction. Subsequently, the full therapeutic dose of vancomycin (1 g diluted in 500 mL normal saline) was initiated via intravenous infusion. As part of intraoperative infection control measures, vancomycin-impregnated beads were also placed locally at the surgical site during procedure. However, immediately after starting the infusion, the patient complained of breathlessness, headache, and anxiety, followed by progressive difficulty in breathing. The patient also developed widespread erythema and urticaria over the chest and upper limbs, facial and eyelid oedema, and hoarseness of voice. His vital signs at this point were as follows: pulse rate, 120 beats/min; blood pressure, 80/36 mmHg; and respiratory rate, 24/min. The final diagnosis of full-thickness ACL tear of the left knee with immediate HSR to i.v. cefuroxime, likely IgE-mediated with RMS was made based on the sudden onset of these signs and symptoms. These features are classically associated with RMS caused by rapid vancomycin administration. The absence of reaction during the earlier test dose (administered after steroid treatment) and the timing of symptom onset shortly after full-dose infusion further support the diagnosis [1].

Vancomycin infusion was immediately discontinued. The patient was promptly managed with 100% oxygen, i.v. mephentermine (30 mg) bolus, i.v. fluids, i.v. noradrenaline infusion, injection hydrocortisone 100 mg i.v., injection dexamethasone 8 mg i.v., and injection pheniramine maleate. Following prompt intervention, the patient showed rapid improvement in blood pressure, respiration, and overall symptoms and his vitals stabilised within the next 30 minutes. The reaction resolved promptly upon stopping vancomycin and initiating supportive treatment, which is consistent with the typical clinical course of RMS. The patient remained stable throughout the postoperative period. His surgical recovery was uneventful. Post-operatively, patient was started on injection piperacillin 4 gm + tazobactum 500 mg and injection amikacin 500 mg. No further

allergic reactions were observed during his hospital stay. Diagnosis of immediate HSR to i.v. cefuroxime, likely IgE-mediated and RMS secondary to rapid i.v. infusion of vancomycin, a non-IgE-mediated histamine release reaction was made. No formal follow-up was conducted after discharge, as the patient recovered uneventfully and did not report back with any complications.

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical information. The patient was assured that all identifying details would be kept confidential and anonymous.

DISCUSSION

Surgical antibiotic prophylaxis plays a pivotal role in preventing surgical site infections, postoperative morbidity, and prolonged hospital stays [2]. Beta-lactam antibiotics, particularly first- and second-generation cephalosporins, are considered the cornerstone of surgical prophylaxis [3]. The i.v. cefuroxime was chosen as the first-line agent for surgical prophylaxis in this case in accordance with institutional protocol and established orthopaedic guidelines. Second-generation cephalosporins like cefuroxime are widely recommended for orthopaedic procedures due to their effective coverage against common skin flora, particularly *Staphylococcus aureus* and *Streptococci*, which are the predominant pathogens in postoperative infections [3]. However, ADRs pose a significant challenge in clinical practice, particularly in the perioperative setting, where multiple drugs are administered in a short period [4]. Beta-lactam antibiotics are one of the leading causes of HSR [5]. When a patient exhibit HSR to beta-lactams, alternative antibiotics such as vancomycin are often used [6]. Following the immediate HSR to cefuroxime, the i.v. vancomycin was selected as an alternative prophylactic antibiotic in this case. Vancomycin is commonly used in patients with a documented beta-lactam allergy or suspected IgE-mediated reactions, as it provides effective coverage against Gram-positive organisms, particularly *S. aureus* and coagulase-negative staphylococci, key pathogens in orthopaedic surgical site infections. This substitution aligns with guideline recommendations for antibiotic prophylaxis in patients with beta-lactam intolerance [7].

Despite its efficacy, vancomycin is known to cause infusion-related reaction 'vancomycin infusion reaction' also called as RMS [1]. RMS is a histamine-mediated reaction characterised by erythema, flushing, pruritus, hypotension, dyspnoea, and angioedema [1]. We report a rare case of a 35-year-old male who developed two consecutive ADRs: first to cefuroxime, followed by a RMS due to vancomycin.

ADR reporting by the treating physician plays a vital role in enhancing patient safety and improving drug use practices [8]. Prompt reporting allows the ADR Monitoring Centre (AMC) like ours to perform causality assessments which contribute to national pharmacovigilance data, help identify rare or unexpected ADRs and can lead to updates in treatment protocols.

ADRs are a significant concern in clinical practice, particularly when they occur sequentially with different antibiotics, as observed in this case. The patient first exhibited a HSR to cefuroxime and subsequently developed RMS due to vancomycin. It is noteworthy that i.v. corticosteroids (hydrocortisone 100 mg and dexamethasone 1 mg) were administered following the HSR to cefuroxime. These were part of the standard management protocol for acute allergic reactions. Subsequently, when vancomycin was administered within two hours of the initial reaction, the patient still developed a severe reaction suggestive of RMS. Notably, when the vancomycin test dose was administered, as the patient had recently received i.v. corticosteroids and antihistamines as part of the management of the preceding cefuroxime-induced HSR, this premedication could have transiently blunted any immediate immunologic or histamine-mediated response to the test dose. However, upon administration of the full therapeutic dose, potentially at a faster infusion rate, the protective effect of the premedication may have waned, leading to the onset of RMS. Furthermore, we believe that the additional placement of vancomycin-impregnated beads locally contributed to rapid increase in blood concentration of vancomycin along with i.v. infusion and gave rise to RMS in this case.

While RMS is typically associated with i.v. vancomycin, unusual presentations have been documented, including RMS following vancomycin-loaded bone cement during primary total knee replacement and even with oral vancomycin therapy [9,10]. To the best of our knowledge, the occurrence of sequential ADR to both cefuroxime and vancomycin within such a short time span has not been previously reported in the literature.

The relationship between hypersensitivity to beta-lactam antibiotics, such as cephalosporins, and the subsequent development of an ADR to vancomycin remains unclear. RMS is a non-IgE-mediated histamine release reaction triggered by rapid infusion rates and differs mechanistically from IgE-mediated allergic responses [11,12]. Current literature does not establish a direct immunologic cross-reactivity between cephalosporin hypersensitivity and vancomycin-induced RMS and is likely coincidental rather than indicative of an underlying shared immunologic mechanism. In scenarios where patients exhibit hypersensitivity to both beta-lactam antibiotics and vancomycin, selecting an appropriate alternative for surgical prophylaxis becomes challenging. Options may include the use of clindamycin [13].

Following the HSR to both cefuroxime and vancomycin, the patient required an alternative broad-spectrum antibiotic regimen for postoperative coverage. Injection piperacillin 4 g + tazobactam 500 mg was chosen due to its extended-spectrum activity against a wide range of Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa*, and its utility in orthopaedic surgical settings where resistant pathogens may be encountered. Injection amikacin 500 mg was added for synergistic Gram-negative coverage, particularly for hospital-acquired flora and to broaden empiric protection while culture results were pending. This combination is widely used in settings where both gram-positive and gram-negative coverage is needed, especially when first-line agents like cephalosporins and glycopeptides cannot be used due to hypersensitivity [14,15].

Expectedly, no adverse reactions were observed with these antibiotics. Several factors may explain the absence of ADRs to these agents. First, neither piperacillin-tazobactam nor amikacin share structural or immunologic cross-reactivity with cephalosporins or glycopeptides, reducing the risk of a sequential HSR. Also, the earlier ADRs may have led to heightened clinical vigilance and tailored administration protocols, thereby preventing additional hypersensitivity. This pattern suggests that the earlier reactions were likely agent-specific rather than reflecting a general drug hypersensitivity predisposition.

To evaluate the likelihood, both the WHO- UMC system and the Naranjo's ADR Probability Scale were applied for causality assessment [16,17]. As per WHO-UMC causality assessment scale, these ADRs were categorised as 'Probable' due to reasonable temporal relationship, and dechallenge. Also, each ADR was independently assessed using the Naranjo scale with total score of seven for cefuroxime ADR and eight for vancomycin ADR indicating 'Probable' category. Hartwig and Siegel's Severity Assessment Scale classifies ADRs into seven levels based on the clinical management and outcomes [18]. ADR due to cefuroxime is level 2 reaction, while reaction to vancomycin fits into the criteria for a level 5 reaction. Also, the Schumock GT and Thornton JP criteria help determine whether an ADR could have been prevented [19]. Accordingly, the ADR to cefuroxime is classified as *not preventable*, while the ADR to vancomycin may be classified as *probably preventable*, considering the infusion rate along with additional simultaneously administered beads might have contributed to the severity of the RMS episode.

[Table/Fig-1] provides a comparative overview of published case reports on RMS and vancomycin-related HSR, alongside the current case [20-22]. While prior reports have described RMS due

Case	Patient demographics	Drug involved	Symptoms	Treatment given	Outcome/ Recovery	Reference
Present case	35-year-old male, ACL tear	Cefuroxime → Vancomycin	Local rash (cefuroxime), followed by flushing, facial oedema, urticaria, hypotension, hoarseness (vancomycin)	i.v. steroids, vasopressors, stopped infusion	Full recovery	Present case
Chen CT et al., (2018)	74-year-old female, Total Knee Replacement (TKR)	Vancomycin in bone cement	Erythema over face, trunk, extremities	Antihistamine, supportive care	Recovery after discontinuation	(Chen CT et al., 2017) [20]
Arroyo-Mercado S et al (2021)	75-year-old female, C. difficile	Oral vancomycin	Flushing, pruritus, erythema of face/neck	Discontinued vancomycin, diphenhydramine	Recovered in 24 hours	(Arroyo-Mercado S et al., 2021) [21]
Polk RE et al., (1988)	Healthy volunteers (n=11)	i.v. vancomycin 1 g over 1 hr	Facial flushing, pruritus, hypotension, ↑ histamine	Monitored; self-resolving	Self-limited; all recovered without sequelae	(Polk RE et al., 1988) [22]

[Table/Fig-1]: Comparative analysis of reported cases of vancomycin-induced Red Man Syndrome (RMS) and current case with sequential antibiotic hypersensitivity [20-22].

to vancomycin administered i.v. or via local bone cement, and even rare occurrences after oral vancomycin, our case is unique in that it involved two distinct HSR; first to cefuroxime and subsequently to vancomycin within a span of less than two hours.

To the best of our knowledge, no published literature has reported such a sequential occurrence of ADRs to both cefuroxime and vancomycin in the same patient, on the same day, in a surgical prophylaxis setting. This case thus adds new insight into the complexity of antibiotic hypersensitivity and the importance of vigilant perioperative monitoring.

Photographic documentation of the HSRs could not be obtained due to the emergency nature of the situation and the need for immediate medical intervention. The treating team prioritised stabilisation of the patient, and hence no images were captured during the acute episode.

Looking ahead, there is a need for continued research into the mechanisms underlying such dual HSR and the development of standardised protocols for managing patients with multiple antibiotic allergies.

CONCLUSION(S)

Timely ADR reporting and AMC-led causality assessment are crucial for enhancing drug safety, optimising future antibiotic use, and promoting a culture of clinical vigilance and institutional learning. This case presents a unique and clinically significant sequential occurrence of ADRs to both cefuroxime and vancomycin, which is likely coincidental and, to the best of our knowledge, previously unreported in such rapid succession. Future research into the mechanisms of dual HSR, as well as pharmacogenomic insights, may pave the way for personalised approaches to antibiotic therapy, reducing the risk of severe ADRs and improving patient safety in perioperative care.

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