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Case Report

Piperacillin-tazobactam fixed dose combination induced skin reaction in a patient with split thickness skin grafting: a case report

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ABSTRACT

Piperacillin is a semi-synthetic ureido-penicillin. It has a broad spectrum against gram negative bacilli particularly *P. aeruginosa*. It is one of the most broadly active of the currently available penicillin with regard to other bacterial species like *proteus, klebsiella, H. influenzae* and *gonococci*. Tazobactam is β-lactamase inhibitor and combined with piperacillin to increase spectrum of the drug. Patient was 25 years old female, admitted in orthopaedic department for treatment of traumatic leg injury of left limb. Leg was amputated in the accident, so after 1-month split thickness skin grafting was done at plastic surgery department. For prophylaxis piperacillin-tazobactam IV 4.5 gm 8 hourly given, on 2nd post operative day patient reported rashes on neck, trunk, both upper and lower extremities, sparing the mucous membrane. Patient was prescribed anti pruritic and anti-allergic medication for ADR management. It is necessary to use such kind of drugs cautiously in patients whose health is deteriorated by this medication.

Keywords: Piperacillin, Semi-synthetic ureido-penicillin, Broad spectrum, β-lactamase inhibitor, Split thickness skin grafting, ADR management

INTRODUCTION

Piperacillin is semi-synthetic ureido-penicillin. It has anti-bacterial action against aerobic and anaerobic bacteria of both the gram positive and gram-negative types. However, β-lactamase producing bacteria are resistant to it, so in recent times its utility is hampered.[1]

Piperacillin is one of the bactericidal drugs, The beta lactam ring is the primary mechanism of action for the antibacterial drug piperacillin. The peptidoglycans found in bacterial cell walls are what give piperacillin and other penicillin their antibacterial properties. The penicillin binding proteins (PBP) on the cell membrane and inside the cell wall are bound by penicillin and inhibited by it. Transpeptidase is one of PBP; it plays a role in the biosynthesis of peptidoglycans.[2]

According to clinical trials in adults**,** an 8:1 ratio of piperacillin to tazobactam is an effective treatment for patients with fever in neutropenic state as well as lower respiratory tract, intra-abdominal, urinary tract, gynaecological, and skin/soft tissue infections. Patients suffering from severe nosocomial infections are treated with combination regimens consisting of piperacillin-tazobactam plus an aminoglycoside. In clinical studies, patients with community-acquired pneumonia responded better to piperacillin-tazobactam than to ticarcillin-clavulanic acid in terms of microbiological and clinical outcomes. Clinical and bacteriological response rates to piperacillin-tazobactam in patients with intra-abdominal infections were considerably greater than those to imipenem-cilastatin (given at a dosage lower than is advised in countries outside Scandinavia). Amikacin with piperacillin/tazobactam was at least as efficacious as ceftazidime plus amikacin in the treatment of ventilator associated pneumonia.[3]

CASE REPORT

Patient was 25 years old female. She got admitted on 14th November 2023 for traumatic leg injury of left lower limb in railway accident. Her left lower limb was amputated in accident. After about 1-month split thickness skin grafting was done at plastic surgery department, government medical college Surat. Results of haematological analysis show a minor decline in the RBC (3.88 million/mcl) and Hb (7.2 gm%) indices, with other parameters falling within the normal range. There is also a slight increase in the lymphocyte count (42.2%) and ESR value (35 mm/1 hr), which may indicate underlying infection.

Medication history

After split thickness skin grafting injection piperacillin-tazobactam was given as antibiotic coverage to prevent the infection. Any other medication was not given to the patient.

ADR**:** After split thickness skin grafting, for prophylaxis injection piperacillin-tazobactam 4.5 gm IV TID was given. On 2nd post operative day patient developed skin rashes on neck, trunk and both upper and lower extremities. There was no involvement of mucous membrane at any place. There was development of diffuse, pruritic, erythematous and non-follicular pin head sized skin rashes (Figure A and B).

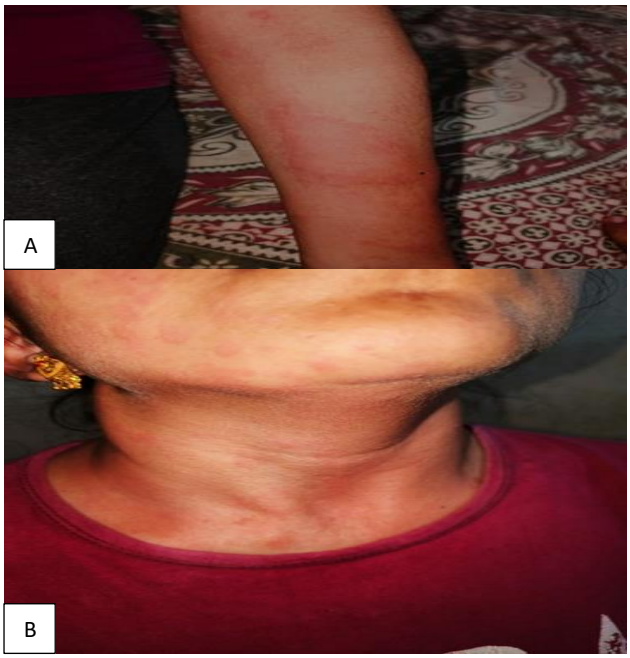

Figure 1 (A and B): Skin rashes present at face, trunk, upper and lower limbs.

Management

Patient was diagnosed clinically as ADR to piperacillin-tazobactam. After the development of skin rashes Piperacillin-Tazobactam was stopped. Symptomatic treatment was given. In treatment, injection pheniramine maleate and dexamethasone IV stat (5 ml) was given. Patient recovered within one day.

DISCUSSION

Gram-positive and gram-negative aerobes as well as anaerobes can all be successfully combatted by the antibiotic piperacillin-tazobactam, hence utilization in various conditions. Headache, rashes, pruritus, and erythema multiforme are among the most frequent adverse responses to piperacillin-tazobactam, but it is typically well tolerated. Other adverse events include diarrhoea. However, there are seldom reports of significant negative effects.[4]

In this case report, patient had only skin rashes due to piperacillin-tazobactam but this drug is responsible for several other adverse drug reactions like neutropenia and thrombocytopenia being the most common haematological adverse reactions.[5]

On the other hand, a rare instance of fever, eosinophilia, and liver damage brought on by piperacillin-tazobactam therapy has been reported in another case.[6]

An instance of cardiac damage due to Kounis syndrome after intravenous piperacillin-tazobactam injection was described by Calogiuri et al.[7]

An uncommon allergic response known as Kounis syndrome causes coronary vasospasm, which can result in angina pectoris or anaphylactic myocardial infarction is also produced by piperacillin-tazobactam.[7]

Individuals who have previously experienced sensitivity to numerous allergens or to penicillin, cephalosporin, or carbapenem are at a higher risk of developing this condition. According to clinical trial data, the medication was stopped in 3.2% of patients because of adverse skin reactions (rash and pruritus), gastrointestinal problems, allergic reactions, and nosocomial pneumonia in 11% of patients. If a patient has previously had hypersensitivity, a thorough examination should be conducted, and the medication should either be stopped or changed if an incidence of allergic response is observed.[8]

There is adequate evidence in the literature to suggest that piperacillin-tazobactam may have caused the allergic response, the suspected medication was submitted to a causality evaluation using the Naranjo scale (Table 1), and the severity of the adverse reaction was evaluated using Hartwig's scale (Table 2).

Through Naranjo evaluation, a total score of "7" was produced, indicating a likelihood that the suspected medication itself is the source of the unpleasant response. According to Hartwig's evaluation, the ADR's intensity is classified as "moderate" severity, meaning it falls beneath level 4.

Table 1: Naranjo probability scale.

Please answer the following questionnaire and give the pertinent score	Yes	No	Don't know	Score
Are there previous conclusive reports on this reaction?	1	0	0	0
Did the adverse event occur after the suspected drug was administered?	2	-1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	1
Did the adverse reaction reappear when the drug was readministered?	2	-1	0	2
Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0	0
Did the reaction reappear when a placebo was given?	-1	1	0	0
Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0
Was the adverse event confirmed by any objective evidence?	1	0	0	1
Total				7
The ADR is assigned to a probability category from the total score as follows: definite	**If the overall score is 9 or greater**			
probable	for a score of 5-8			
possible	for 1-4			
doubtful	if the score is 0			

Causality assessment (to assess the adverse drug reaction)

Table 2: Severity assessment of suspected ADR using Hartwig's scale.

Level	Description
1	An ADR occurred but required no change in treatment with the suspected drug
2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. And/ or An Antidote or other treatment was required. No increase in length of stay (LOS)
4	Any level 3 ADR which increases length of stay by at least 1 day. Or The ADR was the reason for admission
5	Any level 4 ADR which requires intensive medical care
6	The adverse reaction caused permanent harm to the patient
7	The adverse reaction either directly or indirectly led to the death of the patient

[Mild= level 1 and 2, moderate=level 3 and 4, severe=5, 6 and 7]. Report: The suspected ADR found to be moderate on Hartwig's severity scale assessment.

CONCLUSION

According to the Naranjo Causality evaluation, the observed suspected adverse drug response (ADR) has a "Probable" causative association to the usage of "Piperacillin tazobactam" and falls into the "Moderate" severe reaction category according to Hartwig's evaluation. The case report recommends closely monitoring the patient population's use of piperacillin-tazobactam in order to detect any potential ADRs.

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