

Delayed-type of hypersensitivity reaction due to piperacillin/tazobactam causing severe thrombocytopenia

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Received January 12, 2016. Accepted January 27, 2016

ABSTRACT

Piperacillin/tazobactam is a frequently prescribed and well-tolerated β -lactam antibiotic used in various clinical conditions with favorable side effect profile. Very few cases of piperacillin/tazobactam-induced thrombocytopenia have been reported so far. We report a case of piperacillin/tazobactam-induced delayed thrombocytopenia. A 63-year-old female was being treated with piperacillin/tazobactam for aspiration pneumonia after an episode of seizures. While the patient's condition rapidly improved after hospitalization, she developed isolated severe thrombocytopenia on the 12th day. Other possible causes of thrombocytopenia were ruled out by appropriate investigations and the possibility of piperacillin/tazobactam-induced thrombocytopenia was kept. Upon discontinuation of piperacillin/tazobactam, her platelet counts improved rapidly. While treating patients with this drug, clinicians should keep the possibility of thrombocytopenia in mind as a rare but potentially serious side effect. Immediate withdrawal of the drug may be life saving in such situations. Moreover, delayed type of reaction with piperacillin/tazobactam warrants caution for clinicians to continue patients on this drug at home after discharge from the hospital, which is not an uncommon scenario in resource limited countries such as India.

KEY WORDS: Piperacillin/tazobactam; thrombocytopenia; delayed type of hypersensitivity reaction

INTRODUCTION

Piperacillin/tazobactam is a frequently prescribed β -lactam antibiotic for gram positive and negative bacteria as it is useful in various clinical conditions. It is one of the well-tolerated antibiotics due to its favorable side effect profile. Hematological side effects of this drug are very few, the most common being neutropenia. Very few cases of piperacillin/tazobactam-induced thrombocytopenia have been reported so far.

CASE REPORT

A 63-year-old female with past history of hypertension, ischemic cerebro-vascular accident and scar epilepsy presented to the emergency department with an episode of complex partial seizure followed by secondary generalization. She was already taking amlodipine, atenolol, aspirin, atorvastatin, and phenytoin on presentation. There was no past history suggestive of any chronic liver, renal, hematological, or collagen vascular disease. On initial evaluation, she was febrile; she had hypoxia, with pulse rate 106/min, respiratory rate 26/min, and blood pressure 160/90 mmHg. She was admitted to the intensive care unit for further management. Her initial blood investigations showed total leukocyte count 16600/mm³, 89% neutrophils, haemoglobin 13 gm/dl and platelet count 235,000/mm³ with normal renal and liver function tests, normal electrolytes, and normal coagulation profile. Chest X-ray was suggestive of signs of aspiration

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Website: <http://www.njppp.com>

DOI: 10.5455/njppp.2016.6.12012016117

Quick Response Code:



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pneumonia and plain CT brain showed old gliotic changes in the occipital lobe.

Considering a diagnosis of complex partial seizures with secondary generalization with aspiration pneumonia, she was started on injection piperacillin/tazobactam 4.5 g iv 6 h once and injection metronidazole 500 mg iv 8 h once. Her regular medicines were continued. By seventh day of admission, as her clinical, biochemical, and radiological parameters had improved, she was shifted to the general ward. On 12th day of admission, her blood investigation revealed total counts $8500/\text{mm}^3$, neutrophils 72%, hemoglobin 11.2 gm/dL, and platelet count $11,000/\text{mm}^3$. Her blood counts in the intervening period were normal. There was no evidence of bleeding from any site or petechiae on examination. Other causes of thrombocytopenia such as sepsis, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vitamin B12 deficiency, dengue, malaria, human immunodeficiency virus, and cirrhosis of liver were excluded by appropriate investigations. In view of thrombocytopenia developing in a clinically recovering patient treated for aspiration pneumonia with piperacillin/tazobactam and having no clinical or laboratory evidence of other causes of thrombocytopenia in the given clinical setting, a diagnosis of piperacillin/tazobactam induced thrombocytopenia was arrived at. Piperacillin/tazobactam was discontinued immediately and metronidazole was continued. After 12 h, her platelet counts dropped to $6000/\text{mm}^3$. She was given a short course of steroids along with four units of platelet rich plasma.

After 24 h of stopping piperacillin/tazobactam, her platelet count improved to $68,000/\text{mm}^3$ and after 48 h it further improved to $259,000/\text{mm}^3$. She was discharged after 72 h with a platelet count of $347,000/\text{mm}^3$. On follow up after 1 month, patient was reevaluated and her platelet counts were found to be within normal limits.

DISCUSSION

Piperacillin/tazobactam is frequently used antibiotic to treat moderate to severe infections of various sites, with an extended spectrum of action against β -lactamase producing organisms. It is often used to treat infection by *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, Enterobacteraceae, *Citrobacter*, *Salmonella*, and *Shigella*.

Important side effects of this combination include hypersensitivity reactions, hepatotoxicity, neurotoxicity, electrolyte and acid-base disturbances, bleeding disorders, and neutropenia.^[1] Delayed-type hypersensitivity (DTH) is defined as a reaction that manifests only after 10 days of treatment. Most common delayed type of hypersensitivity reaction reported with piperacillin/tazobactam use is neutropenia.^[2] There are previous reports of bone marrow suppression and leucopenia following the use of piperacillin/tazobactam, which is usually reversible after discontinuation of the drug.^[3]

Thrombocytopenia is defined as a platelet count of less than $100,000/\text{mm}^3$ or a drop in platelet count of more than 50% from baseline.^[4] In hospitalized patients, the common causes of

thrombocytopenia are drugs, sepsis, chronic diseases mainly of liver and bone marrow, and disseminated intravascular coagulation. Although bone marrow suppression with leucopenia is mentioned as an important side effect of piperacillin/tazobactam, isolated thrombocytopenia without affection of red cells and leucocytosis has been reported only in few cases.

Macwilliam et al. reported the case of a 48-year-old female treated with an extended course of piperacillin/tazobactam for sepsis secondary to a pelvi-ureteric junction obstruction, who developed thrombocytopenia as a delayed reaction to piperacillin/tazobactam.^[1] Pérez-Vázquez et al. reported the case of a 69-year-old diabetic woman who was admitted for cholecystitis and developed severe thrombocytopenia due to piperacillin/tazobactam on day 11 of starting therapy, which reverted back to normal after stopping the therapy.^[5] However, literature search did not yield any such reports in the Indian scenario.

In our case, patient developed severe thrombocytopenia on day 12 of starting piperacillin/tazobactam therapy, which reverted promptly after discontinuing the antibiotic. Other possible causes of thrombocytopenia were ruled out and piperacillin/tazobactam-induced thrombocytopenia was considered as probable diagnosis. Hemoglobin and total WBC count were not affected. Use of the Naranjo adverse drug reaction probability scale (score of 6)^[6] and George criteria for drug-induced thrombocytopenia (criteria 1, 2 and 3)^[7] indicated a probable relationship between development of thrombocytopenia in this patient and piperacillin/tazobactam as the causal drug. Although our report has level 2 evidence of drug-induced thrombocytopenia as our patient was not reexposed to the same drug, piperacillin/tazobactam has been reported by George et al.^[7] as level 1 evidence for drug-induced thrombocytopenia.

There are reports of platelet dysfunction due to penicillin at high concentration, due to binding of penicillin to adenosine diphosphate receptor sites in platelets, which prevents normal platelet aggregation.^[8] However, mechanism of piperacillin/tazobactam-induced thrombocytopenia in available literature has been mentioned as immune-mediated suppression, and various measures used to treat piperacillin/tazobactam-induced thrombocytopenia include withdrawal of the drug, steroids, intravenous immunoglobulin, and plasmapheresis.

Similar mechanism was likely in our case, as platelet count improved very rapidly within 48 h of omission of drug and a short course of steroids. As potentially serious drop of platelet count is associated with increased risk of spontaneous bleeding, patient was transfused with platelet-rich plasma. However, rapid rise of platelet count from $6,000$ to $259,000/\text{mm}^3$ is unlikely to be due to platelet transfusion. Bleeding due to thrombocytopenia depends upon the severity of thrombocytopenia as well as other host factors. Our patient developed severe thrombocytopenia but did not develop bleeding because she had no other predisposing adverse clinical parameters.

CONCLUSION

Documenting piperacillin/tazobactam as the cause of severe thrombocytopenia is of immense importance for a clinician as

thrombocytopenia can be caused by various medications. It remains an important challenge for clinicians to establish the relationship between thrombocytopenia and the causative drug agent, particularly if the patient is taking several medications. A diagnosis can only be supported if other causes of thrombocytopenia have been ruled out and at the same time thrombocytopenia rapidly resolves after discontinuation of the causative drug. This case highlights the need for clinicians to be aware of thrombocytopenia as a rare but potentially serious side effect of piperacillin/tazobactam. Immediate withdrawal of the drug may be life saving in such situations. In resource-limited countries, it is not uncommon for patients to request clinicians to complete the course of parenteral antibiotics at home with the help of paramedical staff. Due to this delayed type of reaction with piperacillin/tazobactam, it is vital for clinicians to remain alert as thrombocytopenia may manifest after about 7–10 days of therapy, sometimes even after discharge from the hospital.

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How to cite this article: Parekh M, Sheth S, Vaishnav B, Mangalampalli A. Delayed-type of hypersensitivity reaction due to piperacillin/tazobactam causing severe thrombocytopenia. *Natl J Physiol Pharm Pharmacol* 2016;6:266-268

Source of Support: Nil, **Conflict of Interest:** None declared.