Piperacillin- Tazobactam Induced Cutaneous Reaction: A Case Report

Syed Zia Inamdar[1,*], Pradeepthi Katragadda[1], Abhishek Bijjargi[2], Raghavendra Vinayakarao Kulkarni[1], Pooja Bijjargi[2], Bhagyashree Gahtad[2]

[1]Department of Pharmacy Practice, BLDEA's SSM College of Pharmacy and Research Centre, Vijayapura, Karnataka, INDIA.
[2]Pharm D Intern, BLDEA's SSM College of Pharmacy and Research Centre, Vijayapura, Karnataka, INDIA.

ABSTRACT

Piperacillin tazobactum is an extended spectrum pencillin belonging to uriedopencillin class used in the management of polybacterial infections. A 37 year old male patient admitted to the hospital with the chief complaints of breathlessness since 8 days and cough with expectoration since 2 days. The patient was initially managed with nebulization and bronchodilator therapy with subsequent administration of Piperacillin Tazobactum (4.5 gm) antibiotic to treat underlying infection. The patient complained the development of pruritis and red color skin rashes over the back of neck after receiving first dose of Piperacillin Tazobactum, the antibiotic was stopped and supportive treatment with antihistamine and corticosteroid was provided to treat allergic reaction. The symptoms were healed and patient condition was improved on discharge. The suspected drug reaction with Piperacillin Tazobactum was found to have "probable" causal relationship through Naranjo causality assessment and pose "moderate" severity as assessed through Hartwig's Severity scale. The report suggests close monitoring of Piperacillin-Tazobactam usage among patient population.

Key words: Piperacillin- Tazobactum, Uriedopencillin, Pruritis, Adverse drug reaction, Naranjo causality assessment.

INTRODUCTION

Uriedopencillin class of antibiotics are also named as antipseudomonal penicillins. Among these class of drugs piperacillin is more potent and pose superior action against *Klebshiella* and is effective in neutropenic/ immune compromised patients having serious gram-negative infections and in burns.[1] Pharmacokinetics of Piperacillin matches with Tazobactum, which is used in severe infections like peritonitis, pelvic/ urinary/respiratory infections. However, this combination is not effective against piperacillin-resistant Pseudomonas. A dose of 4-12 g/day is required for mild infections and in case of severe infections a higher dose is required (12-24g/day). The combination of Piperacillin- Tazobactum was effective against a range of gram-positive and and gram negative bacterial infections.[1,2]

The poor solubility of the piperacillin and tazobactam co-formulation means that intravenous administration is preferred because of the large volume of fluid required for solubilization (10-20 ml water for injection). Administration is recommended by the product information as a slow

Intravenous injection (3-5 min), or a slow intravenous infusion (20-30 min). Protein binding capacities of piperacillin are [20-30%] and tazobactum [20-23%] respectively.[3] Both piperacillin and tazobactum have small apparent volumes of distribution.[2,3]

A recent systematic study review stated that a variety of adverse reactions has been reported with the piperacillin-tazobactam like hemolytic anemia, bone marrow suppression diseases (such as neutropenia and thrombocytopenia), type 1 hypersensitivity and acute delirium.[4,5] A array of adverse reactions can precipitate within minutes after the hours of exposure to a drug which are of type 'A' or "Augmented' in nature and usually have a low mortality.[6] Others

DOI: 10.5530/ijopp.12.2.33

Address for correspondence:
Dr. Syed Zia Inamdar,
Professor and Clinical Pharmacist, Department of Pharmacy Practice, BLDEA's SSM College of Pharmacy and Research Centre, Vijayapura- 586103, Karnataka, INDIA.
Phone no: :+91-9986666016
Email Id: syedzia.inamdar@gmail.com

www.ijopp.org

pencillin class of drugs are not readily predictable due to high mortality risk (Type 'B' or 'Bizarre').[6] In our case study we describe an unusual case of an immediate reaction to Piperacillin-Tazobactam.

CASE REPORT

A 37 year old male patient was presented to the outpatient clinic of a teaching hospital with the chief complaints of breathlessness since eight days and coughs with expectoration since two days and was later hospitalized. The history of presenting complaints reveals that the patient was apparently alright before he developed breathlessness which was sudden in onset and progressive in nature a week ago and subsequently complaints of cough with expectoration since last two days. The sputum was white in color, non-foul smelling without any blood stain. The patient past medical/medication assessment does not reveal any other concurrent illness or co morbidity. The hematological investigation reveals slight increase in lymphocytes count [42.2%] and ESR value [35mm/1hr] possibly suggestive of underlying infection, there was a moderate decrease in RBC [3.88 m/cmm] and Hb [7.2gm%] indices and other parameters being within normal range.

Patient was initially managed with inj. Deriphylline [Combination of ethophylline and theophylline] twice daily, Duoline nebulization [Ipratropium bromide and salbutamol] 6th hourly to relax and widen airways smooth muscle to make breathing easier, syrup Planokuf two teaspoons twice daily to treat cough, Inj Pantoprazole [40 mg] once daily to relieve symptoms of acidity along with syrup Zincostar forte [Supplements of multi vitamin and minerals] once daily to aid in boosting of immunity and restoring energy levels in the patient and inj. Piperacillin Tazobactum [4.5 gm] an anti microbial given twice daily to treat underlying respiratory and other bacterial infection. After five hours of the first dose of Piperacillin Tazobactum the patient started developing pruritic, red color skin rashes over the back of neck [Figure 1]. The subsequent administration of scheduled second dose of inj. Piperacillin Tazobactum was stopped, as it was suspected to have caused the skin reaction. The anti microbial then was replaced with third generation cephalosporin Ceftriaxone [1 gm] given twice daily to prevent bacterial growth. A third generation non sedating antihistamine tab. Levocetrizine [10mg] and a corticosteroid inj. Dexamethasone [4mg] was used to treat symptoms of allergy, rashes and pruritis.

DISCUSSION

Certain micro organism species like *Pseudomonas aeruginosa*, *Klebsiella* etc have been effectively treated with Piperacillin. A dose of 4 - 12 g/day can treat mild infection but a higher dose within the range of 12-24g/day can effectively counteract serious infections. The antibiotic specifically binds to preferential proteins that bind to penicillin and are present inside the bacterial cell wall resulting into inhibition of cell wall synthesis. Penicillin binding proteins (PBPs) varies among species of bacteria and the susceptibility of piperacillin depends upon its binding capacity to these specific PBPs among various bacterial species. The combined activity of piperacillin and tazobactam has impressive *in-vitro* studies against an array of gram-positive and gram negative aerobic and anaerobic bacteria.

In the current case, the patient was hospitalized with the chief complaints of breathlessness and cough with expectoration with an underlying infection evident from laboratory investigation. The patient condition was indicative for the use of anti microbial therapy. Piperacillin Tazobactum 4.5 gm was prescribed twice daily. After around five hours of receiving first dose of antimicrobial therapy, the patient developed pruritic red colour skin rash over the back of neck prompting the physician to withdraw the anti microbial from patient medication list as a probable suspected drug for the developed adverse skin reaction. The patient was managed symptomatically using antihistamine [Levocetrizine] and corticosteroids [Dexamethasone] for the precipitated allergic reaction. The antibiotic was replaced with third generation cephalosporin [Ceftriaxone] and monitored closely for any unwarranted cross sensitivity with the use of cephalosporin. The symptomatic management of the allergic reaction by the use of antihistamine and corticosteroid resulted in gradual ablation of the

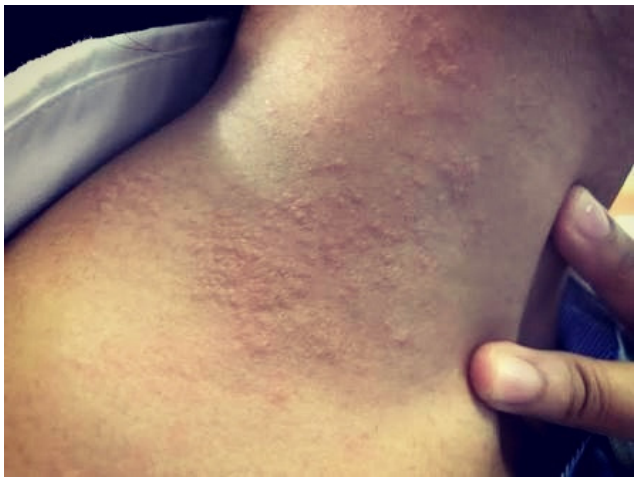

Figure 1: Rashes over Back of Neck.

symptom and the patient condition gradually improved without any fresh complaint and was fully recovered at the time of discharge.

There were report of mild to moderate adverse effects with the use of piperacillin tazobactum that includes diarrhea, rash, erythema, pruritis, allergic reactions, urticaria, superinfection, phlebitis, dyspepsia and insomnia. Serious and occasionally fatal hypersensitivity (Anaphylactic/ anaphylactoid) reactions (Including shock) have also been described to the use of piperacillin tazobactum in patients. Patients with history of sensitivity to penicillin, cephalosporin, or carbapenem or a history of sensitivity to multiple allergens are on the higher risk of incidence. The drug was discontinued in 3.2% of patients due to dermatologic adverse effects [Rash and pruritus], gastrointestinal effects, allergic effects and 11% of patients with nosocomial pneumonia as reported by clinical trial data. A careful investigation should be carried out in patients concerning previous hypersensitivity and the drug should be discontinued or replaced if reported with an allergic reaction incidence.

The literature provides enough evidence to suspect piperacillin tazobactum might have caused the allergic reaction, hence the suspected drug was subjected for causality assessment using Naranjo scale [Table 1] and Hartwig's scale was use to assess the severity of the adverse reaction. [Table 2]. A total score of "7" was obtained through naranjo assessment, which indicates that there is a probability that the adverse reaction is caused due to the suspected drug itself. The severity of the ADR falls under level 4 as a "moderate" severe reaction as per hartwig's assessment.

Table 1: Causality Assessment of Suspected ADR using Naranjo Scale.

Question	Yes	No	Don't Know/NA	Score*
Are there previous conclusive reports on this reaction?	+1	0	0	1
Did the adverse event appear 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 event reappear when the drug was re-administered?	+2	1	0	0
Are there alternative causes (Other than the drug) that could on their own have caused the reaction?	-1	2	0	2
Did the reaction reappear when a placebo was given?	-1	1	0	0
Was the drug detected in 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	0
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 Score				7

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 the 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

The observed suspected Adverse drug reaction [ADR] was found to have "Probable" causal relationship to the use of "Piperacillin tazobactum" as per naranjo causality assessment and falls under "Moderate" severe reaction category as per hartwig's assessment. The case report suggests close monitoring of piperacillin- tazobactum usage among patient population for the possible occurrence of ADR.

CONFLICT OF INTEREST

The authors declare none.

ABBREVIATIONS

PBPs: Penicillin Binding Proteins **ESR:** Erythrocyte sedimentation rate, **RBC:** Red blood corpuscles, **Hb:** Haemoglobin, **ADR:** Adverse drug reaction.

SUMMARY

A patient with underlying respiratory infection was being treated with antimicrobial therapy (Piperacillin-tazobactum), developed skin rashes during the treatment. The skin reaction reported was of drug induced in nature with probable involvement of Piperacillin tazobactum. The suspected antimicrobial was withdrawn and the adverse effect was managed symptomatically.

REFERENCES

1. Lambourne J, et al. Piperacillin/Tazobactum-induced paresthesiae. The Annals of Pharmacotherapy. 2006;4(5):977-9.
2. Wyeth Pharmceticals,, Inc. Zosyn product information. 2009
3. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother. 1993;31 (Suppl_A):39-60.
4. Darwiche D, Iskandar K, Azar A, Hallit R, Hallit S. Piperacillin-Tazobactam-Induced Neutropenia: A Case Report. J Medical Cases. 2017;8(9):280-82.
5. Kucer's. The use of antibiotics: a clinical review of antibacterial, antifungal and antiviral drugs. 6th ed(1). CRC Press Taylor and Francis. 2012. Available from: http://www.academia.edu/16510150/Kucers_The_Use_of_Antibiotics_Sixth_Edition
6. Scheetz MH, McKoy JM, Parada JP, Djulbegovic B, Raisch DW, Yarnold PR, *et al*. Systematic review of piperacillin-induced neutropenia. Drug Saf. 2007;30(4):295-306.