



CASE STUDY

Piperacillin plus Tazobactam induced Drug Hypersensitivity Reaction: A Case Report

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ABSTRACT

Penicillin alone or with combination should be used in hospitalized patients to treat bacterial infections with great precautions since penicillin is known to produce hypersensitivity reactions very commonly. A 53 year old hospitalized male patient having tibia fracture was initially given ceftriaxone plus salbactam and amikacin as an antibacterial therapeutics. Subsequently patient was treated with Pipzo (Inj. Piperacillin plus Tezobactam; 4.5 gm.) on the basis of anti- bacterial sensitivity test of pus culture. It was observed in patient having fever with chills and rigors immediately after injecting Pepzo. Though drug induced these hypersensitivity signs subsided gradually. Later on patient was switch over to inj. Imipenem to cover pseudomonal infection with resulting improvement.

KEYWORDS

Piperacillin, Tazobactam, Hypersensitivity

INTRODUCTION

Adverse drug reaction (ADR) is defined as “response of any type to a drug that is noxious and unintended and that occur at doses used in man for the prophylaxis, diagnosis or treatment of any disease or for modification of physiological function.” There are two ADR – (a) Quantitative ADR (Type A and B) and Qualitative ADR (Type B). Type B reactions are further divided in to (i) idiosyncrasy (Genetic / Unknown mechanism) (ii) Allergy (Immunological) Type I, II, III and IV.¹

Hypersensitivity reactions or Immunologic tissue injury is defined as an exaggerated or inappropriate state of normal immune response with onset of adverse effects on the body.²

Usually when the individual who is sensitized to an antigen gets exposed to same antigen, develops reactions and such reactions are called as hypersensitive reactions. The resulting tissue-damaging reactions include: (a) Type I reactions which are Ig E mediated and immediate hypersensitivity reactions ex; allergic reaction and anaphylaxis. (b) Type II (Cytotoxic) reaction, (c) Type III (Immune complex mediated) reaction and (d) Type IV (Cell Mediated or Delayed Hypersensitivity) reaction.¹

Piperacillin is an extended spectrum ureido penicillin which when combined with the beta lactamase inhibitor tazobactam, is used to treat moderate to severe infections due to susceptible organisms including lactamase producing penicillin-resistant bacteria.³ It has been recorded in the United States that the adverse drug reactions occurring to the administered drug have been estimated to be 10-15% in hospitalized

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persons.⁴⁻⁵ Common adverse reactions with penicillins are allergy and anaphylaxis, skin rashes, a serum sickness like syndrome, renal disturbances, hemopoietic disturbances, anaphylaxis, Jarisch-Herxheimer reaction, superinfection, hyperkalemia, acute non-allergic reactions.¹

MATERIAL AND METHODS

A 53 year old male patient was hospitalized in Dhiraj Hospital of Sumandeep Vidyapeeth, Piparia-391760, Gujarat with the complaints of pain in right leg with yellowish discharge from the site of pain and difficulty in walking since 20 days. He also gave the history of fracture right tibia which was treated with external fixation and flap surgery. On examination, patient had tenderness present over right proximal tibia, flap surgery marks were present with limitation of mobility in the affected limb.

The patient was subjected for the routine hematological investigations and all were found to be within normal limits. Simultaneously, the pus sample was submitted for culture study which showed positive for pseudomonas spp. suggesting osteomyelitis. Therefore, the case was diagnosed as malunited osteomyelitis of right tibia.

Patient was then subjected to sequestrectomy along with illizarov ring fixation. Post operatively he was managed with ceftriaxone + sulbactam, amikacin, flotrip, calcium, multivitamins for the treatment of repeated bacterial infection. Since patient showed positive for pseudomonas spp. on pus culture study, he was treated with inj. Pipzo (piperacillin plus sulbactam; 4.5 gm) to treat the pseudomonas infection.

RESULTS AND DISCUSSION

Immediately after 10-15 minutes of starting inj. Pipzo, patient had complaint of fever with chills with rigors. The intravenous antibiotic-Pipzo (piperacillin-tazobactam; 4.5 gm) was discontinued immediately. Following this, fever with chills and rigors subsided indicating that patient suffered with drug induced hypersensitivity reaction.

Later, patient was prescribed with inj. imipenam on the 6th post operative day to control the pseudomonas infection and it was observed that patient's condition had improved and all the routine investigations were found to be normal. There was no more discharge occurring from the site of infection therefore tab. Imipenam was substituted for inj. imipenam which led to full recovery of the patient from his condition and eventually he was discharged on his improvement on the 22nd day.

Studies have shown that the estimated adverse drug reactions in hospitalized patient are 10-15% of which the penicillin induced reactions are of 5-10% that mainly affecting skin, respiratory tract, gastrointestinal tract, blood and blood vessels.⁴⁻⁸

The distinctive features of allergic reactions are:

- Lack of correlation with known pharmacological properties of the drug.
- Lack of linear relation with drug dose (very small doses may cause very severe effects).
- Rashes, angioedema, serum sickness syndrome, anaphylaxis or asthma; characteristics of classic protein allergy.
- Requirement of an induction period on primary exposure, but not on re-exposure.
- Disappearance on cessation of administration and reappearance on re-exposure to a small dose.
- Occurrence in a minority of patients receiving the drug.
- Possible response to desensitization.

Penicillin is the most important of the antibiotic, belongs to beta-lactam group of antibiotics. It is bactericidal and act by inhibiting the cell wall synthesis. Although penicillin is known to cause all the types of immune mediated reaction, type 4 reaction is usually encountered and cross- allergy with the penicillin is usually common.⁶

Hypersensitive reactions are the major problem in the use of Penicillins. Individuals with an allergic diathesis are more prone to develop

penicillin reactions. Frequent manifestations of penicillin allergy are – rash, itching, urticaria and fever. However, wheezing, angioneurotic edema, serum sickness and exfoliative dermatitis are less common. Anaphylaxis is rare (1 to 4 per 10,000 patients), but many a times fatal. All forms of natural and semisynthetic penicillins can cause allergy, but it is more commonly seen after parenteral than oral administration. The course of penicillin is unpredictable, i.e. an individual who tolerated penicillin earlier may show allergy on subsequent administration and *vice versa*.⁹

Piperacillin is an ureidopenicillin; an extended spectrum penicillin; has a broad spectrum activity against Gram negative bacilli, particularly *Pseudomonas aeruginosa*. It also acts on other bacterial species especially *proteus*, *klebsiella*, *bacteroides*, *fragilis*, *H. influenzae*, and *gonococci*.¹ In combination with the beta lactamase inhibitor tazobactam, it is used to treat moderate to severe infections due to susceptible organisms including lactamase producing penicillin-resistant bacteria.³ It is given parenterally and its adverse effects are similar to those of other penicillins. Although it is useful in a variety of infections, its use is reserved for serious infections, especially those due to *Pseudomonas aeruginosa*.¹

Fever can be the sole symptom or the most prominent symptom of drug hypersensitivity, accompanied in a minority cases by nonurticarial rash or other organ involvement characterized by a febrile response coinciding temporarily with the administration of a drug in the absence of underlying conditions that can be responsible for the fever.^{4,10-12} Fever as an adverse drug reaction following drug administration can occur during or within 24 hours of the administration of a drug.⁴⁻⁵ A key feature that differentiates drug induced fever, from fever of other causes is that, it disappears once the offending drug is discontinued.^{5,13}

Fever may arise from drug's effects on thermoregulation, administration-related reactions, the drug's pharmacologic action, idiosyncratic response and hypersensitivity reactions. Hypersensitive reaction is the most

common mechanism of drug induced fever which include the humoral and cellular response; a mechanism is the release of interleukin-1 by leucocytes into the circulation; this acts on receptors in the hypothalamic thermoregulatory centre, releasing prostaglandin E₁.^{4,6,11,14}

The drug induced fever may occur following the administration of several other drugs for example, azathioprine, sulfasalazine, minocycline, trimethoprim-sulfamethoxazole, sirolimus and tacrolimus. Patients with active HIV infection or cystic fibrosis appear to be at particular risk, with higher rates of drug induced fever to antiretroviral drugs and piperacillin-tazobactam, respectively.¹⁵

If a patient is allergic to penicillin, it is best to use an alternative antibiotic. In situation where continued treatment is required, switching to a chemically unrelated substitute may be performed if possible.¹⁶ However, some drugs do not have an adequate substitute such as during the treatment of a particular type of cancer or a highly drug-resistant microorganism. In such situations, it may be possible to pre-treat the patient with corticosteroids, antihistaminics and/or prostaglandin inhibitors which remaining vigilant for further signs of hypersensitivity.⁴

CONCLUSION

The drug induced hypersensitivity reaction is an immune mediated reaction which is most commonly caused by penicillins with fever as the most prominent symptom accompanied in some of the causes with non-urticarial rashes or the other organ involvements. The reactions have been more prominently and frequently observed in individuals with an immune compromised state. It is therefore essential to be watchful in the use of the drugs in individuals with the existing history of drug allergy. If the individual has once suffered with an allergy to penicillin it may not be suffered once again however, re-challenging is best avoided as it may turn out to be severe reaction and at times fatal.

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