CO-AMOXICLAV: A COMMON ANTIBIOTIC WITH AN UNCOMMON PRESENTATION OF ANAPHYLAXIS- A RARE CASE REPORT

Subish Palaian, PV Kishore, Pranaya Mishra

Manipal Teaching Hospital/ Manipal College of Medical Sciences, Pokhara, Nepal.

Abstract

The use of co-amoxiclav is associated with diarrhoea (most common), nausea and vomiting, rash. Anaphylaxis is also reported with this drug. We report a case of anaphylaxis due to co-amoxiclav in a patient who was not sensitive to Inj. Cefazolin and showed a negative skin test to Co-amoxiclav. The patient was started on Injectable Co - amoxiclav 1.2gms intra venous q12h after giving a test dose, with no notable reaction**.** The patient was also treated earlier with Inj. Cefazolin which he tolerated well. Thirty minutes following the injection, patient developed severe shivering with difficulty in breathing and an elevated body temperature. A diagnosis of anaphylaxis secondary to co-amoxiclav was made. The patient was resuscitated with injection hydrocortisone and salbutamol nebulization and other supportive measures. The causality assessment as per the Naranjo algorithm revealed the ADR to be 'probable', severity assessment as per the Hartwig et al scale revealed the ADR to be moderate (level 3) and the preventability assessment as per the modified Schumock and Thornton scale revealed the ADR to be 'not preventable.'

Key words: Anaphylaxis, Causality, Co-amoxiclav, Preventability, Severity.

Address for correspondence:

Subish Palaian M. Pharm
Assistant Professor
Department of Hospital and Clinical Pharmacy and Pharmacology
Manipal Teaching Hospital/ Manipal College of Medical Sciences
Pokhara, Nepal.

Introduction

Co-amoxiclav is a common drug used widely for various infections. It consists of a fixed dose combination of Amoxicillin and Clavulanic acid in a ratio (2:1 or 4:1). Clavulanic acid is a beta-lactamase inhibitor which increases the antibacterial activity of beta-lactam antibiotics; the drug has been used most frequently with amoxicillin. Clavulanic acid is a beta-lactamase inhibitor produced by Streptomyces clavuligerus. The drug has been shown to inhibit staphylococcal beta-lactamases and numerous beta-lactamases produced by gram-negative organisms. When combined with beta-lactam antibiotics, the activity of the antibiotic is extended against beta-lactamase-producing organisms which would otherwise be resistant [1]. In general it is considered to be a safe drug. The common Adverse Drug Reactions (ADRs) associated with this drug are diarrhoea (most common), nausea, vomiting, rash, urticaria [1].

We hereby report a case of anaphylaxis due to co-amoxiclav in a patient who was not sensitive to Inj. Cefazolin and showed a negative skin test to Co-amoxiclav. We also carried out the causality, severity and preventability of the ADR as per the Naranjo scale, [2] Hartwig et al scale, [3] and modified Schumock and Thornton scales [4] respectively.

Case report

An 85 year old male, ex-smoker and ethanolic, non-hypertensive, non-diabetic with good renal function presented with complaints of swelling in left inguino scrotal region since 3 years gradually increasing in size with no history of fever or pain. Patient was admitted in surgical wards for diagnostic and therapeutic excision of the swelling under general anaesthesia. Routine investigations were done, Hb: 13gm%, RBS: 114Mg/dL, Blood urea: 32Mg/dL, Serum creatinine: 0.9Mg/dL. A histo-pathological diagnosis of de-differentiated liposarcoma from Para testicular area was made from the specimen sent to pathology. Post excision, patient was started on injection Cefazolin 1 gram intra-venous q12h. After 1 week, the surgical flap developed tissue necrosis for which debridement was done and antibiotics were changed empirically to Co-amoxiclav, after sending the pus for culture sensitivity.

The patient was started on Injectable Co - amoxiclav 1.2gms intra venous q12h after giving a test dose, with no notable reaction. However, after 30 minutes of infusion, patient developed severe shivering with difficulty in breathing and an elevated body temperature to 100.6 ^{0}F with no significant change in the blood pressure. A diagnosis of anaphylaxis secondary to co-amoxiclav was made. The patient was immediately resuscitated with injection hydrocortisone and salbutamol nebulization and other supportive measures. The patient improved with the above measures with no recurrence of the symptoms. Subsequently the drug Co - amoxiclav was stopped and initiated on oral Metronidazole 400mg q8h and oral Ciprofloxacin 500mg q12h and continued for one week. Patient had no recurrence of the symptoms and responded well with a healthy healing of the wound. The patient was subsequently managed by the Institute oncologist. Upon reporting the ADR to the Pharmacovigilance cell of the Manipal Teaching Hospital, the Pharmacists carried out the causality, severity and preventability of the adverse drug reactions.

The causality assessment as per the Naranjo algorithm revealed the ADR to be 'probable', severity assessment as per the Hartwig et al scale revealed the ADR to be moderate (level 3) and the preventability assessment as per the modified Schumock and Thornton scale revealed the ADR to be 'not preventable.'

Discussion

Beta lactam antibiotics are a common class of drugs used in many infections. Because of their higher therapeutic index and safety profile, they are one of the preferred drugs. However, hypersensitivity due to this class of drugs is one of the bothersome ADRs. Moreover, penicillin and its derivatives are the commonest cause of drug-induced anaphylaxis, accounting for some 500 deaths per year in the United States [5].

Anaphylaxis is an acute, often explosive, Ig-E mediated systemic reaction that occurs in a previously sensitized person who receives the sensitizing antigen [6]. Anaphylaxis due to penicillins usually occurs within 1 hour after receiving the drug [7]. In case of our patient, the reaction occurred half an hour following the administration of the Injection. Urticaria and angioedema are the most common clinical manifestations of penicillin induced anaphylaxis.[7] Our patient presented with severe shivering with difficulty in breathing and an elevated body temperature.

One of the strategies employed to determining the predisposing factor for developing penicillin induced anaphylaxis is by administering the test dose of the drug. If a patient is likely to develop anaphylaxis due to penicillins, then will develop hypersensitivity reactions to the test dose as well. However, there is evidence suggesting that 1-4% of patients with negative skin reactions may develop non-life-threatening urticarial rashes [5]. In our patient also, the patient was given the test dose of the penicillin drug for which the patient did not develop any reaction. In our case, moreover the patient tolerated very well with the Inj. Cefazolin which is also a beta lactam antibiotic. This shows that though the patient was tolerant to cefazolin and negative to co-amoxiclav sensitivity skin testing, still can develop anaphylaxis to betalactam antibiotics.

The common hypersensitivity reported with this drug included skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions, Stevens - Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and acute generalized exanthematous pustulosis. The manufacturer reports the possibility of anaphylaxis due to this drug [8].

Upon occurrence of hypersensitivity reactions, treatment with antihistamines or, if necessary, corticosteroids may be used and amoxicillin should be discontinued if possible. A history of penicillin hypersensitivity or a history of sensitivity to multiple allergens increases the likelihood of this reactions [8]. In our case the patient needed immediate resuscitation with injection hydrocortisone and salbutamol nebulization and other supportive measures. He improved significantly following the treatment intervention.

Desensitization may be attempted in the patient with a positive skin test for whom there is no alternative to a penicillin-type drug [5]. In such a case, the patient should be desensitized as

per the standard desensitization schedule [9]. *Arroliga and Pied* claims that a history of allergy to penicillin does not necessarily rule out using penicillin again. With skin testing and, in some cases, desensitization, most patients with a history of penicillin allergy can safely receive the drug [7]. In this the authors statement is supported by the evidence from a pilot study which concluded that most patients with histories of allergy to penicillin have negative reactions to skin tests and may receive penicillin safely [10]. In our case, we did not carryout desensitization as there was alternative treatment available in our patient.

Carrying out the causality assessment using standard methods is one of the best ways to establish the causal relationship between drug and effect. The Naranjo algorithm [2] is used widely in carrying out the causality assessment of ADRs. It is based on the score calculated on the basis of points given for each of ten questions that comprises the table. In our case, the causality assessment revealed that the ADR to be 'probably' attributed to Inj. Co-amoxiclav.

In order to take appropriate initiatives towards management of the ADR, it is necessary to study the severity of the ADRs. Hartwig scale [3] is widely used for the purpose. This scale categorizes the reported adverse drug reactions into different levels as mild, moderate or severe based on the treatment and whether or not hospitalization was required for the management of the ADRs. In our patient, the ADR was found to be of 'moderate (level 3)'. This suggest that the ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or on antidote or other treatment is required. There is no increase in length of hospital stay.

The preventability assessment provides an idea to find whether a particular ADR could be preventable. A commonly used scale for this purpose is the Modified Schumock and Thornton scale [4]. In our case this ADR was found to be not-preventable. In our case this ADR was 'not preventable'.

Conclusion

Our case clearly notifies that though a patient tolerates well a beta lactam antibiotic and shown negative allergic testing, still can develop anaphylaxis. This ADR also suggest that clinicians should monitor the patients on beta lactam therapy even if they pose a negative skin reaction.

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