Section: Pharmacology

Case Report

ADVERSE DRUG REACTION DUE TO COMBINATION OF AMOXICILLIN AND CLAVULANIC ACID ALONG WITH ITS CAUSALITY ASSESSMENT: A CASE REPORT

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Abstract

Augmentin is a combination drug. Augmentin contains amoxicillin as the primary ingredient and clavulanic acid, which helps treat infections caused by antibiotic-resistant bacteria. The two antibiotic drugs are the first line of defense against stubborn bacterial infections however, Adverse Drug Reactions [ADRs] are one of the main causes of discontinuation of the therapy. This is a case study of the erythematous rash induced by augmentin along with its causality assessment. A 67-year-old female underwent Left Modified Radicle Mastectomy [MRM] and came with complaints of swelling & discharge from the post-operated site. The patient was then administered augmentin. Augmentin administration caused appearance of erythematous rash on both palms followed by reddening and swelling of the tongue and face. Following this, the drug was then discontinued and a combination of antihistamines, and steroids was given to treat the rashes. Causality assessment was done using the Naranjo scale and indicates a probable relationship. The ADR was reported by VigiFlow in the pharmacovigilance center. Cutaneous adverse reactions can be triggered by any drug class, but they are more commonly associated with various antibiotics. Penicillin-class drugs especially amoxicillin frequently cause cutaneous drug eruptions specifically skin rashes. These immune-mediated, bizarre drug eruptions can range from mild to severe cutaneous responses. Hence, while using augmentin therapy, patient counselling about ADR and monitoring of ADR becomes essential. This case is being shared to provide more evidence of skin reactions caused by amoxicillin.

INTRODUCTION

Amoxicillin-clavulanate (Augmentin) is a mainstay antibiotic in emergency departments and primary care centers throughout the country. It is a combination of two separate drugs: amoxicillin and clavulanic acid.

Amoxicillin is a semi-synthetic, acid-stable drug; that belongs to the penicillin (beta-lactams) class of antibiotics. It is effective against various infections caused by a wide range of gram-positive and gram-negative bacteria.[1] Furthermore, with the addition of clavulanic acid, the spectrum is increased to include beta-lactamase-producing strains as well as broadening the coverage to include other bacterial species. It is used as an effective and safe therapy for acute exacerbations of chronic bronchitis, sinusitis, otitis media, epiglottitis, urinary tract infections, meningitis, salmonella infections, severe skin infections, and other bacterial infections.[2]

Amoxicillin is often the primary treatment for numerous bacterial infections, particularly in infants which is frequently prescribed and considered to be the best drug due to its superior absorptive nature followed by the oral route when compared to other beta-lactam congeners.[3]

Amoxicillin binds to penicillin-binding proteins in the bacterial cell wall, disrupting the synthesis of the cell wall. Clavulanic acid, a β-lactam structurally similar to penicillin, can deactivate certain β-lactamase enzymes.[4]

Beta-lactams regardless of their origin whether they may be naturally produced or synthetic or semi-synthetic are susceptible to provoke immediate or non-immediate allergic reactions.[5]

The ADRs caused by the combination of amoxicillin and clavulanic acid include hypersensitivity reactions like angioedema, anaphylaxis, mild fever, rash, purpura, lymphadenopathy, generalized edema, albuminuria, and hematuria.[6]

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Cutaneous adverse reactions like skin rashes, urticaria, itching, fixed drug eruption, and angioedema are also common among the various adverse drug reactions.[7]

Stevens-Johnson syndrome and Toxic epidermal necrolysis are a rare but fatal form of ADRs affecting patient's life.[8] However, augmentin continues to be the first line of treatment in severe skin infections as it contains clavulanate which widens its spectrum.

This review covers indications, contraindications, administration of amoxicillin-clavulanate, and its potential adverse effects. It also emphasizes the importance of teamwork among healthcare professionals for the effective use of this drug.[9] In the recent past many articles in the form of case reports and case series have been published regarding amoxicillin-induced skin rashes in the pediatric population.[10]

Here we are reporting a non-immediate maculopapular, erythematous rash induced by amoxicillin-clavulanate along with its causality assessment.

CASE REPORT

A 67-year-old woman presented with swelling, discharge, and an abscess on her left breast and was admitted to the surgical ward of a rural tertiary care teaching hospital. She had a history of left-sided breast carcinoma and underwent a left Modified Radical Mastectomy (MRM). Following surgery, she received a regimen of amoxicillin-clavulanic acid tablets (625 mg, three times daily), along with other medications including paracetamol (650 mg as needed) and rabeprazole (20 mg once daily).

Following the second dose of amoxicillin-clavulanate, which was taken 8 to 10 hours after the first dose, the patient experienced itching on both palms and developed maculopapular rashes on them, as shown in [Figure 1].

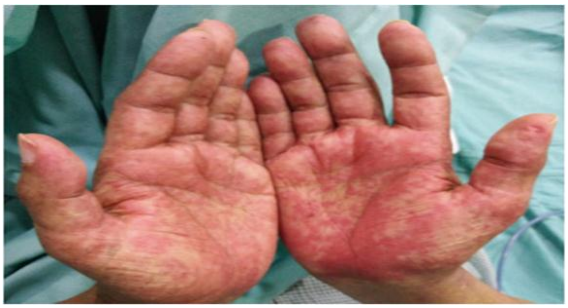

Figure 1: Maculopapular rash on the palms of both the hands

Within half an hour, she also developed swelling on the face, itching in her mouth, swelling and redness of the tongue, as depicted in [Figure 2].

The patient's primary complaints were severe itching and pruritus only with no erosions and hemorrhagic crusting. As a part of history, the patient's attenders revealed that the same instance happened a year ago when the patient was once given antibiotics for some indication.

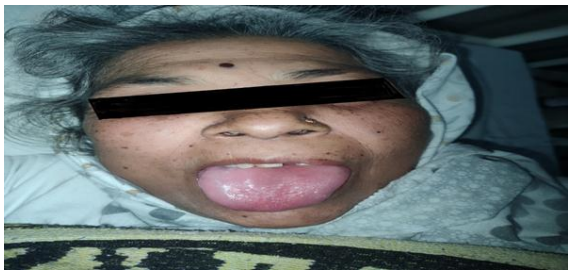

Figure 2: Swelling on face, reddening & swelling of the tongue

Examination & investigation: The patient was conscious, well-oriented, and stable, with a pulse rate of 80 beats per minute. Her blood pressure was within normal limits at 124/78 mm Hg. All other vital signs were also normal.

Upon local examination, numerous irregularly shaped and varying-sized erythematous maculopapular rashes were observed on both palms and the tongue. The affected areas appeared reddish-pink but there were no signs of bullae. Immunoglobulin levels and inflammatory markers were not assessed however all routine laboratory tests were being carried out.

Management: After examining the patient, treatment with amoxicillin-clavulanate was discontinued and the patient was monitored for the progression of erythematous rashes. Immediate treatment included intramuscular injections of corticosteroids and pheniramine maleate. Subsequently, the patient was prescribed prednisolone, a combination tablet of levocetirizine and montelukast, and a steroid ointment (fluticasone propionate) for topical application to the affected areas. Moisturizers and calamine lotion were prescribed for symptomatic relief.

CAUSALITY ASSESSMENT of the ADR:

Causality assessment of the suspected adverse drug reaction was done using the Naranjo scale.[11]

The evaluation indicated that the likelihood of the adverse drug reaction was deemed "probable" with amoxicillin and potassium clavulanate.

Interpretation of scores in the Naranjo scale.[11]

The Naranjo algorithm or ADR probability scale is a method used to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores.

Total score ≥9 [Definite]: The reaction (a) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (b) followed a recognized response to the suspected drug, and (c) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

Total score 5-8: [Probable]: The reaction (a) followed a reasonable temporal sequence after a drug, (b) followed a recognized response to the suspected

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drug. (c) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

Total score 1-4: [Possible]: The reaction (a) followed a temporal sequence after a drug, (b) possibly followed a recognized pattern to the suspected drug, and (c) could be explained by characteristics of the patient's disease.

Total score <0: [Doubtful]: The reaction was likely related to factors other than a drug.

In this case, the causality assessment using the Naranjo scale (Score 7) indicates a "probable" relationship.

Reporting to the ADR monitoring center:

This case of maculopapular erythematous rash caused by amoxicillin-clavulanate was reported to the Regional Pharmacovigilance Centre at MGIMS, Sevagram, as part of the Pharmacovigilance Program of India (PvPI) by the Indian Pharmacopoeia Commission. It was reported by VigiFlow application in the pharmacovigilance center.

Table 1: Naranjo Adverse Drug Reaction Probability Scale.

Questions	Yes	No	Don't know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	Yes
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	Yes
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	Yes
Did the adverse event reappear when the drug was re- administered?	+2	-1	0	DNK
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	No
Did the reaction reappear when a placebo was given?	-1	+1	0	DNK
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	DNK
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	Yes
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	DNK
Was the adverse event confirmed by any objective evidence?	+1	0	0	No
Total Score				7

DISCUSSION

The maculopapular rash caused by amoxicillin and clavulanic acid was identified as crimson red in color and itchy by nature. It was observed that approximately 10% of individuals treated with beta-lactams are susceptible to such allergic reactions, with cases reported in India and other regions.[12]

In the context of skin diseases presenting with clinical signs on the skin, it is crucial to always consider medications as a potential cause of any eruption. Drug-induced eruptions can manifest in various forms of skin lesions.[13] In addition to skin diseases and adverse drug reactions, certain systemic infections are also to be ruled out properly for the correct causality assessment.[14]

The precise pathophysiology of drug-induced skin eruptions is not fully understood; however, immune-mediated reactions are known to occur due to unusual effects which include fatigue, fever, lymph node enlargement, and dysfunction of internal organs such as the liver, kidneys, or bone marrow.[15]

Penicillin (especially amoxicillin) induced skin reactions are said to be classic in nature which are interceded by the involvement of the immune system and categorized as immediate (developing within half an hour to one hour of drug ingestion) and non-immediate (beyond one hour of ingestion).[5]

A previous retrospective analysis revealed that, aside from antibiotics (31%), various other agents can cause severe skin rashes, with antiepileptic drugs being the most common (50%). Among the antiepileptics, carbamazepine was most frequently implicated (27%), followed by phenytoin (13.6%).[16]

Another study conducted in India reported that the most common drugs causing various types of cutaneous adverse drug reactions (ADRs) were antimicrobials, anticonvulsants, and NSAIDs. Among these, anticonvulsants were implicated in 41.6% of maculopapular rashes. Sulfonamides accounted for 43.3% and NSAIDs for 30.7% of fixed drug eruptions. Urticaria was predominantly associated with NSAIDs (24.3%) and penicillin-class drugs (20%).[17]

Augmentin is prescribed for more drug-resistant infections, like skin infections, UTIs, laryngitis, and pharyngitis. Various side effects of Augmentin include diarrhoea, headache, dysgeusia, vulvovaginal mycotic infection, nausea, vomiting, abdominal pain, pruritus, hypersensitivity reaction, rashes, and skin reddening.[6-8]

Maculopapular skin eruptions represent the most frequent type of skin reaction to antibiotics. These reactions exhibit distinct patterns in appearance, ranging from mild skin irritation to severe conditions such as toxic epidermal necrolysis.[9]

Apart from cutaneous reactions, amoxicillin can also cause other ADRs such as acute generalized pustulosis, agranulocytosis, pancreatitis, and Kounis syndrome.[18]

The current study provides new insights into the importance of pharmacist's and clinical pharmacologists' interventions in identifying such scenarios. Additionally, clinical pharmacologists, as

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drug experts, can share their knowledge and experience with other healthcare providers to enhance pharmaceutical care for patients. A drug alert card can also help patients prevent similar reactions in the future.[5]

Reporting adverse drug reactions (ADRs) to the WHO Uppsala Monitoring Centre supports the formulation of drug usage guidelines. In India, the Pharmacovigilance Program of India (PvPI) collects ADR reports from regional PvPI centers and submits them to the WHO center.[19]

The current suspected case of amoxicillin-induced erythematous maculopapular rashes was also submitted to the PvPI. Encouraging the reporting of any adverse drug reaction can aid in preventing and enhancing drug therapy.[7]

CONCLUSION

The current case report highlights gaps in the prescriber's knowledge regarding the evaluation of cutaneous reactions linked to beta-lactams, which are commonly prescribed in emergency as well as surgical departments for many bacterial infections. It also emphasizes the crucial role of clinical pharmacists in the healthcare sector, particularly in such situations, serving as a model for best practices. Literature search shows around 9% prevalence of rashes and hyper-sensitivity reaction of ampicillin but did not show such studies for augmentin. Hence monitoring is essential for any ADRs while using augmentin and in case of ADR one must discontinue the drug and report it to the pharmacovigilance centre.

The cutaneous skin rashes caused by amoxicillin/clavulanic acid are likely responsible for the severe skin eruptions observed in this case. This case report underscores the importance of active pharmacovigilance monitoring. Effective monitoring of adverse drug reactions (ADRs) is crucial for ensuring medication safety. Therefore, spontaneous reporting of such events is essential, with pharmacovigilance playing a pivotal role in this process.

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