International Journal of Pharmacy and Biological Sciences-IJPBS™ (2020) 10 (4):63-66
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Case Report | Biological Sciences | OA Journal | MCI Approved | Index Copernicus

Case Report on Antibiotic Allergy Intolerance

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Received: 02 Jul 2020/ Accepted: 09 Aug 2020 / Published online: 01 Oct 2020
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Abstract
The discovery of antibiotics from 20th century onwards have helped humans to fight against deadly diseases, but the more we use them, it is greater the pressure on bacteria to evolve and flourish. Pathogens emerge different mechanisms and mutations to beat a particular drug where after such population develops among bacterium, evolving resistance. This makes the patients longer to recover or less likely to survive. Other important cofactor on antibiotic use is the allergic reaction that patients develops, diagnosing true drug allergy can be very challenging and it is very crucial that patients are managed appropriately otherwise antibiotics needs to get withheld unnecessarily, which would affect clinical outcomes, increasing healthcare costs and potentially contributing to forth new drug-resistant bacteria. This is a case report of 19-year-old male patient admitted in the hospital for the complaints of reinfection on the site of fracture with ex fix in- situ application. He was newly diagnosed for allergic reaction to ofloxacin and cotrimoxazole. He was initially on INJ. CEFUROXIME 1.5 gm, later based on the culture results, he being resistant to cefuroxime it was mandatory to switch to INJ.OFLOXACIN 200mg. On the test dose patient developed allergic reaction to INJ.OFLOXACIN 200mg consequently INJ.COTRIMOXAZOLE (160/800) mg 1-0-1 was advised as an alternative, unfortunately patient developed allergic episode on cotrimoxazole furthermore. It is challenging for a multidisciplinary team about the possible consequences of labelling a patient with an antibiotic allergy; with their subsequent impacts on patient therapeutic outcomes and how a clinical pharmacist can undertake appropriate investigations and de label patients

Keywords
Allergy, Resistance, Reinfection, de label

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INTRODUCTION:
Drug allergy is a type of the unpredictable ADR that composes of a spectrum of immunologically-mediated hypersensitivity reactions that have different mechanism of action and clinical manifestations. It accounts for approximately 5-10% of all ADRs [(1)] Allergy is defined as an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person. A retrospective analysis of anaphylaxis can be done by evaluating the increase in serum total tryptase levels above baseline or serum mature tryptase. The most useful test for detecting IgE-mediated drug reactions is by the immediate hypersensitivity skin test. The basophil activation test is a recently described method of evaluating the expression of CD63 on basophils after stimulation with an allergen. There are limited data on using this method to evaluate patients with possible allergies to lactam

antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).

The most important causes of immediate hypersensitivity reactions are antibiotics, particularly beta-lactam antibiotics. Approximately 10% of patients report a history of penicillin allergy. However, up to 90% of these individuals can tolerate penicillin and are designated as having penicillin allergy unnecessarily. The use of broad-spectrum antibiotics in patients designated as being allergic can be associated with increased costs, increased antibiotic resistance, and maybe even a compromised optimal medical care. Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy. Both major and minor determinant reagents are used for skin testing. Penicillin challenges of individual's skin test negative to penicilloyl polylysine and penicillin G20, 21 have similar reaction rates compared with individuals skin test negative to the full set of major and minor penicillin determinants [(15)].

Sulfonamide antibiotics rarely cause IgE-mediated reactions and more commonly result in delayed maculopapular exanthem, there is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. The allergic drug reactions to antimycobacterial drugs can induce both minor and life-threatening reactions. Drug allergy should be strongly suspected when the (1) symptoms and physical findings are compatible with an immune drug reaction; (2) there is (or was) a definite temporal relationship between administration of the drug and an adverse event; (3) the class and/or structure of the drug have been associated with immune reactions; (4) the patient had previously received the drug (or a cross-reacting drug) on 1 or more occasions; (5) there is no other clear cause for the presenting manifestations in a patient who is receiving medications known to cause hypersensitivity reactions; and (6) the skin tests and/or laboratory findings are compatible with drug hypersensitivity. The involvement of the skin is often a prominent physical sign of drug allergy. The spectrum of drug-induced skin lesions includes urticaria, morbilliform rashes, papulovesicular and bullous eruptions, and exfoliative dermatitis [(15)].

Diagnosing drug allergy can be challenging and there is considerable variation both in how drug allergy is managed and in geographical access to treatment. This can lead to under-diagnosis, misdiagnosis, and self-diagnosis. This variation may be caused by insufficient awareness of available services or by a lack of local provision of drug allergy specialists. Some people are never offered a referral to specialist services and instead stay in primary care. Therefore, awareness about specialized allergy centres is integral. Key priorities for implementing a drug allergy would be firstly assessing the patient by undergoing a clinical examination and history, documenting the suspected allergic reaction and communicating about the information with other health care professionals. When documenting a new suspected drug allergic reactions it is integral to note the allergic reaction in a structured approach including the generic and proprietary name of the drug, a description about the reaction, indication for which drug was being taken, date and time of the reaction, the number of doses or number of days the drug was taken before the onset of the reaction, the route of administration.

Case Report:

A 19 year old male patient with a suspected history of road traffic accident on 5 November at 2.00 am near his native, suffered an injury to right leg following which he was taken to a private hospital initially and then to an orthopaedic hospital on 5 of November for which he has undergone wound debridement and external fixator application over his right tibia.

On his follow up after 3 months he was noticed with complaints of swelling and discharge from the right leg with ex-fix in situ hence it was diagnosed with the infection on his right leg with ex fix in situ. After considering the infected state and mal-alignment, it was planned for debridement and external fixator removal and limb reconstruction system application. It was suggested with a prophylactic antibiotic INJ.CEFUROXIME 1.5 gm–IV and then de-escalated to 750 mg. After 4 days of Antibiotics, he was switched to INJ.OFLOXACINIV 200 mg1-0-1 based on the culture result with a heavy growth of Klebsiella species. He was soon developed with an allergic reaction (itching) following the first dose and it was advised to replace it with INJ.COTRIMOXAZOLE (160/800) mg 1-0-1 in lieu. But on his test dose developed 5mm induration on the tested site. On the very next day, the patient was suggested with INJ.AMIKACIN (1gm) 1-0-0 for 3 days on clinical pharmacists opinion and was suggested for the further validation of antibiotic allergic labelling to improve the appropriateness of antibiotic use. Later on, the patient was again given with a test dose of OFLOXACIN 200mg in which anaphylactic reaction was reappeared. The clinical pharmacist suggested oral ofloxacin to ensure antibiotic allergy labeling. On day 8 of admission, the patient completed the course of antibiotic treatment and his condition was improved with no soakage at the wound site improved with the completion of the course and no

soakage at the wound site. His examination showed normal vitals: on his discharge he was advised with ORAL.COTRIMOXAZOLE DS (160/800) mg1-0-1 for 10 days as a follow up

DISCUSSION:

All antibiotic has the potential for developing antibiotic resistance. WHO's new Global Antimicrobial Surveillance System (GLASS) revealed that there is a widespread occurrence of antibiotic resistance among the 500000 people with a suspected bacterial infection across 22 countries [8] .Antibiotics are the commonest cause of life-threatening immune-mediated drug reactions that are considered off-target, including anaphylaxis, and organ-specific and severe cutaneous adverse reactions. However, several antibiotic reactions documented as allergies were unknown or not remembered by the patient, body covering reactions unrelated to drug hypersensitivity, drug-interactions, or drugs intolerances. Antibiotic hypersensitivity reaction labels result in the displacement of first-line therapies for antibiotic prophylaxis and treatment [9].The anaphylactic reaction to fluoroquinolones is of immediate type and IgE mediated and usually occurs immediately within one hour of intake [10] .The basic structure of quinolones is a nitrogen-containing eight-member heterocyclic aromatic compound with a carboxylic group at position 3 and a ketone group at the position. The addition of a fluorine substituent at position 6 and a piperazinyl moiety at position 7 gives a ciprofloxacin ring and addition of a methyl substituent on the piperazine ring will give ofloxacin. IgE antibodies interact mainly with the side chains at positions and frequent cross-reactivity among structurally similar quinolones may also occur. Thus, it's been concluded that Ig E-mediated response to the hapten part of ofloxacin is the major pathogenic mechanism underlying ofloxacin hypersensitivity [11]. Cotrimoxazole can induce a large number of different skin reactions mainly of allergic pathogenesis. Immunology of sulfanilamide allergies suggests the mechanism of hypersensitivity reactions involves IgE, occasionally IgG, and different types of T cell-mediated reactions. The best-analysed drug is sulfamethoxazole contained in cotrimoxazole, which is combined with trimethoprim, where this SMX is a prodrug and it is metabolized intra hepatically as SMX-NHOH, which is further then oxidized as SMX-NO. SMX-NO becomes highly reactive when it binds to cysteines, present in soluble and cell-bound proteins. It so will elicit associate immunoglobulin response, a T cell-mediated response, or each to changed proteins, which may end in totally different clinical photos. Intradermal skintest may well be useful in each immediate and non-immediate reactions. SMX at a concentration of 80 mg/mL is shown to be non-irritating in intradermal tests [12].The majority of these reactions, such as urticarial, purpuric, maculopapular, and pustular exanthemas, as well as photoallergic reactions, generally do not endanger the life of the patient [13] ·Cefuroxime resistance mechanisms in Klebsiella pneumonia are the production of extended-spectrum ß-lactamases (ESBL) along with down regulation of porins, especially OmpK35. In the case of Escherichia coli, active efflux is a possible cause of cefuroxime resistance. The efflux pumb AcrAB seems to be important foe efflux mediated resistance on K.pneumoniae. Mutations in the local regulator gene acR are associated with increased expression of acrA in K.pnumonoiae RamA, MarA and SoxS are unit international regulative proteins concerned in multidrug resistance (MDR). RamA is a transcriptional activator in K.pneumoniae involved in regulation of acRAB and in expression of other efflux pumps [14].

Amikacin is a commonly used antibiotic for susceptible pathogens in bone and joint infections and is the reasonable choice when aminoglycoside antibiotics are indicated but it has the impact of inducing eosinophilia and mild systemic symptoms syndrome [2]. Anaphylaxis to amikacin is very rare and has rarely been reported among the literatures. Although skin reactions are the most common physical manifestation of drug-induced allergic reactions, many other organ systems may be involved, such as the renal, hepatic, and haemolytic systems. Multi-organ reactions may also occur and an anaphylaxis of (a serious systemic allergic reaction that would be rapid in onset and may cause death, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, serum sickness, drug-induced lupus erythematosus (DILE) and vasculitis (a heterogeneous group of disorders that are characterized by inflammatory destruction of blood vessels) are some of the other serious reactions that can occur [3]. Cefuroxime is a second-generation semi-synthetic cephalosporin and has been reported to cause anaphylaxis only in a few cases. Cephalosporins will cause a variety of hypersensitivity reactions, from mild, delayed-onset cutaneal reactions to even critical hypersensitivity reaction in patients with immune globulin (IgE)-mediated hypersensitivity reaction[4]. Cotrimoxazole has been used for the treatment of bone and joint infections; a broad spectrum of activity with adequate bone diffusion on oral and intravenous formulations.it is generally effective in bone and joint infections as a salvage therapy also in gram

negative bacilli and poly microbial infections, including orthopaedic device infections [5]. Antibiotic-related anaphylactic reactions usually occurs within minutes after IV injections. A medical history regarding previous antibiotic allergies should be included so as to get a description about the symptoms such as: urticaria; pruritus; angioedema or respiratory difficulties; severity and timing of reaction after drug therapy [6]. Ofloxacin is categorised as a broad-spectrum antibiotic (active against Gram-negative and Gram-positive bacteria) which generally acts by inhibiting bacterial deoxyribonucleic acid gyrase. It is the second generation of the fluoroquinolones group of anti-microbial and can be administered as-oral, injectable or topical. They are one of the commonly used and prescribed antibiotics owing to their broad-spectrum antimicrobial coverage (including anti-tubercular action) and also minimal adverse effects [7].

CONCLUSION:

Antimicrobial resistance is on the rise; however, the evolution of antimicrobial drugs is slowing,' so now more than ever, antimicrobial stewardship is of the utmost importance in optimizing the use of antimicr obials, preventing resistance development and impr oving patient outcomes. Antibiotic Stewardship Program (ASP) helps to reduce inappropriate use of antibiotics and ensures that antibiotic doses, duration of treatment and are used only if required, thus improving patient outcomes and safety with maximum efficacy and lowering adverse events. Validation of antibiotic allergy labelling is also a key step to prevent the inappropriate interventions on medications. A proper history and allergic status investigation should be undertaken by the clinical pharmacist and specialist allergy services to help ensure proper patient outcomes. The hospital should also be encouraged to set up the "systematic generated antibiotic report" in which usage of antibiotics in particular patients will blink on a physician or clinical pharmacist's screen there by timely interventions can be made on cost effectiveness.

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