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Case Series

Pharmacology Section

Ceftriaxone Induced Hypersensitivity Reactions Following Intradermal Skin Test: Case Series

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ABSTRACT

The incidence of cephalosporin induced hypersensitivity reactions in non-penicillin allergic patients is about 1.7% and in penicillin allergic patients it is about 3-5%. Infact, cephalosporins are considered as the first choice in penicillin allergic patients who need antibiotic therapy intraoperatively. Prompt identification of patients with beta-lactam allergy would lead to an improved utilization of antibiotics and reduced occurrence of resistant strains. We hereby attempt to present a series of cases where ceftriaxone has been implicated in the manifestation of various hypersensitivity reactions. We have also tried to highlight some of the errors, risk factors and other drugs that precipitate a hypersensitivity reaction.

Keywords: Adverse drug reaction, Allergic reaction, Broad spectrum antibiotic, Naranjo's scale

Cephalosporin's are one of the most commonly prescribed antibiotics along with penicillin's, because of their broad spectrum of activity. As the therapeutic use of cephalosporin's are increasing, reports of hypersensitivity reactions are also on the rise [1]. Drug induced allergic reactions can be grouped into IgE mediated and non IgE mediated. IgE mediated reactions include angioedema,urticaria, anaphylaxis and bronchospasm which occurs within 72 hours of exposure to the drug. Non IgE mediated reactions are characterized by interstitial nephritis, Steven Johnson syndrome, serum sickness, hemolytic leukemia etc. [2].

CASE 1

A 36-year-old gravida 2, para 1 and abortion 1 was following up in the Obstetrics Outpatient Department (OPD) of our hospital from 29 weeks of gestation. She was a known case of hypertension since conception and has been on low dose aspirin 75 mg according to the risk assessment for Preeclampsia by US Preventive Services Task Force (USPSTF). Anomaly scan, echocardiogram and renal artery Doppler were normal. Later on she was admitted at 31 weeks of gestation with a BP recording 190/110mmHg and was started on alpha-Methyldopa 1500mg and betamethasone to prevent respiratory distress syndrome following premature delivery, 24 hour urine protein was negative, serum sodium-134mmol/L, serum potassium– 3.3meq/L, chloride-99.8mEq/L, fundoscopy and renal Doppler were normal, per abdomen was relaxed and foetal heart sound was present. Further, patient was admitted 24 hours later with the blood pressure recording of 170/100 mmHg with no complaints of headache, epigastric pain and blurred vision. Per abdomen was relaxed with fetal heart rate of 144 beats per minute and amniotic fluid index (AFI) of 11. Urine protein was negative and she was started on oral labetalol 300 mg along with alpha-Methyldopa 1500 mg and was put under continuous BP monitoring. Seven days later, patient was posted for Emergency Lower Segment Cesarean Section (LSCS) under spinal anaesthesia in view of high BP. After obtaining the pre-anaesthetic clearance, at 2:15pm, she was given a test dose of 0.5 ml of 2 gram ceftriaxone intradermally over the left forearm as a part of prophylactic measure against Group B *Streptococcus* postsurgery. Her vitals prior to the procedure were as follows: pulse rate- 82/minute, BP-140/90mmHg and respiratory rate-20/minute. LSCS was performed and she delivered a live female baby weighing 2162 grams with an APGAR score of nine after one minute and five minutes. Soon after the delivery, within 30 minutes she started complaining of rashes and itching over the injected site which subsequently progressed to the shoulder and chest. On examination, urticarial rash and 2 mm wheals were present over the injected site, left shoulder and chest associated with itching. Her vitals were, pulse rate-70/minute and blood pressure- 130/82 mmHg. Her past history did not reveal any allergy to drugs, food or pets. Thus a diagnosis of ceftriaxone induced hypersensitivity reaction was thought of and the full dose was not given. The reaction was treated using injection pheniramine maleate 45 mg and hydrocortisone 100 mg intravenous. Postoperatively, clindamycin 600 mg was administered instead of ceftriaxone for post op surgical prophylaxis and Blood Pressure was managed using clonidine 150 mg and labetalol 300 mg. Rash and itching subsided the next day and patient was discharged on postoperative day five.

CASE 2

A 34-year-old gravida 2, para 1, living 1, death 1 was admitted to the labour ward at 37 weeks of gestation for safe confinement. She had a previous LSCS done two years back for twin pregnancy and with a present history of single umbilical artery in foetus. She did not report any allergy to drugs, no history of anaphylaxis, asthma or eczema or contact sensitivity to metals. All her routine antenatal investigations were within normal limits. Hence, she was planned for an elective LSCS and after obtaining a pre-anaesthetic clearance she was administered a test dose of 0.5 ml of injection ceftriaxone 2 grams at 9:40 am on the day of admission. LSCS was carried out and she delivered a healthy male baby of weight 3840 grams with an Apgar score of nine after one and five minutes. Her vitals prior to the procedure were pulse rate-84/minute, BP-110/70 mmHg, respiratory rate-18/minute. After an hour of test dose, at 10:30 am, she developed dizziness, facial erythema, itching over the face, neck and arms with a heart rate of 108/minute, blood pressure of 116/72 mmHg and respiratory rate-20/minute. Hence, full dose of ceftriaxone was withdrawn and reaction was treated using injection hydrocortisone 100 mg and injection pheniramine maleate 45 mg and intravenous fluids. Postoperatively she was started on ciprofloxacin 400mg for surgical prophylaxis. Itching subsided the next day and she was discharged on postoperative day four.

CASE 3

A 33-year-old gravid 5, para 1, living 1 and abortion 3 at 36 weeks of gestation, presented to the Emergency department of our hospital

with complaints of bleeding per vaginum. She was admitted in the labour ward and a detailed history revealed one episode of bleeding two hours back with no abdominal pain and well appreciated foetal movements. Examination showed no pallor, no oedema, pulse rate of 86 per minute, blood pressure of 112/68 mmHg and respiratory rate of 18 per minute. Abdominal examination revealed a relaxed and term uterus, longitudinal lie, cephalic presentation and foetal heart sound was present. A Trans Abdominal Sonography (TAS) revealed an amniotic fluid index of 10.9, Grade IV placenta previa and active cardiac activity. Hence, she was diagnosed as a case of antepartum haemorrhage and taken up for an emergency LSCS.

As a part of preoperative anaesthetic plan to conduct spinal anaesthesia, she was given a test dose of injection ceftriaxone 0.5 ml of 2 grams, intradermally at 1:30 am over the left forearm. Within a period of 10 minutes, she developed rashes all over the face with redness over the injection site. On examination, heart rate was 90/minute and blood pressure was 124/72 mmHg. However, there was no previous history of allergies, exposure to pets or any other contacts. Full dose of ceftriaxone was not given and the hypersensitivity reaction was treated with injection Phenergan 25 mg. Symptoms subsided the next day. LSCS was performed and she delivered a healthy girl baby weighing 2.5 kg with an Apgar score of nine after one and five minutes.

CASE 4

A 57-year-old female patient, diagnosed as a case of adeno-carcinoma stomach, post-billroth gastrectomy and gastrojejunostomy, presented with complaints of loose stools, vomiting, hiccups and abdominal bloating sensation since four days. On examination, heart rate- 86/minute, blood pressure-122/84 mmHg, Respiratory Rate (RR)- 18/minute. Concomitant medications included pantoprazole 40mg, mebeverine 200 mg for irritable bowel syndrome, multivitamin capsules and a powdered oral nutritional supplement (Fresubin powder) to prevent short bowel syndrome. Laboratory investigations revealed haemoglobin-10.8 g/dl, serum sodium-133 mmol/L, serum potassium- 4.5 meq/L, chloride-98 mEq/L. Hence, it was decided to start injection ceftriaxone empirically after a test dose. Intradermal injection of ceftriaxone 0.5 ml of 2 gram was given over the right forearm. After a period of 15 minutes, she started developing allergic reactions in the form of rashes and urticarial lesions over the injected site. On examination erythematous macular rashes were present over the right forearm and arm along with urticarial rash. However, there was no airway compromise. A detailed history did not reveal any history of allergy to other drugs, pets or dust. Her vitals during the time of reaction were as follows: pulse rate- 90/minute, BP-124/88mmHg and RR–18/minute. Hence, a diagnosis of ceftriaxone induced hypersensitivity was thought of and the full dose was not given. The rashes were treated by lactocalamine lotion and antihistamines phenergan 45 mg intravenous. Patient recovered in one day.

CASE 5

A 48-year-old male patient presented to the Medicine OPD of our hospital with complaints of cough, breathlessness and headache since four days. Cough was productive in nature with occasional frothy sputum, breathlessness was of NYHA Grade 2 and history of orthopnea. There was no history of fever, oliguria or chest pain. Past history revealed hypertension and Grade 3 hypertensive retinopathy for which he was on prazosin 10 mg, clinidipine 40 mg and carvedilol 6.25 mg. On examination, patient was conscious, oriented afebrile with pulse rate-80/minute, BP- 160/90 mmHg and respiratory rate- 20/minute. Auscultation of chest revealed bilateral crepitations and wheeze all over the chest, while all the other systems were within normal limits. Chest X-Ray revealed bilateral patchy infiltrates and air bronchograms. Laboratory investigations revealed leukocytosis (WBC- 11,200 cells/uL). Hence, a diagnosis of lower respiratory tract infection was made and he was started on injection ceftriaxone 2 gram after a test dose. Test dose was given using 0.5ml of 2 gram ceftriaxone over the volar aspect of left forearm. After half an hour, patient started complaining of swelling of lips, facial oedema associated with difficulty in breathing and swallowing. Vitals revealed a heart rate of 110/ min and blood pressure of 170/100 mm/Hg and respiratory rate of 20 per minute, saturation in room air (SpO2) to be 98%. He however, did not have any past history of allergic reactions to dust, drugs or pets. A diagnosis of impending angioedema was thought of and ceftriaxone full dose was withdrawn. Angioedema was treated by steroids hydrocortisone 100 mg intravenously, adrenaline 0.5 ml and antihistamine pheniramine 45 mg along with salbutamol nebulisation every sixth hourly. Angioedema gradually improved within a day and respiratory infection was managed using levofloxacin 500 mg.

DISCUSSION

Cephalosporins have a four membered beta lactam ring, whose structure varies from substitution at the R1 and R2 side chains. Cefotaxime, ceftriaxone, cefepime and cefuroxime have a R1 side chain and the hypersensitivity reactions with the above mentioned drugs are due to the presence of these side chains [1].

Hypersensitive reactions that occur immediately within the first hour of administration are characterized by urticaria, angioedema, rhinitis and anaphylactic shock [3]. Incidence of hypersensitivity reactions with cephalosporins is 1-3% [2]. Most common manifestations are development of maculopapular rash, urticaria and anaphylaxis. In cases where there is no previous exposure to ceftriaxone or other cephalosporin's, an IgE-dependent mechanism could be a possibility for such an occurrence.

Study conducted by Adhikari et al., concluded that rashes and urticaria were the most commonly occurring adverse reaction with intravenous ceftriaxone in children [4]. A thorough patient history is important in the evaluation of cephalosporin allergy. A positive skin testing demonstrates the presence of drug specific IgE antibodies. However, since these skin tests are not standardized, there are chances for false-positive tests from non-specific irritant reactions [3,5]. Study conducted by Shrestha et al., revealed that a prior intradermal test might not reveal hypersensitivity reaction and the incidences of hypersensitivity reactions with cephalosporins is lower compared to the penicillin group [6].

Although skin testing is a highly sensitive test, it is also associated with false positives. Common errors that occur while performing an intradermal (ID) injection are: 1) Wrong site of injection: usually the sensitivity testing is performed intradermally at the flexor aspect of forearm; a subcutaneous injection might not give rise to a bleb formation; 2) Wrong dose: overdose/higher concentrations of the test dose being administered can result in faulty test; 3) Wrong interpretation: appearance of a wheal of >3mm is considered positive; 4) Wrong needle size: a needle size of 25-27 gauge needle is used for performing the ID test; 5) injecting an unsterile solution; 6) splash reactions caused by air injections; 7) intracutaneous bleeding sites could be mistaken as a positive reaction; 8) multiple tests performed at the same site might induce systemic reactions; 9) concomitant administration of drugs such as alpha and beta blockers can itself lead to an exaggerated ID test; 10) expertise of the person performing the test is also important [7].

Some diagnostic tools used in the detection are:

1. In vivo tests like:skin prick test, intradermal test, oral drug provocation test and patch test;
2. Ex vivo tests like: lymphocyte transformation test, drug specific IgE tests that include: radioallergosorbent assay, enzyme linked immunosorbent assay and fluoroenzyme immunoassay [8].

A study conducted by Yoon S A et al., concluded that routine skin testing with a cephalosporin before its administration is not useful for predicting immediate hypersensitivity because of the extremely

low sensitivity and Positive Predictive Value (PPV) of the skin test [9]. Several in vivo studies including measuring the degree of basophil activation to specific allergens and identifying specific IgE have been proposed as alternatives to the skin test. As there are no alternative practical diagnostic tool for predicting immediate hypersensitivity to cephalosporins it is therefore, necessary to investigate adverse drug reactions. Drug induced hypersensitivity reactions are usually described according to the modified Ring and Messmer 4-step grading scale [10].

The American College of Obstetricians and Gynaecologists and the Centers for Disease Control and Prevention have developed strategies for the prevention of neonatal group B Streptococcus infection during labour. One such strategy is to administer antibiotics in labour to all women with prolonged rupture of membranes, pre-term labour, pyrexia during labour or any indication for LSCS [10,11]. The clinical frequency of antibiotic associated hypersensitivity reactions during pregnancy is very low. The typical offending agents in a pregnant female include beta lactam antibiotics, latex, succinylcholine, laminaria and insect stings [11].

Risk factors associated with development of such symptoms could be:

1. Patient related factors such as:

   Age (young/middle aged are more prone>>infants/elderly), Gender (Women>>Men), Genetic polymorphisms, viral infections (human immunodeficiency virus, herpes infections) and previous reactions to drugs/diseases such as presence of asthma, chronic obstructive pulmonary disease, pregnancy, cardiovascular diseases, allergic rhinitis, eczema and mastocytosis [12].

2. Drug related factors such as:

   High molecular weight compounds and hapten forming drugs are more immunogenic, Route of administration (topical>intravenous/intramuscular>oral) and dose of drug administration (frequent exposure to drugs/prolonged> single dose [13].

Drugs that interfere with Drug sensitivity testing:

Certain drugs can suppress an antibiotic susceptibility testing. They are: H1- antihistamines, imipramine, phenothiazines, dopamine, clonidine, monteleukast and corticosteroids.

Also presence of certain diseases like: eczema, urticaria and infectious diseases like leprosy can result in a false positive test [14].

Management of Hypersensitivity reactions:

Mild-moderate hypersensitivity reactions are managed by antihistamines and corticosteroids. Severe hypersensitivity reactions like anaphylactic shock are usually managed by oxygen therapy, intravenous fluids, vasopressors such as corticosteroids, adrenaline and chlorpheniramine [15].

In case 1: patient is a 36-year-old gravida 2 who developed Grade 1 hypersensitivity reaction according to modified Ring and Messmer 4-step grading scale [10], in the form of urticarial rash and 2 mm wheals over the injected site, left shoulder and chest associated with itching within 30 minutes. Her vitals were stable and probably risk factors such as middle aged female, pregnancy and comorbidities like hypertension could have predisposed her to an exaggerated response to the test dose. However, she was not on any drugs which could have interfered with the ID test nor did she have any previous history of allergies. There were no maternal or foetal mortality and reactions subsided within a day.

In case 2: patient is a 34-year-old gravida 2 who developed Grade 1 hypersensitivity reaction according to modified Ring and Messmer four step grading scale [10], in the form of facial erythema, itching over the face, neck and arms within one hour. Her risk factors could have been her age, gender(middle aged pregnant female) and probably she would have been exposed to same/similar class of drugs in her previous pregnancy (details of which are not known). However, she had no comorbidities and no history of allergies. Hypersensitivity reactions subsided in a day.

In case 3: patient is again a middle aged gravida 5 who developed Grade 1 reactions [10] in the form of rashes all over the face with redness over the injection site, within 10 minutes. In this patient, she could have been exposed to the similar antigen previously during her past pregnancy, which could have been a risk factor for developing a reaction in the present pregnancy. However, there were no past history of allergies and patient recovered within a day.

In case 4: patient is a 57-year-old female patient with associated comorbidities (like carcinoma stomach), developed Grade 1 reaction [10] in the form of erythematous macular rashes over the right forearm and arm along with urticarial within 15 minutes. Her vitals were stable, and she recovered on treatment using anti-histamines and corticosteroids within a day.

In case 5: patient is a 48-year-old male with hypertension. He developed a Grade 2 hypersensitivity reaction in the form of an impending angioedema within half an hour [10]. The presence of comorbities, frequent administration of drugs could be some of the risk factors in this case. Concomitant intake of an alpha blocker could have resulted in a false positive test in this case as well. However, promt management of the case did not result in a fatal reaction and patient improved within a day.

In all our cases, an intradermal test was performed using a 27 gauge, injected over the flexor aspect of the forearm at an angle of 5-15° using a diluted sterile solution of the test drug and appearance of a wheal of >3mm within 20 minutes was considered positive along with other signs and symptoms of hypersensitivity reactions. In all our cases an in vivo intradermal skin test was performed as it is the easiest and more sensitive compared to the other in vivo tests. There were no drug interactions and no errors in any of our above mentioned cases. All the above hypersensitivity reactions were managed appropriately according to the standard protocol and hence there was no mortality.

Causality assessment was done as per Naranjo's scale and a probable causal relationship was ascribed to all the five cases [16]. It was also found that the adverse drug reaction was of moderate severity and was not preventable as per Hartwig and Siegel severity and Thornton's scale respectively [17,18].

CONCLUSION

Ceftriaxone is a commonly used antibiotic in both inpatient and outpatient department but have multiple potential adverse events. Clinicians should be aware of the possibility of anaphylaxis occurring with the test dose of ceftriaxone, especially because such a reaction could go unnoticed in patients with life-threatening infections and unstable vital signs. Hence, it is important to recognize it rapidly and treat it effectively.

REFERENCES

[1] Lee SH, Kim MH, Lee K, Jo EJ, Park HK. Hypersensitivity pneumonitis caused by cephalosporins with identical R1 side chains. Allergy, asthma & immunology research. 2015;7:518-22.
[2] Kim MH, Lee JM. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Allergy, asthma & immunology research. 2014;6:485-95.
[3] Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clinical Reviews in Allergy & Immunology. 2013;45:131-42.
[4] Adhikari A, Saha A, Ray M, Bhowal T, Ganguly A, Das AK. Ceftriaxone related adverse drug reactions in children in a tertiary care hospital, Kolkata, West Bengal, India. Exploratory Animal Med Res. 2014;4:444-47.
[5] Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. Journal of clinical anaesthesia. 2001;13:561-64.
[6] Shrestha D, Dhakal AK, Shakya H, Shah SC, Shakya A. A report of near fatal ceftriaxone induced anaphylaxis in a child with review of literature. Nepal Med Coll J. 2013;15:84-86.

[7] Bhagwat AG, Saxena KN. Intraoperative anaphylaxis to inj ceftriaxone: Here we go again. Indian Journal of Anaesthesia. 2008;52(4):462-66.
[8] Rive CM, Bourke J, Phillips EJ. Testing for drug hypersensitivity syndromes. The Clinical Biochemist Reviews. 2013;34(1):15-38.
[9] Yoon SY, Park SY, Kim S, Lee T, Lee YS, Kwon HS, et al. Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge. Allergy. 2013;68(7):938–44.
[10] Hepner DL, Castells M, Mouton-Faivre C, Dewachter P. Anaphylaxis in the clinical setting of obstetric anaesthesia: a literature review. Anaesthesia & Analgesia. 2013;117:1357-67.
[11] Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. Annals of Allergy, Asthma & Immunology. 2010;104(1):55-59.
[12] Del Carpio-Orantes L, Azuara-Trujillo HA. Anaphylactic shock associated with ceftriaxone, case report and literature review. Rev Med Inst Mex Seguro Soc. 2015;53(6):736-41.
[13] Warrington R, Silviu-Dan F. Drug allergy. Allergy, Asthma & Clinical Immunology. 2011;7:S10.
[14] Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67:18-24.
[15] Khan R, Anastasakis E, Kadir RA. Anaphylactic reaction to ceftriaxone in labour. An emerging complication. Journal of Obstetrics and Gynaecology. 2008;28: 751-53.
[16] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions.Clin Pharmacol Ther. 1981;30(2):239- 45.
[17] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. American J Hosp Pharm. 1992;49(9):2229-32.
[18] Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27:538.

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