

Case Report



Ceftriaxone Induced Anaphylaxis Reaction Following Negative Intradermal Skin Tested Patient: A Rare Case Report

Sindhu Devada¹, Saini Bhawna^{2*}, Saini Sandeep³, Dhoot Dipesh Kumar⁴

1. MD, MBBS, Senior Resident, Department of Nephrology, AIIMS, Rishikesh, Uttarakhand, India.

2. MD, DNB, MBBS, Assistant Professor, Department of Pharmacology, Government Doon Medical College, Dehradun, Uttarakhand, India.

3. DM, MD, MBBS, Assistant Professor, Department of Nephrology, AIIMS, Rishikesh, Uttarakhand, India.

4. DM, MD, MBBS, Assistant Professor, Department of Nephrology, AIIMS, Rishikesh, Uttarakhand, India.

*Corresponding author's E-mail: bhanu.gsvm@gmail.com

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ABSTRACT

Anaphylaxis is a severe life-threatening reaction that may be associated with exposure to a variety of drug classes. β -lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are most common classes of drugs causing anaphylaxis. Intradermal skin test (IST) is required in absence of previous history of allergy to antibiotics. In spite of negative intradermal skin testing, our patient had severe anaphylactic reaction after ceftriaxone administration but was managed successfully. This case report reflects the limitations of screening test done preoperatively for the diagnosis of sensitization to ceftriaxone antibiotic drug.

Key Messages: Intradermal skin test is mandatory in all patients receiving first exposure of any new antibiotic drug. When a patient is negative after intradermal skin test, the drug should be given as slow intravenous infusion to prevent sudden and dreadful cardiovascular collapse.

Keywords: Anaphylaxis, Ceftriaxone, Causality assessment, Intradermal skin test.

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INTRODUCTION

According to WHO ICD-11 (2019), Anaphylaxis is defined as severe, life-threatening systemic hypersensitivity reaction. According to a recent study, estimated lifetime prevalence of anaphylaxis is 0.3–5.1%.¹ However, data on epidemiology of anaphylaxis is limited and under-reported. The most common classes of drugs causing anaphylaxis are antibiotics especially β -lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).² Antibiotic administration in a patient depends upon his clinical condition. In absence of previous history of allergy to antibiotics, Intradermal skin tests is required to find out substances responsible for an allergic reaction in patient.

Case History

A 59-year-old female presented to our hospital with chief complaints of facial puffiness, bipedal swelling & abdominal distension for past 7 months. She is a known case of hypertension from 2 years and taking Tab Ramipril 2.5 mg once a day. She has a past history of administration of NSAIDs for a duration of 1 week, 6 months before presentation. She was admitted for evaluation of

nephrotic range proteinuria. She developed in-hospital fever, burning micturition. USG-KUB showed features suggestive of cystitis. She didn't have any documented history of food and drug allergies previously. She was planned for empirical Ceftriaxone administration; hence skin sensitivity test was done. There was no reaction on skin sensitivity testing for ceftriaxone. She was started on Injection Ceftriaxone 1g intravenously. After 5 min of IV injection, she developed generalized itching, shortness of breath, stridor, fall in BP (57/33 mmHg) and SpO₂- 70%. She was diagnosed as a case of severe anaphylactic reaction. Administration of ceftriaxone injection was stopped immediately. She was managed by intramuscular injection of Adrenaline 0.5 ml (1:1000) along with intravenous administration of injection Pheniramine 45.5 mg (1 ampoule) and injection Hydrocortisone 100 mg with NS 500 ml fluid rush. Injection Adrenaline 1mg (1:10000 dilution) was administered by slow flow intravenously. She was nebulized by Salbutamol (2 respules) and Budesonide (1mg respule). Vitals were monitored every 10 minutes. Her vital signs started recovering within 30 minutes with blood pressure and pulse rate 160/80 mm Hg and 112/min respectively. Patient was kept under strict observation for next 24 hours. Within 12 hours of oxygen support and medication administration, she become hemodynamically stable and her fever resolved. She was discharge after two days and advised to take tablet Levofloxacin 750 mg once a day for 7 days.

Adverse drug reaction assessment tools

Causality assessment of the adverse drug reaction was Probable as per Naranjo scale (Table-1) and WHO-UMC



causality scales (Table-2). Severity of ADR was severe (level-5) as per Hartwig's severity assessment scale (Table-3). Preventability was established by Modified Schumock

and Thornton scale that revealed definitely preventable ADR (Table-4). The compiled analysis of ADR is available in Table-5.

Table 1: The Naranjo adverse drug reaction probability scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score				6

Score: ≥ 9 =definite ADR; 5-8=probable ADR; 1-4=possible ADR; 0=doubtful AD

Table 2: WHO-UMC causality scale

Causality term	Assessment criteria (all points should be reasonably compiled)	Case
Certain	<ul style="list-style-type: none"> Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon). Rechallenge satisfactory, if necessary. 	
Probable or likely	<ul style="list-style-type: none"> Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not required. 	✓
Possible	<ul style="list-style-type: none"> Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear. 	
Unlikely	<ul style="list-style-type: none"> Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations. 	
Conditional or unclassified	<ul style="list-style-type: none"> Event or laboratory test abnormality. More data for proper assessment needed. Additional data under examination 	
Unassessable or unclassifiable	<ul style="list-style-type: none"> Report suggesting an adverse reaction. Cannot be judged because information is insufficient or contradictory. Data cannot be supplemented or verified. 	

Table 3: Hartwig's severity assessment scale

Assessment criteria	Case	
Level 1	• An ADR occurred but required no change in treatment with the suspected drug	
Level 2	• The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. • No antidote or other treatment requirement was required. No increase in length of stay (LOS)	
Level 3	• The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. • AND/OR an Antidote or other treatment was required. No increase in length of stay (LOS)	
Level 4	• Any level 3 ADR which increases length of stay by at least 1 day (or) the ADR was the reason for admission	
Level 5	• Any level 4 ADR which requires intensive medical care	✓
Level 6	• The adverse reaction caused permanent harm to the patient	
Level 7	• The adverse reaction either directly or indirectly led to the death of the patient	

Mild=level 1 and 2; Moderate=level 3 and 4; Severe=5, 6 and 7

Table 4: ADR preventability assessment (Schumock and Thornton Preventability Scale)

Assessment criteria		
1. Was there a history of allergy or previous reactions to the drug?		Definitely preventable
2. Was the drug involved inappropriate for the patient's clinical condition?		
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?		
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?	✓	
5. Was there a known treatment for the adverse drug reaction?		Probably preventable
6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?		
7. Was a drug interaction involved in the ADR?		
8. Was poor compliance involved in the ADR?		Not preventable
9. Were preventative measures not prescribed or administered to the patient?		
10. If all above criteria not fulfilled		

Table 5: Analysis of the ADR

Types	Case
Causality- Naranjo	Probable
Causality- WHO-UMC	Probable or likely
Severity- Hartwig	Severe
Preventability-Schumock and Thornton	Definitely preventable

DISCUSSION

Ceftriaxone is a third-generation cephalosporin commonly used for treatment of various serious infections like bacterial meningitis, multidrug resistant typhoid, urinary tract infection, septicaemia. The incidence of ceftriaxone induced hypersensitivity reaction is 1-3%.³ Thus, Intradermal skin test is performed before administration of Ceftriaxone.

Intradermal skin test is sensitive, rapid and inexpensive however it is associated with higher false positive and false

negative results.⁴ Intradermal drug test results are false negative because of faulty techniques, concomitant medications, physiological state of patient and skin test device used. Reactivity of skin test is reduced after drug administration like H1 antihistamines, H2 receptor antagonists, topical glucocorticoids, anti-IgE antibody Omalizumab, Montelukast, Tricyclic antidepressants, topical calcineurin inhibitors, higher doses of methotrexate.⁵ Conversely, false-positive results can arise from certain diseases like eczema, urticaria and infectious diseases like leprosy.⁶ Cephalosporin skin test use



native molecules but on intravenous administration, it undergoes degradation and generate unique haptens or neo-antigens thus skin test can be false negative in patients those are hypersensitive to Ceftriaxone.⁷

In present case, patient was non-reactive for intradermal skin sensitivity test for Ceftriaxone antibiotic. After Ceftriaxone administration patient developed clinical features suggestive of anaphylaxis. A negative skin test result does not rule out the possibility of an immediate-type allergy reaction. Our finding is supported by published case reports of ceftriaxone induced adverse drug reactions like study done by Kumari et al and Hirachan et al.^{8,9}

CONCLUSION

Diagnosis of anaphylaxis is based on clinical history and skin testing which can also be misleading as both false positive and negative reports exist pertaining to the fallacies in the technique or the material. In present case, patient showed anaphylactic reaction to ceftriaxone administration even after showing negative intradermal skin testing but was managed successfully without any residual compromise. This case reflects the limitations of screening test done preoperatively for the diagnosis of sensitization to the drugs. Intradermal skin test is mandatory in all patients receiving first exposure of any new antibiotic drug. If a patient is negative after intradermal skin test, the antibiotic drug should be given as slow intravenous infusion to prevent sudden and dreadful cardiovascular collapse.

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