

A report of near fatal ceftriaxone induced anaphylaxis in a child with review of literature.

D Shrestha, AK Dhakal, H Shakya, C Shah and A Shakya

Department of Pediatrics, KIST Medical College, Imadol, Lalitpur, Nepal.

Corresponding author: Dr. Devendra Shrestha, Lecturer, Department of Pediatrics, KIST Medical College, Imadol, Lalitpur, Nepal; e-mail:devendra.shrestha@gmail.com

ABSTRACT

Ceftriaxone is a widely used antibiotic in pediatric clinical practice. Usually ceftriaxone is well tolerated and serious adverse effect like anaphylaxis is rare. We report a near fatal anaphylaxis reaction in a child after the first dose of intravenous ceftriaxone who revived successfully.

Key words: Anaphylaxis, Ceftriaxone.

INTRODUCTION

Ceftriaxone is a long acting, broad-spectrum, third generation cephalosporin group of antibiotic. Its bactericidal action is through cell wall synthesis inhibition and it exerts in-vitro activity against a wide range of Gram-negative and Gram-positive microorganisms. Intravenous ceftriaxone is generally well tolerated and used for the treatment of serious bacterial infections. Among the few adverse effects, hypersensitivity reactions are the most feared.¹ The incidence of severe allergic reactions related to ceftriaxone is 1-3%, and the incidence of anaphylaxis still lower at 0.1-0.0001%.² Despite the use of ceftriaxone for a wide variety of pediatric infections, there are only few cases reported in the literatures regarding near fatal ceftriaxone anaphylaxis^{3, 4} and fatal anaphylaxis in a neonate.⁵ Similarly, there are scarce reports regarding life threatening anaphylaxis even after negative skin test given during surgical prophylaxis.^{6, 7}

Herein we report a case of near fatal anaphylaxis after the first dose of ceftriaxone in a child admitted in KIST Medical College Teaching Hospital.

CASE REPORT

A nine year old male child presented to KIST Medical College Teaching Hospital with history of high grade fever associated with chills and rigor, and generalized headache for 3 days. This was associated with multiple episodes of non-bilious projectile vomiting. There was no history of seizure, altered sensorium, ear discharge and petechial rash. History of allergy, atopic disease and previous use of β -lactam antibiotics could not be elicited as the child was brought from an orphanage. On examination, he was ill looking but conscious and cooperative. His Glasgow coma scale was 15/15, temperature 100°F, Pulse 102/min, regular and of normal

volume, and BP was 100/60 mmHg. There was no pallor, icterus, cyanosis, clubbing and edema. There was neck rigidity and positive Kernig's sign. Rest of the systemic examination was unremarkable.

After drawing blood for culture and other laboratory investigations, ceftriaxone was given intravenously at the dose of 50 mg/kg/dose. Within 2-3 minutes of intravenous injection, he developed generalized maculopapular pruritic rashes all over body; his heart rate increased to 170/min, and peripheral pulses became feeble. Capillary refill time increased to 6 seconds and systolic blood pressure was 60 mmHg by palpatory method. He developed fever of 103°F and became unresponsive. His SpO₂ was 74% in room air and was immediately put on high flow oxygen via face mask. Inj. adrenaline 0.1ml/kg (1:10000) intravenously, Inj. hydrocortisone 5mg/kg intravenously, Inj. pheniramine 1mg/kg intravenously and Inj. ranitidine 1mg/kg intravenously were given along with two boluses of normal saline at the rate of 20ml/kg. Inj. adrenaline was repeated once at same dose. He was given tepid water sponging for the control of fever. Ceftriaxone was stopped and changed to Inj. chloramphenicol. After 30 minutes of aggressive treatment, he became responsive and was stabilized with pulse rate 114 /min, and BP 100/60 mmHg.

Laboratory investigations were as follows: PCV 38, TLC 8100/mm³ (N 67, L33), ESR 27 mm in 1 hour, platelet count 267000/mm³. Peripheral smear showed normocytic normochromic red cells. Urine analysis, renal function tests and liver function tests were within normal limits. Lumbar puncture for CSF analysis was planned to rule out intracranial infection but could not be done as patient's guardian refused to give consent. Blood culture was sterile after 72 hours.

After 36 hours of hospital admission, he developed bilateral swelling in parotid region with lifting of ear lobules. His fever subsided after this episode. There were no further episodes of vomiting, fever spikes and headache. The child improved remarkably. He was discharged after 7 days of hospital stay with a clinical diagnosis of mumps with aseptic meningitis and a near fatal anaphylaxis to ceftriaxone. He was advised to inform about this incident of ceftriaxone related serious adverse reaction to treating medical professional in the future.

DISCUSSION

Anaphylaxis is a Type I hypersensitivity reaction. It is an IgE mediated reaction also known as an allergic and/or immediate hypersensitivity reaction.^{8,9} This usually occurs within 1 hour of exposure and clinically manifests as urticaria, angioedema, bronchospasm, hypotension and/or anaphylaxis.⁹ Most immediate reactions due to ceftriaxone are IgE mediated.¹⁰ However in some patients, these reactions could be due to mast cell degranulation where IgE against antigen may not be detectable.³

Anaphylaxis is an acute, life threatening reaction which is often associated with dyspnea, angioedema and hypotension, resulting from the release of preformed, newly sensitized bioactive mediators from mast cells and basophils. Anaphylaxis is a medical emergency and usually requires active and prompt resuscitative measures such as airway management, supplemental oxygen, adrenaline, intravenous fluid boluses along with steroids and antihistamines as adjunctive therapy.

The incidence of severe allergic reactions of ceftriaxone is reported to be 1-3% when given to treat infections.² Some authors have even described intraoperative anaphylaxis to ceftriaxone which occurred despite the negative intradermal skin testing to ceftriaxone done one day preoperatively.^{6,7}

Prior skin testing with ceftriaxone was not done in the present case and the role of prior skin testing in predicting allergic reaction is still debatable.^{9,11} The diagnosis of ceftriaxone induced anaphylaxis was made in our case on the basis of typical features of an anaphylactic episode immediately following the intravenous injection of ceftriaxone. The etiological dilemmas due to other possible causes like aspiration or septic shock was also ruled out as the child was hemodynamically stable and fully conscious prior to the intravenous ceftriaxone administration. The casual association to the drug reaction was established using Naranjo ADR probability scale¹², in which the score was 6, suggesting a "probable" relationship of the

reaction with the drug. However, serum IgE level and serum tryptase level estimation could not be done due to lack of facility and we did not perform further challenge with ceftriaxone in this patient. The mechanism of anaphylaxis in our patient may be IgE-dependent, however it is difficult to explain since there was no history of previous exposure to cephalosporin group of antibiotics or penicillin, though the history was not reliable. A similar report of anaphylaxis was reported in a five year child within minutes of first dose of ceftriaxone without prior exposure to cephalosporins.³

Unlike for penicillins, skin testing for cephalosporins is not standardized¹³ and there is no skin test that can reliably predict whether a patient will manifest an allergic reaction to ceftriaxone.¹¹ Cephalosporin skin tests use native molecules, but cephalosporins undergo degradation and lose their ring structure and generate unique haptens or neoantigens making these tests clinically irrelevant.⁹ Also the detection of IgE antibody to penicillin or cephalosporins or of cross-reactive IgE antibody does not predict a definite clinical reaction.⁹

It is also difficult to predict reliably the allergic reactions to cephalosporin after penicillin skin sensitivity test unless the side chain of the penicillin or ampicillin reagent is similar to the cephalosporin side chain being tested and cross reactivity between penicillin and third generation cephalosporins is significantly less.⁹ The frequency of cephalosporin allergy in persons allergic to penicillin decreases as cephalosporin family expands from first generation to third generation.^{9,14}

A patient who has an allergic reaction to a specific cephalosporin probably should not receive that cephalosporin group again. Cross reaction between cephalosporins do occur but at a lower rate.¹⁵ Cephalosporins sharing a similar 7-position (cefotaxime, ceftriaxone and cefipime, cefaclor and cefadroxil) or 3-position side chain (cephalexin and cefadroxil, cefotaxime and cephalothin) are more likely to cross-react with each other.¹⁴ The risk of a reaction with different groups of cephalosporin is very low to nonexistent if the side chains of the two drugs are dissimilar.

The question now raised is whether anaphylaxis to ceftriaxone can be prevented or not. The most important risk factor for allergy to cephalosporins is a history of allergy to penicillin or cephalosporins which increases the risk by eight times.² Detailed history regarding previous antibiotic allergy should include full description of the symptoms such as urticaria, pruritus, angioedema, or respiratory difficulties, severity of reaction as well as the timing of reaction after drug therapy. The positive

and negative predictive values of skin testing results for cephalosporins are not well established.^{11,12} A negative skin test to cephalosporin does not rule out the presence of drug specific IgE antibodies.¹³ On the other hand presence of IgE antibodies to penicillins and cephalosporins is predictive of possible subsequent immediate, IgE-mediated allergic hypersensitivity reactions, but many patients with detectable IgE antibodies do not display a clinical allergic reaction.⁹ Hence the role of both testing for IgE antibody to cephalosporin or penicillin and skin testing prior to administration are still dubious. Test dosing with titrated doses is an option but is still not flawless.² Thus it is really difficult to predict anaphylaxis to cephalosporin and strict vigilance and preparedness is mandatory.

In patients with history of an immediate type reaction to cephalosporin, cephalosporins with similar R-group side chains should be avoided. Treatment with cephalosporins with dissimilar side chains may be considered, but the first dose should be given via graded challenge or induction of drug tolerance, depending on the severity of the previous reaction.¹³

Although the possibility of development of anaphylaxis is very low, deaths following cephalosporin have been reported.^{2,5,6} Anaphylaxis to ceftriaxone is unpredictable and as it is widely used in clinical practice, clinicians should be aware of this potentially life threatening complication which can occur even after first dose and should be vigilant on recognizing anaphylaxis and provide prompt treatment accordingly.

REFERENCES

- Petri WA. Penicillins, cephalosporins, and other β -lactam antibiotics. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's the pharmacologic basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006. p. 1127-54.
- Kelkar PS, Li JT. Cephalosporin allergy. *New Eng J Med* 2001;345(11):804-9.
- Ernst MR, van Dijken PJ, Kabel PJ, Draaisma JM. Anaphylaxis after first exposure to ceftriaxone. *Acta Paediatr* 2002;9(3):355-6.
- Arslanlökylü AE, Kuyucu S, Balci S, Usta Y. Anaphylaxis after the first dose of ceftriaxone injection. *Turk Arch Ped* 2011;46:79-80.
- Baumgartner-Bonnevay C, Choquet-Kastylevsky G, Putet G, Bleyzac N, Vial T, Descotes J. Anaphylactic shock associated with ceftriaxone therapy in a newborn. *Arch Pediatr* 2002;9(10):1050-2.
- Kumar P, Girdhar KK, Anand R, Khera G. Life threatening anaphylaxis to intravenous ceftriaxone after negative skin test. *The Indian Anaesthetists' Forum* [serial online]. 2005 [cited 2012 Dec 17];6(2):1-6. Available from: URL: www.theiaforum.org
- Bhagwat AG, Saxena KN. Intraoperative anaphylaxis to injection ceftriaxone: Here we go again. *Indian J Anesth* 2008;52(4):462-6.
- Fisher M, Sage D. Allergic Reactions. In: Healy TEJ, Knight PR, editors. Wylie and Churchill- Davidson's; A practice of Anaesthesia. 7th ed. London: Arnold; 2003. p. 401-12.
- Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 2005;115(4):1048-57.
- Romano A, Gaeta F, Valluzzi RL, Alonzi C, Viola M, Bousquet PJ. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics* 2008;122(3):521-4.
- Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross reactivity to cephalosporin among patients allergic to penicillins. *Clin Exp Allergy* 2001;31(3):438-43.
- 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.
- Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105(4):259-73.
- Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. *J Fam Pract* 2006;55(2):106-12.
- Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reaction to beta lactam antibiotics. *Ann Intern Med* 1987;107(2):204-15.