

Fatal Anaphylactic Shock Ceftriaxone-Induced in a 4-Year-Old Child

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Abstract: One of the most used cephalosporin in clinical practice is ceftriaxone. Anaphylaxis due to the administration of ceftriaxone is considered a rare event. Here, we report a case of fatal anaphylactic shock after the administration of ceftriaxone in a child who had tolerated the drug in past exposures. The allergic pathogenesis is sustained by the clinical data (short time between the inoculation of the drug and the onset of the symptoms; past exposure to the same molecule and probable sensitization) and the postmortem examination findings (polivisceral congestion and intense eosinophilia found in the histological examination).

Key Words: adverse drug reactions, ceftriaxone, cephalosporins, fatal anaphylaxis, drug allergy

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Cephalosporins, together with penicillins, are the most widely used antibiotics for the treatment of common infections.^{1,2} Among the antibiotics, cephalosporins have been shown to be the cause of severe allergic reactions approximately in 15% of cases. Cephalosporins, belonging to the β -lactams class, are the responsible drugs in 27% of these cases.³ Moreover, reports published since the 1990s indicate that the number of subjects primarily sensitized to cephalosporins were increasing.⁴

Hypersensitivity reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens, although the different epitopes have not been defined.⁵ The most common reactions to cephalosporins are maculopapular rashes and drug fever; urticaria is less frequent, and anaphylaxis is rare.^{6,7} Sometimes after an anaphylactic reaction, cardiovascular complications may occur, especially in subjects with underlying ischemic heart disease. Two cases of stress-induced cardiomyopathy after cephalosporin-induced anaphylaxis were described.^{8,9}

One of the most used cephalosporin in clinical practice is ceftriaxone. The frequency of hypersensitivity skin reactions to ceftriaxone is between 1% and 3%; anaphylaxis is still considered a rare event.⁷

The scientific publications regarding allergic reactions to ceftriaxone are mainly case reports.^{10–14} Among these, only 2 cases of anaphylaxis have been reported after single-dose ceftriaxone without previous exposure to ceftriaxone.^{11,13}

Here, we report a case of fatal anaphylactic shock after the administration of ceftriaxone in a child who had tolerated the drug in past exposures.

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CASE

We observed an interesting case of anaphylactic shock during a retrospective analysis about deaths subjected to legal procedure in Agrigento (Italy). A 4-year-old child, being in a moderate fever (37.5 °C) and exhibiting catarrhal cough and dyspnoea (described as difficulty in breathing without sternal retraction and stridor), about 5 to 6 hours after the beginning of symptoms was visited by a pediatrician who prescribed the administration of ceftriaxone and β -methasone and a local aerosolized therapy with the corticosteroid flunisolide and drops of the β -2-adrenergic agonist salbutamol (each drop contains 187.5 μ g of salbutamol). The local aerosolized therapy was not administered.

Administration of ceftriaxone was made about 12 hours after the beginning of symptoms. A few minutes after the injection of the drugs (a vial of β -methasone 1 mg and about three quarters of a vial of ceftriaxone corresponding to about 180 mg of the drug), the child became cyanotic and had loss of consciousness with the relaxation of the bladder sphincter, so the parents brought him to the local emergency medical service and later to the emergency room of the local hospital. Here, the child arrived already in cardiac arrest.

The child was not asthmatic or allergic but, as reported by the parents and in medical record drawn up by the pediatrician, had already suffered in the past from several episodes of bronchitis and had undergone previously the same therapy with ceftriaxone and bethametasone (the last time, a few months before) without showing signs of hypersensitivity.

Postmortem Examination

In the external examination of the corpse, pale skin and lips, subnails cyanosis in the fingers and toes were found. The right buttock was bearing the presence of the sign of the original site of inoculum of the drug.

The cadaveric dissection highlighted moderate pleural effusion, bilateral tonsillar hypertrophy, especially on the right, congestion and edema of epiglottis and congested laryngeal aditus with supraglottic space slightly reduced and subglottic space extremely reduced, congestion of the tracheal mucosa, paratracheal and parahilar lymph nodes hyperplasia. The cadaveric dissection allowed to put in evidence the absence of traumatic or pathologic encephalic lesions. A polivisceral congestion was also found, emerging in particular pulmonary congestion and edema, severe right ventricular dilatation and left ventricle contraction.

Histological Examination

The histological examination of small fragments extracted from the organs during autopsy and embedded in paraffin showed encephalus congestion and edema with the presence of eosinophil degranulation, intense inflammation of the upper airways with signs of chronic tonsillitis and laryngeal tracheitis, signs of acute bronchitis and mild bronchiolitis, reactive lymphoreticular hyperplasia of the lymph nodes associated with follicular hyperplasia of lymph laryngeal shares, and signs of renal pathosis and hepatic eosinophilic degranulation. The amount of inflammation could seem more than is expected in acute anaphylaxis; however, it is not rare to find in deaths occurring after anaphylactic reactions shock in bronchi the

evidence of mucosal oedema and inflammation together with eosinophilia.¹⁵ Histological findings help to clarify the death of the subject: an intense eosinophilia was found in blood, brain, heart, and liver, and this is a characteristic condition of the allergic reactions.

DISCUSSION

Immediate hypersensitivity reactions have been reported after the administration of a specific cephalosporin, usually after first exposure which has determined the sensitization or for the first time because of cross-reactions to other cephalosporins or β -lactams.¹⁹ Ceftriaxone, a third-generation semisynthetic cephalosporin antibiotic, is used for an ample variety of infectious diseases. Different types of adverse reactions are reported to be induced by ceftriaxone.

The occurrence of anaphylaxis is generally considered a very rare event; however, anaphylactic and anaphylactoid reactions to ceftriaxone are the most frequently severe reactions reported together with cardiac arrest, and the rate of such reactions is much higher than those which have been reported for penicillins.²⁰ Most immediate reactions to cephalosporins appear to be immunoglobulin E (IgE)-mediated. After penicillins, cephalosporins are the β -lactams that more often induce IgE-mediated reactions.²¹ Children are considered more susceptible to adverse reactions to medicines because of less well-developed drug-metabolizing capacity. In a study conducted in hospitalized Iranian children, ceftriaxone and rifampicin were the most frequently implicated antibiotics in observed adverse drug reactions. Because ceftriaxone can induce serious and potentially fatal adverse reactions, it has been suggested that rapid intravenous injection of the medicine, unnecessary administration of the drug, and administration of the drug to patients with a previous history of allergic reactions to cephalosporins or penicillins should be avoided to reduce the frequency of such reactions.²² The risk of anaphylaxis may be increased in subjects with a history of allergy to penicillins and is certainly increased in subjects with a history of allergic reaction to cephalosporins, also without no previous exposure to ceftriaxone or other cephalosporins, and IgE-dependent mechanism could be a possibility.¹¹ Cephalosporin IgE-mediated hypersensitivity may be a transient condition; for this reason, it has been suggested that allergologic examinations should be repeated in patients with negative initial allergologic work-ups, including challenges.²³

CONCLUSION

We described a case reporting death after ceftriaxone administration in a child affected by symptoms leading to the diagnosis of acute bronchitis. First of all, it is noteworthy that the choice of ceftriaxone is common but not the more appropriate prescription because in an outpatient setting, the first line no antibiotics or generally antibiotics are oral amoxicillin or amoxicillin and clavulanic acid are used. In our view, death was caused by anaphylactic shock resulting in acute cardiorespiratory failure after a severe systemic reaction to ceftriaxone with rapid progression to the exitus. The findings of pulmonary congestion and edema, compatible with cardiac arrest, support this hypothesis.¹⁶ Other possible cause of death is viral laryngotracheobronchitis that occasionally result in death in the infant age but we excluded it for the absence of hypoxic-ischemic encephalopathy.¹⁷ The allergic pathogenesis is sustained by the clinical data (short time between the inoculation of the drug and the onset of the symptoms; past exposure to the same molecule and probable sensitization) and the postmortem examination findings. According to the Naranjo algorithm¹⁸ (score 6 for this case), the causality relationship between the adverse reaction and the administration of the suspected drug has been considered as probable.

In conclusion, seen the presence of few cases in literature, especially in pediatric age, we have reported this case in order to warn

against the possible severe and fatal adverse reactions to ceftriaxone, an antibiotic drug with extremely common use.

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