Adverse reaction to ceftriaxone: how far can we go to exclude an allergy?

Abstract:

In the pediatric population, cephalosporins are one of the most often prescribed antibiotic groups. Currently, the European Network for Drug Allergy's (ENDA) standardized diagnostic techniques are widely used to diagnose beta lactam allergic reactions, which help physicians to confirm or exclude the allergy.

Here, we report a case of an incorrectly labeled child of allergy to ceftriaxone after presenting a reaction minutes after the administration of the first dose of ceftriaxone. The allergic pathogenesis was suspected based on the clinical data (brief interval between the drug injection and the appearance of symptoms). we performed skin tests, intradermal tests (IDT) for ceftriaxone, which turn out negatives, then we found an alternative drug for the patient to use by testing ceftazidime and amoxicillin and finally, since the symptoms weren't specific of an allergy reaction and more likely suggesting a vasovagal syncope, we pursued with an intravenous drug provocation test to ceftriaxone, those tests helped us to prove the innocence of ceftriaxone and enabled us to reassure the parents.

Doctors should be mindful of the risks associated with avoiding specific antibiotic classes, particularly beta lactams, which are the most frequently recommended first-line antibiotics for pediatric patients and whose exclusion may complicate the management of certain pathologies.Such an approach may increase the number of infections, have an influence on antimicrobial stewardship, and have negative health economic effects on the public, it is crucial to avoid identifying a child as allergic without first performing an appropriate diagnostic workup.

Key words:cephalosporin – ceftriaxone – allergy – skin test – drug provocation test

Introduction:

Drug hypersensitivity reactions are a significant public health concern, the majority of docum ented drug hypersensitivity responses in children are related to beta lactams, followed by non-steroidal anti-inflammatory medicines and non- beta lactam antibiotics [1].

Antibiotic allergy is often over-diagnosed in children, mostly because many physicians continue to diagnose drug allergies solely based on clinical characteristics, leading to the unjustified avoidance of suspected substances.

The following case report is the description of a falsely labeled allergic child to ceftriaxone based of a non-specific symptom occurred after the first dose of ceftriaxone.

Case presentation:

A seven-years-old girl, with a history of asthma controlled since the age of 6 years under inhaled corticosteroid therapy, and never presented any allergic reaction, was admitted to the pediatric department for an acute episode of lower respiratory tract infection and an asthma exacerbation. At admission, the physical findings were: fever, dyspnea, oxygen saturation was 92%, wheezing with unilateral left crackles rales and blood pressure at 90/60 mmHg.

Based on the clinical finding and a chest x-ray that showed an opacity in the left lower lobe, the enfant had an asthma exacerbation and an acute probably bacterial episode of lower respiratory tract infection. Nebulized salbutamol and systemic corticosteroids were immediately administered, ceftriaxone was given intravenously at a dose of 50 mg/kg. During the injection the child felt dizzy, had nausea and became pale before she fainted for a couple of minutes. The heart rate and blood pressure dropped. The child didn't present any cutaneous signs such as urticaria. An intramuscular injection of 0.01 mg/kg of epinephrine was administered immediately along with 20cc/kg of saline. Within five minutes the circulation was restored. At that time tryptase test wasn't available in the hospital, so the child was labeled allergic to ceftriaxone, Josamycin was given instead for 14 days. The patient was discharged after full recovery.

For further analysis, five months later, the patient was referred to the division of pediatric immunoallergology and infectious Diseases. At first, we performed skin tests and intradermal tests (IDT) for ceftriaxone, then in order to provide a valid alternative to treat the most common pediatric infections, amoxicillin being among the first-choice antibiotic treatments in children, and ceftazidime were also tested.

The prick test and intradermal test were negatives for the three antibiotics as shown in table 1.

Table 1 : Skin prick and intradermal skin tests

Tested antibiotic	Skin prick test (mm)	Intradermal skin test (mm/mm)
Negative control	2	
Positive control	4	
Amoxicillin: 0,25mg	2	5 /5

Amoxicillin: 2,5 mg	2	5 /5
Amoxicillin: 25mg	2	5 /5
Ceftazidime: 0,025 mg	2	3 /3
Ceftazidime: 0,25 mg	2	3 /3
Ceftazidime: 2,5 mg	2	3 /3
Ceftriaxone: 0,025mg	2	4 /4
Ceftriaxone: 0,25mg	2	4 /4
Ceftriaxone: 2,5mg	2	4 /4

We did an oral drug provocation testing by administering gradually increasing doses each 20 minutes of amoxicillin with a total cumulative dose of 80mg/kg (1800mg), then we tested an intravenous drug provocation testing of ceftazidime with a total cumulative dose of 2000 mg, the patient didn't present any allergic reaction to both tests. (as shown in table 2)

The clinical manifestations weren't clear enough to suspect an anaphylaxis, so we pursued with a drug provocation testing (DPT) to ceftriaxone with a total cumulative dose of 1000 mg (table 2), the patient didn't present any allergic reaction.

Table 2: Sequence of Increasing DosesDuring Drug Provocation Tests

Drug	Drug class	Doses increasing/20 minutes	Route	Total cumulative dose
Amoxicillin	Penicillin	10mg, 20mg, 40mg, 80mg, 160mg, 320mg, 640mg, 1200mg	Oral	1800mg
Ceftazidime	Cephalosporin	20mg, 200mg, 1780mg	Intravenous	2000 mg
Ceftriaxone	Cephalosporin	10mg,110mg,890mg	Intravenous	1000 mg

Discussion:

Many studies on pediatric population revealed that only a small proportion of reported cases had their allergy confirmed. [2] Labeling children allergic to antibiotics have resulted in the widespread use of alternative antibiotics, which are typically more expensive, broad-spectrum, and occasionally less effective. [3]

Clinicians should understand the risks of forgoing some antibiotic classes, particularly when they are first-line treatments and an allergy diagnosis has not been properly made.An approach like this may result in an increase in infections caused byantibiotic-resistant species, such as Clostridioidesdifficile, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant enterococcus (VRE). [3]

The diagnosis of cephalosporin allergy is similar to evaluation of other drug-allergic patients, a careful history is mandatory to determine the optimal diagnostic testing strategy. Diagnostic tests differ between those with immediate versus delayed reactions, in our case the reaction was immediate. The international EAACI-ENDA recommendations [4], taking a standardized

clinical history, doing skin prick tests followed by intradermal tests, and if the skin tests were negative provocation testis recommended.

When an allergic reaction is suspected, the EAACI task force suggests measuring serum tryptase thirty minutes to two hours after the start of the reaction, and baseline tryptase at least 24 hours after complete resolution of symptoms, to support diagnosing anaphylaxis retrospectively [5]. In our case it wasn't available at the hospital.

Our patient presented a reduced blood pressure associated to a syncope minutes after the administration of the first dose of ceftriaxone, which led the physician to suspect an allergic reaction to ceftriaxone, however the fact that her symptoms weren't specific of an allergic reaction (no urticaria nor pruritus) and that measuring serum tryptase wasn't an option, the diagnosis couldn't be confirmed.

Prick test and intradermal test were both negative for ceftriaxone.

In our practice the most commonlyused antibiotics for the pediatric population are ceftazidime and amoxicillin, that is the reason why we chose to test those antibiotics as an alternative for our patient.

According to a small number of clinical challenge investigations, patients allergic to one cephalosporin can tolerate other cephalosporins with different R1 side chains. [6] Cefuroxime, ceftriaxone, cefotaxime, and cefodizime share a methoxyimino group in their R1 side chains[7,8], and ceftazidime has an R1 side chain that is slightly different from those of the aforementioned cephalosporins, the ceftazidime R1 side chain has an alkoxyimino group that has greater steric hindrance than the methoxyimino moiety and therefore would not be expected to be recognized by the same IgE molecules [7] .

Prick test, intradermal test and drug provocation test for ceftazidime were all negative for our patient.

We also tested amoxicillin, even though a cross reactivity between ceftriaxone and amoxicillin is unlikely possible, considering that ceftriaxone and amoxicillin do not have the same side chain. [9]

Although the clinical probability of a drug allergy was low,giving that the symptoms were non-specific of an allergy and were more likely vagal symptoms, we had to prove the innocence of the drug, so we pursued with drug provocation test to ceftriaxone, which turned out negative which enabled us to reassure our patient's parents.

The drug provocation tests are widely regardedas the "gold standard "to confirm the diagnosis of hypersensitivity to a certain drug, as it can replicate not only the hypersensitivity symptoms, but also any other adverse clinical manifestation, regardless of the mechanism. [10]

CONCLUSION:

The majority of adverse events in children are likely considered allergic, after a thorough allergy workup, only a small proportion of the suspected reactions are confirmed. A proper diagnostic workup is necessary to confirm the diagnosis before labeling a child as allergic. Physicians should be aware of the danger of incorrectly labeling a child as allergic specially to antibiotics and should refer those patients to an allergy specialist foranappropriateassessment and diagnosis.

Ethical Approval:

As per international standard or university standards written ethical approval has been collected and preserved by the author(s).

Consent

As per international standards, parental written consent has been collected and preserved by the author(s).

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