

Cefaclor anaphylaxis in children

E. Novembre, F. Mori, N. Pucci, R. Bernardini,
A. Romano*

Key words: cefaclor anaphylaxis; children; graded challenge; intradermal tests; skin prick tests.

Immediate hypersensitivity reactions to β -lactam antibiotics are not uncommon in children (1, 2). They are usually induced by an IgE-mediated pathogenic mechanism, occur within the first hour after the last drug administration, and are manifested as urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis. In a study regarding 1170 children with immediate reactions to penicillins and cephalosporins (2), cefaclor was the cephalosporin that presented the highest frequency (29.2%) of positive reactions in both skin prick tests and challenges. Until a few years ago, however, anaphylaxis from cefaclor appeared to be incredibly rare in children, with only a case reported in 1999 by Grouhi et al. (3). In the last few years, nevertheless, numerous anaphylactic reactions to cefaclor have been reported in Italian children (4, 5). This has induced the AIFA (Agenzia Italiana del Farmaco – Italian Drug Agency) to publish an update concerning the safety of cefaclor use in children (4).

We studied all children ranging in age from 3 to 14 years with histories of

immediate reactions to β -lactams seen in the allergy unit of the Azienda Ospedaliero-Universitaria A. Meyer between January 1998 and December 2006. Thirteen (5.1%) of 253 had an anaphylactic reaction (8 to cefaclor, 2 to ceftriaxone, 2 to amoxicillin and 1 to benzyl-penicillin). Anaphylaxis was diagnosed according to the clinical criteria proposed by Sampson et al. (6).

With regard to the eight children with cefaclor-induced anaphylaxis, all experienced symptoms within 30 min after cefaclor ingestion. The mean age at the moment of anaphylaxis was 5 years and the mean time interval between the reaction and our tests was 6.2 months.

According to the European Network for Drug Allergy protocol (7), they underwent allergologic work-ups. The skin testing with penicilloyl-polylysine (PPL) and minor determinant mixture (MDM) was performed on the first day, as previously described (8). Amoxicillin and cefaclor were used on the second day: amoxicillin at concentrations of 2 and 20 mg/ml in normal saline for both prick and intradermal tests, cefaclor at concentrations of 2 and 50 mg/ml in normal saline for prick testing, and 2 mg/ml for intradermal one. We prepared cefaclor sterile solutions no more than 2 h before testing, using the powder obtained from a capsule, as previously described (9).

All of the above reagents were initially tested on volar forearm skin by the prick method at increasing concentrations and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 min later. When prick tests were negative, 0.02 ml of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 min after injections. Results were considered positive when an increase larger than 3 mm in the initial wheal diameter accompanied by erythema was present (8). Positive controls for prick

and intradermal tests were done with histamine (at 10 and 1 mg/ml, respectively). As a negative control for prick and intradermal tests, normal saline was used. Prick and intradermal tests with cefaclor were also administered to 20 healthy control children, ten of whom had previously tolerated cefaclor.

Assays (UniCAP™; Pharmacia Diagnostics AB, Milan, Italy) were performed for specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor. A positive result was defined as a value ≥ 0.35 kU/l. Blood samples were obtained when patients were evaluated and sera were kept at minus 20°C until assayed.

Control subjects showed no positive reactions to cefaclor skin tests. All the eight children displayed negative responses to skin tests with both PPL and MDM and positive ones to those with cefaclor; one child (no. 9) was positive to the intradermal test with amoxicillin at 20 mg/ml. Only two children had detectable serum specific IgE to cefaclor (Table 1). The seven subjects negative to amoxicillin underwent graded challenges with oral amoxicillin and tolerated them.

In the present study, cefaclor was the most frequent cause of β -lactam anaphylaxis in children, confirming the results of the aforesaid study by Romano et al. (5), in which cefaclor was responsible for 16 of the 30 anaphylactic reactions experienced by 43 children with immediate reactions to cephalosporins, followed by ceftriaxone, responsible for nine anaphylactic reactions. This can be explained by the fact that, after amoxicillin, cefaclor is the most frequently prescribed oral antibiotic in Italy (10). However, anaphylactic reactions to cefaclor in a Spanish child (11) and in a Korean adolescent (12) have recently been reported.

It is interesting to note that all the eight children of the present study displayed positive results in allergologic work-ups.

Table 1. Clinical characteristics and results of cefaclor allergologic work-ups

Patient (no.)	Age (years)	Symptoms	Latency (min)	Time (m)	SPT 2 mg/ml (w/e)	SPT 50 mg/ml (w/e)	ID 2 mg/ml (w/e)	UniCAP (kU/l)
1 (GA)	6	Labial-palpebral oedema, urticaria, dyspnoea, cyanosis, dysphonia	5	6	–	3/5	nd	1.89
2 (PM)	4	Giant urticaria, rhino-conjunctivitis, dyspnoea, collapse	1	3	–	9/25	nd	< 0.35
3 (DA)	6	Palpebral oedema, urticaria, hypotension	5	12	4/8	nd	nd	< 0.35
4 (SC)	3	Facial oedema, labial cyanosis, hypotension	5	5	–	4/8	nd	< 0.35
5 (MC)	5	Giant urticaria, facial oedema, dyspnoea	10	2	–	–	7/12	< 0.35
6 (GA)	5	Hand and feet itch, pallor, hypotension	20	4	–	6/15	nd	< 0.35
7 (VF)	3	Urticaria-angioedema, hypotonia, dyspnoea	5	15	–	3/5	nd	< 0.35
8 (BD)	9	Labial-palpebral oedema, urticaria shortness of breath, hypotension	30	5	–	–	11/25	1.10

Latency: time interval (minutes) between cefaclor intake and symptom onset; Time: time interval (months) between reaction and allergologic tests; SPT: skin prick tests; ID: intradermal tests; w/e: wheal/erythema; nd: not done.

In conclusion, anaphylactic reactions to cefaclor in children are not so rare as previously believed, especially in Italy. For this reason, cefaclor therapy in children should only be considered after a careful individual risk/benefit evaluation, as recently advised by the AIFA (4).

*Unità di Allergologia
 Complesso Integrato Columbus
 Via G. Moscati, 31
 00168 Rome
 Italy
 Tel: +39 06 3503782
 Fax: +39 06 3503235
 E-mail: antoninoromano@h-columbus.it

Accepted for publication 11 February 2009
 Allergy 2009

© 2009 John Wiley & Sons A/S
 DOI: 10.1111/j.1398-9995.2009.02043.x

References

- Romano A. Recognising antibacterial hypersensitivity in children. *Paediatr Drugs* 2000;**2**:101–112.
- Atanasković-Marković M, Ćirković Veličković T, Gavrović-Jankulović M, Vučković O, Nestorović B. Immediate allergic reactions to cephalosporins and penicillins and their cross-reactivity in children. *Pediatr Allergy Immunol* 2005;**16**:341–347.
- Grouhi M, Hummel D, Roifman CM. Anaphylactic reaction to oral cefaclor in a child. *Pediatrics* 1999;**103**:e50.
- Cefaclor: aggiornamento sulla sicurezza d'uso nei bambini. *Bollettino d'informazione sui farmaci (Bif)* 2007;**2**:74–75.
- Romano A, Gaeta F, Valluzzi RL, Alonzi C, Viola M, Bousquet JP. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics* 2008;**122**:521–527.
- Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Bránium A et al. Second Symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;**117**:391–397.
- Torres MJ, Blanca M, Fernández J, Romano A, de Weck A, Aberer W et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;**58**:961–972.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;**57**:45–51.
- Romano A, Guéant-Rodríguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP et al. Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy* 2005;**35**:1234–1242.
- Uso dei farmaci in Italia. Ministero della salute, <http://www.ministerosalute.it>.
- Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montañez MI et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006;**117**:404–410.
- Kim SH, Choi JH, Park HS. Heterogeneity of the IgE response to allergenic determinants of cefaclor in serum samples from patients with cefaclor-induced anaphylaxis. *Ann Allergy Asthma Immunol* 2008;**94**:700–704.