Cross-reactivity in IgE-mediated allergy to cefuroxime : focus on the R1 side chain

Cross-reactivity in IgE-mediated allergy to cefuroxime: focus on the R1-side chain

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Clinical implications box

Small differences in the R1 structure may account for the absence of cross-reactivity between cephalosporins. Unlike ceftriaxone, cefotaxime and cefepime, ceftazidime has a very low risk of cross-reactivity in IgE-mediated cefuroxime allergy.

To the editor,

Cephalosporin antibiotics can cause IgE-mediated drug hypersensitivity reactions (DHR) that occur immediately (<1 hour) and mostly present with urticaria and/or angioedema, bronchospasm and even anaphylaxis [1].

After penicillins, cephalosporins are the most important cause of beta-lactam-induced DHR.

For some time, it has been assumed that cross-reactivity among beta-lactam antibiotics related to the beta-lactam ring, common to all beta-lactams. Attached to the beta-lactam ring, cephalosporins have a 6-membered unstable dihydrothiazine ring and two side chains (R1 and R2). Nowadays, it is believed that cross-reactivity among cephalosporins is connected mainly with their R1-side chain structures [2]. Consequently, in finding safe alternative cephalosporins in cephalosporin-allergic patients it is recommended to test molecules with a dissimilar R1-side chain [3]. However, it is not excluded that small differences in R1-side chain structures might result in a lack of cross-reactivity.

This study aims at assessing the cross-reactivity between cefuroxime and other cephalosporins (i.e., ceftazidime, ceftriaxone, cefepime, and cefotaxime) that share similar side chains with it, as well as the tolerability of ceftazidime, in patients with a documented cefuroxime allergy.

This is a retrospective, observational study. Five patients (all female, median age 51.6 years) with histories of immediate DHR to cefuroxime and a positive cefuroxime skin test were included via the outpatients' clinics of Allergology of the Antwerp University Hospital between May 2011 and October 2018. The local ethics committee approved this study (B300201524055) and patients provided an informed consent in accordance with the Declaration of Helsinki.

Prick and intradermal testing with penicillin G, amoxicillin (plus clavulanic acid), amoxicillin, cefuroxime, ceftazidime, ceftriaxone, cefepime, and cefotaxime were performed according to the European Network for Drug Allergy (ENDA) guidelines [1,4]. The final concentrations were 10,000 IU/mL for penicillin G, 20 mg/mL for amoxicillin (plus clavulanic acid) and cefuroxime, and 2 mg/mL for ceftazidime, ceftriaxone, cefepime, and cefotaxime. The median time interval between the skin test cefuroxime and ceftazidime was 0.7 (range 0.3-3.9) months.

Total serum IgE and specific IgE (sIgE) to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor were measured using the ImmunoCAP system FEIA (Phadia Thermo Fisher Scientific, Uppsala, Sweden) with a technical detection limit for sIgE of 0.10 kUA/L.

Graded drug challenges (DC) were also performed administering therapeutic doses of amoxicillin (cumulative dose (CD) 1 g, orally), amoxicillin plus clavulanic acid (CD 875 mg plus 125 mg, orally) and ceftazidime (CD 1 g, intramuscularly), each on a different day, in patients with negative results in the allergy tests concerned. A 4-step protocol (1%, 10%, 25% and 100% of the maximum single unit dose (1000mg)) was applied. After the last dose, patients were kept under close observation for at least 2 hours. A DC was considered positive only when objective symptoms could be observed.

Clinical characteristics and results of diagnostic work-up are shown in Table 1. Skin testing for cephalosporins other than cefuroxime, was positive for ceftriaxone, cefepime and cefotaxime in 4/5, 0/2, and 0/1 patients, respectively. All 5 patients with negative skin testing with ceftazidime underwent an uneventful DC with ceftazidime.

Table E1 in this article's Online Repository, shows an overview of cross-reactivity to other cephalosporins in patients with an IgE-mediated cefuroxime allergy. Cross-reactivity between cefuroxime and other cephalosporins has been mostly studied using skin tests and rarely challenge tests have been performed in patients with a skin test negative for a cephalosporin

with a similar R1-side chain. Actually, cross-reactivity to ceftriaxone (34.5% (10/29)) and cefotaxime (62.1% (18/29)) has been found in a significant proportion of IgE-mediated cefuroxime allergic patients. To a lesser extent, cross-reactivity to cefepime (20% (2/10)) can also occur. All 29 patients had a negative skin test with ceftazidime. A DC with ceftazidime was only performed in 1 case and was negative. In our study, a negative ceftazidime skin test was followed by an uneventful drug challenge in all 5 patients demonstrating that cross-reactivity between cephalosporins may depend on small moieties within the R1 side chain. Cefuroxime, ceftriaxone, cefepime, and cefotaxime share a methoxyimino group in their, further not very similar, R1-side chains (Figure 1), providing a plausible explanation for the observed cross-reactivity between cefuroxime and these cephalosporins. In contrast, to the best of our knowledge, cross-reactivity to ceftazidime has never been observed in cefuroxime-allergic patients possibly because its R1 side chain does not have a methoxyimino group but instead has an alkoxyimino group (Figure 1) [2]. Whether these small structural differences in the R1-side chain absolutely eliminate the risk of cross-reactivity between cefuroxime and ceftazidime needs to be further elucidated in larger studies.

The main limitation of this study is that not all patients underwent a complete diagnostic work-up, especially for alternative cephalosporins. DC with ceftriaxone, cefepime, and cefotaxime were not performed because these cephalosporins all share a methoxyimino group with cefuroxime. However, the strength of this study is that, unlike in other studies [2, 5-7], negative skin testing for ceftazidime was systematically supplemented with a DC (that proved to be negative).

In conclusion, our finding reinforces the concept that cephalosporin hypersensitivity is not necessarily a class hypersensitivity. Moreover, our study shows that, although the R1-side chain accounts for most of the cases of cross-reactivity, small structural dissimilarities that are

not readily apparent when analyzing the R1 side chains in their entirety, might result in a lack of cross-reactivity and clinical tolerance. Therefore, in cephalosporin-allergic subjects, molecules with R1-side chains similar, but not identical, to those responsible for the index reaction should not be a priori excluded or administered using a drug desensitization protocol. In this connection, skin tests allow to detect fine structural differences among cephalosporins in allergic subjects. Moreover, in the present study, the negative predictive value of cephalosporin skin tests appears to be high as in a previous study [3], in which alternative cephalosporins, such as cefazolin, cefaclor, cefuroxime, ceftriaxone, and ceftibuten, found negative in skin testing were administered to cephalosporin-allergic patients. From a practical point of view, in patients with an IgE-mediated cefuroxime allergy who need ceftazidime, skin testing is helpful in predicting tolerance. However, as additional larger-scale studies are needed to further establish the negative predictive value of skin testing, we currently suggest a DC with ceftazidime.

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Figure/table legends

Figure 1: Overview of the chemical structure of cefuroxime, ceftazidime, ceftriaxone, cefepime and cefotaxime. The circles represent a methoxyimino group (full line) or an alkoxyimino group (dashed line).

Table 1: Clinical characteristics and results of diagnostic work-up in IgE-mediated cefuroxime allergic patients.

References

1. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 2009; 64:183-93.
2. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins. J Allergy Clin Immunol 2015; 136:685-91.e3.
3. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PA, Farooque S, et al. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy 2015; 45:300-27.
4. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013; 68:702-12.
5. Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Sanchez F, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol 2000; 106:1177-83.
6. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med 2004; 141:16-22.
7. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montanez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. J Allergy Clin Immunol 2006; 117:404-10.

Table 1: Clinical characteristics and results of diagnostic work-up in IgE-mediated cefuroxime allergic patients

Patient	Sex	Age (years)	Index reaction					Diagnostic delay (months)	tIgE	FEIA ImmunoCAP					Skin testing								Drug challenge		
			Culprit	Administration route	Dose	Delay reaction (hours)	Symptoms			PG	PV	Amp	AmX	Cefac	PG	AmC	AmX	CU	CZ	CT	CP	CX	AmC	AmX	CZ
1	F	53	CU	Oral	First	<1	Vomiting, dyspnoea, itch	5	70	<0.10	<0.10	<0.10	<0.10	<0.10	NP	NP	-	+ (IDT 0.2 mg/mL)	-	+ (IDT 0.2 mg/mL)	NP	NP	-	NP	-
2	F	70	CU	Oral	First	<1	Dyspnoea, nausea, angioedema, itch	3	610	<0.10	<0.10	0.48	0.1	NP	-	NP	-	+ (IDT 0.2 mg/mL)	-	+ (IDT 2 mg/mL)	-	NP	NP	-	-
3	F	32	CU	Oral	First	<1	Vomiting, diarrhoea, palpitations, urticaria, angioedema, dyspnoea	1	120	<0.10	<0.10	NP	NP	<0.10	-	NP	-	+ (SPT 20 mg/mL)	-	+ (IDT 0.2 mg/mL)	NP	NP	NP	NP	-
4	F	52	CU	Oral	First	<1	Dyspnoea, palpitations, dizziness	4	434	<0.10	<0.10	<0.10	<0.10	<0.10	NP	-	NP	+ (IDT 2 mg/mL)	-	-	-	-	-	NP	-
5	F	51	CU	Intravenous	First	<1	Hypotension, urticaria, bronchospasm	4	592	<0.10	0.10	0.38	0.12	0.12	-	-	NP	+ (IDT 20 mg /mL)	-	+ (IDT 2 mg/mL)	NP	NP	-	NP	-

AmC = amoxicillin clavulanic acid; Amp = ampicillin; AmX = amoxicillin; Cefac = cefaclor; CP = cefepime; CT = ceftriaxone; CU = cefuroxime; CX = cefotaxime; CZ = ceftazidime; F = female; IDT = intradermal test; NP = not performed; PG = penicillin G; PV = penicillin V; SPT = skin prick test; tIgE = total IgE; + = positive; - = negative

Table E1. Literature overview of cross-reactivity to other cephalosporins in IgE-mediated cefuroxime allergic patients

Reference	Subjects (N)*	Positive skin test			
		CZ	CT	CP	CX
Romano, 2000[1]	4	0/3	2/3	NP	2/3
Sanchez-Sancho, 2003[2]	2	0/2	0/2	NP	1/2
Romano, 2005[3]	5	0/5	3/5	NP	3/5
Antunez, 2006[4]	8	0/8	2/8	NP	4/8
Hasdenteufel, 2007[5]	1 (axetil)	0/1	1/1	1/1	1/1
Somech, 2009[6]	1	NP	NP	NP	NP
Varela Losada, 2009[7]	1	0/1**	1/1	0/1	1/1
Montannez, 2011[8]	5	0/5	0/5	0/5	2/5
Romano, 2015[9]	3 (2 axetil)	0/3	1/3	1/3	3/3
Tuyls, 2016[10]	1	0/1	0/1**	NP	1/1
Total	31	0/29	10/29	2/10	18/29

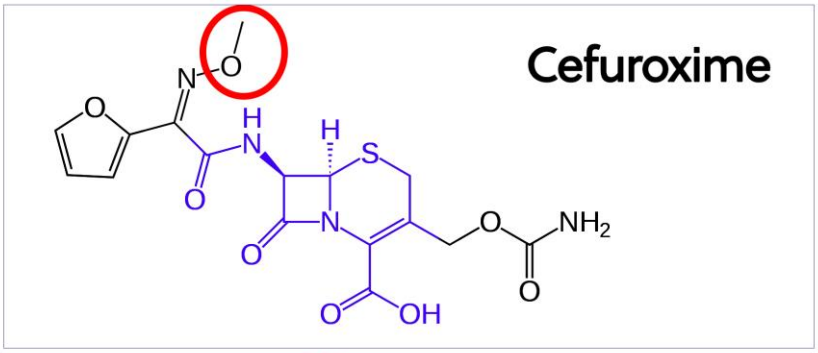
* Cefuroxime allergic patients based on a positive history of an immediate reaction to cefuroxime documented by a positive skin test with cefuroxime

** Negative skin testing was followed by a negative drug challenge. No other drug challenges were performed.

CZ = ceftazidime; CT = ceftriaxone; CP = cefepime; CX = cefotaxime; NP = not performed.

References

1. Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Sanchez F, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol 2000; 106:1177-83.
2. Sanchez-Sancho F, Perez-Inestrosa E, Suau R, Montanez MI, Mayorga C, Torres MJ, et al. Synthesis, characterization and immunochemical evaluation of cephalosporin antigenic determinants. J Mol Recognit 2003; 16:148-56.
3. Romano A, Gueant-Rodriguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP, et al. Diagnosing immediate reactions to cephalosporins. Clin Exp Allergy 2005; 35:1234-42.
4. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montanez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. J Allergy Clin Immunol 2006; 117:404-10.
5. Hasdenteufel F, Luyasu S, Renaudin JM, Trechot P, Kanny G. Anaphylactic shock associated with cefuroxime axetil: structure-activity relationships. Ann Pharmacother 2007; 41:1069-72.
6. Somech R, Weber EA, Lavi S. Evaluation of immediate allergic reactions to cephalosporins in non-penicillin-allergic patients. Int Arch Allergy Immunol 2009; 150:205-9.
7. Varela Losada S, Gonzalez de la Cuesta C, Alvarez-Eire MG, Gonzalez Gonzalez C. Immediate-type allergic reaction to cefuroxime: cross-reactivity with other cephalosporins, and good tolerance to ceftazidime. J Investig Allergol Clin Immunol 2009; 19:164-5.
8. Montannez MI, Mayorga C, Torres MJ, Ariza A, Blanca M, Perez-Inestrosa E. Synthetic approach to gain insight into antigenic determinants of cephalosporins: in vitro studies of chemical structure-IgE molecular recognition relationships. Chem Res Toxicol 2011; 24:706-17.
9. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins. J Allergy Clin Immunol 2015; 136:685-91.e3.
10. Tuyls S, Breynaert C, Schrijvers R. Subgroups in cephalosporin allergy, making a patient-tailored approach redundant? J Allergy Clin Immunol 2016; 137:331.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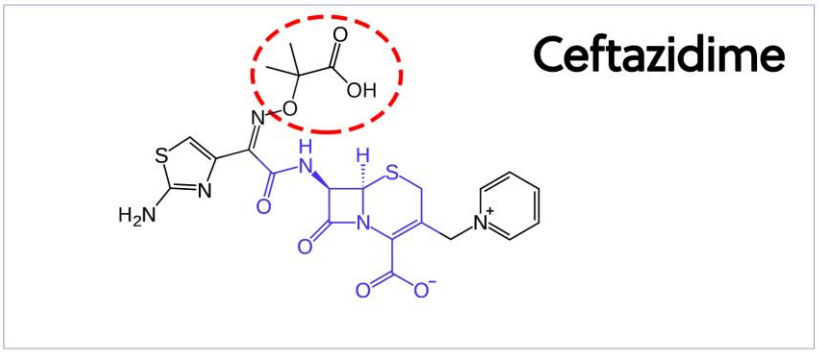
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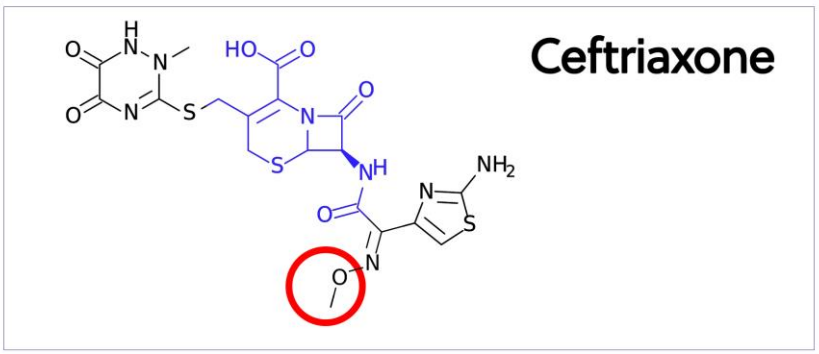
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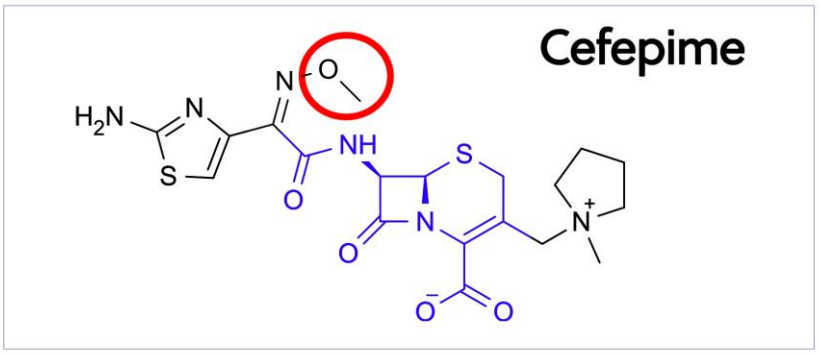
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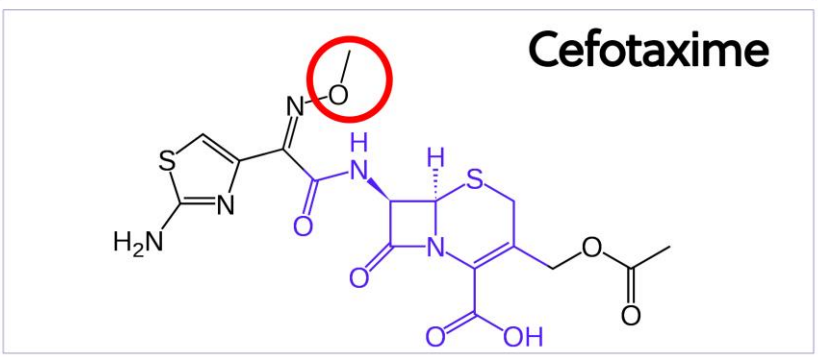
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