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Cefazolin hypersensitivity: towards optimized diagnosis

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Abbreviations:

SPT: skin prick test

IDR: intradermal test

CD: cumulative dose

PyG: penicilloyl G

PyV: penicilloyl V

APy: Ampicilloyl

CL: Cefaclor

PG: penicillin G

PPL: penicilloyl-polylysine

MDM: minor determinant mixture

AX: amoxicillin

AC: amoxicillin-clavulanic acid

AP: ampicillin

CU: cefuroxime

CR: ceftriaxone

CF: ceftazidime

AZ: aztreonam

IM: imipinem

ME: meropenem.

Conflict of interest

There are no known conflicts of interest for the authors.

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Highlight box

What is already known about this topic?

- Up to now the recommended maximum non-irritating concentration for skin testing with cefazolin is 2mg /mL. It seems that cefazolin hypersensitivity is not a class hypersensitivity.

What does this article add to our knowledge?

- Increasing cefazolin concentration for skin tests up to 20 mg/mL increases the sensitivity of the test without affecting its specificity.

How does this study impact current management guidelines?

- We recommend to use 20mg/mL as maximum non-irritating concentration in the diagnostic work up of immediate cefazolin hypersensitivity. This study confirms that cefazolin hypersensitivity is a selective allergy with good tolerance to other β-lactam antibiotics.

Abstract

Background: Correct diagnosis of cefazolin hypersensitivity is not straightforward, mainly because of the absence of in vitro tests and uncertainties concerning the optimal cefazolin concentration for skin testing. Cross-reactivity studies suggest cefazolin hypersensitivity to be a selective hypersensitivity.

Objective: The first objective was to confirm that the application of a higher than 2 mg/mL test concentration could increase skin test sensitivity. A second part aimed at investigating the cross-reactivity between cefazolin and other β-lactam antibiotics.

Methods: 66 patients referred to our clinic after experiencing perioperative anaphylaxis, and exposed to cefazolin, underwent skin testing with cefazolin up to 20 mg/mL. Patients exhibiting a positive skin test with cefazolin had a panel of skin tests with other β-lactams and, if indicated, graded drug challenges to study cross-reactivity.

Results: Increasing skin test concentration from the recommended 2 mg/mL to 20 mg/mL identified an additional 7/19 (27%) patients, who would otherwise have displayed negative skin testing. The concentration was proven non-irritating in 30 cefazolin exposed control individuals in which an alternative culprit for perioperative anaphylaxis was identified. Graded challenge testing, following negative skin testing, displayed that all patients tolerated alternative β-lactam antibiotics (i.e., amoxicillin, cephalosporins, monobactams, carbapenems). Of them, 11 individuals also tolerated an alternative cephalosporin, suggesting cefazolin hypersensitivity (generally) is a selective allergy.

Conclusions: Increasing cefazolin concentration for skin tests up to 20 mg/mL benefits the sensitivity of diagnosis. Furthermore, our data confirm that cefazolin hypersensitivity seems to be a selective allergy with good tolerance to other β-lactam antibiotics.

Introduction

Cefazolin, a first generation cephalosporin, is widely used for preoperative antibiotic prophylaxis [1, 2]. Some studies regarding perioperative anaphylaxis indicate that β-lactam antibiotics are a relevant cause of IgE-mediated hypersensitivity reactions, cefazolin being responsible for the majority of these reactions [3-7].

Although cefazolin hypersensitivity constitutes a potential life-threatening condition with serious consequences, correct diagnosis of cefazolin hypersensitivity is not straightforward for various reasons. First of all, drug provocation tests with this parenteral cephalosporin are hazardous and time consuming. Secondly, no reliable cefazolin-specific IgE antibody assay is available. Therefore, clinical suspicion of cefazolin hypersensitivity is generally confirmed with skin tests [8]. However, for the time being, skin testing with cephalosporins are not entirely standardized and optimal skin test concentrations remain to be established [8]. Actually, sensitivity, specificity and predictive values of this diagnostic method remain unknown, mainly as the maximal non-irritating skin test concentrations need to be established. To date, the European Network on Drug Allergy (ENDA) recommends a maximal non-irritating skin test concentration of 2 mg/mL for all the cephalosporins [9]. On the other hand, as reported in the same guidelines [9], there is evidence that, for several cephalosporins, skin test concentrations up to 20 mg/mL are probably also not irritant. As a matter of fact, for cefazolin a concentration up to 33 mg/mL has been described as being non-irritant in some studies [10-12].

The fact that cephalosporin hypersensitivity is not a class hypersensitivity has recently been reported in a series of patients by Romano et al. [12]. Regarding cefazolin, studies conducted up to now showed that IgE-mediated hypersensitivity towards cefazolin appears to be selective in the great majority of allergic subjects [12-17].

As a first objective of this study, we sought to confirm whether a test concentration higher than 2 mg/mL could increase the sensitivity of the skin tests, and add to the diagnosis in patients who would otherwise yield negative skin test responses. The second part of our study aimed at investigating the cross-reactivity between cefazolin and other β-lactam antibiotics.

Methods

Study population

During the period from January 2013 to December 2015 we evaluated 157 patients who were referred to our outpatients' clinic for diagnostic evaluation after experiencing a perioperative hypersensitivity reaction grade 1-3 according to the Brown criteria [18, 19]. Of them, 66 received cefazolin as a perioperative antibiotic prophylaxis. All these patients underwent the standardized protocol for all potential offenders of perioperative anaphylaxis [20]. Furthermore, all patients underwent skin testing with cefazolin as described below. Patients exhibiting a positive skin test with cefazolin had a panel of skin tests with other β-lactams and, if indicated, graded challenges with some of them.

Skin testing

Skin tests were performed on different days [21]. Firstly, minor determinant mixture ((MDM) consisting of sodium benzylpenicillin, benzylpenicilloic acid, and sodium benzylpenicilloate), penicilloyl-polylysine (PPL), and benzylpenicillin (BP); subsequently amoxicillin (clavulanic-acid) and cefazolin were tested. Finally, patients displaying a positive skin test towards cefazolin underwent skin tests with alternative β-lactams. We applied maximal skin test concentrations recommended by ENDA, except for cefazolin and cefuroxime [9]. For skin testing with penicillin reagents, the maximum non-irritating concentration was $5x10^{-5}$ mM/L for PPL, $2x10^{-2}$ mM/L for MDM, 10 000 UI/mL in normal saline for BP, and 20 mg/mL in normal saline for amoxicillin, ampicillin, and amoxicillin (20 mg/mL) + clavulanic acid (4 mg/mL). For cefazolin and cefuroxime, maximum non irritating concentrations were obtained by performing skin testing with 100 mg/mL and 20 mg/mL in normal saline in 10 healthy controls individuals [10, 12, 22]. As skin testing for cefazolin and cefuroxime using

100 mg/mL yielded irritative positive results in up to 7/10 healthy control individuals, for both drugs, a maximal concentration of 20 mg/mL was subsequently used to test cefazolin exposed patients. Skin testing with the monobactam aztreonam was performed at a concentration of 2 mg/mL, with imipenem-cilastatin at a concentration of 0.5 mg/mL for each component, and with meropenem at a concentration of 1 mg/mL in normal saline. All reagents were diluted no more than 2 hours before testing. Results were considered positive when wheal/flare equaled or exceeded 3/3 mm. IDTs were considered positive when the wheal/flare equaled or exceeded 5 mm.

Total and specific IgE measurement

In all patients total IgE and sIgE levels for the commercially available β-lactam determinants i.e. penicilloyl G, penicilloyl V, amoxicilloyl, ampicilloyl and cefaclor were quantified by FEIA ImmunoCAP system (ThermoFisher Scientific, Uppsala, Sweden). Results equalling or exceeding 0.35 kUA/L were considered positive.

Graded challenges

When indicated, a graded challenge up to a cumulative dose (CD) equalling or exceeding the therapeutic dose, was performed in order to study cross-reactivity and to identify a safe alternative β-lactam antibiotic for the future. Oral challenges were performed with amoxicillin (CD 901 mg), amoxicillin-clavulanic acid (CD 901 mg) and cefuroxime axetil (CD 661 mg). Intramuscular challenges were performed with aztreonam (CD 1 g) and ceftriaxone (CD 1 g).

Results

Skin testing

Figure 1 displays the results of the skin testing. In total, 66 cefazolin exposed patients who experienced a perioperative anaphylaxis underwent the standardized diagnostic protocol for all potential offenders. In 30 patients a cause other than cefazolin was found (e.g. curares, latex, chlorhexidine). These 30 patients received the maximal non irritating cefazolin skin testing up to 20 mg/mL. In all these individuals, skin testing with cefazolin was negative. These patients were considered as exposed control individuals. In contrast, 19 of the remaining 36 individuals exposed to cefazolin, in whom no other cause for perioperative anaphylaxis was found, displayed positive skin test responses to this cephalosporin. 12 patients had a positive intradermal test at a concentration up to 2 mg/mL, as recommended by current guidelines, and an additional 7 (27%) had a positive intradermal test at a ten-fold higher concentration of 20 mg/mL. In the remaining 17 patients, no causative agents responsible for the perioperative anaphylaxis could be identified (Fig. 1).

All the patients with an IgE-mediated hypersensitivity towards cefazolin displayed negative skin tests for a panel of β-lactam antibiotics as displayed in table 1.

Total and specific IgE measurement

Total and specific IgE results are displayed in table 1. Only one patient displayed a weak positive specific IgE toward penicilloyl V (0.36 kUA/L).

Graded challenges

Challenges with alternative β-lactams were performed in 16/19 patients (Table 1). Five patients were challenged with only amoxicillin or amoxicillin-clavulanic acid; 2 with only

cefuroxime axetil, whereas in 9 patients, controlled administrations of amoxicillin or amoxicillin-clavulanic-acid, as well as one or more cephalosporins and/or aztreonam were performed. All challenges were negative.

In 3/30 skin test negative patients a challenge test with cefazolin was negative.

Discussion

To our knowledge, this is the largest monocentric study about immediate perioperative hypersensitivity to cefazolin. It demonstrates that increasing cefazolin concentration for skin testing up to 20 mg/mL probably improves the sensitivity of the test without affecting its specificity. This observation is in line with previous studies [10, 12]. As a result, 7 additional patients could be identified as possibly cefazolin allergic who would otherwise have not been diagnosed because of negative skin testing. Moreover, in our series these additional patients represent almost one-third of the cefazolin allergic population. Hitherto, current guidelines [9, 23, 24] have recommended a maximal non-irritating concentration for all cephalosporins of 2 mg/mL. Therefore, we believe that the observation that a concentration of 20 mg/mL that allows to identify an additional 30% of patients is relevant, especially as this concentration was established by using a titrated skin test procedure. However, to really calculate the negative predictive value of the maximal non irritating skin test concentration for cefazolin one should perform challenge tests in patients displaying a negative skin test to 20 mg/mL. The main limitation of this study is that we did not challenge the majority of patients displaying a negative 20mg/mL intradermal test.

One could argue that increasing cefazolin concentration could entail a risk for false positive skin test results. Although the determination of the precise test accuracy (sensitivity/specificity) would require provocation tests in all patients including those with a positive skin test, such an approach cannot be justified and has been dissuaded for obvious reasons [25]. Therefore, as an alternative approach, it is common practice to identify non-irritating skin test concentrations, ideally by enrolling at least 20 control individuals [9]. We have followed these recommendation and have performed titrated skin testing up to 100

mg/mL that was found irritative, whereas 20 mg/mL did not trigger a skin test response in 30 exposed control individuals.

Previous cross-reactivity studies [12-17] demonstrated that cefazolin hypersensitivity is mainly a selective hypersensitivity, i.e., it does not involve cross-reactivity with other cephalosporins and/or penicillins. In effect, in these studies, the great majority, namely 20/22, of patients suffering from an IgE-mediated hypersensitivity to cefazolin displayed a pattern of selective response to it [12-17]. Our study of 19 cefazolin skin test-positive patients, confirms this data as no patient reacted to an alternative β-lactam antibiotic and none of the patients except one displayed positive results in the ImmunoCAP. Of them, 11 individuals tolerated alternative cephalosporins; specifically, 9 patients were able to tolerate cefuroxime axetil. In Belgium this is the only (second generation) cephalosporin available in oral formulation. The patient displaying positive specific IgE towards penicilloyl V with a specific/total IgE ratio of 0.0029 [25] tolerated an oral challenge with amoxicillin clavulanic acid pointing to a false positive IgE result [26].

Regarding evaluation of cross-reactivity, a limitation of this study is that, since some data was collected in retrospect, not all the patients received the same battery of skin testing and drug provocations with alternative β-lactams. These data confirm that in the majority of cases cefazolin hypersensitivity seems to be an isolated allergy with tolerance for alternative β-lactam antibiotics. This probably relates to the fact that cross-reactivity of cephalosporins is mainly determined by the R1 side-chain structure [12]. The R1 side-chain of cefazolin consists of a heterocycle *N*-methylthiodiazole structure [13] which is different to other cephalosporin R1 side chains [8, 12, 27].

In conclusion, our study demonstrates that diagnosis of cefazolin hypersensitivity benefits from a drug-specific intradermal test concentration up to 20 mg/mL. Furthermore, study of cross-reactivity reveals that, according to literature data, cefazolin hypersensitivity in the great majority of cases is a selective allergy with tolerance to other β-lactam antibiotics.

References

1. Unger NR, Stein BJ. Effectiveness of pre-operative cefazolin in obese patients. Surg Infect (Larchmt). 2014;15(4):412-6.
2. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. Surg Infect (Larchmt). 2013;14(1):73-156.
3. Dong S, Mertes P, Petitpain N, Hasdenteufel F, Malinovsky J, GERAP. Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). Minerva Anestesiol. 2012;78:868-79.
4. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia: a 10-year survey 1 at the University Hospital of Antwerp. P Belg Roy Acad Med. 2013;2:88-100.
5. Gonzalez-Estrada A, Pien LC, Zell K, Wang XF, Lang DM. Antibiotics are an important identifiable cause of perioperative anaphylaxis in the United States. J Allergy Clin Immunol Pract. 2015;3(1):101-5 e1.
6. Antunes J, Kochuyt AM, Ceuppens JL. Perioperative allergic reactions: experience in a Flemish referral centre. Allergol Immunopathol (Madr). 2014;42(4):348-54.
7. Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, et al. Allergic reactions during anesthesia at a large United States referral center. Anesth Analg. 2011;113(5):1202-12.
8. Kim M-H, Lee J-M. Diagnosis and Management of Immediate Hypersensitivity Reactions to Cephalosporins. Allergy Asthma Immunol Res. 2014;6(6):485-95.
9. 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(6):702-12.
10. Testi S, Severino M, Iorno M, Capretti S, Ermini G, Macchia D, et al. Nonirritating concentration for skin testing with cephalosporins. J Investig Allergol Clin Immunol. 2010;20(2):170-6.
11. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol. 2003;112(3):629-30.
12. 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(3):685-91.e3.
13. Pipet A, Veyrac G, Wessel F, Jolliet P, Magnan A, Demoly P, et al. A statement on cefazolin immediate hypersensitivity: data from a large database, and focus on the cross-reactivities. Clin Exp Allergy. 2011;41(11):1602-8.
14. Igea J, Fraj J, Davila I, Cuevas M, Cuesta J, Hinojosa M. Allergy to cefazolin: study of in vivo cross reactivity with other betalactams. Ann Allergy. 1992;68(8):515-9.
15. Weber EA. Cefazolin specific side chain hypersensitivity. J Allergy Clin Immunol. 1996;98(4):849-50.
16. Somech R, Weber EA, Lavi S. Evaluation of immediate allergic reactions to cephalosporins in non-penicillin-allergic patients. Int Arch Allergy Immunol. 2009;150(3):205-9.
17. Warrington RJ, McPhillips S. Independent anaphylaxis to cefazolin without allergy to other beta-lactam antibiotics J Allergy Clin Immunol. 1996;98(460-2).
18. Mertes PM, Malinovsky JM, Jouffroy F, Aberer W, Terreehorst I, Brockow K, et al. Reducing the Risk of Anaphylaxis During Anesthesia: 2011 Updated Guidelines for Clinical Practice. J Investig Allergol Clin Immunol. 2011;21(6):442-53.
19. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6.
20. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. Allergy. 2007;62(5):471-87.
21. 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(9):1234-42.

22. Romano A, Gaeta F, Valluzi RL, Caruso C, C. A, Viola M, et al. Diagnosing nonimmediate reactions to cephalosporin. J Allergy Clin Immunol. 2012;129(4):1166-9.
23. 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.
24. Dickson S, Salazar K. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clin Rev Allergy Immunol. 2013;45:131-42.
25. Vultaggio A, Virgili G, Gaeta F, Romano A, Maggi E, Matucci A. High serum beta-lactams specific/total IgE ratio is associated with immediate reactions to beta-lactams antibiotics. PLoS One. 2015;10(4):e0121857.
26. Johansson SG, Adedoyin J, Van Hage M, Grönneberg R, Nopp A. False-positive penicillin immunoassay: An unnoticed common problem. J Allergy Clin Immunol. 2013;132(1):235-7.
27. Baldo BA, Pham NH. Drug Allergy. Clinical Aspects, Diagnosis, Mechanisms, Structure-Activity Relationships. New York: Springer; 2013.

Legends of the figure and table

Fig 1. Flowchart displaying skin test results in patients and control individuals

Table 1. Allergologic test results of the 21 individuals with cefazolin allergy . *concentration at which the IDR with cefazolin was positive, TOT: total IgE, PyG: penicilloyl G, PyV: penicilloyl V, APy: Ampicilloyl, CL: Cefaclor, PF: penicillin G, PPL: penicilloyl-polylysine, MDM: minor determinant, AX: amoxicillin, AC: amoxicillin-clavulanic acid, AP: ampicillin, CU: cefuroxime, CR: ceftriaxone, CF: ceftazidime, AZ: aztreonam, IM: imipinem, ME: meropenem.