

CLINICAL PRACTICE

Cefalotin as antimicrobial prophylaxis in patients with known intraoperative anaphylaxis to cefazolin

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Abstract

Background: The most common trigger for intraoperative anaphylaxis in Western Australia for the period 2014–5 was an antibiotic used for surgical prophylaxis, cefazolin. In these patients who subsequently present for surgery, alternative cephalosporins are forbidden by current guidelines because of concerns regarding an increased risk of anaphylaxis. However, consideration of the structure–activity relationships relevant to anaphylaxis suggests that cefalotin is a safe alternative because of structural dissimilarities, although there are no published clinical data relevant to the perioperative setting.

Methods: Patients diagnosed with intraoperative anaphylaxis to cefazolin at the Western Australian Anaesthetic Allergy Clinic were tested with intradermal cefalotin and, if negative, subsequently challenged i.v. If tolerated, cefalotin was recommended for subsequent surgery, and subjects were followed up to determine the safety of subsequent intraoperative doses.

Results: Twenty-one subjects diagnosed with immediate hypersensitivity to cephazolin, including 19 subjects with confirmed anaphylaxis, participated. None tested positive to intradermal cefalotin, and all received a graded i.v. challenge to cefalotin without developing signs or symptoms of anaphylaxis. Three subjects subsequently received intraoperative cefalotin 12–139 days later without adverse events.

Conclusions: A negative intradermal cefalotin skin test has a good negative predictive value in patients who have previously suffered anaphylaxis to cefazolin, allowing the rational and desirable use of this alternative cephalosporin for future surgery and the avoidance of less desirable antimicrobial agents.

Key words: anaphylaxis; cephalosporins; surgery

Editor's key points

- Prophylactic cefazolin is a common cause of intraoperative anaphylaxis for which guidelines dictate avoidance of future β -lactam antibiotics.
- Of 21 patients with immediate hypersensitivity reactions to cefazolin, none reacted to testing with cefalotin and three subsequently received intraoperative cefalotin uneventfully.
- Negative intradermal testing to cefalotin can predict subsequent successful use in cefazolin allergic patients.

Cefazolin was the most common individual drug responsible for intraoperative anaphylaxis in Western Australia in 2014–5, reflecting its status as first-line choice for the prevention of surgical site infections where Gram-positive organisms are common contaminants. Although cefalotin, an alternative first-generation cephalosporin with similar antimicrobial properties and a desirable side-effect profile, is available, guidelines state that β -lactam antibiotics should be avoided.^{1–3}

Local, regional, and national guidelines recommend vancomycin or clindamycin for patients with major β -lactam hypersensitivity,

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but these agents have several disadvantages when compared with a first-generation cephalosporin. The emergence of vancomycin-resistant enterococci, vancomycin-intermediate *Staphylococcus aureus*, and vancomycin- and clindamycin-resistant *S. aureus* makes the availability of alternative agents for the prevention of surgical site infections increasingly important.^{1,4}

We have previously noted a lack of cross-reactivity on skin testing to cefalotin in patients referred to our clinic with confirmed IgE-mediated intraoperative anaphylaxis to cefazolin. Current practice in our hospital is that a graded challenge is required before prescribing alternative β -lactam antibiotics. Although it is stated in all guidelines on surgical antibiotic prophylaxis that β -lactam antibiotics are precluded in this situation, there is increasing awareness that, in certain circumstances, alternative cephalosporins can be administered safely.

We sought to determine the predictive value of a negative intradermal test to cefalotin in subjects with known intraoperative anaphylaxis to cefazolin by administering an immediate i.v. challenge and monitoring subjects to determine the safety of subsequent cefalotin doses.

Methods

Twenty-one subjects with a history of intraoperative immediate hypersensitivity to cephalosporins underwent intradermal testing to cefalotin and, if negative, were given a graded i.v. cefalotin challenge. The diagnosis of cefazolin hypersensitivity had previously been made on the basis of a positive clinical history and intradermal testing that indicated hypersensitivity to cefazolin with an absence of hypersensitivity to other identified potential pharmaceutical triggers administered within 30 min of the intraoperative episode (drug dilutions are provided in Supplementary data, Table S1). Subjects were graded according to our modification of the guidelines for clinical practice developed by the Societe Francaise d'Anesthesie et de Reanimation and Societe Francaise d'Allergologie (SFAR/SFA; see Table 1).⁵ Anaphylaxis was defined as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, equivalent to immediate hypersensitivity of grade 2, 3, or 4.⁶

Our intradermal testing protocol is consistent with SFAR/SFA guidelines, consisting of an intradermal injection into the volar forearm of ~0.02 ml of 1 mg ml⁻¹ of the cephalosporin solution via a 29 gauge hypodermic needle to produce a 4 mm intradermal bleb. A positive test result requires the appearance of an erythematous wheal of at least 8 mm diameter (twice the initial size) at 15 min. A positive control skin-prick test with histamine 0.8% (wheal of ≥ 3 mm) and negative intradermal control indicate normal skin sensitivity for interpretation of the intradermal tests.

Table 1 Grades of immediate hypersensitivity. Adapted from Mertes and colleagues⁵

Grade	Features
1	Cutaneous signs: generalized erythema, urticaria, angioedema
2	Measurable but not life-threatening signs: hypotension (<30% of baseline). Tachycardia. Respiratory disturbances: poor respiratory compliance
3	Life-threatening signs: severe (<50% of baseline) hypotension, malignant arrhythmias, severe bronchospasm
4	Cardiac arrest (absence of palpable pulses)

Exclusion criteria were the use of β -blockers or antihistamines in the 72 h before testing, and age <16 yr. All subjects received information about the possible risks associated with cefalotin skin testing and the i.v. challenge, and written informed consent was obtained from each subject. Testing was conducted in a tertiary hospital with immediate access to resuscitative staff and equipment. Ethics approval was granted on January 25, 2015 as Project 11 057 by the Sir Charles Gairdner Group Human Research Ethics Committee.

If a cefalotin intradermal test was negative, subjects underwent a graded i.v. challenge. The challenge protocol consisted of a subject-blinded i.v. injection of normal saline 0.9% 2.5 ml (negative control), followed by cefalotin at incremental doses during 30 min (2.5, 7.5, 25, 65, 250, and 650 mg). A positive i.v. provocation test was defined by any signs or symptoms of respiratory, cardiovascular, skin, gastrointestinal, or cerebral dysfunction. The subject was then observed for a further 60 min before discharge home.

All subjects were contacted at the completion of the study (May 2016) to determine whether they had been administered cefalotin since their diagnosis of cefazolin anaphylaxis and, if so, the clinician involved was contacted to determine whether the drug was safely tolerated, and copies of the perioperative record were obtained.

Results

From November 2014 to May 2016, 21 patients seen at the Sir Charles Gairdner Hospital, Western Australia Anaesthetic Allergy Clinic were diagnosed with intraoperative immediate hypersensitivity to cefazolin and were subsequently administered an i.v. challenge with cefalotin. Characteristics of the subjects are summarized in Table 2. Only one (Subject 16) had a previous history of allergy to a β -lactam antibiotic (amoxycillin). The severity of intraoperative immediate hypersensitivity to cefazolin was grade 1 in two subjects, grade 2 in five subjects, grade 3 in 11 subjects, and grade 4 in three subjects. Nineteen of the 21 subjects therefore met the criteria for intraoperative anaphylaxis. Epinephrine was administered i.v. by bolus, infusion, or both in 15 of the 19 subjects with anaphylaxis, and 11 required unplanned admission to intensive care for IPPV. An acute mast cell tryptase was measured in 18 of the 19 instances of anaphylaxis, with an average value of 32.5 $\mu\text{g litre}^{-1}$ (upper limit of reference range 11.4 $\mu\text{g litre}^{-1}$).⁷

Subjects were interviewed and tested 26–205 days (mean 59 days) after the intraoperative event. Skin testing was conducted within 2 months of the hypersensitivity reaction in 15 of 21 subjects, and all except one were tested within 4 months. Subjects had negative responses to all potential triggers except cefazolin.

There were no instances of cross-reactivity with intradermal cefalotin, with all 21 subjects having negative intradermal skin tests.

Graded i.v. cefalotin challenge was tolerated without evidence of anaphylaxis or adverse reaction in all subjects [negative predictive value of skin testing 100% (95% confidence interval 86–100%)].

During the study period, four subjects had reoperation, of whom three were administered cefalotin for antimicrobial prophylaxis and one clindamycin. There were no adverse drug reactions.

Discussion

We observed that 21 subjects with negative pretreatment intradermal tests to cefalotin were safely administered an i.v. challenge despite a history of intraoperative immediate hypersensitivity to cephalosporins, 19 of whom had suffered intraoperative anaphylaxis. Three of these subjects were subsequently administered cefalotin

Table 2 Study subjects with known intraoperative immediate hypersensitivity or anaphylaxis to cefazolin. ICU, intensive care unit; IDT, intradermal test; N/A, not applicable; MCT, mast cell tryptase

Patient no.	Age (yr)	Grade	Adrenaline i.v. dose (mg)	ICU (IPPV)	MCT ($\mu\text{g litre}^{-1}$)	Baseline MCT ($\mu\text{g litre}^{-1}$)	MCT ratio	Interval before testing (days)	Cefazolin wheal (mm)	Cefazolin flare (mm)	Cefazolin IDT	Cefalotin challenge	Subsequent prophylaxis given (days after challenge)
1	18	3	No	Yes	31	5.0	6.2	52	8×5	30×25	Negative	Negative	N/A
2	31	3	100 μg	No	15.8	3.0	5.3	29	8×6	30×30	Negative	Negative	Cefalotin (27)
3	22	2	80 μg	No	3.6	2.5	1.4	30	8×7	25×25	Negative	Negative	Clindamycin (166)
4	41	1	No	No	–	–	–	205	9×10	40×30	Negative	Negative	N/A
5	77	3	700 μg +infusion	No	88	10.3	8.5	29	12×8	20×20	Negative	Negative	Cefalotin (139)
6	22	3	500 μg +infusion	Yes	37.8	3.3	11.5	27	12×12	30×30	Negative	Negative	N/A
7	24	1	No	No	14	2.9	4.8	51	8×8	28×28	Negative	Negative	N/A
8	60	3	Infusion	Yes	17.6	5.9	3.0	97	8×8	20×20	Negative	Negative	N/A
9	16	2	50 μg +infusion	No	24.1	8.5	2.8	43	8×8	25×25	Negative	Negative	N/A
10	20	3	600 μg	No	11.5	6.7	1.7	36	12×12	25×25	Negative	Negative	N/A
11	29	2	No	No	–	5.6	–	96	8×6	40×30	Negative	Negative	N/A
12	60	3	Infusion	Yes	82.8	4.8	17.2	48	11×10	35×30	Negative	Negative	N/A
13	44	4	2000 mg+infusion	Yes	22.7	3.6	6.3	26	10×10	45×40	Negative	Negative	N/A
14	36	3	No	Yes	6.1	2.3	2.7	45	13×10	35×30	Negative	Negative	N/A
15	54	2	No	No	8.8	3.3	3.8	70	13×8	40×30	Negative	Negative	N/A
16	44	2	Yes	Yes	66.1	23.4	2.8	30	8×8	32×34	Negative	Negative	Cefalotin (12)
17	19	4	1.5 mg+infusion	Yes	39	3.3	11.8	57	8×6	20×30	Negative	Negative	N/A
18	25	3	500 μg +infusion	Yes	11	–	–	59	8×6	18×22	Negative	Negative	N/A
19	52	4	1.2 mg+infusion	Yes	25.3	4.2	6.0	110	12×10	30×20	Negative	Negative	N/A
20	20	3	2 mg+infusion	No	86.9	6.0	14.5	41	8×8	25×25	Negative	Negative	N/A
21	29	3	180 μg +infusion	Yes	6.4	3.0	2.1	62	8×8	30×30	Negative	Negative	N/A

without adverse events when presenting for surgery that required antibiotics for prevention of surgical site infections. This result is consistent with our understanding of the structure–activity relationships of β -lactam drug hypersensitivity, and has the potential to change current prescribing practice to the benefit of patients. The availability of cefalotin as a safe alternative to vancomycin or clindamycin in patients with cefazolin anaphylaxis could reduce costs, improve compliance with pre-incision antibiotic dosing, reduce the development of vancomycin and clindamycin resistance, and reduce side-effects for patients.

The recommended antibiotic in Western Australia for prevention of surgical site infections where Gram-positive cocci are likely to contaminate wounds is cefazolin. This includes orthopaedic, cardiothoracic, abdominal (with co-administration of metronidazole), vascular, and neurosurgical procedures. As a consequence, cefazolin is now the most common cause of intraoperative anaphylaxis in our region. Current guidelines recommend vancomycin as the appropriate substitute for cefazolin in these patients, and indeed in all patients with a major β -lactam allergy.^{2,8} Vancomycin is frequently administered for surgical prophylaxis in Western Australia.

When compared with first-generation cephalosporins, vancomycin has several disadvantages. The ideal prophylactic agent would have the narrowest antibiotic spectrum required to cover causative organisms adequately, be the least expensive, have the lowest toxicity, and be easily administered. One should also avoid antibiotics that are likely to be used in the treatment of severe sepsis.¹ Vancomycin has a slower bactericidal activity, is less effective against Gram-negative pathogens, is more expensive, and is associated with potentially serious side-effects, including 'red-man syndrome' and hypotension.^{9,10} Plasma pharmacokinetics, protein binding, and tissue penetration vary according to surgical site and co-morbid disease, and it is difficult to administer the loading dose before surgical incision because of limits in infusion rates required to minimize infusion-related adverse events, resulting in a high observed frequency of non-compliance with dosing recommendations (including the

administration of prophylaxis before skin incision).^{9,11} The unnecessary use of vancomycin also favours emergence of vancomycin-resistant enterococcus and *S. aureus*.

Advances in the understanding of β -lactam cross-reactivity and increasing confidence in the predictive value of cephalosporin skin testing have led the authors to reconsider the possibility of using alternative first-generation cephalosporins for surgical prophylaxis in patients with known cefazolin anaphylaxis. Cefalotin is widely available in Western Australia and has a similar *in vitro* bactericidal activity for Gram-positive and Gram-negative organisms.¹² It has been recommended as a suitable antibiotic choice for surgical prophylaxis in upper respiratory tract surgery, cardiac surgery, and orthopaedic surgery.¹

Cephalosporins share a basic β -lactam structure condensed with a dihydrothiazine ring.¹³ Antibodies can be directed to this basic structure or, more frequently, to the R1 (7-position) or R2 (3-position) side-chains, which can be unique to a particular cephalosporin. Cefazolin and cefalotin have dissimilar R1 and R2 side-chains (Fig. 1). Among the β -lactams, cefazolin has unique R1 and R2 side-chains, whereas cefalotin shares an identical R1 side-chain with cefoxitin and cephaloridine, and has R2 side-chain similarity with cefotaxime only.¹³ Cross-reactivity between cefalotin and benzyl penicillin has been attributed to classical ring bioisosteres (thiophene and benzene, respectively) present in their R1 side-chains.¹⁴ A major hurdle to the use of cefalotin in patients with cefazolin anaphylaxis was the observation that cross-reactivity among the first-generation cephalosporins was higher than that observed among the second- or third-generation cephalosporins.^{15,16} Rather than being a consequence of their antimicrobial spectrum, this observed cross-reactivity is a consequence of the higher frequency of similar R1 side-chains within the first generation compared with other generations of cephalosporins.^{14,16}

After *i.v.* administration, the cephalosporin antibiotics conjugate with penicillin-binding proteins by β -lactam ring opening. When this occurs, the R2 side-chain is lost, and fractionation of the dihydrothiazine ring leaves only the R1 side-chain and part of the β -lactam ring bound to the carrier protein.¹³ This is thought to

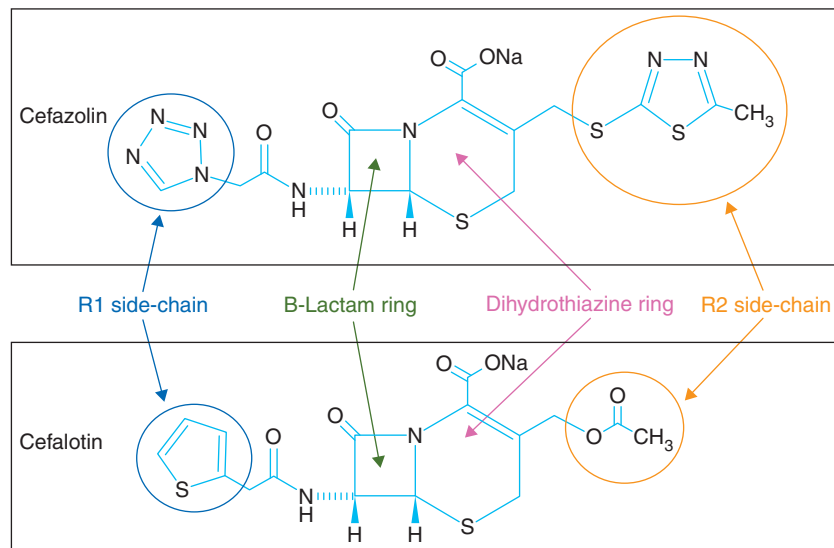


Fig 1 Outline of the major structural differences between cefazolin and cefalotin. © Dr Russell Clarke.

form the allergenic epitope. It follows that if a patient with anaphylaxis to cefazolin has hypersensitivity to its unique epitope, they are unlikely to cross-react with cefalotin. Although less common, it is possible that a patient could be hypersensitive to a portion of the β -lactam or the thiazolidine rings common to both cefazolin and cefalotin, or a common breakdown product. However, the absence of a positive pretreatment intradermal test to cefalotin in the presence of a positive intradermal test to cefazolin would make this unlikely. Likewise, the presence of coexisting hypersensitivities, unrelated to shared structure–activity relationships, would be expected to produce a positive pretreatment intradermal test to cefalotin.

Previous studies have demonstrated the ability of skin testing to reduce the frequency of vancomycin use in patients with a history of penicillin allergy,¹⁷ and it seems reasonable that cephalosporin skin testing will have similar benefits for patients with cefazolin anaphylaxis. We used the recommended maximal concentration for intradermal testing with cephalosporins (1–2 mg ml⁻¹).¹⁸ Our findings support the hypothesis that cephalosporin hypersensitivity is not a class hypersensitivity, and that patients can be treated with agents with different side-chain determinants if they have negative pretreatment skin test responses.¹⁶ Whether penicillins can also safely be prescribed in these patients (even if only benzyl penicillin, which shares a similar R1 side-chain with the tolerated cephalosporin, cefalotin), is a subject for further studies. It has previously been recommended that penicillins can be administered safely to patients with allergy to cephalosporins if they have a negative skin test to penicilloyl polylysine and minor determinant mix and if the penicillin has different side-chains from the offending cephalosporin.¹⁸

We did not observe false-negative skin tests to cefalotin in this population of subjects with a demonstrated positive skin test to cefazolin. The true rate of a false negative is therefore likely to be low (95% confidence interval 0–14%). Our sample size is similar to previous series investigating a rare condition, and there are no previous instances reported in the literature. Coexisting sensitivities can occur, as can cross-reactivity between cephalosporins with dissimilar side-chains or completely unrelated drug classes, so we would encourage clinicians to ensure that patients have a negative pretreatment skin test, and that challenging occurs in an environment in which resuscitation equipment and skilled staff are readily available. It is also important to note that all our subjects except one were tested within 4 months of the episode of anaphylaxis, and all had a positive skin test to cefazolin at the time of testing with cefalotin. This is relevant because the natural evolution of β -lactam skin-test sensitivity is that the longer the interval between the reaction and testing, the lower the chances are of detecting IgE antibodies (whether by skin testing or *in vitro* tests).²⁰ An additional important finding of this study was that *i.v.* challenge, or intradermal testing, with cefalotin did not result in immune sensitization within the period in which three subjects had subsequent surgery and cefalotin dosing.

Cefalotin has some pharmacokinetic qualities that might be less desirable for prophylaxis of surgical site infections compared with cefazolin. After similar *i.v.* doses, cefalotin results in a lower peak concentration in blood, attributable to higher serum and renal clearance and a larger apparent volume of distribution. This is offset by a lower degree of protein binding (the bound drug being inactive).^{12–21} The redosing interval might need to be shorter compared with cefazolin to compensate for this, as is suggested for other cephalosporins used for surgical prophylaxis with shorter plasma half-times (e.g. cefoxitin, which is redosed at 2 h, compared with 4 h for cefazolin).²²

In summary, intradermal testing with cefalotin in patients who have previously suffered intraoperative anaphylaxis to cefazolin appears to predict the tolerability of *i.v.* cefalotin. This knowledge will improve access to appropriate antibiotic agents for these patients, reduce emergence of drug-resistant organisms, and supports the hypothesis that cephalosporin anaphylaxis is not necessarily a class hypersensitivity, but related most commonly to the R1 side-chain.

Author's contributions

Planning the investigation; recruiting and testing subjects; reviewing and contributing to the final manuscript: P.H.M.S., R.C.C., P.R.P.

Literature review: P.H.M.S., P.R.P.

Manuscript preparation: P.H.M.S.

Contribution to manuscript preparation: R.C.C., P.R.P.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

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