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Are changes in antibiotic prophylaxis recommendations responsible for an increased risk of cefazolin allergy?

Running title: Cefazolin hypersensitivity

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Authors contribution

NC, LDC, AGC contributed to the design of the work. LDC, SA, FL, PM, CN and AGC contributed to the acquisition, the analysis, and the interpretation of the data. AGC and NC wrote the first draft of the manuscript. LDC, SA, FL, PM and CN revised it afterwards. All authors gave their final approval of the submitted version and agreed to be accountable for all aspects of the work.

Ethical statement

The study was approved for all centers by an Institutional Review Board (ethical committee “Comité Ethique pour la Recherche en Anesthésie Réanimation”, reference IRB 00010254 - 2023 – 035, on April 16, 2023).

Word count

Title: 14 words

Abbreviated title: 2 words

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Key Words

Allergy; Anaesthesia; Antibiotics; Cefazolin; Chemoinformatics; Cross-reactivity; Prophylaxis; Surgery

Abstract

Background

The first line of prevention of surgical site infection relies on the timely administration of antibiotic prophylaxis. First- and second-generation cephalosporins are the most recommended antibiotics in elective surgery. The incidence of cefazolin allergy has increased worldwide over the years. The sensitization mechanism of cefazolin is currently unknown, and data supporting cross-reactivity between penicillins and cephalosporins are lacking. Sensitization could occur through previous exposure either to cefazolin or to structurally related chemical agents. The objective of this study was to evaluate sensitization agents for cefazolin.

Methods

The OpenBabel chemoinformatics toolbox was used to search for similarities between cefazolin and other molecules in an extensive drug database. Using the pholcodine-rocuronium similarity score as a threshold, we selected drugs with the most similar structure to that of cefazolin. Exposure to those drugs and cefazolin was assessed in a cohort of patients with skin test-proven cefazolin allergy at a specialized allergy centre via a self-administered anonymous questionnaire.

Results

Using the pholcodine-rocuronium similarity score as a threshold (score \geq 0.7), 42 molecules were found to be similar to cefazolin (all cephalosporins). Only eight were marketed in France. None of the 14 cefazolin-allergic patients who answered the questionnaire (65% female, median age 56 years) reported exposure to any identified antibiotics. In contrast, 11 (78%) had at least one previous surgery requiring cefazolin before the index case.

Conclusion

Direct previous cefazolin exposure was identified in 78% of cefazolin-allergic patients. Cefazolin started to take a central place in antibiotic prophylaxis after 2010, when cefamandole usage decreased drastically. Changes in antibiotic prophylaxis over the past 14 years in France could have been the turning point for the increased incidence of cefazolin allergy.

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Introduction

Surgical site infection (SSI) remains a major health issue, the prevalence of which is estimated to be stable at approximately 3%. First-line prevention of SSI relies on timely administration of antibiotic prophylaxis, with first- and second-generation cephalosporins being the most widely recommended antibiotics in elective surgery, except for eye surgery [1]. Therefore, to follow the evolution of scientific knowledge and avoid SSI, most organizations, such as the French Society for Anaesthesiology and Intensive Care, the World Health Organization, and the American Society of Anesthesiologists, have regularly updated their antibiotic prophylaxis recommendations (every 6-9 years in France).

The incidence of first-generation cephalosporin (cefazolin) allergy has been increasing worldwide [2]. Beta-lactam sensitization patterns can vary according to consumption trends and among countries [3]. In the beta-lactam family, cross-reactivity between penicillins and cephalosporins is considered weak [4]. Cephalosporins differ from penicillins in terms of their heterocyclic ring and R2 side chain in addition to the R1 side chain. The R1 side chain and the opened beta-lactam ring are central to immunogenicity. Several studies have suggested that cephalosporin-allergic individuals most often tolerate other cephalosporins with different R1 side chains [5]. This tolerance could be predicted based on the degree of similarity between side chains. The exact cross-reactivity rate between penicillins and cephalosporins has not yet been established, with values estimated to be lower than 1% [2,5,6]. Interestingly, cefazolin has a unique combination of R1 and R2 side chains, which are also found only in ceftazole (solely available in Asia). However, the sensitization process against cefazolin remains unknown.

IgE hypersensitivity reactions require at least one exposure before the index reaction (although previous sensitization could be unsuspected or due to cross-reactivity) [7]. Since cefazolin is mainly used in perioperative settings, sensitization through direct exposure during previous surgery seems to be the most likely explanation. In a small case report, Warrington et al. could not identify any cefazolin exposure before cefazolin anaphylaxis in 4 patients [8]. We hypothesized that cefazolin sensitization could also occur through other structurally related chemical agents. Such a pathway has been observed with sensitization to rocuronium (a neuromuscular blocking agent, NMBA), which can be acquired through pholcodine exposure [9]. The objective of our study was thus to identify potential sensitization agents to cefazolin.

Material and Methods

The 5903 “approved drugs in major jurisdictions, including the FDA” database was downloaded on January 3rd, 2023, from the ZINC15 website (<https://zinc15.docking.org/substances/subsets/world/>). All those drugs are used in healthcare. The OpenBabel chemoinformatics toolbox [10] was used to look for similarities between rocuronium and the drugs in the database. Every molecule was assigned a structural fingerprint, which is a series of boolean numbers that describe the structure of the molecule. Different fingerprints were tested, and only MACCS provided satisfactory results. The MACCS fingerprint (Molecular ACCess System) describes the structure of a molecule through 166 features, which are mainly the presence or absence of various chemical substructures. Fingerprints were subsequently compared between pairs of molecules, with the Tanimoto similarity score set to the default value, which is a number between 0 and 1 (1 for identical molecules) [11]. As a reference, we used the rocuronium-pholcodine similarity. Pholcodine was found to be the 8th closest structure to rocuronium out of 5903 (with a score of 0.735) after the exclusion of stereoisomers

with the MACCS fingerprint (other fingerprints were tested and did not provide a satisfactory ranking). This method takes into account both the structural similarities (such as the steroid cycle) and specific aspects of the molecule (such as the quaternary ammonium epitope in NMBAs) and has the advantage of being very fast (a few minutes to compare one molecule with the full drug database). Applying the same method to cefazolin, based on the pholcodine score, 42 molecules had similarity scores above 0.7, all of which were from the cephalosporin family. Among these, only 8 are marketed in France and were retained for this study: cefamandole, ceftriaxone, ceftazidime, cefotaxime, ceftazidime, cefotiam, cefixime, and cefpodoxime. Amoxicillin is by far the most commonly used antibiotic in the beta-lactam family in outpatients. Years ago, cephalosporin formulations were contaminated with penicillin, leading to high estimates of beta-lactam cross-reactivity [12]. Based on knowledge about immunogenicity, penicillin and cephalosporin cross-reactivity is now recognized to be quite low in the absence of similar side chains (below 1%), although some cross-reactivity might still exist. However, this belief persists, especially among nonallergist specialists [13]. We thus decided to add amoxicillin to the questionnaire for exhaustivity reasons.

We then investigated the exposure of 20 well-documented cefazolin-allergic patients selected from a specialized allergy center in France to these 9 molecules. The inclusion criteria were a clinical history of perioperative hypersensitivity reaction (POH) subsequent to cefazolin exposure and a positive cefazolin skin test during the allergy workup. The exclusion criterion was the absence of consent. Patients were asked to complete an electronic anonymous questionnaire that collected demographic, comorbidity, previous surgery, previous hospitalization for infectious reasons and antibiotic exposure data.

This study was approved by an Institutional Review Board (CERAR 00010254–2023–035, April 16, 2023). This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for the reporting of observational studies in epidemiology (STROBE, <http://www.strobe-statement.org/>; see Supplemental Table 1). The results are presented as values or medians [interquartile ranges (IQRs)]. Additional information about the study methods and findings are available in the following repository: https://osf.io/q7s6c/?view_only=c4ff9070699849c3a75f9c4027dc2117.

Results

Fourteen patients (mainly female, median age of 56 years; Table) returned the questionnaire. From January 2017 to June 2022, patients underwent different surgery types: gynaecological (n=4), urological (n=3), orthopaedic (n=4), abdominal (n=1), mixed gynaecological with an elective appendicectomy (n=1) or vascular surgery (n=1). Three (21%) patients presented with a grade 1-2 POH, and eleven (78%) presented with a grade 3 POH (three of whom were subsequently admitted to the intensive care unit). Surgery was resumed after POH in 57% of the patients. Twelve (86%) patients had at least one previous surgery, and the recommended antibiotic prophylaxis was cefazolin for 11 patients (78%). The median exposure delay was 6 years (minimum, 1; maximum, 22). None of the patients reported exposure to any of the eight antibiotics identified. Three patients (22%) had previously been hospitalized for a bacterial infection, with no indication of the type of antimicrobial agent received (one of them had no previous surgery). Eight of the patients (57%) reported previous amoxicillin exposure. As part of the routine allergy work-up, five patients received both amoxicillin and ceftriaxone drug challenge, two patients received ceftriaxone drug challenge and one patient received amoxicillin drug challenge. All the treatments were well tolerated.

Discussion

Our report suggests that previous cefazolin exposure could be the main cause of cefazolin allergy, which has surprisingly never been reported thus far. Cefazolin started to take a central place in antibiotic prophylaxis recommendations in France after 2010 when cefamandole usage decreased drastically. The changes in antibiotic prophylaxis over the past 14 years could have been the turning point of the increase in the incidence of cefazolin allergy, as these changes also occurred in other countries, such as Spain and Japan. Analysing the epidemiology of anaphylaxis in each specific country reinforces this hypothesis. Indeed, teicoplanin is highly used for antibiotic prophylaxis in the United Kingdom, as it is the alternative recommended agent for patients with penicillin allergy. It is also one of the most common causative agents of POH in the United Kingdom, which has never been reported in other countries. This finding sustains how antimicrobial recommendations could influence local allergy epidemiology.

In 22% of patients of the present study, we were not able to find any previous exposure explaining the sensitization, neither through perioperative exposure nor through antimicrobial regimens for infectious diseases. Other factors not explored here could be responsible, such as other molecules (below the 0.7 ratio similarity score), sustaining the requirement for epidemiologic studies with well-conducted questionnaires to evaluate all antimicrobial regimen exposures.

Notably, eight patients (57%) were exposed to amoxicillin before the hypersensitivity reaction. As previously stated, cross-reactivity relies on the R1 side chain (which is different between amoxicillin and cefazolin) and on the opened beta-lactam ring. In penicillins, the beta-lactam ring is known to be unstable, leading to spontaneous opening of the ring, allowing the highly reactive carbonyl group to easily bind to the amino groups of plasma and cell-surface proteins.[14] As the core cephalosporin structure is less reactive, the opening of the beta-lactam ring is less frequent, and when this occurs, it leads to the production of highly unstable protein conjugates that are rapidly degraded. As such, very few reports have identified the beta-lactam ring in cephalosporins to be responsible for IgE-mediated allergies.[15] However, this cannot be completely excluded and should be considered.

Another explanation could be the overall increased exposure to cefazolin. To evaluate the number of surgical procedures performed per year, we analysed the official French data available online (data.drees.solidarites-sante.gouv.fr). As a surrogate marker of the number of surgeries performed, we used the number of hospitalizations in surgical units (out- and inpatients), which increased from 7.54 million in 2000 to 8.47 million in 2019 (Supplemental Figure 4). This 11% increase is in accordance with the 10% increase in the French population over the last 20 years.

Although the chemical structure of cephalosporin antigens is not completely understood, in our attempt to identify close molecules through fingerprint analysis, we did not identify any previous intake of the suspected molecules in cefazolin-allergic patients.

Even though our approach has some limitations (number of patients, retrospective questionnaire, no direct access to anaesthesia charts), it proposes the first-in-kind structural comparison between cefazolin and marketed drugs. No exposure to drugs similar to cefazolin could be found, while a likely direct previous cefazolin exposure was identified in 86% of patients. While other yet unidentified molecules could be involved, these data suggest that cefazolin itself might be the main factor responsible for its own sensitization.

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Table legends

Table: Patients' characteristics. Results are presented as medians (interquartile ranges) or absolute values (percentages). ASA: American Society of Anesthesiologists; ICU: intensive care unit; POH: perioperative hypersensitivity reaction.