CEFAZOLIN USE IN PATIENTS WHO REPORT A NON-IGE MEDIATED PENICILLIN ALLERGY: A RETROSPECTIVE LOOK AT ADVERSE REACTIONS IN ARTHROPLASTY

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ABSTRACT

Background: A large number of patients presenting for total hip and knee arthroplasty report an allergy to penicillin. The reported incidence of cross reactions with cephalosporins in patients with penicillin allergy ranges from 3% to 18%. Perioperative antibiotic prophylaxis practices range from using cephalosporins to substituting clindamycin or vancomycin. The purpose of this study was to determine whether cefazolin can be used safely in the perioperative setting in patients with reported non-IgE mediated reactions to penicillin.

Methods: We retrospectively reviewed all primary total hip and knee arthroplasty (2012) and revision (278) cases done at a Canadian university hospital from 2007 to 2010. We calculated the prevalence of reported penicillin allergy, the specific reaction reported, and the observed reaction rate in penicillin allergic patients given cefazolin.

Results: The prevalence of reported penicillin allergy was 9.9%. There was a wide range of reported reactions, with 25% IgE mediated and 75% non-IgE mediated. Only 27% of patients reporting penicillin allergies were given cefazolin. There were no adverse reactions when non-IgE mediated penicillin allergy patients received cefazolin.

Conclusion: Surgical patients with reported non-IgE allergic reactions to penicillin have a low chance of adverse reaction to perioperative administration of cefazolin. Only a fraction of surgical patients with reported non-IgE mediated reactions to penicillin receive cefazolin perioperatively.

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INTRODUCTION

Prior to 1995 penicillins were the most utilized antibiotics, and had the highest prevalence of drug allergy[1]. Cephalosporins, especially cefazolin, a first generation cephalosporin, is currently used as the antibiotic of choice for the prophylaxis of surgical infections due to its effectiveness against gram-positive bacteria and its action against most clinically important aerobic gram-negative bacilli and nonbacteroid anaerobes[2]. On a chemical level, cephalosporins and penicillins share a beta-lactam ring as well as certain side-chains believed to be the antigenic determinants responsible for cross-reactivity between these drugs[3,4,5]. However, recent research and clinical reviews, aided by a better understanding of the chemistry and purer drug preparation, support the notions that the allergy overlap between them is much more limited than previously thought and that cephalosporin use should not be as restricted in penicillin allergic patients[6].

The reported incidence of allergic reactions to first generation cephalosporin antibiotics ranges from 0.0001% to 0.1%[7]. The reported incidence of cross reactions with these medications in patients with penicillin allergy ranges from 3% to 18%[8,9]. Because of these wide variations, practice recommendations range from using these medications if the allergy is mild to automatically substituting clindamycin or vancomycin regardless of the nature of the adverse reaction to penicillin.[9] This mirrors the current practice for all surgical cases at our center for cefazolin use in patients with a reported penicillin allergy.

Substitution of cefazolin raises several concerns. Vancomycin exposure increases the risk of vancomycin resistant *Enterococcus* (VRE) infections and its use should be restricted to centres where methicillin resistant *Staphylococcus aureus* is endemic[1,10]. *Clostridium difficile* infections can occur with the use of any broad spectrum antibiotic but is particularly associated with the use of clindamycin[10]. Finally, cefazolin is the most cost effective drug per dose at our center (cefazolin – $0.85, clindamycin - $1.41, vancomycin - $7.60). Therefore, we hoped to be able to maximize the future safe use of cefazolin by determining if there is a subgroup of penicillin allergy patients that can be given Cefazolin without cross-reaction.

Table 1: Summary of reaction types and rates.

Type of Reaction	Number of patients reporting the reaction	Proportion of all reactions	Number of patients who received cefazolin
Urticaria*	20	10%	0
Immediate airway compromise*	14	7%	0
Anaphylaxis*	10	5%	0
Angioedema*	5	3%	0
Rash	77	39%	36
Unknown or "Cannot Remember"	27	14%	4
Swelling	11	6%	4
Itching	8	4%	3
GI upset	8	4%	4
Blisters and boils	3	2%	1
Mouth Sores	3	2%	0
Colitis	1	<1%	0
Coma	1	<1%	0
Convulsions	1	<1%	0
Hiccups	1	<1%	0
Fever	1	<1%	0
Lumps on Feet	1	<1%	1
Positive Penicillin Allergy test	1	<1%	1
Racing heart	1	<1%	0
Serum Sickness	1	<1%	0

* indicates IgE mediated reactions

METHODS AND MATERIALS

We retrospectively collected data from 1962 patients who underwent 2290 hip and knee arthroplasty procedures between 2007 and 2010 at our University Health Sciences Centre, Ontario, Canada. We noted the presence of a patient reported penicillin allergy. The patient's reported reaction was recorded. Reactions were characterized as IgE and non-IgE mediated. Urticaria, immediate airway compromise, angioedema, and anaphylaxis were considered IgE mediated[11], whereas all other reactions fell under the category of non-IgE mediated (Table 1). The prophylactic antibiotic administered was recorded, as well as any resultant adverse reactions. The patients' paper charts and electronic charts were searched for a record of adverse reactions. This included the anesthetic record (recorded by the anesthetist), the operative note (recorded by the surgeon), the operative record (recorded by the nursing team in the operating room), the progress notes (recorded by the surgical team rounding on the ward post-operatively until discharge from hospital), and the inpatient nursing notes (recorded by the bedside nurse post-operatively until discharge from hospital).

Penicillin allergy prevalence was calculated, and a chi-square analysis was performed. Hospital appointed program directors, with the support of the Departments of Anesthesiology and Perioperative Medicine, Medicine (Infectious Diseases), Surgery, and the Ethics Review Board at our center approved this retrospective study.

RESULTS

From 2007 to 2010, 1962 patients underwent 2290 arthroplasty procedures. These procedures were 1093 primary total knee replacements, 919 primary total hip replacements, 131 revision total knee replacements, and 147 revision total hip replacements.

The prevalence of reported penicillin allergy was 9.9% (196 patients). There was a wide range of reported reactions with IgE mediated allergies such as anaphylaxis, urticaria, angioedema and airway compromise accounting for 25% (49) of those reported (Table 1). Non-IgE reactions comprised 75% (147) of patients. Rash and unknown reactions were among the highest reported non-IgE mediated reactions at 39% and 14%, respectively.

No patients reporting an IgE mediated allergy received cefazolin. Of the 54 non-IgE mediated penicillin allergic patients who received cefazolin, no adverse reactions were reported, which was significantly different from the reported literature rates of 3% to 18%[8,9] by chi-square analysis ($p<0.03$). We also noted that fewer penicillin allergic patients received cefazolin (54 of 196, 27%) compared to those who reported no penicillin allergy (1691 of 1826, 93%, $p= <0.001$).

DISCUSSION

Despite finding a similar prevalence for penicillin allergy to that reported in the literature, we observed a significantly decreased reaction rate to cefazolin among patients who report a penicillin allergy compared to the literature[1]. Based on a reported cross-reactivity rate of 3% to 18%[8,9] we would have expected between two and ten patients (out of 54) to experience an adverse reaction. Our study saw zero adverse reactions which was noted to be significant ($p<0.03$). This could potentially be explained by the fact that only non-IgE mediated allergies received cefazolin at our institution.

Another possible explanation is that older studies overestimated the cross-reactivity rate between penicillins and cephalosporins since early cephalosporin antibiotics contained trace amounts of penicillin which had led to a frequent avoidance of cephalosporins in penicillin allergic patients, even after developments in purification techniques eliminated the contamination problem in the 1970's[9,12,13]. This is supported by a study by Novolbos et al., which noted that of 41 patients with IgE mediated penicillin allergy who received a cefazolin intramuscularly, no patients experienced an adverse reaction.[12]

We noted that merely reporting a penicillin allergy (regardless of the reaction type) significantly decreased a patient's chances of receiving cefazolin prophylactically. Despite an established guideline at our institution that permits cefazolin administration in non-IgE mediated penicillin allergic patients, there was little adherence to this counsel. This practice is likely historical, based on previous manufacturing practices whereby cephalosporin antibiotics contained trace amounts of penicillin. This has given rise to the propensity to substitute for cefazolin in these cases. We believe this illustrates a need for education amongst surgeons, anesthesiologists, and the entire surgical team regarding cefazolin administration in penicillin allergic patients.

Vancomycin is often administered over a prolonged period to avoid "Red Man Syndrome". If vancomycin were not started in a timely manner and the full dose was not administered prior to incision then the prophylactic benefit of the antibiotic would be compromised. Studies have emphasized the importance for full dosing of prophylactic antibiotics prior to skin incision[14,15,16,17]. To date there is no literature to support whether cefazolin is inherently better at preventing infection than vancomycin or clindamycin, only that cefazolin has a lower drug risk profile. The increasing use of vancomycin and clindamycin comes with the associated risks of vancomycin resistant enterococcus infection[18], nephrotoxicity[19] and *C.difficile* infection[20,21]. Number needed to harm (NNH) can be used to help assess negative reactions between drugs with a higher NNH indicating lower risk. Clindamycin harbors a NNH of eight for *C. difficile* infection[20,21], while vancomycin exhibits a NNH of 14 for nephrotoxicity[19]. Cefazolin's NNH for *C.difficile* infection is 28[20,21]. Because of these risks the Healthcare Infection Control Practices Advisory Committee has previously stated in their guideline "the routine use of vancomycin in antimicrobial prophylaxis is not recommended for any kind of operation."[16] Minimizing other adverse reactions is one reason why orthopaedic surgeons may opt for cefazolin pre-operatively.

Our study is limited by its retrospective nature and reliance on previously recorded data. Underreporting of adverse events is one limitation of collecting data retrospectively. Another limitation is that we draw conclusions about safety of cefazolin use for the non-IgE mediated allergy group as a whole. Though we provide convincing data demonstrating a lack of adverse-reaction of our 36 patients with penicillin rash allergies, many of the other allergy subgroups were small. However, because of the large number of potential reactions and the high unlikelihood that penicillin cross-reactivity for these rarer reactions would exist, combining these into a single non-IgE mediated reaction group ultimately improves the analysis.

We find the disparity in antibiotic choice based on reporting a penicillin allergy and the lack of adverse reactions in certain penicillin allergic patients to be worthy of note. It appears that many patients who could otherwise receive cefazolin perioperatively are being presribed an alternative antibiotic despite evidence to support the contrary. We believe that we have identified a group of patients who can be screened to receive cefazolin based on a history of non-IgE mediated penicillin allergy. Based on our findings it appears that cefazolin is safe to administer to patients reporting a non-IgE mediated penicillin allergy. However further prospective studies are warranted to further examine our findings.

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