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Cephalosporins Can Be Given to Penicillin-allergic Patients Who Do Not Exhibit an Anaphylactic Response

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Study Objectives: *To assess the risk of intraoperative allergic reactions to cephalosporins in patients who claim to be allergic to penicillin.*
Design: *Retrospective chart review.*
Setting: *University-affiliated hospital.*
Measurements: *2,933 intraoperative anesthesia records of all adult orthopedic patients treated at our institution during a 14-month period (7/96–8/97) were reviewed for antibiotic use and allergic reactions.*
Main Results: *Most of the 2,933 orthopedic patients, including 413 patients who were allergic to penicillin, received a cephalosporin (usually cefazolin) during their procedure. Only one of the penicillin-allergic patients may have had an allergic reaction to the cephalosporin, because diphenhydramine and hydrocortisone were given at the beginning of the case. However, no mention was made on the chart about itching or a rash or hives. One of the non-penicillin-allergic patients did develop a rash while the cephalosporin was infusing, requiring discontinuation of the antibiotic.*
Conclusions: *Given the low incidence of allergic reactions, it appears to be safe to administer cephalosporins to patients who claim to be allergic to penicillin. However, no conclusion can be made concerning patients who report severe or anaphylactic reactions to penicillin, because these patients probably were excluded from the study.*

Keywords: Allergy, anaphylaxis, cephalosporin, cross-reactivity, penicillin, reaction.

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Presented in part at the Annual Meeting of the International Anesthesia Research Society, Los Angeles, CA, March, 1999.

Received for publication September 5, 2000; revised manuscript accepted for publication August 12, 2001.

Introduction

Initial tests of the first cephalosporins found them to be safe antibiotics, even in patients with a history of penicillin allergy.[1,2] It was hoped that the resistance of cephalosporins to penicillinase and the subsequent different paths of degradation for cephalosporins and penicillins would protect penicillin-allergic patients from antigens that could initiate an allergic reaction. However, case reports then appeared that raised doubts about the earlier findings.[3,4] Patients who had

655 Avenue of the Americas, New York, NY 10010

0952-8180/01/$–see front matter
PII S0952-8180(01)00329-4

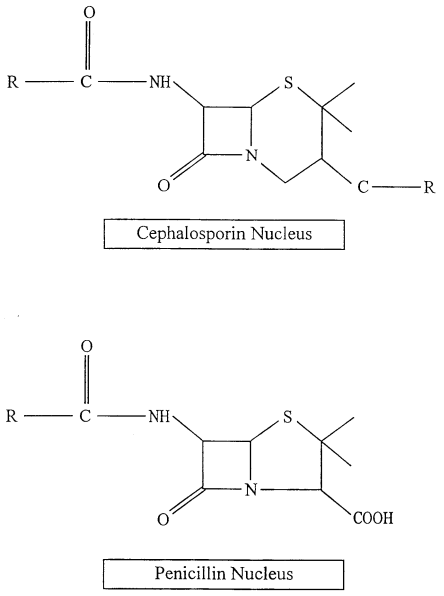

Figure 1. The similarity between the cephalosporin and penicillin structures.

reacted to penicillin in the past seemed to be at higher risk for having difficulty with a course of a cephalosporin antibiotic.

Cross-reactivity between the two families of antibiotics had been feared from the beginning because of the similarity in their structures (*Figure 1*). Both have a β-lactam ring, which is largely responsible for the antibiotic activity, and each has another ring structure containing sulfur. Cephalosporins have a six-member dihydrothiazine ring, whereas penicillins have a five-member thiazolidine ring.

In vitro experiments confirmed the antigenic similarity between penicillin and some of the cephalosporins. The leukocyte challenge test, lymphocyte stimulation test, hemagglutination inhibition test, and the quantitative leukocyte histamine release test demonstrated a 40% to 75% antigenic cross-reactivity.[5,6] Mixed inhibition studies also showed that there was a considerable degree of cross-reaction between the benzyl penicilloyl haptenic determinant, which is the main antigenic determinant of penicillin, and antigens on cephalosporins.[7]

Clinical studies, on the other hand, were far from conclusive. Issues concerning the reliability of a history of penicillin allergy, as well as the significance of skin testing and levels of antibodies to antibiotics, made interpreting results difficult.

This study examines the incidence of reactions to cephalosporins during orthopedic procedures. In our hospital, cephalosporins are given routinely before orthopedic procedures. Patients who have a history of penicillin allergy also receive cephalosporin antibiotics, unless their reaction is of a more severe anaphylactic type.

Materials and Methods

After approval from our hospital's Institutional Review Board for Human Investigation, intraoperative anesthesia records of all adult orthopedic patients over a period of 14 months (July 1996—August 1997) were searched. The number of patients receiving cephalosporins was noted, as was the type of antibiotic given to the penicillin-allergic patients. Only intraoperative antibiotics were considered. The charts were scanned for signs that an allergic reaction had occurred, such as a report of itching, sudden changes in blood pressure not related to interoperative events, the administration of H_1 blockers or steroids, or the premature discontinuation of the antibiotic. The age, gender, and other drug allergies of the penicillin-allergic patients were also recorded. Patients who had questionable penicillin allergies or who had an allergy to "an unknown medication" were not considered truly allergic to penicillin.

A sample (or "subset") population was examined more closely to determine what should be expected to be the average age, the average number of allergies, and the normal ratios of males and females in our orthopedic population. This sample population consisted of all orthopedic patients during three complete months (February 1997—April 1997). The age and gender of these patients were noted, as was the number of medications on their list of allergies.

Statistical significance was determined using Chi-square analysis for the nominal data (gender distribution, number of allergies) and the two-tailed *t*-test was used for the interval data (age distribution).

Results

Almost 3,000 patients had orthopedic surgery procedures performed during the 14-month period studied (*Table 1*). A majority of all orthopedic, including the penicillin-allergic patients, received a cephalosporin during their procedure. All but two of the penicillin-allergic patients who received a cephalosporin were given only the first-generation cephalosporin, cefazolin. One patient received the third-generation cephalosporin, ceftazidime, and another received cefazolin plus gentamycin. The other penicillin-allergic patients received the following antibiotics: erythromycin (3), ampicillin and sulbactam (1), vancomycin (51), gentamycin (4), nafcillin (1), and clindamycin (2).

The average age of the penicillin-allergic patients did not differ significantly from those in the non-penicillin subset (*Table 2*). However, a significantly larger ($p < 0.001$) proportion of the penicillin-allergic patients were women. Of the subset population with at least one drug allergy (*Table 3*), the proportion with more than one allergy was 47% (67/143). This figure was not significantly different from the penicillin-allergic patients, in whom 50% had additional drug allergies (207/413).

Only one of the penicillin-allergic patients may have had an allergic reaction to the cephalosporin. Just after the cephalosporin was given at the beginning of the case (just after a spinal anesthetic was placed), diphenhydramine and hydrocortisone were given. However, no mention was made on the chart about itching, hives, or a rash. Furthermore, the steroids may have been given as a stress

Table 1. Number of Patients Receiving Antibiotics

	Type of Patient	
	All Patients	**Penicillin-Allergic Patients**
Total patients	2933	413
Received a CSP	2431 (83%)	300 (73%)
Received a non-CSP antibiotic	124 (4%)	59 (14%)
Received no antibiotic	378 (13%)	54 (13%)

CSP = cephalosporin.

dose because the patient was taking chronic steroid therapy. The diphenhydramine may have been used as a sedative. One of the non-penicillin-allergic patients did develop a rash while the cephalosporin was infusing, requiring discontinuation of the antibiotic.

Discussion

The incidence of allergic reactions to cephalosporins in penicillin-allergic people has been reported to be approximately 8% by both Petz[8] and Thoburn et al.[9] Most of the reactions involved skin manifestations. Petz found the rate of reactions to be 1.7% in non-penicillin-allergic patients. Anaphylaxis was exceedingly rare, occurring in only 0.4% of penicillin-allergic patients. However, this figure was higher than the rate in the non-penicillin-allergic patients, in whom only 2 of 9,388 (or 0.02%) patients experienced anaphylaxis to a cephalosporin.

The increased rate of cross-reactivity can be explained at least partly by the higher incidence of allergic reactions to antigenically unrelated compounds in penicillin-allergic patients.[10] Penicillin allergy itself is unlikely to predispose to a greater than usual degree of cross-reactivity, because in the current study (*Table 3*), a similar fraction of patients were allergic to other medications if they were penicillin-allergic (207/413, or 50%) than if they were not allergic to penicillin but to at least one other medication (67/143, or 47%). It is possible that allergy to *any* medication predisposes to an increased likelihood of a reaction to any other medication.

In the current study, all patients who claimed to be penicillin-allergic were assumed to be allergic to penicillin. Although this often is not the case, one rarely has the luxury of reviewing results of skin testing (or other indicators of allergy) between one's first encounter with a patient and the beginning of the planned anesthetic. One usually is forced to rely on the patient's word and possibly faulty recollection, and then proceed in an appropriate manner. This study attempted to clarify the risks of administering cephalosporins under typical clinical conditions.

Table 2. All Penicillin-Allergic Patients Compared with the Subset Population

	Male	**Female**	**Avg. Age (± SD)**
Penicillin-allergic patients:	131 (32%)	282 (68%)	58 (± 17)
Subset (non-penicillin allergic)	242 (47%)	272 (53%)	52 (± 20)

Table 3. Penicillin-Allergic Patients Compared with the Subset Population

	No. of Medicinal Allergies					**Total Patients**
	0	**1**	**2**	**3**	**≥4**	
Penicillin-allergic patients:	0	206	105	57	45	413
Subset (non-penicillin allergic)	371	76	34	22	11	514

The absence of allergic reactions found in this study has several explanations. First, the cefazolin that most of the patients received may cross-react weakly, if at all, with penicillin. Skin tests demonstrate that cephalosporins vary considerably in their cross-reactivity with penicillin.[11] For example, cephalothin has a higher affinity to the antipenicillin antibodies than does cephalexin.[8] Antibodies to cephalexin are primarily to the 7-amino-cephalosporanic acid nucleus and do not cross-react with the penicillin nucleus.[6] Furthermore, the concentration of penicillin G necessary to inhibit antibodies to cephalexin is 600 times the concentration of cephalexin necessary for inhibition.

Contamination of the first cephalosporins with traces of penicillin (or penicilloyl proteins) may have contributed to early reports of reactions to cephalosporins in penicillin-allergic patients.[12] However, this type of impurity is unlikely to be present in the cephalosporins currently in use.

Another explanation for the lack of reactions found in this study involves the number of patients claiming to be allergic to penicillin who will not develop a reaction on repeat exposure to this drug. Only a minority of patients who have had a reaction to penicillin will have difficulty taking it years later.[7]

Establishing sensitivity to penicillin and then sensitivity to cephalosporins has proven to be a difficult task. Antibodies to penicillin can be demonstrated in nearly all people who receive the drug,[13] whether or not an allergic reaction appears. If only those who have clinical allergic reactions to penicillin are considered, the incidence of positive skin tests to cephalosporins may be as low as 1 in 30[2] or as high as 30% to 50%.[7,14] The wide range of values may be due to the choice of cephalosporins tested in each study and their differing immunogenicities.

However, skin tests are not entirely dependable. Scholand et al.[15] reported a case of a man who was skin-test positive for penicillin and skin test-*negative* for cephalothin, and yet who developed anaphylaxis to intravenous cephalothin as soon as the drug was started. Although this case could be explained by assuming that the minor antigenic determinants were to blame,[16] it highlights the limitations of skin testing.

When one is presented with a patient who has a history of penicillin allergy, every attempt should be made to elucidate the evidence for such a claim. The symptoms associated with the reaction, when the reaction occurred, and the therapy used to treat the patient should be explored. Inquiries also should be made as to any subsequent diagnostic tests that may have been performed, such as allergic skin testing.

The present study relied solely on the allergy claims of the patients. This situation is what normally is encountered. Rarely, if ever, does one have skin test results to confirm penicillin allergy and cross-reactivity with cephalosporins. Instead, therapy must be guided by the probability of a patient's allergy to penicillin and the likelihood of its leading to a reaction if a cephalosporin is given.

All but two of the penicillin-allergic patients in this study received cefazolin, which is a first-generation cephalosporin. It is possible that only the safety of this drug in penicillin-allergic patients was demonstrated. However, the literature seems to indicate otherwise. If a reaction occurred, it would be expected to manifest itself as a minor skin eruption of some variety. Anaphylactic reactions are rare,[10] and their incidence is in the same range as the incidence for anaphylaxis to cephalosporins in the general population (0.02%–0.1%). Furthermore, as shown by others and as confirmed in this study, allergy to any medication increases the likelihood of allergy to any other drug. The clinician must be more vigilant when dealing with these patients and prepared to treat manifestations of allergy as they appear.

The alternative medications that are given in place of cephalosporins often expose the penicillin-allergic patient to other serious side effects. For example, the nephrotoxicity and ototoxicity of the aminoglycosides and the hypotension that can occur with vancomycin administration are well known. The dangers these medications pose must be weighed carefully against the small risk of cross-reaction between penicillin and a cephalosporin.

In conclusion, cephalosporins (and cefazolin in particular) should be considered a first choice in penicillin-allergic patients who need antibiotic therapy intraoperatively. The practice of trying a small amount of cephalosporin first ("test-dosing") before administering the whole dose is wise. It may elicit a more limited reaction before the rest of the drug is given. Although small amounts of drug can elicit major allergic reactions, it is possible that the dose of drug given can determine the magnitude of histamine release in anaphylactic or anaphylactic reactions.[17]

In the small population of patients who report a history of anaphylaxis to penicillin, other appropriate medications should be substituted. The risk of administering a cephalosporin to this type of patient outweighs the possible benefits. Anaphylactic reactions in a patient given anesthesia are particularly dangerous, because pulmonary manifestations may challenge ventilation and oxygenation of the patient. In addition, symptoms of anaphylaxis can be subtle or nonspecific and not easily linked to their cause. Patients receiving general anesthesia or sedation may not be able to assist by alerting the anesthesiologist that something is awry.

It is possible that patients who reported anaphylactic reactions to penicillin essentially were excluded from the study. The anesthesiologist in charge of their care may have feared the reaction these medications could cause and did not administer a cephalosporin. Some day it may be shown that cephalosporins are safe in these patients, as well.

Acknowledgments

We would like to thank Dr. Cascorbi for his assistance in editing the manuscript and for encouraging research in our department. We would also like to thank Mrs. Esther Goodman for her artistic rendition of Figure 1, Mrs. Leslie Henry for her help with background information and references, and Mrs. Molly Durden for skillfully taking care of many of the tasks involved in preparing the manuscript.

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