

Review of the use of cephalosporins in children with anaphylactic reactions from penicillins

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OBJECTIVE: It is a widely accepted practice that children with anaphylaxis from penicillins should avoid cephalosporins. The purpose of the present study was to determine whether there is evidence in the literature to support this practice.

DATA SOURCES: MEDLINE, EMBASE, Toxline, International Pharmaceutical Abstracts and PubMed were used to search the literature published from 1966 to 2001. The Canadian Medical Protective Association, Health Canada and the Boston Collaborative Drug Surveillance Program were also contacted to determine whether there were any unpublished cases of cross-reactivity between penicillins and cephalosporins.

DATA EXTRACTION: Cases describing the use of cephalosporins in adults and children with positive penicillin skin tests or anaphylaxis from penicillin were evaluated. Case reports of anaphylaxis from cephalosporins in paediatric patients were identified.

DATA SYNTHESIS: There have been five reported cases of serious reactions from cephalosporins in patients with a history of anaphylaxis from penicillins. All cases occurred in adults; three developed anaphylaxis from the older, first-generation cephalosporins, cephalothin and cephaloridine; one developed anaphylaxis from cefamandole; and one developed anaphylaxis

from cefaclor. There have been 12 other published reports of anaphylaxis from cephalosporins in adults with a history of penicillin allergy or a positive penicillin skin test, but with no history of anaphylaxis from penicillin. In seven studies, in which a total of 158 patients with positive penicillin skin tests were administered cephalosporins, seven had apparent immunoglobulin E-mediated reactions when they were given a cephalosporin. When the class of cephalosporin was able to be determined, none of the reports of reactions from cephalosporins in patients with allergies to penicillin involved third-generation cephalosporins. There have been 13 case reports of anaphylaxis from cephalosporins in paediatric patients.

CONCLUSION: There are no published case reports of anaphylaxis from cephalosporins in children with anaphylaxis from penicillin, and there are only a small number of such reports in adults. Anaphylaxis from cephalosporins appears to be incredibly rare in children. There is minimal evidence in the literature to support the avoidance of cephalosporins in children with anaphylaxis from penicillins.

Key Words: *Anaphylaxis; Antibiotic allergy; Antibiotic hypersensitivity; Cephalosporins; Cross-reactivity; Drug allergy; Drug hypersensitivity; Penicillin*

Résumé à la page suivante

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Le point sur les céphalosporines chez les enfants ayant des réactions anaphylactiques aux pénicillines

OBJECTIF : Il est en général accepté dans la pratique d'éviter les céphalosporines chez les enfants qui manifestent des signes d'anaphylaxie avec les pénicillines. Le but de la présente étude est de vérifier si cette pratique s'appuie sur des sources dans la littérature.

SOURCES DES DONNÉES : Les réseaux Medline, Embase, Toxline, *International Pharmaceutical Abstracts* et PubMed ont été interrogés au sujet des publications parues entre 1966 et 2001. L'Association canadienne de protection médicale, Santé Canada et le *Boston Collaborative Drug Surveillance Program* ont aussi été contactés afin de déterminer si des cas non publiés de réactivité croisée étaient survenus entre les pénicillines et les céphalosporines.

EXTRACTION DES DONNÉES : Les cas décrivant l'utilisation de céphalosporines chez des adultes et des enfants ayant présenté des résultats positifs aux tests de réaction cutanée à la pénicilline ont été évalués. Les rapports faisant état de réactions anaphylactiques aux céphalosporines chez des enfants ont été recensés.

SYNTHÈSE DES DONNÉES : Cinq cas de réaction grave aux céphalosporines ont été rapportés chez des patients qui avaient des

antécédents d'anaphylaxie avec les pénicillines. Tous les cas sont survenus chez des adultes : trois ont développé une anaphylaxie avec les anciennes céphalosporines de première génération, céphalothine et céphaloridine; un a développé une anaphylaxie avec le céphamandole et le dernier avec le céfador. Douze autres rapports ont été publiés sur l'anaphylaxie associée aux céphalosporines chez des adultes ayant des antécédents d'allergie à la pénicilline ou un test cutané à la pénicilline positif sans antécédents d'anaphylaxie à la pénicilline. Dans sept études, au cours desquelles en tout 158 patients ayant des tests positifs à la pénicilline ont reçu des céphalosporines, sept sujets ont apparemment présenté des réactions modulées par l'immunoglobuline E au moment de recevoir leur céphalosporine. Lorsqu'il était possible de déterminer la classe de céphalosporine, aucun des rapports de réaction aux céphalosporines chez les patients allergiques aux pénicillines ne concernait les céphalosporines de 3^e génération. Treize cas d'anaphylaxie liés aux céphalosporines ont été rapportés chez des enfants.

CONCLUSION : Il n'y a pas de rapports de cas publiés quant à l'anaphylaxie liée aux céphalosporines chez des enfants ayant une anaphylaxie aux pénicillines et seul un petit nombre de rapports ont porté sur des adultes. L'anaphylaxie semble incroyablement rare chez les enfants. Très peu de preuves dans la littérature préconisent d'éviter les céphalosporines chez les enfants allergiques aux pénicillines.

A common problem in paediatrics is determining whether a cephalosporin can be used in a child with a history of a serious reaction from a penicillin, and whether a penicillin can be administered to a child with a history of a serious reaction from a cephalosporin. In many cases, such patients are prescribed antibiotics that are less effective, more toxic, have a broader spectrum or are more expensive than the drug of choice for their condition.

Diagnostic tests for antibiotic allergies are limited and are standardized only for penicillin.

When penicillin is metabolized, the beta-lactam ring opens to form a penicilloyl derivative that, when bound to serum and tissue proteins, accounts for more than 90% of immunologically active penicillin metabolites (the major determinants). However, about 16% of allergic reactions to penicillin involve multiple, different antigens that result from further penicillin metabolism. These antigens are referred to as minor determinants (1). In patients who have a history of penicillin allergy but negative skin test results using major and minor determinants, studies have shown that the chance of a serious allergic reaction to penicillin is negligible (1). Skin testing for cephalosporin allergy is sometimes performed, but is not standardized because the antigenic determinants of a serious allergic reaction have not been established.

Standard teaching is that patients who have had possible anaphylaxis from penicillin should be given cephalosporins only with extreme caution, because their risk of developing anaphylaxis from cephalosporins is increased (2). Penicillins have a beta-lactam ring attached to a thiazolidine ring with one side chain, while cephalosporins have a beta-lactam ring attached to a dihydrothiazine ring with two side chains (1) (Figure 1). Because of the similar struc-

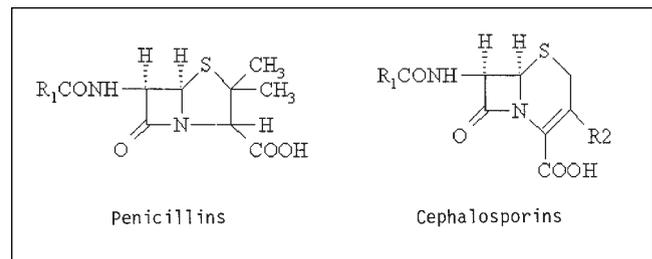


Figure 1) Comparison of chemical structure of penicillins and cephalosporins. R Side chain

tures, there is a theoretical risk of cross-reactivity between penicillins and cephalosporins.

Soon after cephalosporins were introduced, there were reports of anaphylaxis in patients who were given cephalosporins and who had also experienced anaphylaxis from penicillin. Furthermore, during the initial clinical trials with first-generation cephalosporins and cefamandole, 8.1% of patients with a history of allergy to a penicillin had a possible allergy to a cephalosporin, compared with 4.5% of patients with no such history (3). However, in those initial trials, no attempt was made to ensure that the reaction to the penicillin or to the cephalosporin was truly allergic. The purpose of the present study was to determine whether there is further evidence in the literature to support the avoidance of cephalosporins in children with suspected penicillin allergies. If the risk of cross-reactivity between penicillins and cephalosporins is low in the adult population, the same is probably true for the paediatric population. Therefore, the incidence of case reports of anaphylaxis from cephalosporins in adults or children with anaphylaxis from penicillin or a positive penicillin skin test was studied. The results of cephalosporin challenge in patients with pos-

TABLE 1
Summary of case reports of anaphylaxis to cephalosporins in patients with a history of penicillin allergy or a positive penicillin skin test

Year, Reference	Age (years)	Sex	Reaction to penicillin	Anaphylaxis to penicillin (yes/no)	Cephalosporin	Reaction to cephalosporin
1965, Kabins et al (4)	47	F	Pruritis and angioneurotic edema	Yes	Cephalothin	Hypotensive, wheezing and unresponsive within 2 min
1966, Rothschild and Doty (23)	56	M	Pruritis and urticaria	No	Cephalothin	Apnea and hypotension within minutes
1966, Drug Letter (24)	40	F	Rash*	No	Cephalothin	Pruritis, dyspnea and angioneurotic edema
1968, Scholand et al (5)	65	M	Urticaria, angioneurotic edema and dyspnea	Yes	Cephalothin	Wheezing and hypotension within 30 s
1968, Girard (6)	1 patient [†]		Anaphylaxis*	Yes	Cephaloridine	Mild anaphylactic shock*
1971, Petz (25)	2 patients [†]		Unknown*	No	Cephalothin	Anaphylaxis*
1974, Spruill et al (10)	59	M	Unknown*	Unknown	Cephalothin	Cardiac arrest within 5 min
1980, Zeok and Tsueda (26)	1 patient [†]		Urticaria	No	Cephalothin	Hypotension, bradycardia, diminished respiratory excursions and wheezing, generalized edema, urticaria
1989, Blanca et al (7)	22	F	Angioedema of the mouth and eyes	No	Cefamandole	Hypotension
1989, Blanca et al (7)	50	F	Hypotension, pruritis of the lips, breathing difficulties	Yes	Cefamandole	Hypotension, dysphonia, generalized pruritis, and upper airway obstruction
1989, Macnab (27)	35	F	Unknown*	No	Cephalexin and cephalothin	Urticaria, dyspnea, nausea and severe headaches
1999, Pumphrey and Davis (8)	76	F	Anaphylaxis to amoxicillin*	Yes	Cefaclor	Fatal anaphylaxis*
1999, Pumphrey and Davis (8)	3 patients [†]		Two allergic to amoxicillin and 1 allergic to penicillin*	Unknown	Unknown	Fatal anaphylaxis*
1999, Nordt et al (28)	32	F	Unknown*	Unknown	Cephalexin	Rapid onset of throat tightness and urticaria

*No further details of the reactions were given; [†]Ages unknown. F Female; M Male

itive penicillin skin tests were also reviewed. If it is exceedingly rare for children to develop anaphylaxis from cephalosporins, it may not be necessary to avoid their use in children who are allergic to penicillins. Therefore, the total number of published case reports of anaphylaxis from cephalosporins in all children was also researched.

DATA AND METHODS

The literature was reviewed for results of cephalosporin challenge in adults or children with anaphylactic reactions from penicillin or with positive penicillin skin tests. Case reports of anaphylaxis from cephalosporins in paediatric patients (up to 16 years of age) were also researched. MEDLINE, EMBASE, Toxline, International Pharmaceutical

Abstracts and PubMed were used to search the literature published from 1966 to 2001, using 'anaphylaxis', 'penicillin', 'cephalosporin', 'beta-lactams', 'cross-reactivity', 'cross-sensitivity', 'drug allergy' and 'drug hypersensitivity' as keywords, and by referencing the bibliographies of related papers. Cases with urticaria or life-threatening symptoms (apnea, bronchospasm or hypotension) were considered to be anaphylaxis. We also contacted Health Canada, the Canadian Medical Protective Association (CMPA) and the Boston Collaborative Drug Surveillance Program to determine whether they were aware of any unpublished cases of cross-reactivity between penicillins and cephalosporins, and anaphylaxis from cephalosporins in children.

TABLE 2
Summary of studies of cephalosporin challenge in patients with positive skin tests for allergies to penicillin

Reference (year)	Patients challenged with cephalosporins	Patients with negative challenge	Patients with positive challenge	Cephalosporin	Reaction if positive challenge
Assem and Vickers (29) (1974)	2*	0	2*	Cephaloridine	Anaphylactic reaction [†] in first patient, extensive urticaria in second patient
Warrington et al (30) (1978)	3	3	0	Not applicable	Not applicable
Solley (31) (1982)	27	27	0	Not applicable	Not applicable
Rohr (32) (1987)	62	61	1	Not specified	Mild urticaria and bronchospasm [†]
Blanca et al (7) (1989)	12 [‡]	10	2	Cefamandole	In one patient, profound and sustained hypotension; in the other patient, transient hypotension, dysphonia, generalized pruritus, and upper airway breathing difficulties
Shepherd and Burton (33) (1993)	9	9	0	Not applicable	Not applicable
Pichichero and Pinchichero (9) (1988)	43 [§]	41	2	Not specified	Mild IgE-mediated reactions [†]

*Although three patients had positive challenges with cephalosporins, only two patients had suspected IgE-mediated reactions; [†]No further details were provided; [‡]Three penicillin skin-test-negative patients were selected on the basis of positive penicillin challenge; [§]Treatment courses with cephalosporins. IgE Immunoglobulin E

RESULTS

A review of case reports of anaphylaxis from cephalosporins in adults or children with a history of penicillin allergy or a positive penicillin skin test is presented in Table 1. In five cases (4-8), patients with a history of anaphylaxis from penicillin developed anaphylaxis from a cephalosporin. Three of the cases involved anaphylaxis from the older, first-generation cephalosporins, cephalothin and cephaloridine, while two cases involved anaphylaxis from the second-generation cephalosporins, cefaclor and cefamandole. There were 12 other published reports of anaphylaxis from cephalosporins in adults with a history of penicillin allergy or a positive penicillin skin test but with no history of anaphylaxis from penicillin. In nine of these cases, the class of cephalosporin was known (six were cephalothin, one was both cephalothin and cephalexin, one was cephalexin and one was cefamandole). The CMPA was not aware of any legal action in Canada that resulted from the administration of a cephalosporin to a patient with an allergy to penicillin. Health Canada's Adverse Drug Reaction Monitoring Program and the Boston Collaborative Drug Surveillance Program had no additional unpublished reports of anaphylaxis from cephalosporins in patients who were allergic to penicillin.

Table 2 summarizes the studies of cephalosporin challenge in children and adults with positive penicillin skin tests. Only one study (9) focused on paediatric patients. Of

a total of 158 patients, there were seven positive challenges with cephalosporins. Four of the seven suspected immunoglobulin E (IgE)-mediated reactions were mild (one reaction to cephaloridine and three reactions in which the cephalosporin was not specified), while three were serious reactions that consisted of anaphylaxis from cephaloridine or cefamandole.

There were 13 reported cases of anaphylaxis from cephalosporins in children (Table 3). One case involved the old, first-generation cephalosporin cephalothin (10), four cases involved second-generation cephalosporins (cefaclor, cefamandole, cefotetan and cefuroxime) (11-13) and eight cases involved a third-generation cephalosporin (ceftriaxone in seven patients and ceftazidime in one patient) (14-16).

DISCUSSION

There have been only 17 published case reports of anaphylaxis from cephalosporins in patients with a history of penicillin allergy or a positive penicillin skin test. All cases occurred in adults. In nine of the 14 cases in which the class of cephalosporin could be determined, anaphylaxis was from first-generation cephalosporins, while the other five cases were anaphylaxis from second-generation cephalosporins. However, one limitation of the present study was that the reporting of cases was sporadic. Therefore, the infrequency of case reports may have been due to the fact that physicians

TABLE 3
Case reports of anaphylaxis from cephalosporins in children

Reference	Age (years)	Sex	Cephalosporin	Reaction to cephalosporin
Romano et al (14) (1999)	15	Male	Ceftriaxone	Urticaria, dyspnea, tachycardia and severe hypotension within 5 min
Grouhi et al (11) (1999)	2	Male	Cefaclor	Vomiting, generalized hives, shortness of breath, wheezing with grunting and loss of consciousness
Wessel (12) (1998)	6	Female	Cefamandole	Anaphylactic shock*
Spruill et al (10) (1974)	11	Male	Cephalothin	Hypotension and shock
Romano et al (15) (2000)	6	Male	Ceftriaxone	Urticaria
	7	Female	Ceftriaxone	Anaphylactic shock*
	14	Male	Ceftriaxone	Anaphylactic shock*
	12	Female	Ceftriaxone	Anaphylactic shock*
	5	Female	Ceftriaxone	Anaphylactic shock*
	9	Female	Ceftriaxone	Anaphylactic shock*
Romano et al (16) (2001)	16	Female	Ceftazidime	Anaphylactic shock (urticaria, rhinitis, wheezing, dyspnea and hypotension)
Health Canada (13) (2001)	10	Female	Cefotetan	Flushing, hypotension, atrial arrhythmia and tachycardia
Health Canada (13) (2001)	8	Female	Cefuroxime	Urticaria and edema

*No further details were provided

are very compliant about not prescribing cephalosporins to patients with suspected penicillin allergies, the cases of cross-reactivity between penicillins and cephalosporins that occur are often not reported, or that it is very rare for cross-reactivity to occur.

There have been seven studies in which 158 patients with positive penicillin skin tests were administered cephalosporins; seven had IgE-mediated reactions when they were administered a cephalosporin. Four of the reactions were mild (one reaction was to cephaloridine and three were in reaction to a cephalosporin that was not specified). There was one serious reaction to cephaloridine and two serious reactions to cefamandole in patients with allergies to penicillin. A possible explanation for the three serious reactions is that of all the cephalosporins, cephaloridine and cefamandole have side chain structures that are most similar to penicillin and, thus, cross-reactivity may have occurred (2).

When the class of the cephalosporin was specified, none of the serious reactions to cephalosporins in patients with positive penicillin skin tests involved third-generation cephalosporins. The risk of serious allergic reactions from cephalosporins in the general population appears to be less than 0.02%, and the risk is lowest for third-generation cephalosporins (possibly because cephalosporins are thought to be only antigenic if the side chain is bound to a serum protein, and free side chains compete with bound side chains for binding to IgE antibodies) (17,18).

Anaphylaxis from cephalosporins appears to be incredibly rare in children, with only 13 case reports in the literature. However, it is likely that not all cases would have been

reported or even recognized. It is interesting that eight of those case reports came from Romano (15,16). He also mentioned a six-year-old with an immediate reaction to a cephalosporin in another paper (19), but it is not clear if this was an additional case. A recent review article found only 54 published cases of anaphylaxis to cephalosporins in both adults and children, but did not include all of the paediatric cases found in the present study (12,15,16).

The reason why a high incidence of cross-reactivity between penicillins and cephalosporins was thought to be likely is that both have a beta-lactam ring. However, there is increasing evidence that, in most allergic reactions to cephalosporins, it is the side chain rather than the beta-lactam ring that is the antigen (2). It is only the older, first- and second-generation cephalosporins (cephalothin, cephaloridine and cefamandole) that have a side chain that is similar to that of penicillin, while cephalexin has a side chain that is identical to that of ampicillin. In addition, older, first-generation cephalosporins were sometimes contaminated with penicillin before 1980 (20). These two facts may account for some of the early reports of cross-reactivity between penicillins and cephalosporins. Furthermore, the results of penicillin skin testing are not predictive of cephalosporin allergy, which again suggests that there is limited cross-reactivity (3).

There is evidence that patients with a history of penicillin allergy have three times the rate of patients in control groups of having an allergic reaction to any other antibiotic (17). Therefore, even if the risk of patients with a history of penicillin allergy having a serious reaction to cephalosporins is double that of patients in control groups,

this risk may be lower than the risk of them having a serious reaction to any alternative antibiotic (2). It has been suggested that the low incidence of serious allergic reactions to cephalosporins may relate to the lack of stability of immunogenic metabolites (16).

CONCLUSIONS

There is minimal evidence in the literature to support the avoidance of cephalosporins in children with anaphylaxis from penicillins. Despite published guidelines to the contrary (20), a child or adult with a previous mild reaction to a peni-

cillin can probably safely be administered a cephalosporin. If a more serious reaction to a penicillin has occurred, yet the patient has a negative penicillin skin test, it is probably safe to administer a cephalosporin (21). However, if skin testing cannot be done or if a patient is known to have had a positive penicillin skin test, it is not advisable to administer a full dose of an intravenous cephalosporin in the face of standard recommendations against this practice (20). However, it would appear to be safe to administer a supervised, graded challenge with a nonfirst-generation cephalosporin other than cefamandole or to embark on desensitization (22).

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