

Comment

Surgery was postponed in our case until the second trimester of pregnancy to avoid the greater possibility of spontaneous abortion or other hazard to the conception stemming from anesthesia and a major surgical procedure during the first trimester. The present case is, to our knowledge, only the second to be described in which successful parathyroid exploration has been performed during pregnancy with the subsequent delivery of a normal infant at term. In a previous report⁶ summarizing the complications of maternal hyperparathyroidism during pregnancy, the recommendation was made that surgical exploration for a parathyroid adenoma should be carried out when the diagnosis is made during the pregnancy. That extensive surgical exploration for a parathyroid adenoma is feasible during pregnancy, without harm to the mother or the fetus is demonstrated by the case reported here, as well as by the previous case of Petit and Clark.⁶

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Anaphylaxis to *Clonidine* in a Patient Allergic to *Penicillin*

Joseph F. Mohr

CEPHALOTHIN is an antibiotic because of its antibacterial activity. Its toxicity is due to its reactivity with the amino acid tyrosine. It is a good drug for penicillin-resistant infections. Subcutaneous injections have been reported to cause severe allergic reactions. Because apparently no other cases have been reported, we are reporting this reaction on first exposure. It is not known to be allergic in nature. The literature suggests that reactivity is not an allergic reaction.

From the departments of medicine and surgery of the Ohio State University Medical Center, Columbus.
Reprint requests to University Hospital, Columbus, Ohio 43210 (Dr. Tennenbaum).

cinat, without incident, and was discharged. Other medications, given less than six hours before the reaction, included digitalis, heparin sodium, morphine sulfate, and tetracycline hydrochloride.

Approximately one year earlier, generalized pruritus developed immediately following an injection of penicillin for bronchitis. Ten months before admission, the patient experienced severe conjunctival irritation while mixing a vial of penicillin. Several days later, when the patient was walking through a room where a penicillin injection had been administered intramuscularly to a patient in the nursing home, severe dyspnea and itching developed. At a local hospital, angioneurotic edema of the face and lips and generalized urticaria were documented. This cleared with appropriate therapy. The patient denied a history of hay fever or asthma and was not known to be allergic to any other drugs.

A prick test subsequently performed to penicilloyl-polylysine (12×10^{-6} M) was positive three weeks after the anaphylactic reaction. A prick test with cephalothin sodium (0.15 mg/ml) was negative. Further prick and intradermal testing with this drug and penicillin were not done because of the known cardiac disease. Passive transfer tests were performed with the patient's serum and with use of a healthy adult who had no background of atopy. Immediate positive reactions to intradermal administration of penicillin G (10^{-2} M) and penicilloyl-polylysine (12×10^{-5} M) were obtained 24 hours after transfer. No response was found to cephalothin in concentrations below those which produce nonspecific irritant reactions in control skin sites.

Comment

Three previously reported cases of anaphylaxis to cephalothin in patients with a history of penicillin allergy⁶⁻⁸ are summarized in the Table. It is noteworthy that three of these four patients had previously experienced an immediate allergic reaction to penicillin, suggesting that this type of patient has a greater risk of a severe reaction from cephalothin therapy.

The chemical structure of both penicillin G and cephalothin includes a four-membered B-lactam ring between two cyclic portions. The similarity in structure is readily appreciated in the Figure. Because of this structural resemblance, the clinical evaluation of cephalothin, the first widely available cephalosporin C derivative, was closely observed in patients allergic to penicillin for evidence of possible cross-reactivity. Early reports indicated a lack of cross-allergenicity between cephalothin and penicillin by both skin tests performed in patients with known allergy to penicillin⁹ and in a survey of cephalothin usage in such patients.⁵ However, recent evidence has accumulated to demonstrate that cross-allergenicity does occur both in humans and in laboratory animals.

In addition to the four cases summarized here, several investigators have reported patients with known allergic reactions to penicillin in whom positive intradermal skin tests to cephalothin developed. Among eight patients who had had anaphylactic reactions to penicillin, Perkins and Saslaw⁴ found one who reacted to intradermal administration of cephalothin. None of 14 patients who experienced delayed serum sickness reaction to penicillin showed cross-allergenicity. Two other isolated cases of patients with allergy to penicillin showed



Comparison of cephalothin and penicillin G, showing the form with penicillin G. The structure of cephalothin is formed with a fused ring system, and the structure of penicillin G is formed with a fused ring system. The central portion of the penicillin G molecule is the same as the central portion of the cephalothin molecule, which is the basis for the cross-allergenicity of this pair of drugs.

a reaction to intradermal administration of cephalothin.^{11,10} Recently, a patient in whom immune hemolytic anemia during penicillin therapy, was observed to have a severe reaction to cephalothin, a drug to which he had never received.¹² Hemagglutination tests with penicillin and cephalothin have demonstrated the presence of an antibody to penicillin in this patient which cross-reacts with cephalothin. Furthermore, in this same patient, a mixture of erythrocytes labeled with ⁵¹Cr and sensitized with a mixture of shortened half-life penicillin and cephalothin with cephalothin or penicillin alone, showed a significant cross-reactivity. This cross-reactivity suggested the presence of antibodies demonstrating a degree of cross-allergenic significance. Another study found that sera from eight patients with demonstrable skin sensitizing reactions to penicillin G, responded to challenge with cephalothin by the Prausnitz-Küstner test. In the same study, four to six patients from the same sources and with similar histories, but who were not allergic to penicillin, did not show cross-allergenicity in humans have been reported.

In spite of this, cephalothin is allergenic in many patients who have had allergy to penicillin. These observations suggest that patients who are allergic to penicillin include certain populations, one of which involves cross-allergenicity, and that antigenic determinants can be formed by cephalothin in vivo. These observations have been particularly helpful in determining the nature of the common antigenic determinants.

At least two groups of investigators have shown cross-reaction between penicillin and cephalosporin C derivatives conjugated to serum proteins in animals.^{14,15} Significantly, this cross-reaction is inhibited by benzylpenicilloyl haptene to a considerable degree. Earlier, it had been assumed that penicillins were converted to the corresponding penicilloyl only through an intermediate penicil-

Cases of Anaphylaxis*				
Case No., Author	Age and Sex	Primary Disease	Reaction to Penicillin	Reaction to Cephalothin
1 Kabins et al ⁶	47, F	Urinary tract infection; non-seasonal hay fever; post-cholecystectomy	Penicillin Puritus and angioneurotic edema 10 minutes after injection	Hypotensive, wheezing, and unresponsive within 2 minutes
2 Rothschild and Doty ⁷	56, M	Cellulitis; hidradenocarcinoma of the axilla	Pruritus and urticaria 10 minutes after methicillin sodium injection	Apeas and no blood pressure within minutes
3 Drug letter ⁸	47, F	Tooth abscess; sarcoidosis; convulsive disorder	History of "rash"; no other details	Pruritus, dyspnea, and angioneurotic edema
4 Scholand et al	65, M	Cellulitis; post-myocardial infarct; embolectomy	Generalized pruritus, urticaria, angioneurotic edema, and dyspnea	Wheezing and absent blood pressure within 30 seconds

*Summary of the important features of the reported anaphylactic reactions to cephalothin in patients who are allergic to penicillin. All patients recovered after receiving appropriate therapy.

lenic acid. As cephalosporin C could not be converted to this intermediate, it was reasoned that the penicilloyl group would not be important in allergic manifestations to these drugs. Reinvestigation,¹⁶ however, has suggested that the direct penicilloylation of carrier protein is a relatively easy and general route to the penicilloyl antigenic determinants in vivo. Cephalosporin C derivatives react with epsilon-amino groups, giving conjugates with certain physical properties resembling the penicilloyl conjugates.¹⁷ The Figure compares the structure of the penicilloyl protein conjugate with the proposed cephalothin analogue. The central identity, oriented between two similar ring systems, is apparent.

As the animal studies suggest that the penicilloyl group is important in this cross-reactivity, it should be noted that our patient gave an immediate positive skin test with penicilloyl-polylysine and that the skin sensitizing antibody directed to this determinant could be passively transferred to the skin of a normal recipient. Two of the three patients discussed previously, who were allergic to penicillin and who gave positive intradermal skin tests to cephalothin, also exhibited immediate positive intradermal skin tests to penicilloyl-polylysine.^{4,11} The third, who is probably identical to the patient in case 3 in the Table, gave a positive delayed reaction.¹⁰ The reaction of this patient was also the least severe of the four summarized in the Table.

With the number of patients who are allergic to penicillin and who have probably been treated with cephalothin on the basis of the early reports of safety, it is indeed surprising that only four severe anaphylactic reactions apparently have been reported. This suggests the antibody in penicillin allergy has less affinity for cephalothin than for penicillin. Only if the antipenicillin antibody has a very high affinity in cross-reaction to cephalothin will a clinical reaction develop in the patient when he is treated with this drug. Indeed in most of the reports demonstrating cross-allergenicity and

where quantitation has been possible, the reaction is weaker with cephalothin or requires a larger dose to produce a comparable response. The possibility is that most anaphylactic reactions to penicillin are mediated through minor determinants, not the major or penicilloyl group, and therefore, it is only the patients with the latter exceptions who are at risk from severe allergic cross-reactions with cephalothin.

Although few severe reactions have occurred, it is apparent cephalosporin C derivatives must be used with caution in patients who are allergic to penicillin. Preliminary evidence suggests that patients with immediate anaphylactic reactions to penicillin and who exhibit positive penicilloyl-polylysine skin tests are the patients at the highest risk of reaction from cephalothin. Further observations will be necessary to confirm this impression.

Cephalothin and Penicillin

Cephalothin sodium—Keflin
Chloramphenicol sodium succinate—Chloromycetin
Tetracycline hydrochloride—Sumycin
Hydrocortisone sodium succinate—Solu-Cortef
Methicillin sodium—Diminil

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