

# Perioperative Anaphylaxis to Cefazolin

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## ABSTRACT

*The incidence of generalized reactions during anesthesia has been reported to range from 1 in 5000 to 1 in 25,000 cases with a mortality rate of up to 6%. The most common causes are neuromuscular blocking agents, latex, and antibiotics. Identification of the offending agent may be difficult because multiple medications are administered over a short period. Furthermore, up to 40% of all generalized reactions during anesthesia are non-immunoglobulin E mediated and therefore can not be evaluated by skin testing. We report a case of perioperative anaphylaxis to cefazolin. Sensitization to cefazolin was determined through skin testing, and the patient underwent successful surgery subsequently with the avoidance of cefazolin. (Allergy and Asthma Proc 25:23–26, 2004)*

## CASE REPORT

A 46-year-old woman with no history of atopy or drug allergies was admitted to the hospital to undergo laminectomy. During surgery, multiple medications—pancuronium, propofol, midazolam, fentanyl, and cefazolin—were administered in this order over a 10-minute interval. Within 15 minutes, the patient developed hypotension, generalized urticaria, and angioedema of the extremities and eyelids without any signs of bronchospasm. Surgery was aborted and symptoms were resolved after treatment with epinephrine, diphenhydramine, and methylprednisolone.

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Mature ( $\beta$ ) tryptase drawn 2 hours after the reaction was 12 ng/mL (normal <1 ng/mL) with a total tryptase of 35 ng/mL (normal <11 ng/mL). Latex and penicillin-specific immunoglobulin E (IgE) antibodies were negative by ImmunoCAP (Pharmacia Diagnostics, Kalamazoo, MI) measurement. Skin test performed 2 months after the reaction was positive to cefazolin only. Skin tests to the penicillin derivatives were negative along with negative responses to pancuronium, propofol, midazolam, and fentanyl (Table I). The patient underwent successful laminectomy subsequently, receiving all the foregoing reagents except cefazolin.

## CAUSES OF GENERALIZED REACTIONS DURING ANESTHESIA

The incidence of generalized reactions during anesthesia has been reported to range from 1 in 5000 to 1 in 25,000 cases with a mortality rate of up to 6%.<sup>1,2</sup> The most common causes are neuromuscular blocking agents (NMBAs), latex, and antibiotics (Table II).<sup>3</sup> NMBAs account for 50–70% of all cases of generalized reactions during anesthesia.<sup>4</sup> The quaternary ammonium ions shared by NMBAs are the immunodominant epitopes recognized by the IgE antibodies,<sup>5</sup> leading to significant cross-sensitivity of ~75% among the NMBAs.<sup>3</sup> NMBAs can be classified by their risk of sensitization as high (succinylcholine and rocuronium), medium (pancuronium, vecuronium, and mivacurium), and low (atracurium and cisatracurium).<sup>4</sup> Atopy is not a risk factor for sensitization, but there is a 3:1 female predominance in reactions to NMBAs, suggesting sensitization to quaternary ammonium ions that may be in personal care products.<sup>5</sup> Routine skin testing to NMBAs is not recommended for adults in the general population given the low incidence of generalized reactions during anesthesia (0.02–0.004%) compared with the high prevalence of sensitivity to NMBAs (9.3%) in the general population.<sup>6</sup>

TABLE I

| Concentration of Reagents Used for Skin Testing in the Case Vignette |                      |                      |
|----------------------------------------------------------------------|----------------------|----------------------|
|                                                                      | Prick                | Intradermal          |
| Pancuronium                                                          | 1 mg/mL              | 0.001–0.1 mg/mL      |
| Propofol                                                             | 1 mg/mL              | 0.001–0.1 mg/mL      |
| Midazolam                                                            | 1 mg/mL              | 0.001–0.1 mg/mL      |
| Fentanyl                                                             | 50 ng/mL             | 0.05–5 ng/mL         |
| Cefazolin                                                            | 2.5 mg/mL            | 2.5 mg/mL            |
| Penicillin G                                                         | 5000 U/mL            | 5000 U/mL            |
| Penicilloyl-polylysine                                               | $6 \times 10^{-5}$ M | $6 \times 10^{-5}$ M |
| Penilloate/penicilloate                                              | 10 mM                | 10 mM                |

The second most common cause of generalized reactions during anesthesia is latex, accounting for 10–16% of cases.<sup>4</sup> Atopy and asthma are more common in patients with latex allergy.<sup>3</sup> Individuals at increased risk include health care workers, surgical patients with spinal bifida and urogenital abnormalities, and patients with a history of multiple surgeries.<sup>7</sup> Careful medical assessment of patients with latex allergy may reveal allergies to several fruits that cross-sensitizes with latex: banana, avocado, chestnut, kiwi, and papaya.<sup>7</sup>

The third most common cause of generalized reactions during anesthesia are the antibiotic drugs, accounting for ~15% of cases.<sup>4</sup> Other causes are the hypnotic induction agents (thiopental, propofol, and etomidate), colloids, opioids, radiocontrast, and local anesthetics. These other agents combined account for ~10% of all reactions.<sup>4</sup>

#### CHARACTERISTICS OF GENERALIZED REACTIONS DURING ANESTHESIA

Recognition of generalized reactions during anesthesia may be difficult. Multiple medications are administered sequentially over a short period, making the temporal relationship between drug administration and clinical reactions less helpful. Patients are sedated and can not communicate the presence of cutaneous symptoms of itch and flushing and surgical drapes may obscure cutaneous findings.<sup>5</sup> Reactions may be well established before the signs are recognized.

Generalized reactions may be secondary to IgE (anaphylactic) or non-IgE (anaphylactoid) mechanisms. Differentiation of the two mechanisms is important because the severity of anaphylactoid reactions tends to be similar with repeat administration whereas the severity of anaphylactic reactions may worsen with repeat administration of the causal agent.<sup>5</sup> Of the 789 patients who experienced generalized reactions during anesthesia, 66% of cases were IgE mediated and 34% were non-IgE mediated.<sup>3</sup> Cardiovascular and respiratory signs were more common in anaphylactic reactions whereas cutaneous findings were more frequent in anaphylactoid reactions. However, absence of cutaneous findings did not rule out the presence of generalized reac-

TABLE II

| Causes of Generalized Reactions to Anesthesia |                                                                                    |
|-----------------------------------------------|------------------------------------------------------------------------------------|
| 50–70%                                        | Muscle relaxants                                                                   |
| 10–16%                                        | Latex                                                                              |
| 10–15%                                        | Antibiotics                                                                        |
| 10%                                           | Hypnotic induction agents, colloids, opioids, radiocontrast, and local anesthetics |

tions.<sup>3</sup> There was a significant female predominance in both anaphylactic and anaphylactoid reactions of 66 and 70%, respectively.<sup>3</sup>

#### PATHOGENESIS OF $\beta$ -LACTAM ALLERGY

The case vignette illustrates a patient with perioperative anaphylaxis to cefazolin. The  $\beta$ -lactam antibiotics—penicillin, cephalosporin, carbapenem, and monobactam—are responsible for 80% of all generalized reactions to antibiotics.<sup>3</sup> Most studies on  $\beta$ -lactam antibiotics focus on penicillin and its derivatives. Penicillin has a low molecular weight and is coupled covalently to host carrier proteins to form multivalent haptenic immunogenic complexes capable of initiating immune responses.<sup>8</sup>

The haptenic complexes are formed because the  $\beta$ -lactam ring is unstable and readily acylates with lysine residues in proteins. This covalent bond forms the major antigenic determinant of penicillin—the penicilloyl epitope.<sup>9</sup> Other minor forms of haptination may occur by the isomerization of penicillin and covalent binding through carboxyl and thiol groups, forming the minor determinants.<sup>10</sup> Most tissue-bound penicillin is in the form of the major determinant and a small fraction is in the form of minor determinants. Although the major determinant accounts for 90% of IgE-mediated reactions to penicillin, reactions to the minor determinants are associated more frequently with anaphylactic reactions whereas reactions to the major determinant are more often urticarial in nature.<sup>10</sup>

#### CROSS-SENSITIVITIES AMONG $\beta$ -LACTAM ANTIBIOTICS

All  $\beta$ -lactam antibiotics contain the four-membered  $\beta$ -lactam ring. Except for the monobactam group, the shared  $\beta$ -lactam structure is joined to another five- or six-membered ring, forming the nucleus with the side chains attached to the nucleus.<sup>9</sup> Most IgE antibodies are formed against the neodeterminants of the nucleus; however, side-chain-specific IgE antibodies also may be formed.<sup>11</sup> The clinical significance of the specificity of the immune response is that cross-sensitization among the  $\beta$ -lactam antibiotics may be theoretically possible if the IgE antibodies recognize the neodeterminants of the common nucleus structure. On the other hand, if the immune response only recognizes the side chains, then cross-sensitivities are less likely unless the antibiotics have the same side chain.<sup>9</sup>

Clinical cross-reactivity among the  $\beta$ -lactam drugs is complex. Patients with a history of allergy to the penicillins have cross-reactivity to the cephalosporins of up to 10%.<sup>12</sup> Extensive cross-sensitivity exists between carbapenem and penicillin. Saxon *et al.*<sup>13</sup> skin tested patients with a history of penicillin allergy to penicillin derivatives and imipenem, a carbapenem. Of the patients who had positive skin tests, 50% were positive to imipenem. In contrast, cross-sensitivity between monobactam and penicillin is low because allergic reactions to the monobactam are attributed to side-chain specificity. In theory, cross-sensitivity between aztreonam (monobactam) and ceftazidime (cephalosporin) exists because both drugs share the same side chain.<sup>9</sup>

Side-chain-specific immune responses are important determinants of immunologic responses and may predict potential cross-reactivity between  $\beta$ -lactam antibiotics with the similar side chain.<sup>9</sup> Silviu-Dan *et al.*<sup>11</sup> skin tested patients with a history of penicillin allergy to penicillins and semisynthetic penicillins. Of the subjects who tested positive, 38.1% had positive skin tests to ampicillin only. In another study, patients with known IgE-mediated allergic reaction to amoxicillin and negative responses to penicillin were challenged to cefadroxil, a cephalosporin with the identical side chain as amoxicillin.<sup>8</sup> More than one-third of the patients (38%) had positive challenge results to cefadroxil, suggesting a high degree of cross-reactivity between cephalosporins and penicillins with an identical side chain.

### IG E-MEDIATED REACTIONS TO CEF AZOLIN

In the case vignette, cefazolin was found to be the culprit based on skin testing. Cefazolin, a first generation cephalosporin, is a widely used antibiotic for surgical prophylaxis because of its efficacy against gram (+) and some gram (–) bacteria. Cefazolin, like other  $\beta$ -lactam antibiotics, has the characteristic four-membered  $\beta$ -lactam ring. However, the immune response to cefazolin is determined mostly by specificity of antibodies against the side chains rather than against the neodeterminants of the nucleus.<sup>9</sup> Igea *et al.*<sup>14</sup> reported two patients with hypersensitivity to cefazolin who had positive skin tests to cefazolin and negative skin tests to penicillin derivatives. The two patients further tolerated oral challenge to other  $\beta$ -lactam antibiotics. Warrington *et al.*<sup>15</sup> also reported four cases of anaphylactic reactions to cefazolin with positive skin tests to cefazolin but negative skin test to penicillin derivatives. Similar to the case vignette, these patients were thought to have side-chain-specific anaphylactic sensitivity.

### $\beta$ -LACTAM SKIN TEST

Skin testing is a useful and safe diagnostic approach to identify sensitized individuals. A negative skin test is highly predictive of patients who can safely receive the antibiotic at the time of testing and permits retreatment of a large number of patients previously labeled as penicillin

allergic.<sup>10</sup> Fewer than 20% of patients with a history of allergy to penicillin will have positive skin tests to penicillin derivatives.<sup>9–11</sup> Skin tests may be negative in patients with history of penicillin allergy including non-IgE-mediated allergic reactions, loss of penicillin sensitivities, and inadequate  $\beta$ -lactam determinants for skin testing.<sup>16</sup>

Most patients with previous penicillin allergy but current negative penicillin skin tests are able to tolerate full-dose penicillin therapy. Fewer than 3% of these patients develop IgE-mediated reactions that are mild and self-limited.<sup>17,18</sup> On the other hand, patients with prior history of penicillin allergy and skin test sensitivity to penicillin derivatives are at substantial risk for allergic reactions on subsequent exposure. The positive predictive value of the penicillin skin test is ~50–70% in subsequent challenge studies.<sup>17,18</sup>

Adult patients with a history of IgE-mediated penicillin allergy but current negative skin tests are at minimal risk of resensitization after subsequent exposures to penicillin. In one study, the resensitization rate was 0% among patients with a history of penicillin allergy but negative skin tests who were rechallenged with three oral courses of penicillin.<sup>19</sup> Another study of healthy children with a history of penicillin allergy showed resensitization of <1%.<sup>20</sup> Hospitalized patients requiring intravenous doses of  $\beta$ -lactam may have higher rates of resensitization. In one study, hospitalized patients with a history of penicillin allergy and negative skin test had a resensitization rate of 16% after receiving intravenous doses of  $\beta$ -lactam antibiotics.<sup>21</sup>

### CASE SUMMARY

In the case vignette, the patient's clinical reactions, elevated  $\beta$ -tryptase, and positive skin test to cefazolin are evidence that the generalized reaction during anesthesia was caused by an anaphylactic response to cefazolin. The negative skin tests to penicillin derivatives in this case suggest a side-chain-specific immune response. Future oral challenge to penicillin antibiotics and to other cephalosporins is needed to safely permit the use of other  $\beta$ -lactam antibiotics in this patient.

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