



Immunologic Evaluation of Patients with Cefotetan-Induced Anaphylaxis

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Cefotetan is a commonly prescribed second-generation cephalosporin that acts against a wide range of bacteria. However, cefotetan-induced hypersensitivity has rarely been reported. We report 2 cases of cefotetan-induced anaphylaxis with immunologic evaluation. The first case was a 70-year-old asthmatic woman who had dyspnea and hypotension during administration of cefotetan, in which high serum-specific IgE to cefotetan-human serum albumin (HSA) conjugate was detected by enzyme-linked immunosorbent assay. The second case was a 63-year-old asthmatic woman who complained of chest tightness and dyspnea during cefotetan infusion, in which high serum-specific IgG1 and IgG4 with no serum specific IgE to cefotetan-HSA conjugate was detected. The basophil activation test using basophils from the patient showed a significant up-regulation of CD63 with the addition of anti-IgG4 antibody compared with that in non-atopic healthy controls. In conclusion, cefotetan can induce anaphylaxis, which may involve both IgE- and IgG4-mediated responses in the pathogenic mechanism.

Key Words: Anaphylaxis; cefotetan; specific IgE; specific IgG4

INTRODUCTION

Cefotetan, a second-generation cephalosporin, is commonly prescribed for use in infections caused by a wide range of bacteria. Although several cases of cefotetan-induced hypersensitivity have been reported, to date, no published report has investigated the immunologic mechanism of cefotetan-induced hypersensitivity. We experienced 2 cases of cefotetan-induced anaphylaxis and investigated the pathogenic mechanisms.

CASE REPORT

Patient 1 was a 70-year-old asthmatic woman who had no history of a drug allergy. Cefotetan had been administered several times previously with no adverse reaction. On this occasion, she was admitted because of aggravated cough, dyspnea, and fever, and cefotetan was administered intravenously under the impression of pneumonia. A few minutes later, she developed chest tightness, wheezing, urticaria, and decreased blood pressure. Systemic corticosteroids were administered along with intramuscular injection of epinephrine, and she subsequently re-

covered. One week later, a skin prick test (SPT) and an intradermal test were performed using cefotetan at concentrations of 0.1-10 mg/mL in 0.9% NaCl. Skin tests were considered positive when a wheal larger than 3 mm with surrounding erythema was present 15 minutes after exposure. She showed negative responses to all common inhalant allergens on SPT. A positive response was noted on the intradermal test with 10 mg/mL cefotetan, but there was no response on SPT.

Patient 2 was a 63-year-old woman diagnosed with reactive airway dysfunction syndrome, due to 2,2-dichlorovinyl dimethyl phosphate 11 years ago. She was non-atopic and had no history of allergic disease. She visited the emergency room due to pneumonia and cefotetan was administered intravenously. Immediately, she complained of aggravated dyspnea and chest

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tightness, followed by a significant fall in blood pressure and loss of consciousness. The patient was intubated and resuscitated with the administration of intravenous fluid, epinephrine, and inotropes.

The diagnosis in both cases was cefotetan-induced anaphylaxis. To investigate the underlying pathogenic mechanisms, we prepared cefotetan-human serum albumin (HSA) conjugate and detected serum-specific IgE and IgG antibodies to cefotetan-HSA conjugate using ELISA as described previously.^{1,2} When the positive cut-off value was determined from the mean + 3 SD of non-atopic healthy controls, patient 1 showed high serum-specific IgE to cefotetan-HSA conjugate (Figure A), whereas serum-specific IgG1 (data not shown) and IgG4 antibodies to cefotetan-HSA conjugate were not detected (Figure B).

By contrast, serum-specific IgE to cefotetan-HSA conjugate was not detected in patient 2 (Figure A), whereas high serum-specific IgG1 (data not shown) and IgG4 antibodies were noted (Figure B), compared with controls. To evaluate a possible mechanism of IgG4-mediated basophil activation, we performed a basophil activation test (BAT) with cefotetan and anti-IgG4 antibody using peripheral basophils from patient 2, as described previously.³ The patient's basophils were incubated for 30 minutes with various concentrations of cefotetan and anti-IgG4. Anti-IgE antibody (1 µg/mL; Sigma-Aldrich, St. Louis, MO, USA) and no drug incubations were used in positive and negative control treatments, respectively. A significant up-regulation of CD63, a marker of activated basophils, was noted upon serial addition of cefotetan (from 10% to 57.6%) and anti-IgG4 antibody (from 12.6% to 27.7%) compared with that in healthy controls (Figure C and D). However, no significant response was noted when the anti-IgG1 antibody was added (data not shown).

DISCUSSION

Cefotetan-induced anaphylaxis has rarely been reported.^{4,5} The incidence of cefotetan-induced anaphylactic reaction was 1.4% for surgical prophylaxis in cesarean sections and hysterectomies at a single hospital.⁴ All of the reactions developed immediately and were life threatening, consistent with those in our 2 cases.

Most immediate reactions to cephalosporins are IgE mediated, which has been supported by positive results with skin tests and detection of serum-specific IgE antibodies.^{6,7} Previously, Lee *et al.*⁵ reported a case of cefotetan-induced anaphylaxis; this case was only confirmed by SPT. Skin tests have been the most generalized approach for diagnosing immediate hypersensitivity to beta-lactams; however, the sensitivity of the tests is not optimal. A wide range of sensitivity has been noted from 30.7% to 69.7% in recent studies.^{7,8} The rates of positive detection of IgE using radioimmunoassays and CAP-FEIA (fluorescence enzyme immunoassay; Viracor-IBT Laboratories, Summit, CO, USA) were 74.3% and 58.6%, respectively⁷; however, cefaclor is the only cephalosporin commercially available as an IgE detection system. In the present study, patient 1 showed a positive response to the intradermal test, and we confirmed the presence of serum-specific IgE to cefotetan-HSA conjugate. A SPT is recommended 4-6 weeks after the reaction; however, in the present study, a SPT was performed 1 week after the event, possibly inducing a false-negative response. Although we did not repeat the skin test, we suggest that the IgE-mediated response is the pathogenic mechanism involved in the immediate hypersensitivity to cefotetan for patient 1 based on the positive skin test result and high serum-specific IgE antibody.

Various studies have indicated that this classical pathway does

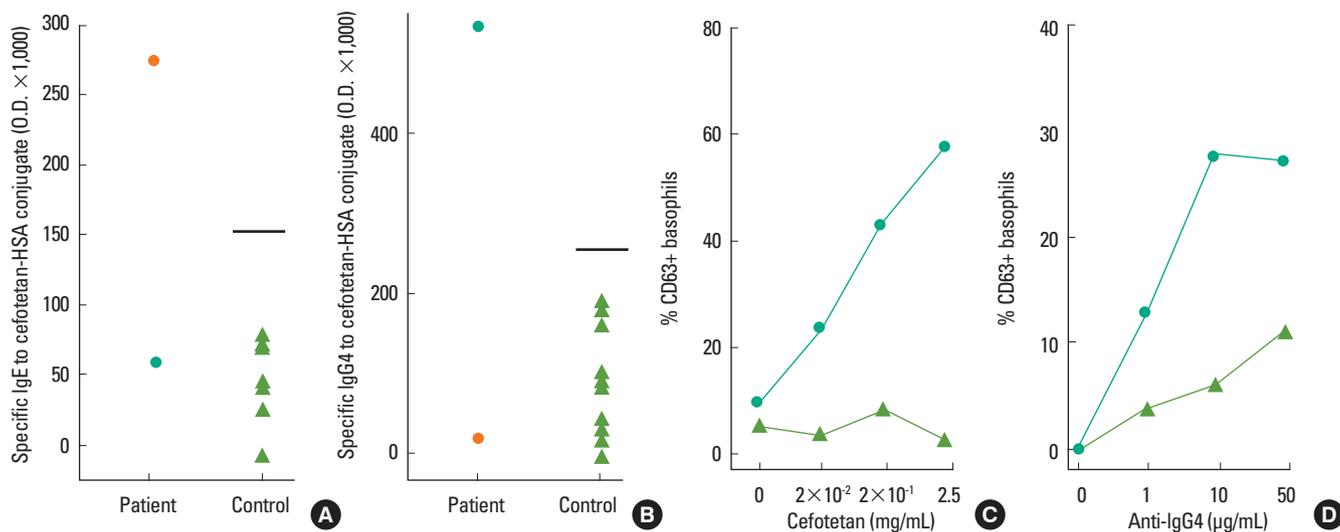


Figure. Serum-specific IgE (A) and IgG4 (B) to cefotetan in patient 1 (●), patient 2 (●) and healthy controls (▲) as determined by ELISA, as well as the results of basophil activation tests using free cefotetan extracts (C) and anti-IgG4 antibody (D) in patient 2 (●) and healthy controls (▲). The horizontal bar indicates the mean + 3 SD absorbance values of healthy controls.

not account for all anaphylactic reactions,⁹ and a modified Th2 response defined as a condition with IgG4 antibodies but with no demonstrable IgE antibodies has been reported. Additionally, an alternative pathway mediated by IgG has been suggested in which basophils play a major role by releasing platelet-activating factor upon stimulation with allergen-IgG complexes.¹⁰ Platelet-activating factor increases vascular permeability with a much higher potency than histamine, resulting in systemic anaphylaxis. IgG4 is a subclass of IgG that is produced after prolonged antigen exposure, and it is elevated in atopic diseases.¹¹ Although serum-specific IgG has been found more frequently in patients with beta-lactam allergy than in those with allergic reactions to other antibiotics, the pathogenic role for specific IgG in its pathogenic mechanism is not fully understood. The prevalence of serum-specific IgG was found to be 8% in patients with suspected penicillin allergy,¹² 14.7% in health care workers exposed to cephalosporins,¹³ and 3% in patients with monobactam allergy.¹⁴ It is suggested that IgG-mediated reactions may be more frequent in cephalosporins, including cefotetan, than in other beta-lactams and non-beta-lactams.¹⁵

BAT represents a potential diagnostic method for evaluating immediate hypersensitivity to antibiotics. Basophils are activated via membrane-bound IgE and up-regulate the expression of specific activation markers, such as CD63 and CD203c, which can be detected by flow cytometry.¹⁶ The BAT sensitivity was 50%, and its specificity ranged from 89% to 97% in patients with immediate allergic reactions to beta-lactams.¹⁷ In the present study, patient 2 showed high levels of serum-specific IgG1 and IgG4 antibodies but not of specific IgE. BAT with cefotetan and anti-IgG4 antibody showed significant up-regulation of CD63 in a dose-dependent manner, suggesting that the patient's anaphylaxis may be mediated by an IgG4-mediated mechanism.

In conclusion, we report 2 cases of cefotetan-induced anaphylaxis in which IgE- and IgG4-mediated responses appear to be involved in the pathogenic mechanism, respectively.

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