A Case of Piperacillin-induced Occupational Anaphylaxis: Detection of Serum IgE to Piperacillin-HSA Conjugate

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INTRODUCTION

Piperacillin is an extended-spectrum beta-lactam antibiotic of the ureidopenicillin family. Piperacillin is widely used in conjunction with tazobactam, a beta-lactamase inhibitor. Some penicillins have been reported to cause occupational diseases, including bronchial asthma (1, 2), anaphylaxis (3), contact urticaria (4), contact dermatitis (5), and hypersensitivity pneumonitis (6), in pharmaceutical workers and health care professionals. Most of these penicillins belong to the benzylpenicillin or aminopenicillin family. Occupational contact urticaria and anaphylaxis induced by cephalosporins have often been reported (7). With regard to piperacillin, there is only one published report of occupational asthma, rhinitis, and urticaria in a pharmaceutical worker (1). However, to our knowledge, there has been no report of occupational anaphylaxis induced by piperacillin. Furthermore, no evidence of a serum IgE antibody response to piperacillin has been published. This is thus the first report of occupational anaphylaxis due to piperacillin and detection of a serum IgE response to a piperacillin-HSA conjugate.

CASE DESCRIPTION

The subject was a 24-yr-old female nurse who worked in the intensive care unit at a University Hospital. She had handled piperacillin/tazobactam without gloves or a mask since March 2003. Eighteen months later (October 2004), she experienced generalized urticaria with onset immediately and repeatedly after she had administered piperacillin. Nevertheless, she continued to work and finally experienced chest tightness, dizziness, sweating, generalized urticaria, abdominal pain, and diarrhea 10 min after giving a piperacillin injection in April 2005. Her blood pressure was 80/50 mmHg with a pulse rate of 104 beats/min. Her breath sounds were clear. The symptoms resolved completely after treatment with epinephrine, diphenhydramine, and methylprednisolone. She had a previous history of atopic dermatitis, and her hand eczema had become exacerbated after she had begun to work at the hospital.

Skin prick tests and measurement of serum total IgE

Skin prick tests using 80 common inhalant and food allergens (Bencard, Brentford, UK) were all negative. We did not perform a skin prick test with piperacillin/tazobactam because of the risk of anaphylaxis (8). Serum total IgE, measured using an immunoCAP® system (Phadia, Uppsala, Sweden), was 283 IU/mL.

Assay of serum IgE and IgG levels

To assay piperacillin-specific serum IgE and IgG, we prepared...
piperacillin-human serum albumin (HSA) conjugates in our laboratory and performed an ELISA as described previously (11). Piperacillin-specific IgE and IgG levels in an initial serum sample and the IgE level in a serum sample obtained 5 yr later (May 2010) were measured. In brief, the wells of a 96-well ELISA microplate (Corning, New York, NY, USA) were coated by incubation with piperacillin-HSA conjugate at 10 μg/mL in phosphate-buffered saline (PBS) overnight at 4°C. After the wells were washed four times with 350 μL of PBS containing 0.05% Tween 20 (PBST; Sigma-Aldrich, St. Louis, MO, USA), nonspecific binding sites were blocked by incubation with 200 μL of 10% fetal bovine serum (FBS; Gibco/Invitrogen, Carlsbad, CA, USA) in PBS at room temperature for 2 hr. After washing four times with 0.05% PBST, 50 μL of diluted serum (1:3) were added to each well, followed by incubation for 2 hr at 37°C. The plate was washed four times with 0.05% PBST; then 100 μL of goat anti-human IgG antibody (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD, USA) diluted 1:1,000 with 10% FBS-PBS were added to each well, and the plate was incubated for 1 hr at room temperature. After washing four times with 0.05% PBST, 100 μL of alkaline phosphate-conjugated rabbit anti-goat IgG antibody (ReserveAPTM; Kirkegaard & Perry Laboratories) diluted 1:500 with 10% FBS-PBS were added to each well, and the plate was incubated for 1 hr at room temperature. PNPP (p-nitro-phenyl phosphate; Sigma-Aldrich) substrate was added, and the reaction was stopped by the addition of 1 N NaOH. The optical density of the solution in each well was measured at 405 nm using a microplate reader (Synergy HT; Bio-Tek, Winooski, VT, USA). The final absorbance value of piperacillin was determined by subtracting the absorbance value of a control crosslinker-HSA conjugate, which was obtained using a procedure identical to that described above, except that a crosslinker-HSA conjugate was used in place of piperacillin-HSA conjugate. The positive cutoff value was determined as the mean plus three standard deviations of the absorbance values in serum samples from 11 unexposed, non-atopic healthy controls. For the inhibition ELISA, increasing amounts (1-100 μg/mL) of free piperacillin, piperacillin-HSA conjugate, and HSA alone, dissolved in 10% FBS-PBS, were incubated with serum overnight, and an ELISA was performed as described above. The percentage inhibition was calculated as follows: % inhibition = (1 − absorbance with inhibitor/absorbance without inhibitor) × 100. For the ELISA of piperacillin-specific serum IgG levels, alkaline phosphate-conjugated rabbit anti-human IgG antibody (Kirkegaard & Perry Laboratories) was used instead of goat anti-human IgG antibody and alkaline phosphate-conjugated rabbit anti-goat IgG antibody. A high level of specific IgE antibody to piperacillin-HSA conjugate was detected in the initial serum sample from the subject; however, this had decreased markedly after 5 yr (Fig. 1). Significant inhibition by both free piperacillin and piperacillin-HSA conjugate occurred in a dose-dependent manner, with minimal inhibition by HSA alone (Fig. 2). High levels of piperacillin-HSA conjugate-specific IgG were also detected in the initial serum sample (data not shown).

Based on these findings, the subject was diagnosed with occupational anaphylaxis and urticaria caused by piperacillin. The subject was transferred to a different department and has not again experienced anaphylaxis or urticaria.

**DISCUSSION**

Although we did not perform provocation and skin prick tests with piperacillin, we diagnosed this patient with occupational anaphylaxis because: 1) the temporal correlation between handling piperacillin and anaphylaxis; 2) a history of recurrent urticaria after handling piperacillin; and 3) detection of piperacillin-specific IgE in the serum. The complete disappearance of anaphylaxis and the reduction of serum IgE after avoidance of
piperacillin further support this diagnosis. These findings suggest that occupational exposure to piperacillin induced IgE-mediated anaphylaxis in this subject.

Piperacillin can induce allergic reactions such as bronchial asthma, rhinitis (1), urticaria, anaphylaxis (9, 12), immune hemolytic anemia (10), maculopapular exanthem (13, 14), acute generalized exanthematous pustulosis (15), and drug hypersensitivity syndrome (16). Several reports used skin prick, provocation, and serologic tests to demonstrate that piperacillin induced these reactions (1, 9, 10). A previous study reported that two of 311 tertiary hospital nurses showed a positive skin prick test to piperacillin (0.6%) (17). Two studies attempted to measure piperacillin-specific IgE levels in serum (1, 9). One involved a case of anaphylaxis, urticarial, and angioedema after intravenous piperacillin injection in an acute bronchitis patient, and the other was a case of occupational asthma, rhinitis, and urticaria induced by piperacillin powder exposure in a pharmaceutical worker. In those reports, a radioisotope test was used to detect IgE levels, but the assay failed. In the present study, we successfully detected piperacillin-HSA conjugate-specific serum IgE by ELISA in a patient with suspected piperacillin-induced occupational anaphylaxis. Furthermore, the binding specificity of the IgE was confirmed by inhibition ELISA. As significant inhibition by both free piperacillin and piperacillin-HSA conjugate was detected, it is likely that the hapten component of piperacillin is the antigenic determinant. High serum piperacillin-HSA conjugate-specific IgG levels were also detected in this patient, while levels in controls were minimal (data not shown). Although one study has sought to evaluate penicillin-specific IgG levels in the sera of patients with penicillin allergies, the significance of IgG levels remains unclear (18). Further studies are needed to investigate the role of specific IgG or its subclasses in occupational allergic diseases induced by piperacillin.

Nontherapeutic exposure to antibiotics, including penicillins, can occur by various routes (3). Contact with spilled drugs and inhalation of powder or foam are the most common routes. Exposure by the contact route usually induces contact urticaria (4), anaphylaxis (19), or dermatitis (5), whereas the inhalation route induces most commonly asthma or rhinitis (2, 20). Inhalation can also induce urticaria (1). Piperacillin, an intravenous antibiotic, is provided as a powder in a bottle and should be dissolved prior to administration. When dissolved, piperacillin develops little foam, but emits a more obvious odor than other intravenous antibiotics. The subject in the present report sometimes suffered from urticaria without direct contact with the solution, suggesting that inhalation of evaporated piperacillin may be the major route of sensitization. However, considering the reported exacerbation of hand eczema that occurred prior to the anaphylaxis, we speculate that exposure by direct contact with piperacillin solution may also have been a factor.

In conclusion, we report a case of a nurse with anaphylaxis and generalized urticaria caused by piperacillin and mediated by an interaction of IgE with the hapten of piperacillin. Sensitization was suspected to have occurred through inhalation of piperacillin vapor. Given that an ELISA was capable of detecting piperacillin-specific serum IgE, this system could be used for detecting piperacillin-HSA conjugate-specific IgE in the serum of occupational anaphylaxis or asymptomatic sensitized patients.

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