

Cefotiam-induced IgE-mediated occupational contact anaphylaxis of nurses; case reports, RAST analysis, and a review of the literature

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Summary

Cefotiam (CTM) is one of the most popular cephem antibiotics in Japan. Recently we experienced two cases of nurses with CTM-induced contact anaphylaxis. When they were preparing drip infusions of antibiotics or working around other nurses doing so, they suddenly fell into shock with other symptoms such as flushing, urticaria, abdominal distress, vomiting, dyspnoea and/or loss of consciousness. The symptoms never occurred after they avoided exposure to CTM. Passive cutaneous or open patch tests were positive for CTM. Histamine release was induced by CTM from washed leucocytes. RAST analysis using CTM-human serum albumin-coupled discs showed high % RAST count, suggesting that these reactions were mediated by IgE antibodies. A RAST inhibition test suggested that the methyl-thiotetrazol side-chain was the main antigenic determinant. Both patients had hand dermatitis that had appeared preceding the episodes of anaphylaxis. Although the dermatitis had been resistant to treatments, it also disappeared after they avoided exposure to CTM. It seemed likely that it was also induced or exacerbated by CTM and facilitated the penetration of CTM to cause anaphylaxis. The literature is also reviewed.

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Introduction

A few agents such as latex gloves and penicillins [1,2] have been reported to cause anaphylactic shock among the medical staff who were occupationally exposed to them.

Cefotiam (CTM) is one of the most popular second generation cephem antibiotics in Japan. Recently, we [3] and others [4–10] have experienced cases of nurses with anaphylactic shock due to occupational contact exposure to cefotiam. No such case, as far as we know, has been described except in Japan.

Here we report two such cases and the results of RAST analysis. The literature is also reviewed.

Case reports

Case 1 (YO)

A 26-year-old nurse had experienced generalized redness, itching of skin, palpitation, and abdominal distress followed by transient loss of consciousness, soon after she dissolved an antibiotic and installed a drip infusion set in January 1985. She recovered without any treatment within 30 min. In February and April 1985, she suddenly had itching of eyes, lacrimation, generalized redness of skin, and abdominal cramp, but without loss of consciousness, when she was writing nursing records in the nurse room where others were preparing drip infusions of antibiotics nearby. In March 1985, when she was injecting an antibiotic by drip infusion that she had prepared by herself several minutes before, she was seized by restlessness, wheezing dyspnoea, and loss of consciousness in addition to the previous symptoms. Physical examination

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revealed generalized flushing of the skin, profuse lacrimation with conjunctival injection, tachycardia and wheezing rales on the whole chest. The maximal blood pressure was 60 mmHg. She recovered about an hour after treatment with epinephrine, steroid, and fluid infusions. Laboratory examination, including urine 5-hydroxyindole acetic acid (5-HIAA), serum 5-hydroxytryptamine (5-HT), and EEG after the recovery, showed no abnormality except for the increased serum IgE levels of 320 U/ml. She again experienced similar but more severe symptoms on October 1, 1985. After these episodes she noticed that she had been affected by such symptoms only after exposure to CTM, although other cepheims such as cefazolin, cefalothin (CET), cefmetazol, cefsulodin, and latamoxef were also used in the department. A drug-induced lymphocyte stimulation test conducted by a commercial medical laboratory on October 7 showed a positive reaction to CTM and cefazolin. She was referred to us on October 24 for detailed examination. She had had infantile asthma until 12 years of age, suffered from rheumatic fever at 14 years of age without any sequelae, and had had hand dermatitis since she was 20 years old. She had never been treated with CTM, but had been exposed occupationally to CTM for 2 years in the department. She had to handle antibiotics two to three times a week. Her paternal grandfather, father, and an uncle had bronchial asthma. Her mother had a past history of penicillin-induced shock and showed a positive skin test against it. Physical examination showed nothing particular except for the hand dermatitis with redness and desquamation which had been resistant to corticosteroid treatment. Routine laboratory tests showed no abnormality except for the elevated serum level of IgE (590 U/ml). As there were no relatives as recipients for passive cutaneous transfer testing, a rhesus monkey was used as a recipient. Positive reactions were evoked by 10^{-2} M CTM at the sites where the patient's serum had been injected 24 h before and by *D. farinae* extract at the sites with a highly sensitive patient serum (positive control), but not either by CTM at the sites with normal control sera or saline at the sites with the patient's serum (negative controls), indicating that she was sensitized with anti-CTM IgE antibody. She changed her work from inpatient care to the health care division where no antibiotic was used. Since then, she has had no more such incidents and her hands became clear without any treatment in a few months.

Case 2 (HK)

A 23-year-old nurse was seized suddenly by epigastric distress, nausea, generalized urticaria, and diarrhoea in a nurse station in April 1986, 3 years after she had started

her work as a staff nurse. She recovered in an hour by rest without medication. In May 1986 she had itching of the ear followed by generalized urticaria, abdominal pain, nausea and vomiting, restlessness, and palpitation, when she was preparing a drip infusion of CTM. Her maximal blood pressure was 72 mmHg, which returned to normal with treatments including epinephrine and steroid. In the next month she realized that she always had hives when she was exposed to CTM on the normal skin. She then also recognized that she also had hives when she smelt CTM on passing by her colleagues preparing the infusion. The systemic symptoms occurred only when she handled CTM solution, although cefazolin, CET, cefmetazol, cefotaxime, ceftazidime, CPZ, cefuzoname, sulperazon, and latamoxef were also used in the department. She consulted a dermatologist in the same hospital. Prick test showed positive reaction for CTM, but the intracutaneous test was negative for the other cephem antibiotics, such as CET and cefazolin. Hyposensitization therapy was started by the prick with 30 µg/ml CTM solution. She had no systemic reaction during four courses of a once weekly therapy with the same concentration of CTM. However, she fell into shock with dyspnoea when the skin was pricked with 60 µg/ml CTM solution one week later. She was referred to us in March 1988. She had had atopic dermatitis since her infancy and had had bronchial asthma for 2 months at 18 years of age. She had never therapeutically received CTM but had been exposed to CTM for 5 years since the practice in the nurse school. She had been in charge of drip infusion of antibiotics at least three times a week. Allergic disease was not noted in the family history. Physical examination showed nothing particular except for hand dermatitis and dry skin that had been resistant to treatments with anti-histamine and topical corticosteroid. An open patch test on the normal skin was negative for 0.05 ml of 3, 30, and 300 µg/ml CTM. She, however, had positive weal-and-flare reaction, when 0.05 ml of 30 µg/ml CTM was placed on the dry skin. Furthermore, she experienced restlessness, palpitation, abdominal pain and dyspnoea in addition to the local skin reactions when the skin was pricked with 0.05 ml of 30 µg/ml CTM placed on the apparently normal skin. In contrast, the prick tests with 300 µg/ml CTM were negative in 20 normal volunteers and in eight normal nurse controls who were similarly exposed to CTM without any reaction. The histamine release test (as described in Materials and methods) showed a maximal percentage histamine release of 11.4% at the CTM concentration of 100 µg/ml. The anaphylactic reaction disappeared after the department stopped using CTM on her behalf and she left the hospital to enter a public health nurse school. Her hand dermatitis was also dramatically relieved.

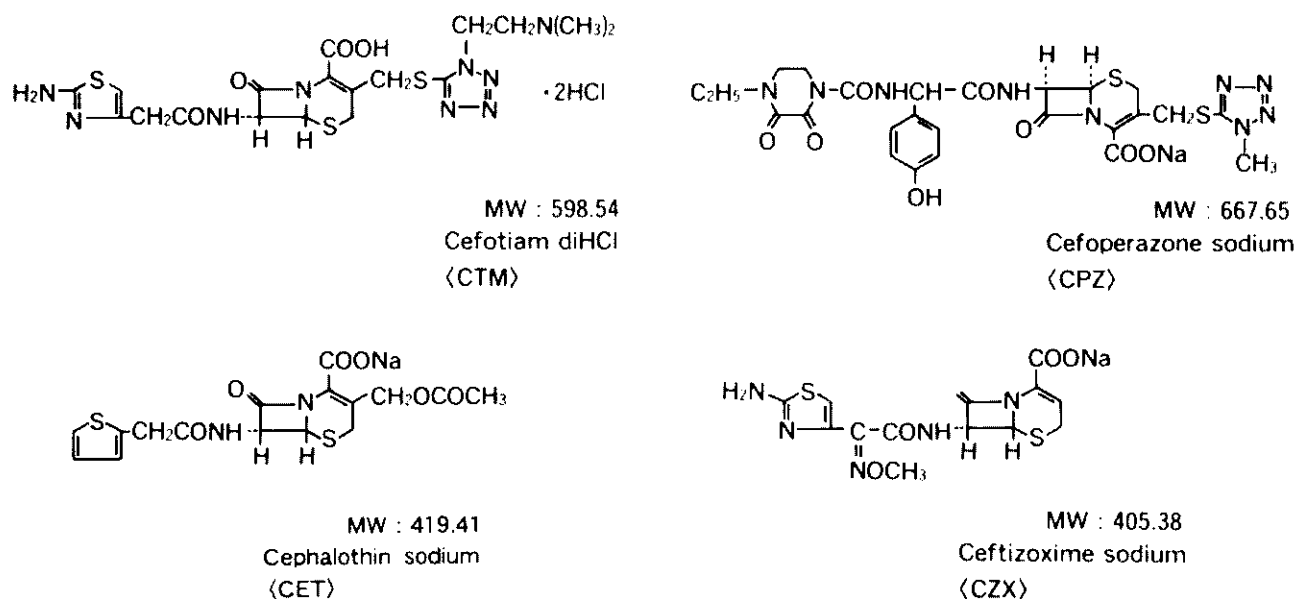


Fig. 1. Molecular structures of CTM and other cepheims. CPZ has a methyl-thiotetrazol side-chain similar to that of CTM

Materials and methods

Materials

Two CTM preparations, Pansporin[®] and Halospore[®], were purchased from Takeda Pharmaceutical Co. (Osaka, Japan) and Ciba-Geigy Co. (Basel, Switzerland). Cephalothin, ceftizoxime (CZX), and CPZ were also commercially available.

Conjugation of CTM to human serum albumin (HSA)

CTM-HSA conjugate was prepared with a slight modification of the method of Levine and Redmond [11], as previously described [12]. In brief, 300 mg CTM were mixed with 100 mg HSA in 20 ml saline for 90 min at pH 11.5. The mixture was then dialysed against 1.15 M phosphate-buffered saline (PBS). Conjugation of CTM with HSA was confirmed photometrically [13].

RAST analysis

Two mg ml of CTM or CTM-HSA in 10 ml PBS was conjugated to 100 paper discs (5 mm diameter, Toyo Roshi Co., Japan) activated by cyanogen bromide [14]. Fifty μ l of each serum sample was applied to a Phadebas RAST kit[®] (Pharmacia) in order to determine anti-CTM IgE antibodies. The per cent RAST (% RAST) count was determined using the following equation [15]:

$$\% \text{RAST count} = \frac{\text{patient's serum (cpm)} - \text{background (cpm)}}{\text{total } ^{125}\text{I-anti-IgE (cpm)} - \text{background (cpm)}} \times 100$$

In the RAST inhibition assay, sera were pre-incubated with various concentrations of inhibitors or saline (negative control) for 1 h in preparation for the assay. The per cent inhibition was determined by the following equation: % inhibition =

$$\left(1 - \frac{\text{inhibitor (\% RAST count)}}{\text{saline (\% RAST count)}} \right) \times 100$$

All experiments were performed in duplicate.

Histamine release test

Histamine release tests were performed as previously described [16]. In brief, 20 ml of venous blood were mixed with 5 ml of 6% clinical dextran and 2 ml of 0.1 M EDTA and allowed to sediment for 90 min at room temperature. The leucocyte-containing plasma overlayer was removed, washed two times with HEPES-buffered balanced salt solution (20 mM HEPES, 125 mM NaCl, 5 mM KCl, 0.5 mM glucose, pH 7.3) and then resuspended in the above buffer supplemented with 0.6 mM CaCl_2 and 1 mM MgCl_2 (HCM). The mixed leucocytes containing basophils were challenged by incubation at 37 °C for 45 min with HCM alone or different concentrations of CTM from 0.1 μ g ml to 1 mg ml. After the challenge, the supernatants were removed by centrifugation at $200 \times g$ for 10 min, acidified with perchloric acid to a final concentration of 4%, and stored at 4 °C. Histamine was determined by the automated fluorometric assay of Siraganian [17]. The results

were based on the means of duplicate determinations and expressed as a percentage of total histamine corrected for spontaneous release.

Results

RAST analysis and determination of the antigenic substance

Anti-CTM IgE antibody was determined by RAST assay using CTM-HSA-coupled discs. The mean % RAST counts of case 1 (YO) and case 2 (HK) were 2.3% and 1.3%, respectively, which were significantly high ($P < 0.01$ by unpaired *t*-test) in comparison with those of 10 normal controls ($0.84 \pm 0.09\%$; mean $\pm$ SD) who had been neither occupationally nor therapeutically exposed to CTM. To investigate the specificity of the antibody, the sera were pre-incubated with four different cepheids, i.e. CTM, CPZ, CET, and CZX. The molecular structures are shown in Fig. 1. The counts were significantly ($P < 0.01$ by two-way layout analysis of variance) decreased in a dose-dependent fashion by CTM. The 50% inhibition dose (ID₅₀) was 0.7 $\mu\text{g/ml}$ (YO) and 0.1 $\mu\text{g/ml}$ (HK), respectively. This result indicated that the reactions were mediated by anti-CTM IgE antibodies. Among the other three cepheids, CPZ, that has a methyl-thiotetrazol side-chain similar to that of CTM, showed significant ($P < 0.05$) % RAST inhibition in case 2 and the highest, though not significant, inhibition in case 1 (Fig. 2), suggesting that this side-chain was the main antigenic determinant.

Discussion and review of the literature

Various materials such as foods, cosmetics, disinfectants, or antibiotics are known to cause immediate contact urticaria [18]. Contact urticaria can be divided into immunologic and non-immunologic mechanisms [19]. Severe cases of immunologic contact urticaria may develop not only the local weal-and-flare reaction but also the systemic reactions such as angioedema, generalized urticaria, bronchospasm, and/or anaphylactic shock. Only a few materials such as latex gloves or penicillin [1,2] have been reported to cause anaphylactic shock among medical staffs after occupational exposure.

However, nine cases of CTM-induced contact urticaria have been reported since 1986 in Japan (Table 1). Five of them, including our two cases, were accompanied by shock with or without loss of consciousness (Table 1). Symptoms appeared within 15 min of exposure, usually on the hands, to CTM solution splashed or leaked while it was being filled into the drip infusion line or injected into patients. Shock was preceded or accompanied by other

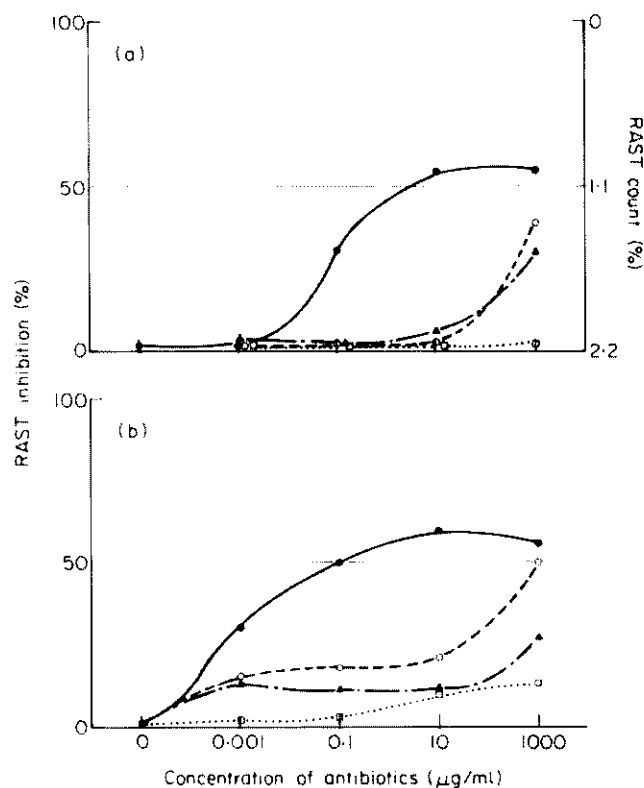


Fig. 2. RAST inhibition test. Sera were pre-incubated with different concentrations of cefotiam (CTM) or other cephalosporins at 37 C for 1 h and then applied for RAST assay using CTM-human serum albumin-coupled discs. (a) Case 1 (YO); (b) case 2 (HK). ●, CTM; ○, cefoperazone; □, cefprozime; ▲, cephalothin.

symptoms of anaphylaxis such as local and generalized urticaria with itching, lacrimation, restlessness, gastrointestinal distress, broncho-spasm, palpitation, and/or cold diaphoresis. However, sometimes, especially in severe cases, local urticaria was not noted by the patients. One of our patients was initially suspected of epilepsy until the causal relation between the symptoms and exposure to CTM was noted.

Our two patients were seized by systemic reactions while they were working in the nurse station where other nurses were preparing CTM solution. Inhalation of CTM mist or contact with tiny droplets produced during the preparation of drip infusion sets, seemed to have elicited anaphylaxis. Prick test with 30 $\mu\text{g/ml}$ CTM provoked systemic symptoms in our second patient (HK). Usually, approximately 0.03 μl of antigen is introduced in the prick test. Therefore, as little as 1 ng of CTM seemed enough to provoke the systemic reactions.

The symptoms, histamine release test, and positive

Table 1. Case reports of CTM-induced contact urticaria with or without anaphylaxis among nurses

Case no.	Age	Start of work (age)	Symptoms	Skin test for CTM	Family history	Dermatitis (age of onset)	Prevention	Reference
1	26	21	Flushing, abdominal pain, dyspnoea, shock, LOC	Passive cutaneous positive	Penicillin allergy (mother)	Hand (20)	Avoidance	Present
2	23	19	Abdominal pain, vomiting, urticaria, shock	Open patch positive, prick positive with shock	Nothing	Atopic (1)	Hyposensitization failed then avoidance	Present
3	22	18	Generalized itching, urticaria, laryngoedema	Intradermal positive with shock	ND	ND	Oral hyposensitization	4
4	24	22	Urticaria, abdominal pain, shock, LOC*	Open patch positive	Nothing	Atopic (2)	Avoidance	5
5	40	21	Angioedema of hands and peri-orbids	Open patch positive	AD (son), AR (sister)	Hand (28)	Avoidance	6
6	26	21	Abdominal pain, vomiting, shock	Unknown positive	ND	Hand (ND)	Avoidance	7
7	20	19	Generalized itching	Prick positive	ND	Hand (19.5)	Avoidance	8
8	47	ND	Hand and generalized urticaria, dyspnoea, shock	Semi-closed patch	ND	ND	ND	9
9	23	21	Hand and generalized urticaria, dyspnoea	Open patch positive	Nothing	Hand (22)	Latex gloves	10

ND, Not described; LOC, loss of consciousness; AD, atopic dermatitis; AR, allergic rhinitis; CTM, cefotiam.

immediate skin test including passive transfer test suggested that the reactions were anaphylaxis-mediated by anti-CTM IgE antibody. The increased % RAST count and positive RAST inhibition test with CTM in our two cases further substantiated this mechanism.

None of the patients described so far had ever therapeutically received CTM. Symptoms appeared after several months to years of bed-side work in which they handled antibiotics including CTM, indicating that they were sensitized during repeated occupational exposure.

It is noteworthy that eight of the nine patients described had hand dermatitis which in most cases preceded the appearance of anaphylaxis. The open patch test (HK) was positive on dry skin but not on apparently normal skin. Dermatitis seemed to have allowed the penetration of CTM and facilitated the sensitization against it as well as the elicitation of anaphylaxis. Although it had been resistant to local steroid treatment in most cases, it disappeared or was relieved after the avoidance of exposure to CTM, suggesting that CTM was at least one of the causal agents inducing and/or exacerbating hand dermatitis. However, it has not been confirmed whether the dermatitis was induced and/or exacerbated by immunologic or irritant mechanism, because it appeared extremely dangerous to conduct the usual closed patch test.

In our RAST inhibition test CPZ, which also has a methyl-thiotetrazol side-chain, showed some inhibition. Other reports [5,6,9,10] have shown that piperacillin and cepheims which have *N*-methyl-thiotetrazol side-chains or chemically similar side-chains (i.e. cefazolin, cefatridine, cefroxime, cefamandole, cefmetazole, CPZ, cefmenoxime) had showed positive reactions in the prick test or scratch test. These observations suggested that the methyl-thiotetrazol side-chain is the major antigenic determinant in these patients. Our results further substantiate these observations.

Cefotiam is, as far as we know, the only cephem that has been reported in the last 10 years to elicit occupational contact urticaria with anaphylaxis among nurses. Although some patients were positive in the prick test, but not in the open patch test, for other cepheims with a similar methyl-thiotetrazol side-chain, anaphylaxis has not been induced by contact exposure to these substances. On the other hand, the incidence of anaphylaxis in patients who received CTM by the parenteral route is not outstanding among beta-lactam antibiotics. The serum and skin concentrations of CTM after intramuscular injection were not different from those of other cepheims [20]. Recently, it was reported that CTM elicited non-specific skin reactions most frequently among beta-lactam antibiotics when they were injected intradermally at the concentration of 1 mg/ml into normal volunteers

[21]. Such skin irritability of CTM might have some relevance to the occurrence of hand dermatitis and the resultant easy penetration of CTM and sensitization against it.

It was recently reported that wearing latex gloves while working was an effective prevention of anaphylaxis for a nurse with CTM-induced generalized urticaria and dyspnoea, but without shock [10]. However, our two patients had been seized by anaphylaxis when other nurses were preparing drip infusions of CTM. They had experienced the reactions even when they used latex gloves and masks. Including these two cases, six of the eight nurses described either changed their work from inpatient care to a health care unit, out-patient clinic, or other to avoid exposure.

Two patients received hyposensitization treatment, as they wished to continue their work in the inpatient division. One failed as described in the text. The other was successfully hyposensitized. She ingested 2 µg of CTM at the beginning, and doubled the dose every 15 min, receiving epinephrine treatment on the appearance of systemic symptoms, until she had no symptom with a maintenance dose of 500 mg/day. She had reportedly worked with in-patients for 9 months without generalized symptoms, although she had sometimes had one or two hives. Naclerio [1] also reported a case of a nurse's successful desensitization to penicillin. However, hyposensitization should be the last and transient treatment, because fatal anaphylaxis may occur in the course of treatment and because the long-term sequelae of hyposensitization with CTM are not known, especially as the majority of the patients were young women likely to become pregnant in the future.

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