

## IgE-mediated anaphylactic reaction to imipenem

Z. Chen\*, X. Baur, F. Kutscha-Lissberg, R. Merget

**Key words:** anaphylaxis; drug allergy; IgE; imipenem.

• IMIPENEM is a very broad-spectrum antibiotic commonly used as a mixture with the enzyme inhibitor cilastatin in the multi-infected septic patient (1). Imipenem is a  $\beta$ -lactam antibiotic. But, of the  $\beta$ -lactam antibiotics such as the penicillins and the cephalosporins, imipenem is thought to be the least allergenic (2). So far, there has been no report of IgE-mediated anaphylactic reactions to imipenem. In the present study, we describe a patient who had severe anaphylactic reactions after intravenous imipenem treatment.

**Negative skin tests to penicillin make this case unusual.**

The patient, a 52-year-old man, had been operated for severe comminuted fracture of the distal right tibia and fibula after an accident at work which led to severe soft-tissue damage. Primary closure of the medial soft-tissue damage was not possible, and open wound management was initiated with topical application of imipenem-cilastatin sodium (Zienam<sup>®</sup>, MSD, Haar, Germany) by mixing 1 g of imipenem-cilastatin dissolved in 250 ml aqua with 45 g of a hydroxyethyl-cellulose gel (renewal twice a day). Intravenous cephazolin (Gramaxin<sup>®</sup>, Boehringer, Mannheim, Germany) was given for 10 days. The topical imipenem application was stopped after 25 days. Due to persistent inflammation 7 weeks after the accident, both topical

Zienam and cephazolin were resumed, and the latter was replaced after 3 days by oral ciprofloxacin (Ciprobay<sup>®</sup>, Bayer, Germany). After 10 days, the patient developed marked itching mainly on his back with concomitant generalized rash. Ciprofloxacin was immediately withdrawn, and application of topical imipenem treatment was continued. The topical steroid treatment was initiated without beneficial effects. After another 14 days, the rash was unchanged. The topical Zienam<sup>®</sup> therapy was discontinued, and an immediate improvement was observed.

Eight weeks later, the diagnosis of chronic osteomyelitis made further surgical interventions necessary. During spinal anesthesia, intravenous Zienam<sup>®</sup> was given. Ten minutes after the beginning of the infusion (30 min after spinal anesthesia), the patient developed severe arterial hypotension with consequent cardiac arrest. After orotracheal intubation and external cardiopulmonary resuscitation for a period of 20 min, his condition stabilized. Two weeks later, the patient was admitted for further evaluation. During the immunologic tests, he was without medication that might have altered the test results.

Skin prick tests (SPT) showed a reproducible 9.5-mm wheal with surrounding flare reaction with individual solutions (1 mg/ml) of imipenem-cilastatin sodium and imipenem alone, but the SPT were negative with cilastatin sodium (all from MSD, Haar, Germany). SPT were negative with common environmental allergens (Scherax, Hamburg, Germany) as well as with individual solutions (1 mg/ml) of 12 antibiotics including benzylpenicillin, cephazolin, amoxicillin, cefotaxime, meropenem, and ciprofloxacin (all from the manufacturers or distributors in Germany).

Histamine (10 mg/ml) and saline were used as positive and negative controls and showed normal skin reactivity. Twenty control subjects showed negative SPT results with imipenem reagents at a concentration of 1 mg/ml.

Specific IgE antibodies to imipenem were tested by enzyme-linked allergosorbent test (EAST). First, protein-conjugate of imipenem was prepared by incubating HSA with imipenem (1 mg/ml) for 5 h at room temperature. After separating imipenem by ultrafiltration through a Millipore membrane filter (molecular weight cutoff: 3000), the imipenem-HSA conjugate was coupled to CNBr-activated cellulose disks. The specific IgE to imipenem-HSA was 8.49 kU/l (mean of four measurements, range 7.98–8.95). Autoinhibition assays showed a dose-related inhibition of IgE binding up to 90% by preincubating of serum with imipenem (10  $\mu$ g). No IgE binding to HSA alone could be detected. Twelve serum samples from unrelated patients with a total IgE of 180–2000 kU/l were used as control, and no significant IgE binding to HSA-imipenem was detectable (mean 0.35 kU/l).

The cross-reactivity of imipenem with other  $\beta$ -lactam antibiotics was also studied by immune inhibition assay in EAST. We found no significant inhibition of IgE binding to imipenem when cephalothin, cephalosporin C, cephacloz, cefoxitin, cefotaxime, and cephalexin were used as inhibitors at a concentration of <500 nmol.

In association with the case history, skin, and *in vitro* test results, we conclude that the IgE-mediated allergy to imipenem was the cause of the anaphylactic reaction. To our knowledge, this is the first reported case of IgE-mediated anaphylactic reaction to imipenem. A previous study by Saxon et al. (3) indicated that 50% of subjects ( $n=20$ )

allergic to penicillin on skin testing also reacted to imipenem reagents in SPT. But, in the present study, we did not find cross-reactivity of imipenem to penicillin determinants with SPT in the subject studied.

\*BGFA

Buerkle de la Camp Platz 1  
44789 Bochum  
Germany  
Tel. +49-234-3074 628  
Fax: +49-234-3074 505  
E-mail: chen@bgfa.ruhr-uni-bochum.de

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## Pyrethroid syndrome in an animal keeper

T. Mitsche, H. Borck, B. Horr, N. Bayas,  
H. W. Hoppe, F. Diel\*

**Key words:** interferon-gamma; interleukin-4; intoxication; nonallergic hypersensitivity; pyrethroids.

● PYRETHROIDS are used as insecticides all over the world. For many years, there has been controversy over the toxic and allergic effects of the compounds, especially in connection with the so-called pyrethroid syndrome (1).

We here report the case of a 45-year-old female animal keeper who was exposed to

pyrethroid insecticides over a period of 13 years at her workplace in activities such as feeding, maintenance of hygienic conditions, and application of insecticides).

Clinical history revealed mainly neurologic and allergy-like symptoms which developed in a progressive manner, as well as pain syndrome in muscles and joints. These

symptoms had been apparent for about 5 years. Furthermore, the patient suffered from abnormalities of

the vegetative neural behavior (e.g., loss of strength and performance, abnormal tiredness, loss of interest, sensation of coldness, dysphoria, heart arrhythmia, rapid pulse, malfunction of memory and concentration, nausea, headache, decreased olfactory sensitivity, and low blood pressure), hair loss, hypothyreosis, and vitiligo.

Ten years before, the patient had had an anaphylactic reaction after administration of the nonsteroidal analgetic Valoron® (Tilidin, Naloxon). In previous epicutaneous tests, she had a positive reaction to paracetamol, neomycin, kanamycin, and framycetin, and substances such as procaine, Coffein (in Impletol®), Tilidin, Naloxon (in Valoron), and gentamycin were suspected to cause allergy-like responses in this patient.

Several attempts to clarify the causes of her complaints failed; a specialist orthopedic clinic suspected the patient to be suffering from pesticide intoxication. It was not possible to determine any sign of radiologic correlation for the complaints. During treatment and examination in a special rheumatologic clinic, there was evidence of grades I to II morbus Scheuermann.

The animal keeper is now incapable of work due to the severity of the complaints.

After completing an extensive questionnaire, the patient was examined clinically. Data from the following laboratory examinations are reported.

### Intoxication and allergy-like response to pyrethroid insecticides and piperonyl-butoxide (PBO).

- 1) Pyrethroids and their metabolites were measured in urine and hair samples (2).
- 2) Scratch tests were performed on the volar forearm with the following allergen extracts of pyrethroids:  $4 \times 10^{-7}$  to  $2.5 \times 10^{-4}$  M S-bioallethrin and permethrin as well as  $10^{-4}$  M synergist piperonyl-butoxide (PBO) (Fluka, Deisenhofen, Germany), and S-bioallethrin/PBO mixture under standardized conditions (2).
- 3) Peripheral blood/mononuclear cells (PBMNC) were cultured for 3 days after stimulation with T-cell mitogen phytohemagglutinin (PHA). The proliferation of lymphocytes was estimated by the MTT test; the cytokines interleukin (IL)-4 and interferon (IFN)- $\gamma$  were determined by ELISA, as outlined previously (3).

In the urine samples, the pyrethroid metabolites 1.3  $\mu\text{g/l}$  *cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (BR2CA) and 5.5  $\mu\text{g/l}$  3-phenoxybenzoic acid (mPBA) were measured, and the hair analysis showed positive pyrethroid contamination.

Skin (scratch) tests resulted in flares of >5 mm and wheals of >2 mm in response to histamine, grass, and mite allergens, and showed dose-dependent response to S-bioallethrin as well as to permethrin. No significant differences were observed with the pyrethroid/PBO mixture in comparison with the single agents ( $P=0.05$ ,  $n=4$  pairs).

The blood lymphocyte count was abnormally low (<20%) and the lymphocyte-stimulating test (MTT test) showed an irregular 3-day time course. The pyrethroids caused a significant decrease in cell proliferation ( $P<0.001$  ranked pair test, Wilcoxon matched-pairs signed-ranks test), whereas the mixed agents S-bioallethrin and PBO (< $10^{-4}$  M) did not show this effect.

The determinations of IL-4 and IFN- $\gamma$  in the supernatants of the MTT test samples also indicated abnormal lymphokine kinetics.