

Table 1. Results of prick tests with various human insulin (rDNA) preparations

Preparation	Additives	Results (diameter in mm) (wheal/flare)
Insulatard NPH ¹	Protamine	5/15
	Zinc	
	Metacresol	
	Phenol	
	Glycerol	
	Sodium phosphate	
Mixtard 20 Novolet ¹	As above	4/18
Humulina NPH rDNA ²	As above	4/27
Humapilus 20:80 rDNA ²	As above	9/21
Actrapid ¹	Zinc	5/16
	Metacresol	
	Glycerol	
Monotard ¹	Zinc	4/10
	Methylparabenzoate	
	Sodium chloride	
	Sodium acetate	
	Metacresol	
Humulina Regular rDNA ²	Glycerol	4/18
	As above	
Humapilus Regular rDNA ²	As above	7/20
Humalog ^{2,3}	Zinc	3/27
	Metacresol	
	Glycerol	
	Sodium phosphate	

All insulins were tested at concentration of 40 UI/ml.

Prick histamine (10 mg/ml): wheal diameter 4 × 4 mm.

¹ *Saccharomyces cerevisiae* is used for synthesis (Novo Nordisk, Denmark).

² *E. coli* is used for synthesis (Lilly SA, Madrid, Spain).

³ Insulin lispro (Lilly SA, Madrid, Spain): new rDNA human insulin analog which differs from human insulin in order of amino acids of β -chain at positions 28 and 29.

identified rDNA HI as the cause of cutaneous reactions that occurred in our patient. We confirmed that the injection technique was correct, and we ruled out infection or irritant responses and sensitization to latex or additives. The immune response to rDNA HI is determined by both the insulin administered (changes in tertiary structure or modifications during the administration route) and the individual receiving it. Thus, high levels of insulin antibodies were found to be associated with HLA-DR4, and patients who are intermittently exposed to insulin appear to be at a higher risk of more persistent and severe allergic reactions (1). Our patient was DR4 positive, the insulin therapy had not been interrupted, and the first cutaneous reaction appeared 45 days after starting insulin. Although, in most cases, allergic reactions to HI occur after previous administration of animal insulins, they can occur (as in our report) after rDNA HI administration exclusively (2, 4, 5). The presence of specific IgE against animal insulins in our patient could be explained by the cross-reactivity that occurs between animal insulin and HI. Local reactions due to insulin are usually mild and most improve or resolve spontaneously within the first

months of treatment (1). In our case, they were persistent, and it was not possible to stop cetirizine for the moment.

■ In summary, we report a patient with local cutaneous reactions to rDNA HI due to an IgE-mediated mechanism. Special features of this case include:

- 1) the absence of treatment interruptions
- 2) the persistence of the reaction
- 3) the development of specific IgE against human and animal insulins (although the patient had not been treated with animal insulins previously)
- 4) the control of the reaction by oral antihistamines
- 5) the sensitization to insulin lispro (a new rDNA HI analog).

Key words: diabetes mellitus; drug hypersensitivity; insulin; recombinant proteins; skin.

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Hypersensitivity reaction to clarithromycin

WE report the case of a 25-year-old woman who came to our clinic because of an adverse reaction 3 years ago to clarithromycin (Klacid

comprimidos 500[®], Abbott, Spain) taken for acute tonsillitis. Approximately 8 h after taking the twelfth 500-mg tablet, she developed a symmetric, pruriginous, maculopapular rash involving the entire body but sparing the mucous membranes, palms, and soles, without fever, malaise, or arthralgia; she also reported lip angioedema and a sensation of throat fullness. At the emergency department, laryngeal edema was excluded and she received treatment with i.m. methylprednisolone. The patient had taken clarithromycin and other macrolides before without problems. The rash resolved completely in 4 weeks.

The patient had nonallergic, noneosinophilic chronic rhinitis but no personal or familial history of atopy. Ten years before, she had had an allergic reaction to amoxicillin confirmed by positive intradermal tests to benzyl penicilloyl and to the minor determinant mixture. Therefore, she had received other medication, usually macrolides, to treat respiratory infections.

■ After the patient gave written consent, an allergy study was carried out. Skin tests were performed with the following drugs: clarithromycin, erythromycin lactobionate, spiramycin, and diacetyl-midecamycin. The concentrations used in prick tests were 10 mg/ml and in intradermal tests 1 mg/ml. Positive (histamine) and negative (normal saline) controls were also carried out. Furthermore, patch tests were performed with the same drugs at 20% in petrolatum, and were read at 48 and 96 h. All these concentrations proved to be nonirritant in a group of 10 control subjects.

The results of all these skin tests in our patient were negative. Therefore, we performed single-blind, placebo-controlled oral challenge tests with all these macrolides by the oral route, starting with a dose of 62.5 mg and doubling it every 24 h to a maximum dose of 500 mg. The tests were made on an outpatient basis with a 2-h observation period in our clinic after each dose. The challenge tests with the second dose of 125 mg of clarithromycin resulted in the development within 3 h of pruriginous, maculopapular rash on the trunk that resolved with administration of 30 mg of deflazacort once a day for 5 days. The challenge test with placebo and the other macrolides was negative. Finally, a new challenge test with the excipients of Klacid comprimidos 500 was also negative.

■ Macrolides are widely prescribed antibiotics with a low risk of sensitization; only a few cases of hypersensitivity reactions to erythromycin and spiramycin have been described (1, 2). Recently, in order to improve gastrointestinal tolerance and antibacterial activity, new macrolides have been

developed which can be classified according to the number of carbon atoms in the lactone ring: 14 carbon atoms, as in erythromycin (clarithromycin and roxythromycin); 15, as in azithromycin; and 16, as in spiramycin (diacetyl-midecamycin). To our knowledge, no hypersensitivity reactions to these new macrolides have been reported except for one case of reaction to diacetyl-midecamycin (3).

We hereby describe the first known hypersensitivity reaction to clarithromycin. The symptoms suffered by the patient, the latency of the reaction, and the reproducibility of the clinical picture in the challenge test strongly suggest an underlying hypersensitivity mechanism. As in previous reports, skin tests had no value as a diagnostic tool except for anecdotal cases of occupational asthma attributed to spiramycin (4). Only the challenge test can confirm the causal relationship between the adverse reaction and the macrolide, with a few, reversible side-effects at the moment.

Since the clinical characteristics of the adverse reaction did not suggest type I hypersensitivity, we did not look for specific IgE to clarithromycin. In

fact, only one report found specific IgE to erythromycin in the serum of a patient with two episodes of immediate urticaria after the administration of the drug and a positive skin prick

A skin-prick-test-negative but challenge-positive patient allergic to β -lactam.

test (5); the clinical picture of this patient was clearly different from the other reports of macrolides-allergic subjects.

It is interesting that our patient tolerated the administration of the other macrolides, especially erythromycin. This macrolide and clarithromycin share the same 15-carbon-atom lactone ring with only minor differences in their molecules. This fact has been observed previously (1, 3) and points to a probable limited cross-reactivity among macrolides.

In summary, we have presented the first case of a very probable hypersensitivity reaction to clarithromycin with good tolerance of other macrolides in a patient allergic to β -lactam antibiotics. In the *in vivo* study performed, only the oral challenge test helped us to make the diagnosis with minor morbidity.

Key words: clarithromycin; hypersensitivity; β -lactam; macrolides.

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Anaphylaxis to millet

CEREAL grains are the staple food of most of the world, providing almost half of the world's supply of human dietary protein. Millet seed is one of the oldest cultivated crops. In the USA, approximately 500 000 acres of millet are grown per year, mostly for use as birdseed. In China, India, and equatorial Africa, this cereal is mainly cultivated for alimentary purposes, as millet seeds contain high-quality proteins. Millet belongs to the Poaceae family (syn. Gramineae), which is subdivided into many subfamilies (Table 1). Common millet (*Panicum miliaceum*) is mainly used for birdseed. Japanese and Italian millet is grown for human consumption.

The patient was a 32-year-old, otherwise healthy woman. A few minutes after ingestion of a "natural food" consisting of a cookie containing millet, she developed laryngeal pruritus and edema with stridor, tightness of the throat, pruritus of palms and soles, conjunctivitis, facial swelling, and, a few minutes later, bronchospasm and hypotension, as measured in an emergency unit (values not recorded). She was treated with epinephrine, intravenous corticosteroids, and intravenous antihistamines. The symptoms resolved within 1 h. She had previously had laryngeal itching after ingestion of a pastry containing millet, as well as an episode of swelling of the tongue in childhood related to ingestion of a particular but unknown cereal. She had never noticed reactions to common cereals (including barley and wheat). The positive control was histamine (100 µg/ml) and the negative, glycerine in water. Skin prick tests (SPT) were negative for grass pollen, tree pollen, house-dust mites, cat and dog allergens, parrot, molds, carrot, celery, parsley, soya, almond, banana, peanut, other nuts,

nut mix, apple, tomato, milk, whole egg, and egg yolk. SPT were positive for barley grains (++) and wheat flour (++) and negative for barley flour, corn grains, corn flour, oat grains, and oat flour. The wheal observed after prick-prick testing with the millet seeds, freshly prepared according to Ortolani et al. (1), was classified as strongly positive (wheal: 0.8×1 cm). Neither of the two nonatopic control subjects showed a positive reaction, ruling out a nonspecific irritant reaction. No specific serum IgE to barley, corn, oats, and wheat was found (<0.35 UI/ml, CAP Pharmacia®). In contrast, a test for specific IgE to common millet was positive (1.7 UI/ml; class 2, CAP Pharmacia).

With the increasing interest in "natural" food and "alternative" diets, more vegetable products not commonly used as food are beginning to be consumed in Western countries. Allergic reactions to different cereals have been widely described. Serologic reactions to different cereals exist, but their clinical relevance is unknown. In 1995, Jones et al. (2) performed double-blind, placebo-controlled food challenges (DBPCFC) in children with suspected cereal allergy and positive or negative SPT. They found only 20% with positive DBPCFC;

of these, 80% had reactions to only one cereal, although sera from SPT-positive and -negative allergic patients, and even SPT-positive subjects without allergy to cereals exhibited serum IgE to multiple cereals. In 1994, immunoblotting studies by Varjonen et al. (3) suggested cross-reactivity between oats, wheat, rye, and barley. Urisu et al. (4) demonstrated that a 16-kDa protein is one of the major aller-

The case of a patient who developed anaphylaxis after ingestion of food containing millet suggests that the introduction of this grain into the Western diet may result in the occurrence of apparently new allergic reactions.

gens in rice-grain extracts and showed evidence of cross-reactivity between rice and some cereal grains such as wheat and grains of the Poaceae family (corn, Japanese millet, Italian millet). This protein showed sequence homology to wheat α-amylase inhibitor and barley trypsin inhibitor (5). Thus, cross-reactive epitopes within conserved regions of these proteins may explain serologic cross-reactivity. It is of note that our patient had positive SPT to wheat and barley grain but

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