

detected as the provoking agent. Afterwards, he had been asymptomatic, as he avoided consumption of or contact with linseed-containing products.

Linseed contains many potential allergens. In a recent case study of linseed hypersensitivity (1), five allergens with mol. wt. of 38, 35, 30, 22, and 20 kDa were found by SDS-PAGE immunoblotting. In contrast, by SDS-PAGE immunoblotting under nonreducing conditions, we have found that allergens with a higher mol. wt. (150–175 kDa) intensely bound with IgE, and other more discrete bindings were noted with lower mol.-wt. allergens (90–100 kDa). With SDS-PAGE immunoblotting under reducing conditions, the high-mol.-wt. bands disappeared and discrete bands of lower mol. wt. (35–100 kDa) were detected. The results of SDS-PAGE are also in agreement with these findings. This may suggest that allergens of high mol. wt. that bind intensely with IgE separate into various subunits under reducing conditions, and that, upon separating, they lose the major part of their binding capacity.

Key words: anaphylaxis; food; linseed; specific IgE.

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Cutaneous allergy to human (recombinant DNA) insulin

THE introduction of insulin therapy was soon followed by the report of cutaneous reactions. Nowadays, the biosynthesis of human insulin (HI) by recombinant DNA technology (rDNA) has greatly reduced the incidence of adverse reactions (1). We report here an unusual case of persistent local immediate-type allergy to rDNA HI at initial insulin therapy.

■ A 32-year-old woman was diagnosed as having insulin-dependent diabetes in November 1995. She

began treatment with rDNA HI (Actrapid® Novolet® and Mixtard® 20 Novolet®) and had no problems for 45 days. She then developed local reactions at the injection sites with pruritus and wheal and flare 5 min after every injection of insulin. This reaction reached a diameter of 8–10 cm within 1 h, resolved within 1–2 h, and was followed by an indurated lesion that lasted for 48 h. Treatment with cetirizine (10 mg/24 h) provided considerable relief, but could not check the disorder for the moment. The patient had no previous history of atopy.

■ The patient was admitted to our department for evaluation in February 1996. Her informed consent was obtained before the study. Prick tests with different insulin preparations proved positive (Table 1), and negative with latex (ALK-Abelló, Madrid, Spain), protamine sulfate (Rovi SA, Madrid, Spain), and other additives included in insulin preparations. Intra-dermal tests with protamine from 0.1 µg/ml to 0.1 mg/ml were negative. Ten normal subjects were used as a control group. Total serum IgE (ALASTAT, DPC, Los Angeles, CA, USA) was normal (45 UI/ml). Specific IgE to bovine, porcine, and human insulins

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(ImmunoCAP, Pharmacia, Sweden) were elevated to 7.78, 6.78, 8.11 kU/l, respectively. Specific IgE against latex and protamine were negative (ImmunoCAP, Pharmacia, Sweden). Hematologic, biochemical, and urine tests; immunoglobulins; and C3, C4, CH50, and circulating immune complexes were normal, except for fasting blood glucose (260 mg/dl). The HLA phenotype was A24,26/B38,39/ Bw4,6/ Cw7,X/ DR4,8/ DRw53,X/ DQw4,8. Skin biopsy showed a perivascular infiltrate consisting of lymphocytes, monocytes, and especially eosinophils, mild edema affecting the superficial dermis; and slight edema of endothelial cells.

■ Cases of local allergy against HI have been rarely reported (2–6). Some authors describe a cell-mediated hypersensitivity reaction (2); others an IgE-mediated mechanism (3–6). On the basis of the results of cutaneous and *in vitro* tests, we

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 U/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

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