Insulin Allergy Treated with Human Insulin (recombinant DNA)

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Two insulin-dependent diabetic subjects treated with pork and beef insulin during a period of 6 mo developed severe local reactions. Both patients had an important allergic history (asthma, urticaria, drug reactions, rhinitis). Skin-testing revealed type I allergy to beef and pork insulin. Specific IgE-insulin binding was demonstrated with both insulins. After negative skin testing with NPH Lilly human insulin (recombinant DNA), treatment was started with this compound and remained successful during a period of 6–9 mo. In one patient a local reaction occurred when regular human insulin (recombinant DNA) was added to NPH in order to obtain better control. Skin testing with regular human insulin was positive, but not with NPH human insulin alone. The mechanism of this phenomenon remains unsolved. DIABETES CARE 5 (SUPPL. 2): 168–170, 1982.

Insulin allergy has clinical importance in some insulin-treated patients.

Local reactions are due to 1. immediate hypersensitivity (type I allergy) with formation of skin-sensitizing IgE antibodies; 2. delayed hypersensitivity after T-lymphocyte stimulation.

Systemic reactions are rare and due to IgG antibody formation. In most individuals beef insulin is more antigenic than pork, NPH insulin more than Lente types, and monocomponent and Desphe-insulins less antigenic than classical ones.[1-4]

The recent introduction of biosynthetic and semisynthetic human insulins could perhaps offer an alternative in patients suffering a severe allergic reaction to other insulins.

We had the opportunity to test and treat two patients with an insulin allergy.

CASE 1

A 47-yr-old man, asthmatic since childhood, was known to have a moderate degree of diabetes mellitus since 1976. Hyperglycemia was severe (200 mg/dl fasting) only during episodes of asthma-bronchitis when he was treated with corticosteroids and Actrapid pork MC insulin.

Till 1981 diet was sufficient to maintain an acceptable glucose tolerance (fasting blood sugar 130 mg/dl; MBG 180 mg/dl). After several severe attacks of bronchial spasm, necessitating admission at the intensive care unit, a continuous daily administration of 20 U of Novolente MC became necessary. In July 1981 he developed a severe local reaction at the injection site with general allergic symptoms such as urticaria. Intradermal skin testing showed an immediate and delayed positive response to pork and beef insulin, but no significant reaction could be observed with human semisynthetic and human (recombinant DNA) insulins (Table 1). Successful treatment was started with two injections of Lilly NPH insulin (recombinant DNA) daily, which maintained an acceptable degree of diabetes control even during bronchitis and respiratory distress episodes. No local reactions were noted during a 6-mo period of treatment, followed by 3-mo of Monotard HM without reaction.

CASE 2

A 57-yr-old man had had allergic rhinitis for 20 yr, with a significant eosinophilia (10% of total WBC). Type I diabetes was diagnosed in May 1981 and treated with diet and Actrapid MC i.v. for 1 wk till good control was achieved. For 3 mo satisfactory carbohydrate tolerance was maintained (HbA_1, 7%) with 20 U of Ultralente MC and 10 U of Actrapid MC. In October 1981 a severe immediate local reaction (erythema and induration with a diameter of 5 cm) was observed at the injection site after 10 min. Skin testing revealed a significant immediate reaction with MC pork and beef insulins as well as with Desphe pork and beef insulins, semisynthetic human insulins, and regular human insulin.

TABLE 1
Intradermal testing (0.1 ml + 0.1 U insulin): patient 1

Allergen	Species	Reaction after 20 min		Reaction after 24 h	
		Erythema (cm)	Induration (cm)	Erythema (cm)	Induration (cm)
NaCl (9%)		—	—	—	—
Actrapid MC	pork	1.8	1.4	0.4	—
Semilente MC	pork	1.8	0.8	0.7	—
Monotard MC	pork	1.4	0.5	1.0	1.0
Lente MC	pork + beef	1.4	0.5	1.5	0.5
Ultralente MC	beef	1.2	1.0	1.0	1.0
Actrapid HM	human	1.5	—	—	—
Monotard HM	human	0.8	—	—	—
Regular human insulin (recombinant DNA)	human	0.5	—	—	—
NPH human insulin (recombinant DNA)	human	0.8	0.8	—	—

TABLE 2
Intradermal testing (0.1 ml + 0.1 U Insulin): patient 2

Allergen	Species	Reaction after 20 min		Reaction after 24 h	
		Erythema (cm)	Induration (cm)	Erythema (cm)	Induration (cm)
NaCl 9%		0.6	—	—	—
Actrapid MC	pork	2.5	2.5	—	—
Monotard MC	pork	1.2	1.2	0.3	0.1
Desphe O_1S	pork	1.5	1.8	—	—
Desphe O_5S	pork	1.2	1.2	0.2	0.2
Novolente MC	pork + beef	1.5	1.5	0.6	0.6
Desphe O_1R	beef	2.0	1.6	—	—
Actrapid HM	human	2.0	2.0	0.5	0.6
Monotard HM	human	1.2	1.2	0.4	0.2
Regular human insulin (recombinant DNA)	human	2.0	2.0	—	—
NPH human insulin (recombinant DNA)	human	1.0	0.9	—	—

TABLE 3
RAST (insulin-specific IgE Binding, %)

Insulin	Species	Normal controls	Patient 1	Patient 2
Actrapid MC	pork	1.13	2.61	4.21
Monotard	pork	1.90	5.82	7.74
Lente Novo	pork + beef	0.93	4.16	5.62
Lente Novo MC	pork + beef	1.28	4.12	4.48

NPH human insulin gave only a discrete reaction (Table 2). The patient was successfully treated with 25 U of this insulin, and during 9 mo no significant local allergic reaction was observed. A remarkable fact was noted: when regular human insulin was added in order to obtain a better postprandial blood glucose value, a local induration of 3-cm diameter was observed together with severe itching. NPH human insulin alone never gave rise to such a reaction.

This could be explained by a better protection of the insulin molecule against antibody fixation in loco while using the NPH preparation. This allergy can usefully be demonstrated by RAST testing measuring the percentage of binding of the patient's serum with insulin-specific IgE (Table 3).

In conclusion, despite the fact that local reactions to human insulin have already been described, these insulins may offer a therapeutic alternative for insulin-dependent, type I diabetic patients allergic to the commercially available classical insulins.

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