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A Case of Newly Diagnosed Non-Insulin-Dependent Diabetes Associated with Immediate-Type Allergy Against Human Insulin

Key Words

Insulin allergy
Human insulin
Non-insulin-dependent
diabetes mellitus

Abstract

A case of newly diagnosed non-insulin-dependent diabetes mellitus with immediate-type allergy against semisynthetic human insulin is reported. She experienced immediate-type allergy 2 months after initial insulin treatment. A skin test showed that she had allergy against the insulin itself but not the additives. The amino acid sequence of the semisynthetic human insulin was identical to that of endogenous native insulin and, moreover, the patient had not been treated with animal-derived insulin previously, so a structural change to the semisynthetic formulation at the injected subcutaneous site might have antigenicity. An H₁ histamine blocker markedly diminished the skin reaction to insulin, and her plasma glucose and glycosylated hemoglobin A_{1c} became well controlled. In summary, we experienced a diabetic patient with human insulin allergy at the time of initial insulin treatment, emphasizing that the possibility of human insulin allergy should be considered whenever a patient is started on insulin therapy.

Introduction

Insulin allergy is a common finding, manifested by 5–10% of diabetic patients at the initial phase of therapy during the last 20 years [1]. However, the recent biosynthesis of human insulin by recombinant DNA technology, its semisynthesis from porcine insulins, and its purification as a pharmacologic agent have greatly reduced the incidence of this allergic response. We report here a very rare case of newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM) with immediate-type allergy against semisynthetic human insulin at the initial insulin therapy.

Patient and Methods

A 58-year-old female patient was admitted to our hospital for poor control of plasma glucose and body weight loss. She had experienced anaphylactic reactions to ephedrine 5 years previously and had shown immediate skin reactions, such as urticaria, to canned meat since childhood. On physical examination, the patient appeared healthy. Her temperature was 36.8 °C, pulse 78 per minute and blood pressure 112/70 mm Hg. The lungs and heart were clear. The abdomen was normal. There was no peripheral edema. Neurologic examinations were negative except that the knee and ankle jerks were diminished. The urine gave a + test for protein and a ++ test for glucose, but the sediment was normal. She had no diabetic retinopathy on funduscopic examination. She was diagnosed as having NIDDM complicated by mild peripheral neuropathy and nephropathy.

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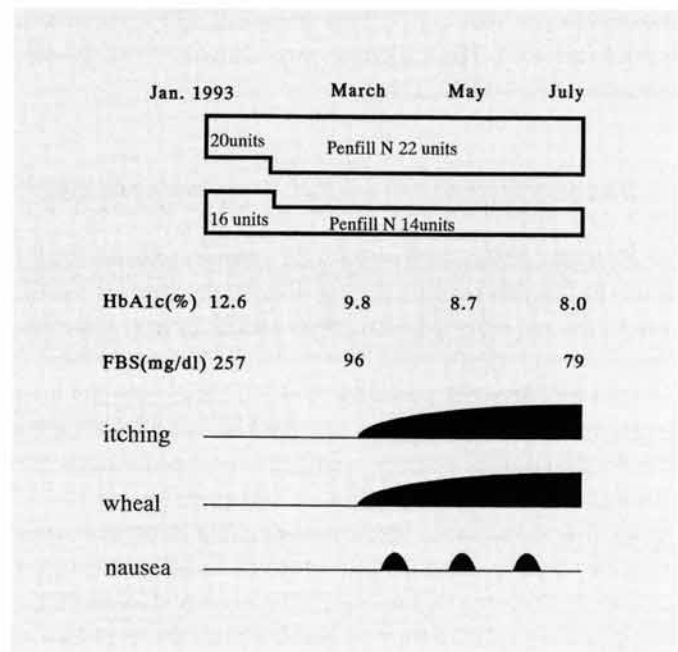
Table 1. Intradermal skin test

Preparation	Erythema, mm	Wheal, mm
Human insulin (biosynthetic)		
Before	52 × 40	15 × 17
After	12 × 10	–
Human insulin (semisynthetic)		
Before	42 × 42	20 × 15
After	12 × 10	–
Porcine insulin		
Before	40 × 48	17 × 20
After	22 × 22	–
Bovine insulin		
Before	50 × 50	40 × 30
After	23 × 21	–
Paraben medium		
Before	–	–
After	–	–
Phenol medium		
Before	–	–
After	–	–
Medium for insulin: zinc suspensions		
Before	–	–
After	–	–
Medium for insulin: NPH suspensions		
Before	–	–
After	–	–
<i>m</i> -Cresol medium		
Before	–	–
After	–	–
Protamine sulfate		
Before	–	–
After	–	–
0.9% NaCl		
Before	–	–
After	–	–

Reactions were read after 20 min. – = <5 mm.

She had not been treated with insulin previously, but started semisynthetic human insulin therapy (Penfill N[®], Novo Nordisk, Denmark) at this admission, when her plasma glucose (FPG) and glycosylated hemoglobin A_{1c} (HbA_{1c}) were poorly controlled, but the routine blood biochemistry was normal. After initial insulin treatment, her FPG and HbA_{1c} showed a marked improvement.

However, 2 months later, she developed itchy skin wheals at the insulin injection sites and sometimes experienced generalized allergic reactions, such as nausea and vomiting, to insulin, and so allergy against human insulin was suspected (fig. 1).

**Fig. 1.** Clinical course of the patient.

To evaluate possible insulin allergy, intradermal skin tests were performed with an insulin allergy skin-testing kit (Novo Nordisk), containing different insulins, the various additives in the insulin preparations (protamine sulfate, zinc suspension, NPH suspension, and preservative agents such as paraben, cresol, and phenol), and saline. 0.05 ml of 5 U/ml of human synthetic, semisynthetic, porcine, bovine insulin and 0.05 ml of the various additives were injected intradermally. The size of the erythema and wheal at the injection site was recorded 20 min after injection. A size less than 5 mm in diameter was considered negative.

Results

The titer of insulin-specific IgE antibody (measured by a Pharmacia CAP system) was less than 0.34 UA/ml, and that of total IgE antibody was also within the normal range (IgE: 22 mg/dl). Moreover, eosinophilia was not detected, but the ¹²⁵I-insulin-binding rate was 51.9% (normal range: 0–15%). The skin test with human synthetic or semisynthetic insulin resulted in local immediate skin reactions, such as itchy erythema and wheal (table 1), but generalized reactions to insulin itself were not observed. Furthermore, porcine and bovine insulins also induced local allergic reactions. However, the additives in the insulin preparations (prolongation or preservative agents) did not result in allergic reactions at the injection site. A

negative test was also noted after control testing with saline (table 1). HLA phenotyping showed the following antigens: HLA-DR2, DR4.

Discussion

Because of the antigenicity of animal-derived insulin and the additives and contaminants present in insulin preparations, many insulin-treated diabetic patients experienced local skin reactions [1]. However, since human insulin has become available, few diabetic patients have experienced allergy against insulin [2]. We report here a newly diagnosed diabetic patient with immediate-type insulin allergy at the initial human insulin therapy.

In this case, there were considerable local skin reactions to various insulins, but not to the additives (prolongation or preservative agents). The amino acid sequence of the semisynthetic human insulin is identical to that of endogenous native insulin [3] and, moreover, this female patient had not been treated with animal-derived (bovine or porcine) insulin previously, and the first manifestations of immediate-type allergy appeared 2 months after the initial insulin treatment. These facts indicated that the antigenicity of human semisynthetic insulin was probably due to a tertiary structural change during the unphysiologic subcutaneous administration.

This patient had experienced anaphylactic reactions to ephedrine 5 years previously and also allergy against can-

ned food since childhood, and her HLA phenotyping showed the following antigens: HLA-DR2, DR4. Moreover, recent studies suggest that insulin allergy is under genetic control and an immune response to insulin is associated strongly with HLA-DR4, but weakly with HLA-DR2 and DR3 [2, 4]. These findings suggest that she might have a genetic predisposition to insulin allergy.

Since skin reactions to not only human, but also to bovine and porcine insulin were positive, allergy to a common epitope of these various insulins was suspected. Amino acid sequences of animal-derived (bovine or porcine) insulins are different from those of endogenous circulating human insulin, and so skin tests to the former insulins might result in prominent allergic skin reactions.

In this patient, insulin-specific IgE antibody and non-specific IgE antibody were also negative. However, local skin allergic reactions to insulin do not always parallel the titer of IgE-insulin antibody [5] and the sensitivity of the measurement of this antibody is not very high. Moreover, the fact that this allergic reaction to insulin was well controlled by an H₁ histamine blocker (ketotifen fumarate, Zaditen®, Sandoz, Switzerland) also indicated the presence of a specific allergy to insulin in this patient.

In summary, we experienced a very rare case of a newly diagnosed diabetic patient with immediate-type allergy against human insulin. The possibility of allergic reactions to human insulin should be kept in mind when a patient is started on human insulin therapy.

References

- 1 Arkins JA, Engbring NH, Lennon EJ: The incidence of skin reactivity to insulin in diabetic patients. *J Allergy* 1962;33:69-72.
- 2 Schernthaner G, Ludwig H, Jarisch R, Bruneder H: Immediate-type allergy against insulin itself: Clinical and immunologic studies on a diabetic patient with insulin intolerance. *Diabetes Care* 1981;4:196-201.
- 3 Fireman P, Fineberg SE, Galloway A: Development of IgE antibodies to human (recombinant DNA), porcine, and bovine insulins in diabetic subjects. *Diabetes Care* 1982;5:119-125.
- 4 Irvine WJ, DiMario U, Gray RS, Morris PJ: Insulin antibodies in relation to islet antibodies and HLA antigens in type 1 diabetes. *J Clin Lab Immunol* 1978;7:111-114.
- 5 Wiles PG, Guy R: Allergy to purified bovine, porcine, and human insulins. *Br Med J* 1983; 287:531.