

Immediate-Type Human Insulin Allergy Successfully Treated by Continuous Subcutaneous Insulin Infusion

Takashi NAGAI, Yoko NAGAI, Takashi TOMIZAWA and Masatomo MORI*

A 63-year-old insulin-dependent diabetic woman was hospitalized with itchy skin wheals at the injection sites of human insulin. After intradermal skin testing was performed, the erythema and wheal was recorded immediately. The increased titer of human insulin-specific IgE antibody indicated immediate-type allergy against human insulin. Administration of an anti-allergic drug or desensitization for human insulin every 2 hours was not effective. After continuous subcutaneous insulin infusion (CSII) therapy was performed, both the itching and wheal disappeared. The process may be a desensitization through CSII. CSII may be useful in the treatment for human insulin allergy.

(Internal Medicine 36: 575–578, 1997)

Key words: insulin-dependent diabetes mellitus, desensitization

Introduction

Immunological complications of insulin therapy such as insulin allergy have decreased since the advent of human insulin treatment. Allergic symptoms to human insulin are now found in less than 1% of de novo-treated patients, but still may occur when human insulin is used in the insulin-allergic patient (1). Cutaneous insulin allergy remains a clinical problem despite the use of highly purified human insulin. It is likely that insulin aggregates (e.g., covalent dimers) contribute to the insulin antibody formation (2, 3). Continuous subcutaneous insulin infusion (CSII) therapy has been well accepted by insulin-dependent diabetes mellitus (IDDM) patients and can result in improvement of metabolic control (4), and delay or prevent diabetic complication (5). Here, we report a case of IDDM associated with immediate-type allergy against human insulin which was successfully treated by CSII.

Case Report

A 63-year-old woman came to our hospital complaining of thirst and general malaise for about one month. A 5 kg loss of body weight was noted over one month. None of her family had diabetes mellitus. She had no history of diabetes or allergy to other drugs before this episode. Her fasting blood glucose level was 16.3 mmol/l and her urine ketone was 3+. Acidosis was not noted. She was diagnosed as diabetic ketosis and was admitted

September 7, 1995. After treatment with diet therapy, semisynthetic human insulin therapy (Penfill N, Novo Nordisk, Denmark: 30 minutes prior to breakfast: 14u, dinner: 6u) and 0.9 mg/day of voglibose for 4 weeks after admission, her blood glucose levels improved. However, 4 months later, she developed itchy skin wheals at the insulin injection sites 20 minutes to 5 hours after injection, without lipoatrophy or lipohypertrophy remaining. After administration of 20 mg daily epinastine hydrochloride (Boehringer-Ingelheim, Kawanishi), which possesses an anti-histaminergic effect, her itching generally improved. The wheal, however, remained unchanged. As her blood glucose levels became worse, she had to be re-hospitalized on March 5, 1996.

Physical findings included height 156 cm, body weight 46 kg and blood pressure 144/88 mmHg. She had no diabetic retinopathy on funduscopic examination. There was no abnormality in chest and abdomen. Neurological findings were normal. Laboratory findings were as follows: Urinalysis showed glycosuria (4+) and ketonuria (±). The white blood cell counts were within the normal range (4,500–5,800/μl), however, eosinophilia was detected (320–350/μl). Liver function, renal function and electrolyte levels were normal. The chest X-ray revealed no abnormality and the electrocardiogram showed a normal range. Urine-C peptide levels were 8 μg/day. Anti-GAD antibodies were positive (73.9–95.9 U/ml, by RIP Anti-GAD Hoechst), indicating IDDM.

To evaluate possible insulin allergy, intradermal skin testing

From the Department of Internal Medicine, Public Tomioka General Hospital, Tomioka and *the Department of Internal Medicine, Gunma University School of Medicine, Maebashi

Received for publication October 29, 1996; Accepted for publication April 25, 1997

Reprint requests should be addressed to Dr. Takashi Nagai, the Department of Internal Medicine, Public Tomioka General Hospital, 2073-1 Tomioka, Tomioka, Gunma, 370-23

was performed with an insulin allergy skin testing kit (Novo Nordisk) containing 0.05 ml of 5 U/ml of different insulin (human, porcine or bovine insulin), 0.05 ml of the various additives in the insulin preparations and saline. The skin test with human, porcine and bovine insulin resulted in itchy erythema and wheals at the injection sites after 20 minutes and lasted for 5 hours (Table 1). Moreover, the titer of human insulin-specific immunoglobulin E (IgE) antibody (measured by a Pharmacia CAP system) was 14.8 UA/ml (normal range: ≤ 0.34 UA/ml), indicating immediate-type allergy against human insulin. The desensitization for human neutral insulin (Novolin R) every 2 hours showed the threshold of insulin was 0.1 units from March 15 to March 18 (Table 2). After starting CSII (used by SP-3HQ, Nipro, Osaka) therapy from March 25, which involved basal 0.36 u/h and an additional (30 minutes prior to breakfast: 10u, lunch: 4u, dinner: 8u) insulin dose, both the itching and wheal disappeared. Moreover, the control of blood glucose improved (Fig. 1). The skin test with human,

porcine and bovine insulin resulted in itchy erythema and wheals at the injection sites after 20 minutes and lasted for 5 hours. Three hundred and five days later, the results were repeated (Table 1). Sixty-three days and 303 days after starting CSII, intradermal skin testing showed the threshold of insulin had become 0.2 units (Table 2).

The property of insulin binding antibody was observed. Double antibody precipitation technique using ^{125}I -insulin was employed. IgG-insulin binding antibodies were detected (28.2%: normal range $\leq 3.1\%$), however, IgM-insulin binding antibodies were not detected (1.9%: normal range $\leq 1.9\%$). Moreover, at 3 and 6 months, the percentage of IgG-insulin binding antibodies increased (34–35%), although IgM-insulin binding antibodies were not detected (1.9%). The titer of human insulin-specific IgE antibody decreased (7.4–8.3 UA/ml) (Fig. 1).

Table 1. Intradermal Skin Testing

Preparation	before CSII		305 days after CSII	
	Erythema (mm)	Wheal (mm)	Erythema (mm)	Wheal (mm)
Human insulin (biosynthetic)				
20 minutes after	30 × 27	26 × 20	32 × 29	27 × 22
60 minutes after	35 × 20	26 × 20	31 × 22	25 × 22
Porcine insulin				
20 minutes after	30 × 20	26 × 19	32 × 22	25 × 20
60 minutes after	30 × 20	25 × 15	31 × 22	24 × 17
Bovine insulin				
20 minutes after	26 × 25	21 × 20	29 × 28	22 × 21
60 minutes after	30 × 20	20 × 16	29 × 25	21 × 19
Paraben medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
Phenol medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
Metacresol medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
Zinc medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
Isophane medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
Protamine medium				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0
0.9% NaCl				
20 minutes after	5 × 5	0 × 0	5 × 5	0 × 0
60 minutes after	0 × 0	0 × 0	0 × 0	0 × 0

Normal erythema diameter: less than 5 mm.

Table 2. Desensitization for Human Insulin (Novolin R)

Day	Insulin dose	Erythema (mm)	Wheal (mm)
1st day	0.001u	5 × 5	0 × 0
	0.002u	10 × 8	0 × 0
	0.004u	5 × 5	0 × 0
	0.01u	10 × 10	0 × 0
	0.02u	5 × 5	0 × 0
	0.04u	5 × 5	0 × 0
	0.1u	25 × 15	15 × 10
2nd day	0.04u	5 × 5	0 × 0
	0.1u	12 × 10	5 × 5
	0.1u	10 × 10	0 × 0
3rd day	0.1u	5 × 5	0 × 0
	0.2u	25 × 22	8 × 7
	0.2u	25 × 20	7 × 6
4th day	0.1u	5 × 5	0 × 0
	0.2u	24 × 19	8 × 7
	0.2u	23 × 19	8 × 6
63rd day after starting of CSII			
	0.1u	5 × 5	0 × 0
	0.2u	5 × 5	0 × 0
	0.4u	25 × 20	10 × 9
	0.4u	25 × 20	11 × 8
	1u	170 × 50	40 × 40
303rd day after starting of CSII			
	0.1u	5 × 5	0 × 0
	0.2u	5 × 5	0 × 0
	0.4u	25 × 19	11 × 10
	0.4u	24 × 20	11 × 10
	1u	165 × 55	45 × 40

Normal erythema diameter: less than 5mm.

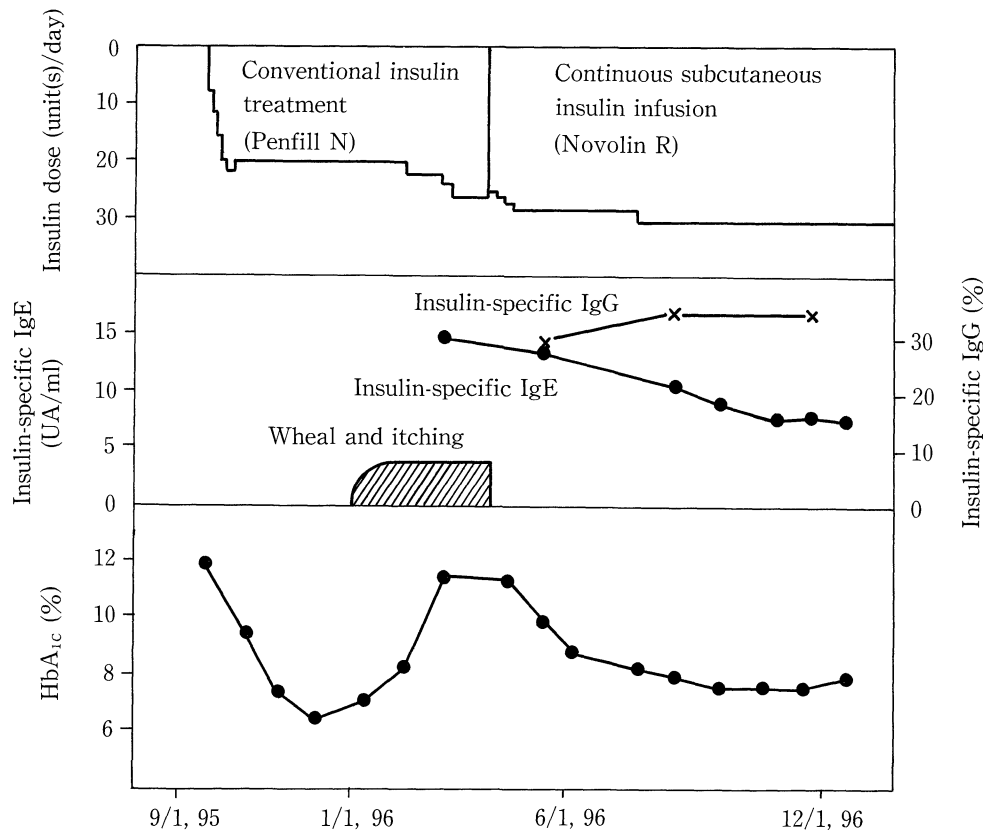


Figure 1. Clinical course of the patient.

Discussion

Since human insulin has become available, few diabetic patients have experienced an allergic reaction against insulin (1). We report an IDDM patient with immediate type insulin allergy after 4 months of the initial human insulin therapy. The amino acid sequence of the semisynthetic human insulin is identical to that of endogeneous native insulin (6). Moreover, the patient had not been treated with animal-derived insulin previously. Therefore, the antigenicity of human semisynthetic insulin was probably due to a tertiary structural change (2, 3). Although in general, human insulin allergy can be well controlled by an H₁ histamine blocker (7), it was not successfully treated in the present case. Conventional insulin treatment may cause spontaneous desensitization to insulin allergy (8). However, about 10 months' after CSII, the skin test with human, porcine and bovine insulin resulted in itchy erythema and wheals. Moreover, the human insulin threshold remained at 0.2 units, indicating the allergy remained unchanged. Why wheals do not result from bolus insulin injection over 0.2 units (4 to 10 units) is unclear, however, the basal insulin injection may cause a desensitization through continuous insulin infusion. It seems to involve depletion of the chemical mediators of hypersensitivity from mast cells and basophils (9) at the continuous injection site. Insulin autoantibodies in newly diagnosed IDDM

patients are frequently detected (10). Therefore, IgG-insulin binding antibodies or insulin-specific IgE antibodies may not always be due to exogenous human insulin. However, here, the percentage of IgG-insulin binding antibodies increased, while the titer of human insulin-specific IgE antibody tended to decrease after CSII therapy. Insulin IgG blocking antibodies (IgG4), which we had not measured, may have developed to prevent the binding of insulin to IgE on mast cells that triggers the immediate hypersensitivity response (9, 11). Moreover, human insulin-specific IgG may have deteriorated glycemic control due to insulin resistance (12) in this patient with a short duration of insulin therapy. Also the decrease of insulin-specific IgE antibody (13), which causes immediate type insulin allergy (14), may be due to the desensitization resulting from CSII therapy. CSII may improve not only the blood glucose level in diabetic patients, but also may be useful in treating human insulin allergy.

References

- 1) Scherthaner G Immunogenicity and allergenic potential of animal and human insulins *Diabetes Care* 16 Suppl 3: 155, 1993.
- 2) Robbins DC, Cooper SM, Fineberg SE, Mead PM. Antibodies to covalent aggregates of insulin in blood insulin-using diabetic patients *Diabetes* 36: 838, 1987
- 3) Patner RE, Phillips TM, Steiner M Persistent cutaneous insulin allergy resulting from high-molecular-weight insulin aggregates *Diabetes* 39:

- 728, 1990.
- 4) Home PD, Capaldo B, Burrin JM, Worth R, Alberti KG. A crossover comparison of continuous subcutaneous insulin infusion (CSII) against multiple insulin injections in insulin-dependent diabetic subjects: Improved control with CSII. *Diabetes Care* **5**: 466, 1982.
 - 5) The Kroc Collaborative Study Group: Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. *JAMA* **260**: 37, 1988.
 - 6) Fireman P, Fineberg SE, Galloway JA. Development of IgE antibodies to human (recombinant DNA), porcine and bovine insulins in diabetic subjects. *Diabetes Care* 5 Suppl **2**: 119, 1982.
 - 7) Yamagishi S, Abe T, Sawada T. A case of newly diagnosed non-insulin-dependent diabetes associated with immediate-type allergy against human insulin. *Horm Res* **43**: 300, 1995.
 - 8) deShazo RD, Mather P, Grant W, et al. Evaluation of patients with local reactions to insulin with skin tests and in vitro techniques. *Diabetes Care* **10**: 330, 1987.
 - 9) Patterson R, Lucena G, Metz R, Roberts M. Reaginic antibody against insulin: demonstration of antigenic distinction between native and extracted insulin. *J Immunol* **103**: 1061, 1969.
 - 10) Palmer JP, Asplin CM, Clemons P, et al. Insulin antibodies in insulin-dependent diabetics before insulin treatment. *Science* **222**: 1337, 1983.
 - 11) Aalberse RC, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. *J Immunol* **130**: 722, 1983.
 - 12) Grammer LC, Roberts M, Buchanan TA, Fitzsimons R, Metzger BE, Patterson R. Specificity of immunoglobulin E and immunoglobulin G against human (recombinant DNA) insulin in human insulin allergy and resistance. *J Lab Clin Med* **109**: 141, 1987.
 - 13) Lichtenstein LM, Ishizaka K, Norman PS, Sobotka AK, Hill BM. IgE antibody measurement in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. *J Clin Invest* **52**: 472, 1973.
 - 14) Falholt K. Determination of insulin specific IgE in serum of diabetic patients by solid-phase radioimmunoassay. *Diabetologia* **22**: 254, 1982.
-