

DIABET 00492

Case Report

A case of insulin allergy: the crystalline human insulin may mask its antigenicity

Hiroshi Takatsuki, Hidehiro Ishii, Teruaki Yamauchi, Naoki Nakashima, Shouji Nagase,
Akitaka Hisatomi, Fumio Umeda and Hajime Nawata

Third Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, Japan

(Received 17 October 1990)

(Revision accepted 26 December 1990)

Summary

We report an unusual case of insulin allergy. A 48-year-old man with non-insulin-dependent diabetes mellitus receiving biosynthetic isophane human insulin (Humulin N) developed itchy wheal-and-flare reactions at the sites of injection. When Humulin N was changed to a semi-synthetic crystalline human insulin zinc (Novolin U), the allergic reactions completely disappeared. Evaluation of his serum showed a high level of insulin-specific IgE. Skin testing with all commercially available insulins showed immediate local reactions to all agents tested except for Novolin U. In addition, decrystallized Novolin U prepared by lowering the pH with acetic acid also induced a positive reaction. These observations suggest that the crystallized structure of human insulin may mask its antigenicity for allergic reactions.

Key words: Insulin allergy; Crystalline human insulin

Introduction

There have been many reports of allergic reactions following the injection of insulin preparations, for which various factors have been held responsible. These include biological contaminants, e.g., proinsulin [1] and additives, e.g., zinc [2] or protamine [3]. Allergic reactions can occur

even with human insulin, although in most cases this is seen following previous short-term administration of less purified preparations of bovine or porcine insulin [4]. In general, patients who are allergic to one human insulin preparation react similarly to all other human insulins when the allergic reactions are induced by insulin itself. However, in this report, we present a patient who showed positive skin-test reactions to all insulin preparations except for a crystallized human insulin. The mechanism for this unusual observation is discussed.

Correspondence to: Fumio Umeda, Third Department of Internal Medicine, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan.

Case report

A 48-year-old man with no history of allergy was diagnosed as having non-insulin-dependent diabetes mellitus in 1984. In October 1988, because of poor glycemic control, treatment began with injections of monocomponent bovine/porcine insulin zinc (Insulin Novo Lente MC, Novo) with subsequent improvement. However, after one month, he decided to discontinue the insulin injections. By December 1988, he had a noticeable weight loss and there was general fatigue. At that time he was seen again by a physician who prescribed treatment with biosynthetic isophane human insulin (Humulin N, Lilly). While using that preparation, he noticed local, itchy, wheal-and-flare reactions at the sites of injection and occasionally felt nausea. He was admitted to our hospital for evaluation in October 1989.

The patient was 172 cm tall and weighed 47 kg. On physical examination the Achilles tendon reflex could not be elicited and there was paresthesia in the lower and upper extremities. The ocular fundus photography revealed preproliferative retinopathy. The complete blood count was within normal limits (eosinophils 0% of $6.7 \times 10^3/\mu\text{l}$). The fasting blood glucose was 200–300 mg/dl and the daily profile of blood glucose was within the range of 150 to 300 mg/dl. The HbA_{1c} level was 10.7%. The urinary excretion of C-peptide was 20–50 µg/day. An intravenous glucagon tolerance test (1 mg) showed a slightly lowered response of the serum C-peptide level from 1.3 ng/ml at base to 2.9 ng/ml at 6 min. The total serum IgE concentration was 7.3 IU/ml (normal <120 IU/ml), but the bovine, porcine and human insulin-specific bound IgE was elevated to 1.4, 2.6 and 2.9%, respectively (normal <0.8%). Insulin-specific IgG was also elevated to 1.595 (OD at 492 nm) for bovine insulin, 1.529 for porcine insulin and 1.550 for human insulin (normal 0.155 ± 0.042 , and 0.152 ± 0.058 and 0.151 ± 0.057 , respectively). Intradermal testing for insulin allergy was performed with seven commercially available preparations of human, porcine and bovine insulin. As shown in

Table 1, only one preparation, semi-synthetic crystalline human insulin zinc (Novolin U, Novo), did not produce allergic reactions. However, when Novolin U was decrystallized by lowering the pH from 7 to 3.5 by adding acetic acid [5], a positive reaction was again observed. Based on these skin test results, Humulin N was changed to Novolin U. All allergic reactions then disappeared completely. However, the glycemic control grew progressively worse despite an increase in insulin dosage to 48 U/day. We therefore tried administering a combination of Novolin U, 38 U/day, with gliclazide 120 mg/day. After four weeks, the levels of fasting blood glucose improved to 100–140 mg/dl and the HbA_{1c} to 9.5%. The urinary excretion of C-peptide increased to 40–70 µg/day.

TABLE 1

Results of skin testing with various insulin preparations

Insulin preparation	Flare size (cm)		Itching
	15 min	60 min	
Actrapid Human (Novo)	4.5	4.5	+++
Humulin R (Lilly)	4.5	3.5	+++
Monotard Human (Novo)	3.5	3.0	+
Humulin N (Lilly)	0.9	1.6	+
Insulin Novo Lente MC (Novo)	1.5	4.0	+
Insulin Novo Ultralente MC (Novo)	0.9	1.5	+
Novolin U (Novo)	0	0	–
Novolin U, decrystallized*	4.5	4.8	++
Acetic acid (pH 3.5)	0.4	0.4	+
Carrier solution of Actrapid Human	0	0	–

One unit (25 µl) of each insulin preparation was injected intradermally and the size of flare was measured at 15 min and again at 60 min after the injection. Actrapid Human; semi-synthetic neutral human insulin, Humulin R; biosynthetic regular human insulin, Monotard Human; semi-synthetic human insulin zinc, Humulin N; biosynthetic isophane human insulin, Insulin Novo Lente MC; monocomponent bovine/porcine insulin zinc, Insulin Novo Ultralente MC; monocomponent crystalline bovine insulin zinc, Novolin U; semi-synthetic crystalline human insulin zinc. *Novolin U was decrystallized by lowering the pH from 7 to 3.5 by the addition of acetic acid before injection.

Discussion

Wheal-and-flare reactions at the site of insulin injection are recognized as indicators of dermal insulin hypersensitivity. It is considered that insulin allergy in diabetic patients results from an insulin-specific IgE antibody [6,7]. In our patient, the results of skin tests clearly indicated that insulin itself and not contaminants or additives caused the allergic reactions. This was supported by the presence of a high level of insulin-specific IgE. Although crystallized insulin preparations are generally accepted as having more antigenicity than non-crystallized preparations [6], our patient reacted negatively to skin tests only with a semi-synthetic crystalline human insulin (Novolin U). In particular, the decrystallized preparation of Novolin U induced skin allergy, suggesting that the crystallized structure [8] of this human insulin may mask its antigenicity for skin allergy. However, we could not exclude the possibility that a change in the 3-dimensional conformation of crystallized insulin [9] may inversely reduce its antigenicity. Our patient had a positive skin reaction to a crystalline monocomponent bovine insulin zinc (Insulin Novo Ultralente MC, Novo). Since our patient had been treated with bovine and porcine insulin for one month, part of his anti-insulin IgE antibodies may have reacted to the amino acid sequence of bovine insulin which differs from that of human insulin. The type of insulin allergy we observed has not previously been described and could lead to unnecessary treatment for insulin allergy such as glucocorticoid administration.

The satisfactory glycemic control of our patient was not accomplished by 48 U/day of Novolin U injection, probably because short-acting insulin preparations could not be used and insulin-specific IgG may induce insulin resistance [10]. Therefore we tried administering a combination of Novolin U with an oral sulfonylurea, which was reported to be effective in improving

glycemic control in non-insulin-dependent diabetic patients with a short duration of insulin therapy or with a sufficient residual endogenous insulin secretion [11]. This regimen improved his glycemic control and the daily excretion of C-peptide in urine increased, suggesting that the combined therapy proved effective in this patients.

References

- 1 Kahn, C.R. and Rosenthal, A.S. (1979) Immunologic reactions to insulin: insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diabetes Care* 2, 283–295.
- 2 Feinglos, M.N. and Jegasothy, B.V. (1979) Insulin allergy due to zinc. *Lancet* 1, 122–124.
- 3 Shore, R.N., Shelly, W.B. and Kyle G.C. (1975) Chronic urticaria from isophane insulin therapy. *Arch. Dermatol.* 11, 94–97.
- 4 Home, P.D. (1987) Insulin injection therapy. In: K.G.M.M. Alberti and L.P. Krall (Eds.), *The Diabetes Annual*, 3, Elsevier, Amsterdam, Netherlands, pp. 94–106.
- 5 Cunningham, L.W., Fischer, R.L. and Vestling, C.S. (1985) A study of the binding of zinc and cobalt by insulin. *J. Am. Chem. Soc.* 77, 5703–5707.
- 6 Falholt, K. (1982) Determination of insulin specific IgE in serum of diabetic patients by solid-phase radioimmunoassay. *Diabetologia* 22, 254–257.
- 7 Falholt, K., Hoskam, J.A.M., Karamanos, B.G., Susstrunk, H., Viswanathan, M. and Heding, L.G. (1983) Insulin-specific IgE in serum of 67 diabetic patients against human insulin (Novo), porcine insulin, and bovine insulin. Four case reports. *Diabetes Care* 6 (Suppl. 1), 61–65.
- 8 Blundell, T., Dodson, G., Hodgkin, D. and Mercola, D. (1972) Insulin: the structure in the crystal and its reflection in chemistry and biology. *Adv. Protein Chem.* 26, 279–402.
- 9 Bentley, G., Dodson, E., Dodson, G., Hodgkin, D. and Mercola, D. (1976) Structure of insulin in 4-zinc insulin. *Nature* 261, 166–168.
- 10 Patterson, R., O'Rourke, J., Roberts, M. and Suszko, I.M. (1973) Immunologic reactions against insulin: IgG anti-insulin and insulin resistance. *J. Immunol.* 110, 1126–1134.
- 11 Lewitt, M.S., Yu, V.K.F., Rennie, G.C. et al. (1989) Effects of combined insulin-sulfonylurea therapy in type II patients. *Diabetes Care* 12, 379–383.