



A case of primary and generalized allergy to human insulin with no history of any prior insulin exposure

Hiroshi Takuma*, Takahiko Kawagishi, Ikuo Kyogoku, Yasuhisa Okuno,
Yoshiki Nishizawa, Hirotoshi Morii

Second Department of Internal Medicine, Osaka City University Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545, Japan

Received 7 April 1995; revision received 24 August 1995; accepted 27 September 1995

Abstract

A generalized hypersensitivity reaction against human insulin was demonstrated in a non-insulin dependent diabetic man treated with only human insulin. The patient had no history of previous insulin exposure or atopy. Because of negative reactions to intracutaneous tests of constituents of the formulation and the presence of insulin-specific IgE antibody, this generalized allergic reaction seems to have been caused by the human insulin itself. Although desensitization was not effective, this allergic reaction was improved both by the treatment with oral antihistamines and desensitization. Cases of generalized and primary allergy against human insulin have been rarely reported making this a very rare case.

Keywords: Primary allergy; Human insulin; Generalized

1. Introduction

Allergic reactions to animal-derived insulin have been reported [1]. Since human insulin has no immunogenicity, its availability would have seemed to potentially eliminate the problem of insulin allergy, but this has decreased only to some extent, and several cases of allergic reactions to human in-

sulin have been reported [2]. Most patients with allergic reactions to human insulin had received animal derived insulin previously [3]. We report here a rare case of allergy to human insulin without any previous history of insulin exposure. To our knowledge, only five cases [4–6] that show primary allergy to human insulin have been reported. Most allergic reactions to insulin are of the local type, but generalized allergic cases are rare. Local symptoms have been described in 5–10% of insulin treated patients [7], and general symptoms in one series were found in only 0.07% (4 of 5880 insulin treated patients) [8]. In this report we demonstrate a case of a generalized aller-

* Corresponding author, Department of Neurology, Institute for Brain Research, School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. Tel.: +81-3-3815-5411, ext. 3783; fax: +81-3-3813-2129.

gic reaction and sensitization to human insulin without a history of previous insulin exposure. This generalized and primary allergy to human insulin is one of the few very rare reported cases.

2. Case presentation

The patient was a 63-year-old man with a 15-year duration of non-insulin-dependent diabetes mellitus. He had no history of any drug or food allergy, or atopy. Since he was diagnosed to have diabetes mellitus in 1976, he had received the oral hypoglycemic agent, glibenclamide. Five months before his admission, glibenclamide was no longer effective for glycemic control, resulting in fasting blood glucose values >290 mg/dl (HbA_{1c} , 11.1%). Daily insulin therapy was initiated on March 25, 1991. He had no prior history of any kind of insulin exposure. He required initially a morning dose of 4 U of semisynthetic human insulin (Penfill N; Novo Nordisk Pharma Ltd., Bagsraerd, Denmark) which was gradually increased to 30 U. At first he self-injected subcutaneously in the anterior region of the thigh or abdomen, but reddening and swelling of the region occurred for about 24 h after the injection. He had no itching. Subsequently he changed the injection site to his upper arm, but on May 8 he had the same type of skin reaction at the new injection site and felt itching. On August 21 nausea, generalized skin rashes with redness, itching, swelling, tingling paresthesia and sweating

appeared just after the injection. These symptoms disappeared within about 1 h. Insulin therapy was stopped and the patient was admitted to our hospital to search for a more suitable insulin preparation or to undergo an insulin desensitization procedure.

After his admission, we first performed a series of intracutaneous tests to determine if true allergy to human insulin existed. Intracutaneous tests with the following preparations were carried out. Insulin was diluted in sterile diluent (0.9% NaCl) to 1 U/ml and other substances/constituents were added as indicated: (a) semisynthetic human insulins; Monotard Human (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark), Novolin U (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark), Penfill R and Penfill N (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark); (b) recombinant human insulins; Humulin R and Humulin N (Eli-Lilly and company, Indianapolis, USA); (c) highly purified pork insulins; Actrapid MC (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark); (d) highly purified beef insulins; NPH Iszilin (Shimizu Pharmaceutical Co., Ltd., Shimizu, Japan); (e) other protein preparations; 0.05 U/l glucagon (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark), 1 U/ml secretin (Eisai Co. Ltd., Tokyo, Japan), 0.01 mg/ml protireline tertrate (thyrotropin releasing

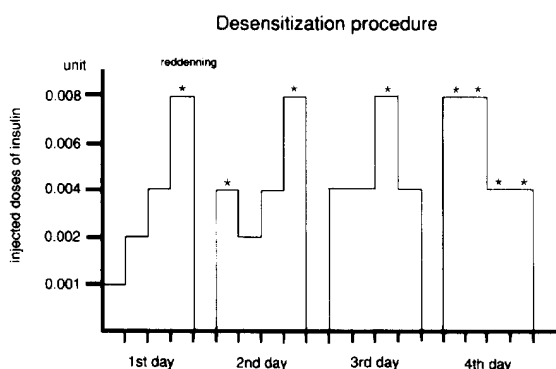


Fig. 1. The injected dose of semi-synthetic human insulin (Penfill N) and the patient's reaction. Injections were given at 3 h intervals each day. *Shows when an allergic reaction occurred. All these reactions were limited to only local reddening.

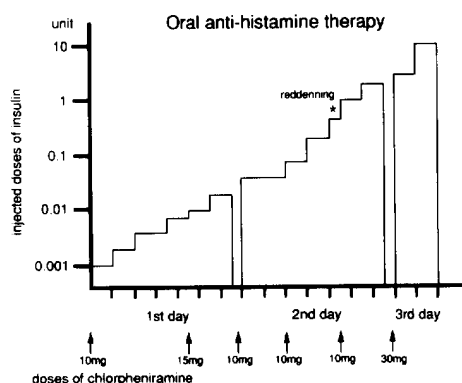


Fig. 2. The injected dose of semi-synthetic human insulin (Penfill N) and the patient's reaction during treatment with the oral anti-histamine (chlorpheniramine). The started doses of chlorpheniramine were administered at the points indicated by the arrows. One unit of the X-axis indicates 2 h. *Means the same as in the Fig. 1.

hormone, Takeda chemical industries Ltd., Osaka, Japan); (f) insulin preparation components (diluted 1:100 to normal commercial use with saline); paraben medium (0.01 mg/ml methyl parahydroxybenzoate, 0.014 mg/ml sodium acetate, 0.07 mg/ml sodium chloride), phenol medium (0.02 mg/ml phenol, 0.16 mg/ml glycerol), *m*-cresol medium (0.03 mg/ml *m*-cresol, 0.16 mg/ml glycerol), zinc medium (0.5 µg/ml zinc as chloride, 0.01 mg/ml methyl parahydroxybenzoate, 0.014 mg/ml sodium acetate, 0.07 mg/ml sodium chloride), NPH medium (0.024 mg/ml disodium phosphate, 0.016 mg/ml glycerol, 0.015 mg/ml *m*-cresol, 6.5 µg/ml phenol), 0.1 mg/ml protamine sulfate (Novo Nordisk Pharma Ltd., Bagsraerd, Denmark). Normal saline (0.9% NaCl) and histamine were injected as controls. Intracutaneous skin tests were judged positive if the wheal diameter was larger than 10 mm and an area of erythema was

noted about the wheal. At the sites of each insulin injection, positive reactions occurred almost immediately (after 15 min) but there were no delayed reactions (after 24 h and 48 h). Other substances, i.e., other proteins, insulin components, produced neither immediate nor delayed reactions. As discussed later, these results indicated that the patient's allergic reaction to the insulin preparation was caused by the insulin itself. We decided to place the patient on a desensitization protocol. A schedule of intracutaneous injections of semi-synthetic human insulin (Penfill N) at increasing concentrations, starting with 0.001 IU (0.01 IU/ml) administered every 3 h, was applied. There was no reaction initially, but on the fourth injection (0.008 IU; 0.08 IU/ml), an immediate allergic reaction occurred. The concentration was repeatedly stepped down and subsequently increased for 4 days, but a high enough dosage could

Table 1
Results of intracutaneous skin testing with various components of insulin preparations

	Species of insulin			Prot- amine	Zinc	Phenol	Cresol	Methyl para hydroxy benzoate	Glycerol	Allergic reaction	
	Human		Bovine								Porcine
	Semisyn- thetic	Recom- binant									

Penfill N	○			○		○	○		○	+
Penfill R	○					○			○	+
Novolin U	○				○			○		+
Monotard										
Human	○				○			○		+
Humulin N		○		○		○	○		○	+
Humulin R		○					○		○	+
Iszilin			○				○	○	○	+
Novo Actorapid				○				○		+
MC										
Paraben medium								○		-
Phenol medium						○			○	-
m-Cresol medium							○		○	-
Zinc medium					○			○		-
Protamine thiosulphate				○						-

Open circles (○) indicate the components in each medium.

not be reached to desensitize the patient. We, therefore, stopped this procedure.

Next we chose a program of insulin injections with oral antihistamine [9]. The patient was given orally the antihistaminic agent, chlorpheniramine maleate. To determine the proper dosage of chlorpheniramine maleate, after receiving regular doses, the patient took an injection at a lower concentration of human insulin (0.001 IU/0.1 ml) and desensitization was performed as follows. When an allergic reaction occurred, increased dosage of antihistamine was given. Finally the patient could accept an injection of 10 IU/0.1 ml of insulin by taking 30 mg of oral chlorpheniramine maleate. The side effect of the administration of 30 mg of chlorpheniramine maleate was only slight sleepiness. The generalized allergic reaction was no longer present.

At this stage he has achieved good diabetes control with semisynthetic human insulin (Penfill N) while taking chlorpheniramine 18 mg/day. During the antihistamine treatment, the dose of his insulin requirement has not been changed and no allergic reaction has been found. The side effect of the antihistamine has gradually reduced.

Specific IgE antibodies for human insulin measured by fluorescent enzyme immunoassay (BML; Saitama, Japan) gave highly positive values (8.66 Phadebas RAST unit/ml, class 3) on October 15 (<0.35, class 0). Anti-insulin-antibody (IRI binding rate) was 8.8% on May 31 and 68.3% on September 5 (0–10%).

3. Discussion

Almost all cases of insulin allergy have previous histories of animal-derived insulin exposure, but this case had no history of such exposures. After the first treatment with human insulin, the allergic reaction appeared in this patient. We suggest that the allergic reaction of this case was caused primarily by human insulin solution, for the following reasons. First, after beginning treatment with human insulin, the titer of specific IgE antibodies for human insulin was high. Although the anti-insulin-antibody (IRI binding rate) was normal at the start of insulin exposure, it reached a very high value about 5 months later. Second, semisynthetic human, recombinant human, bovine or porcine insulin all caused allergic reactions, whereas the con-

stituents of the formulations — methyl parahydroxybenzoate, phenol, glycerol, cresol and zinc, did not. For example, Penfill N caused a positive reaction and contains protamine, phenol and glycerol, but none of these constituents caused reactions. For these reasons, we suggest that the allergic reaction in the case was caused by the human insulin itself. Other proteins which we tested, i.e., glucagon, secretin and thyrotropin releasing hormone, did not cause any reaction. The allergic reaction in this case was extremely specific to insulin.

It is still unknown generally why human insulin is immunogenic, but some speculation has been made. For example, it has been suggested that there are differences in tertiary structure between synthetic and endogenous insulin, and that these differences produce immunogenicity [2]. It has been shown that insulin molecules will aggregate, and that these aggregates result in immunogenicity [10]. Most cases of allergy to human insulin have histories of animal insulin exposure [3]. It has been suggested that antibodies to animal insulin are produced after exposure to it and that they cross-react with human insulin [11]. Some additives, such as zinc or protamine, are included in insulin preparations, and in some cases may be a cause of immunogenicity [12]. The early insulin preparations were found to contain significant quantities of biological contaminants, such as proinsulin or hormonal contaminants [13,14], and it has been suggested that they can induce allergic reactions. In the present case, cross-reaction is unlikely because there was no prior history of receiving any type of insulin. Since none of the additives in the insulin preparations induced allergic reactions, they are unlikely to be the cause of the allergic reaction in this case. The fact that insulin preparations, currently, are highly purified [15] argues against contaminants having a role. We suggest that either immunogenicity caused by the tertiary structure of synthetic insulin or of aggregates of insulin molecules may have contributed to the allergic reaction in this case.

Several kinds of treatments for insulin allergies are possible. Desensitization is undertaken to produce anti-insulin IgG-blocking antibodies [16]. To blunt the histamine-induced effect, antihistamines are administered orally [7,17] or subcutaneously [17,18]. Glucocorticoids would be effective as anti-

inflammatory agents and to inhibit cellular lymphokine production, they can be taken orally [7], subcutaneously [7,9], and topically [9]. Continuous subcutaneous insulin infusion (CSII) may be used, on the supposition that the infusion of insulin microdoses at a continuous basal rate could represent a desensitization method [19]. Non-steroidal anti-inflammatory agents, such as aspirin, could be used to antagonize vascular mediators of the allergic response [20]. There is, however, no authorized method. The desensitization procedure is popular, but it is unsuccessful in about 10% of all patients [21]. We selected this procedure first, but it was not effective. We, therefore, chose oral antihistamines for the next procedure because the allergic reaction was generalized, and a treatment that affected only the local region would not have been effective in controlling it. We thought that it would be hard to control the severe allergy of our patient using CSII because an allergic reaction occurred at a low dose of insulin in the desensitization procedure. Furthermore, our patient found it difficult to comply with CSII, and the cost of this procedure is personally expensive as it has not been approved for national insurance reimbursement in Japan. Finally, we chose the treatment with the anti-allergic agent rather than with CSII. The patient had problems of compliance in following other procedures, and the long term administration of glucocorticoids caused us anxiety concerning their effects on the patient's glycemic control.

Primary allergy to human insulin is very rare. Generalized allergy is much rarer and more severe, but it can occur as this case indicates. We should be alert to the possibility of insulin allergy, even in patients who are receiving human insulin.

References

- [1] Lamkin, N., Lieberman, P., Hashimoto, K., Morohashi, M. and Sullivan, P. (1976) Allergic reaction to insulin. *J. Allergy Clin. Immunol.* 58, 213–223.
- [2] Grammer, L.C., Metzger, B.E. and Patterson, R. (1984) Cutaneous allergy to human (recombinant DNA) insulin. *J. Am. Med. Assoc.* 251, 1459–1460.
- [3] Blandford, R.L., Sewell, H., Sharp, P. and Hearnshaw, J.R. (1982) Generalized allergic reaction with synthetic human insulin. *Lancet* 2, 1468.
- [4] Grammer, L.C., Roberts, M., Buchanan, T.A., Fitzsimons, R., Metzger, B.E. and Patterson, R. (1987) Specificity of immunoglobulin E and immunoglobulin G against human (recombinant DNA) insulin in human insulin allergy and resistance. *J. Lab. Clin. Med.* 109, 141–146.
- [5] Balsells, M.C., Corcoy, R.M., Leonart, R.B. et al. (1991) Primary allergy to human insulin in a patient with gestational diabetes. *Diabetes Care* 14, 423–424.
- [6] Nagel, C., Talaular, M., Humbert, I. and Willms, B. (1988) Allergie gegen Humaninsulin. *Dtsch. Med. Wschr.* 113, 1013–1016.
- [7] Ganz, M.A., Unterman, T., Roberts, M. et al. (1990) Resistance and allergy to recombinant human insulin. *J. Allergy Clin. Immunol.* 86, 45–51.
- [8] Granic, M., Renar, I.P., Metelko, Z. and Skrabalo, Z. (1986) Insulin allergy. *Diabetes Care* 9, 99–100.
- [9] Loeb, J.A., Herold, K.C., Barton, K.P., Robinson, L.E. and Jaspan, J.B. (1989) Systematic approach to diagnosis and management of biphasic insulin allergy with local anti-inflammatory agents. *Diabetes Care* 12, 421–423.
- [10] Ratner, R.E., Phillips, T.M. and Steiner, M. (1990) Persistent cutaneous insulin allergy resistant from high-molecular-weight insulin aggregates. *Diabetes* 39, 728–733.
- [11] Grammer, L.C., Roberts, M. and Patterson, R. (1985) IgE and IgG antibody against human (recombinant DNA) insulin in patients with systemic insulin allergy. *J. Lab. Clin. Med.* 105, 108–113.
- [12] Bruni, B., Barolo, P., Gamba, S., Grassi, G. and Blatto, A. (1986) Case of generalized allergy due to zinc and protamine in insulin preparation. *Diabetes Care* 9, 552.
- [13] Bruni, B. (1978) Proinsulin and A-component antibodies in diabetics after long term monocomponent insulin. *Diabetologia* 14, 165–169.
- [14] Bloom, S.R. (1979) Autoimmunity in diabetics induced by hormonal contaminants of insulin. *Lancet* 1, 14–16.
- [15] Markussen, J., Damgaard, U., Pingel, M., Suel, L., Sorensen, A.R. and Sorensen, E. (1983) Human insulin (Novo): Chemistry and characteristics. *Diabetes Care* 6 (suppl 1), 1–5.
- [16] Bachmann, W., Hasche, H. and Mehnert, H. (1982) Intradermal desensitization with human insulin (recombinant DNA) in a patient with severe allergic skin reaction due to insulin. *Diabetes Care* 5 (suppl. 2), 165–167.
- [17] Yosino, G., Yamochi, W., Moriyama, H. et al. (1990) Pancreatic diabetes with severe generalized allergy to purified beef, pork, and human insulins. *Diabetes Care* 13, 1093–1094.
- [18] Kahn, C.R. and Rosental, S. (1979) Immunologic reactions to insulin: Insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diabetes Care* 2, 283–295.
- [19] Valentini, U., Cimino, A., Rocca, L., Perizzari, R., Rotondi, A. and Tosoni, C. (1988) CSII in management of insulin allergy. *Diabetes Care* 11, 97–98.
- [20] Holdaway, I.M. and Wilson, J.D. (1984) Cutaneous insulin allergy responsive to oral desensitisation and aspirin. *Br. Med. J.* 289, 1565–1566.
- [21] Galloway, J.A. (1980) When the patient is resistant or allergic to insulin. *Med. Times* 108, 91–94, 96, 101.