

Severe anaphylactic reaction to human insulin in a diabetic patient

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Abstract

A 46-year-old nonatopic woman who had been suffering from type 2 diabetes for 17 years was hospitalized at the Endocrinology Department of Selcuk University due to very high glucose levels after recovery from acute hepatitis A infection. She had never used insulin before. After first subcutaneous dose of human regular insulin, severe local allergic reaction developed. Desensitization to insulin was tried. One day later, ketoacidosis developed. Human regular insulin was again subcutaneously injected to the patient. Severe anaphylactic reaction occurred, and in spite of all the medical attempts to save the patient, she died.

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1. Introduction

Immunogenic reactions to insulin were not uncommon in the past, with purified animal insulin such as porcine or bovine preparations. The commercial insulin preparations are often physically altered by additives, lubricants, and contaminants such as protamine, latex, and zinc (Bloom, Barnes, Adrian, & Polak, 1979; Chance, Root, & Galloway, 1976; Feinglos & Jegasothy, 1979; Kumar, Rosenquist, Parameswaren (1979); Kurtz & Nabarro, 1980; Patterson, Mellies, & Roberts, 1973; Witters, Ohman, Weir, Raymond, & Lowell, 1977). These preparations are capable of eliciting a variety of immunologic responses, including local and systemic allergy and insulin resistance. The most common clinical symptoms of insulin allergy are usually local and appear a few minutes after injection, such as red blotch, indurations, pruritus, and burning sensation at the injection site, but general and serious allergic reactions from urticaria to anaphylactic shock to insulin are very rare. Systemic allergic reactions are also known as hypersensi-

tivity reactions that are IgE-mediated, local or systemic anaphylactic-type reactions (Patterson, Lucena, Metz, & Roberts, 1969), IgG-mediated insulin resistance (Patterson et al., 1973), a combination of these reactions (Patterson, Mellies et al., 1973), or very rarely, serum sickness (Arkins, Engbeing, & Lennon, 1962; Patterson, Roberts, & Grammer, 1990). New recombinant human insulin preparations and insulin analogs have lowered but have not yet fully eliminated immunogenic reactions (Gonzalez, Guillausseau, Pecquet, & Gayno, 2003; Takata et al., 2003). We report a case wherein a patient with diabetic ketoacidosis died due to serious anaphylactic reaction to human insulin.

2. Case

A 46-year-old woman with a history of type 2 diabetes for the past 17 years was consulted with our department of Endocrinology and Metabolism for the management of uncontrolled diabetes. She had been hospitalized at the infection disease clinic department due to acute viral hepatitis A infection for a month. She had been instructed to follow a diet and had been treated with oral agents such as sulfonylurea and metformin for 17 years. These oral agents had been stopped because of very high liver enzymes, and

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Fig. 1. Dermatological reactions.

she was on a diet for a month. She was hospitalized with the diagnosis of uncontrolled diabetes mellitus in our department. At the time she was hospitalized in our department, she had fully recovered from her acute hepatitis. Except for serum glucose levels, all the laboratory parameters including liver enzymes were in the normal range.

On physical examination, she was 160 cm tall and weighed 65 kg. Her blood pressure was 110/70 mmHg; her pulse rate was 104/min, and her temperature was 37.2°C. Except for a 2-cm soft and tender hepatomegaly, all other systemic physical findings were normal. Blood glucose level was 280 mg/dl. There was mild ketonuria, but she did not have ketoacidosis. After she had been hospitalized in our department because of the high serum glucose levels, she was ordered to follow an intensive insulin regimen: three times daily injection of recombinant human regular insulin (Humulin R, Lily) and a one-time injection of recombinant human neutral protamine Hagedorn insulin (Humulin N, Lily). Forty-five minutes after the first subcutaneous injection of 4 IU human regular insulin, extensive erythematous dermal reactions were noticed nearly all over the body and insulin therapy stopped (Figs. 1–3). Well-circumscribed, raised, bordered erythematous pruritic wheals were defined as urticaria by dermatologist. The wheals had a tendency to be coalescent and



Fig. 2. Dermatological reactions.



Fig. 3. Dermatological reactions.

blanched with pressure. On laboratory examination, blood glucose level was approximately 380–400 mg/dl, and there were ketonemia and ketonuria. Parenteral liquid and antihistaminic therapies were performed. Insulin desensitization was tried with frequent injection of diluted regular insulin according to reports by Blanco et al. (1996) and Thompson and Ronco (1993). We used the desensitization scheme of Galloway (1988).

In emergencies such as the presence of diabetic ketoacidosis, rapid desensitization should be considered using the dilutions of neutral regular insulin below:

1. Make a 1:1 dilution of single-space insulin (50 U/ml),
2. Add 0.5 ml of the above dilution to 4.5 ml of diluent (5 U/ml)
3. Add 0.5 ml of the 5-U/ml dilution to 4.5 ml of diluent (0.5 U/ml)
4. Add 0.5 ml of the 0.05-U/ml dilution to 4.5 ml of diluent (0.05 U/ml)

Desensitization was started by giving 0.02 ml of the 0.05-U/ml concentration (1/1000 U) intradermally. The procedure proceeded to the next greater concentration (0.5 U/ml) while giving 0.02, 0.04, and 0.08 ml of the concentration at 20- to 30-min intervals. Following protocol and notwithstanding mild reactions (wheal, flare, or inductions <1 cm), with evidence of a dermal or systemic response, we went back two steps and continued the process. The following day, all the dermal lesions were recovered, and the patient was in diabetic ketoacidosis. In those times, analog insulin preparations were not yet available to the world market; hence, commercial human regular insulin preparation (4 IU; Actrapid, Novo Nordisk) was subcutaneously injected for the second time. After injection, severe anaphylactic reaction developed rapidly, and the patient had died because of anaphylaxis in spite of all medical attempts to save her, including adrenaline, corticosteroid, and antihistaminic therapies, parenteral liquid support, and intubation. We did not have enough time to perform an intradermal skin test, as well as to assay IgE, IgG, and eosinophilia, to evaluate the patient for insulin allergy.

3. Discussion

In the past, it was reported that immunogenic reactions to insulin could occur in at least 5–10% of insulin-treated patients. Most of these reactions were mild and local and often disappeared with continuation of therapy. Only 1–2% of all reactions to insulin were reported as systemic and often presented as anaphylaxis (Hanauer & Bateson, 1961; Lamkin, Lieberman, Hashimoto, Morohashi, & Sullivan, 1976; Shipp, Cunningham, Russel, & Marble, 1965). With the use of human recombinant insulin, the incidence of allergic reactions to insulin is now reported in less than 1% of diabetic patients (Davidson & DeBra, 1978). Systemic allergic reactions to insulin are uncommon, especially since new human recombinant DNA insulin is being used, with a reported incidence of 0.1–2%. Systemic anaphylactic reactions to insulin most commonly occur after an interruption of insulin therapy and after progressively larger local reactions at the injection site (Blanco et al., 1996).

Immunologic insulin resistance defined as a systemic response to insulin manifests primarily as elevated (>200 U/day) insulin requirements (Davidson & DeBra, 1978). Shipp et al. (1965) had reported 84 patients with insulin resistance; of whom, 14 had diabetic ketoacidosis and 19 had allergy manifesting as dermal reactions or eosinophilia. Our patient, who had no history of atopy, presented with local cutaneous and systemic allergy manifested by anaphylaxis and consecutive diabetic ketoacidosis, like what Shipp et al. (1965) and Ross et al. (1984) reported. The difference from our case with theirs was that there was no immunologic resistance to insulin in our case. As of August 2005, the medical literature search (PubMed) has not yielded any previous case report of any human insulin-induced death due to anaphylactic reaction.

It was shown in literature that there was immunologic cross-reactivity between human recombinant insulin and bovine and porcine insulins; thus, these insulins were suggested in case of allergy to human insulin (Baur, Bossert, & Koops, 2003; Fernandez, Duque, Montalban, & Bartolome, 2003).

In literature, it had been shown in some cases that among several insulin preparations, short-, intermediate-, and biphasic-acting insulins caused allergic reactions while long-acting insulin did not. Although in some reports, long-acting insulin was found to induce allergic symptoms in such patients. It was shown that there was specific unresponsiveness to crystallized long-acting insulin and that some patients were treated safely (Adachi, Atsushi, & Horikawa, 2004).

The human insulin analogs lispro and aspart are thought to be an alternative for human-insulin allergic patients, and certain insulin allergic patients can use these insulin analogs safely. There were some reports about the safety of short-acting insulin analogs, that is, to not cause insulin allergy, but there were also contrasting reports in the literature (Takata et al., 2003).

Immunotherapy (hyposensitization) by porcine as well as by bovine insulin was reported to be successful, but there were also contrasting reports. The use of anti-IgE antibodies (Omalizumab) in therapy in the future shows great promise (Baur et al., 2003).

We conclude that insulin analogs and long-acting insulin can be an alternative in some patients, but it cannot be effective in some patients with insulin allergy, as in our case. In a case of serious insulin allergy, physicians must be aware of the anaphylaxis risk involved.

References

- Adachi, A., Atsushi, F., & Horikawa, T. (2004). A case of human allergy induced by short-acting and intermediate-acting insulin but not by long-acting insulin. *Cameo*, 43, 597–599.
- Arkins, J. A., Engbeing, N. H., & Lennon, E. J. (1962). The incidence of skin reactivity to insulin in diabetic patients. *Journal of Allergy*, 33, 69.
- Baur, X., Bossert, J., & Koops, F. (2003). IgE-mediated allergy to recombinant human insulin in a diabetic. *Allergy*, 58, 676–678.
- Blanco, C., Castillo, R., Quiralte, J., Delgado, J., Garcia, I., Pablos, P. D., & Carrillo, T. (1996). Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy*, 51, 421–424.
- Bloom, S. R., Barnes, A. J., Adrian, T. E., & Polak, J. M. (1979). Autoimmunity in diabetics induced by hormonal contaminants of insulin. *Lancet*, 1, 14–17.
- Chance, R. E., Root, M. A., & Galloway, J. A. (1976). The immunogenicity of insulin preparations. *Acta Endocrinologica*, 83 (Suppl. 205), 185–198.
- Davidson, J. K., & DeBra, D. W. (1978). Immunologic insulin resistance. *Diabetes*, 27, 307–318.
- Feinglos, M. N., & Jegasothy, B. V. (1979). “Insulin” allergy due to zinc. *Lancet*, 1, 122–124.
- Fernandez, L., Duque, S., Montalban, C., & Bartolome, B. (2003). Allergy to human insulin. *Allergy*, 58 (12), 1317.
- Galloway, J. A. (1988). Chemistry and clinical use of insulin. In J. A. Galloway, J. H. Potvin, & C. R. Shuman (Eds.), *Diabetes mellitus*, (9th ed.). Indianapolis: Eli Lilly and Company.
- Gonzalez, K. N. D., Guillausseau, N., Pecquet, C., & Gayno, J. P. (2003). Glargine insulin is not an alternative in insulin allergy. *Diabetes Care*, 26 (7), 2216.
- Hanauer, L., & Bateson, J. M. (1961). Anaphylactic shock following insulin injection. *Diabetes*, 10, 105–109.
- Kumar, D., Rosenquist, R. J., Parameswaren, V. (1979). *Journal of Clinical Endocrinology and Metabolism*, 49, 252–254.
- Kurtz, A. B., & Nabarro, J. D. N. (1980). Circulating insulin binding antibodies. *Diabetologia*, 19, 329–334.
- Lamkin, N., Lieberman, P., Hashimoto, K., Morohashi, M., & Sullivan, P. (1976). Allergic reactions to insulin. *Journal of Allergy and Clinical Immunology*, 58, 213–223.
- Patterson, R., Lucena, G., Metz, R., & Roberts, M. (1969). Reaginic antibody against insulin: Demonstration of antigenic distinction between native and extracted insulin. *Journal of Immunology*, 103, 1061.
- Patterson, R., Mellies, C. J., & Roberts, M. (1973). Immunologic reactions against insulin: II. IgE anti-insulin antibodies, insulin allergy and combined IgE and IgG immunologic insulin resistance. *Journal of Immunology*, 110, 1135–1145.
- Patterson, R., O'Rourke, J., Roberts, M., et al. (1973). *Journal of Immunology*, 110, 1126.
- Patterson, R., Roberts, M., & Grammer, L. C. (1990). Insulin allergy: Re-evaluation after two decades. *Annals of Allergy*, 64, 459–462.

- Ross, J. M., Murali, M. R., Delara, T. C., & Cheron, R. G. (1984). Anaphylaxis and immunologic insulin resistance in a diabetic woman with Ketoacidosis. *Diabetes Care*, 7 (3), 276–279.
- Shipp, J. C., Cunningham, R. W., Russel, R. O., & Marble, A. (1965). Insulin resistance: Clinical features, natural course and effects of adrenal steroid treatment. *Medicine*, 44, 165–186.
- Takata, H., Kumon, Y., Osaki, F., Kumagai, C., Arie, K., Ikeda, Y., Suehiro, T., & Hashimoto, K. (2003). The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care*, 26 (1), 253–254.
- Thompson, D. M., & Ronco, J. J. (1993). Prolonged desensitization required for treatment of generalized allergy to human insulin. *Diabetes Care*, 16, 957–958.
- Witters, L. A., Ohman, J. L., Weir, G. C., Raymond, L. W., & Lowell, F. C. (1977). Insulin antibodies in the pathogenesis of insulin allergy and resistance. *American Journal of Medicine*, 63, 703–709.