

Systemic allergy to endogenous insulin during therapy with recombinant DNA(rDNA) insulin

Linda Alvarez-Thull, MD*; Lanny J Rosenwasser, MD†; and Todd D Brodie, MD*

Background: Clinically significant allergic reactions with insulin therapy are known to occur. There have been rare reports of allergic reactions to endogenously secreted insulin manifested as insulin resistance. No reports of systemic or local allergic reactions to endogenous insulin have previously been cited, and no immunologic reactions to endogenous insulin have been reported during therapy with recombinant(rDNA) insulin.

Methods: We report a case in which the patient, a 28-year-old black woman who initially presented with gestational onset diabetes but postpartum continued to require insulin, developed generalized allergic reactions during therapy with subcutaneously injected rDNA insulin. Similar reactions occurred with sulfonylurea therapy. She was unable to tolerate any pharmacologic therapy for diabetes without concurrent use of at least 10 mg of prednisone per day.

Results: Skin testing with the insulin preparations were positive, while skin testing to the sulfonylurea hypoglycemic agents were negative. IgE antibodies to insulin were present in high titer. Oral challenge to sulfonylurea hypoglycemic agents produced generalized urticarial reactions coinciding with time of peak insulin secretion. Oral challenge to other medications containing sulfa produced no adverse reaction. Biphasic hypersensitivity reactions occurred during attempts at desensitization which were futile without simultaneous glucocorticoid therapy.

Conclusions: This is the first report of local and systemic allergic reactions to endogenously secreted insulin in association with rDNA insulin therapy. Although immunologic complications with rDNA therapy appear less frequently than with other insulin preparations, this case illustrates the need for continued awareness for potential allergic complications occurring with rDNA insulin therapy.

Ann Allergy Asthma Immunol 1996;76:253-256.

INTRODUCTION

Clinically significant immunologic reactions to exogenous insulin have been reported extensively.¹⁻⁵ Among the various antibody-mediated reactions to exogenous insulin are local cutaneous reactions, systemic reactions, and insulin resistance. Immunologic reactions to endogenous insulin are rare. The three case reports of immunologic reactions to endogenously secreted insulin have all been of insulin resistance.⁶⁻⁸ Local, systemic, or biphasic

allergic reactions to endogenous insulin have not been reported previously.

We report a patient who had not only generalized allergic reactions during therapy with rDNA insulin, but also similar reactions during subsequent therapy with oral hypoglycemic agents. Since rDNA insulin has been in use for clinical therapy, there has been no report of allergic reactions to endogenous insulin attributed to sensitization to rDNA insulin or precipitated by oral hypoglycemic agents.

CASE REPORT

A 28-year-old black woman with noninsulin dependent diabetes mellitus had had a history of asthma since childhood that often required treatment with glucocorticoids. At age 26 years, during her sixth pregnancy and while receiving

prednisone for asthma, she developed gestational diabetes requiring insulin therapy. Following an uncomplicated delivery, the patient continued to require prednisone and insulin therapy, but remained in good health for the following 2 1/2 years. As her asthma improved, the prednisone was tapered gradually over 3 months from 50 mg to 5 mg per day; it was during this taper the patient first experienced symptoms consistent with insulin allergy.

The patient initially developed a wheal and flare reaction at the site of subcutaneous injection after 15 minutes with her usual rDNA human insulin. This progressed to a generalized urticarial reaction involving her face, chest, and upper extremities. It occurred on the first day the patient's prednisone dose was tapered from 7.5 mg to 5 mg a day. After a period of two days during which she had repeated attacks of urticaria, she presented to the emergency room where insulin was stopped and she was started on glipizide, 10 mg a day. Within two hours after each dose of glipizide she developed similar generalized urticarial reactions occasionally with tongue swelling. The glipizide was also stopped, so the patient received no glucose lowering medications.

Attempts at desensitization to recombinant insulin were futile; she developed local cutaneous and urticarial reactions starting with the most dilute dose and was unable to receive more than 5 units of insulin without developing similar reactions despite the addition of diphenhydramine to the injection. Prednisone was increased to 60 mg/day, and she was subsequently able to receive her usual mixed split dose of insulin without any allergic reactions. She continued to remain free of cuta-

* Maricopa Medical Center, Department of Medicine, Phoenix, Arizona.

† National Jewish Center for Immunology and Respiratory Medicine, Division of Allergy and Clinical Immunology, Denver, Colorado.

Received for publication December 21, 1994.

Accepted for publication in revised form May 25, 1995.

neous reactions to insulin on this dose of prednisone.

To test the hypothesis that the immune reactions were to endogenous insulin, the prednisone was tapered to 7.5 mg a day, and she was then challenged with oral doses of glipizide, tolbutamide, and chlorpropamide, as described in "Methods". Each of these produced generalized urticarial reactions. Prick skin tests with these medications did not elicit reactions.

She was then evaluated for allergy to other sulfa-containing medications. While on 7.5 mg of prednisone she received varying oral doses of trimethoprim-sulfamethoxazole, furosemide, and finally the combination of trimethoprim-sulfamethoxazole plus furosemide, none of which produced allergic reactions. At doses of prednisone of 10 mg or greater the patient could receive insulin therapy without allergic reactions.

METHODS

Three days after all glucose lowering medications were discontinued, prick skin tests with human, pork, and beef regular insulin (Eli Lilly and Co., Indianapolis, IN and NOVO Nordisk, Princeton, NJ) were administered at concentrations of 1 unit per mL of diluent (0.9% sodium chloride) placed on the anterior aspect of the forearm with histamine (0.1 mg/mL) and saline controls. Dermal responses were recorded at 15 minutes. A wheal of greater than 3 mm was considered positive.

Desensitization to insulin was begun with an initial dose of 0.001 unit of

regular insulin which was given subcutaneously with incremental increases in administered dose every hour (0.002, 0.004, 0.01, and 0.02 units).

IgE antibody titers were determined during systemic desensitization by radioimmunoassay using polyethylene glycol (PEG) for precipitation of the insulin-antibody complexes.⁹

Oral challenge tests with sulfa-containing medications began with a single 10-mg dose of glipizide (Pfizer Laboratories). Twenty-four hours later she was challenged with 500 mg of tolbutamide (Upjohn); 250 mg chlorpropamide (Pfizer Laboratories) was administered 24 hours after tolbutamide challenge.

Prick skin tests to glipizide, tolbutamide, and chlorpropamide were placed at a concentration of 1 mg/mL, 50 mg/mL, and 25 mg/mL respectively, and interpreted as described above.

Evaluation for allergy to sulfa containing medications was begun with administration of four double strength (800 mg trimethoprim/160 mg sulfamethoxazole each tablet) trimethoprim-sulfamethoxazole tablets (Roche Laboratories) followed by 40 mg of oral furosemide (Hoechst-Roussel), and finally with two double strength trimethoprim-sulfamethoxazole tablets plus 40 mg of oral furosemide while she was receiving a maintenance dose of 7.5 mg of prednisone.

RESULTS

Fifteen minutes after application of prick skin tests, the patient developed

wheal and flare reactions of 21/38 mm to beef, 18/32 mm to pork, and 9/28 mm to recombinant human insulin. Likewise, intradermal skin tests with the same insulin preparations were also positive (Table 1).

During desensitization she developed a 25-mm induration within 20 minutes after the first injection which contained 0.001 unit of regular insulin. This became firm and painful four to five hours later. After a period of two days she was unable to receive more than 5 units of insulin without developing similar reactions despite the addition of diphenhydramine to the injections.

Hypoglycemia occurred as she was receiving 5 units of insulin per hour and she was treated with intravenous glucose for this reaction. She continued to experience cutaneous urticarial reactions to insulin administration.

Oral challenge to glipizide produced a generalized urticarial reaction within two hours, tolbutamide produced an urticarial reaction within one and one-half hours, and chlorpropamide produced an urticarial reaction within six and one-half hours of oral administration (Table 1). Prick skin tests with these medications did not elicit reactions. Oral challenges with trimethoprim-sulfamethoxazole and furosemide did not produce allergic reactions.

IgE antibodies against insulin during this time were present at a titer of 1:5,000.

DISCUSSION

Since the beginning of exogenous insulin therapy in 1922, cutaneous aller-

Table 1. Summary of Challenges and Skin Tests

Medication	Prick Skin Tests	Intradermal Skin Test	Systemic Allergy Reaction	Onset of Allergic Reaction	Peak Levels of Oral Agents
Human regular insulin	Positive	Positive	Positive	20 minutes	N/A*
Pork regular insulin	Positive	Positive	Not given in large enough dose	N/A*	N/A*
Beef regular insulin	Positive	Positive	Not given in large enough dose	N/A*	N/A*
Glipizide	Negative	Negative	Positive	120 minutes	1-2 hours
Chlorpropamide	Negative	Negative	Positive	360 minutes	3-6 hours
Tolbutamide	Negative	Negative	Positive	90 minutes	3-4 hours
Lasix	Negative	ND*	Negative	N/A*	N/A*
Trimethoprim-sulfamethoxazole	Negative	ND*	Negative	N/A*	N/A*

* ND = not done and N/A = not applicable.

gic reactions and insulin resistance have become commonly known complications of therapy, although they have become much less frequent with the technical advances in insulin production. Both of these reactions are immunologically mediated, predominantly by antibodies to various components of insulin preparations and the molecule itself.¹⁰⁻¹² Clinical syndromes of the immunologic reactivity of insulin and their mechanisms have been described.^{13,14}

Systemic reactions to exogenous insulin are believed to occur as a result of IgE antibodies against various components of the insulin molecule.⁴ In insulin resistance, the confounding antibody is of the IgG isotype, which binds to exogenous insulin, producing a non-functional complex.^{15,16} In the previous reports of insulin resistance to endogenous insulin, the apparent mechanism has been cross-reactivity of the IgG antibody to exogenous insulin with endogenous insulin.

In this case report, insulin allergy is proposed to occur by cross-reactivity of anti-insulin IgE antibodies to the endogenous insulin molecule. The patient initially exhibited typical local and systemic allergic reactions during therapy with human rDNA insulin in the presence of high titer anti-insulin IgE, with amelioration of symptoms occurring with glucocorticoids. This could be attributed to IgE antibody to the exogenous insulin; a mechanism that is supported by positive prick skin tests. At the time when the patient theoretically had no circulating exogenous insulin, however, she sustained both local and systemic reactions when she was stimulated to secrete endogenous insulin with administration of oral hypoglycemic agents (Table 1). This implies that the patient had developed antibodies that reacted to her own endogenously secreted insulin. Allergy to the sulfa component of the oral hypoglycemic agents appears less likely in view of the fact that the patient had no allergic reactions to challenges with other sulfa based medications.

The initial event in development of insulin hypersensitivity in our patient

is unknown. She could have developed "autoimmunity" to her own insulin that was masked by glucocorticoid therapy. Alternatively, she may have become sensitized by the rDNA insulin. In either case the insulin hypersensitivity did not become clinically apparent until the dosage of prednisone was reduced to 5 mg daily.

A second point for consideration is that the urticarial responses were "idiopathic" and unrelated to insulin therapy. The temporal relationship between development of urticaria and administration of insulin or oral hypoglycemic agents make this alternative unlikely.

Prior to this report, no cross-reactivity between IgE antibody to rDNA human insulin and endogenous human insulin has been reported. This finding is not surprising since recombinant human DNA derived insulin should be entirely analogous to secreted endogenous insulin from human pancreas. It is well known from animal studies and in vitro studies that IgE antibodies raised during exogenous therapy with beef insulin, for example, could cross-react with human insulin.¹⁷ Since diabetic and asthmatic patients are known to have diseases of immunoregulation it is not surprising that a break in "tolerance" could occur even with exogenous human insulin with antibodies developed to the human insulin molecule, even antibodies of the IgE isotype.

Our patient did not demonstrate insulin resistance, another immunologic complication of exogenous insulin therapy. Although anti-insulin IgG antibodies are typically produced during therapy with insulin¹⁸⁻²⁰ and are responsible for insulin resistance,^{14,21} our patient exhibited no clinical evidence of cross-reactivity of anti-insulin IgG antibodies. This is a phenomenon that theoretically could occur.

Differences in amino acid sequences of the various exogenous insulins is one of the major contributors to exogenous insulin allergy.^{20,22} Porcine and bovine insulin differ from human insulin by 1 and 3 amino acids, respectively. Clinically, allergic reactions oc-

cur more often with bovine insulin therapy than with porcine insulin therapy reflecting greater antigenicity of beef insulin as compared with pork insulin.^{20,23}

With the advancement in DNA technology that led to the development of recombinant DNA (rDNA) human insulin²⁴ came the hope that allergic reactions to insulin therapy would become a historical curiosity. Despite the homologous amino acid sequence of rDNA insulin with endogenous human insulin, continued antibody formation to insulin occurred,²⁵⁻²⁷ as did allergic reactions^{2,28,29} and immunologic insulin resistance.³⁰ Shared antigenic determinants of human, porcine, and bovine insulin,³⁰ and tertiary structure of rDNA insulin are implicated as contributing causes of continued allergic reactions to rDNA insulin.^{9,17}

CONCLUSIONS

This patient demonstrates a complication of therapy with rDNA insulin that has not previously been recognized. Because of the homology between rDNA human insulin and endogenous human insulin, this complication may be unique to rDNA insulin.

In this patient, anti-insulin IgE antibodies to rDNA insulin cross-reacted with the patient's endogenous insulin resulting in local cutaneous and systemic allergic reactions. Desensitization to insulin failed to alleviate the allergic reactions. Concurrent administration of glucocorticoids continues to be necessary for this patient to receive her insulin regimen and oral hypoglycemic therapy, if warranted.

Immunologic complications with rDNA therapy appear less frequently than with other insulin preparations. As this case illustrates, however, awareness for potential allergic complications from rDNA insulin still needs recognition.

ACKNOWLEDGMENTS

Special thanks to Dr. Charles H. Kirkpatrick for his critical review of this manuscript.

REFERENCES

1. Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979;1: 122-4.
2. Gossain VV, Rovner DR, Mohan K. Systemic allergy to human (recombinant DNA) insulin. *Ann Allergy* 1985; 55:116-8.
3. Silverstone P. Generalised allergic reaction to human insulin. *Br Med J* 1986;292:933-4.
4. Grammer L. Insulin allergy. *Clin Rev Allergy* 1986;4(2):189-200.
5. Simmond JP, Russell GI, Cowley AJ et al. Generalized allergy to porcine and bovine monocomponent insulins. *Br Med J* 1980;281:355-6.
6. Howard JE. In: Mote JR, ed. *Proceedings of the second clinical ACTH conference*. vol. 1 Research. Blakiston Co 1951:327-31.
7. Karam JH, Grodsky GM, Forsham PH. Insulin resistant diabetes with autoantibodies induced by exogenous insulin. Successful treatment by insulin withdrawal. *Diabetes* 1969;18(7):445-54.
8. Rendell M, Hamilton RG, Drew HM, Adkinson NF. Exacerbation of diabetes mellitus by antibodies to exogenous insulin. *Am J Med Sci* 1981;282: 18-26.
9. Grammer LC, Roberts M, Patterson R. IgE and IgG antibody against human (recombinant DNA) insulin in patients with systemic insulin allergy. *J Lab Clin Med* 1985;105:108-13.
10. Lowell FC. Immunologic studies in insulin resistance: The presence of a neutralizing factor in the blood exhibiting some characteristics of an antibody. *J Clin Invest* 1944;23:233-40.
11. Ross JM. Allergy to insulin. *Pediatr Clin N Am* 1984;31:675-87.
12. Deckert T. The immunogenicity of new insulins. *Diabetes* 1985;34(2): 94-6.
13. Rosenwasser LJ. Immunologic reactivity to insulin: animal models and clinical syndromes. *Clin Immunol Rev* 1981-82;1:311-35.
14. Kahn CR, Rosenthal AS. Immunologic reactions to insulin: insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diabetes Care* 1979; 2:283-95.
15. Berson SA, Yalow RS. Insulin inhibitors and insulin resistance. *NY State J Med* 1960;60:3658.
16. Davidson JK, DeBra DW. Immunologic insulin resistance. *Diabetes* 1978; 27:307-18.
17. Patterson R, Lucena G, Metz R, Roberts M. Reaginic antibody against insulin: demonstration of antigenic distinction between native and extracted insulin. *J Immunol* 1969;103: 1061-71.
18. Berson SA, Yalow RS, Bauman A, et al. Insulin-131 I metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin treated subjects. *J Clin Invest* 1956;35:170-90.
19. Deckert T, Grundahl E. The antigenicity of pig insulin. *Diabetologia* 1970; 6:15-20.
20. Chance RE, Root MA, Galloway JA. The immunogenicity of insulin preparations. *Acta Endocrinol* 1976; 83(Suppl 205):185-99.
21. Patterson R, Mellies CJ, Roberts M. Immunologic reactions against insulin: IgE anti-insulin, insulin allergy and combined IgE and IgG immunologic insulin resistance. *J Immunol* 1973; 110:1135-45.
22. Lieberman P, Patterson R, Metz R. Allergic reactions to insulin. *JAMA* 1971;215:1106-15.
23. Reeves WG. Immunology of diabetes and insulin therapy. In: Thompson RA, ed. *Recent advances in clinical immunology*. Edinburgh: Churchill Livingstone Inc., 1980:No. 2,182-200.
24. Miller WL, Baxter JD. Recombinant DNA—a new source of insulin. *Diabetologia* 1980;18:431-6.
25. Velcovsky HG, Federlin KF. Insulin-specific IgG and IgE antibody response in type I diabetic subjects exclusively treated with human insulin (recombinant DNA). *Diabetes Care* 1982;5(Suppl 2):126-8.
26. Fireman P, Fineberg SE, Galloway JA. Development of IgE antibodies to human (recombinant DNA), porcine, and bovine insulins in diabetic subjects. *Diabetes Care* 1982;5(Suppl 2): 119-25.
27. Fineberg SE, Galloway JA, Fineberg NS, et al. Immunogenicity of recombinant DNA human insulin. *Diabetologia* 1983;25:465-9.
28. Wiles PG, Guy R, Watkins SM, Reeves WG. Allergy to purified bovine, porcine, and human insulins. *Br Med J* 1983;287:531.
29. Grammer LC, Metzger BE, Patterson R. Cutaneous allergy to human (rDNA) insulin. *JAMA* 1984;251: 1459-60.
30. Grammer LC, Roberts M, Buchanan TA, et al. Specificity of immunoglobulin E and immunoglobulin G against human (recombinant DNA) insulin in human insulin allergy and resistance. *J Lab Clin Med* 1987;109:141-6.

*Request for reprints should be addressed to:
Linda Alvarez, MD
National Jewish Center for Immunology &
Respiratory Medicine
Division of Allergy & Clinical Immunology
1400 Jackson St
Denver, CO 80206*