

Cutaneous Allergy to Human (Recombinant DNA) Insulin

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• We report two cases of cutaneous allergy to human (recombinant DNA) insulin. Each patient had a history of systemic allergic reactions to porcine insulin and was at least as reactive to human as to porcine insulin by end-point cutaneous titration. Both patients' insulin allergy was managed with animal insulins and both have done well. Our experience with these two patients indicates that human insulin (rDNA) should not be expected to be efficacious in all patients with systemic allergy to insulin.

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SYSTEMIC insulin allergy is an infrequent medical problem that can be managed by adhering to certain guidelines.^{1,2} The availability of human insulin (rDNA) has raised expectations that this insulin not only is the treatment of choice for allergic complications of insulin therapy but will be uniformly successful. It has been shown that patients who are switched from animal insulins to human insulins have a decline in their titers of antibody to insulin.³ It is also known that patients who initially begin therapy with human insulin have lower levels of IgE against insulin than patients initially beginning therapy with animal insulins.⁴ While there have been patients with systemic allergy to animal insulins who have responded favorably to human insulin (rDNA),⁵ there are patients who react to human insulin.⁶

We have recently seen two patients

with systemic allergic reactions to animal insulins who did not tolerate human (recombinant DNA) insulin. In one case, the patient experienced a large cutaneous reaction during an attempt to desensitize her to human insulin. She was desensitized to porcine insulin without reaction. In the other case, as the patient was equally reactive on cutaneous end-point titer to porcine and human insulin and as human insulin was not then commercially available, we desensitized her to porcine insulin without reaction.

Report of Cases

CASE 1.—A 73-year-old woman had a five-month history of fasting blood glucose levels above 200 mg/dL and elevated levels of glycosylated hemoglobin, ranging from 14% to 16% (reference range, 6% to 8%) despite oral hypoglycemic therapy and dietary manipulation. In 1973, the patient had generalized urticaria while being treated with mixed beef-pork insulin. She was hospitalized for several weeks while her physician attempted to desensitize her to insulin. Because of recurrent urticaria with insulin injections, the insulin therapy was discontinued and the patient was treated with oral hypoglycemic therapy. Using "purified" porcine insulin in 1979, another attempt was made to desensitize her but was unsuccessful.

Except for mild hypertension (160/90

mm Hg) and grade I retinopathy, the physical examination results were unremarkable. The Endocrinology Service deemed administration of insulin essential to this patient's diabetic control. The patient was tested by the prick method to pure bovine, porcine, and human insulins at 100 units/mL. She had a 4+ reaction to bovine but had no reaction to porcine or human insulin. Using a previously published desensitization schedule,¹ we attempted to desensitize her to human insulin. However, on subcutaneous injection of 0.01 unit of human insulin into the right forearm, a site the patient had not used previously for insulin injection, a local 15-mm wheal and 35-mm flare reaction developed. We then performed cutaneous end-point titration to bovine, porcine, and human insulin and found that the patient was more reactive to human than to porcine insulin. All insulins were diluted in 0.1% human serum albumin. The patient was desensitized using porcine insulin without difficulty and has done well during three months of observation.

CASE 2.—A 26-year-old woman was eight weeks pregnant with her second child. She had gestational-onset diabetes treated with mixed bovine-porcine insulin during her first pregnancy two years earlier. Her physician had reinstituted insulin therapy nine days previously when she was found to have hyperglycemia. She was transferred to our medical center because urticaria, angioedema, and chest tightness developed on the seventh day of insulin therapy. Two days before admission, her physician had switched her to purified porcine insulin and had started giving her diphenhydramine, but the allergic reactions to insulin continued.

Physical examination results were not remarkable except for generalized urticaria, a large local reaction at the site of injected insulin, and periorbital angioedema. The endocrinology service deemed insulin essential for control of hyperglyce-

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mia during her pregnancy. Prick testing was performed, and she was found to have a 4+ reaction to bovine and to be nonreactive to porcine or human insulin. On end-point titration she was equally reactive to porcine and human insulin. As human insulin was not commercially available at that time, she was treated with porcine insulin. When her dose was reduced to 10 units of porcine isophane insulin suspension (NPH), she still experienced generalized urticaria, but she had no reaction when the dose was reduced to 5 units of porcine NPH insulin. Her dose was then increased by 2 units, morning and evening, until diabetic control was achieved with a daily dose of 18 units. As her pregnancy advanced and insulin requirement increased, her dose could be increased by 2 to 3 units every other day. She had no further allergic reactions to insulin during three months of observation.

Comment

These two patients had systemic allergic reactions to mixed bovine-porcine and porcine insulin, respectively. In the first case, there had been a hiatus of four years since the allergic reaction. As a consequence of the hiatus and the insulin allergy, desensitization was required. Several desensitization schedules have been published.^{1,2,7,8} Desensitization to human insulin was considered but not attempted because of the strongly positive skin test result to a minimal dose of human insulin. As the patient experienced a large local reaction on subcutaneous injection of 0.01 unit of human insulin and as the patient was more reactive on cutaneous titration to human insulin than to porcine, the desensitization was performed with porcine insulin.

In the second case, the patient had received insulin within the past 24 hours. Consequently, desensitization from minuscule doses was not necessary; it was necessary only to reduce the dose to half, or for extreme caution, to one fifth of the dose that caused the reaction. Each day the insulin dose could be increased by 2 to 5 units. Once it was determined that insulin was essential for diabetic control, it was important that the insulin therapy not be discontinued, since a desensitization would have been required. In both cases, the patients have done well over three months of observation receiving animal insulins.

The fact that each of these patients

was at least as reactive to human insulin as to porcine insulin may seem paradoxical. However, a review of the composition of insulin and of the immunology of insulin allergy reveals that this is not unexpected. Insulin allergy is a classic type I, IgE-mediated immediate hypersensitivity. The insulin molecule is made up of two peptide chains, A and B, convoluted into a tertiary structure. Beef insulin differs from human insulin sequence by three amino acids, while pork differs by only one. Standard commercial insulin contains less than 50 ppm of impurities, while "purified" insulin contains less than 10 ppm of impurities.

In insulin-allergic patients, the antigen to which the IgE is made is variable. In one study by Lieberman et al⁹ of five patients who had systemic reactions to insulin, it was demonstrated that beef insulin was more allergenic than pork, which was more allergenic than human (extracted from human pancreas) or "purified" beef insulin. Therefore, the allergenicity in some patients may be contributed by the difference in primary amino acid sequence or by non-insulin impurities.

However, in one case, the IgE was definitely demonstrated to be directed against the tertiary structure of insulin altered by extraction procedures.¹⁰ The particular patient studied was found to be reactive to human insulin extracted from the pancreas with acid alcohol but was not reactive to endogenous insulin. As the primary amino acid sequence of human (recombinant DNA) insulin is the same as endogenous insulin, we believe that the alteration of tertiary structure also explains the reactivity of our two

Material	Example	Characteristic	Possible Reactions
Heterologous insulin	Beef insulin	Foreign protein	IgE- and IgG-mediated allergic reactions; IgG-mediated insulin resistance
Altered heterologous insulin	Beef insulin	Foreign protein plus new antigenic determinants	Same as above
Protein contaminants in insulin	Noninsulin beef proteins	Foreign proteins	IgE- and IgG-mediated allergic reactions
Nonprotein additives	Zinc	Nonprotein antigens	Incriminated in late skin reactions
Altered homologous insulin	Human (recombinant) DNA	Altered tertiary structure	IgE and IgG have been demonstrated

patients to human insulin. The Table is a synopsis of the possible antigenic materials in insulin preparations.

In conclusion, availability of human (recombinant DNA) insulin will not eliminate the problem of insulin allergy in every case because there are patients like ours who are at least as reactive to human (recombinant DNA) insulin as to porcine insulin. Moreover, there are allergic patients in whom an animal insulin may actually be preferable to human (recombinant DNA) insulin.

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