

Insulin desensitization with insulin lispro and an insulin pump in a 5-year-old child

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Background and objective: Allergic reactions to insulin, though rare, can have serious consequences in children with type I diabetes mellitus. We report a case of insulin allergy in a 5-year-old child in whom insulin desensitization was accomplished using an insulin pump.

Methods and results: A 5-year-old girl with insulin-dependent diabetes mellitus (IDDM) developed progressive reactions to insulin and was found to have positive intradermal skin tests to regular and NPH insulin. Addition of oral antihistamine and co-administration of subcutaneous dexamethasone along with the insulin failed to control her symptoms. The patient was therefore hospitalized and desensitized to insulin using an insulin pump and insulin lispro.

Conclusion: An insulin pump can be used for insulin desensitization in selected children. The slow constant infusion rate provided by the pump may be an ideal means of achieving insulin desensitization. In addition, insulin lispro, a synthetic insulin analog, should be considered for use in insulin-allergic individuals.

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INTRODUCTION

Allergic reactions to insulin were fairly common in the past when bovine and porcine insulin were in use. The use of recombinant human insulin has reduced the frequency of allergic reactions, but cutaneous insulin allergy still remains a clinical problem in less than 1% of the diabetic population.^{1,2} Indeed, recombinant human insulin can induce IgE antibodies in diabetic patients and allergic reactions to insulin may occur in patients receiving only recombinant human insulin.^{3–5} Further, insulin aggregates are thought to play a role in insulin allergy by promoting the formation of anti-insulin antibodies.⁶

Continuous subcutaneous insulin infusion by means of insulin pumps is well tolerated by patients, may result

in improvement of metabolic control,⁷ and delay or prevent metabolic complications. Pumps, however, are not often used in younger children due to difficulty with compliance, the need for bolusing before lunch at school, and the increased danger of insulin overdose in this age group. The use of an insulin pump to desensitize an adult patient with insulin-dependent diabetes mellitus (IDDM) and immediate hypersensitivity to insulin has been reported previously.¹ Here we report a case in which we successfully desensitized a 5-year-old girl with type-I insulin allergy using an insulin pump.

CASE REPORT

The patient is a 5-year-old girl with diabetes mellitus who was diagnosed at 18 months of age. Treatment with human insulin was initially tolerated without a problem. Three years later, she gradually developed local reactions (2 to 5 cm areas of swelling 30 to 120 minutes following her injections) which were associated with a stinging and burning sensation. Her injections became extremely painful which complicated her insulin therapy. In addition to these local reactions, she devel-

oped an evanescent lacy pink rash across her chest and trunk with occasional pruritus and burning. The rash typically peaked 1 to 2 hours after her insulin injections, and was sometimes accompanied by generalized flushing, pruritus, hives, and/or nasal congestion. Attempts to avoid these problems were made by changing from human to pork insulin, with only transient relief. Insulin was also obtained in latex-free vials, as there was a suspicion that latex in the vials may have contributed to her symptoms, however, no improvement was observed.

The patient had additional medical problems including Pierre Robin syndrome, cleft palate, allergic rhinitis, recurrent sinusitis, and obstructive sleep apnea. She had several hospitalizations for these various problems including cleft palate repair, sinus surgery, and diabetic-ketoacidosis related to infections. She had previously developed skin rashes after administration of penicillin, sulfa, and clindamycin. Immediate hypersensitivity skin testing for penicillin was negative.

An initial exam at our clinic revealed mild rhinitis and a fading 3 to 4-cm wheal from her morning dose of insulin. Prick skin testing was negative for diluent, NPH, and regular insulin; however, intradermal tests with NPH and regular insulin were both positive (Table 1). Prick skin and RAST tests for latex were negative. A trial with the H₁ anti-histamine cetirizine provided

Table 1. Skin Test Results* (wheal and flare)

	Regular	NPH
Prick	0/0 cm	0/0 cm
ID	0.7/3.5 cm	0.5/3.0 cm

* Controls: Skin testing with the diluent was negative while histamine showed a strong positive reaction.

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partial relief. Adding dexamethasone (2 to 4 $\mu\text{g}/\text{U}$ of insulin) to the human insulin provided transient relief from the local reactions. Over the subsequent few weeks, the allergic reactions returned and the child's insulin requirements increased, suggesting insulin or lack of efficacy due to antibodies.

A decision was made to attempt desensitization and to improve metabolic control using insulin lispro, a recombinant analog of human insulin administered with an insulin pump. She was hospitalized and pre-treated with cetirizine, 10 mg po, just before the desensitization. Her blood sugar level prior to the desensitization was 300 mg/dL. An insulin lispro infusion was started at a rate of 0.1 units/hour, and the rate was gradually increased every hour to her therapeutic daytime basal level (Fig 1). The patients' blood sugars were checked every hour as were her vital signs. No adverse effects were observed during the infusion. Her daily insulin requirements also decreased from 30 units (1.7 $\mu\text{g}/\text{kg}$) prior to the desensitization to about 17 units (0.9u/kg). After discharge, pruritus and local reactions were almost absent. Her glycemic control also improved and her blood sugar levels range between 100 to 200mg/dL. Our patient tolerated the use of the pump very well and her mother did not report problems with supervision or compliance. She experienced significant relief of her symptoms for about 8 months after which she again started to develop local re-

actions. With a combination of cetirizine and the insulin lispro delivery via the pump, her reactions are currently manageable.

DISCUSSION

The manifestations of insulin allergy can vary in severity from mild local reactions to systemic reactions such as urticaria and anaphylaxis.⁸ Systemic reactions result from the interaction of insulin and insulin-specific IgE antibodies. The offending antigen responsible for insulin allergy usually is the insulin molecule itself,³ although insulin hexamers or contaminants present in animal insulins can also cause adverse effects. Because beef, pork, and human insulins share similar epitopes, patients who are allergic to one type of insulin may react to all types.³ When insulin allergy is suspected, the diagnosis should be established by identifying a temporal relationship between the insulin injections and the occurrence of allergic signs and symptoms, and by documenting the presence of insulin-specific IgE antibodies with positive skin or RAST tests. Insulin allergy can be treated, often with limited success by switching to a different type of insulin, use of oral antihistamines, or by adding glucocorticoids such as dexamethasone to the insulin. If these techniques fail, or if systemic reactions are severe or persistent, then desensitization can be attempted, and is often successful. In one series, de-

sensitization to pork insulin failed in only 17 of 295 cases.⁸

Insulin lispro is a recombinant analog of insulin that may be less antigenic for people with insulin allergy as it does not aggregate to form polymers. It was developed by transposing two amino acid residues at positions B-28 and B-29.⁹ This involves the dimerization site of the insulin molecule and self-association and dimerization are markedly reduced.^{6,10} The insulin molecule has well-defined immunogenic epitopes, which map at specific amino acids, and remain unchanged in the insulin lispro molecule. It is unlikely that there are significant antigenic differences between the insulin lispro and human insulin monomers.⁹ Unlike human insulin, however, insulin lispro does not aggregate to form polymers and may thus be less immunogenic than human insulin.

There are also indicators that insulin lispro may be less immunogenic *in vivo*. For example, there are at least two reported cases in which insulin lispro has caused a reduction in insulin-binding antibodies and a concomitant decline in daily dosages, suggesting reduced immunogenicity for insulin lispro.^{11,12} Furthermore, insulin lispro has been successfully used to treat allergy to human insulin.¹⁰ In our patient, insulin lispro resulted in less severe clinical reactions, but this effect was only temporary, thus making insulin desensitization necessary. Our patient required lower daily doses of insulin when treated with insulin lispro and an insulin pump. A reduction in insulin dosages, however, is frequently observed following initiation of the insulin pump. It is therefore not clear whether the decrease in insulin dosage truly represents a reduction in the immunogenicity of the insulin lispro.

We decided to use an insulin pump in our patient for several reasons. First, most desensitization protocols involve the frequent administration of small and incrementally increasing doses of the offending medication in order to obtain low constant blood levels that gradually increase to therapeutic levels. Second, insulin lispro has a shorter

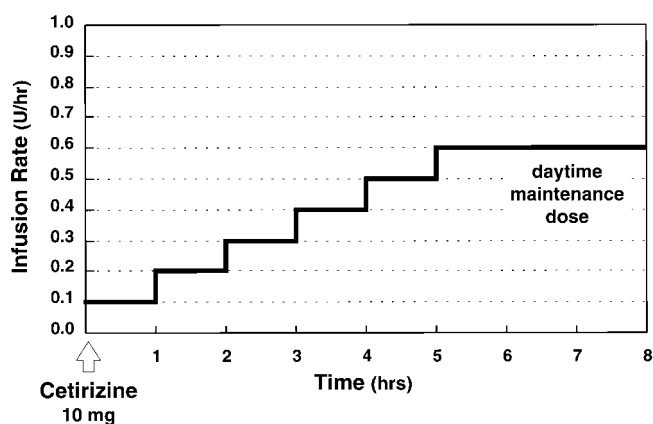


Figure 1. Regimen for insulin desensitization using an insulin pump.

half-life than insulin, and is not available in a long-acting form. Continuous delivery was therefore needed to avoid repeated injections with the use of insulin lispro. The continuous and adjustable delivery provided by the insulin pump would be an ideal method of desensitization. Finally, although our patient was relatively young to use an insulin pump, her family was extremely motivated and committed to her care, and carefully monitored for signs and symptoms of insulin overdose.

In summary, insulin lispro delivered via an insulin pump was used successfully to desensitize a child with insulin allergy. The slow constant infusion rate provided by the pump might be an ideal method for achieving insulin desensitization, and this option should be considered in the treatment of children with insulin allergy.

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