

Case report

Primary systemic allergy to human insulin: recurrence of generalized urticaria after successful desensitization

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Primary systemic allergy to human insulin is rare. We report a case of recurrent immediate local reactions followed eventually by generalized urticaria to recombinant human insulin (Humulin) in an insulin-dependent diabetic. Skin test to Humulin R was positive, and the patient was successfully desensitized using a modified rapid desensitization protocol. Two weeks later, he had another episode of generalized urticaria after Humulin R injection. His treatment was resumed at a lower dose, and within a week he was able to tolerate his usual regimen of insulin. To our knowledge, this is the first report of a recurrence of systemic reaction after successful desensitization.

H. H. Chng¹, K. P. Leong¹, K. C. Loh²

Departments of ¹ Rheumatology and Immunology, and ² General Medicine, Tan Tock Seng Hospital, Singapore

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Dr Hiok Hee Chng
Dept of Rheumatology and Immunology
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130

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Animal insulins became available for the treatment of diabetes mellitus in 1922. This was followed by reports of immunologic complications associated with their use. The introduction of highly purified monocomponent porcine insulin and, subsequently, semisynthetic and recombinant human insulins has significantly reduced, but not removed, the problem of insulin hypersensitivity. Cases of human insulin allergy occurred mainly in patients treated previously with animal insulins. Primary human insulin allergy is rare, and a Medline search from 1976 to 1994 revealed only six cases (1, 11, 15, 20).

We report a recently diagnosed, insulin-dependent diabetic who developed systemic allergic reaction soon after recombinant human insulin was introduced. We successfully desensitized him to human insulin using a modified rapid desensitization protocol. Two weeks later, he experienced another episode of generalized urticaria after Humulin injection. He resumed Humulin at a lower dose and within a week was able to tolerate his usual regimen. To our knowledge, this is the first report of a recurrence of systemic reaction after successful desensitization.

Case report

Mr D., a 22-year-old Malay, was found to have insulin-dependent diabetes mellitus in November 1993 when he presented to a government polyclinic with symptoms of lethargy, weight loss, polyuria, and polydipsia. He resisted insulin therapy despite poor diabetic control with oral hypoglycemic agents. Eventually, in September 1994, he was admitted to our hospital because of hyperglycemia. He was dehydrated with a random blood glucose level of 42.0 mmol/l on admission. There was no evidence of diabetic ketoacidosis or infection, and he was eventually discharged with Humulin R8 units tid (pre-meal) and Humulin N 10 units at 10 pm.

Three weeks after initiation of insulin therapy, he experienced immediate local reactions with both regular and isophane Humulin. The reactions would settle within 20 min. He continued to have these reactions even after a change in the source of Humulin, and on 15 December 1994, he developed generalized urticaria soon after the appearance of a local reaction. There was no history of angioedema, wheeze, dyspnea, or dizziness. The reaction resolved spontaneously in about 1 h. He contacted a diabe-

tes care nurse, who advised him to discontinue insulin. He was on an oral hypoglycemic agent until readmission on 30 December 1994 for the evaluation and management of the hypersensitivity reaction. His serum total IgE was elevated at 461 IU/ml, but specific anti-insulin IgE was not measured. Intradermal skin test using Humulin R was positive at 0.1 unit/ml concentration (Table 1). He did not react to both Humulin R and N diluents on skin testing. He was initially started on a slow desensitization protocol with three insulin doses per day, beginning with the first dose of 0.1 ml of Humulin R at 0.01 unit/ml concentration (Table 2). This was modified to four doses per day, and on day 5 a modified rapid desensitization at hourly intervals was carried out, as the patient was tired of being in hospital. He was able to tolerate the original regimen of 8 units Humulin R tid (premeal) and 10 units Humulin N at 10 pm on day 12 of desensitization. He continued to have small local reactions (less than 10 mm wheal size) and was discharged 13 days after desensitization was begun. It is interesting to note that the local reactions were always larger when Humulin was injected into the abdominal wall, and he was taught to administer Humulin into the deltoid area of either arm. He did not require any antihistamine, as the reactions were mild.

Two weeks after discharge, he developed generalized urticaria again within 3 min of subcutaneous injection of Humulin R into his abdominal wall. The reaction cleared within a few hours. There was no increase in intensity of local reaction prior to the recurrence of urticaria. He was advised to reduce his Humulin R to 6 units tid and Humulin N 6 units at 10 pm and to avoid injecting into his abdominal wall. He subsequently had only small local reactions, and a week later was able to resume his usual dose. He continued to have small local reactions of less than 10 mm diameter 6 weeks later.

Table 1. Intradermal skin test using Humulin R (100 units/ml)

Dilution	Units/ml	Units administered	Wheal size (mm)
1:100 000 000	0.000 001	0.000 000 002	4
1:10 000 000	0.000 01	0.000 000 02	3
1:1 000 000	0.000 1	0.000 000 2	4
1:100 000	0.001	0.000 002	5
1:10 000	0.01	0.000 2	3
1:1000	0.1	0.002	8
<i>Controls</i>		<i>Wheal size (mm)</i>	
Humulin R diluent		0	
Humulin N diluent		0	
Negative control (sterile water)		2	
Histamine (1 mg/ml)*		4	

* Given by prick method.

Table 2. Desensitization protocol*

Day 1	0.1 ml (0.01 unit/ml) at 9 am 0.1 ml (0.1 unit/ml) at 1 pm and 6 pm
Day 2	0.1 ml (0.1 unit/ml) at 9 am 0.5 ml (0.1 unit/ml) at 1 pm, 5 pm, 9 pm
Day 3	0.5 ml (0.1 unit/ml) at 9 am, 1 pm, 5 pm, 9 pm
Day 4	0.5 ml (0.1 unit/ml) at 9 am, 1 pm, 5 pm, 9 pm
Day 5	0.1 ml (1 unit/ml) at 9 am, 11 am, 12 noon, 1 pm, 2 pm, 3 pm, 4 pm
Day 6	0.1 ml (1 unit/ml) at 10 am 0.2 ml (1 unit/ml) at 11 am, 12 noon, 1 pm, 2:30 pm, 4 pm 0.5 ml (1 unit/ml) at 5 pm
Day 7	0.5 ml (1 unit/ml) at 11 am, 12 noon, 2 pm, 3 pm 0.1 ml (10 unit/ml) at 4:30 pm, 5:30 pm
Day 8	0.1 ml (10 unit/ml) at 10:30 am, 11:30 am, 12:30 pm, 2 pm 0.2 ml (10 unit/ml) at 4 pm, 5 pm
Day 9	4 units Humulin R at 8:30 am, 11:30 am, 4:30 pm 4 units Humulin N at 9:30 am
Day 10	4 units Humulin R at 8:30 am, 11:30 am, 4:30 pm 6 units Humulin N at 8:30 am, 10:30 pm
Day 11	6 units Humulin R at 8:30 am, 11:30 am, 4:30 pm 2 units Humulin N at 8:30 pm 8 units Humulin N at 10:30 pm
Day 12	8 units Humulin R at 8:30 am, 11:30 am, 4:30 pm 10 units Humulin N at 10 pm

* Dose administered remains same if local wheal reaction is greater than 3 mm in diameter.

Discussion

Immunologic reaction to insulin may take several forms. Immediate local and systemic reactions are mediated by IgE antibodies. With continued insulin therapy, immediate local reaction usually resolves spontaneously after several weeks. In rare instances, however, it progresses to a systemic state, as in our patient. Other immunologic reactions are delayed local reactions, insulin resistance, and serum sickness; all are uncommon. Patients have also been reported to have more than one type of hypersensitivity reaction (13, 17).

Human insulin (biosynthetic and semisynthetic) is less immunogenic than animal insulin (6) and has significantly reduced the problem of hypersensitivity reactions. The presence of specific IgG and IgE insulin antibodies which do not cause clinical manifestation is common (40% and 10%, respectively), but primary clinical allergy to human insulin is exceptional (21). The antigenic determinant recognized by the antibody induced by human insulin may also be present in bovine and porcine insulin (3, 10, 11). Patients have also been reported to show greater sensitivity to human insulin than porcine insulin on skin testing (9).

It is not known why human insulin is immunogenic. It has been suggested that changes in tertiary

structure are related to immunogenicity (16, 19). In the past, reactions to insulin were caused by contaminants such as preinsulin (12) and other peptides. Biosynthetic human insulin (Humulin) is prepared by using recombinant DNA technology and special strains of nonpathogenic *Escherichia coli*. A theoretic source of protein contaminant could be derived from *E. coli*. However, commercially available Humulin contains less than 4 ppm of immunoreacting *E. coli* polypeptide; thus, reaction to bacteria polypeptide is unlikely.

Patients given insulin may react to zinc, protamine, or the preservative used, rather than the insulin (2, 4, 5, 18). In our patient, the reaction occurred to both regular and isophane Humulin; thus, it is unlikely he reacted to zinc or protamine. In addition, he did not show any reaction when skin tested with the diluents provided by the manufacturer.

The management of immune reactions to insulin depends on the mechanism of reaction and the insulin used. In our patient with *de novo* type I hypersensitivity, desensitization was the treatment of choice, as he was insulin dependent (8). Since there was no urgent need for insulin in this patient, slow desensitization was initially carried out. As the process was slow, we switched to a modified rapid desensitization schedule. We were unable to give the insulin every 15–30 min as recommended (14), because the patient's local reaction sometimes reached a maximum only after 30 min and took another 30 min to subside. It took 12 days to complete the desensitization in our patient. In the last reported case of systemic reaction to human insulin (20), the patient was successfully desensitized only after 350 injections. Mr D. continued to have small local reactions that did not require antihistamine. The disorder did not resolve, and we were surprised at the recurrence of generalized urticaria 3 weeks later. In normal circumstances, we would have expected him to be free of these local reactions after several weeks. In addition, there was no increase in intensity of these local reactions to warn the patient of impending systemic reaction. One possible explanation could be the inadvertent injection of Humulin into the circulation. However, there was no ecchymosis at the injection site to suggest this.

The mechanism of desensitization is unknown. It probably involves the depletion of mediators and the induction of blocking IgG antibodies (7). No data are available on the success of desensitization for human insulin allergy because the disorder is rare.

Conclusion

This case illustrates the immunogenicity of human insulin (recombinant DNA), the potential for progression of immediate local to systemic reaction, and

the value of desensitization. More importantly, allergists should be aware of the potential for recurrence of systemic reaction if a patient continues to have mild local reactions after desensitization, and immediate local reaction may persist much longer than the few weeks usually mentioned.

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