

A case of generalised allergic reaction to human insulin



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Allergic reactions to insulin are distinctly unusual with recombinant human insulin. When they occur, however, they can be associated with severe symptoms, making it difficult to treat patients who are insulin-dependent. We report here on a patient with generalised allergy to human insulin who underwent successful desensitisation.

Case history

A 57-year-old man with type 2 diabetes mellitus on insulin treatment because of oral agent failure presented to the emergency department at Groote Schuur Hospital, Cape Town, with a generalised, itchy rash which he related to his insulin injection. He had had diabetes for about 10 years, and had been switched to insulin 1 year previously because of poor control with an HbA_{1c} of 9.5% (normal range < 5.8%) on maximal doses of metformin and glibenclamide. At the time of presentation he was taking human premixed insulin (Actraphane), 40 units in the morning and 22 units in the evening. There had been symptomatic improvement after starting the insulin, although his best HbA_{1c} was still poor at 8.8%. He had never before been on insulin, and there was no reason to suspect intermittent compliance. Insulin was well tolerated until 1 month before presentation, when he noted a very itchy rash appearing 1 - 2 hours after injecting. This persisted for a few hours, improved, and then recurred after his next injection. The rash had become progressively more severe over the last month. There was no allergic history otherwise.

Ten units of short-acting human insulin (Humulin R) were administered subcutaneously in the emergency unit and the patient was kept under observation. About 30 minutes after the injection he developed a generalised and severe urticarial reaction. There was no nasal irritation, peri-orbital oedema or swelling of the tongue or lips. There was no wheeze or shortness of breath. Maximum doses of oral agents were recommenced and strict dietary habits maintained. However, glycaemic control deteriorated (HbA_{1c} 12.7%) and symptoms of hyperglycaemia developed again. He was therefore admitted for insulin desensitisation.

Skin testing was performed intradermally using dilutions of human short-acting insulin (Actrapid). The

skin testing confirmed allergy to the insulin molecule itself, with a wheal and flare reaction developing at 0.001 units of insulin. The patient had positive immunoglobulin E (IgE) antibodies to porcine (1.77 kU/l) and human insulin (1.29 kU/l).

Desensitisation was carried out over 4 days using subcutaneous injections of increasing concentrations of human Actrapid prepared by the hospital pharmacy. On day 2, a minor papular urticarial reaction developed on the neck only. The dose of insulin was reduced and desensitisation continued successfully. After desensitisation the patient tolerated the insulin for 2 weeks without allergic reaction. Allergic symptoms recurred thereafter as the insulin dose was increased. A sulfonylurea and metformin were recommended together with insulin in lower doses and although occasionally still plagued by allergic reactions these have been milder and controlled with antihistamines.

Discussion

Soon after the introduction of animal insulin for the treatment of diabetes in 1922, immunological complications of insulin became evident. Insulin allergy was particularly common, with local symptoms occurring in up to 50% of patients treated with unchromatographed insulin.¹ However, early insulins were very impure, and were either single species or mixtures of bovine and porcine insulin, and contained several islet-cell peptides, proinsulin, C-peptide, pancreatic polypeptide, glucagon, or somatostatin, all of which are immunogenic. With the introduction of highly purified porcine insulin and recombinant human insulin, allergic reactions were far less common, occurring in about 3% and less than 1% of cases respectively.²

Allergic reactions to insulin occur as one of three types (Table I).³ By far the most common is a type I

Table I.	Allergic reactions to insulin, using the Gell and Coombs classification
Type I, immediate-type hypersensitivity reaction (mediated by IgE antibodies)	
Clinical presentation	
1. Local reaction: immediate and/or biphasic (immediate and late reactions)	
Marked induration, erythema and continuous pruritus	
2. Generalised reaction: urticaria to anaphylaxis	
Type III immune complex-type hypersensitivity reaction (mediated by IgG antibodies). Very rare	
Clinical presentation	
1. Arthus-type localised reaction. Pruritic, painful reaction 6 - 12 hours after injection	
2. Serum sickness type: generalised	
3. Immunogenic insulin resistance	
Type IV delayed-type hypersensitivity reaction (lymphocyte-mediated late local reaction)	
Clinical presentation	
Induration 12 - 24 hours after injection	

hypersensitivity reaction mediated by IgE, also called the 'late phase reaction' which can result in local or generalised reactions. This biphasic reaction has a typical time course characterised by an immediate wheal and flare, followed about 6 hours later by a repeat reaction that may persist for days. Allergy is usually to the insulin molecule itself, rather than to contaminating animal proteins in the insulin preparations and IgE and to insulin are invariably raised and are usually found in high titre in patients with generalised allergy.^{4,5} IgE antibodies to insulin may develop in people with no manifestations of allergy to insulin, and are therefore not helpful in diagnosing insulin allergy.⁴ However, in the absence of IgE to insulin, allergy is unlikely. Protamine (which acts as a complexing agent to prolong the duration of action of insulin) and zinc (stabiliser) have also been implicated in insulin allergy.⁶⁻⁸ Zinc is a constituent in all current formulations of human insulin, but is present in high concentrations in longer-acting lente insulin. IgE antibody directed to protamine is common in patients treated with protamine-containing insulin, but the prevalence of clinically evident protamine allergy is low. It is interesting to note that a serious generalised reaction to protamine, given to neutralise heparin anticoagulation following cardiac surgery, has been described in patients with antibodies to protamine.⁹⁻¹¹ Most episodes of insulin allergy become manifest after at least 7 days and usually within 6 months after the start of treatment.¹² People who develop insulin allergy, whether systemic or localised, have an increased incidence of allergies to penicillin and other drugs.¹³ Interrupted insulin therapy is a further factor influencing the development of allergy.¹³ Intravenous

insulin seems to be less immunogenic than subcutaneous insulin and the newer insulin analogues (which tend not to associate as dimers/polymers) have been reported as being useful in patients with allergy to recombinant human insulin.¹⁴⁻¹⁸ The presence of insulin in monomer form instead of aggregated form is likely to be less antigenic. Alternatively, position 28 of the insulin B-chain, modified in both insulin lispro and insulin aspart, may be a common immunogenic epitope in insulin allergy.

Treatment of local reactions

Local reactions to insulin tend to be self-limited, with improvement seen in 1 - 2 months with continued use of insulin. However, if reactions persist for more than 2 weeks it is reasonable to attempt the strategies outlined in Table II. With such a technique 90% will improve in 2 months, and over half of the remainder will improve spontaneously over 6 - 12 months.¹² If there is deterioration in the severity of the local reaction it may herald a generalised reaction, and management as for such a reaction is appropriate. An adrenalin delivery device, e.g. EpiPen (Merck), should be issued to manage symptoms of anaphylaxis.

Table II.	Treatment of local reactions (modified from Galloway and deShazo ¹²)
1. Rule out poor injection technique, impurities in cleansing alcohol and infection	
2. Switch to human insulin. Consider insulin analogues lispro, aspart or glargine	
3. If no improvement	
Reduce the dose given at a single site by 50%, by using two injection sites	
Consider zinc-free insulin (available from manufacturers)	
Use local steroids in low doses	
4. Oral long-acting antihistamine at night may offer some palliation	

Treatment of generalised insulin allergy

Features of generalised allergy to insulin range in severity and include urticaria, angio-oedema, pruritus, paraesthesiae, pallor, flushing, palpitations, bronchospasm, respiratory distress due to laryngeal oedema and frank circulatory collapse.

If evaluated within 24 - 48 hours of a mild, generalised allergic reaction, consider continuing the insulin, hospitalising the patient and reducing the dose to 1/3 or 1/4 of the original and then gradually increasing the dose over several days.¹⁹ If available, it would be prudent to change to insulin analogues.

If insulin therapy has been interrupted by an interval of more than 48 hours, or if previous allergic reactions have been particularly severe, then skin testing and possible desensitisation are indicated. For such a procedure, the patient is hospitalised and adrenalin is kept at the bedside. Advice from an experienced diabetologist or allergologist is recommended. In the presence of significant hyperglycaemia and/or deteriorating metabolic condition desensitisation should be started immediately. In a patient with ketoacidosis, intravenous insulin is generally tolerated and can be given until metabolically stable before subcutaneous desensitisation takes place. In patients who are metabolically stable, desensitisation may be performed on an elective basis.

The appropriate starting dose and type of insulin can be determined using preliminary skin prick testing to find the least reactive insulin for the patient and the level of sensitivity. For this procedure drugs, e.g. antihistamines and steroids, which might obscure an allergic reaction, should be withheld. Serial dilutions of human insulin (chosen because of its lower immunogenicity) are prepared or are obtainable from the insulin manufacturers. Skin testing should include the insulin analogues. Controls for such skin prick testing include a positive control (histamine) and a negative control (saline). Ordinarily, the initial insulin dose is 1:1 000 U and is administered intradermally. If this dose does not elicit an allergic response, increase the concentration 10-fold and repeat. If the skin test is not positive to 1 U of insulin, then the patient probably does not have insulin allergy.¹²

Subsequent doses of the dilutions are given three times a day, or can be given in a rapid schedule every 30 minutes for more unstable patients. An example of a suitable schedule is set out in Table III. Such a schedule should be flexible, e.g. if any type of reaction occurs the dose should be decreased by half, and

increased thereafter in smaller increments. Following such a protocol, 94% of patients with allergy to pork insulin were successfully desensitised.¹² One would expect similar figures for human insulin, although data are not available, presumably because of the rarity of such reactions.

In patients who fail to be desensitised, options for further management include strong reinforcement of non-medical management such as weight loss and exercise, acceptance of mild hyperglycaemia, enduring mild to moderate reactions, or combining insulin with antihistamines and/or systemic steroids.²⁰ It is particularly important to emphasise that patients should not stop insulin again, as restarting thereafter could result in a more serious reaction occurring.

Conclusions

We have described a case of IgE-mediated generalised allergy to human insulin. Although rare, many diabetologists and general physicians may come across patients with localised insulin allergy. This case and discussion illustrate the need for continued awareness of complications arising from insulin allergy to human insulin. Whether the increased use of insulin analogues will further reduce the allergic manifestations first seen with animal insulin remains uncertain.

Table III. Representative subcutaneous insulin desensitisation schedule

Day	Dose number	Dose (units)
1	1	0.00001
	2	0.0001
	3	0.001
2	4	0.01
	5	0.1
	6	1.0
3	7	2.0
	8	4.0
4	9	8.0
	10	12.0
	11	16.0

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