

# Insulin allergy: a rare diagnostic and management dilemma

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## ARTICLE POINTS

**1** Insulin allergy is rare and difficult to diagnose.

**2** Three types of reaction have been described: localised, systemic and insulin resistance.

**3** Localised reactions are the most common, and still occur in 5% of patients receiving insulin.

**4** Systemic reactions may be life-threatening and require desensitisation programmes with resuscitation equipment to hand.

**5** It is important to consider insulin allergy if insulin therapy has been periodic.

## KEY WORDS

- Insulin
- Allergy
- Diabetes
- Insulin resistance

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## Introduction

**Insulin allergy is a rare occurrence which can present diagnostic and management dilemmas for the clinician. Three types of reaction have been reported: localised, generalised (systemic) and insulin resistance. All need to be considered in cases of suspected insulin allergy. Careful evaluation and early identification of the problem are important. The case study described in this paper serves as a focus for discussion of insulin allergy, and highlights the need to take into account the patient's individual circumstances. Some management strategies are suggested.**

Subcutaneous injection of insulin is an effective means of controlling blood glucose levels in patients with type 1 diabetes and many with type 2 diabetes.

There are sporadic reports of insulin allergy in the literature, particularly to the 'older' insulins of animal origin, such as neutral protein Hagedorn (NPH), protamine zinc insulin (PZI) and biphasic insulins. Localised allergic reactions are the most frequently reported and are thought to occur as a result of the impurities contained in the older insulins, particularly pro-insulin, C peptide and other peptides (Bruni et al, 1988; Loeb et al, 1989).

More recently, allergies to the insulin components protamine, metacresol and phenol have been reported in a series of five patients (Brooks and Roseveare, 1994).

Only a small number of generalised reactions to insulin, or of insulin resistance as a consequence of insulin administration, have been reported (Patrick and Williams, 1993). Investigations for insulin resistance include radioallergosorbent testing (RAST), skin testing and blood tests to detect antibodies to insulin.

Localised reactions to insulin still occur in 5% of patients receiving insulin, despite it now being available in a highly purified state and having the same molecular structure as human insulin (Ganz et al, 1990).

Insulin resistance occurring as a result of high levels of insulin antibodies is rare. Although antibodies to biosynthetic and semi-synthetic human insulin are rare,

occurring in less than 1% of patients, immunoglobulin G (IgG) and immunoglobulin E (IgE) can develop. It has been suggested that the crystalline structure of human insulin may mask its antigenicity for allergic reactions (Schemthaner, 1993).

Although the majority of reactions occur in people who were initially commenced on animal insulin, those who have had interrupted treatment with insulin of animal and human origins may also develop allergic reactions (Takatsuki et al, 1991). It is suggested that antibodies to animal insulins may cross-react when patients are changed to human insulin (Blanco et al, 1996).

The case study presented here describes an episode of suspected insulin allergy and the diagnostic difficulties encountered. Some management strategies are suggested.

## Discussion

Insulin allergy is rare and difficult to diagnose. It is still not clear whether the subject of this case report had a genuine insulin allergy. 'Wheal and flare' reactions are common histamine-related reactions to the injection itself, and most cases of patient-reported insulin allergy are not proven. However, it is important to consider the possibility of insulin allergy in susceptible individuals.

Three types of reaction — localised reaction, generalised (systemic) reaction, and insulin resistance — have been described and should be considered.

- Localised reactions display a 'wheal and

## CASE STUDY

The patient is a 48-year-old woman who is overweight and has insulin-requiring type 2 diabetes. She has been treated with insulin since diagnosis at 31 years of age (17 years). She has non-proliferative retinopathy and has always had suboptimal glycaemic control, often with polyuria and polydipsia.

She has numerous long-standing psychosocial problems. She lives in a flat behind her parents' home, alleges verbal and sexual abuse by her parents and reacts to family stresses by taking narcotics and ethanol. Psychiatric assessment indicated that she manipulates her somatic complaints, including diabetes, to deal with her psychosocial and emotional problems.

The patient raised the question of possible insulin allergy on several occasions over a 12-month period while attending outpatient appointments, and described local urticaria after injecting Protaphane, Human Actrapid and Monotard insulins. She stated that the reaction had not occurred when she was treated with bovine and porcine insulins. On one occasion she claimed to have experienced generalised urticaria, orofacial swelling and respiratory difficulties after injecting Protaphane insulin (HM). The reaction was not observed by any other person and she did not seek medical attention at the time. Protaphane insulin was ceased at this time and a 4-hourly Actrapid regimen instituted.

Her glycaemic control was very erratic on this

regimen, with frequent hypoglycaemic episodes followed by rebound hyperglycaemia. Allergy testing was undertaken and a positive skin reaction to zinc and protamine was demonstrated on one of two occasions.

The patient was admitted to hospital to recommence Protaphane insulin under test conditions. She complained of generalised itch after injections, but no urticaria, oedema or respiratory problems occurred. Cortisone 100 mg was added to each dose of Protaphane to depress the inflammatory reaction for five doses. An explanation of the treatment and counselling took place.

It was not practical to continue this combined insulin/cortisone regimen at home with the patient adding the steroids to the insulin, because of her impaired vision and the complexity of the process. Hydrocortisone 1% cream was therefore applied to the intended injection site before injecting the insulin dose and the patient was transferred to another brand of insulin (Humulin NPH and Humulin R). No further reactions have occurred and the patient has not used the hydrocortisone cream since changing the brands of insulin.

Following resolution of the possible insulin allergy the patient presents on a regular basis to the orthopaedic clinic and her family doctor with chronic back pain. The treating doctors consider that many of the visits are attention seeking and attempts to escape difficult social circumstances.

flare' appearance, consisting of redness occurring within 30 minutes of insulin administration, which peaks and lasts for about 2 hours. The reaction may be IgE-mediated. In some cases, where the injection sites are not rotated, the local reaction may be associated with lipoatrophy. Insulin injection technique and the insulin sites should be examined.

Localised reactions usually disappear if insulin treatment is continued. If insulin is stopped there is a risk that generalised reactions may occur when insulin is re-introduced.

Local application of antihistamine creams and reassurance can be helpful in the treatment of localised reactions.

● **Systemic reactions** are rare and

can be life-threatening. The patient may present with some, or all, of the following symptoms: generalised urticaria, nausea, angio-oedema, asthma, hypotension, cardiac arrhythmia, gastrointestinal cramps, bronchospasm and shock.

A desensitisation programme may be required and should be carried out in a controlled setting with resuscitation equipment available. The aim is to gradually achieve a therapeutic dose of insulin. Patients with elevated IgE and IgG levels may be more likely to experience generalised reactions (Blanco et al, 1996; Skelhy and Van Son, 1987).

● **Insulin resistance** as a consequence of insulin therapy is rare, but may develop if insulin antibodies (IgG) neutralise the

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**1** People with insulin resistance have an increased risk of developing long-term complications of diabetes.

**2** Although true insulin allergy is rare, hypersensitivity can occur at any time.

**3** Management of suspected insulin allergy should include a careful history of drug allergies and previous insulin treatment.

**4** Skin and blood tests may be necessary to identify the specific allergen(s).

**5** Individual factors need to be taken into account when deciding on management.

effects of exogenous insulin, leading to hyperglycaemia and the need for very large doses of insulin. Insulin resistance increases the risk of the individual developing long-term complications of diabetes and is difficult to manage.

Prednisolone 60–100mg daily has been used to treat severe cases of insulin resistance, with variable success. It is difficult to ascertain whether the patients with insulin resistance reported in the literature also had allergies to other substances.

A number of factors complicated the diagnosis and management of possible insulin allergy in the case reported here, including:

- The patient's psychological history, which made health professionals reluctant to accept the possibility that the symptoms may have an organic basis
- The long duration of insulin treatment before any localised reaction was reported
- A familial history of asthma made it difficult to attribute the self-reported generalised reaction to insulin allergy
- The self-report of a systemic reaction to insulin causing respiratory distress but no other symptoms of anaphylaxis was not observed, and the patient did not seek medical treatment.

'Insulin allergy' was a recent occurrence in this patient and it was difficult to attribute her symptoms to insulin allergy, because of her long duration of uninterrupted insulin therapy (17 years). There was no evidence of any problem when insulin was initiated, which would be the expected presentation. However, although true insulin allergy is rare, it should be borne in mind that hypersensitivity can occur at any time.

The local reactions reported by the patient while in hospital under nursing and medical supervision were not significant and not consistent with the literature descriptions of insulin allergy. The management that was instituted was effective for this patient, but individual factors need to be considered when deciding management for other patients.

**Management strategies**

The recommendations for management in cases of suspected insulin allergy are not clearly defined, but should include:

- An awareness of the possibility of insulin allergy, although it is a rare phenomenon
- A careful history before re-commencing insulin therapy, particularly a history of allergies (especially drug allergies and drug rechallenges) and previous treatment with insulin (e.g. during illness, surgery or pregnancy), to identify those few patients who may develop an allergic reaction
- Documenting the time elapsed between the administration of insulin and the onset of the reaction, an accurate description of the episode, the treatment used, and the patient's response to the treatment
- Skin and blood tests, if necessary, to identify the specific allergen(s)
- Changing the patient to another brand of insulin and noting the response
- Desensitisation under supervision with resuscitation equipment available, if necessary.

**Conclusion**

Insulin allergy is rare, but may occur in susceptible individuals. Early identification of the problem is desirable. The possibility of insulin allergy should be considered when first commencing a patient on insulin, especially if interrupted insulin therapy has been administered in the past. ■

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