

Review article

Insulin allergy: clinical manifestations and management strategies

Insulin allergy in patients with diabetes mellitus on insulin treatment is a rare condition. It is suspected upon noticing immediate symptoms following insulin injections. The immediate vital implications for the patient call for prompt diagnosis and management of insulin allergy. We review current knowledge and procedures based on four diabetic patients who presented in our clinic. Insulin allergy was suspected as they showed immediate symptoms after insulin injection (urticaria, rash, angioedema, hypotension, dyspnea). A detailed allergologic work-up was performed and adequate therapy was initiated. In three of the four patients, a specific immunotherapy was started whereas in one patient a switch to oral antidiabetics was possible and consequently initiated. By standard prick testing and measurement of specific IgE antibodies, a type 1 IgE-mediated allergy was confirmed. After initiation of insulin immunotherapy, the symptoms completely resolved in two out three of patients and significantly improved in the third patient. The fourth patient was successfully switched to oral antidiabetics. Insulin allergy is a rare but severe condition that calls for immediate allergological work-up. It can be managed well in close cooperation between the diabetologist and the allergologist. Specific immunotherapy is efficient and should be considered.

**L. Heinzerling^{1,2}, K. Raile³,
H. Rochlitz⁴, T. Zuberbier¹, M. Worm¹**

¹Department of Dermatology and Allergy, Charité Universitätsmedizin, Berlin, Germany; ²Harvard School of Public Health, Boston, MA, USA; Departments of ³Pediatric Endocrinology and Diabetes; ⁴Endocrinology, Diabetes and Nutrition, Charité Universitätsmedizin, Berlin, Germany

Key words: drug reaction; IgE; skin prick test; specific immunotherapy; tolerance; type 1 allergic reaction.

Lucie Heinzerling
Harvard School of Public Health
677 Huntington Avenue
Boston
MA 02115
USA

Accepted for publication 19 September 2007

Adverse reactions to insulin have significantly decreased since the introduction of human insulin preparations (1). However, cases with insulin allergy continue to present in the clinic. Symptoms range from local injection site reactions to severe generalized anaphylactic reactions (2). Allergic reactions to insulin include immediate type IgE-mediated reactions, type 3 immune complex type (Arthus reaction-localized or serum sickness-generalized) or delayed type hypersensitivity reactions. Furthermore, reactions with a delayed onset, i.e. 6 h after injection of insulin may develop (3). These delayed reactions include induration at the injection site with histological signs of leukocytoclastic vasculitis (4). Finally, some reactions are even more delayed with onset after 8–24 h and may be on account of delayed hypersensitivity. This has been reported most frequently for insulin preparations containing zinc (5) or protamine (6). It is important to distinguish insulin allergy that manifests with allergic symptoms from immune-complex mediated insulin resistance due to IgG antibodies that bind to insulin to produce a nonfunctional complex (7).

This review focuses on the type 1 allergy with an immediate reaction to insulin preparations. As insulin is a vital drug for the insulin-dependent patients, a quick diagnostic work-up and adequate management is critical for diabetic patients presenting with symptoms suspected to be of allergic origin. Upon diagnosis, most patients can be satisfactorily managed with various treatment options

at hand. Rarely, insulin allergy can be fatal despite appropriate interventions (8).

In this review, the diagnostic procedures and management options for insulin allergy are reviewed in the light of four severe cases of IgE-mediated allergic reaction to insulin and/or insulin components. We suggest a detailed allergological work-up and discuss a management protocol.

Clinical presentation

The clinical presentation of insulin allergy can range from minor local symptoms to a severe generalized allergic reaction. IgE-mediated symptoms occur immediately after insulin injection. Skin reactions vary from local erythema and swelling at the injection site to generalized reactions like urticaria and angioedema (9, 10). Interestingly, flare reactions can also be elicited at the former injection sites upon insulin injection (11). Furthermore, pruritus of soles and palms, generalized flushing, and itching can occur (12). In rare severe cases, anaphylaxis with dyspnea and hypotension has been observed (2, 13). In one case, a diabetic patient developed a severe anaphylactic reaction in which symptoms could not be managed, despite attempts to desensitize and the patient succumbed upon reintroduction of insulin (8).

The four patients presented in this review were between 12 and 87 years of age with different types of diabetes mellitus and varying local and systemic symptoms (Table 1).

Diagnostic work-up

The presence of an insulin sensitization can be proven by skin prick test and determination of specific IgE (14). A diagnostic algorithm in suspected insulin allergy has been suggested by Jaeger et al. (15) including intradermal skin testing, quantification of insulin-specific IgG and IgE in the serum, and analysis of the time-dependent binding/dissociation curves of the insulin-neutralizing antibodies in an *ex vivo/in vitro* assay.

Diagnostic work-up for the four patients included skin prick testing, assessment of specific IgE and IgG4, and diagnostic tests to exclude other causes of the allergic symptoms. Skin prick testing included the insulin preparations used, alternative insulin preparations, additives and the components of the skin test kits provided by the pharmaceutical companies (Sanofi aventis, Bad Soden am Taunus, Germany; Novo Nordisc, Bagsvaerd, Denmark). Positivity was defined as wheal diameter of more than 3 mm after 15 min. Histamine (10 mg/ml) and diluent (0.9% NaCl) served as positive and negative control. Insulin-specific IgG antibodies were assessed with the CentAK anti-IA (Medipan, Selchow, Germany) which determines specific antibodies against human insulin. The estimate for normal values determined by Jaeger et al. (15) was around 0.038 mU/ml (95% CI 0.025–0.052 mU/ml). Additionally, specific IgE against latex, protamine and penicilloyl G and V were assessed (CAP system; Pharmacia, Uppsala, Sweden).

Management

First line management of insulin allergy besides symptomatic therapy with antihistamines calls for a switch to a different insulin preparation. Especially in patients that show allergic reactions to components of the preparation a switch to a preparation which does not contain the specific agent can lead to a cessation of symptoms (16). To offer alternatives to the patient allergic to insulin analogues, lispro, aspart and glargine with the exchange of two (B28-proline and B29-lysine), one (B28-aspartate) or the exchange of one (A21-glycine) and addition of two amino acids (B31-arginine and B32-arginine), respectively, have been used (17–20). Although these represent options for patients with allergy to insulin (21) they have also been known to provoke hypersensitivity reactions including type 1 allergies in clinical practice (22–25). Detemir, a long-acting insulin analogue, differs from native insulin by the deletion of amino acid B30 and addition of a myristic acid residue at B29 and has also

Table 1. Patient characteristics, symptoms, management, and outcome

Patient Nr.	Age, gender (M/F)	Diabetes mellitus	Symptoms	Other (allergic) conditions	Trial attempts	Management	Outcome
1	36, F	Type I	Urticaria, pruritus, angioedema, diplopic images, general malaise with palpitations, confusion, paresthesia (hands and mouth), induration at injection site, maculous macular exanthema, insulin resistance	Allergic rhinitis (cat, grass), allergic drug reaction to penicillin	Change of insulin preparation (regular insulin (Insuman Infusat/Actrapid), NPH-insulin (Protaphane), insulin aspart, insulin lispro, and insulin glargine), change to insulin pump, symptomatic therapy with antihistamines and corticosteroids	Specific immunotherapy with human insulin (Insuman Rapid)	Improvement of symptoms, but worse perception of hypoglycemia with human insulin preparation
2	13, F	Type I	Urticaria, nausea, paleness, angioedema, dyspnoea	Sickle cell anemia (splenectomy and continuous treatment with low dose penicillin)	Immediate monitoring in hospital	Specific immunotherapy with human insulin (Huminsulin normal)	Cessation of symptoms
3	83, F	Type II	Urticaria, pruritus, erythema, induration and swelling at injection site, diplopic images, insulin resistance	Hypertension, coronary artery disease, apoplexapoplexy	Symptomatic therapy with antihistamines	Change to oral antidiabetics	Cessation of symptoms
4	60, M	Type II	Urticaria, pruritus, erythema	Allergic rhinitis (cat, house dust mite, grass, birch), food allergy (hazelnut, oat flour), allergic drug reaction to penicillin	Change of insulin preparation, symptomatic therapy with antihistamines	Specific immunotherapy with insulin analogue (Novo-Rapid)	Cessation of symptoms

been reported to elicit allergic reactions (26, 27). One report even implied the potential of insulin analogues to be more allergenic than insulin (28), which led to a debate on this preposition (29).

One method to induce tolerance is the application of insulin as continuous subcutaneous insulin infusion (CSII). Several case reports describe the beneficial effect of this form of application in allergic diabetic patients (30–34). Furthermore, the use of specific immunotherapy for the treatment of insulin allergy has been reported previously and was successful in many cases (35). In our patients, prior to the specific immunotherapy, various treatment options including change of insulin, change of insulin application and symptomatic therapy with antihistamines had been attempted (Table 1). Specific immunotherapy consists of successive subcutaneous injections of insulin under close monitoring with preparation for emergency intervention in an in-patient setting. The initial dose for the specific immunotherapy depends on the grade of sensitization and the duration is usually up to 2 days. In our patients who presented with severe symptoms, the initial dose was 0.00001 units, with subsequent doses progressively increasing 10-fold up to 1 unit, then 2, 4, 8, 12, 16, and 20 units. In case of local allergic reactions, the last dose is repeated until no reaction occurs and then the dose increases are continued. If systemic reactions occur the dose is reduced to one half. During the specific immunotherapy, blood sugar is closely monitored and controlled via diet, oral antidiabetics (in type 2 diabetic patients) or insulin pump treatment using insulin analogues, different from insulin preparations used for immunotherapy. At high insulin doses, a 10% glucose solution can be given to counteract the glucose-lowering effect. Specific immunotherapy is often effective although effects may not be permanent and symptoms may recur (9).

Recently, insulin tolerability in a severely insulin-allergic patient with diabetes was achieved by the use of intravenously injected insulin (36). In this patient, treatment attempts of specific immunotherapy with subcutaneous insulin injections, with continuous subcutaneous injection of insulin analogue lispro, and with oral anti-allergic agents did not prevent frequent life-threatening allergic symptoms. Ultimately, the authors applied the required insulin intravenously over a central line at a dose of 100 U per 500 ml with a portable pump delivering 5–10 ml/h, adjusted according to self-monitored blood glucose levels.

Clinical history

Patient #1

A 36-year-old female patient, with type 1 diabetes for more than 5 years, developed symptoms of urticaria and angioedema, palpitations, and paresthesia in the hands and in the mouth. Symptoms started 5–10 min after

insulin injections. Additionally, the local injection site showed an induration upon physical examination. Furthermore, intermittent diplopia without periorbital edema was present. Insulin therapy with human insulin was increasingly less effective in controlling the glucose level and showed progressively more intense side effects. The following insulin preparations had been used: regular insulin (Insuman Infusat or Actrapid), NPH-insulin (Protaphane), insulin aspart, insulin lispro, and insulin glargine. At the time of admission to our unit, the patient was treated with porcine regular insulin (Actrapid suis MC) in an infusion pump. Besides the acute symptoms, the patient had a seasonal allergic rhinoconjunctivitis with sensitization to grass pollen and a history of allergic reaction to penicillin. The immunological evaluation revealed: (1) positive skin testing for the additives zinc and protamine, and insulin preparations Insulin novo semilente, Insuman rapid, and insulin glargine in intracutaneous testing. The porcine insulin Actrapid suis MC showed a reaction, though of insufficient magnitude to be classified as positive. (2) High titers of insulin-specific IgE with CAP class 4 (30.6 kU/l) but no protamine-specific IgE (<0.35 kU/l). ANAs, insulin-specific IgG, and circulating immune complexes were within normal limits. The initial treatment with oral antihistamines had improved symptoms. Additionally, the patient had taken oral corticosteroids on occasions of more severe symptoms. As symptoms could not be controlled sufficiently with the symptomatic treatment, a specific immunotherapy was initiated with human regular insulin (Insuman Rapid) by a dose-escalation scheme over 2 days. Two days after initiation, no further allergic symptoms occurred and the patient was treated with human insulin without any continuing allergic symptoms.

Patient #2

A 13-year-old female patient presented with type 1 diabetes for 3 months on insulin therapy (12 months at present). On account of a homozygous sickle cell disease, the patient had received splenectomy and continuous antibiotic treatment with low dose oral penicillin. Half a minute after bolus injections of insulin, she reacted with paleness, nausea, urticaria, angioedema and dyspnea. The intensity and frequency of these attacks increased continuously. (1) Skin testing revealed a sensitization to insulin glargine, regular insulin (Actrapid Penfill and Huminsulin Normal), and NPH-insulin (Huminsulin Basal). Insulin aspart showed a small reaction, which was not classified as positive. (2) Anti-insulin IgE antibodies were 7.49 kU/l (CAP class 3) and total IgE was 185 kU/l. Due to the severity of the symptoms and these findings, a specific immunotherapy was initiated followed by insulin pump treatment with insulin aspart. After the 5-day course the symptoms did not recur. Furthermore, the patient showed 0.56 kU/l (CAP class 1) IgE antibodies against penicilloyl V without clinical signs of penicillin

allergy. Currently, insulin pump treatment with insulin aspart continues and metabolic control is good.

Patient #3

An 83-year-old female patient with type 2 diabetes [body mass index (BMI), 25] received insulin treatment for 10 months with regular and NPH-insulin (Actrapid and Protaphane). She had hypertension, coronary artery disease, and had previously suffered from an apoplexy. The leading allergic symptoms were erythematous reactions, urticaria, and pruritus immediately after injection. Additionally, her glucose levels were increasingly hard to control. Furthermore, the injection site showed induration. Oral antihistamine treatment improved the condition but did not completely resolve it. Immunological evaluations revealed: (1) positive skin prick testing for regular insulin (Actrapid), mix insulin (Berlinsulin H 30/70, Huminsulin Profil 30/70), NPH-insulin (Basal Hoechst, Huminsulin Basal, Berlinsulin Basal), zinc insulin (Novo Ultratard), insulin aspart and insulin lispro. Skin prick testing for the compounds with the Novo Nordisc insulin allergy kit was negative. Intracutaneous testing was positive for porcine, bovine and more positive for human insulin. (2) Insulin-specific IgE against human CAP class 2 (2.39 kU/l), bovine CAP class 2 (2.06 kU/l) and porcine CAP class 1 (2.61 kU/l) insulin were present. Insulin-specific IgG were normal. The patient was successfully transferred from insulin to oral antidiabetics (metformin and repaglinide) and allergic symptoms resolved completely.

Patient #4

A 60-year-old male patient with type 2 diabetes was treated with insulin for 5 months and presented to our outpatient department because of the onset of urticaria, erythema, flush, and pruritus. He had been treated with insulin glulisine. After the symptoms started he was switched to insulin aspart. However, the allergic symptoms did not improve. Since 1 month he received NPH-insulin (Protaphane) in addition. Oral antihistamines had improved the symptoms but not resolved them. Additionally, he suffered from allergic rhinitis and asthma and reported a drug reaction to penicillin. The immunological evaluations revealed the following: (1) positive skin testing showed an urticaria factitia with equally positive reactions for NaCl, human insulin, and cresol. (2) Quantification of insulin-specific antibodies showed insulin-specific IgE CAP class 1 (0.43 kU/l) while insulin-specific IgG was normal. Interestingly, the patient showed penicillin-specific antibodies: penicilloyl V CAP class 1 (0.56 kU/l), ampicilloyl CAP class 1 (0.47 kU/l) as well as latex-specific antibodies CAP class 2 (2.24 kU/l) with a total IgE of 210 kU/l. Other triggers for the urticaria, e. g. *Helicobacter pylori* infection were excluded. Furthermore, the patient had sensitizations to house dust mite, grass pollen, cat and birch. Because of a suspected IgE-mediated allergy to

insulin that provoked symptoms despite intensive antihistamine therapy, a specific immunotherapy with regular insulin (Insuman Rapid) was performed. After the 2-day course the symptoms did not recur.

Results

At our department, we diagnosed four patients with a type 1 sensitization towards insulin (Table 2) and allergic symptoms in clinical use of insulin. Respective insulin IgE antibodies were present in these four patients (Table 2). Furthermore, all patients showed a positive skin prick test or intracutaneous test to insulin preparations and/or insulin analogues. Two patients presented with a sensitization to additives in the insulin preparations (one to protamine and zinc, and one to cresol). Three out of three patients tested had IgE against penicillin and two patients had a history of allergic reactions to penicillin.

During the specific immunotherapy regimen that each of the three patients underwent, no complications occurred and symptoms improved in one patient and completely disappeared in the other two patients. In the fourth patient, a change to oral antidiabetics was sufficient to control blood glucose and insulin treatment could be stopped with no further allergic symptoms.

Immunologic mechanisms

Type 1 allergic reactions are mediated by IgE against insulin or components of the insulin preparations. These immunologic reactions can be elicited by different antigenic determinants in the recombinant proteins, which are not present in the endogenous human insulin (37) or they may also be on account of the immunogenicity of one of the nonprotein components (38). It has also been assumed that some modification of insulin, such as aggregation, may lead to the immunologic reactions (39, 40). In rare cases, the IgE is directed to the endogenous insulin of the patient (41, 42). The following additives in insulin preparations have been observed to induce allergic reactions or sensitizations: zinc, protamine (42, 43), and cresol (44). Protamine can act as adjuvant (45), and the crystalline zinc solutions can alter immunogenicity by changing the structure of the B-chain (46, 47). Interestingly, Madero et al. report a case of a diabetic patient with IgE-mediated allergic reactions to recombinant human insulin and a positive skin test for glargine possibly mediated by specific IgG4 (48).

The route of administration also determines whether allergic symptoms occur as described in a patient by Asai et al. who showed no symptoms upon intravenous injection of insulin, whereas symptoms on subcutaneous injection persisted (36).

Specific immunotherapy induces tolerance in many patients with IgE-mediated immediate allergic reactions.

Table 2. Diagnostic work-up

Patient Nr.	Prick test results/intracutaneous test (i.c.)	Specific IgE	Total IgE (kU/l)	Circulating immune complexes	Other findings
1	Prick test negative for Humalog Mix, Lantus, Insuman, glargine; i.c. test positive for zinc, protamine, insulin Novo semilente, Insuman Rapid, Lantus; components: phenol-cresol, protamine-cresol-phenol, protamine sulphate; i.c. test slight reaction to Actrapid MC suis; i.c. test negative for glargine, glargine components, Humalog Mix Prick test positive for Huminsulin normal, Huminsulin Basal, prick test slight reaction for Novo Rapid Penfill	Human insulin Cap 4 (43.9 kU/l) Protamine Cap 0 (<0.35 kU/l) Penicilloyl G Cap 1 (0.38 kU/l) Penicilloyl V Cap 1 (0.53 kU/l) Latex Cap 0 (< 0.35 kU/l) Human insulin Cap 3 (7.5 kU/l) Protamine Cap 2 (1.42 kU/l) Penicilloyl G Cap 0 (<0.35 kU/l) Penicilloyl V Cap 1 (0.56 kU/l) Latex Cap 0 (<0.35 kU/l)	69.8	37.8 µg/ml (normal) <55 µg/ml	IgG insulin antibodies: positive; tyrosin antibodies: 1.2 U/ml (normal) <0.75 U/ml; ANA: negative; C3c/C4: normal
2			185	Not done	
3	Prick test positive for Berlinsulin H 30/70, Huminsulin Profil 30/70, Berlinsulin Basal, Humalog, Basal Hoechst, Huminsulin Basal, Actrapid, Novorapid, Novo retard; prick test slight reaction porcine and human insulin; i.c. test positive for porcine, bovine and human insulin I.c. test positive for human insulin, metacresol, NaCl; i.c. test negative for Novo Rapid, protaphane, protamine, isophane, zinc, phenol, paraben	Porcine insulin Cap 2 (2.6 kU/l) Bovine insulin Cap 2 (2.1 kU/l) Human insulin Cap 2 (2.4 kU/l)	54.8	30 µg/ml (normal) <55 µg/ml	IgG insulin antibodies: negative; ANA: 1 : 320
4		Human insulin Cap 1 (0.6 kU/l) Penicilloyl G Cap 0 (<0.35 kU/l) Penicilloyl V Cap 1 (0.56 kU/l) Ampicilloyl Cap 1 (0.47 kU/l) Latex Cap 2 (2.24 kU/l)	227	Not done	IgG insulin antibodies: negative; ANA: negative; helicobacter pylori: negative; anti-TPQ: negative

Even though the mechanism of specific immunotherapy has not been fully elucidated, the induction of anergy or depletion of specific T cells has been suggested as well as the induction of T-regulatory cells and the modulation of antibody production by cytokines (49). Specific immunotherapy has been associated with a fall in IgE antibodies (50). The fall in serum IgE levels, however, does not exclude the appearance of allergic symptoms (36). In this case, despite the decrease in insulin-specific IgE and IgG to normal levels after intravenous application of insulin, the subcutaneous injection of regular insulin still caused immediate allergic reactions (36).

Conclusion

In summary, when insulin allergy is suspected, a careful history may give first indication as to whether the symptoms are allergic, whether it is a type 1 or type 3 reaction, and which agents are the most likely cause of these symptoms. Allergologic work-up for IgE-mediated allergy includes skin prick testing or intracutaneous testing, assessment of specific IgE and IgG4, and the exclusion of other causes of the symptoms (Fig. 1). Exclusion of other causes has been shown to be particularly important as a retrospective study in 22 patients with suspected insulin allergy indicated that 59% of the patients did not have an allergic cause of their symptoms (51). Furthermore, allergy to latex has to be excluded as allergic symptoms have been described to be caused by trace amounts of latex from the vial membranes (52, 53) although sensitization is not always relevant (52). However, none of the patients who reported here were sensitized to latex.

Skin test results have to be evaluated with care as nonallergic diabetic subjects have previously been documented to have a positive skin prick test to protamine and less frequently to human insulin (2, 14). In fact, positive prick test results and low specific IgE titers may occur in up to 28% of diabetes patients without any clinical relevance (54). Positive antibody titers indicate sensitization only and thus always must be viewed in conjunction with the clinical symptoms. Interestingly, all three patients who were assessed, additionally showed IgE antibodies to penicillin, and two of the four patients had a history of a drug reaction to penicillin, a condition that has previously been shown to have a higher prevalence in insulin-allergic patients (55).

Human insulin is less immunogenic than animal insulin, and porcine insulin is less immunogenic than bovine insulin. Bovine insulin differs from human insulin in three amino acids (2 in the A chain) and porcine insulin in only one (human A chain and pork A chain are identical). When sensitization is limited to one origin of insulin or one additive, the allergen can be avoided by choosing a different preparation suitable for the patient (Table 3). Importantly, antibodies to protamine have

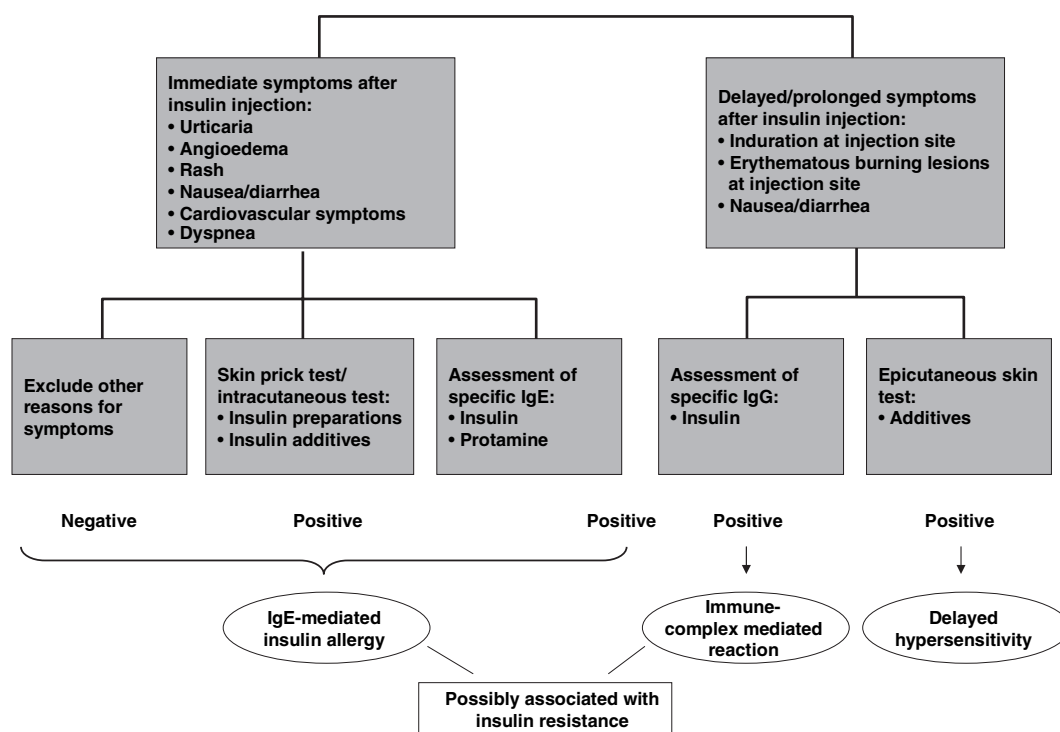


Figure 1. Diagnostic approach in suspected insulin allergy.

Table 3. Insulin preparations with respective additives

Name of insulin	Type of insulin	Additives				Duration of action
		Zinc	Protamine	Cresol	Other	
Actrapid	Human	×		×	Glycerol	2–8 h
Berlinsulin H Normal	Human			×	Glycerol	2–8 h
Huminsulin Normal	Human			×	Glycerol	2–8 h
Insuman Rapid	Human			×	Glycerol	2–8 h
Insulin B Braun	Human (enzymatically produced from porcine insulin)			×	Glycerol	2–8 h
Velosulin	Human	×		×	Glycerol	2–8 h
Insulin S Berlin-Chemie	Porcine				Methyl-4-hydroxybenzoat	2–8 h
Insulin S.N.C. Berlin-Chemie	Porcine			×	Glycerol	2–8 h
Novorapid	r-DNA insulin aspart	×		×	Phenol, glycerol	2–5 h
Apidra optiset	Analogum (glulisin)			×	Trometamol	2–5 h
Humalog	Analogum (lispro)	×		×	Glycerol	2–5 h
Actraphane	Human	×	×	×	Phenol, glycerol	Up to 24 h
Berlinsulin H	Human	×	×	×	Phenol, glycerol	Up to 24 h
Huminsulin Basal for pen	Human		×	×	Phenol, glycerol	Up to 24 h
Huminsulin Basal	Human	×	×	×	Phenol, glycerol	Up to 24 h
Huminsulin Profil	Human		×	×	Phenol, glycerol	Up to 24 h
Insulin B Braun Basal	Human (enzymatically produced from porcine insulin)	×	×	×	Phenol, glycerol	Up to 24 h
Protaphane	Human	×	×	×	Phenol	Up to 24 h
Insuman Basal	Human	×	×	×	Phenol, glycerol	Up to 24 h
Monotard	Human	×			Methyl-4-hydroxybenzoat	Up to 24 h
B Insulin S	Porcine				Methyl-4-hydroxybenzoat, Aminoquinurid	Up to 24 h
Insulin Novo Semilente MC	Porcine	×			Methyl-4-hydroxybenzoat	Up to 24 h
Humalog Mix	Analogum (lispro)	×	×	×	Phenol, glycerol	Up to 24 h
NovoMix 30	Insulin aspart-protamin crystals	×	×	×	Phenol	Up to 24 h
Levemir	Insulindetemir	×		×	Phenol	Up to 24 h
Ultratard	Human	×			Methyl-4-hydroxybenzoat	More than 24 h
Lantus	Analogum (glargin)	×		×	Glycerol	More than 24 h

been associated with anaphylaxis during reversal of intraoperative heparin anticoagulation by protamine in cardiac catheterization (42, 56, 57). Treatment options for insulin allergy include the symptomatic therapy with antihistamines. However; sensitization may be accentuated over time. Especially when local symptoms are increasing in intensity they may precede systemic reactions. When symptomatic therapy is not sufficient, and change of insulin preparation not feasible due to multiple sensitizations or difficulties in stabilizing the blood sugar with a certain insulin preparation, specific immunotherapy is a good option for the patient. In severe cases it has previously been combined with prednisolone (35, 58).

In accordance with results from other groups (31, 35), specific immunotherapy was effective in reducing symptoms of type 1 allergy to insulin or insulin components in all three patients described here. It was also associated with a decrease in IgE titers as has been described before (59). Our regimen used several ascending single doses, whereas there are also reports of successful specific immunotherapy with continuous subcutaneous infusion

(32, 33, 60) and surprisingly one case of intravenous therapy (36). The specific immunotherapy regimen was effective and well tolerated. However, a few cases of ineffective specific immunotherapy (61) and short duration of effect have also been reported (9). A rare complication has been described in the induction of insulin IgG antibodies leading to insulin resistance (62).

In conclusion, insulin allergy is a rare condition that calls for a quick allergological work-up. It can be managed well in close cooperation between the diabetologist and the allergologist. Specific immunotherapy should be considered if a type 1 allergy to insulin is diagnosed and may lead to a complete resolution of symptoms.

Acknowledgements

We thank Dr Elsbeth Oestmann and Dr Christian Hessel from the Charité University Hospital, Department of Dermatology and Allergy, for patient care. We also thank Jeff Berens for language editing of the manuscript.

References

- Fernandez L, Duque S, Montalban C, Bartolome B. Allergy to human insulin. *Allergy* 2003;**58**:1317.
- Blanco C, Castillo R, Quiralte J, Delgado J, García I, de Pablos P et al. Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996;**51**:421–424.
- deShazo RD, Boehm TM, Kumar D, Galloway JA, Dvorak HF. Dermal hypersensitivity reactions to insulin: correlations of three patterns to their histopathology. *J Allergy Clin Immunol* 1982;**69**:229–237.
- Mandrup-Poulsen T, Molvig J, Pildal J, Rasmussen AK, Andersen L, Skov BG et al. Leukocytoclastic vasculitis induced by subcutaneous injection of human insulin in a patient with type 1 diabetes and essential thrombocytemia. *Diabetes Care* 2002;**25**:242–243.
- Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979;**1**:122–124.
- Raap U, Liekenbrocker T, Kapp A, Wedi B. Delayed-type hypersensitivity to protamine as a complication of insulin therapy. *Contact Dermatitis* 2005;**53**:57–58.
- Goldfine AB, Kahn CR. Insulin allergy and insulin resistance. *Curr Ther Endocrinol Metab* 1994;**5**:461–464.
- Kaya A, Gungor K, Karakose S. Severe anaphylactic reaction to human insulin in a diabetic patient. *J Diabetes Complications* 2007;**21**:124–127.
- Chng HH, Leong KP, Loh KC. Primary systemic allergy to human insulin: recurrence of generalized urticaria after successful desensitization. *Allergy* 1995;**50**:984–987.
- Gonzalo MA, de Argila D, Revenga F, García JM, Diaz J, Morales F. Cutaneous allergy to human (recombinant DNA) insulin. *Allergy* 1998;**53**:106–107.
- Wessbecher R, Kiehn M, Stoffel E, Moll I. Management of insulin allergy. *Allergy* 2001;**56**:919–920.
- Baur X, Bossert J, Koops F. IgE-mediated allergy to recombinant human insulin in a diabetic. *Allergy* 2003;**58**:676–678.
- Scheer BG, Sitz KV. Suspected insulin anaphylaxis and literature review. *J Ark Med Soc* 2001;**97**:311–313.
- Lee AY, Chey WY, Choi J, Jeon JS. Insulin-induced drug eruptions and reliability of skin tests. *Acta Derm Venereol* 2002;**82**:114–117.
- Jaeger C, Eckhard M, Brendel MD, Bretzel RG. Diagnostic algorithm and management of immune-mediated complications associated with subcutaneous insulin therapy. *Exp Clin Endocrinol Diabetes* 2004;**112**:416–421.
- Rajpar SF, Foulds IS, Abdullah A, Maheshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. *Contact Dermatitis* 2006;**55**:119–120.
- Airaghi L, Lorini M, Tedeschi A. The insulin analog aspart: a safe alternative in insulin allergy. *Diabetes Care* 2001;**24**:2000.
- Kumar D. Lispro analog for treatment of generalized allergy to human insulin. *Diabetes Care* 1997;**20**:1357–1359.
- Lluch-Bernal M, Fernandez M, Herrera-Pombo JL, Sastre J. Insulin lispro, an alternative in insulin hypersensitivity. *Allergy* 1999;**54**:186–187.
- Moriyama H, Nagata M, Fujihira K, Yamada K, Chowdhury SA, Chakrabarty S et al. Treatment with human analog (GlyA21, ArgB31, ArgB32) insulin glargine (HOE901) resolves a generalized allergy to human insulin in type 1 diabetes. *Diabetes Care* 2001;**24**:411–412.
- Panczel P, Hosszufalusi N, Horvath MM, Horvath A. Advantage of insulin lispro in suspected insulin allergy. *Allergy* 2000;**55**:409–410.
- Barranco R, Herrero T, Tornero P, Barrio M, Frutos C, Rodriguez A et al. Systemic allergic reaction by a human insulin analog. *Allergy* 2003;**58**:536–537.

23. Durand-Gonzalez KN, Guillausseau N, Pecquet C, Gayno JP. Glargine insulin is not an alternative in insulin allergy. *Diabetes Care* 2003;**26**:2216.
24. JiXiong X, Jianying L, Yulan C, Huixian C. The human insulin analog aspart can induce insulin allergy. *Diabetes Care* 2004;**27**:2084–2085.
25. Takata H, Kumon Y, Osaki F, Kumagai C, Arii K, Ikeda Y et al. The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003;**26**:253–254.
26. Blumer IR. Severe injection site reaction to insulin detemir. *Diabetes Care* 2006;**29**:946.
27. Darmon P, Castera V, Koeppl MC, Petitjean C, Dutour A. Type III allergy to insulin detemir. *Diabetes Care* 2005;**28**:2980.
28. Sola-Gazagnes A, Pecquet C, M'Bemba J, Larger E, Slama G. Type I and type IV allergy to the insulin analogue detemir. *Lancet* 2007;**369**:637–638.
29. Dejgaard A, Larsen J, Pedersen CR. Type I and type IV allergy to insulin detemir. *Lancet* 2007;**369**:1926–1927.
30. Eapen SS, Connor EL, Gern JE. Insulin desensitization with insulin lispro and an insulin pump in a 5-year-old child. *Ann Allergy Asthma Immunol* 2000;**85**:395–397.
31. Moyes V, Driver R, Croom A, Mirakian R, Chowdhury TA. Insulin allergy in a patient with type 2 diabetes successfully treated with continuous subcutaneous insulin infusion. *Diabet Med* 2006;**23**:204–206.
32. Naf S, Esmatjes E, Recasens M, Valero A, Halperin I, Levy I et al. Continuous subcutaneous insulin infusion to resolve an allergy to human insulin. *Diabetes Care* 2002;**25**:634–635.
33. Nagai T, Nagai Y, Tomizawa T, Mori M. Immediate-type human insulin allergy successfully treated by continuous subcutaneous insulin infusion. *Intern Med* 1997;**36**:575–578.
34. Radermecker RP, Scheen AJ. Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues. *Diabetes Metab Res Rev* 2007;**23**:348–355.
35. Yokoyama H, Fukumoto S, Koyama H, Emoto M, Kitagawa Y, Nishizawa Y. Insulin allergy; desensitization with crystalline zinc-insulin and steroid tapering. *Diabetes Res Clin Pract* 2003;**61**:161–166.
36. Asai M, Yoshida M, Miura Y. Immunologic tolerance to intravenously injected insulin. *N Engl J Med* 2006;**354**:307–309.
37. Scherthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993;**16**(Suppl. 3):155–165.
38. Grammer L. Insulin allergy. *Clin Rev Allergy* 1986;**4**:189–200.
39. Brange J, Andersen L, Laursen ED, Meyn G, Rasmussen E. Toward understanding insulin fibrillation. *J Pharm Sci* 1997;**86**:517–525.
40. Maislos M, Mead PM, Gaynor DH, Robbins DC. The source of the circulating aggregate of insulin in type I diabetic patients is therapeutic insulin. *J Clin Invest* 1986;**77**:717–723.
41. Alvarez-Thull L, Rosenwasser LJ, Brodie TD. Systemic allergy to endogenous insulin during therapy with recombinant DNA (rDNA) insulin. *Ann Allergy Asthma Immunol* 1996;**76**:253–256.
42. Porsche R, Brenner ZR. Allergy to protamine sulfate. *Heart Lung* 1999;**28**:418–428.
43. Bollinger ME, Hamilton RG, Wood RA. Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999;**104**:462–465.
44. Clerx V, Van Den KC, Kochuyt A, Goossens A. Drug intolerance reaction to insulin therapy caused by metacresol. *Contact Dermatitis* 2003;**48**:162–163.
45. Kahn CR, Rosenthal AS. Immunologic reactions to insulin: insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diabetes Care* 1979;**2**:283–295.
46. Ratner RE, Phillips TM, Steiner M. Persistent cutaneous insulin allergy resulting from high-molecular-weight insulin aggregates. *Diabetes* 1990;**39**:728–733.
47. Yip CM, Brader ML, DeFelippis MR, Ward MD. Atomic force microscopy of crystalline insulins: the influence of sequence variation on crystallization and interfacial structure. *Biophys J* 1998;**74**:2199–2209.
48. Madero MF, Sastre J, Carnes J, Quirce S, Herrera-Pombo JL. IgG(4)-mediated allergic reaction to glargine insulin. *Allergy* 2006;**61**:1022–1023.
49. Jutel M, Akdis M, Budak F et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;**33**:1205–1214.
50. Child DF, Johansson SG. IgE antibody studies in a case of generalized allergic reaction to human insulin. *Allergy* 1984;**39**:630–633.
51. Bodtger U, Wittrup M. A rational clinical approach to suspected insulin allergy: status after five years and 22 cases. *Diabet Med* 2005;**22**:102–106.
52. Danne T, Niggemann B, Weber B, Wahn U. Prevalence of latex-specific IgE antibodies in atopic and nonatopic children with type I diabetes. *Diabetes Care* 1997;**20**:476–478.
53. Roest MA, Shaw S, Orton DI. Insulin-injection-site reactions associated with type I latex allergy. *N Engl J Med* 2003;**348**:265–266.
54. Velcovsky HG, Federlin KF. Insulin-specific IgG and IgE antibody response in type I diabetic subjects exclusively treated with human insulin (recombinant DNA). *Diabetes Care* 1982;**5**(Suppl. 2):126–128.
55. Jegasothy BV. Allergic reactions to insulin. *Int J Dermatol* 1980;**19**:139–141.
56. Sharath MD, Metzger WJ, Richerson HB, Scupham RK, Meng RL, Ginsberg BH et al. Protamine-induced fatal anaphylaxis. Prevalence of antiprotamine immunoglobulin E antibody. *J Thorac Cardiovasc Surg* 1985;**90**:86–90.
57. Stewart WJ, McSweeney SM, Kellett MA, Faxon DP, Ryan TJ. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984;**70**:788–792.
58. Grant W, deShazo RD, Frenzt J. Use of low-dose continuous corticosteroid infusion to facilitate insulin pump use in local insulin hypersensitivity. *Diabetes Care* 1986;**9**:318–319.
59. Mattson JR, Patterson R, Roberts M. Insulin therapy in patients with systemic insulin allergy. *Arch Intern Med* 1975;**135**:818–821.
60. Pratt EJ, Miles P, Kerr D. Localized insulin allergy treated with continuous subcutaneous insulin. *Diabet Med* 2001;**18**:515–516.
61. Frigerio C, Aubry M, Gomez F, Graf L, Dayer E, de Kalbermatten N et al. Desensitization-resistant insulin allergy. *Allergy* 1997;**52**:238–239.
62. Witters LA, Ohman JL, Weir GC, Raymond LW, Lowell FC. Insulin antibodies in the pathogenesis of insulin allergy and resistance. *Am J Med* 1977;**63**:703–709.