Insulin allergy: clinical manifestations and management strategies

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 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.

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...
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 antihistamines 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 Nordic 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.
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, 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 IgG, and the exclusion of other causes of the symptoms. Fig. 1 depicts the exclusion of other causes of the symptoms and the importance of a retrospective study in patients with suspected insulin allergy (51). Furthermore, an allergic cause of their symptoms (51). 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). How-
Figure 1. Diagnostic approach in suspected insulin allergy.

Table 3. Insulin preparations with respective additives

<table>
<thead>
<tr>
<th>Name of insulin</th>
<th>Type of insulin</th>
<th>Zinc</th>
<th>Protamine</th>
<th>Cresol</th>
<th>Other</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actrapid Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Berlininsulin H Normal</td>
<td>Human</td>
<td>×</td>
<td></td>
<td>×</td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Huminsulin Normal</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Insulin B Braun Human</td>
<td>Human (enzymatically produced from porcine insulin)</td>
<td>×</td>
<td></td>
<td></td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Velosulin Hum</td>
<td>Human</td>
<td>×</td>
<td></td>
<td></td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Insulin S Berlin-Chemie</td>
<td>Porcine</td>
<td></td>
<td></td>
<td>×</td>
<td>Methyl-4-hydroxybenzoat</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Insulin S.N.C. Berlin-Chemie</td>
<td>Porcine</td>
<td></td>
<td></td>
<td>×</td>
<td>Glycerol</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Novorapid r-DNA insulin aspart</td>
<td>r-DNA insulin aspart</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Phenol, glycerol</td>
<td>2–5 h</td>
</tr>
<tr>
<td>Apidra optiset Analogum (glulisin)</td>
<td>Analogum (glulisin)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Trometamol</td>
<td>2–5 h</td>
</tr>
<tr>
<td>Humalog Analogum (lispro)</td>
<td>Analogum (lispro)</td>
<td></td>
<td></td>
<td>×</td>
<td>Glycerol</td>
<td>2–5 h</td>
</tr>
<tr>
<td>Actraphane Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Berlinsulin H Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Huminsulin Basal for pen Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Huminsulin Profil Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Insulin B Braun Basal Human (enzymatically produced from porcine insulin)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
<td></td>
</tr>
<tr>
<td>Protaphane Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Insulin Basal Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Monotard Human</td>
<td>Human</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Methyl-4-hydroxybenzoat</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>B Insulin S</td>
<td>Porcine</td>
<td></td>
<td></td>
<td>×</td>
<td>Methyl-4-hydroxybenzoat, Aminoquinurid</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Insulin Novo Semilente MC</td>
<td>Porcine</td>
<td>×</td>
<td></td>
<td></td>
<td>Methyl-4-hydroxybenzoat</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Humalog Mix Analogum (lispro)</td>
<td>Analogum (lispro)</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol, glycerol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>NovoMix 30 Insulin aspart-protamin cristals</td>
<td>Insulin aspart-protamin cristals</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Phenol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Lentevirc</td>
<td>Insulindetemir</td>
<td>×</td>
<td></td>
<td>×</td>
<td>Phenol</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Ultratard Human</td>
<td>Human</td>
<td>×</td>
<td></td>
<td>×</td>
<td>Methyl-4-hydroxybenzoat</td>
<td>More than 24 h</td>
</tr>
<tr>
<td>Lantus</td>
<td>Analogum (glargin)</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Glycerol</td>
<td>More than 24 h</td>
</tr>
</tbody>
</table>
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, with a decrease in IgE titers as has been described before (59). 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

Insulin allergy


