

Anaphylactic shock to defibrotide

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Key words: anaphylactic shock; defibrotide; hypersensitivity.

Defibrotide, a polydeoxyribonucleotide with antithrombotic and profibrinolytic properties, was originally used in patients with chronic venous insufficiency (CVI), but was recently shown to have protective effects during cardiac arrest (1), to resolve or prevent thrombotic microangiopathy and hepatic veno-occlusive disease after allogeneic stem cell and/or bone marrow transplantation (2, 3). Finally, defibrotide was successfully used in cases of catastrophic antiphospholipid syndrome (4).

Several adverse reactions to this drug have been described: vomiting and diarrhoea, thrombophlebitis at infusion site and cutaneous reaction (5).

We present a case of reaction to defibrotide with different clinical manifestation: anaphylactic shock. We studied a 66-year-old woman who suffered from CVI and experienced anaphylactic shock (generalized urticaria, vomiting, fall in blood pressure, collapse, loss of consciousness) within 15 min after intravenous administration of the first dose (200 mg) of Prociclide® (defibrotide, Prociclide, Crinos SpA, Milan, Italy). After treatment with anti-shock therapy in the emergency department, her symptoms were considerably reduced within 2 h and completely resolved after 24 h.

Eight months earlier, she had tolerated oral defibrotide. The patient had no personal or family history of allergic disease.

Four months later she was referred to our Allergy Unit for allergologic investigation.

After obtaining informed consent, we investigated the patient and five healthy nonatopic control subjects. All these patients underwent skin test (prick and intradermal) with defibrotide diluted in

0.9% NaCl and administered at increasing concentration every 15–20 min, as previously described (6).

The patient responded positively to prick testing with defibrotide (wheal 3×10 mm) as undiluted drug (200 mg/ml) and to intradermal testing at concentration of 2 mg/ml (wheal 13×20 mm).

Control intradermal tests with defibrotide were also administered to five healthy subjects without any adverse effect.

Clinical findings and positive skin test with defibrotide imply that the patient developed type-1 hypersensitivity. To the best of our knowledge, this is the first documented case of immediate hypersensitivity to defibrotide: this shows that also drugs potentially nonallergenic as deoxyribonucleic acid derivative can induce severe allergic reaction.

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IgG₄-mediated allergic reaction to glargine insulin

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Key words: allergy; glargine; hypersensitivity; IgG₄; insulin.

Allergic reactions to recombinant and semisynthetic insulins are uncommon.

Insulin glargine is a recombinant human insulin (rhI) analogue, produced by DNA technol-

ogy. Although glargine insulin has been proposed as an alternative in cases of insulin allergy, immunoglobulin E (IgE)-mediated reactions to glargine insulin have been published (1, 2).

We report on a 35-year-old woman, who was diagnosed with type 1 diabetes at the age of 7 years. She was first treated with monocomponent insulin and then with rhI. Seven years ago she developed immediate skin reactions to rhI. The immunological study at that time demonstrated an IgE-independent mechanism (3). She started treatment with Lyspro insulin and later on with Humalog NPL® insulin (Eli Lilly, Indianapolis, IN, USA), without any adverse effects up to now. Before deciding to change to glargine insulin in order to provide a better diabetes control, a skin test with glargine insulin was performed. This skin

Allergy to glargine insulin mediated by IgG₄.

test elicited an immediate skin reaction at the site of injection. She continued on treatment with Lyspro insulin without any ill effect.

Intradermal skin tests were performed on the patient's forearm according to European Academy of Allergology and Clinical Immunology (EAACI) recommendations with commercial glargine insulin (100 IU/ml) at concentrations of 1/1, 1/10 and 1/100. Intradermal skin tests with glargine insulin showed a strong positive immediate reaction at a concentration of 1/100 and 1/10 (wheal diameter of 11 and 15 mm, respectively), without late phase reaction.

The patient's serum and the sera from eight patients treated with glargine insulin for more than 6 months without any adverse effects and from one atopic patient (control subjects) were evaluated by direct enzyme-linked immunosorbent assay (ELISA) to determine specific IgE, IgG and IgG₄ binding against glargine insulin, as previously described (4). The results were expressed in optical densities (OD). The laboratory tests revealed high titers of specific IgG and IgG₄ (ELISA) to glargine insulin (maximum OD 2.5 and 1.4 respectively) in the patient's serum. Sera from subjects treated with glargine insulin showed high titers of specific IgG in only two patients (maximum OD 1.2 and 1.4), but specific IgG₄ was not demonstrated in any of the control sera (mean OD 0.11). Specific IgE to this insulin was negative in the patient's serum and in all control subjects. Serum from the atopic subject did not demonstrate specific IgE, IgG or IgG₄ to glargine insulin.

IgG and IgG₄ immunoblotting analysis for specific binding using peroxidase-conjugated monoclonal anti-human IgG and IgG₄ (Menarini Diagnostics, Florence, Italy) to glargine, rhI and Lyspro insulin under natural and reducing conditions were performed. Immunoblotting with glargine insulin in natural condi-

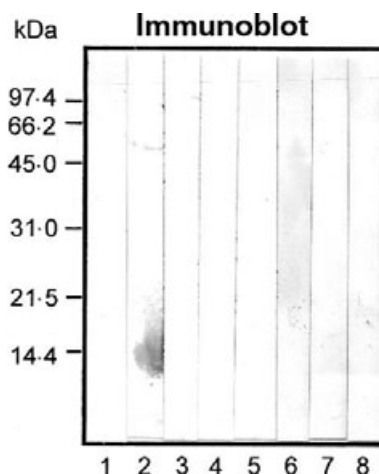


Figure 1. IgG₄ immunoblotting with insulin glargine, human insulin recombinant and Lyspro insulin. Lane 1: glargine insulin. Reducing conditions (60 µg). Lane 2: glargine insulin. Natural condition (60 µg). Lane 3: human recombinant insulin. Reducing conditions (60 µg). Lane 4: human recombinant insulin. Natural condition (60 µg). Lane 5: Lyspro insulin. Reducing conditions (60 µg). Lane 6: Lyspro insulin. Natural condition (60 µg). Lane 7: sera pool of patients treated with glargine insulin. Lane 8: atopic serum. Serum dilution 1 : 2. kDa: molecular weight markers.

tions with patient's serum, showed a unique 8 kDa band that bound IgG to glargine insulin and rhI, and IgG₄ only to glargine insulin (Fig. 1). No bands were observed when insulin was used in reducing conditions.

To the best of our knowledge, this is the first case report of an immediate local reaction to glargine insulin, probably mediated by an IgG₄ mechanism. In this case, the patient was not previously exposed to glargine insulin, but she had had a previous allergic reaction to rhI that was mediated by an IgE-independent mechanism. Specific IgG and IgG subclasses, mainly IgG₁, IgG₃ and IgG₄, antibody responses to insulin in diabetic patients may be a common finding. In most occasions it is

associated with no complications and has no adverse clinical consequences. However, in some cases it has been associated with insulin resistance or allergic reactions. IgG₄ antibodies may bind to human basophils and promote the release of histamine from sensitized cells, and therefore they may be considered as anaphylactic antibodies (5).

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