OBSERVATIONS

Immunologic Tolerance to the Insulin Analogue Glulisine

Systemic allergy to insulin is a rare but severe condition. The introduction of human insulin analogues lispro and aspart has considerably decreased the severity of a reaction to insulin (1). However, cases of an allergic reaction to these analogues have also been reported (2). We describe the case of a patient in which severe systemic allergy subsided after glulisine, the latest insulin analogue, was administered.

A 33-year-old man was referred to our hospital for the management of type 1 diabetes and insulin allergy. Previously, we showed that intravenous administration using a portable device for parenteral nutrition resolved systemic reactions in a patient due to a severe allergic reaction caused by subcutaneous insulin administration (3). In trouble with sepsis in September 2005, he has received treatment with continuous subcutaneous insulin lispro; the allergic reaction weakened to a greater extent with insulin lispro than with recombinant human insulin. However, the patient developed a local wheal and itching at the site of subcutaneous injection; administration of oral antiallergic agents and prednisolone was required, which led to poor glycemic control. To determine the efficacy of the latest insulin analogues, we recently performed skin tests for glulisine, glargine, and detemir. The results of the intracutaneous test were negative for glulisine and detemir but positive for glargine. A skin test performed earlier had shown that all forms of commercially available insulin and insulin analogues were present and solvent and additives were absent (3). In October 2009, the allergy symptoms completely subsided after insulin lispro was replaced with glulisine. Moreover, antiallergic agents and prednisolone were no longer required, and glycemic control gradually improved to reduce the dose of insulin (A1C: from 9.0% in September to 7.0% in November). Furthermore, total immunoglobulin E antibody decreased to the normal range (from 338 to 167 IU/ml; standard value <202 IU/ml).

The insulin analogue glulisine was considered suitable for treatment because a negative result was obtained in a skin test for glulisine. Subsequently, we observed that the patient was immunotolerant to glulisine. Rather than native monomers of insulin, insulin aggregates have been known to cause cutaneous allergy, and immunogenicity of insulin preparations is correlated with the concentration of aggregates (1). Furthermore, the severity of the allergic reaction depends on the rate at which insulin forms monomers and is absorbed (2). Structural changes and pharmacological kinetics of insulin analogues contribute to low immunogenicity in vivo (1). Compared with other insulin analogues, glulisine shows both low self-association and stability in monomeric and dimeric forms in solution in the absence of zinc due to amino acid replacements (4). Accordingly, as well as intravenous administration, the efficacy of subcutaneous injection of glulisine demonstrates the pathogenesis of immunological response to insulin and the importance of monomeric forms in immunological tolerance.

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