

Short Reports

Systematic Approach to Diagnosis and Management of Biphasic Insulin Allergy With Local Anti-Inflammatory Agents

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In this report, we present a patient with a rarely encountered form of biphasic insulin allergy refractory to a conventional desensitization procedure. We describe a systematic approach to this clinical problem with a set of insulin preparations containing antihistamine and/or corticosteroid to verify the type of hypersensitivity reaction and identify treatment options. The approach taken here may be of use for patients with similar conditions who require insulin for adequate diabetic management but who would otherwise be forced to discontinue insulin because of allergic reactions. *Diabetes Care* 12:421–23, 1989

immediate reactions (2). Some of these patients have been forced to discontinue insulin therapy (4). In addition to desensitization procedures, local and systemic antihistamines and corticosteroids have been used to treat insulin allergies with variable success (2,3,6). In this study, we describe a patient who presented with a combination of immediate and delayed hypersensitivity to human insulin. A systematic approach for verification and treatment of these reactions with local antihistamine and corticosteroid therapy is described.

Allergic reactions to insulin pose a difficult dilemma for the management of insulin-requiring diabetic patients. The benefits of glucose homeostasis have to be weighed against the adverse effects of the insulin allergic reaction, which may vary from a local pruritic skin eruption to life-threatening anaphylaxis (1,2). Whereas most local allergic reactions are immediate and occur within 30 min after injection, isolated cases of delayed hypersensitivity have been reported in which reactions occur 24 h after injection, sometimes with and without a preceding immediate reaction (3–5). These delayed reactions have been reported to be refractory to insulin desensitization procedures, which generally succeed in preventing the

CASE REPORT

The patient is a 65-yr-old hypertensive woman with a 10-yr history of diabetes and a history of myocardial infarction and stroke. When she first presented with symptoms of polydipsia and polyuria, she was treated with beef-pork insulin, but after she developed local pruritic skin eruptions, an oral hypoglycemic agent (glipizide) was initiated. Her diabetes was managed with glipizide for ~3 wk (before admission to the hospital) when a maximal dose of glipizide (40 mg/day) was no longer effective in controlling her diabetes, resulting in fasting blood glucose values >205 mg/dl; subsequently, insulin therapy was reinstituted. She required a morning dose of 25 U of human Novolin 70/30 (Squibb-Novo, Princeton, NJ) and an evening dose of 5

U of the same preparation to achieve good blood glucose control. However, she again developed local pruritic reactions at injection sites in response to various different human insulin preparations, including Humulin (Lilly, Indianapolis, IN) and Novolin. These reactions were most likely due to an epitope on the insulin molecule because the vehicles for both regular and NPH Humulin (provided by J. Anderson of Lilly) by themselves produced neither immediate nor delayed reactions.

The patient's allergic response to insulin was biphasic and approximately proportional to the amount of insulin injected. A typical reaction consisted of a pruritic wheal and flare at the site of injection that was most severe 30 min after injection and then subsided over the next 1–2 h, followed by a pruritic indurated and often painful lesion that was maximal at 24 h and subsided over the next few days. The patient found the delayed reaction to be more bothersome than the immediate reaction due to the persistent pain and pruritus.

She was admitted to the hospital to undergo an insulin-desensitization procedure similar to the one recommended by Lilly (2). In this procedure, increasing doses of regular human insulin were administered subcutaneously at 0.5-h intervals, starting with 1/10,000 and up to 1 U for a total of 6 h. Unfortunately, this procedure failed to prevent either the immediate or delayed reaction.

RESULTS

To verify the type of hypersensitivity reactions and use this information to design a rational treatment plan, a set of insulin-containing solutions with and without added antihistamine and corticosteroid were injected into the patient. The rationale behind the use of these agents is that the antihistamine would be expected to prevent an immediate type 1 hypersensitivity reaction by preventing local IgE-mediated histamine release, whereas the corticosteroid would prevent a delayed type 4 hypersensitivity reaction by effects that include the inhibition of cellular lymphokine production.

The patient was simultaneously given four subcutaneous injections in separate sites on her midforearms and thighs. The first site was injected with a solution of insulin (8 U NPH, 4 U Regular Humulin; Lilly) and 0.1 ml of sterile water. The second site was injected with a solution containing the same amount of insulin with 0.1 ml of sterile water containing 1 mg of diphenhydramine. The third site had the same amount of insulin with 0.1 ml of sterile water containing 1 mg of hydrocortisone, and the fourth site was injected with a solution containing only sterile water. Both subjective measurements of pruritus, from 0 to 3+, and objective measurements of the diameter of the immediate wheal and flare and the delayed induration, in centimeters, were recorded (Fig. 1).

It was found that insulin alone caused both an im-

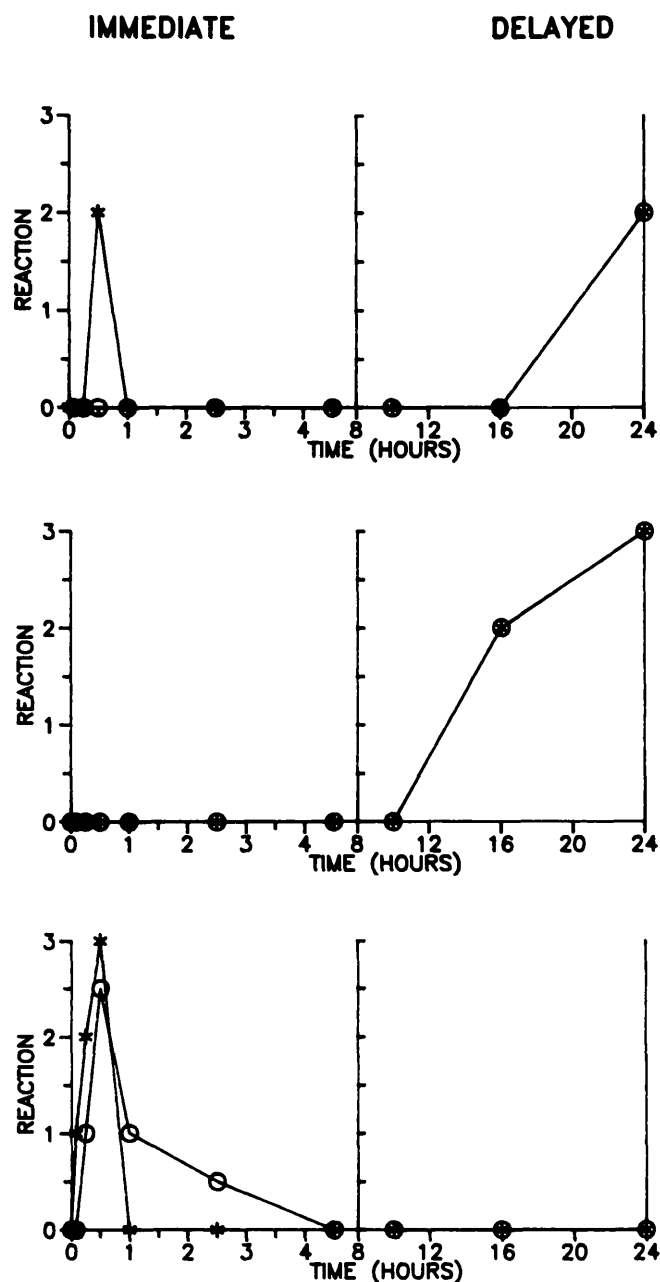


FIG. 1. Effect of diphenhydramine and hydrocortisone on immediate and delayed hypersensitivity reactions induced by insulin. The extent of the reaction is indicated by amount of pruritus from 0 to 3+ (*) and by diameter of the lesion in centimeters (○). *Top*, insulin; *middle*, insulin and diphenhydramine; *bottom*, insulin and hydrocortisone.

mediate wheal and flare reaction with pruritus and a delayed indurated pruritic reaction. The addition of diphenhydramine to the insulin entirely prevented the immediate (IgE-mediated) reaction but had no effect in reducing the delayed response. Conversely, the presence of hydrocortisone completely prevented the delayed (cell-mediated) but not the immediate reaction.

Sterile water alone induced no reaction. In a separate test performed the next day, diphenhydramine was injected into the same site as the insulin and hydrocortisone mixture. This combination prevented both immediate and delayed reactions. In conclusion, the results clearly demonstrate that our patient displayed both immediate and delayed hypersensitivity to human insulin, which could be prevented by simultaneous administration of local antihistamine and corticosteroid, respectively.

DISCUSSION

Based on these clinical observations, it was decided that optimally a mixture containing adjusted proportions of insulin, diphenhydramine, and hydrocortisone could be injected together to prevent local reactions. However, although this simple set of skin tests both defines the types of allergic reactions and suggests a mode of treatment, management of these reactions is beset by numerous complicating factors. It has been suggested that a solution of diphenhydramine and insulin is incompatible due to precipitation of insulin probably related to lowering the pH (2,6). Moreover, hydrocortisone is not stable for >3 days in aqueous solution and is even less stable when mixed with diphenhydramine (7). Thus, the patient was sent home with instructions to apply a high-potency topical corticosteroid preparation (0.05% fluocinonide) to her injection site 30 min before injection and to take terfenadine (60 mg), an oral antihistamine lacking the side effects of drowsiness characteristic of other antihistamines. Although providing considerable relief, this regimen was not completely effective, presumably because of lower local concentrations of antihistamine and corticosteroid attained at the injection site and variability in the application of the corticosteroid cream. We subsequently have been able to overcome some of these problems by the administration of a stable mixture containing insulin and dexamethasone at a concentration of 1 µg dexamethasone/1 U insulin. This preparation prevents the more disturbing delayed reaction, but systemic antihistamines are still required to minimize the immediate hypersensitivity reaction. With this treatment protocol, our patient has been able to achieve good

diabetic control on insulin, free of bothersome side effects. After 6 mo on this therapeutic program, her glycohemoglobin level was 6.6% (normal range 4–6.3%). This suggests that the addition of dexamethasone to insulin does not affect the bioavailability and efficacy of insulin.

Glucose 1 mM = 18 mg/dl

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Effect of Sucrose-Containing Snacks on Blood Glucose Control

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To determine whether ingestion of sucrose-containing snacks would affect blood glucose (BG) control, 16 subjects with insulin-dependent diabetes mellitus participated in a 5-day double-blind study at a diabetes camp. Eight subjects in the sucrose group ate sucrose-

sweetened snacks twice a day, and 8 subjects in the control group ingested snacks that were sweetened with aspartame. The percentage of total daily calories derived from added sucrose was 7% for the sucrose group and 1% for the control group. Metabolic control