

Evaluation and management of insulin allergy

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Dr. Chen: Systemic^{1,2} and local³ allergic reactions have been recognized since the early use of exogenous insulin in diabetes. Local reactions, consisting of erythema, pruritus, and induration at the injection site, are common and therefore many physicians have experience in their management. Because systemic insulin allergy is rare, many physicians have not seen a case. To clarify features of the immunologic characteristics, differential diagnosis, diagnostic procedures, and therapeutic modalities of systemic insulin allergy, three illustrative cases will be presented for discussion.

CASE PRESENTATIONS

Patient 1

Dr. Chen: A 19-yr-old white diabetic woman treated with insulin since age 5 presented with a 3 mo history of daily generalized urticaria. There was no relationship to foods or physical factors (e.g., exercise, cold). She denied the use of any drugs except insulin and had no other medical complaints. There was no hiatus in insulin therapy and no history of a local reaction at the site of insulin injection. Physical examination was normal except for the presence of urticaria over legs and trunk. Chest radiograph, complete blood count, SMA-20, erythrocyte sedimentation rate, and urinalysis were normal. A change to purified insulin had not changed her symptoms. She had a negative skin test to full-strength purified pork insulin, and a diagnosis of idiopathic urticaria was made. The patient is presently well controlled on hydroxyzine (25 mg every 6 hr) and prednisone (10 mg q.o.d.).

Patient 2

A 38-yr-old white woman with known vasculitis requiring long-term corticosteroids for control had diabetes that

had been treated for 2 mo with NPH pork insulin. Subsequently, the insulin was discontinued as the steroid requirement to control her vasculitis decreased.

Two years later her vasculitis required higher doses of prednisone for control and her diabetes returned. Without hospital admission, NPH pork insulin was reinstituted and the dose was adjusted. One month after initiation, the patient experienced a wheal and flare at the site of the injection of 60 U of insulin. This was accompanied by generalized pruritus and wheezing. On her way to the emergency room she ingested two Tedral tablets that improved her symptoms. She was admitted with a diagnosis of insulin allergy for continuation of insulin therapy under medical supervision. She was skin tested with regular pork insulin intradermally (0.0001, 0.001, and 0.01 U) with no reaction; at 0.1 U she had a 10 mm wheal and a 20 mm flare. The next day she was given one third of the dose of NPH pork insulin that had caused the adverse reaction, 20 U, without difficulty. The dose was increased by 5 U each day until the fifth day, when she received 45 U and developed a large local reaction at the injection site. Her next dose was reduced by 5 U and she tolerated 40 U without difficulty. She was discharged on this amount with good diabetic control.

Patient 3

A 53-yr-old white man who presented with polyuria, polydipsia, polyphagia, weight loss, and a fasting glucose level of 400 mg/dl was started on lente insulin. One week later the therapy was terminated by the patient because he did not like injecting himself. He remained on a diet and oral hypoglycemics for the next 7 mo. Symptoms then recurred and the patient's fasting glucose level was found to be 300 mg/dl despite diet and oral medication.

Lente insulin (30 U) was reinstituted, and 12 days after initiation of therapy the patient developed urticaria at the insulin injection site, followed by generalized urticaria and angioedema of the hands. He again stopped taking his insulin and presented to the emergency room 2 wk later with a fasting glucose level of 400 mg/dl. Because there was a 2 wk lapse in therapy after the systemic allergic reaction to insulin, insulin therapy was reinstituted with a desensitization schedule (Table I). No reactions occurred and the patient has continued to do well on 30 U of insulin each morning.

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TABLE I. Desensitization schedule

Day	Time	(min)	Route	Dose (U)
1	A.M.	0 min	Scratch	10^{-4}
		10	ID	10^{-5}
		20	SQ	10^{-4}
2	P.M.		SQ	10^{-3}
	A.M.		SQ	10^{-2}
	P.M.		SQ	10^{-1}
3	A.M.		SQ	1
	P.M.		SQ	5
4	A.M.		SQ	10
	P.M.		SQ	20
5	A.M.		SQ	30
6	A.M.		SQ	30

ID = intradermal; SQ = subcutaneous.

DISCUSSION

Dr. Grammer: Whenever a patient on insulin develops a generalized urticarial reaction like patient 1, the question of insulin allergy is likely to arise. The differential diagnosis includes the usual etiologies of generalized urticaria: other drug allergy, food allergy, physical urticaria, and systemic illnesses, including infections, malignancy, and connective tissue diseases. In addition to the usual history and physical examination in the evaluation of such patients, it is important to ascertain whether there was a local reaction at the site of the insulin injection and whether there was a hiatus in therapy, since, with rare exception,⁴ the absence of a local reaction and hiatus makes insulin allergy very unlikely. The patient with classic insulin allergy had been on insulin months or years before and the insulin had been discontinued. Upon reinstitution, the patient usually has progressively larger local reactions that culminate in a systemic reaction.⁵

Patient 1 has idiopathic adult-onset urticaria. The insulin had been incriminated by the patient's physician, but because the patient had a negative skin test to insulin, insulin allergy was easily excluded. It is important to note that 40% to 50%^{6, 7} of diabetics on insulin with no clinical evidence of systemic insulin allergy do have positive skin tests to insulin. Thus a negative skin test confirms the absence of insulin allergy but a positive skin test does not confirm the presence of systemic insulin allergy. The majority of patients on insulin for a few weeks have detectable IgE against insulin in their serum in the absence of clinical manifestations of systemic insulin allergy,⁸ and thus detection of IgE against insulin is of no diagnostic significance.

Dr. Patterson: In patients 2 and 3 the diagnosis of

TABLE II. IgE binding of ^{125} I bovine insulin by sera of patients with insulin allergy or insulin resistance and normal controls; inhibition of binding by IgE and unlabeled insulin demonstrates IgE antibody and specificity for insulin

Patient	Clinical state	Binding of 1.0 ng ^{125} I bovine insulin added to coated tubes	
		cpm Added	cpm Bound*
1	Systemic immediate reaction to insulin	53,029	11,700
2	Systemic immediate reaction to insulin	62,342	3,200
3	Systemic immediate reaction to insulin	62,676	7,030
4	Systemic immediate reaction to insulin	67,746	7,980
5	Systemic immediate reaction to insulin and immunologic insulin resistance	67,402	33,498
6	Systemic immediate reaction to insulin and immunologic insulin resistance	63,996	21,725
7	Immunologic insulin resistance	62,818	352
8	Immunologic insulin resistance	59,893	840
9	Immunologic insulin resistance	60,920	696
10	Diabetes mellitus treated with insulin; no allergy or resistance	61,654	0
11	Normal	58,982	0
12	Normal	62,983	0
13	Volunteer used for passive transfer recipient; multiple skin tests with insulin for 5 yr	58,739	44

*Corrected for total IgE concentration of serum.

insulin allergy was made on the basis of temporal relationship of insulin injection to systemic allergic symptoms, occurrence of a large local reaction, and the hiatus in therapy prior to the reaction. In each case the absolute necessity for insulin was ascertained before proceeding with the management by insulin administration.

As a preface to discussing the management of patients who require insulin and have had a systemic reaction to insulin, certain salient features of the immunology of insulin allergy should be reviewed. It is well known that insulin allergy is a classic type I

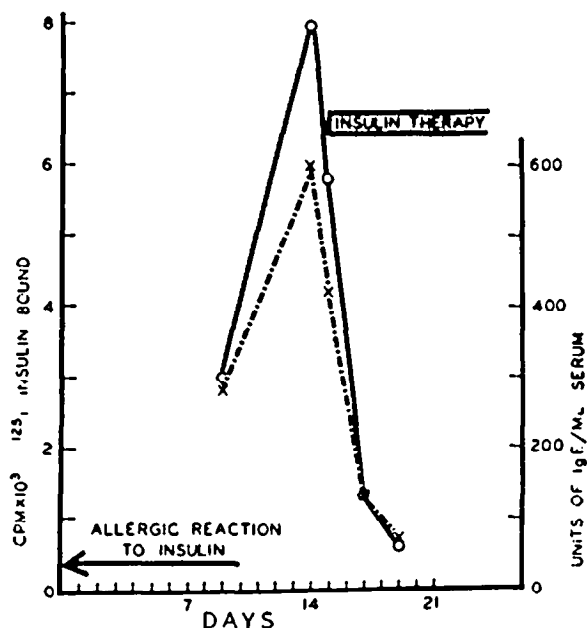


FIG. 1. Changes in serum IgE concentration and IgE anti-insulin activity in a patient after a systemic allergic reaction to insulin and rapid insulin desensitization. x, Serum IgE concentration; O, ^{125}I insulin bound by serum IgE.

IgE-mediated reaction. The allergen against which the IgE is directed is variable, although it has been clearly shown in one case to be directed against insulin that has been altered by acid alcohol extraction.⁹

The insulin molecule is comprised of two chains, A and B, intertwined in a tertiary structure. Beef insulin sequence differs from human in three amino acids, while pork differs by only one. Most standard commercial insulin sold in this country is resolved by gel chromatography to contain less than 50 ppm of impurities.¹⁰ "Purified" insulin, sometimes referred to as "monocomponent" or "single component," is standard commercial insulin that has been further refined. The Food and Drug Administration criteria for the term "purified" is that it contains less than 10 ppm of impurities.¹⁰ This is to be contrasted with earlier preparations that, before 1972, had more than 1000 ppm of impurities. Historically, it was thought that the allergenicity of insulin was most likely due to non-insulin protein contaminants and that the newer purified insulins would eliminate insulin allergy. However, the purified insulins are still immunogenic,¹¹ and more importantly, anaphylaxis has been reported to purified pork insulin.¹²

Certainly, allergenicity can be attributed to the insulin molecule itself, whose tertiary structure is altered by the acid alcohol procedure used to extract it from the pancreas. This was demonstrated in the study of a patient allergic to heterologous insulins

who was found to be reactive against human insulin extracted by acid alcohol.⁹ In another study of five patients who had systemic reactions to insulin, it was found by skin titration that beef insulin was more allergenic than pork insulin, which was more allergenic than human insulin or purified beef insulin.⁶ Thus some of the allergenicity may be contributed by heterologous insulin and by non-insulin protein contaminants.

Patients such as patient 2, who have had systemic reactions to insulin within 24 hr, can simply be given one third, or for extreme caution, one sixth of the dose that caused the reaction. In any event, the insulin should not be discontinued once it is determined that it is essential for diabetic control. These patients should be hospitalized, the risks of anaphylaxis should be explained, and there should be immediate availability of resuscitative drugs and equipment during insulin administration. Each day the insulin dose can be increased by 5 U. If, as happened with this patient, a reaction occurs, the dose is reduced to that previous dose that did not cause a reaction. Then, if necessary for control of diabetes, another attempt should be made to slowly increase the dose. In rare cases the dose cannot be increased and the patient must be treated with divided doses. The principle of management here is that the patient had a mild systemic reaction to a dose of insulin. If there is no delay in insulin administration the dose can be reduced and rapidly increased to therapeutic levels. A delay of weeks may result in a more sensitive subject due to increased IgE antibody and then desensitization is required as the safest procedure.

In the third patient, 2 wk had elapsed since the patient had taken his insulin. Thus the dose could not merely be reduced, but the patient had to be desensitized as described. There are several available desensitization schedules^{6, 13} (Table I).

In a case of suspected insulin allergy the question of in vitro tests for IgE antibody against insulin may be raised. Such tests have been established and used to demonstrate that the reaction is IgE mediated and that various immunologic changes occur during a course of desensitization. Table II shows the demonstration of IgE antibodies by a radioimmunoassay in IgE-mediated allergy. Fig. 1 shows the rise of IgE antibodies after an allergic reaction. IgE antibodies then declined during desensitization. Such an assay is of value for research purposes but is of little additional value in diagnosis over history and possibly skin testing and is so rarely necessary that it is inappropriate for most laboratories to have it set up. Finally, in cases of systemic allergic reactions where continued insulin therapy is required, the appropriate

management is reduction in dose with continued therapy, as described above. This does not permit the delay required for *in vitro* assays to be of any practical value. In summary, *in vitro* assays are neither necessary or even desirable for diagnosis and management of insulin allergy.

The choice of which insulin to use for desensitization is probably not crucial, since the patient's IgE is most likely directed against a tertiary structural alteration from acid alcohol extraction, a procedure that is common to all commercially available insulin. In general, only beef, pork, or mixed insulins are available; that is, except as a research procedure, skin testing for whale or chicken insulin is not helpful, since those insulins are not commercially available and patients thus cannot be maintained on them for long periods. One can test patients with intradermal injections of serial dilutions of various insulins and use the least allergenic, or one can use the insulin that the patient is already taking. We have successfully desensitized 28 of 28 people to various insulins. In another series, 84 of 84 patients with systemic insulin allergy were desensitized to various insulins.¹⁴ No matter which insulin is used, desensitization eventually results in a decrease in IgE against insulin in the serum,⁶ since the patient's IgE is bound by the injected insulin. In general, the mechanism of desensitization does not appear to involve IgG or blocking-antibody production. However, there have been patients with insulin allergy who have been desensitized and who have developed IgG-mediated insulin resistance.¹⁵ In an emergency situation, e.g., ketoacidosis, the desensitization can be performed intravenously at 10 min intervals rather than subcutaneously at 12 hr intervals. Besides anaphylaxis to insulin, there are several other forms of immunologic reactions to insulin that should be mentioned.

Dr. Grammer: Although not life threatening, local reactions to insulin mediated by IgE can occasionally be bothersome. In general, with reassurance and continuation of insulin, symptoms will subside. Rarely, one must resort to oral antihistamines, change to a purified insulin,¹⁴ or divide the injection over two or three sites. Occasional patients have biphasic reactions in which the early phase is IgE mediated and the later phase has some histologic characteristics of an Arthus reaction.¹⁶ Subsequently patients with biphasic reactions have been described whose biopsies are histopathologically identical to "late-phase reactions" seen with ragweed^{17, 18} and whose skin reactivity can be transferred by Prausnitz-Küstner testing.¹⁹ Management of biphasic reactions is similar to that of monophasic IgE-mediated reactions. Desensitization is not indicated for the treatment of local allergy.

Delayed skin tests of two types have been described. A patient may develop erythema and induration 4 to 6 hr after insulin injection. The reaction peak is 12 hr and the histologic appearance is that of an Arthus reaction.¹⁹ Finally, patients may develop reactions compatible with type IV delayed hypersensitivity at 12 to 24 hr. This has been described in patients receiving zinc insulin,²⁰ and the reactions have been alleviated by change to insulin that does not contain zinc. Delayed hypersensitivity has also been described in which changing to zinc-free insulin was not helpful in ameliorating the reaction.¹⁹

There are also rare patients in whom serum sickness has been reported from insulin.²¹ These patients also had insulin resistance mediated by IgG directed against insulin. Insulin-IgG-anti-insulin complexes were demonstrated in the serum. Both symptoms and insulin requirement decreased with steroid therapy. Patients may, of course, have insulin resistance alone that is mediated by IgG against insulin, without serum sickness.

Dr. Patterson: In general, IgE-mediated immediate-type anaphylaxis is the most significant allergic problem associated with insulin. It can be handled by a temporary dose reduction if the lapse in therapy is short or by insulin desensitization if the lapse is long. Local IgE-mediated reactions are more common but generally subside spontaneously and thus do not create significant clinical problems. Insulin resistance with or without serum sickness, both mediated by IgG to insulin, are exceedingly rare and respond to prednisone therapy.

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