Managing Generalised Insulin Hypersensitivity*

Yam Cheng Chee, M.B., B.S., M.Med., M.R.C.P.

SUMMARY **A 35-year-old woman with non-insulin-dependent diabetes mellitus from the age of 10 eventually required insulin to control her condition. At first she was given protamine zinc insulin and soluble insulin only during pregnancy. After subsequent exposures to available insulins (Novo regular insulin, zinc insulin and monocomponent insulin of beef and pork origin), she developed generalised allergic reactions. Finally, her condition could be controlled only with the use of recently available human insulin which gave negative skin-prick tests.**

These results suggest the use of skin-prick test with the insulin solutions for immunological evaluation where the determination of IgE antibody is not readily available, as in Singapore.

ASIAN PACIFIC J ALLERG IMMUN 1984; 2 : 113-115.

Generalised allergic reactions to insulin were recognised soon after its introduction into medicine. Because insulin is generally a foreign protein, it is no surprise that it can induce the same manifestations of hypersensitivity as other antigens. Allergy to insulin is a disturbing and not uncommon complication of diabetes treatment. The reported frequency of local cutaneous reactions range from 14 to 55.8 per cent.[1] These reactions, which may be quite painful, consist of erythema, induration, pruritus and occasional wheal formation at the injection site. The local reaction usually occurs early in the course of insulin therapy and usually disappears with continued insulin administration due to automatic desensitisation. However, they may persist and be a harbinger of a systemic reaction. In one of the largest series of patients with systemic reactions to insulin, 14 of 15 patients had clinically apparent local reactions preceding the systemic outburst.[2]

Systemic reactions to insulin are rare. Their importance, however, lies not in their frequency but in the fact that they may be a serious obstacle to the proper treatment of diabetes when insulin administration becomes essential. Antibodies to insulin have been demonstrated in all immunoglobulin classes except IgD; IgG antibodies seemingly relate to insulin resistance, and IgE antibodies to insulin allergy.[3,4]

This report details the management of a case of familial diabetes mellitus, non-insulin dependent type, who after 26 years on oral hypoglycaemic therapy required insulin for proper control of her disease. Administration of insulin resulted in a Type I anaphylactic reaction.

CASE REPORT

A 35-year-old Chinese woman, with diabetic parents and a diabetic sister, herself developed non-ketotic diabetes mellitus at the age of 10 years, which was stabilised on oral chlorpropamide and later tolbutamide. There was no personal or family history of atopic diseases. She delivered a baby girl at the age of 18 and a baby boy at 22. Five years later she was pregnant again, and was put on protamine zinc insulin 74 units and soluble insulin 8 units daily. Delivery was by lower Caesarian section. Thereafter she continued on oral glibenclamide and metformin.

In 1982, at the age of 35, she entered the hospital because of chronic cervicitis with menorrhagia; her diabetes was found to be uncontrolled (a random blood sugar was 358 mg/dl). Physically she was well built (weight 64 kg) with blood pressure of 130/80 torr and no abnormal signs. Chest radiograph and electrocardiogram were normal. Blood urea nitrogen and serum electrolytes were within normal limits. Urine sugar ranged from orange to yellow colour on testing with Benedict's solution and blood sugar from 275 to 312 mg/dl while on a restricted diabetic diet. Tolbuta-

*From the Department of Medicine III, Tan Tock Seng Hospital, Moulmein Road, Singapore 1130.

mide with metformin were given without adequate control. She was then given 16 units of insulin zinc suspension (IZS) lente subcutaneously and promptly developed generalised urticaria and a choking sensation which subsided with parenteral antihistamine. She was next changed to subcutaneous injection with 4 units of monocomponent soluble insulin (neutral porcine-Actrapid, Novo) which immediately gave her numbness of fingers, flushing of face and chest, epigastric pain, diarrhoea and generalised urticaria typical of anaphylactic reaction. She responded to parenteral adrenaline and promethazine.

Knowing of her hypersensitivity (IgE-type) to both bovine and porcine insulin, as determined by skin-prick tests, and that she was not insulin-dependent, a variety of available oral hypoglycaemic drugs, i.e., glicazide, glibenclamide and glibournuride plus metformin, were tried in succession on an outpatient basis. She was finally stabilised on chlorpropamide 500 mg and metformin 3 g daily; her lowest blood sugar level was 185 mg/dl. Desensitisation to insulin was offered but the patient was very fearful of insulin injections.

In February 1983, she was rehospitalised due to an infected ovarian cyst. Pre-operative blood sugar (while on oral hypoglycaemics) ranged between 132 mg and 246 mg/dl without ketosis. She recovered uneventfully and her diabetes was stable.

In October 1983, her diabetes became worse again (urine sugar on Benedict's testing was consistently orange and blood sugars were around 370 mg/dl). At this time human insulin was obtainable, and the patient was then put on Humulin S (Eli Lilly), 4 and then 8 units subcutaneously thrice daily, after skin testing yielded negative results. She was also maintained on oral chlorpropamide 250 mg once and metformin 500 mg thrice daily. With this regimen, blood sugar levels came down satisfactorily. In January 1984, the injections were replaced by Monotard HM 20 units daily without untoward effects.

Skin testing with insulins

Both a delayed-type hypersensitivity and an immediate-type hypersensitivity to insulin have been described.[4,5] These reactions are rare and have been reported even with monocomponent insulins[6] and highly purified porcine insulins.[7] In order not to risk another anaphylactic experience, the patient consented to have skin-prick tests carried out on her. This was done by a universal method as previously reported.[8] Instead of using Bencard manufactured allergens, one drop each of various locally available insulin solutions was used together with a positive control solution of histamine, and normal saline as negative control. By this method, wheal development within 15-20 minutes implies a type I IgE mediated allergy, and oedema at the prick site 4-6 hours after the prick suggests a type III IgG-mediated allergy. No intracutaneous testing was done with these insulin solutions.

Skin-prick testing was carried out on four occasions. In April 1982 the patient was determined to be non-atopic by skin-prick tests but showed wheals at 15 minutes to bovine soluble insulin (SI) 80 units per ml (Novo), bovine insulin zinc suspension (IZS) lente 80 units per ml (Novo) and monocomponent porcine soluble insulin 80 units per ml (Actrapid, Novo). In November 1982, the above three solutions gave even larger wheals and monocomponent porcine IZS 80 units per ml (Novo) was also positive (Table 1). In December 1983, she was tested with Humulin S, which gave no wheal at 15 minutes. Finally, in January 1984, she exhibited no wheal with Monotard™ HM 100 units per ml (Novo). There was no reaction at 4-6 hours on any test.

DISCUSSION

Insulins are commercially obtained from bovine and porcine pancreas although very recently new semi-synthetic human insulins and recombinant human insulins have become available. Biologically prepared insulins are not pure chemical substances but contain three not easily separable components comprising: (a) natural material of high molecular weight; (b) proinsulin and intermediates; and (c) insulins, arginine insulin, ethyl ester of insulin and desaminoinsulin. It was therefore only to be expected that component (a) caused most of the allergic problems of insulin use. Conventional or regular insulins contain bovine 52 per cent and porcine insulin 48 per cent and these are combined with zinc compounds (IZS) or complexed with proteins e.g. protamine (PZI) to prolong their action. Human and porcine insulins are identical except for substitution of one amino acid of the B chain whereas beef insulin differs

Table 1 Positive wheals to bovine and porcine insulins on skin-prick tests

Insulin tested	Wheal sizes* April 1982	Nov. 1982
Bovine SI		
Bovine IZS		
Porcine monocomponent Actrapid SI		
Porcine monocomponent IZS	not tested	

*Half of actual sizes

from human insulin in three amino acid positions. Of the various animal species used routinely for therapeutic purposes, porcine insulin is probably the least antigenic but with combined bovine and porcine insulins in commercial preparations, there is a significant response in most patients. Mixtures of bovine and porcine insulins may have greater antigenicity than either alone.[9] Reaginic antibody activity against bovine and porcine protein has been shown in about half of a group of patients who had positive skin tests to the insulin they were receiving but no clinical evidence of insulin allergy.[4]

The patient reported in this study received both PZI and SI eight years previously and it is likely that antigenic stimulation was provided by the combined bovine and porcine insulin, the protamine, the zinc[10] or other protein contaminants. After a lapse of eight years she was given insulin again of bovine and porcine origin and she developed systemic reactions. In the largest series of five cases of systemic reactions to insulin,[4] there had been a discontinuation of previous insulin injections in all cases, resulting in a lapse of insulin therapy. The authors of this study stated that, *"Therefore the danger of anaphylaxis must always be considered whenever insulin therapy is resumed, even after a prolonged period with no treatment."* Nowadays, there are many patients on short-term insulin who may subsequently require insulin again, for example pregnant diabetics and diabetics undergoing major surgery, and they are at risk of insulin anaphylaxis.

The case reported by Leslie[6] had a strong family history of allergy and was herself allergic to penicillin, salmon and trout. Another case gave a history of hay fever.[7] On the other hand, the patient in this report was not atopic. It is of note that in none of the recent case reports was eosinophilia found.[6,11] Patients with generalised insulin allergy have high concentrations of insulin-specific IgE which is independent of total IgE and insulin-specific IgG.[12] It was not possible to measure total or specific IgE in the present patient. She had raised IgE level to bovine and porcine insulins, as indicated by large wheals by skin-prick test.[13]

To assess specific IgE to various antigens including insulin, the skin-prick test is a good, reliable and cheap alternative to radioimmunoassay. Intracutaneous testing with insulin solutions used to be the choice method to detect allergy *in vivo*[4,6,7,10], but skin-prick testing is more reliable.[14] The second prick test showed larger wheals than the first done seven months previously, suggesting an exacerbation of the allergy, which indicates that skin testing is not without risk.

Purification of insulins by chromatography and ion exchange have given rise to newer brands of purer insulins such as monocomponent and single-peak types. Thus, newer types and brands of insulin may solve the allergy problem. Even then, "highly purified" porcine monospecies insulin is not a pure chemical entity of insulin. The case reported here had IgE antibodies to these "purer" preparations, but luckily for her, she was not allergic to human insulin, although this too has been reported.[11]

Humulin S (Eli Lilly) is a recombinant short-acting human insulin. Because the long-acting counterpart is not available in Singapore, Monotard HM (Novo) has been used instead. The confidence to use these insulins was based on negative skin-prick tests. Had these been positive in the present case, an alternative was to desensitise her to one of the more freely available monocomponent porcine insulins. The practice of continuing insulins under protection with an antihistamine and dexamethasone was considered to be too risky.

REFERENCES

1. Lamkin N, Lieberman P, Hashimoto K, Morohashi M, Sullivan P. Allergic reactions to insulin. J Allergy Clin Immunol 1976; 58:213-23.
2. Mattson JR, Patterson R, Roberts M. Insulin therapy in patients with systemic insulin allergy. Arch Intern Med 1975; 135: 818-21.
3. deShazo RD. Insulin allergy and insulin resistance. Postgrad Med 1978; 63:85-92.
4. Lieberman P, Patterson R, Metz R, Lucena G. Allergic reactions to insulin. JAMA 1971; 215:1106-12.
5. Goldstein HH. In: Joslin's Diabetes mellitus. Philadelphia: Lea & Febiger, 1971: 701.
6. Leslie D. Generalised allergic reaction to monocomponent insulin. Br Med J 1977; 2:736-7.
7. Reisner C, Moul DJ, Cudworth AG. Generalised urticaria precipitated by change to highly purified porcine insulin. Br Med J 1978; 2:56.
8. Chee YC. Skin-prick tests for atopy in asthmatic adults in Singapore. Asean J Clin Sci 1982; 3:259-64.
9. Kurtz AB, Nabarro JDN. Circulating insulin-binding antibodies. Diabetologia 1980; 19:329-34.
10. Feinglos MM, Jegasothy BV. "Insulin allergy" due to zinc. Lancet 1979; 1:122-4.
11. Wiles PG, Guy R, Watkins SM, Reeves WG. Allergy to purified bovine, porcine and human insulins. Br Med J 1983; 287:531.
12. Falhort K. Determination of insulin specific IgE in serum of diabetic patients by solid phase radioimmunoassay. Diabetologia 1982; 22:254-7.
13. Steinus W, Wilde L, Seymour WM, Holford-Stevens V, Pepys J. Clinical significance of specific IgE to common allergens. Clin Allergy 1971; 1:37-55.
14. Pepys J. Laboratory methods in clinical allergy. Proc Roy Soc Med 1972; 65:271-4.