Use of Sheep Insulin in Insulin Allergy

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SUMMARY

A case of mild diabetic ketoacidosis and severe allergy to beef-pork NPH insulin is described. Intradermal tests using insulin derived from various species led to the successful use of sheep insulin. DIABETES *20*:774-75, November, 1971.

The pathogenesis of allergy to insulin is still unclear. In 1966, Devlin et al. reported evidence of antibody involvement in cutaneous allergy to insulin but, paradoxically, they were unable to identify that antibody as being of the reaginic or skin sensitizing type.[1] Nevertheless, intradermal testing with insulin preparations obtained from various species has proven helpful in the management of insulin allergy.[2] In this connection it is useful to be aware that all commercially available insulin preparations are derived from beef pancreas, pork pancreas or both. All Squibb insulins, all insulins formerly manufactured by Merck, Sharp and Dohme, all Eli Lilly insulins labeled SPECIAL and Eli Lilly Semilente and Ultralente insulins are derived from beef pancreas exclusively, whereas all other insulins that are commercially available in the United States are derived from both beef and pork pancreases. In addition, the Eli Lilly Company makes commercially available crystalline pork insulin, pork NPH and pork Lente insulins.

It is the present purpose to describe a patient with mild diabetic ketoacidosis and severe allergy to beef-pork insulin in whom intradermal testing gave information which led to the successful use of sheep insulin.

METHODS

Direct intradermal tests were performed by injecting 0.05 ml. of each test substance intradermally into the upper back. The injected sites were examined at 15, 30, and 60 min. for the development of erythema, induration and pseudopods. The results were graded as follows:

0—No erythema and/or induration, or erythema and/or induration at 15 min. but none at 30 min.
1+—Induration of less than 1 cm. without pseudopods or erythema.
2+—Induration greater than 1 cm. without pseudopods but with erythema of less than 2 cm.
3+—Induration greater than 1 cm. without pseudopods but with erythema greater than 2 cm.
4+—Induration greater than 1 cm. with pseudopods and erythema greater than 2 cm.

Dilutions of insulin were prepared in 0.9 per cent saline so that 0.05 ml. contained 0.001 U.

Passive transfer tests [Prausnitz-Kuestner (PK)] were performed by injecting 0.1 ml. quantities of sterile serum from the allergic patient intradermally into the upper back of his apparently healthy wife. Forty-eight hours later the sites were challenged by intradermal tests as described above.

CASE REPORT

D. H., a forty-three-year-old salesman, was admitted to the hospital on September 9, 1969, because of generalized urticaria and uncontrolled diabetes mellitus.

In 1964, the patient had experienced generalized urticaria following a penicillin injection. He was then well until August, 1969, when excessive thirst, excessive urination and a 10-lb. weight loss led to the diagnosis of diabetes mellitus. Initially, treatment was given with a diet of 2000 calories plus 40 U. of NPH insulin daily, but after six weeks the apparent requirement for insulin decreased to only 6 U. per day. Long-acting phenformin, 50 mg. twice daily, was then substituted for insulin but the symptoms of uncontrolled diabetes recurred and, on August 30, 1969, phenformin was discontinued and treatment was reinstated with 40 U. of NPH insulin daily. Five days later, generalized urticaria developed and worsened each day despite treatment with diphenhydramine HCl.

On admission to the hospital, the physical examination was normal except for severe generalized urticaria and numerous excoriations. The hemoglobin was 13.9 gm./100 ml. and the WBC 7,800 per mm.^{3} of which 60 per cent were mature polymorphonuclear leukocytes, 13 per cent stab forms, 21

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per cent lymphocytes, 4 per cent eosinophils and 2 per cent basophils. The urinalysis was unremarkable except for the presence of 5 per cent glucose and a trace of albumin. The blood sugar was 450 and the BUN 24 mg./100 ml. respectively. The serum sodium was 133, potassium 5.1, chloride 97 and CO_2 21 mEq./L. respectively.

NPH insulin was discontinued and an attempt was made to control the diabetes with a very restricted diet of only 1200 calories plus a combination of 100 mg. of long-acting phenformin and 500 mg. chlorpropamide daily. The urticaria promptly subsided but the diabetes steadily worsened. Forty-eight hours later, the blood sugar was 480 mg./100 ml. and the CO_2 was 18 mEq./L.; ketones were present in the plasma in small amount and in the urine in large amount. Intradermal sensitivity tests were then performed with 0.9 per cent saline, and crystalline sheep, beef, pork and dealaninated pork insulins.* The reaction to beef, pork and dealaninated pork insulins was 4+ whereas that to saline and to sheep insulin was negative. Accordingly, treatment was initiated with crystalline sheep insulin and during the ensuing twelve hours a total of 200 U. was administered subcutaneously. Ketosis and glycosuria cleared and urticaria did not recur. Thereafter, the diet was liberalized to 2000 calories and 10 U. of sheep insulin was administered subcutaneously before breakfast, 20 U. before lunch and 15 U. before supper, each day. On this regimen the urine remained essentially sugar free and daily late afternoon serum sugar values were 216, 163, 80, 106 and 46 mg./100 ml. respectively.

Passive transfer (PK) tests were performed with serum obtained from the patient thirty-six hours after the first injection of sheep insulin. The patient's apparently healthy wife served as recipient and was given direct intradermal tests as well. The direct intradermal tests with saline, sheep, beef, pork and dealaninated pork insulins and the indirect test with saline were negative but the PK tests with sheep, beef, pork and dealaninated pork insulins, after injection of the patient's serum, were all 3+ or 4+. The direct intradermal tests were then repeated in the patient on the fifth day of treatment with sheep insulin, and at that time the tests with sheep, beef, pork and dealaninated pork insulins were all 4+.

One week later, because of the short supply of sheep insulin, crystalline pork insulin was cautiously substituted without the patient's knowledge. At first no adverse reaction was noted, but a few days later mild pruritus developed at each injection site. This minor reaction was avoidable by administering the pork insulin intramuscularly via 22-gauge needles. A month later, crystalline beef insulin and then beef Lente insulin were substituted and were also well tolerated except for the local pruritus that was avoidable by intramuscular injection. Finally, pork Lente insulin was given subcutaneously and this has been well tolerated during twelve months of follow-up.

In January, 1970, while the patient was taking pork Lente insulin, intradermal tests were made with normal saline, beef, sheep, pork, dealaninated pork, pork proinsulin, pork single component (molecular weight 6,000) and human insulins. The reaction to saline was $\mp$ but that to each of the other materials was 3+ or 4+.

*Sheep insulin is presently not available commercially in the U.S.A.

DISCUSSION

Several confusing findings of the present case merit discussion. First, the PK tests performed with serum obtained from the patient after only thirty-six hours of treatment with sheep insulin gave an unexpected strongly positive reaction to sheep insulin, suggesting that antibody to sheep insulin had already developed during that very short time. The subsequent demonstration in the patient of a strongly positive direct reaction to sheep insulin supported that conclusion although, strangely, sheep insulin was being well tolerated subcutaneously at the same time. A possible explanation for this paradox might be that the skin sensitizing antibodies which presumably were demonstrated by the direct intradermal and the PK tests are not the same as, and do not necessarily even indicate the presence of, those antibodies which cause generalized hypersensitivity. Remission of allergy, which occurred in this case, is also confusing but it has been reported previously.[2] Analogous remissions have also been observed in insulin-resistant diabetes wherein a lessening of insulin requirement followed a short period during which insulin was withdrawn and treatment was given with intravenous fluids and electrolytes only.[5] Finally, the significance of the positive intradermal reactions to human insulin, pork single component insulin and pork proinsulin is unknown.

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