Case report

Chronic urticaria secondary to insulin allergy

Report of a case treated with a portable subcutaneous insulin infusion pump

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Although insulin allergy is usually limited, this patient had an 8-year history of urticaria, which resolved after the subcutaneous infusion of insulin.

Case report

A 47-year-old machinist had a 12-year history of diabetes mellitus. After an unsuccessful trial of chlorpropamide, Neutral Protamine Hagedorn (NPH) insulin was used for the first time in 1970. Six months later pruritus developed, which transiently improved with the use of beef lente insulin. In 1975 a single injection of oxytetracycline (Terramycin) precipitated generalized urticaria, and concomitant insulin allergy was suspected. Trials of various single peak, single component, zinc-free insulin and insulin densensitization in combination with hydroxyzine hydrochloride (Atarax) and diphenhydramine hydrochloride (Benadryl) provided temporary relief.* Thorough studies at the Cleveland Clinic and the National Institutes of Health did not reveal another cause.

Pertinent medical history included severe childhood asthma that resolved when the patient was an adult. Vitiligo, which had been present for several years, was also noted. In 1978 primary hypothyroidism was diagnosed and treated with 0.15 mg of L-thyroxine.

In February 1979 the patient was hospitalized for repeat desensitization to alleviate disabling urticaria. In-

* *Single peak, single component, zinc-free insulin, and desensitization kits were made available through the courtesy of Dr. John A. Galloway of the Eli Lilly Company, Indianapolis, Indiana.*

sulin was withdrawn, and the patient was placed on a regimen of tolbutamide, bicarbonate supplement, and a 300-calorie protein formula diet to prolong the insulin-free period. Allergic symptoms quickly abated, but 4 days later the serum glucose value was 220 to 285 mg/dl with associated ketonuria and a plasma bicarbonate of 12 mEq/dl. Under careful supervision, desensitization was successfully performed with the use of repeated small doses of single peak pork regular insulin. While the patient was receiving 2 units every 2 hours, hives developed, which ceased with hourly injections. At the time of discharge, the patient was asymptomatic while receiving insulin injections every 4 hours.

When symptoms recurred one week later, the subcutaneous infusion of insulin was considered to maintain the desensitized state. A portable open loop battery-operated infusion pump was devised* that could deliver 0.2 to 0.5 cc/24 hr (*Figure*). Pulse therapy could be added to the basal infusion as desired. A 25-gauge butterfly needle that could be reinserted subcutaneously daily was attached to the connector tubing.

The patient was hospitalized again in August 1979 and prepared for desensitization in a similar manner. Three days after insulin had been withdrawn, the initial intradermal injection of 0.001 unit of single peak pork regular insulin produced a wheal and flare response. Single component pork regular insulin was obtained. Subsequently, repeated intradermal injections of 0.001 unit and 0.002 unit produced a slight wheal. With careful supervision the patient received 0.001, 0.002, 0.004, 0.01, 0.02, 0.04, 0.1, 0.2, and then 0.5 units of insulin every 30 minutes without further allergic symptoms. Insulin was then infused subcutaneously at 20 units/24 hr. Since the postprandial blood glucose values ranged from 200 to 280 mg/dl, pulse therapy of 5 units was administered before meals. When the insulin precipitated pruritus, the basal infusion rate was adjusted to 40 units/24 hr. Three weeks after discharge, the patient was asymptomatic with fasting and noon serum glucose levels of 65 and 104 mg/dl, respectively.

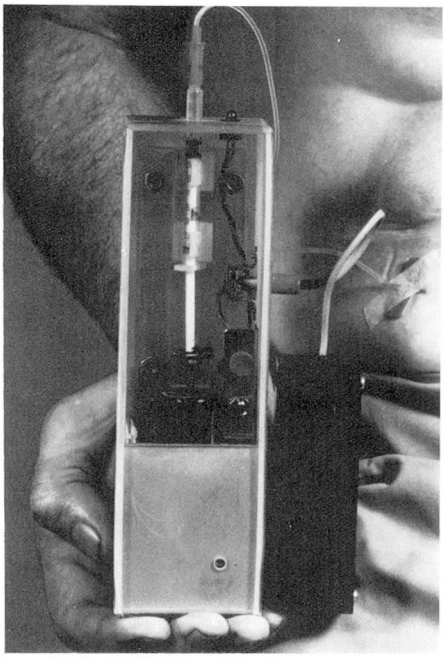

Figure. Portable open loop battery-operated infusion pump.

Discussion

Insulin allergy, usually manifested by mild erythema, induration and pruritus at the injection site, frequently abates with continued insulin administration.[1–3] Occasionally, severe focal reactions or systemic reactions including anaphylaxis may occur.[2, 4–6] Impurities, insulin additives or insulin itself may generate the allergic response.

With improved insulin purification, fewer adverse reactions develop. Before 1974 U.S.P. insulin preparations were 92% pure. With the use of a molecular sieve, 98% to 99% pure single peak insulin may be identified by gel chromatography.[7] Further purification by DEAE ion exchange chromatography produces greater than 99% pure single

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* *The infusion pump was devised by Ronald W. Sukalac and Setsuo Takatani, Department of Artificial Organs.*

component insulin.[7] Davidson et al[8] reported 70% improvement of the local allergic response when single peak or single component pork insulin was used. However, small amounts of impurities, including proinsulin, insulin dimers, and monodesamido insulin, remain in single component insulin and may contribute to antigenicity.[9]

Insulin-containing additives, including protamine, zinc, and globin have an associated higher incidence of hypersensitivity reactions.[3, 10-12] Although protamine alone is a weak antigen, protamine-bound insulin may potentiate insulin allergy.[12, 13] Chronic urticaria precipitated by isophane beef insulin has been described.[12] Urticaria resolved after single peak beef lente insulin was administered. Local allergy secondary to insulin-containing zinc has also been reported.[11] In this instance, the use of zinc-free neutral regular insulin eliminated the local reaction. Regular insulin without additive proteins has a lower incidence of allergic symptoms.[10]

Since single component pork regular insulin has generated generalized urticaria and anaphylactoid reactions, the insulin molecule alone may generate the allergic response.[14, 15] Our case is not unlike those previously reported. Definite local reactions to human insulin have also been described.[8] The amino acid difference that exists among bovine, porcine, and human insulin may initiate the immune response. Patterson et al[16] reported that human and commercial insulins extracted by acid alcohol appear to have an altered antigenic structure that may also produce an allergic phenomenon.

In our patient, persistent urticaria resolved with subcutaneous insulin infusion. Previous reports have shown that continuous intravenous or subcutaneous infusion of insulin effectively and safely controls diabetes.[17-20] Although pulse dose supplements before meals improve the control of diabetes physiologically, our patient experienced pruritus from the insulin bolus. However, diabetes remained controlled by adjusting the basal infusion rate. The efficacy of continuous infusion devices in preventing long-term microvascular complications is presently unknown. Our case presents another use for a continuous infusion pump.

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