abscesses. Anaerobic and aerobic bacteriology and outpatient management. Ann. Intern. Med. 1977; 87:145–49.

# Use of Low-Dose Continuous Corticosteroid Infusion to Facilitate Insulin Pump Use in Local Insulin Hypersensitivity

Hypersensitivity reactions may occur at the site of insulin injection and can cause painful local reactions, which complicate insulin therapy.[1] Furthermore, hypersensitivity reactions to insulin continue to be reported despite the use of highly purified animal and human insulins.[2] We report the results of investigation and management of a patient who had persistent local reactions at the sites of insulin injection with either intermittent or continuous subcutaneous insulin infusion (CSII) therapy. The patient's local reactions to insulin disappeared when low doses of corticosteroid were mixed with insulin administered by CSII.

The patient is a 16-yr-old women who had type I diabetes mellitus diagnosed 6 yr before our evaluation. She was first placed on lente beef-pork insulin without complication but began to have frequent hospitalization for diabetic ketoacidosis at 14 yr of age. She was started on twice daily subcutaneous injections of Iletin II purified pork regular and NPH insulins, but continued to have unstable diabetes mellitus. Her control improved for ~6 mo with CSII of Iletin II purified pork regular insulin administered by an insulin pump (Autosyringe 6C, Travenol, Deerfield, Illinois). She objected to continued use of the insulin pump and was placed on multiple daily subcutaneous injections of Iletin II purified pork regular and NPH insulins, and later on beef-pork ultralente and regular insulins. After requiring five hospitalizations for diabetic ketoacidosis in a 7-mo period, she was again placed on CSII, using Lilly Humulin regular insulin. After ~1 mo on this routine, she began to develop reactions at the insulin infusion site. Observation of skin test sites injected with single doses of insulin revealed that persistent induration resulted from the fact that the dermal reactions were "biphasic" in type. That is, wheal-and-flare (hive) reactions developed at the site of CSII within 15 min, peaked during the ensuing 15 min and decreased in size without complete resolution over the remaining 1–2 h. During the 2- to 6-h period after insulin injection, the site again became erythematous and pruritic and induration gradually developed. Reactions appeared fully developed by 6 h, at which time they were circumscribed, intensely pruritic, edematous, and painful to touch. These reactions frequently persisted for up to 24 h. *Staphylococcus aureus* was not cultured from the needle site used for CSII. Actrapid human insulin (Squibb-Novo, Princeton, NJ) was substituted for the Lilly preparation, but reactions still occurred. Reactions became progressively larger and more painful with continued insulin therapy. Attempts to block these local reactions with oral antihistamine therapy were unsuccessful. Also, changing the needle from the usual stainless steel needle to a plastic catheter failed to affect the size of the reaction. Reactions were especially large at the site of needle placement when it was left in place for >24 h. Further evaluation was initiated at that time.

The patient was skin tested with a battery of 14 insulin preparations using 0.02 ml of a 50-U/ml insulin solution prepared from U 100 insulin by diluting insulin with equal volumes of buffered phenol saline.[1] Appropriate control skin tests with phenol saline and histamine (1 mg/ml) were performed. Skin tests were positive at 20 min for all insulins tested, including zinc-free insulins, protamine-free insulins, and human insulins. No reactivity to zinc acetate or to the insulin diluents was noted. Reaction sites were observed at 6 h with local induration present at all insulin skin test sites. Insulin-specific IgE was measured (courtesy of Dr. Phillip Fireman) using a radioallergoabsorbent test.[2] Results were expressed in RAST units calculated as percentage counts bound to total counts. Insulin-specific antibodies of the IgE class were detectable to beef (6.5 U/ml), pork (5.4 U/ml), and human (5.5 U/ml) insulins. Values for IgE-anti-insulin in nondiabetic individuals average <4 U/ml and those for insulin-requiring diabetic individuals without reactions average <5 U/ml in this system. Insulin-specific IgG was measured using $^{125}$I-labeled insulin in an insulin-antibody binding assay where results are reported as percent binding,[3] and was detectable in the two regular insulins tested: beef (24.7%) and pork (16.5%). Control values for nondiabetic individuals are <3% binding in this system.

Since previous reports have suggested that incorporation of small amounts of corticosteroids into insulin preparations are useful in patients with local insulin reactions who are receiving intermittent insulin therapy,[4,5] 0.22 mg methylprednisolone was added to each 5 U of human insulin placed in the pump (0.04 mg methylprednisolone/1 U insulin). The addition of this preparation resulted in immediate and complete resolution of the dermal reactions previously noted. Subsequently, lower doses of methylprednisolone (0.02 mg methylprednisolone/1 U insulin) were found to be equally effective. After several months, corticosteroid was gradually discontinued and reactions did not recur.

Two types of local reactions have been reported in patients on continuous insulin infusion—local hypersensitivity reactions and cutaneous abscesses associated with *Staphylococcus aureus* infection at the needle site.[6] The latter reactions are characterized by a pustule and on occasion may require incision, drainage, and antibiotic therapy. Four types of local hypersensitivity reactions to insulin have been reported.[1] These include immediate wheal-and-flare reactions, biphasic reactions with a wheal and flare followed by a late reaction at 6–12 h, and delayed hypersensitivity reactions and Arthus reactions. The timing and appearance of the reactions that occurred in this patient were biphasic-type insulin reactions, the more common type of dermal hypersensitivity to insulin.[1] In general, biphasic reactions appear to be decreased in size by oral antihistamine therapy, although in our experience

doses of antihistamine required to suppress these reactions are frequently associated with sedation.[7] We and others[8] have suggested simultaneous injection of small amounts of corticosteroids with insulin in patients experiencing these reactions, and recent reports have found this useful in treating reactions to the human insulins administered by intermittent injection.[8]

The mechanism by which corticosteroid therapy blocked the local reactions in our patient is unclear. It is impossible to rule out the possibility that immunologic insulin "desensitization" occurred, but it is improbable that it would have occurred simultaneously with the administration of corticosteroid. In this regard, previous reports (summarized in ref. 9) have demonstrated that late-phase reactions may be blocked by corticosteroid treatment. Use of corticosteroids in small doses mixed with insulin appears to facilitate insulin therapy in patients with local hypersensitivity to human insulin.

This study was supported in part by an Institutional Research Grant from the Squibb-Novo Company, Princeton, New Jersey.

WILLIAM GRANT, M.D.
RICHARD D. DESHAZO, M.D.
JOHNNETTE FRENTZ, M.D.

**From the Departments of Medicine and Pediatrics and the Herbert F. Harvey Laboratory, Tulane University School of Medicine, New Orleans, Louisiana 70112.**

**Address reprint requests to Richard D. deShazo, M.D., Departments of Medicine and Pediatrics, Tulane University School of Medicine, 1700 Perdido Street, New Orleans, Louisiana 70112.**

REFERENCES

[1] deShazo, R. D., Boehm, T. M., Kumar, O., Galloway, J. A., and Dvorak, H. F.: Dermal hypersensitivity reactions to insulin: correlations of three patterns to their histopathology. J. Allergy Clin. Immunol. 1982; 66:229–37.

[2] Fireman, P., Fineberg, S. E., and Galloway, J. A.: Development of IgE antibodies to human (recombinant DNA), porcine, and bovine insulins in diabetic subjects. Diabetes Care 1982; 5:119–25.

[3] Skom, J. H., and Talmage, D. W.: The role of nonprecipitating insulin antibodies in diabetes. J. Clin. Invest. 1958; 37:787–93.

[4] Pyke, D. A., and Watkins, P. J.: Allergy to purified bovine, porcine, and human insulins. Br. J. Med. 1983; 287:531.

[5] Watkins, P. J.: Generalized allergic reaction with synthetic human insulin. Lancet 1982; 2:1287.

[6] Pietri, A., and Reskin, P.: Cutaneous complications of chronic continuous subcutaneous insulin infusion therapy. Diabetes Care 1981; 4:624–26.

[7] Galloway, J. A., and deShazo, R. D.: The clinical use of insulin and complications of insulin therapy. *In* Diabetes Mellitus. Ellenburg, E., Ed. New Hyde Park, NY, Year Book, 1983:591.

[8] Wiles, P. G., Guy, R., Watkins, S. M., and Reeves, W. G.: Allergy to purified bovine porcine and human insulins. Br. Med. J. 1983; 287:531.

[9] deShazo, R. D., Levinson, A. I., and Dvorak, H. F.: The late phase skin reaction: paradigm or epiphenoma. Ann. Allergy 1983; 51:166–77.

# A Precision Index for Evaluation of Techniques for Self-Monitoring of Blood Glucose

Diabetic patients must maintain a delicate equilibrium between diet, exercise, and hypoglycemic medication to control blood glucose homeostasis. Until a practical glucose sensor is developed, self-monitoring of blood glucose (SMBG) provides the essential feedback for day-to-day therapeutic adjustments.[1–5] Most of the SMBG methods are relatively accurate provided the technique is carefully respected.[6–8] The patients use these self-generated data to make critical decisions such as insulin dose adjustments. Therefore, it is important to perform a quality control of the individual patient's technique. For that purpose, blood should be sampled for laboratory analysis at the time the patient performs his SMBG technique and this should be repeated many times. Most of these patients are outpatients, and therefore it is difficult to obtain more than 5–12 corresponding values for an individual patient. The coefficient of correlation, currently used in the evaluation of SMBG methods, may be an inadequate tool to assess individual patient reliability.

Recently, we made a quality control assessment of the SMBG techniques of 18 randomly selected type I or type II diabetic patients. These patients measured capillary blood glucose with visual reading strips for periods varying from 2 wk to a few months. We made no attempt to improve their technique. Their SMBG results were compared with laboratory glucose (G) measurements made on filter paper blood spot[9,10] sampled at home at the corresponding time (Table 1).

A case-by-case analysis indicated that neither the coefficient of correlation nor the mean of the differences were good indexes to achieve our goal. Indeed, a good correlation depends partially on a good dispersion of the values from the low range to the high range. In individual case studies, the 5–12 corresponding values available were not always dispersed, particularly in well-controlled patients whose values ranged from 70 to 120 mg/dl. Some well-controlled patients had very small (G − SMBG) differences but a poor correlation due to lack of dispersion (patient 8: $r = .451$, difference = −22.3 mg/dl; patient 11: $r = .104$, difference = 9.2 mg/dl). Inversely, some patients with good correlations ($r > .80$) owing to a good dispersion had significant (G − SMBG) differences (for example, patient 4: $r = .912$, difference = −63.9 mg/dl; patient 6: $r = .823$, difference = −62.3 mg/dl). Moreover, a difference of 30 mg/dl does not have the same significance at 100 mg/dl and at 300 mg/dl levels.

Thus, to evaluate the quality of the SMBG technique with respect to G, we derived the following precision index, $PI = 1 - [\Sigma(|G - SMBG|/G)]/N$, which represents the extent to which the SMBG technique deviates (in absolute values) from the linear regression G = SMBG going through