Comparison of Plasma Insulin Profiles After Subcutaneous Administration of Insulin by Jet Spray and Conventional Needle Injection in Patients With Insulin-Dependent Diabetes Mellitus

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The characteristics of plasma free insulin profiles after conventional subcutaneous injection of regular insulin (10 units) and after jet injection of this amount of insulin were compared in eight subjects with insulin-dependent diabetes mellitus. Although administration of insulin with the jet injector resulted in peak plasma free insulin concentrations (45 ± 4 μU/ml) similar to those achieved after conventional injection (47 ± 5 μU/ml), it produced more rapid increases in plasma free insulin concentrations (time to peak concentration, 76 ± 11 minutes versus 152 ± 16 minutes; $P<0.01$) and less prolonged hyperinsulinemia. Variability in the peak insulin concentrations and the time to peak concentration was comparable for both methods of administration of insulin. Thus, insulin administered by jet injector may improve control of postprandial hyperglycemia and diminish the risk for late hypoglycemia in some patients with insulin-requiring diabetes mellitus treated with conventional injections of insulin.

Currently, attempts to lessen the frequency and severity of the long-term complications of diabetes mellitus rely predominantly on the maintenance of near normoglycemia in patients with this disorder.[1] Such optimization of glycemic control is generally thought to be most readily achieved either by use of subcutaneous infusion pumps, which deliver premeal boluses of insulin supplemented by a basal insulin infusion, or by administration of preprandial subcutaneous injections of regular insulin along with a single daily injection of an intermediate (NPH or lente) or a long-acting insulin (for example, protamine zinc or ultralente) to provide intraprandial and overnight requirements, respectively.[2-4]

These two methods of administration of insulin produce almost identical plasma insulin profiles[2,5] that, compared with prandial profiles of endogenous insulin in nondiabetic persons, increase less rapidly and remain elevated longer.[2,6,7] In addition to variability in the absorption of subcutaneously administered insulin,[7] this slow increase in plasma insulin concentration and the subsequent prolonged hyperinsulinemia not only make it difficult to prevent excessive postprandial hyperglycemia but may also predispose patients to the development of late hypoglycemia.[6]

Recently, it has been shown that earlier preprandial administration of insulin can at least partially overcome these limitations.[7] Because the rate of subcutaneous insulin absorption increases as the surface area to which the insulin is exposed increases,[8] we wondered whether subcutaneous administration of insulin as a spray with use of a jet injector, similar to devices used for mass inoculations in the military, would result in a more rapid increase in plasma insulin concentration. The current studies were therefore undertaken to compare the characteristics of plasma insulin profiles achieved by this mode of administration of insulin and those achieved after needle injections of insulin.

MATERIAL AND METHODS

Informed written consent was obtained from eight insulin-dependent diabetic subjects (seven women and one man) whose ages ranged from 20 to 48 years (mean

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age, 32 ± 9 years). In these patients, the duration of disease ranged from 3 to 45 years (mean, 21 ± 8 years). Four patients had C-peptide deficiency substantiated by the glucagon stimulation test;[9] the other four were presumed to be C-peptide deficient on the basis of the duration of their diabetes, the age of the patients at the onset of diabetes, or a history of diabetic ketoacidosis. All subjects were apparently healthy and were within 15% of their ideal body weight. None had lipodystrophy in the abdomen, and their insulin requirements were stable throughout the course of the study.

Each subject was studied on six different mornings in the outpatient section of the Clinical Study Unit at the Mayo Clinic. Their long-acting insulin (NPH or lente) had been withheld for 24 to 48 hours; the dose of short-acting insulin (regular or semilente) for the previous day had been reduced and was given a minimum of 12 to 24 hours before the morning of the study. On three occasions, each subject was given a 10-unit injection of regular insulin (U-100 Actrapid, Novo) subcutaneously on the left side of the abdomen with use of a B-D Lo-Dose syringe (Becton, Dickinson and Company, Rutherford, NJ). The same physician administered each injection. On three additional occasions, the same amount of regular insulin was administered in the same area with use of the Medi-Jector (Derata Corporation, Minneapolis, MN), a spring-powered insulin jet spray device. One of two persons at our institution expert in the use of the device administered each injection. For each subject, the appropriate depth of injection was determined on the initial visit by up to four saline test injections. Too shallow a depth of injection was indicated by blistering of the skin or appearance of blood or fluid at the injection site; too deep a depth of injection (that is, intramuscular) was indicated by elicitation of pain at the time of injection.

On the morning of each study, an 18-gauge plastic catheter was placed in a forearm vein for withdrawal of blood specimens. Samples for determination of plasma free insulin were obtained 30 minutes before and at the time of the insulin administration and thereafter at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, and 300 minutes. The subjects remained seated during the entire study. Samples for plasma glucose determination (glucose oxidase, Yellow Springs Instrument glucose analyzer, Yellow Springs, OH) were withdrawn before and intermittently after administration of insulin so that steps could be taken to prevent hypoglycemia. The subjects drank 237 ml (8 oz) of fruit juice at the beginning of the study and any time thereafter when either symptoms of hypoglycemia occurred or a plasma glucose concentration of less than 80 mg/dl was encountered.

Blood for determination of free insulin concentration was collected in 3 ml of tripotassium ethylenediaminetetraacetic acid in tubes (Vacutainer, Becton, Dickinson and Company) to which 0.3 ml of benzamidine had been added. The tubes were placed in ice until the end of the study, at which time the plasma was separated and frozen at −20°C until assayed. Plasma free immunoreactive insulin was measured after polyethylene glycol extraction by radioimmunoassay.[10] The data in the text and the figure are given as means ± SEM and were evaluated by using analysis of variance corrected for repeated measurements or paired *t* tests.[11]

RESULTS

Mean plasma free insulin concentrations for the three occasions on which insulin was administered by jet injector or needle were calculated for each patient (Fig. 1). Baseline insulin concentrations were not significantly different before jet injection (12 ± 2 μU/ml) and needle injection (13 ± 2 μU/ml) of insulin. Between 10 and 60 minutes after administration of insulin, however, plasma free insulin values were greater ($P<0.05$) after jet injection than after needle administration. Although plasma free insulin concentrations between 75 and 150 minutes after injection were not significantly different with the two modes of administration of insulin, subsequent concentrations were less after jet injector administration of insulin than after needle administration ($P<0.05$).

Neither total areas under the curve for plasma free insulin concentrations (6.5 ± 0.7 mU/ml·300 minutes after jet injection versus 6.9 ± 0.8 mU/ml·300 minutes after needle administration) nor the magnitude of peak plasma free insulin values differed significantly after jet injector administration (45 ± 4 μU/ml) and needle administration (47 ± 5 μU/ml). Nevertheless, peak concentrations occurred significantly earlier after jet injector administration than after needle administration of insulin (76 ± 11 minutes versus 152 ± 16 minutes, respectively, $P<0.01$).

To assess the reproducibility of the plasma free insulin levels resulting from jet injector- and needle-administered insulin, we determined the coefficient of variations for the peak free insulin concentration and the time to peak concentration for the three times each subject had been administered insulin by these methods. For peak plasma free insulin concentrations, the coefficients of variation were almost identical (15 ± 2% versus 14 ± 3% for jet injector and needle, respectively). The coefficient of variation for time to peak concentration was significantly greater ($P<0.05$) for the jet injection (36 ± 6%) than for the needle administration of insulin (23 ± 4%). Because the time to peak concentration was twice

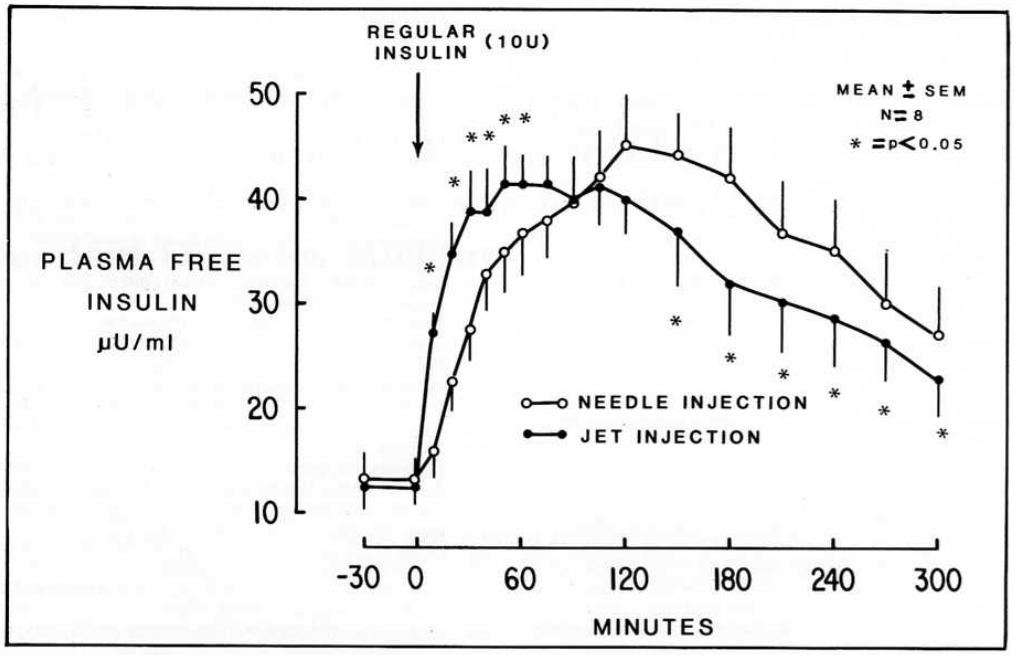

Fig. 1. Plasma free insulin concentrations after conventional subcutaneous needle injection of insulin and after subcutaneous jet injection of insulin in eight subjects with insulin-dependent diabetes mellitus.

as great for needle-administered insulin, however, the actual variations in minutes (27 for the jet injector and 32 for the needle) were comparable.

Administration of insulin by the jet injector was well tolerated; some patients remarked that they could not tell when the insulin was given.

DISCUSSION

The current study demonstrates that administration of insulin with use of a jet injector to patients with insulin-dependent diabetes mellitus produces more rapid and less prolonged increases in plasma free insulin concentrations than does conventional subcutaneous injection of insulin. Similar results have recently been reported by Taylor and associates,[12] but these investigators did not compare the reproducibility of plasma insulin profiles achieved with each mode of administration of insulin. Our data confirm that considerable variability is found in absorption of regular insulin after subcutaneous injection[8] but indicate that comparable variability results when insulin is administered by jet injector.

Although postprandial hyperglycemia was not directly assessed in the current study, one would expect on the basis of previous studies[7] that the earlier increase in plasma free insulin concentrations achieved by using the jet injector should result in less postprandial hyperglycemia than would the same amount of insulin administered by subcutaneous injection. Furthermore, the lower late plasma free insulin levels that occur after jet injection of insulin should diminish the likelihood of late hypoglycemia, to which some patients who undergo intensified insulin therapy are predisposed.[13,14] Indeed, a recent preliminary report indicated that patients given jet spray-delivered insulin preprandially had superior glycemic control compared with patients who received twice-daily subcutaneous injections of mixtures of regular and intermediate-acting insulin and concluded that jet spray-administered insulin was "effective, painless, and convenient."[15] Furthermore, multiple daily jet injections of insulin have recently been shown to produce glycemic control comparable to that achieved by using an insulin infusion pump.[16]

Thus, administration of insulin with a jet injector may be considered as a useful alternative to subcutaneous needle injection of insulin or pump administration of insulin in patients who prefer not to use these modes of insulin delivery or in whom these methods do not produce satisfactory glycemic control.

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