Comparison of Insulin Levels After Injection by Jet Stream and Disposable Insulin Syringe

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Intermediate-acting biosynthetic human (NPH) insulin was administered by disposable insulin syringe into the right upper thigh of nine insulin-dependent diabetic youths. Seven days later, the same amount and type of NPH insulin was given in the same anatomic site with a Medi-Jector II, which delivers insulin as a jet stream. Blood was collected before insulin injection and at hourly intervals subsequently for the measurement of glucose and insulin. The total serum insulin measured before the first morning dose with the needle and syringe and the Medi-Jector II was 41.2 ± 10.7 μU/ml and 46.2 ± 10.7 μU/ml, respectively. During the next 9 h, the areas under the respective total insulin curves were not different, but the area under the free-insulin curve after jet injection was greater than the free-insulin area after needle injection ($P < .01$). The ratio of free/total serum insulin was 0.31 ± 0.02 after needle injection and 0.40 ± 0.03 after jet injection ($P < .0025$). The peak of total insulin concentration occurred 4.2 h after jet injection of NPH: 1 h earlier than the peak after needle injection. The plasma glucose at time zero was 197 ± 15 mg/dl before needle injection and 242 ± 19 mg/dl before jet injection. Although the diet consumed by each subject on the 2nd study day was identical to that of the 1st day, the mean glucose increase was greater after needle-injected insulin than after jet-spray injection. This indicates that the greater amount of free insulin observed after jet-injected insulin had a direct effect in lowering the plasma glucose. Jet injection may reduce insulin requirements by increasing the availability of free insulin. DIABETES CARE 1986; 9:637–40.

Efforts to help patients with insulin-dependent diabetes mellitus (IDDM) attain near-normal blood glucose levels have focused on different methods of insulin delivery.[1,2] One method currently receiving attention is jet injection of insulin. This procedure forces insulin through a fine nozzle at high pressure, producing a microjet stream that penetrates the skin with a minimum of pain for the patient. Two previous studies report insulin levels after jet-stream injection of regular unmodified insulin.[3,4] Free-insulin levels seem to increase faster after jet injection compared with needle injection, but peak levels were not different. This suggests more rapid absorption of jet-injected regular insulin but provides no information about the influence of jet injection on a protein-bound insulin such as NPH. Enough users of insulin jet injectors [e.g., Medi-Jector (Derata, Minneapolis, MN)] have reported a reduction in insulin requirements that the manufacturer has included a "caution" note in the operating procedure manual that is included with the instrument.[5] If NPH insulin (10-μm crystals) is forced under high pressure through a 0.163-mm nozzle, there is a possibility of physical modification of the NPH insulin that may affect its action. We therefore performed this study to evaluate the influence of jet injection on the absorption of NPH insulin.

METHODS

Nine IDDM children (6 boys, 3 girls) aged 13.5 ± 0.74 yr (range, 10.6–16.0 yr) with clinical diabetes for 2.8 ± 0.6 yr (range, 1.2–6.5 yr) agreed to participate in a study to compare insulin levels achieved after needle injection with a disposable insulin syringe with levels occurring after jet-spray injection with a Medi-Jector II. Stimulated C-peptide response after 8 oz of Sustacal (Mead Johnson, Evansville, IN) was <0.1 pmol/ml in each case. The usual insulin program followed at home by each of the subjects was NPH insulin (Humulin, Lily, Indianapolis, IN) given twice each day. This form of insulin had been used for at least 4 mo before the study by each subject. The dose of 0.52 ± 0.06 U/kg (0.32–0.78 U/kg) and type of insulin administered on each study day were identical to that used routinely. The study was explained to the children and their parents in compliance with the protocol approved by the institutional Review Board of the University of South Florida. The morning of each study day, blood was collected after a 12-h fast and before insulin administration as well as at hourly intervals after insulin injection for the measurement of plasma glucose and free and total insulin. The insulin (NPH Humulin) was carefully administered into the right upper thigh the 1st day with a low-dose disposable insulin syringe, and the same dose was administered 7 days later in the same anatomic site with the Medi-Jector II. Each dose was measured and the injection given by one investigator (J.I.M.) to ensure consistency of technique. Each individual then ate his or her usual breakfast and 4 h later ate lunch. An identical diet was consumed 1 wk later. The participants played sedentary board games during the study, which limited the influence of physical activity on plasma glucose and insulin levels. All results are presented as the mean ± SE. The significance of differences between the two groups was determined by the paired *t* test.[6] Analysis of covariance was used to compare the rate of increase of free insulin from time zero until the 4th h after needle and jet injection,[7] as well as the rate of decrease in concentration from the 5th to the 9th h of the study. Plasma was prepared immediately on sample collection and frozen at −20°C. The plasmas from both studies were maintained at −20°C until the day (8 days after each study) that insulin antibodies were removed with 25% (wt/vol) polyethyleneglycol. The antibodies were removed by the addition of 25% polyethylene glycol (1:1, vol/vol) after incubating the plasma at 37°C for 2 h to approximate the in vivo free-insulin level.[8] Total insulin was measured after acid hydrolysis as previously described.[9] Insulin levels were measured in each sample during the same assay. Glucose was measured in plasma with glucose oxidase with a Beckman glucose analyzer (Fullerton, CA).

During the first 9-h study after the needle injection of insulin, the children and families were taught the use of the Medi-Jector II. At the conclusion of the first study they were instructed to give the same insulin dose by jet injection daily for the next week. They returned 1 wk later to repeat the study with the Medi-Jector II.

RESULTS

Total insulin levels were compared in the same subjects before needle and jet injection and there were no differences (needle injection = 41.2 ± 10.7 μU/ml, jet injection = 46.2 ± 10.7 μU/ml). Total insulin levels after injection were as follows. Peak minus basal levels: needle injection = 54.3 ± 12.2 μU/ml, jet injection = 51.0 ± 9.6 μU/ml; time to peak levels: needle injection = 5.2 ± 0.9 h, jet injection = 4.2 ± 0.4 h; and area under the total insulin curve: needle injection = 261.5 ± 70.1 $\mu U \cdot h^{-1} \cdot ml^{-1}$, jet injection = 238.3 ± 47.5 $\mu U \cdot h^{-1} \cdot ml^{-1}$ (Table 1).

In contrast, several differences were noted in free-insulin concentrations. Although basal free-insulin levels were lower before jet injection, the peak minus basal levels were higher after jet injection (Table 1, Fig. 1). The area under the free-insulin curve was 97.2 ± 24.0 $\mu U \cdot h^{-1} \cdot ml^{-1}$ after needle injection and 194.0 ± 29.5 $\mu U \cdot h^{-1} \cdot ml^{-1}$ after jet injection ($P < .01$). Although the peak level of total insulin occurred ~1 h earlier after jet injection, the mean time to peak free-insulin level after both needle and jet injection was nearly identical.

The mean rate of increase of free insulin from basal levels to peak level was 3.5 ± 1.0 $\mu U \cdot ml^{-1} \cdot h^{-1}$ after needle injection and 8.1 ± 1.4 $\mu U \cdot ml^{-1} \cdot h^{-1}$ after jet injection ($P < .001$). Free insulin disappeared from plasma at a rate of 4.3 ± 1.0 $\mu U \cdot ml^{-1} \cdot h^{-1}$ after jet injection and 1.6 ± 0.9 $\mu U \cdot ml^{-1} \cdot h^{-1}$ after needle injection ($P <$ .001) (Fig. 1*B*). The mean free-insulin to total-insulin ratio after jet injection (0.40 ± 0.03) was greater than the ratio after needle injection (0.31 ± 0.03) ($P < .003$). Because ratios are usually distributed binomially, arcsine transformation was applied to the free- to total-insulin ratios to obtain a normal distribution.[10] There was a significant difference between the transformed area under the curve for needle injection (1.59 ± 0.66 h) and jet injection (4.23 ± 0.79 h), indicating the greater availability of free insulin ($P < .05$).

The biologic effect of free insulin was assessed by comparing changes in free- and total-insulin levels with the change in plasma glucose during the next hour. A negative correlation was noted between the change in free-insulin concentration and the change in the glucose concentration during the next hour ($r = -.42$; $P < .0001$); no correlation

TABLE 1
Total and free insulin after needle and Medi-Jector insulin administration

	Needle	Jet	*P*
Total insulin			
Time to peak (h)	5.2 ± 0.9	4.2 ± 0.4	NS
Basal (μU/ml)	41.2 ± 10.7	46.2 ± 10.7	NS
Peak minus basal (μU/ml)	54.3 ± 12.2	51.0 ± 9.6	NS
Area under curve ($\mu U \cdot h^{-1} \cdot ml^{-1}$)	261.5 ± 70.1	238.3 ± 47.5	NS
Free insulin			
Time to peak (h)	4.3 ± 0.8	4.2 ± 0.4	NS
Basal (μU/ml)	5.3 ± 1.6	2.9 ± 1.1	NS
Peak minus basal (μU/ml)	18.5 ± 3.5	33.7 ± 5.5	<.02
Area under curve ($\mu U \cdot h^{-1} \cdot ml^{-1}$)	97.2 ± 24.0	194.0 ± 29.5	<.01
Rate of increase (0–4 h)	3.5 ± 1.0	8.1 ± 1.4	<.001
Rate of decrease (5–10 h)	−1.6 ± 0.9	−4.3 ± 1.0	<.001
Free/total insulin (transformed area under curve)	1.59 ± 0.66	4.23 ± 0.79	<.05
Glucose			
Basal (mg/dl)	197.1 ± 15.3	241.8 ± 18.9	<.05
Basal minus nadir (mg/dl)	24.9 ± 23.0	108.3 ± 19.7	<.02

Values are means ± SE.

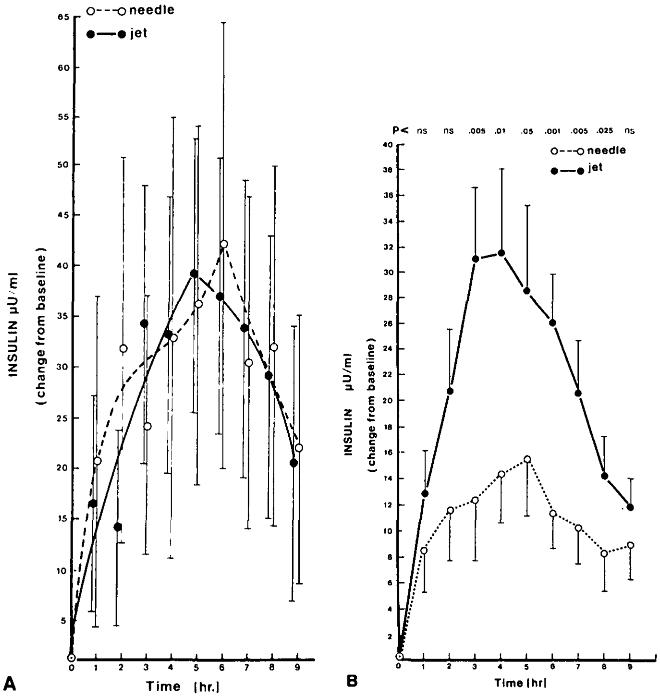

FIG. 1. Total- and free-insulin levels. *A*: change in total-insulin levels from baseline at time 0. P < NS. *B*: change in free-insulin levels from baseline at time 0.

was found between total insulin and glucose levels. Although the food consumed on each study day was identical, the level of plasma glucose was depressed more at each time point after jet injection of insulin, suggesting that the increased levels of free insulin had a direct biologic effect (Fig. 2).

DISCUSSION

The total insulin delivered by jet spray and its time of distribution in the serum were no different from those that occurred after needle injection. This indicates that jet injection does not disrupt the physical composition of NPH insulin. The mean peak level of total insulin occurred 1 h earlier after jet injection than after needle injection, but this apparent difference was not statistically significant. The method of delivery, however, did influence the quantity of unbound (free) insulin. A greater proportion of free insulin was noted after jet injection (Fig. 1). This indicates that less insulin was antibody bound. We cannot explain the reduced binding of insulin after jet injection. Insulin polymers have been shown to be a potent stimulus to insulin-antibody production.[11] We speculate that the wide dispersion of insulin in the subcutaneous fat after jet injection[12] may reduce the tendency for self-aggregation reported to occur when insulin is concentrated in the subcutaneous fat after needle injection.[13] Pehling and Gerich[3] as well as Taylor et al.[4] did not observe any difference between the areas under the curve or the peak free-insulin levels achieved after needle or jet injection of regular unmodified insulin. Total-insulin levels were not measured by these investigators, therefore an appropriate comparison of their results with ours is not possible. Moreover, those investigators evaluated insulin levels after jet injections that were isolated events preceded by routine daily injections with a needle and syringe. The fact that those previous reports[3,4] found nearly identical free-insulin levels after both needle and jet injection may indicate that jet-spray dispersion of insulin is not sufficient by itself to reduce antibody binding. The reduced insulin binding, observed in our study, may be secondary to reduced antibody production in response to a decline in insulin aggregates during the 7 days of jet-spray insulin delivery preceding the study day.

The greater availability of free insulin was not a measurement artifact because its increased presence was accompanied by greater reductions of blood glucose levels at each point measured. The disappearance of free insulin, however, appeared to be greater after jet injection. It was noted after 1 wk of NPH insulin administration with the Medi-Jector II that free-insulin levels were lower (2.9 ± 1.1 vs. 5.3 ± 1.6 µU/ml) and the plasma glucose levels higher ($P < .05$) 14–15 h after jet-injected insulin. This occurred even though the free-insulin levels 3–8 h after jet injection were higher

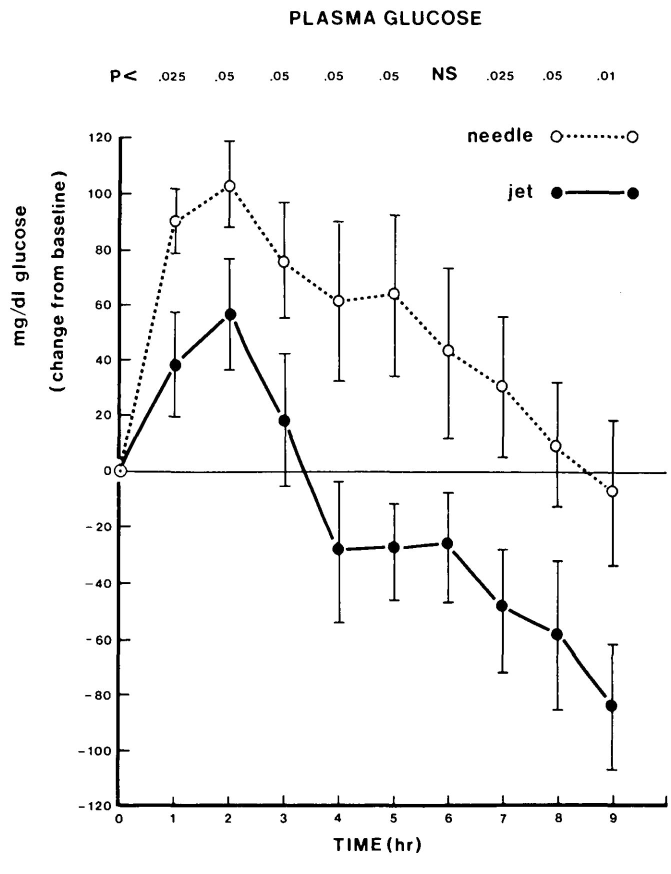

FIG. 2. Change in plasma glucose from baseline (which was before insulin) and breakfast at time 0. Lunch was eaten at hour 4, which altered rate of decline in plasma glucose.

than the free-insulin levels after syringe injection (Fig. 1B); the more rapid disappearance of free insulin noted during the 9 h after jet injection seems to explain this observation. This indicates that the greater concentrations of free insulin results in a shortened duration of action for insulin delivered by jet spray.

In summary, the total insulin absorbed after injection by the Medi-Jector II is identical to that absorbed when the same dose is delivered by syringe and needle (Table 1). The initial increase of circulating insulin is not modified by jet injection of NPH insulin, but more free insulin is available, which has a greater effect in lowering plasma glucose. The larger quantity of free insulin seems to disappear more quickly, which results in reduced duration of insulin effect. The more rapid disappearance of free insulin may cause a deterioration in metabolic control 12–14 h after jet-spray injection of NPH insulin. These observations must be remembered when changing a patient from needle to jet injection of insulin with the Medi-Jector II because more frequent smaller insulin doses may be required.

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