Brief Communications

Plasma Free Insulin Profiles After Administration of Insulin by Jet and Conventional Syringe Injection

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Plasma free insulin profiles in insulin-dependent diabetic subjects were compared after jet and syringe injection of insulin. Jet injection of insulin resulted in a shift of the free insulin profile to the left. Thus higher plasma free insulin levels were found over the first 30 min after injection ($P < 0.05$), while after 240 min plasma free insulin levels were lower than those seen following syringe injection ($P < 0.05$). Significant differences in the response of blood glucose and 3-hydroxybutyrate levels reflected the differances in plasma free insulin levels. Jet administration results in more rapid absorption of insulin and could be useful in providing a more physiologic postprandial insulin profile than that seen after conventional injection. DIABETES CARE 4: 377–379, MAY–JUNE 1981.

Adequate control of the postprandial rise in blood glucose has proved difficult to attain using intermittent subcutaneous injections of insulin.[1] Continuous intravenous infusion of insulin can diminish the magnitude and duration of this rise by allowing a sharp increase in the rate of insulin infusion when blood glucose levels tend to rise.[2,3] Continuous intravenous infusion of insulin is not practical for the routine management of diabetes mellitus and hence an alternative method of achieving a rapid rise in plasma insulin at meal times is required.

The Med-E-Jet injector gun (Med-E-Jet Corp, Cleveland, Ohio) causes insulin to be deposited subcutaneously in a dispersed fashion,[4] and may result in altered insulin pharmacokinetics.[5] The present study was undertaken to determine the plasma free insulin profile after jet injection and to compare it with the profile after conventional syringe injection of insulin.

MATERIALS AND METHODS

Five insulin-dependent diabetic subjects aged 21–47 yr gave informed consent to participate in the study. Details of sex, body weight, duration of diabetes, and usual insulin regimen are given in Table 1.

Each subject was studied on two consecutive days. In order to ensure that fasting plasma insulin levels were minimal, short-acting insulin only was given on the evening before each test day. Insulin was administered by jet injection on one day and by syringe injection on the other in random order. The dose of insulin was the same on both days for each individual and was determined by the individual's usual insulin requirements (mean dose administered 16.4 U, range 12–20 U). The fasting subjects reported at 0730 h and an indwelling catheter (Abbocath, Abbots Medical Ltd.) was sited in a forearm vein. At 0800 h a single dose of short-acting insulin (Actrapid, Novo, or soluble, Wellcome) was given subcutaneously into the midpoint of the anterior surface of the thigh. The same doctor administered all insulin injections. Breakfast was provided at 15 min, a snack at 135 min, and lunch at 255 min after the injection, each individual receiving his or her normal diet. Blood samples were withdrawn at 15-min intervals from 0745 to 1100 h and at 30-min intervals until 1400 h. The patients remained seated throughout each study.

The Med-E-Jet injector gun was used for jet injection of insulin. This device is powered by compressed carbon dioxide and delivers a fine stream of insulin at high velocity which penetrates the skin.

Blood glucose and 3-hydroxybutyrate were assayed by standard fluorimetric techniques.[6] Plasma free insulin was measured after extraction with polyethylene glycol.[7] Analysis of data was carried out using Student's paired *t* test. Results are stated as mean ± SE.

RESULTS

Fasting plasma free insulin levels before administration of insulin were similar on the two days (Figure 1). After jet injection, free insulin levels rose by 6.1 ± 1.6 mU/L at 15 min and by 9.5 ± 0.4 mU/L at 30 min. These levels were signifi-

TABLE 1
Characteristics of the five insulin-dependent diabetic subjects studied

Subject	Sex	Age (yr)	Ideal body weight (%)	Duration of diabetes (yr)	Normal insulin therapy (U/day)
1	F	41	111	25	Actrapid/Retard 32
2	F	28	103	17	Actrapid/Retard 50
3	M	47	105	24	Soluble/Isophane 48
4	F	29	102	1	Actrapid/Retard 42
5	M	21	85	14	Actrapid/Retard 120

cantly different ($P < 0.05$) from those observed after syringe injection, when the respective rises were 0.8 ± 0.8 mU/L and 4.7 ± 1.5 mU/L.

By 60 min after injection the methods gave similar free insulin levels, but peak levels were achieved earlier after jet injection (135 min) than after syringe injection (165 min) ($P < 0.05$). From 240 to 360 min after injection free insulin levels were higher after syringe injection ($P < 0.05$).

The changes in blood glucose are shown in Figure 2. There was a significant rise in blood glucose over the 90 min following syringe injection, but jet injection controlled the postprandial increase with no change in blood glucose over the same period. This difference was significant ($P < 0.05$). The early effect was reversed by midmorning, mean blood glucose from 150 to 240 min after jet injection being significantly higher ($P < 0.05$). This trend continued after lunch ($P < 0.05$).

3-Hydroxybutyrate levels were suppressed more rapidly ($P < 0.05$) after jet injection of insulin (Figure 2). This was not merely a function of higher starting levels, as 3-hydroxybutyrate levels after jet injection continued their more rapid decline even when the absolute values fell below those seen between 30 and 45 min after syringe injection. Although 3-hydroxybutyrate levels in the 90–150-min period were lower ($P < 0.05$) after jet compared with syringe injection, concentrations were not significantly different after 150 min.

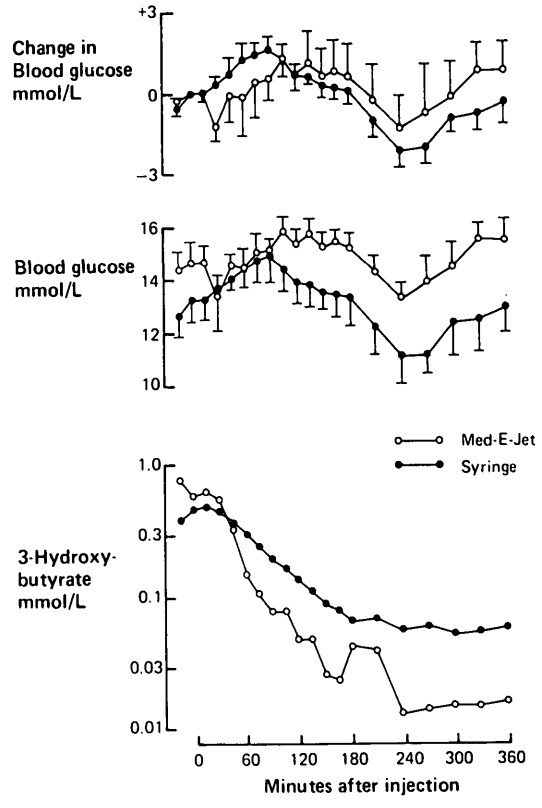

FIG. 2. Change in blood glucose levels, absolute blood glucose levels (mean ± SE), and blood 3-hydroxybutyrate levels after jet (O—O) and syringe (X—X) injection of insulin.

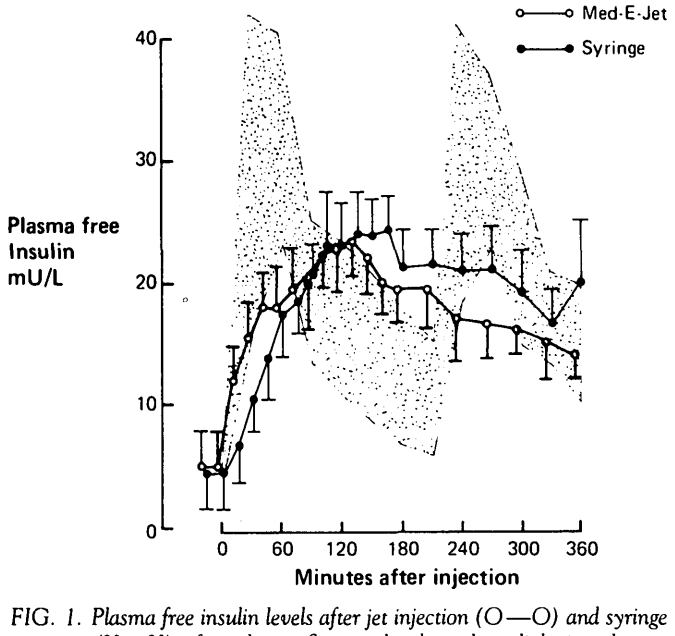

*FIG. 1. Plasma free insulin levels after jet injection (O—O) and syringe injection (X—X) of insulin in five insulin-dependent diabetic subjects. Mean ± SE. *P < 0.05. The shaded area indicates the 95% confidence limits of plasma insulin in normal subjects (D. G. Johnston, unpublished observations).*

DISCUSSION

Jet injection of insulin brought about a more rapid rise in plasma free insulin when compared with conventional syringe injection. This effect was seen in the first 45 min following injection, but by 60 min after the injection plasma free insulin levels were similar. The more rapid increase in plasma free insulin after jet injection was matched by lower levels during the period of decline in plasma insulin concentration. Thus the dynamics of insulin absorption after jet injection were found to be significantly different from those after syringe injection. More rapid absorption of the dispersed insulin pool produced by jet injection was expected as it is known that small volume deposits of insulin are absorbed more rapidly than large volume de-

posits.[8] Nevertheless, the plasma free insulin profile after jet injection does not approach the fast rise and fall of the physiologic response to meals, as shown in Figure 1 (refs. 9 and 10; D. G. Johnston, unpublished observations). The decline in free insulin concentration is even slower than the decline in insulin concentrations in normal subjects given subcutaneous insulin,[11,12] although consistent with reported results in diabetic patients.[13,14] On a jet injection regimen snacks would still be essential between meals.

The effect of the different plasma insulin profiles can be seen when considering the blood glucose and 3-hydroxybutyrate data. The slower rise in plasma insulin following syringe injection allowed an early rise in blood glucose after breakfast, while jet injection largely controlled this postprandial rise. The higher plasma free insulin levels resulting from syringe injection then caused a greater fall in blood glucose during the postabsorptive phase despite the snack. The observed short duration of insulin action after jet injection has been previously reported.[5] 3-Hydroxybutyrate concentrations follow the pattern expected from the above changes in plasma insulin, jet injection of insulin bringing about a more rapid suppression of blood 3-hydroxybutyrate levels.

The results of this comparative study suggest that jet injection of insulin before each meal could bring about better control of blood glucose than could thrice daily syringe injection of insulin. With either method a once daily injection of a very long-acting insulin would be necessary to provide adequate basal insulin levels. However, any advantage conferred by the use of the jet injector must be weighed against the inconvenience of carrying around and using this device.[5]

ACKNOWLEDGMENTS: We thank the Sister and staff of Ward 15, Freeman Hospital, Newcastle upon Tyne, and V. A. Hurst, dietitian, for their help. Dr. J. Burrin and L. Ashworth performed the metabolite assays. Philip Home is very grateful for the support of Novo Laboratories Ltd.

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