The Intravenous, Intraperitoneal, and Subcutaneous Routes of Insulin Delivery in Diabetic Man

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SUMMARY

Successful implantation of an artificial pancreas requires the infusion of insulin into an appropriate anatomic site. Three sites being actively investigated include (1) intravenous (i.v.), (2) intraperitoneal (i.p.), and (3) subcutaneous (s.c.). This study compared the rate, magnitude, and duration of insulin absorption from these three absorption sites as assessed by the appearance of "free" insulin into the plasma of 10 insulin-dependent diabetic subjects. The biologic effectiveness of insulin was assessed by the suppression of plasma glucose concentration following a 750-calorie meal.

Our results suggest that i.v. delivered insulin provides the most rapid increase in plasma free insulin concentration, followed by the i.p. and s.c. routes, respectively. In contrast, the elevation of plasma free insulin concentration was most prolonged with the s.c. route, followed by i.p. and i.v. routes, respectively. Compared with the i.v. and s.c. routes of insulin delivery, only 50% of the i.p. delivered insulin appeared in the plasma. The onset of the biologic activity of the insulin delivered by the three different routes during the 4½-h observation period was most rapid for the i.v. and least rapid for the s.c. route. These results suggest that all three routes may be appropriate sites for delivery of insulin from an artificial pancreas. However, because of the difference in absorption kinetics and the onset of biologic effectiveness of the delivered insulin, different quantities and timing of insulin delivery may be needed. DIABETES 28:1069–1072, December 1979.

The successful development and implantation of an artificial insulin delivery system into diabetic man requires an appropriate site for the infusion of insulin. The major anatomic sites being actively investigated include (1) intravenous (i.v.),[1,2] (2) intraperitoneal (i.p.),[3] and (3) subcutaneous (s.c.).[4,5] Although there are advantages and disadvantages to each administration site, to date no studies are available that compare the rate and degree of insulin absorption as measured by the appearance of insulin into the peripheral circulation.

This study examined the increase in plasma free insulin concentration in diabetic subjects receiving a preprogrammed infusion of exogenous insulin. Regular insulin (40 U/ml) was infused into either the i.v., i.p., or s.c. site by means of a portable, rotary solenoid microliter-infusion pump. An assessment of the rapidity, magnitude, and duration of insulin absorption from these three sites was made using a randomized paired-study protocol in 10 diabetic men lacking endogenous insulin secretion (no C-peptide secretion). In addition, the change in plasma glucose concentration following ingestion of identical meals was also examined as a measure of the onset of biologic activity of the insulin delivered during the 4½-h observation period.

METHODS

Subject population. Ten healthy, normal weight, male, insulin-dependent diabetic subjects participated in the 13½-h studies. Ages ranged from 22 to 39 yr and all subjects were receiving either one or two injections per day of isophane insulin with or without the addition of regular insulin. On the evening before study, the subjects were admitted to the Clinical Research Center of the University of New Mexico School of Medicine. No subject received insulin between 7:30 p.m. and the start of the studies at 7:30 a.m. the next day. Before initiating these studies, informed written consent was obtained from each volunteer, and all studies were approved by the University of New Mexico Human Research Review Committee.

Protocol. On the day of study, each subject received three identical meals, which corresponded in time to breakfast, lunch, and supper at 7:30 a.m., noon, and 4:30 p.m. Each meal consisted of ham, fruit, bread, and milk comprising 750 calories (40% carbohydrate, 40% fat, and 20% protein).

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Between meals, free access to water was allowed but no food was ingested.

The 13½-h protocol was divided into three equal time periods of 4½ h each, during which each subject received one i.v., one i.p., and one s.c. insulin infusion study in randomized sequence. The protocol used in all studies employed an initial 30-min high dose insulin infusion of 5 U of regular insulin beginning simultaneously with the start of the meal. Following the 30-min high dose insulin infusion, the infusion pump reverted to the low dose insulin infusion rate of 2 U/h for three additional hours. At the end of the 3½ h, the insulin delivery catheter was removed. The subsequent 60-min "no insulin" period permitted an assessment of continued insulin absorption from the infusion site.

All insulin protocols used a mini, peristaltic rotary solenoid pump to deliver the insulin.[6] This pump was portable (6.0 × 7.5 × 10 cm) and battery operated. The pump was driven in a pulsatile fashion by a rotary solenoid, each pulse rotating the pump head by 10 degrees and delivering a volume of 2 μl/pulse. Reproducibility of the pump was ± 5% for a delivery volume of 72 μl. In all infusion studies, the insulin was stored in a 50-ml plastic reservoir connected by a 10-cm plastic tube to the rotary solenoid pump. Before starting the individual infusion studies, 1 ml of the U40 insulin in the reservoir was pumped through the plastic tubing to saturate insulin absorption sites.

Infusion technique. Insulin in all three studies was delivered through a 22-gauge plastic Intracath (Deseret Pharmaceutical Company, Sandy, Utah), 20 cm in length, attached to the insulin pump via a 40-cm connecting tube. In the i.v. delivery of insulin study, the 19-gauge trocar was inserted into an antecubital vein, permitting placement of the plastic catheter approximately 5 cm into the vein.

In the i.p. insulin infusion studies, the 22-gauge Intracath was inserted 3 cm below the umbilicus into the i.p. space through a locally anesthetized area. The flexible plastic Intracath catheter was "threaded" through a 19-gauge trocar into the peritoneal space to a depth of approximately 5 cm. This catheter was not rigid enough to pierce either a blood vessel or the wall of the intestine. Once the catheter was threaded through the trocar, the trocar was removed and taped to the abdominal skin. Sterile technique was used throughout the procedure. Following the 3½-h peritoneal infusion, the catheter was removed and cultured. In the 10 subjects undergoing this procedure, no complications or infections were encountered. Our experience indicates that this procedure is both safe and painless and agrees with published reports in the literature on the safety of this technique.[7]

In the s.c. insulin infusion study, an identical Intracath was placed subcutaneously approximately 4 cm above the umbilicus. The trocar was inserted approximately 5 cm into the s.c. tissue and then withdrawn, leaving the plastic catheter approximately 4 cm within the s.c. space.

Assay methodology. Plasma glucose concentration was measured by glucose oxidase and plasma free insulin by double antibody radioimmunoassay following precipitation with 25% polyethylene glycol to remove endogenous insulin antibodies as previously described.[3] C-peptide was assayed with a kit from Calbiochem (Van Nuys, California).[8]

Statistical assessment. The changes in plasma free insulin concentration in these diabetic subjects were assessed by frequent venous blood sampling from the arm contralateral to that which received the i.v. insulin. Four-milliliter blood samples were withdrawn via a #19 scalp vein needle every 15 or 30 min throughout the study, as shown in Figure 1. Patency of this scalp vein needle was maintained by continuous infusion of isotonic saline (1 ml/min).

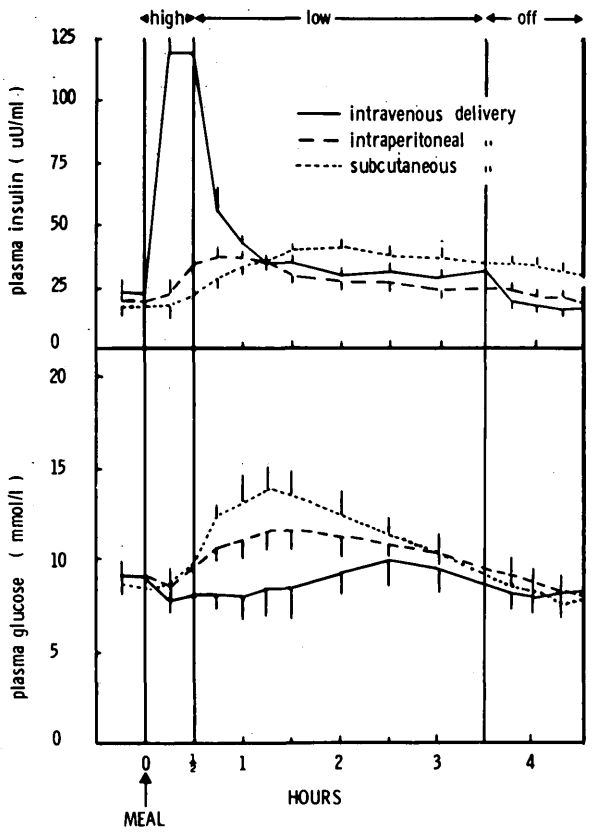

Figure 1. The changes in plasma free insulin concentration (top) and glucose concentration (bottom) during programmed delivery of 11 U of regular insulin by three different routes in diabetic man. The infusion of insulin (U40-regular) was begun at a high dose (10 U/h) at time 0 and continued for 30 min, when the infusion pump automatically reverted to the low dose (2 U/h) for an additional 3 h. Simultaneously with the start of the high dose insulin infusion, each of the 10 diabetic subjects began to eat a 750-calorie meal (arrow). At the end of the infusion period (3½ h) the insulin infusion was stopped for 60 min (off). Each of the 10 diabetic subjects participated in an intravenous, intraperitoneal, and subcutaneous insulin infusion study in a randomized sequence. The mean ± SEM of these 10 subjects is shown in the figure.

The mean ± SE for insulin and glucose for all studies are plotted in Figure 1. To quantitate the amount of insulin appearing in the peripheral circulation during the 4½-h period, the increase in insulin concentration above the initial starting concentration at time 0 was assessed by integration. To estimate the rapidity of onset of biologic effectiveness of the administered insulin, the increase of plasma glucose concentration over baseline levels was compared with Student's *t* test for paired data.

RESULTS

Mean plasma free insulin concentration (Figure 1). In the i.v. insulin infusion study, mean plasma free insulin concentration rose to a maximum of 119 ± 13 μU/ml by 15 min post initiation of infusion and then decreased rapidly following termination of the high dose infusion to an approximate background level of 30 μU/ml. When the insulin infusion

was stopped at 3½ h, the plasma free insulin concentration decreased further to approximately 18 μU/ml, 5 μU/ml below the initial starting basal free insulin concentration of 22 ± 3 μU/ml ($P < 0.01$).

In the i.p. insulin infusion study, mean plasma free insulin concentration rose to a maximal concentration of 37 ± 6 μU/ml by 45 min postinitiation of the high dose insulin infusion followed by a slow decline over a period of approximately 1 h, attaining a level of 26 μU/ml during the low dose insulin infusion. Following termination of the infusion, a further decline in plasma free insulin concentration was observed to a level of 18 ± 1 μU/ml, not different from the initial starting basal free insulin concentration of 19 ± 3 μU/ml ($P > 0.05$).

In the s.c. insulin infusion study, mean plasma free insulin concentration rose to 40 ± 4 μU/ml by 2 h postinitiation of high dose infusion followed by a slow decline in plasma free insulin concentration. After the infusion of insulin had ceased for 60 min, the plasma free insulin concentration remained elevated at 29 ± 2 μU/ml ($P < 0.001$).

In each study, plasma free insulin concentration demonstrated a rise and subsequent fall. However, the timing and magnitude of this change depended on the route of insulin delivery. At 30 min following the initiation of insulin infusion, plasma free insulin concentration in the i.p. study (34 ± 4 μU/ml) was significantly greater than in the s.c. one (21 ± 2 μU/ml) and significantly less than in the i.p. study (117 ± 10 μU/ml) ($P < 0.05$) (Figure 1). By 2 h, however, the plasma free insulin concentration in the s.c. study (41 ± 3 μU/ml) had exceeded the concentration in both the i.p. (26 ± 3 μU/ml) and i.v. studies (29 ± 2 μU/ml) ($P < 0.05$). This late elevation in plasma free insulin concentration persisted throughout the remainder of the study such that at 4½ h, the insulin concentration in the s.c. study (29 ± 2 μU/ml) was significantly greater than in the i.p. (18 ± 1 μU/ml) and the i.v. ones (16 ± 2 μU/ml) ($P < 0.01$).

Integrated insulin concentration (Table 1). Although the same quantity of exogenous insulin was infused into all subjects in each study (11 U), the quantity of insulin appearing in the plasma significantly differed, depending on the route of administration. During the 4½-h i.v. infusion study, 8743 ± 1046 μU/ml · h/100 of insulin appeared in the plasma. This quantity was twice that of insulin appearing in the plasma when delivered via the i.p. route (3636 ± 480 μU/ml · h/100) ($P < 0.001$). When the 11 U of insulin was delivered via the s.c. route, 7383 ± 743 μU/ml · h/100 appeared in the plasma, significantly greater than that during the i.p. route ($P < 0.001$) but not different from that quantity appearing during the i.v. infusion of insulin ($P > 0.05$).

TABLE 1
Integrated area of free insulin above basal concentration (μU/ml · h/100)

Subject	Intravenous	Intraperitoneal	Subcutaneous
1. N.V.	4,825	2,275	8,187
2. E.G.	12,837	5,262	8,300
3. J.A.	5,437	1,040	9,362
4. M.P.	13,975	5,625	9,162
5. J.G.	4,437	3,537	3,262
6. J.D.	8,175	2,112	3,525
7. D.B.	9,262	3,050	5,650
8. J.S.	8,850	4,862	8,637
9. L.P.	11,637	4,775	9,150
10. D.B.	8,000	3,850	8,600
Mean	8,743	3,638	7,383
Sem	± 1,046	± 480	± 743
	← $P < 0.001$ →	← $P < 0.001$ →	
	← $P > 0.05$ →		

Plasma glucose concentration (Figure 1). Plasma glucose concentration rose in all studies following ingestion of the 750-calorie meal. However, the rise was most rapid during the s.c. administration of insulin and least rapid during i.v. administration. Statistically, this difference became significant at 45 min when plasma glucose concentration had risen by 4.1 ± 1.2 mmol/L in the s.c. study, 1.6 ± 0.7 mmol/L in the i.p. study, and declined by −0.9 ± 0.8 mmol/L in the i.v. study ($P < 0.05$ for all comparisons). This statistical difference remained throughout the initial 75-min observation period. This rate of rise corresponded inversely to the rate of rise in plasma free insulin concentration in the three different delivery route studies (Figure 1, top).

Plasma C-peptide concentration. Plasma C-peptide concentration was assayed in all plasma samples. In no subject was C-peptide detectable in the plasma at any observation point during these studies.

DISCUSSION

This study compared the rapidity, duration, and magnitude of insulin absorption during insulin infusion via the i.v., i.p., and s.c. delivery routes. Our results demonstrate that i.v. insulin attains maximal plasma concentration by 15 min, followed by the i.p. (45 min) and the s.c. routes (120 min), respectively. With respect to the duration of insulin absorption, absorption from the s.c. site was most prolonged in contrast to the very rapid decline in plasma insulin concentration following termination of i.v. insulin delivery. The magnitude of the integrated rise in plasma insulin was comparable in both the i.v. and s.c. infusion routes, but was reduced by 50% with peritoneal delivery of insulin. In spite of this "loss," i.p. delivery of insulin was as effective, if not more effective, than s.c. delivery in suppressing the meal-related hyperglycemia.

This is the first study demonstrating that i.p. insulin delivery may control postprandial hyperglycemia in healthy diabetic men. Intraperitoneal insulin delivery has several characteristics that make it an attractive alternative to i.v. and s.c. insulin delivery. First, the absorption of insulin is relatively rapid such that rapid control of hyperglycemia may be achieved. Second, the peritoneal space is extravascular such that catheter thrombosis is minimized.[9] Third, the peritoneal space is a potentially large anatomic space into which an artificial pancreas could be implanted without disfigurement of the recipient.

In these studies, only short-term insulin absorption kinetics were examined, which may not necessarily reflect kinetics of long-term delivery. Furthermore, because our protocol was not designed to optimize glucose control by the three routes of insulin delivery, additional studies will be required to determine the most effective route in controlling plasma glucose concentration. However, since a relationship exists between the timing of the insulin increase in the plasma and the rise of plasma glucose concentration,[10] our results sug-

gest that the infusion of s.c. insulin be begun before the start of the meal, as has been employed.[4,5] Furthermore, since both our results and the results of others[11] demonstrate a prolonged absorption of insulin at the s.c. site following termination of the insulin infusion, a reduced rate of delivery between meals should be evaluated when using this route. Our results also suggest that improved glucose control might be achieved during the i.p. route if the insulin is administered at a greater concentration for a shorter period of time following the initiation of the meal. Whatever the route of insulin delivery used by an artificial pancreas, knowledge of the kinetics of insulin absorption and the onset of biologic activity should result in improved control of meal-induced hyperglycemia.

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