Changes in Glucagon Levels After Four to Five Weeks of Glucoregulation by Portable Insulin Infusion Pumps

PHILIP RASKIN, ANGEL PIETRI, AND ROGER UNGER

SUMMARY

Near-normal glucoregulation was maintained in five patients with juvenile-onset diabetes mellitus for 4–5 wk with a preprogrammed, continuous, subcutaneous insulin infusion using a portable battery-powered infusion pump. This form of therapy significantly lowered immunoreactive glucagon (IRG) levels below those observed while on conventional insulin treatment at several times during the 24-h profile. The maximum IRG levels were also reduced in all five subjects. Thus, a flexible system of insulin delivery, as is provided by certain open-loop pump systems, can overcome inappropriate glucagon secretion that occurs with conventional insulin therapy. DIABETES *28*:1033–1035, NOVEMBER 1979.

The treatment of juvenile-onset diabetics with portable "open-loop" insulin infusion pumps makes possible the maintenance of normal or near-normal around-the-clock glucose profiles[1–3] and has corrected certain of the metabolic and endocrine abnormalities that are present in diabetics receiving insulin by conventional delivery methods.[4–6] However, the effect of the improved glucoregulation by this new therapeutic method on the relative hyperglucagonemia and A-cell dysfunction that persists in diabetic patients despite liberal doses of conventionally administered insulin[7–10] has not been reported. Because of the important role of abnormal A-cell function in the hyperglycemia and ketonemia of insulin-treated diabetics,[11–13] studies of daily glucagon profiles were conducted in five juvenile diabetic patients before and after 4–5 wk of near-normal glucoregulation by an open-loop pump.

From Dallas Veterans Administration Medical Center and The University of Texas Health Science Center at Dallas, Southwestern Medical School, Department of Internal Medicine.
Address reprint requests to Philip Raskin, M.D., The University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235.
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MATERIALS AND METHODS

Five nonobese patients with ketoacidosis-prone juvenile-onset diabetes mellitus were admitted to the Clinical Research Unit at Parkland Memorial Hospital in Dallas, Texas. The clinical data on the diabetic patients are listed in Table 1. On admission to the hospital they consumed a metabolic diet containing 45% carbohydrate, 35% fat, and 20% protein. Two-sevenths of the daily calories were given at breakfast (0800), two-sevenths at lunch (1200), two-sevenths at dinner (1700), and one-seventh as an evening snack (2100). The diet was calculated to be similar to the caloric intake of the patients' diet consumed at home. The initial "profile day" occurred on the third hospital day, with each patient receiving his or her usual daily insulin dose (which in most cases consisted of two injections of a mixture of NPH and regular insulin) (Table 1). On the following day, continuous, subcutaneous insulin infusion (CSII) by a portable battery-powered infusion pump was started. In four of the patients the Auto-Syringe pump model AS2C (Auto-Syringe, Inc., Hooksett, New Hampshire) was used and in one patient the Mill-Hill Infuser (Muirhead Ltd., Beckenham Kent, England) was employed. The operational features of both of these pumps have been previously described.[1,2] Regular insulin was infused through a thin (external diameter 0.4 mm, internal diameter 0.19 mm) nylon canula (Portex Ltd, Hythe-Kent, England) inserted in the subcutaneous tissue of the abdomen as described by Pickup et al.[1] Each patient received a constant basal infusion rate of insulin, and 30 min before each meal, a predetermined insulin bolus was administered. After the administration of the preprandial insulin dose, the basal rate was then resumed. The patients' dose of insulin was adjusted from day to day during the first week of hospitalization. Each patient's daily insulin dose and its distribution between basal rate and preprandial doses (Table 1) was determined by the glycemic response to the previous day's insulin dose. After the first week only periodic modifications in insulin dosage were required. The patients' activities consisted of free ambulation within the Clinical Re-

TABLE 1
Clinical characteristics of the diabetic patients

	Age	Sex	Race	Duration of diabetes (yr)	Insulin dose: conven. insulin therapy (U)	Insulin dose: continuous s.c. insulin infusion total (U)	%Basal*	%Breakfast†	%Lunch†	%Dinner†	%Snack†
S.S.	16	F	W	11	35	77	46	18	13	13	10
P.S.	19	F	W	11	40	56	25	32	16	18	9
J.A.	30	M	W	14	51	46	22	42	22	17	5
J.B.	18	M	B	4	65	74	32	24	19	19	6
J.B.	39	M	W	17	47	51	58	18	10	10	4
				Average	48 ± 5	61 ± 8	41 ± 6	23 ± 3	14 ± 2	15 ± 2	7 ± 1

* Percent of total daily CSII insulin dosage given as a basal rate.
† Percent of total daily CSII insulin dosage given before meals.

search Unit and was essentially constant in each patient throughout the study.

One patient was hospitalized for the entire period in which he participated in the study. The other four patients were hospitalized for at least the first 2 wk of the CSII therapy, after which time they were sent home. All managed to continue with their usual daily activities while receiving insulin with the portable infusion pump outside the hospital. They were readmitted to the Clinical Research Unit periodically for reevaluation, during which time another "profile" was done. Two of the patients were studied after 35 days of CSII therapy and three patients after 28 days of therapy.

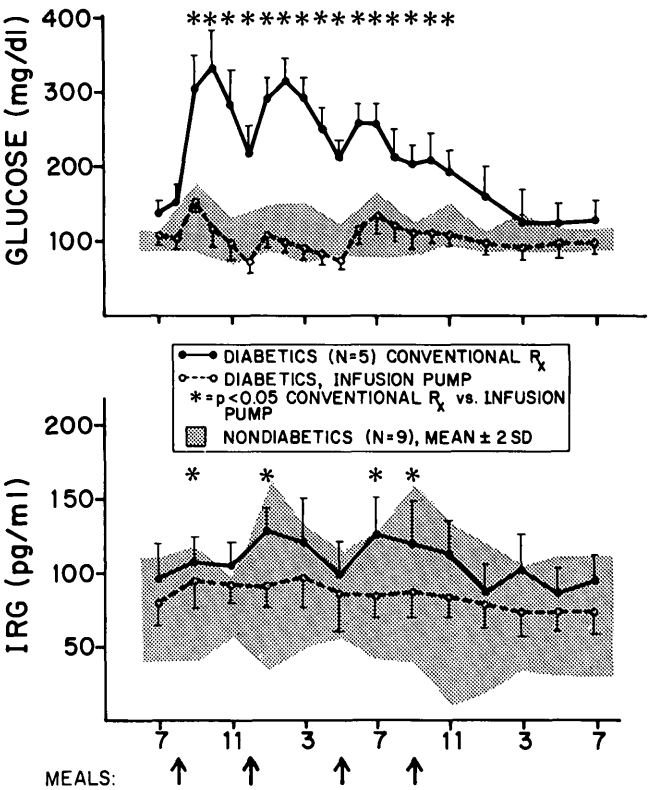
Blood samples for a 24-h profile were obtained at hourly intervals from 0700 to 2300 and then at 2-h intervals from 2300 to 0700 through an indwelling 19-gauge butterfly needle placed in a large forearm vein. Glucose was measured in all specimens. Blood for immunoreactive glucagon (IRG) measurements was collected at 2-hour intervals in chilled tubes containing 12 mg EDTA and 1 ml Trasylol (500 Kallikrein inhibitor units/ml of blood) and centrifuged promptly at 4°C. Plasma was separated and stored at −20°C until the time of the hormone assay. Plasma IRG was determined by a previously described method using antibody 30K.[14] All samples from each individual patient were measured in the same assay run. The glucose was measured immediately on the Beckman Glucose Analyzer. In addition, total glycosylated hemoglobin was determined by ion exchange chromatography using a prepacked microcolumn. (Quik-Column, Helena Laboratories, Beaumont, Texas).

The statistical analysis of the effect of continuous subcutaneous insulin infusion on plasma glucose and IRG was made by computing the mean values for each 24-h period in each patient. These were then averaged (mean of the means). The Student's *t* test for paired groups was used for statistical analysis.

RESULTS

Effect of normalization of glycemia by CSII on the IRG profile. Figure 1 shows the mean of the five 24-h profiles of plasma glucose and IRG levels obtained while on conventional therapy and after 4–6 wk of CSII. At this time the glucose profiles had been reduced to a normal range (73 ± 12 to 151 ± 10 mg/dl) and the total glycosylated hemoglobin had been reduced from 12 ± 1.6% to 6.2 ± 0.4%. Glucose values were significantly below ($P < 0.05$) the corresponding value of the profile obtained while the patients were receiving conventional insulin therapy at 16 of 21 time points (Figure 1). Symptomatic hypoglycemia occurred only rarely while the patients received CSII. It was most often seen during the initial portion of the study before the final insulin program was established. In most circumstances when it did occur, it was before lunch. Previously published profiles of nondiabetics[15] who consumed a similar diet are also shown for comparison (mean ± 2 SD ranged from 164 to 10 pg/ml). The mean of all IRG levels averaged 83 ± 15 pg/ml on CSII, significantly below the value of 105 ± 20 pg/ml while on conventional insulin therapy ($P < 0.05$). The mean of the

FIGURE 1. Mean (±SEM) plasma glucose and IRG profiles during 24 h of conventional insulin treatment (●——●) and after 4–5 wk of continuous subcutaneous insulin infusion (○----○) with portable insulin infusion pumps in five juvenile-onset diabetics. Asterisks indicate $P < 0.05$ in the diabetics with insulin infusion versus conventional therapy. The shaded area represents the mean ± 2 SD of values from nine nondiabetics on a similar diet[15] included for comparison. Times of meals are indicated by arrows.



maximal values was significantly reduced ($P < 0.05$) (115 ± 19 versus 141 ± 23 pg/ml).

DISCUSSION

Maintenance of glycemia within a near-normal range significantly lowered IRG levels below those observed while on conventional insulin treatment at several time points of the 24-h profiles. It should be noted that most of the diabetics, while on conventional insulin therapy, demonstrated relative hyperglucagonemia. That is to say, although their absolute IRG levels fell within the normal range (for normoglycemic nondiabetics), they were still elevated relative to their plasma glucose levels. The maximum IRG levels were also reduced in all five subjects. This is not surprising since it has been reported previously that IRG levels in such patients fall during conventional subcutaneous insulin therapy.[15] In this previous study,[15] although plasma IRG levels fell in response to aggressive conventional insulin therapy, they were never made completely normal. The use of CSII resulted in a fall in IRG levels to the middle of the nondiabetic range, a result that suggests an additional advantage in this type of insulin delivery over conventional methods. It should be kept in mind, however, that a fall in IRG levels does not necessarily indicate that A-cell function has been restored to normal. For example, in juvenile-onset diabetes a constant insulin infusion has been shown to correct one abnormality of A-cell function, the excessive A-cell response to arginine,[16,17] but does not restore to normal another abnormality, namely, the ability of hyperglycemia to abolish the protein-induced rise in IRG.[9] Specific studies of A-cell function will therefore be required to determine if such abnormalities are corrected by long periods of euglycemia or whether they persist despite such treatment.

The importance of correcting abnormal A-cell function, such as inappropriate meal-induced rises in glucagon, has been established in diabetics treated by an inflexible method of insulin delivery.[12] In such patients a rise in IRG, when unaccompanied by a change in insulin, causes an increase in glucose and ketone production and in hyperglycemia.[11–13] However, with a flexible system of insulin delivery, provided by certain insulin pump systems, the hyperglycemic effect of inappropriate glucagon secretion, like that of a glucose load, can be overcome by an appropriately timed increase in insulin delivery,[18] and glucagon suppression, which is so effective in maintaining normoglycemia when insulin is delivered at a fixed rate,[12] is unnecessary. However, glucagon-suppressing agents such as somatostatin, which can reduce the production of both endogenous glucose from the liver[19] and the entry of exogenous glucose from the gut,[20] may yet prove therapeutically useful in selected patients as a supplement to CSII when optimal glucoregulation is not attainable with a program using insulin alone.

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