Evaluation of Exogenous Insulin Homoeostasis by the Artificial Pancreas in Insulin-Dependent Diabetes

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Summary. With the artificial pancreas used by the authors, insulin was delivered through a venous infusion and the rate of delivery was adjusted according to data provided by a continuous blood glucose monitor. After different trials we selected control algorithms integrating two parameters: instantaneous blood glucose concentration and increasing or decreasing patterns of blood glucose. A constant basal insulin infusion rate was added and improved the control of glycaemic excursions. Different parameters concerning exogenous insulin homoeostasis were determined. The delay to reach an insulin effect was 18 ± 2 min and was shortened by a priming-dose at the beginning of the infusion. The insulin effect remained for 28 ± 2 min after the infusion had been stopped, but differences were noted in the morning (21 ± 2 min), in the afternoon (32 ± 2 min) and during the night (25 ± 3 min). Insulin needs were evaluated during meals. Related to the amount of carbohydrates, the doses fell from 0.53 units/hr/g of carbohydrate for breakfast to 0.15 for dinner. From these data, it appears that the efficiency of exogenous insulin exhibits a circadian rhythm.

Key words: Insulin infusion, artificial betacell, artificial endocrine pancreas, control algorithms, continuous blood glucose measurement.

The artificial pancreas or external artificial beta cell corresponds to a device developed in order to reach better control of spontaneous or provoked glycaemic excursions. This aim can be achieved by using an insulin and/or glucose infusion adjusted to blood glucose levels as measured by rapid chemical determinations on continuous blood sampling. This technique has been successfully developed and previously described by a number of authors [1, 2, 3, 4, 18, 19, 20, 10, 5, 6]. In the present work, we describe a new system and its quantitative evaluation in relation to exogenous insulin homoeostasis in insulin-dependent diabetics.
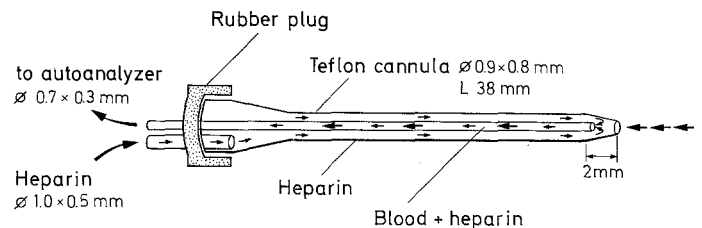
Materials and Methods

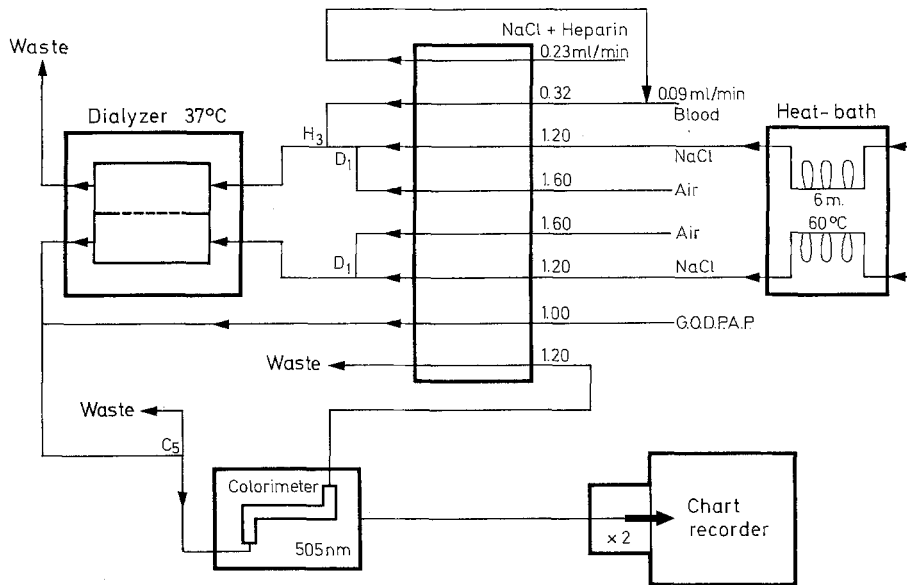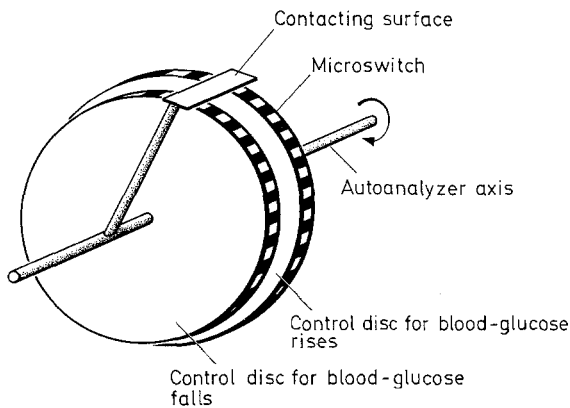*The artificial pancreas* that we use consists of 3 subsystems (Fig. 1).
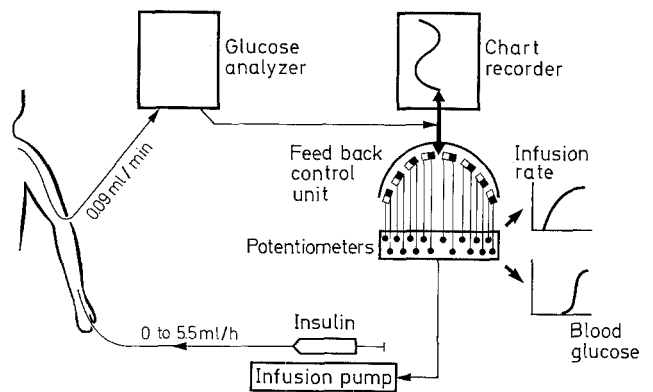
Fig. 1. Apparatus used for automated regulation of blood glucose. For description of the feed back control unit (right hand part of the figure), see Fig. 4
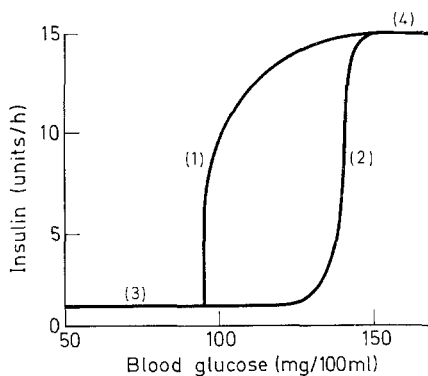

Fig. 2. Double lumen catheter for continuous blood sampling

Fig. 3. Flow diagram used for rapid continuous measurement of whole blood glucose

Fig. 4. Detail of the feed-back control unit used as an interface between blood glucose recording and insulin infusion unit


Fig. 5. Control algorithms relating insulin infusion and blood glucose. 1) control algorithms for blood glucose rises; 2) control algorithms for blood glucose falls; 3) basal insulin flow-rate (0.25–1.5 units/h); 4) maximum insulin flow-rate (15 units/h)

1. the continuous blood glucose measurement,
2. the automatic adjustment system,
3. the insulin pump.

Blood samples were withdrawn through a double lumen catheter (Fig. 2). Into the outer lumen between the tubing and the cannula, heparin (50 u/ml 0.154 mol/l saline) was pumped at a rate of 0.23 ml/min. The heparin when reaching the tip of the tube mixed with the blood entering the cannula and the blood-heparin mixture was pumped through the inner tube to the autoanalyzer at a rate of 0.32 ml/min. The total blood loss amounted to 0.09 ml/min, i. e. 129 ml/24 h.

Continuous blood glucose measurement was achieved by means of a Technicon autoanalyzer using a modified glucose-oxidase method (G.O.D-P.A.P. Boehringer) (Fig. 3). Routine recalibration after 12 h of continuous blood glucose analysis shows a small positive baseline drift of 0.5 mg/100 ml/h and no reduction in the sensivity of the calibration curve. The lag time between blood sampling and obtaining a blood glucose result was less than 3 min, despite the presence of a 2 metre line between the patient and the measuring device. The presence of this long line allowed a certain amount of physical activity for the subject.

The insulin infusion was prepared by diluting Actrapid insulin (Novo 40 units per ml) with saline to a final concentration of 2–4 units per ml. It was delivered by a 50 ml plastic syringe with the aid of a multispeed infusion pump (Sage model 240, range 0 to 5.5 ml/hr). Albumin was not added because adsorption is negligible when insulin is present in relatively high concentrations in plastic syringes [17]. The mixture was infused into a superficial vein of
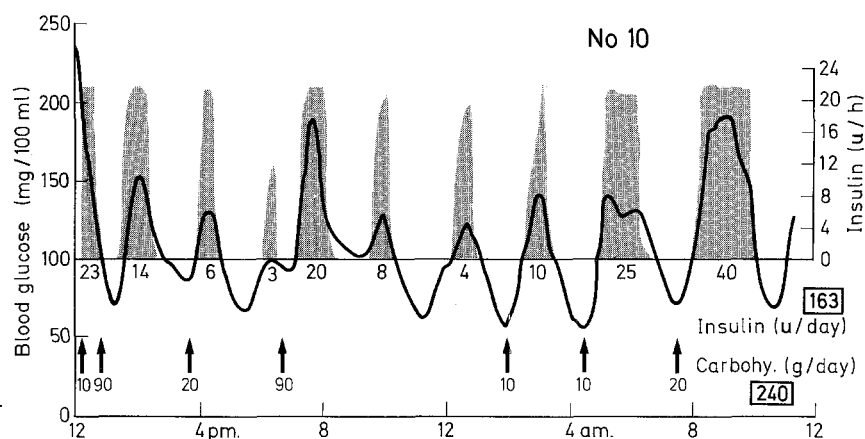
Fig. 6. Continuous record of blood glucose (black)controlled by artificial pancreas (grey). Note absence of a constant basal insulin infusion

the forearm through an indwelling tube (diameter 5.5 mm, length 200 cm, Braun) fitted to a siliconed needle (Abbott).

The feed back control unit (Fig. 4) consisted of two series of microswitches located on two disks directly on the axis of the recorder. Each microswitch was connected to a preselected potentiometer which governs the rate of the pump. One of the discs was connected when blood glucose concentration rose, the other when blood glucose concentration fell. By this means, the system provided a range of infusion rates according to blood glucose concentration and increasing or decreasing pattern of blood glucose curve.

The control algorithms (Fig. 5) allowed a rapid response of insulin infusion, to a maximal rate when blood glucose rises. On the other hand, the infusion rate falls rapidly as soon as blood glucose begins to fall. A basal insulin infusion rate for low blood glucose concentrations was added subsequently.

Patients

Twenty insulin-dependent diabetics were studied over a 12 to 48 h period. During the day preceding the investigation, the patients were treated with 3 daily injections of regular insulin, in order to avoid any overlap between the insulin infusion on the day of investigation and the prolonged activity of lente insulin injected on the day before. Their main clinical characteristics are summarized in Table 1. None of the patients presented with degenerative or infectious disease.

Results

The time course of blood glucose recordings as adjusted by the artificial pancreas are shown on Figures 6, 7 and 8.

Table 1. Clinical data of patients studied with the artificial pancreas. — N_o 1 to 10: without basal insulin flow rate; N_o 11 to 20: with basal insulin flow rate

N°	Sex	Age (years)	Duration of Diabetes (years)	Carbohydrate regimen (g/24 hr)	Usual subcutaneous insulin requirements (U/24 hr)
1	M	26	3	160	67
2	M	32	6	180	25
3	F	50	2	220	50
4	F	51	5	295	42
5	M	33	9	220	25
6	M	32	0.1	225	14
7	M	42	10	270	41
8	M	20	2	225	42
9	M	25	0.1	250	30
10	M	38	3	220	32
11	M	18	0.3	295	85
12	M	25	0.1	160	36
13	F	29	1	130	32
14	F	54	6	130	28
15	F	53	3	165	34
16	M	28	10	280	67
17	M	41	2	180	32
18	M	14	2	250	63
19	F	14	0.1	200	42
20	M	41	0.6	150	64
Mean		33	3.3	206	43
± S.E.M		3	0.7	11	4

Figure 6 shows the results for a poorly controlled patient. Blood glucose concentrations varied from 55 to 195 mg/100 ml during the infusion period. This could be considered satisfactory control but severe hyperglycaemic surges occurred throughout and the overall insulin requirement for the day was large. It should be noted that there was no basal insulin infusion in this case. By adding such a basal infusion, better control could be achieved in another difficult patient (Fig. 7). However, the basal rate ap-
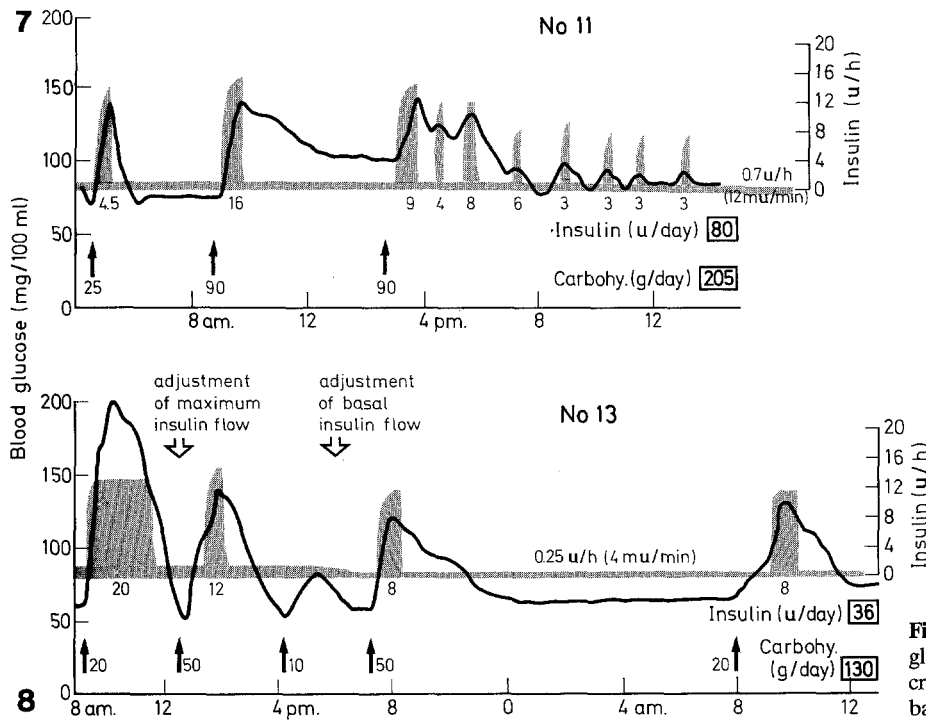
Fig. 7 and 8. Continuous record of blood glucose (black), controlled by artificial pancreas (grey). Note presence of a constant basal insulin infusion
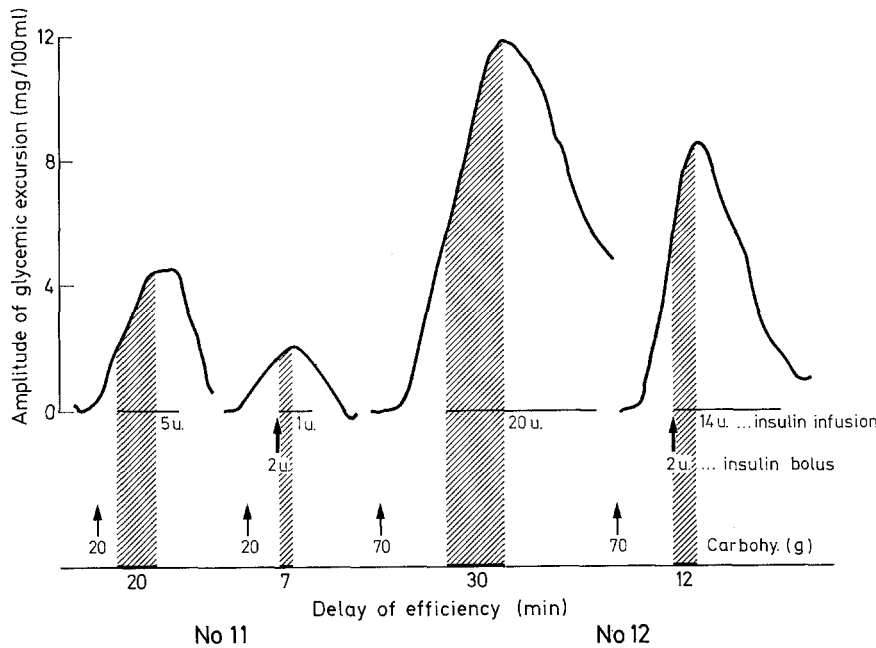

Fig. 9. Effect of a priming dose on the insulin infusion efficiency. Stippled areas represent the delay of insulin efficiency i. e. the lag time between beginning of the infusion and discontinuation of the blood glucose rises

peared to be insufficient. This was probably responsible for small hyperglycaemic episodes immediately corrected by the modulated insulin infusion programme, but it resulted in an oscillating pattern of timecourse recording during the night. The controlled recording as shown in Figure 8 gives evidence that an accurate adjustment of basal and modulated infusion rates is required. Currently the dietary hyperglycaemic episodes are controlled by a

maximal infusion rate of 15 units per hour. On the other hand, the basal infusion needs to be adjusted to each particular case and its value varies from 0.25 to 1.5 units per hour.

The delay to reach an insulin effect (i. e. the lagtime between the beginning of the infusion and discontinuation of spontaneous or meal induced blood glucose rises) was equal to 18 ± 2 min. In the absence of a priming dose the hypoglycaemic effect of
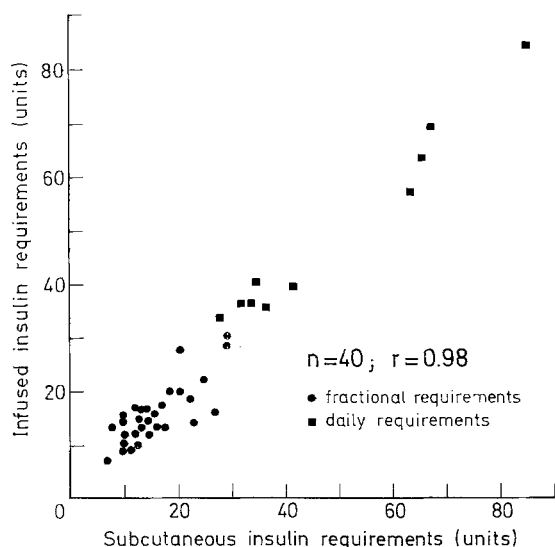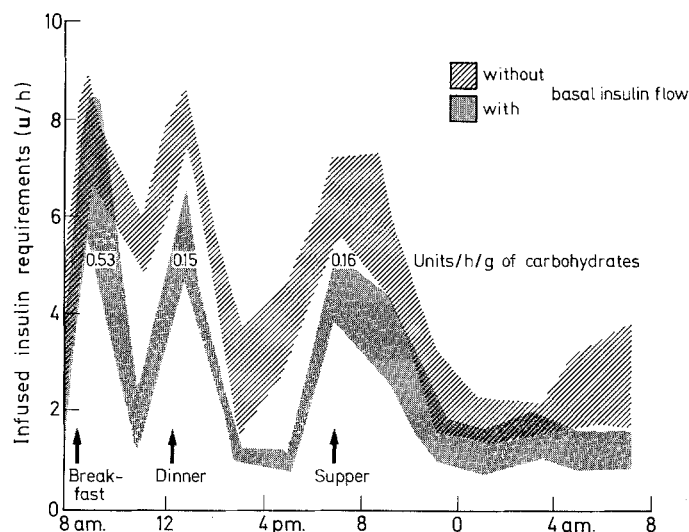
Fig. 10. Comparison between subcutaneous and infused insulin requirements

Fig. 11. Infused insulin requirements: diurnal variations

insulin was delayed when the infusion was started again. In Figure 9, this phenomenon is demonstrated in two cases (11 and 12) given similar carbohydrate loads (20 g in case 11 and 70 g in case 12) without and with an IV bolus at the beginning of the insulin infusion.

The prolonged insulin effect (i. e. the lag-time between the end of the infusion and discontinuation of spontaneous or post hyperglycaemia blood glucose falls) was not dependent on the quantity of insulin previously infused and averaged 28 ± 2 min after the infusion had been stopped. However, differences were noted with the time of monitoring: 21 ± 3 min in the morning, 32 ± 3 min in the afternoon, 25 ± 3 min during the night. The difference between the effect in the morning and in the afternoon was significant (P < 0.01).

The exact evaluation of insulin requirements during infusion and subcutaneous treatment (Fig. 10) showed that at times of good control, a highly significant correlation existed between the subcutaneous and intravenous insulin doses needed (N_o 10 to 20).

However the hourly insulin requirements were variable over the day. Their absolute values were slightly greater for breakfast than for lunch and dinner (Fig. 11). The doses remained in a similar range, but slightly lower, when a basal insulin infusion was added. The differences in insulin doses were more obvious when the number of units delivered was related to the amount of carbohydrates given: the doses fell from 0.53 unit per hour per g of carbohydrates for breakfast, to 0.15 for lunch and to 0.16 for dinner.

Discussion

Our artificial pancreas [14, 15] includes a continuous blood glucose recording controlling both a modulated and a basal insulin infusion flow rate, the latter maintaining a steady blood glucose between meals. These features are similar to some [4, 6, 20] but not all [7] others. However our artificial pancreas differs from the others in the following:

- the information is transmitted to the infusion pump by a noncomputerized analog system.
- the computerization of the rate of blood glucose change (dynamic control) is replaced by two static control algorithms which regulate separately the increase and decrease of blood glucose concentration. The reliability of our system is confirmed by the excellent correlation (r = 0.98) between subcutaneous and infused insulin requirements (Fig. 10). Thus the artificial pancreas provides accurate information about the daily amounts of insulin required by the patient.
- hyperglycaemic substrate (glucagon or dextrose) is not added to the insulin infusion. Therefore the efficiency of the infused insulin can be easily analysed from the blood glucose curve.

Furthermore, the blood glucose recording and the insulin release are perfectly stable (Fig. 8) except for meal-induced peaks. This almost physiological pattern seems more difficult to reach with the double-infusion technique [1, 18]

The delay in initial action (18 ± 2 min) and discontinuation (28 ± 2 min) of effect of the infused insulin agrees with previous studies of the hormone half-life [12, 16, 21, 22]. However, important differ-

ences between patients were noted [12] making an adequate feed-back control quite difficult.

An IV bolus added at the beginning of any insulin infusion (Fig. 9) results in a more physiological profile [9] of the insulin release and improves the efficiency of the device.

Diurnal variations of insulin efficiency and/or requirements have been noted in normal and diabetic subjects [8, 11, 13]. In diabetics, diurnal analysis is difficult because of the intermittent and often inadequate insulin therapy. The artificial pancreas avoids this problem. Results show that the duration of effect of the infused insulin (which can be considered an index of the biological half-life) is significantly longer in the afternoon (32 ± 3 min) than in the morning (21 ± 3 min). Furthermore, hourly insulin requirements per g of carbohydrate (Fig. 11) are much greater for breakfast (0.53 µ/hr/g) than for lunch (0.15 µ/hr/g) or dinner (0.16 µ/hr/g) despite similar carbohydrate composition.

It appears from these results that this technique is of considerable value in evaluation of exogenous insulin homeostasis in insulin dependent diabetics.

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