

# Development and Application of Insulin Infusion Profiles for Therapy of Type-I Diabetics with Portable Insulin Infusion Systems

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## INTRODUCTION

The metabolism of insulin-dependent diabetics (IDDs) cannot always be normalized by the conventional subcutaneous insulin regimen that usually provides only two injections of regular and intermediate-acting insulin per day, but glucose-controlled intravenous insulin infusion ensures almost normal glycaemia all day long. However, glucose-controlled insulin infusion systems (GCIS) are available only for inpatient treatment<sup>1,7,8,12</sup> because, at present, in vivo glucose measuring systems are not suitable for portable devices. Thus only open-loop devices are considered for outpatient treatment for brittle IDDs. There is no difficulty in finding the right dosage for the basic insulin requirement, but control of the postprandial blood glucose increase presents a greater problem since the preprandial blood glucose level should be restored within two hours postprandially, without risking severe hypo- or hyperglycaemia. It is obvious that insulin dosage alone is insufficient for this, but the timing of the insulin infusion may be important<sup>10,13</sup>.

The aim of this study was to clarify the importance of different insulin infusion profiles on daily and postprandial blood glucose levels.

## METHODS AND MATERIALS

### Patients

We studied seven (step vs rectangular profile) and five (with vs without initial insulin bolus) normal-weight type-I diabetics. The patients had no measurable residual insulin secretion as assessed by C-peptide measurement (0.2 ng/ml). Some patients had measurable insulin-antibody titres but these did not cause any insulin resistance. Additional diseases or severe late complications of diabetes mellitus did not occur (Table 1).

### Materials

The already well established insulin infusion device Promedos E1 (Siemens AG; Figure 1) provided the rectangular infusion profiles. The individually programmable insulin infusion device (Figure 2) is the prototype of our own development.

Table 1. Clinical data of the patients

No.	Sex (m/f)	Age (years)	Height (cm)	Weight (kg)	BROCA (%)	Duration of diabetes (years)	Retinopathy (Y/N)	Neuropathy (Y/N)	C-peptide (Y/N)	IRI-AB (Y/N)	Insulin dose s.c. (iu/day)
1	m	23	180	64	88.9	18	Y	N	N	Y	42
2	f	23	165	65	116.2	3	N	N	N	Y	38
3	f	32	170	53	84.1	5	N	N	N	Y	49
4	m	31	178	58	92.6	3	N	N	N	N	54
5	m	26	183	82	109.8	5	N	N	N	Y	54
6	m	28	181	80	109.7	18	Y	Y	N	N	58
7	m	29	182	82	111.1	3	N	N	N	Y	58
8	m	19	186	62	80.1	0.5	N	N	N	Y	66
9	f	23	158	56	107.3	1	N	N	N	Y	60
10	m	23	168	63	102.9	9	N	N	N	Y	52
11	m	19	188	77	97.2	2	N	Y	N	Y	62
12	m	26	180	71	98.6	8	N	N	N	Y	48
Mean	9/3	25.2	176.6	67.8	99.9	6.3	2/10	3/9	0/12	9/2	53.4
s.c.m.		1.2	2.7	3.0	3.3	1.7					2.4

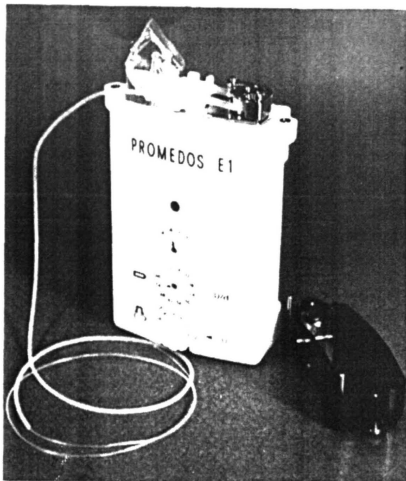


Figure 1. Promedos E1 (Siemens) insulin infusion device providing rectangular profiles.

The external dimensions of the latter are  $19.5 \times 7.8 \times 5.0$  cm, weighing 800 g. An electric stepping motor propels the piston of a reusable Hamilton glass syringe. Communication with the processor is possible via a keyboard; basal rates and meal programmes can be activated by typing-in a numerical code. An LCD indicates the time or activated programme. Two programmable basal rates automatically change within 24 hours. Two hundred and fifty-four different infusion rates ( $0.1 \mu\text{l}/\text{min}$  to  $25.4 \mu\text{l}/\text{min}$ ) can be read back following a mode programmed in EPROM that stores up to eight different meal programmes and two basal rates. Most programmes have a duration of two hours. EPROM was programmed by an Apple II+ computer. Insulin was administered by a Siemens catheter inserted into a deep brachial vein. We used NOVO Actrapid regular insulin in concentrations of 40 iu/ml for the Siemens pump and 25 iu/ml for the individually programmed system containing 2500 iu/ml heparin for prevention of local thrombophlebitis.

For comparison of rectangular and individually programmed infusion profiles blood glucose was measured hourly in capillary blood by a Y 23a glucose analyser (glucose oxydase method). For comparison of profiles with and without initial insulin bolus the patients were connected to the blood glucose measuring system of Biostator, monitoring intravenous blood glucose levels every minute.

The data were depicted as mean value curves with standard error of mean (s.e.m.). The Student *t*-test was chosen for the intra-individual comparison of different profile types.

### Methods

Individual insulin requirements were oriented in accordance with the data provided by Biostator. However, the insulin consumption of the glucose-controlled

system could not be directly transferred to the open-loop devices. Practice from simple Millhill-Infusors<sup>11</sup> and the rapid adjustment of diabetics<sup>3</sup> demonstrated that insulin requirements when GCIIS are used are 15 to 20 per cent higher than are insulin requirements when open-loop systems are used. Therefore, the total insulin dosage had to be reduced.

The basal insulin requirement can be estimated by analysing the insulin requirements between midnight and 3 a.m. A linear correlation between basal insulin requirement (BIR) and total insulin requirement (TIR) is  $TIR = 0.0327 \times BIR - 0.5061$ , calculated from a greater number of patients, enabled the final determination of the daily insulin dosage<sup>19</sup>.

The postprandial amount of insulin minus the basal requirement measured by GCIIS was converted into rectangular profiles having a duration of 1 h, and into individually programmed step profiles having a duration of 2 to 2.5 h. The shape of the step profiles was oriented along two characteristic points of the postprandial blood glucose curve as monitored by the GCIIS (Figure 3): the beginning of blood glucose increase after 10 to 20 min and the maximum after 30 to 40 min. We compared the effect of step and rectangular profiles on the blood glucose profiles in seven IDDs intra-individually.

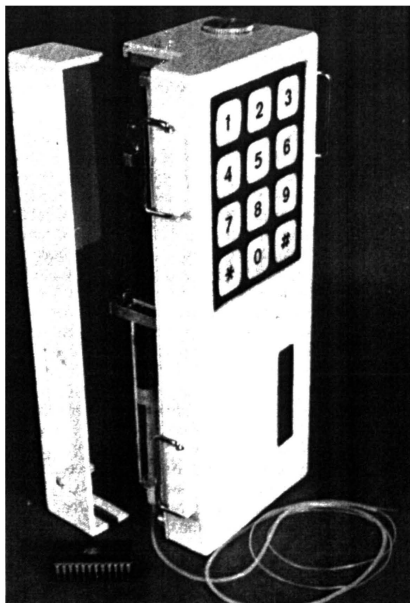


Figure 2. Individually programmed insulin infusion system.

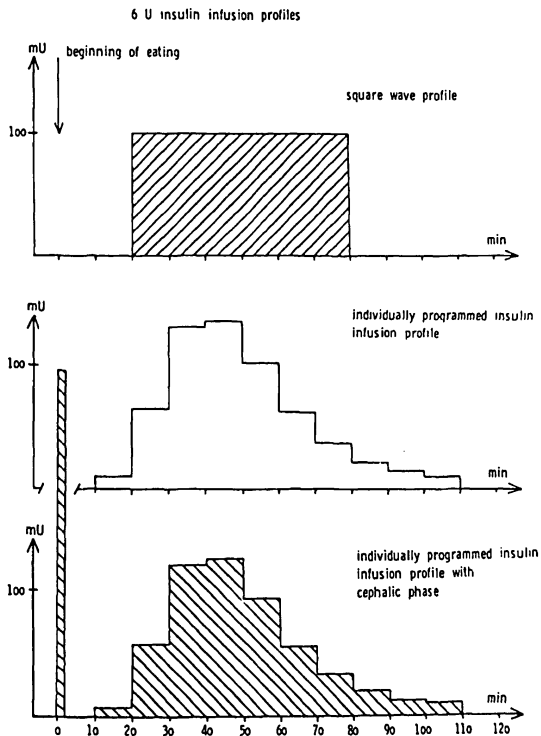


Figure 3. Rectangular and individually programmed step profiles with and without cephalic phase bolus.

An initial insulin bolus was added to the step profile and was intra-individually compared with a pure step profile in five patients. The individually programmed step profile is based upon a mathematical model proposed by E. Cerasi<sup>4,5</sup>, which simulates functional properties of the postprandial pancreatic insulin secretion by an analogue computer model.

The insulin infusion rate (IIR) is proportional to three factors:

1. A hyperbolic tangent function  $f(g)$  calculating the initial phase of IIR.
2. An exponential function  $\exp(p)$  computing the second phase of IIR.
3. An exponential function  $\exp(-b)$  simulating the refractory period of the islets of Langerhans.

Thus, the formula is  $IIR = f(g) \times \exp(p-b)$ .

The numerous constants were empirically determined by analysis of the Bio-stator data. Finally, a monophasic insulin profile results, in accordance with experimental results<sup>6</sup>. However, this model merely considers the insulin secretion characteristics modulated by a blood glucose rise; the preabsorptive insulin secretion or cephalic phase of insulin secretion is presumably controlled by neural and gastrohormonal mechanisms<sup>2,16</sup> simulated by an initial 2-min bolus in this programme. The values of the blood glucose curve and of the corresponding IIR

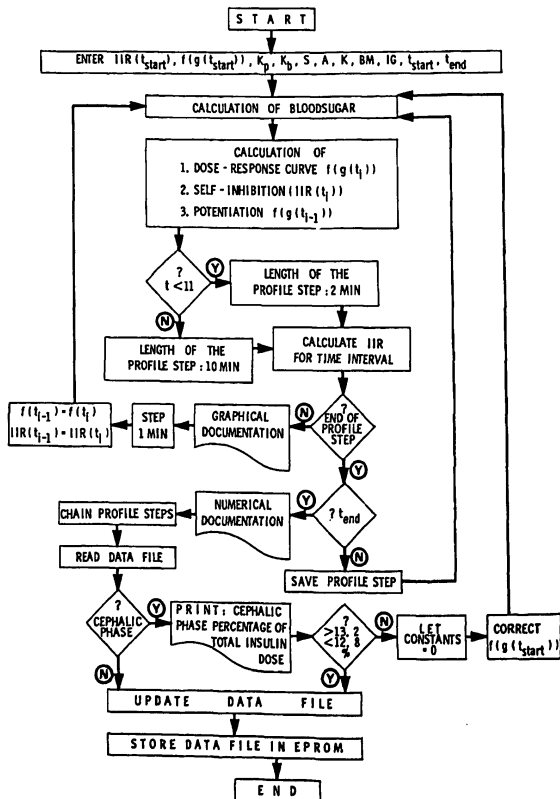


Figure 4. Flow diagram of the computer program.

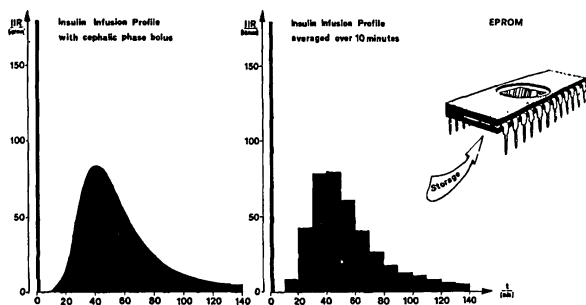


Figure 5. Example of an individually programmed insulin infusion profile with optional cephalic phase bolus.

are computed for every minute (Figure 4); IIR is graphically monitored. Two-minute blocks are computed for the first 10 min to permit the interpolation of the initial insulin bolus. All other values are successively averaged over 10 min. The mean values form 10-min blocks, creating a step-like shape of the infusion profile. Finally, the data are arranged in a chain and stored on a floppy disc, ready for transfer to EPROM (Figure 5).

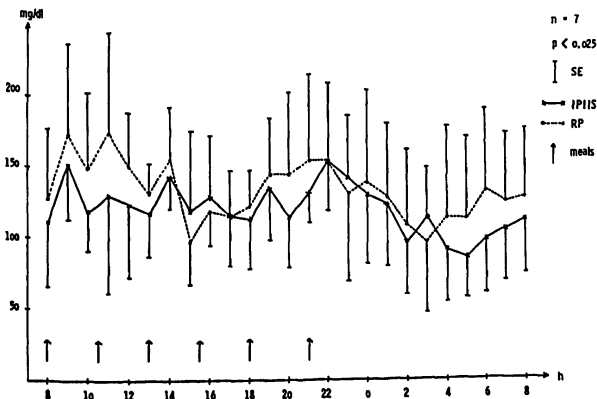


Figure 6. Mean blood glucose values of seven patients treated with individually programmed and rectangular profiles during 24h.

Table 2. Comparison of M value and MAGE of seven IDD patients treated with rectangular and individually programmed insulin infusion profiles

Patient	M value		MAGE (mg/dl)	
	IPIIS	RP	IPIIS	RP
AM	8.5	10.3	60.0	83.5
LG	7.1	11.2	51.0	108.0
LR	14.8	9.5	50.5	64.0
MJ	11.7	9.8	40.0	44.0
RE	7.7	18.9	105.6	165.0
SH	11.9	8.2	38.8	70.0
MK	6.3	10.6	43.0	66.0

$P < 0.3$ 
 $P < 0.005$

## RESULTS

Rectangular and step profiles provided a good blood glucose control without the occurrence of hypoglycaemia or severe hyperglycaemia. Complications such as clogging or rupture of the catheter were not observed. Insulin requirements and mean blood glucose levels were significantly lower when step profiles were used ( $P < 0.05$  vs  $P < 0.025$ ; Figure 6). The M-value<sup>18</sup>, a measure for the quality of blood glucose control that indicates hypoglycaemic periods especially well, did not differ. However, the MAGE<sup>20</sup>, considering blood glucose fluctuations, was

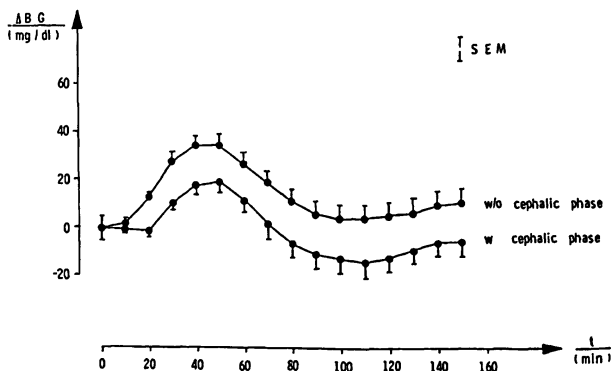


Figure 7. Comparison of postprandial blood glucose profiles produced by step profiles with and without cephalic phase ( $n = 24$  meals of 6 IDD).



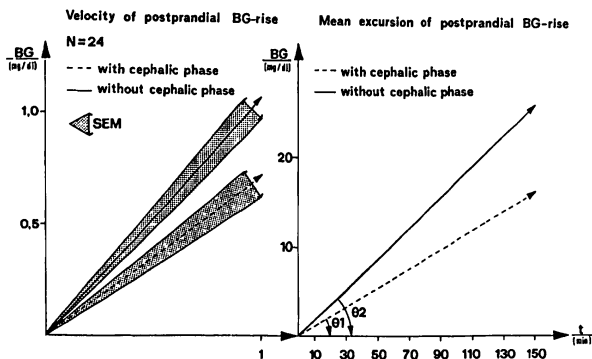


Figure 8. Comparison of velocity and amplitude of postprandial blood glucose profiles produced by step profiles with and without cephalic phase ( $P < 0.01$ ).

significantly lower for the individually programmed step profiles ( $P < 0.005$ ; Table 2). When the step profiles were combined with an initial insulin bolus, postprandial blood glucose levels were significantly lower than when applying only a postprandial step profile ( $P < 0.01$ ; Figure 7). Velocity and mean excursion of the postprandial blood glucose rise were also decreased if the cephalic phase insulin infusion preceded the postprandial step profile (Figure 8).

## DISCUSSION

Open-loop infusion devices succeeded well in improving blood glucose control of diabetics whose metabolism could not be adjusted by the conventional subcutaneous insulin therapy<sup>9,11</sup>. Some effects of continuing hyperglycaemia, such as decreased nerve conduction velocity or increased lipoprotein levels, became normal<sup>14,15</sup>. However, this success should not obscure the fact that the blood glucose levels of patients treated with portable insulin infusion devices are not comparable with the levels found in non-diabetics, even if the effects of hyperglycaemia are reversible. Schade, Eaton and Spencer<sup>17</sup> demonstrated that the blood glucose levels of patients treated with continuous insulin infusion were abnormal despite quite normal intravenous insulin levels. Kraegen, Chrisholm and McNamara<sup>10</sup> also emphasized the importance of the timing of insulin delivery. A small delay in insulin delivery can lead to significantly higher blood glucose levels.

Wavy step profiles cover the period of maximal enteric glucose resorption particularly well, but less insulin is infused in the following postprandial period. Perlman et al<sup>13</sup> used a similar profile but without defining it mathematically. They produced similar results by using a three-block insulin infusion profile.

Numerous animal tests showed that the preabsorptive increase in insulin secretion<sup>2</sup> was caused mainly by nervous factors<sup>16</sup>, and it is therefore called 'cephalic phase' secretion.

Individually programmed step profiles, combined with cephalic insulin infusion, can decrease blood glucose levels and smooth blood glucose fluctuations. Moreover, the preabsorptive insulin infusion may also reduce insulin consumption and thus prevent hyperinsulinism.

### SUMMARY

We studied the insulin requirements of seven insulin-dependent diabetics applying a glucose controlled insulin infusion system. The data were transformed into individually programmed and rectangular profiles. The MAGE, a measure of blood sugar fluctuations, was significantly lower when individually programmed step profiles were used ( $P < 0.005$ ) than it was when rectangular profiles were applied:  $57.7 \pm 24.8$  mg/dl vs  $89.0 \pm 42.9$  mg/dl. The average of measured blood glucose levels was significantly lower in individually programmed infusion profiles ( $P < 0.025$ ). The combination of individually programmed profiles and preprandial insulin bolus significantly reduced the postprandial blood glucose level and increase ( $P < 0.001$ ). Our investigations suggest that individually programmed insulin infusion profiles are able to smooth blood glucose fluctuations. When combined with an initial insulin bolus they may lead to a reduced insulin consumption after meals.

### APPENDIX

For the computation of the Cerasi formula by the Apple II+ computer the differential equations have to be integrated. For  $p(t)$ , the equation is:

$$p(t) = k_p \times f(t)_{t-1} \times \left[ T_p \times T_{p1} \times \left( 1 - \exp\left(-\frac{t}{T_p}\right) \right) - \frac{T_p \times T_{p1}^2}{T_{p1} - T_p} \times \left( \exp\left(-\frac{t}{T_p}\right) - \exp\left(-\frac{t}{T_{p1}}\right) \right) \right]$$

in which  $T_p$ ,  $T_{p1}$  and  $k_p$  are constants. A similar equation gives  $b(t)$ :

$$b(t) = k_b \times IIR_{t-1} \times \left[ T_b - T_{b1} \times \left( 1 - \exp\left(-\frac{t}{T_b}\right) \right) - \frac{T_b \times T_{b1}^2}{T_{b1} - T_b} \times \left( \exp\left(-\frac{t}{T_b}\right) - \exp\left(-\frac{t}{T_{b1}}\right) \right) \right]$$

in which  $T_b$ ,  $T_{b1}$  and  $k_b$  are constants.

Since the open-loop insulin infusion system does not measure the actual blood glucose concentration a rigid model has to simulate the postprandial behaviour of the blood glucose. Its ascending part simulates the slow rise of blood glucose after an oral food intake:

$$BG_{asc} = \frac{C_1 \times \exp(k_1 \times t_1) - C_2 \times \exp(k_2 \times t_1)}{C_1 \times \exp(k_1 \times t_1) + C_2 \times \exp(k_2 \times t_1)}$$

in which  $C_1$ ,  $C_2$ ,  $k_1$  and  $k_2$  are constants. The descending part of this curve takes the blood glucose lowering effect of the infused insulin into account:

$$BG_{desc.} = C_3 \times \exp(k_3 \times t_i)$$

in which  $C_3$  and  $k_3$  are constants. Thus the formula for the simulated postprandial blood glucose curve reads as follows:

$$BG = BM \times BG_{asc.} \times BG_{desc.}$$

in which BM is a factor proportional to the amount of carbohydrates taken in.

The sigmoidal dose-response curve is approximated by a hyperbolic tangent function:

$$f(G) = \tanh(G), \text{ whereby } G = a \times \exp(k \times BG)$$

in which a and k are constants.

#### ACKNOWLEDGEMENTS

This article is part of the doctoral thesis of T. Strack. The study was supported by BMFT (Dismed 13).

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