Incidence of Hypoglycemic Episodes in Diabetic Patients Under Continuous Subcutaneous Insulin Infusion and Intensified Conventional Insulin Treatment: Assessment by Means of Semiambulatory 24-hour Continuous Blood Glucose Monitoring

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The incidence and magnitude of hypoglycemia (i.e., blood glucose values <50 mg/dl) were assessed by continuous blood glucose monitoring over 24 h in 10 insulin-dependent diabetic (IDD) patients treated with continuous subcutaneous insulin infusion (CSII) and 9 IDD patients under intensified conventional treatment (ICT). A newly developed, battery-powered blood glucose monitor was employed. Patients were thus enabled to move freely in the hospital premises. Despite similar quality of previous blood glucose control (HbA_1: 8.0 ± 0.05% CSII versus 8.0 ± 0.3% ICT, $\bar{x}$ ± SEM), the obtained profiles showed better regulation under CSII treatment (mean blood glucose [MBG], 99.6 ± 10.0 versus 133.1 ± 7.4 mg/dl; M-value, 12.3 ± 3.5 versus 26.2 ± 4.1; mean amplitude of glycemic excursion [MAGE], 71.9 ± 8.7 versus 132.9 ± 14.2 mg/dl; CSII versus ICT, $\bar{x}$ ± SEM). The incidence of blood glucose values <50 mg/dl was 9/10 patients (CSII) and 5/9 patients (ICT). In both groups, hypoglycemia was most frequent at noon and was related to elevated pre- and postprandial free insulin levels. Patients became aware of hypoglycemia only in 6/23 episodes (CSII) and 6/8 episodes (ICT). Our data indicate that CSII as well as ICT may result in postprandial hyperinsulinemia leading to frequent hypoglycemic episodes of variable length, reassessing the traditional experience of close correlation between aggressive insulin therapy and enhanced hypoglycemic risk. DIABETES CARE 1985; 8:134–40.

Intensified conventional insulin therapy[1] and continuous insulin infusion, either i.v.,[2,3] s.c.,[4] or i.p.,[5] have been increasingly employed in the last 5 yr in an attempt to improve blood glucose control in insulin-dependent diabetic individuals, and thus to prevent or postpone the development of microangiopathic complications. Although the primary goal, namely the lowering of the blood glucose values, has been attained, the influence of long-term blood glucose normalization on vascular disease remains controversial.[6–10]

In the last 2 yr, attention has been focused on the increasing number of severe hypoglycemic complications recorded in patients treated with intensified insulin regimens.[11,12] These complications include unconsciousness and even death related to the hypoglycemic attacks[13,14] (European Study Group on Artificial Insulin Delivery Systems and Pancreas-Islet Transplantation, unpublished observations).

All patients treated with insulin pumps or intensified conventional therapy (ICT) perform self-monitoring of blood glucose more or less frequently during the day, but, obviously, this method cannot provide complete, thorough information about daily glycemic fluctuations, leaving many "black holes" at different times of the day, and mainly during the rest hours.

Given the lack of sensitivity emerging from punctual blood glucose measurements, we developed this protocol to assess the incidence, magnitude, duration, and distribution of hypoglycemic episodes, i.e., blood glucose values <50 mg/dl, emerging as a consequence of continuous subcutaneous insulin infusion (CSII) treatment and ICT throughout a 24-h period.

PATIENTS AND METHODS

Patients. Nineteen IDD patients, whose clinical features are listed in Table 1, gave written consent for participating in this study. Patients 1–10 had been on CSII for at least 3 mo. Patients 11–19 were successfully treated with two daily injections of mixtures of regular and long-acting insulins, adjusting the dose according to the blood glucose values measured at least two times daily. Table 2 summarizes the treatment features of the investigated IDD patients.

Study protocol. Twenty-four-hour blood glucose monitor-

TABLE 1
Anthropometric and clinical data of the investigated patients

Therapy	Patient no.	Age (yr)	Broca index*	Duration of diabetes (yr)	Late diabetic complications		
					Retinopathy†	Neuropathy‡	Nephropathy§
CSII	1	25	0.81	19	+	+	+
	2	18	0.82	9	−	−	−
	3	33	1.07	10	−	−	−
	4	22	0.96	12	−	−	−
	5	46	0.72	1	−	−	−
	6	45	0.95	5	−	−	−
	7	23	0.96	18	+	−	−
	8	18	0.74	1	−	−	−
	9	23	0.98	20	+	−	+
	10	31	0.98	10	−	−	−
	$\bar{x}$	28.4	0.90	10.5			
	SEM	3.2	0.04	2.2			
ICT	11	53	1.01	22	−	−	−
	12	22	0.79	8	−	−	−
	13	25	0.99	6	−	−	−
	14	27	0.96	15	−	−	−
	15	28	1.10	11	+	−	−
	16	24	0.83	11	−	−	−
	17	34	0.94	30	+	−	−
	18	29	0.84	8	−	−	−
	19	39	0.97	8	−	−	−
	$\bar{x}$	31.2	0.97	13.2			
	SEM	9.7	0.10	7.9			

*Broca index = weight (kg):(height [cm] − 100).
†Background and proliferative funduscopic changes.
‡Reduction of nerve conduction velocity.
§Persistent proteinuria (>0.3 g/dl).

ing began at 6 p.m. Thirty minutes before, an indwelling cannula (18 g, 44.5 mm, Jelco Laboratory, Raritan, New Jersey) had been inserted into a superficial vein of the patient's forearm, thus allowing continuous blood sampling through a double-lumen catheter (Life Science Instruments, Munich, West Germany).

The CSII-treated patients received their usual food intake at 7 p.m., 8 a.m., and 1 p.m. These meals contained approximately 37.5%, 25%, and 37.5%, respectively, of the total carbohydrate intake. Low-carbohydrate–containing snacks were given at 10 p.m., 11 a.m., and 4 p.m. In the ICT group each of the main meals, administered according to the same schedule, contained 22%, and the three snacks 11% each of the total carbohydrate intake, respectively.

While patients treated with motor-driven syringe pumps (AS6C, AS6MP, AutoSyringe, Hooksett, New Hampshire; CPI 9100, CPI Lilly, Indianapolis, Indiana) administered their premeal boluses 30 min before the main meals, patients carrying peristaltic pumps (Promedos E1, Siemens, Erlangen, West Germany) switched on the corresponding high-infusion rate 45 min before. Patients under ICT injected themselves with their usual insulin doses in the deltoid region 30 min before breakfast and supper.

During the second hour after the main meals the patients walked within the hospital's limits pushing the blood glucose monitor in front of them, thus trying to mimic a normal day's activity.

Analytics and statistics. Blood glucose monitoring was performed with the mobile fashion of the glucose monitor, taken from the Ulm version of the artificial endocrine pancreas or glucose-controlled insulin infusion system (GCIIS),[15] which later became commercially available as a GCIIS Biostator.[16,17] This monitor has been modified in our biotechnical laboratory. The modifications included 24 V DC supply from an accumulator and continuous registering of the blood glucose data in a cassette memory unit. Calibrations with baseline and standard solutions[15] performed every 2 h showed a minimal sensor drift. The accuracy of the blood glucose monitor used in this study had been investigated previously: blood glucose values measured with this device correlated well with the reference (hexokinase) method ($r = 0.95$, $N = 299$; unpublished data).

Glycosylated hemoglobin levels were measured from blood samples taken immediately after connecting the patients to the glucose monitor by microcolumns (Panchem, Kleinwallstadt, West Germany). The normal range ($\bar{x} \pm 2SD$) for this method was 5.1–7.1%.

Blood samples for the determination of free insulin were

TABLE 2
Treatment features of the investigated patients

CSII	Patient no.	Pump model	Duration of treatment (days)	Insulin doses: Basal (IU/d)	Breakfast (IU)	Lunch (IU)	Supper (IU)	HbA_1 (%)
	1	CPI	494	8/12*	6	6	6	6.3
	2	P E1	371	42/36†	10	10	10	7.0
	3	AS6C	150	16/20†	4	6	2	9.1
	4	AS6C	90	12	6	5	5	7.4
	5	AS6C	370	22	5	4	4	7.8
	6	AS6C	242	26	15	9	11	8.3
	7	CPI	146	13/11†	10	4	6	7.1
	8	AS6C	308	17/12†	6	8	11	8.2
	9	P E1	120	12	2	4	3	10.4
	10	AS6MP	130	19/31*	4	4	4	10.3
	$\bar{x}$							8.0
	SEM							0.5

ICT	Patient no.	Morning doses (IU): Long acting	Morning doses (IU): Regular	Evening doses (IU): Long acting	Evening doses (IU): Regular	HbA_1 (%)
	11	20	—	8	4	7.9
	12	16	14	8	8	9.4
	13	24	12	22	8	7.1
	14	10	12	6	6	6.8
	15	20	8	8	4	7.8
	16	24	16	8	4	8.2
	17	8	6	14	6	7.6
	18	30	6	20	4	8.2
	19	12	6	6	10	8.8
	$\bar{x}$					8.0
	SEM					0.3

*Early morning basal rate (4–7 h).
†Nocturnal basal rate (0–6 h).

obtained at regular intervals through a second Jelco cannula placed in an elbow flexure vein of the arm already connected to the glucose monitor. They were kept at room temperature for 1 h and then serum was separated and deep frozen. Free insulin was assayed according to Nakagawa et al.[18]

To assess the degree of blood glucose regulation, the MBG value, M-value, and MAGE[19] were calculated from the obtained profiles.

A hypoglycemic episode was defined by blood glucose values persisting for 3 min or more under a reference level of 50 mg/dl. The areas of the registered episodes were then integrated according to the trapezoidal rule. For this calculation the difference of the actual blood glucose value from the mentioned reference level was used (integrated value = 50 − actual BG). The results, expressed in mg/dl/min, reflect not only the magnitude or depth, but also the duration of the hypoglycemic episodes. Finally, the distribution of these episodes throughout the day was analyzed by considering the number of patients showing blood glucose values <50 mg/dl at any time during the 24-h period.

Statistical evaluation was performed by one-way analysis of variance.[20]

RESULTS

Blood glucose and free insulin profiles. The mean blood glucose curves, as well as the measured free insulin levels of both groups are depicted in Figure 1. ICT patients showed higher blood glucose values throughout the day. This difference increased in the early morning and late afternoon hours, as the activity of the injected long-acting insulin seemed to fade away. The calculated blood glucose regulation parameters were: MBG, 99.6 ± 10.0 and 133.1 ± 7.4 mg/dl; M-value, 12.3 ± 3.5 and 26.2 ± 4.1; MAGE, 71.9 ± 8.7 and 132.9 ± 14.2 mg/dl for the CSII and ICT groups, respectively.

Under CSII, the administration of the evening insulin bolus at 6:30 p.m. resulted in a significant ($P < 0.01$ versus 6 p.m. value) increase of the free insulin concentrations that reached its peak 90 min thereafter; insulin levels then decreased slowly, returning to baseline values at 12 p.m. Between midnight

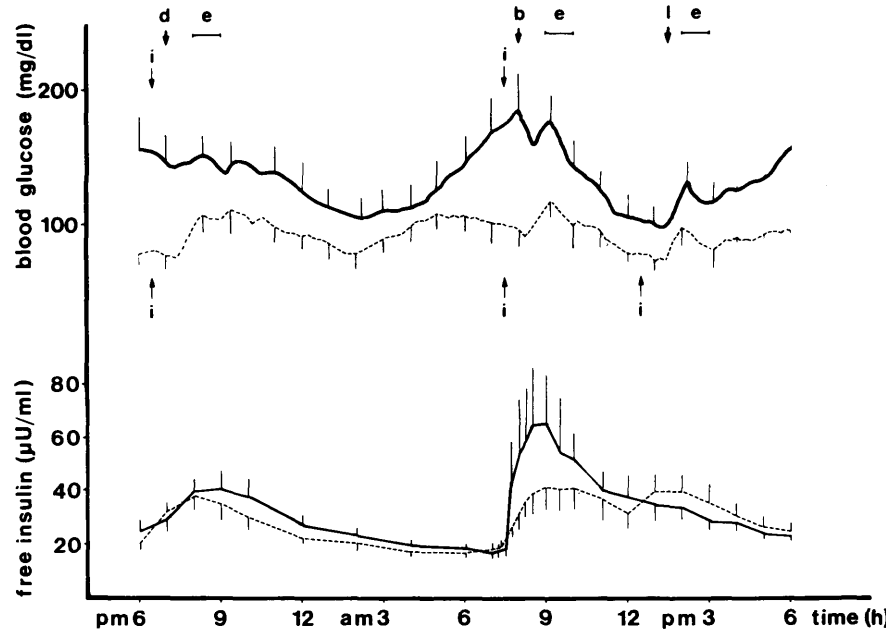

FIG. 1. Circadian blood glucose and free insulin levels in ICT (solid line) and CSII (dotted line) patients ($\bar{x} \pm SEM$). d, Dinner; b, breakfast; l, lunch; e, exercise; i, insulin injection (either bolus or conventional).

and 7 a.m. insulin concentrations fluctuated slightly around 20 μU/ml. A significant rise of the insulin levels was again observed after breakfast bolus administration ($P < 0.01$ versus 7:30 a.m. value). The injection of the midday bolus promptly reversed the falling insulin levels. Insulin concentrations were thus raised to 40 μU/ml at 1 p.m. and remained elevated (>30 μU/ml) until 4 p.m. Somewhat higher free insulin levels were observed in the ICT group after supper, during the night, and mainly, after breakfast, when a steep rise (up to 60 μU/ml, $P < 0.05$ versus 7:30 a.m. value) was registered. The insulin concentrations gradually fell thereafter till 6 p.m., that is to say, no rise in insulin revels concomitant to lunch administration occurred.

Hypoglycemic episodes. Regarding the incidence of hypoglycemic episodes, these were observed in 9 of 10 patients in the CSII-treated group and in 5 of 9 patients under ICT. The mean cumulative duration of the hypoglycemic phases and the mean area under the 50 mg/dl edge, as well as the blood glucose nadir registered during the study, are shown in Table 3.

We did not find an increased incidence of hypoglycemic episodes during the nocturnal period in pump-treated patients. Indeed, the early morning rise in the insulin requirements (the so-called "dawn phenomenon") was accompanied by a complete absence of low glycemic values between 4 and 6 a.m. Hypoglycemia was more frequent immediately before and after meals, especially after lunch. In the ICT group no hypoglycemic episodes were registered after 2 a.m. Concomitantly with the elevated fasting blood glucose levels depicted in Figure 1 the morning hours were also free of hypoglycemia in this group. Maximal incidence of hypoglycemia was also found in this group around the lunch hours (12 a.m.–2 p.m.).

Clinical findings. Mild hypoglycemic symptoms, leading to supplementary carbohydrate intake, were noted by the CSII patients during 6 of the total 23 registered hypoglycemic episodes, and during 6 of the 8 episodes documented in ICT patients.

DISCUSSION

After more than 60 yr of insulin replacement therapy, hypoglycemia is still its most feared complication. Old therapeutic approaches that considered permanent slight glycosuria as an optimal goal have been overcome. Urged by modern premises that emphasize the importance of blood glucose near normalization in diabetic individuals, we must face the consequences of "aggressive" insulin regimens.

Until now, the incidence of hypoglycemia in patients under ICT and CSII had not been established on the basis of an accurate registration method. Continuous 24-h blood glucose monitoring under semiambulatory conditions enabled us to show an impressively high incidence of hypoglycemic episodes in IDD patients under intensified insulin regimens, since blood glucose fell below 50 mg/dl at least once during the study in 9 of 10 CSII, and in 5 of 9 ICT patients.

Any comparison between the two groups regarding blood glucose control and incidence, duration, and severity of the documented hypoglycemias has been avoided, given the small sample size and the lack of randomization of the investigated subjects to the ICT and CSII groups. Besides, the incidence of hypoglycemia would probably have been increased in the ICT group if a more intensive insulin treatment had been used. Another source of variation is given by the differences in carbohydrate administration. We considered, in accordance with others,[21] that carbohydrate-containing snacks were

TABLE 3
Incidence, duration, and magnitude of the registered hypoglycemic episodes in CSII patients (1–10) and ICT patients (11–19)

Patient no.	Number of episodes	Cumulated duration (min)	Integrated area (mg/dl · min)	BG nadir (mg/dl)
1	3	180	2322	32
2	5	284	1623	38
3	3	384	3129	34
4	0	0	0	65
5	1	24	78	44
6	1	3	6	48
7	1	20	105	45
8	*5*	*422*	*3105*	*29*
9	1	110	360	45
10	3	41	234	37
$\bar{x}$	2.3	146.8	1096.2	41.7
SEM	0.6	51.4	416.9	3.3
11	2	48	333	37
12	0	0	0	75
13	0	0	0	88
14	1	20	135	43
15	1	13	18	42
16	1	6	6	48
17	3	200	1722	31
18	0	0	0	65
19	0	0	0	61
$\bar{x}$	0.9	31.9	246.0	54.4
SEM	0.4	21.7	188.2	6.3

not necessarily mandated in CSII patients receiving only short-acting insulin. Furthermore, and given the existence of day-to-day variations in blood glucose profiles of IDD patients, and the possible influence of hospitalization upon metabolic regulation, this brief period of in-hospital monitoring does not enable us to assume that the obtained blood glucose profiles are representative of the degree of diabetes control attained outside the clinic under both therapeutic approaches.

Of all factors contributing to hypoglycemia in the investigated patients we will consider first the circadian insulin levels. Bolus administration in CSII patients resulted in significant increases of the free insulin concentrations, basal levels being regained only 5–6 h thereafter. These data are supported by the previous work of Lauritzen et al.,[22] concerning the pharmacokinetics of CSII. Similar or slightly higher free insulin levels have been described in CSII-treated patients.[23–26] Protracted hyperinsulinemia leading to late postprandial low blood glucose values seems to be the unavoidable consequence of subcutaneous insulin bolus administration.

The elevated free insulin levels registered during the morning hours in the ICT group can be attributed to the higher mean regular insulin quantities given by these patients before breakfast to cope with the higher fasting blood glucose values. During the afternoon and night hours the insulin levels decline gradually according to the described pharmacokinetics of injected long-acting insulins.[27,28]

Independently of the insulin concentrations, five patients (1, 2, 3, 8, and 17) show longer-lasting and deeper hypoglycemias, duration ranging from 180 to 422 min (Table 3). As shown previously, these prolonged, and sometimes deep, hypoglycemic episodes could be related to a defective glucose counterregulatory response,[29–32] and reflect a potential danger of severe, acute, and, perhaps, chronic neuroglycopenia. In fact, patients 1, 2, 3, and 8 have suffered from hypoglycemic attacks leading to unconsciousness at least once in their averge 1.9 yr of CSII treatment. Concerning the distribution of hypoglycemic episodes throughout the day, only patients 1, 2, 3, 8, and 17 showed low blood glucose values between 12 p.m. and 6 p.m. These results are in accordance with those reported by White et al.[30] But the highest incidence of hypoglycemia was registered before and after lunch, linked to the persistently elevated free insulin levels.

Clinical findings during the 24-h study indicate that the perception of hypoglycemia is blunted in patients under intensified insulin regimens. Only 25% of the registered low blood glucose values were noted by the pump-treated patients, while in the conventionally treated group this percentage was raised to 75%. The wider blood glucose fluctuations shown in this group could account for this difference. Nevertheless, an increased tolerance to low blood glucose values in CSII-treated patients, as suggested by our own clinical experience and also by Barbosa et al.,[33] cannot be ruled out.

We may conclude from the present data that: (1) subcutaneous insulin delivery, both by means of conventional in-

jection or continuous infusion, leads to postprandial hyperinsulinemia that results in low blood glucose values, irrespective of the employed therapeutic regimen and further confirming the old experience that tight regulation results in an enhanced hypoglycemic risk; (2) this condition seems to be aggravated in some particular cases of both groups, probably linked to a defective counterregulatory response, and resulting in far more extended and deeper hypoglycemias; (3) the true incidence of hypoglycemic episodes can be appreciated only by continuous blood glucose monitoring. Asymptomatic hypoglycemia will not otherwise be detected by occasional blood glucose measurements.

Reducing the risk of developing hypoglycemia in IDD patients treated with intensified insulin regimens hardly seems to be an attainable goal, given the inadequacy of present insulin therapy and, at least in some cases, the existence of defective counterregulatory mechanisms. Nevertheless, and according to our results, a few strategies might be suggested. The incidence of bolus-related hypoglycemia can be lowered by shortening the bolus meal delay (30 min in our cases) to 15 min or less, according to the preprandially measured blood glucose values, and by adding carbohydrates to the snacks to neutralize postprandial hyperinsulinemia. Increasing the frequency of blood glucose monitoring to 4–5 determinations/day (before meals, before going to bed, and, when necessary, at 3 a.m.) can be of paramount importance in patients lacking adequate counterregulatory mechanisms. The identification of these patients by means of a reproducible insulin tolerance test seems desirable. Still, unless it is indicated after a thorough evaluation of the individual risk/benefit ratio, we do not consider that patients with altered glucose counterregulation should be promptly ruled out of intensified therapy programs. Finally, aiming at higher blood glucose levels, not only fasting but also before lunch and supper, will obviously lower the incidence of hypoglycemic episodes induced by CSII and ICT. Restoring the disrupted feedback relationship between glycemic levels and insulin administration by means of islet cell or pancreas transplantation, or a portable, closed-loop insulin infusion system seems to be the only safe way of achieving normoglycemia in insulin-dependent diabetes.

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