A 6-Hour Nocturnal Interruption of a Continuous Subcutaneous Insulin Infusion: 1. Metabolic and Hormonal Consequences and Scheme for a Prompt Return to Adequate Control

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Summary. Interruption of a continuous subcutaneous insulin infusion, most often due to technical problems occurring during the night, is a not uncommon event whose metabolic consequences have received relatively little attention until now. We have therefore investigated the changes in blood glucose, plasma non-esterified fatty acids, 3-hydroxybutyrate, glucagon and free insulin in eight C-peptide negative Type 1 diabetic patients whose pumps were deliberately stopped between 23.00 h and 05.00 h. A control test with the pump functioning normally was carried out in each patient and the studies were randomized. Considering the values at 23.00 h as reference, interruption of the insulin infusion resulted in (1) a rapid decrease in plasma free insulin significant after 1 h and reaching a nadir of 6 ± 2 mU/l after 6 h; (2) a rise in blood glucose which was significant at hour 3 and reached 17.4 ± 1.9 mmol/l at hour 6; (3) a moderate increase in plasma non-esterified fatty acids which remained in the range of $700–800$ μmol/l; (4) an early and linear rise in plasma 3-hydroxybutyrate, significant after 1 h and averaging 1290 ± 140 μmol/l after 6 h; (5) a late increase (hour 5) in plasma glucagon. The second aim of our study was to provide for the patient a precise scheme of insulin supplements administered via the pump and based on blood glucose monitoring (Dextrostix – Glucometer) and semi-quantitative evaluation of ketonuria (Acetest). Resetting the pump at its basal rate at 05.00 h and giving insulin supplements (2–8 U) at 06.45 h (with the usual breakfast dose) and again at 10.00 h have proved efficacious in restoring satisfactory metabolic control by noon the day after starting the experiment. These results form practical recommendations to patients undergoing this type of accident.

Key words: Continuous subcutaneous infusion, Type 1 diabetes, glucagon, insulin, management, non-esterified fatty acids, pump.

The major importance of good metabolic control in all forms of diabetes is now well documented [1]. In Type 1 (insulin-dependent) diabetic patients, continuous subcutaneous insulin infusion (CSII), using small portable pumps, has been proposed to attain this goal, with encouraging results [2–5]. A hazard of this treatment is the fortuitous interruption of the subcutaneous insulin delivery due to failure of the pump or delivery system. Until the recent publication of Pickup et al. [6], this question had received relatively little attention [7]. The aim of the present study was (1) to perform a detailed analysis of the hormonal and metabolic changes occurring during a 6 h nocturnal interruption of CSII in Type 1 diabetic patients; (2) to provide a precise scheme for a prompt return to adequate control. For this second part of the study, the scheme was designed to be usable by the patient himself on the basis of blood glucose monitoring and semi-quantitative evaluation of ketonuria.

Material and Methods

Subjects

The study was approved by the Ethical Committee for Human Investigations of our Institution and all subjects gave their free and informed consent. Eight Type 1 C-peptide negative diabetic patients participated in the study. Individual data are given in Table 1.

Experimental Procedures

The patients, who had been accustomed to their 1001 HM Mill Hill Infuser for 5–10 days, used it at 17.45 h to deliver their usual pre-dinner insulin dose (8.4 ± 1.1 U); dinner was taken from 18.00 to 18.30 h. At 22.00 h, a catheter was inserted in an antecubital vein. At 23.00 h, the pump was stopped by removing the battery. At 05.00 h, the pump was reactivated at its basal rate (1.1 ± 0.2 U/h). At 06.45 h, the subjects made their usual pre-breakfast 'clicks' (handling the knob of the Mill-Hill Infuser to deliver boluses of insulin makes a 'click' which corresponds to the delivery of a certain amount of insulin depending upon the insulin concentration in the syringe; in the present investigation,

Table 1. Clinical characteristics of eight Type 1 diabetic patients

| Subjects	1	2	3	4	5	6	7	8	Mean ± SEM
Sex	F	F	M	M	M	F	M	M	3 F; 5 M
Age (years)	33	41	44	53	31	51	41	49	43 ±3
Height (cm)	167	165	169	167	170	170	173	166	168 ±1
Weight (kg)	60	65	72	73	64	71	61	53	65 ±2
% Ideal body weight	104	116	114	119	100	119	92	87	106 ±4
Duration of diabetes (years)	12	30	23	23	28	18	16	7	20 ±3
Plasma creatinine (mmol/l)	0.08	0.11	0.09	0.10	0.11	0.06	0.10	0.10	0.09 ± 0.02
Basal insulin delivery rate (U/h)	0.9	0.8	1.2	1.3	1.0	1.2	1.0	1.2	1.1 ±0.2
Insulin before breakfast (U)	7	3	9	9	6	12	9	12	8.4 ±1.1
Insulin before lunch (U)	5	4	8	7	6	9	6	8	6.6 ±0.6
Insulin before dinner (U)	7	3	7	6	5	9	7	8	6.5 ±0.7
Anti-insulin antibodies (U/l)	0.82	0.55	0.07	1.32	0.10	0	–	0.35	0.46 ± 0.18
2-h post-prandial C-peptide (nmol/l)	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025	< 0.025
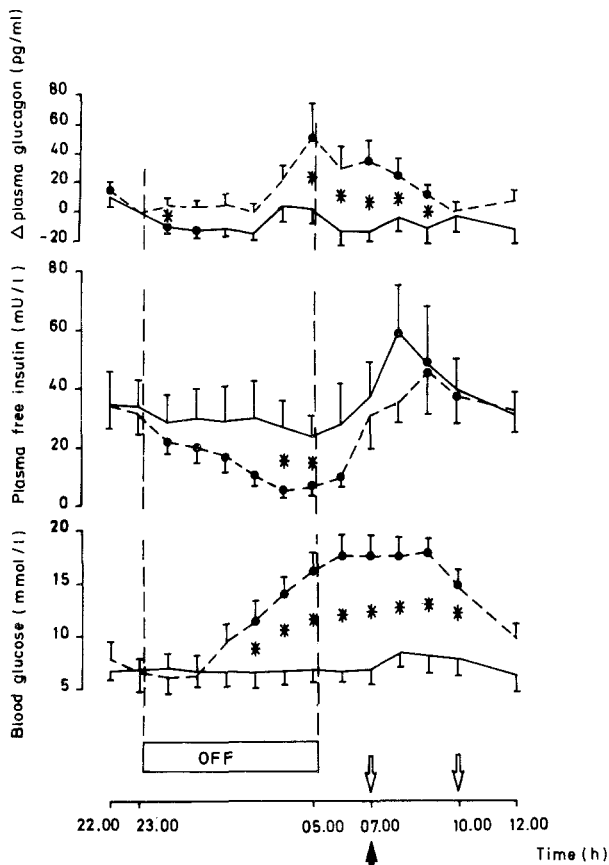
Fig. 1. Changes in blood glucose, plasma free insulin and plasma glucagon levels during normal functioning of the CSII (———) and during interruption (- - - -). Results are expressed as mean ± SEM. * = $2p < 0.05$ 'on' *versus* 'off'; • = $2p < 0.05$ *versus* 23.00 h value; $n = 8$ ▲ = breakfast; ⌂ = 'clicks' (boluses of insulin)

each 'click' corresponded to 0.6–1.0 U of insulin; mean 0.9 ± 0.2 U) together with additional 'clicks' whose numbers were based on a capillary blood glucose determination using a Dextrostix read on a Glucometer and a ketonuria test using Acetest (Ames Division, Miles Laboratories, Elkhart, Indiana, USA). The additional amounts of insulin were 8 U administrated via the pump if blood glucose was > 22 mmol/l (whether or not ketonuria was present), 6 U if blood glucose was > 16.5 mmol/l with ketonuria; 4 U if blood glucose was > 16.5 mmol/l without ketonuria and 2 U if blood glucose > 11 mmol/l.

At 07.00 h, the patients ate their usual breakfast; at 10.00 h the same scheme of insulin supplements was applied if blood glucose was > 11 mmol/l and the protocol ended at 12.00 h. Each subject underwent two tests at random: one as just described (pump off or 'off') and the other which was identical (same timetable; same meals) but without interruption of the CSII (pump on or 'on'). The two tests were separated by at least 2 days. The subjects were asleep in both conditions tested.

Blood Samples and Determinations

Blood samples were drawn every hour from 22.00 till 12.00 h the next day (except at 11.00 h). Blood glucose was measured using the hexokinase method adapted to the Technicon autoanalyzer, plasma non-esterified fatty acids (NEFA) according to Dole and Meinertz [8], plasma 3-hydroxybutyrate (3-OHB) using an enzymatic assay (β-hydroxybutyrate dehydrogenase, Boehringer, Mannheim, FRG), plasma glucagon according to Luyckx [9] using 30K antibody (Dr R. H. Unger, Dallas, Texas, USA), plasma growth hormone using the HGHK kit (CIS International, Sorin, Italy), plasma cortisol according to Sulon et al. [11] and plasma C-peptide according to Heding [12]. Plasma free insulin was assayed according to Nakagawa et al. [10]; in each assay, two standard-curves were performed one in the presence, the other in the absence of polyethylene glycol. After adaptation for dilution, both curves fitted perfectly ($r = 0.99913$). The detection limit was 5 mU/l; the intra-assay coefficient of variation was ± 4.1% and the interassay coefficient ± 9.6%. For all determinations, samples for the same subjects were assayed in the same radioimmuno- or enzymatic assay.

Statistical Evaluation

The results are expressed as mean ± SEM. Statistical evaluation was performed according to the Student's t-test for paired values. All data are compared both between the 'on' and 'off' tests and, within a given test, versus the value recorded at 23.00 h, considered as baseline. For this last comparison, preliminary analysis of variance, using the Anova test, allowed the subsequent use of the Student's t-test.

Results

Blood Glucose (Fig. 1)

During the control test ('on'), blood glucose remained constantly within the normal range. In the interruption test ('off'), blood glucose values remained unchanged during the first 2 h after stopping the pump, and then in-

Table 2. Plasma cortisol and growth hormone levels in the eight Type 1 diabetic patients without interruption ('on') and with interruption ('off') of CSII

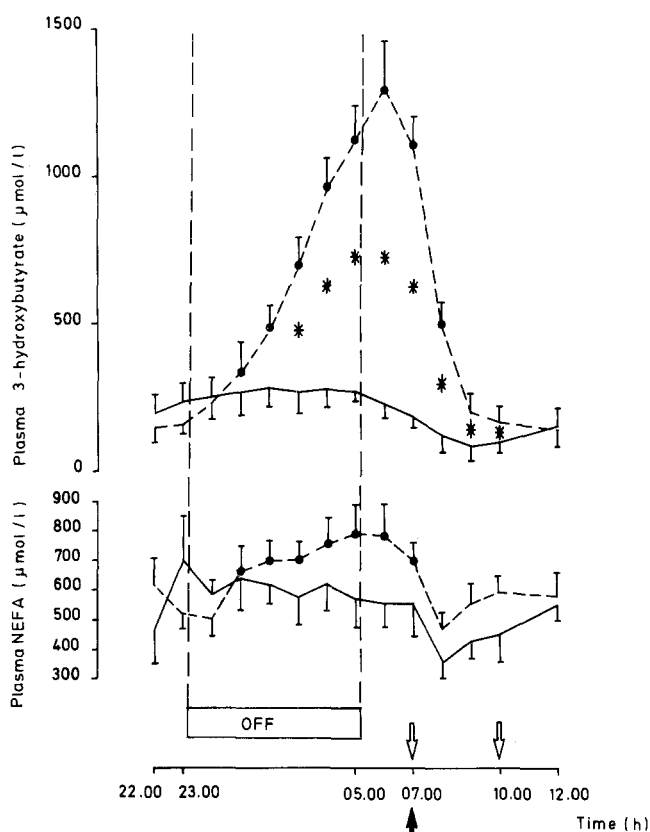|	23.00 h	03.00 h	05.00 h	08.00 h	12.00 h
Plasma cortisol (µg/dl)					
'on'	3.7 ± 0.9	6.1 ± 1.3	10.9 ± 1.4	14.0 ± 1.6	11.1 ± 1.4
'off'	5.1 ± 1.6	4.9 ± 1.1	13.6 ± 2.7	14.1 ± 1.4	9.2 ± 1.0
Plasma growth hormone (ng/ml)					
'on'	3.7 ± 1.5	3.2 ± 1.2	2.3 ± 0.8	1.3 ± 0.2	5.6 ± 2.2
'off'	3.7 ± 3.4	2.7 ± 1.0	2.1 ± 0.7	3.8 ± 1.8	1.6 ± 0.3

Results are given as mean ± SEM

Fig. 2. Changes in plasma non-esterified fatty acids (NEFA) and plasma 3-hydroxybutyrate levels during normal functioning of the CSII (———) and during the interruption test (- - - - -). Results are expressed as mean ± SEM. $* = 2p < 0.05$ 'on' *versus* 'off'; $\bullet = 2p < 0.05$ *versus* 23.00 h value; $n = 8$ ▲ = breakfast; ⌂ = 'clicks' (boluses of insulin)

creased regularly from hour 3 after interruption until 1 h after resetting the pump at its basal rate. The rate of this linear blood glucose rise averaged 0.032 ± 0.003 mmol·l^{-1}·min^{-1} between 02.00 and 06.00 h. From 06.00 to 09.00 h, blood glucose values remained stable at approximately 17.5 mmol/l and then decreased rapidly to reach 10 mmol/l at 12.00 h. The blood glucose levels in the 'off' tests were significantly different from the 23.00 h value and from the values recorded in the 'on' test from 03.00 to 10.00 h.

Plasma Free Insulin (Fig. 1)

During the control test ('on'), plasma free insulin concentration decreased slightly, but not significantly from 35 to 25 mU/l during the night; it increased markedly and significantly after the breakfast 'clicks' to reach a value of 60 mU/l at 08.00 h and then decreased progressively, reaching 30 mU/l at the end of the study. In the interruption test ('off'), plasma free insulin concentration decreased significantly 1 h after stopping the pump to reach a nadir of 6 ± 2 mU/l at 04.00 and 05.00 h; after resetting the pump at its basal rate between 05.00 and 06.45 h, and after administration of the morning 'clicks', plasma free insulin increased markedly to 45 ± 15 mU/l and then decreased at the end of the study to reach a concentration identical to that observed in the control test. Plasma free insulin values were significantly lower in the interruption test ('off') versus the control test ('on') at 04.00 and 05.00 h.

Plasma Glucagon (Fig. 1)

Results of plasma glucagon determinations were expressed as changes versus the value recorded at 23.00 h considered as baseline for each subject; these basal values were not significantly different in the two tests (63 ± 22 'on' versus 45 ± 22 pg/ml 'off'). In the control test ('on'), plasma glucagon levels showed no major fluctuations, except a significant decrease between 23.00 and 01.00 h. In the interruption test ('off'), plasma glucagon levels decreased significantly between 22.00 and 23.00 h but remained stable until 03.00 h; later, glucagon increased by 45 pg/ml between 03.00 and 05.00 h and thereafter decreased progressively to reach basal values at the end of the study. Plasma glucagon levels in the interruption test ('off') were significantly different from the basal values (23.00 h) at 05.00, 07.00, 08.00 and 09.00 h and control test ('on') at 24.00 h and for all values collected between 05.00 and 09.00 h.

Plasma Non-esterified Fatty Acids (Fig. 2)

During the control test ('on'), plasma NEFA values remained between 500 and 700 µmol/l until breakfast (07.00 h) after which NEFA decreased temporarily to

350 ± 62 µmol/l to reach 550 µmol/l again at the end of the study. In the interruption test ('off'), plasma NEFA values were not significantly different from those observed during the normal functioning of the pump ('on'). Nevertheless, levels did increase significantly versus baseline from the hours 2–6 of interruption of the CSII; plasma NEFA levels remained stable for 1 h and then decreased rapidly until 1 h after breakfast. At the end of the study, NEFA levels averaged 575 ± 95 µmol/l.

Plasma 3-hydroxybutyrate (Fig. 2)

During the control test ('on') plasma 3-OHB levels remained between 100 and 250 µmol/l throughout the study. In the interruption test ('off'), plasma 3-OHB values increased rapidly and steadily after the interruption of the CSII reaching 1290 ± 140 µmol/l at 06.00 h. They then decreased quickly until 09.00 h and, afterwards, remained stable at about 150 µmol/l until the end of the investigation. In the interruption test ('off'), the rise in plasma 3-OHB was statistically significant versus basal value (23.00 h) from 01.00 to 08.00 h and the plasma 3-OHB levels were significantly higher than those observed in the control test ('on') from 03.00 to 10.00 h.

Plasma Cortisol and Growth Hormone (Table 2)

In the control test ('on') as well as in the interruption test ('off'), plasma cortisol levels exhibited their classical circadian variations, without any statistically significant difference between the two experimental conditions.

No significant changes were observed between the growth hormone levels in both conditions.

Discussion

Numerous recent investigations have emphasized the use of portable pumps for continuous subcutaneous insulin delivery in Type 1 diabetic patients [2–5]. In the present investigation, CSII achieved adequate control of blood glucose, plasma NEFA and 3-hydroxybutyrate but as reported by others [13, 14] and confirmed here, at the cost of moderate peripheral hyperinsulinaemia. Most groups with long-term experience of this type of treatment have encountered problems related to inadequate insulin delivery due to battery, motor, syringe or other catheter-needle defects. However, few studies until now have dealt systematically with this crucial question [7, 6].

Gerich et al. [15] reported the consequences of abrupt cessation of an *intravenous* insulin delivery in otherwise perfectly controlled Type 1 diabetic patients: prompt increase in blood glucose, plasma NEFA and 3-hydroxybutyrate, rapid fall in plasma alanine and al-

most immediate increase in plasma glucagon. Changes occurring after cessation of a *subcutaneous* insulin infusion obviously have a different pattern. Champion et al. [7] reported that, in four patients, discontinuation of insulin infusion for 12 h at night resulted in a moderate increase in blood glucose to reach a mean level of 11.9 mmol/l (with a range of 8.9–23.3 mmol/l) while 3-hydroxybutyrate rose to about 2 mmol/l. More recently, Pickup et al. [6] reported their findings in nine patients investigated after deliberately stopping the pump at 09.00 h, the subjects remaining supine and fasting (an attempt to mimic nocturnal conditions) for the next 9 h. A preliminary account of this study on six patients had been published separately by Keen et al. [17]. They reported a virtually linear rise in plasma 3-hydroxybutyrate, while, in contrast, blood glucose did not change during the first hour, rose at a diminishing rate for the next 5 h and then surprisingly levelled off spontaneously at a plateau of about 5.5 mmol/l above baseline. It should be pointed out that two of these patients had residual C-peptide secretion. We believe that the interest of our study lies in its particularly strict conditions: patients were all without residual endogenous insulin secretion; subjects were studied at night, a time when this type of incident is more likely to occur and when the hormonal milieu might be quite different from the daytime; a control study with the pump operating has been performed in each patient; and, finally, more metabolites and hormones have been investigated. We have observed that plasma free insulin levels start to decline as soon as 1 h after interruption of the insulin infusion to reach a nadir during hours 5 and 6 of the interruption. Interestingly, blood glucose remained unchanged during the first 2 h after discontinuation of the insulin infusion. This observation, in agreement with the findings of Pickup et al. [6], has important implications: a 1–2 h interruption of CSII seems to be well tolerated in terms of blood glucose in well controlled diabetic patients. It remains, however, to investigate the consequences of a 2 h interruption of CSII followed by a reactivation of the pump at its basal rate. At hour 2 after discontinuation of the insulin infusion, plasma NEFA and 3-hydroxybutyrate levels are clearly increased when compared to the values recorded at 23.00 h. During the last 4 h of the interruption, plasma NEFA remain elevated while plasma 3-hydroxybutyrate exhibit a steady increase at a rate of 3.3 ± 0.4 µmol·l^{-1}·min^{-1}. During this period, plasma free insulin levels are falling to minimal values, while, in contrast, plasma glucagon remains unchanged until the last 2 h of the interruption period when a mean increase of 45 pg/ml occurs. In agreement with a current theory on the respective roles of insulin and glucagon in the control of hepatic ketogenesis [16], it is suggested that the fall in circulating insulin plays the major role in promoting NEFA mobilization through lipolysis, whereas the fall in the insulin: glucagon ratio (due to both the drop in insulin levels and the later rise in glucagon levels) is involved in

orienting to ketone body formation the NEFA made available to the liver.

One aim of the present study was to provide patients on CSII with guidelines to restore adequate metabolic control after accidental interruption of the insulin infusion. We have considered that return to control should be achieved: (1) by the patient himself; (2) using the pump as a means of insulin delivery; and (3) on the basis of simple determinations performed by the patient. This scheme, included addition of insulin to the usual pre-breakfast dose (at a moment when, in ordinary conditions, correction should be made) and, if necessary, more supplementary insulin given via the pump 3 h later. These guidelines have been extremely efficient since, at noon blood glucose had returned from 17.5 to 10 mmol/l (despite eating a normal breakfast), plasma NEFA and 3-hydroxybutyrate levels were corrected as were circulating insulin and glucagon levels.

In conclusion, the present study has permitted precise characterization of the hormonal and metabolic consequences of a 6-h nocturnal interruption of CSII mimicking spontaneous incidents that indeed occur with this type of treatment [18]. Moreover, precise guidelines have been established which permit the patient to restore adequate metabolic control within a few hours on the basis of simple blood and urine determinations performed by the patient himself.

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