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Post-prandial administration of the insulin analogue insulin aspart in patients with Type 1 diabetes mellitus

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Abstract

Aims In intensified insulin therapy, the recent development of short-acting insulin analogues with a very rapid onset of action forces a new discussion in terms of the optimal injection–meal interval. This study evaluated prandial glycaemia in patients with Type 1 diabetes following the subcutaneous injection of soluble human insulin (HI) and the insulin analogue insulin aspart (IAsp) at different injection–meal intervals and investigated whether administration of IAsp after the meal might provide satisfactory metabolic control.

Methods In a randomized, double-blind, double-dummy, four-period crossover study, 20 Type 1 diabetic patients were investigated. Prandial insulin was administered 15 min before the start of the meal ($HI_{(-15min)}$), immediately before the meal ($HI_{(0min)}$; $IAsp_{(0min)}$) and 15 min after the start of the meal ($IAsp_{(+15min)}$).

Results Plasma glucose excursions from baseline levels during the 4 h (PG_{exc}) were highest with $HI_{(0min)}$ (17.9 mmol.l^{-1}.h; $P < 0.05$ vs. other treatments) and were not statistically different for $HI_{(-15min)}$, $IAsp_{(0min)}$ and $IAsp_{(15min)}$ (13.6, 11.9 and 14.2 mmol.l^{-1}.h, respectively). Maximum concentration of plasma glucose (PG_{max}) was lowest with $IAsp_{(0min)}$ (11.2 mmol/l; $P < 0.05$ vs. other treatments). PG_{max} was comparable with $HI_{(-15min)}$, $HI_{(0min)}$ and $IAsp_{(+15min)}$ (13.3, 14.1 and 13.2 mmol/l, respectively).

Conclusions With regard to prandial glycaemia $IAsp_{(+15min)}$ is as effective as $HI_{(-5min)}$ and superior to $HI_{(0min)}$. Thus, post-prandial dosing of the insulin analogue IAsp offers an attractive and feasible therapeutic option for well-controlled patients with Type 1 diabetes mellitus.

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Keywords injection–meal interval, insulin analogue, insulin aspart, insulin therapy, soluble human insulin

Abbreviations ANOVA, analysis of variance; AUC, area under the curve; BMI, body mass index; HI, soluble human insulin; IAsp, insulin analogue insulin aspart; PG_{exc}, plasma glucose excursions from baseline values; PG_{max}, maximum concentration of plasma glucose

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Introduction

Near normoglycaemia can reduce the incidence of long-term complications in Type 1 diabetes mellitus [1]. To achieve this goal, the majority of patients perform intensified insulin therapy with subcutaneous injection of long-term insulin (basal insulin) and short-acting insulin (bolus insulin) [2]. However, owing to the late onset and long duration of action of subcutaneously injected soluble human insulin, prandial glycaemia that is comparable to non-diabetic subjects is rarely achievable for diabetic patients [3]. Thus, short-acting insulin analogues with a more rapid onset of action have been developed in the past few years [3–5]. In several investigations [6,7], the accelerated and improved absorption kinetics after subcutaneous injection led to significantly reduced post-prandial glucose excursions. Moreover, owing to the rapid onset of action of short-acting insulin analogues, the injection–meal interval could be considerably reduced [8]. Recently it has been proposed that these analogues might also be injected post-prandially without a subsequent deterioration of blood glucose control [9]. The administration of bolus insulin after the meal might bring about greater flexibility in insulin therapy and thus improve quality-of-life for diabetic patients [10]. Furthermore, post-prandial injection could allow improved adjustment of the insulin dosage according to the amount of ingested carbohydrates and composition of the meal.

The aim of the present study was to evaluate prandial glycaemia following the subcutaneous injection of soluble human insulin and the insulin analogue insulin aspart at different injection–meal intervals and to investigate whether the administration of insulin aspart after the meal might provide satisfactory metabolic control.

Patients and methods

Subjects

Twenty Type 1 diabetic patients (12 males, eight females) completed the trial. All patients had a body mass index (BMI) $\leqslant$ 35 kg/m^2, HbA_{1c} levels $\leqslant$ 8.5% and were on an intensive program with multiple daily injections [2]. None of the patients had overt diabetic nephropathy (albumin excretion > 300 mg/24 h) or any evidence of rapidly progressing complications. The main characteristics (mean $\pm$ SD) of the patients were the following: age 36.4 $\pm$ 11.2 years; BMI 25.0 $\pm$ 2.9 kg/m^2; HbA_{1c} 7.6 $\pm$ 0.8%. The study was approved by the ethical commitee of the Karl-Franzens University and all subjects gave written informed consent before entry into the trial.

Study design

The patients were studied on four different occasions, 1 week apart, in random order. On study days, patients had dinner and their usual pre-prandial short-acting insulin before admission to the research ward of the Department of Internal Medicine at 21.00 h. No long-acting insulin was injected on the evening of admission. After arrival, patients were put to bed and studied in the supine position until the end of the experiment. At 22.00 h an intravenous catheter was inserted into each of the patients' forearms. One of these catheters was used for blood sampling and kept patent with 0.9% NaCl. The other intravenous line was used for a variable infusion of insulin as previously described [11]. By this variable infusion of insulin, plasma glucose levels were kept stable at approximately 6.7 mmol/l (range 5.6–7.8 mmol/l) during the night. At 08.30 h (time zero), a standardized breakfast was served (543 kcal; 55% carbohydrates, 17% protein, 28% fat). This standardized breakfast was identical for all patients on all study days. To cover prandial insulin requirements for the test meal, the patients were subcutaneously injected soluble human insulin (HI, 100 IU/ml) or insulin analogue insulin aspart (IAsp, 100 U/ml) at different injection–meal intervals:

- soluble human insulin 15 min before the meal ($HI_{(-15min)}$)
- soluble human insulin immediately before the meal ($HI_{(0min)}$)
- insulin aspart immediately before the meal ($IAsp_{(0min)}$)
- insulin aspart 15 min after the start of the meal ($IAsp_{(+15min)}$)

Injections of the test substances were performed by a study nurse and the individual dosage of HI/IAsp for each individual patient was the same on all study days (mean 9 IU, range 6–12 IU). All investigators and patients were blinded with regard to the respective type of insulin treatment (HI vs. IAsp). To blind for the injection–meal interval, each patient received three subcutaneous injections on each study day (–15 min, 0 min, +15 min). Two injections consisted of placebo and only one injection consisted of HI/IAsp (double-dummy design). In order to avoid any influence of variable absorption kinetics of long-acting insulin [12], patients omitted their usual injection of basal insulin [2] in the morning. Basal insulin requirements during the 4 h after the test meal (08.30–12.30 h) were covered by a continuous intravenous infusion of insulin: adjustment of the overnight infusion of insulin was allowed until 07.00 h (–90 min) and kept constant thereafter. Experiments were only performed if plasma glucose values remained stable between 5.6 and 7.8 mmol/l during this 90-min-period prior to the test meal (idealized basal insulin requirements). For the evaluation of prandial glycaemia, blood samples for the determination of plasma glucose were drawn from –15 min to 240 min at 15 min intervals. All experiments were performed in random order (Latin square design). Between experiments the patients continued their usual intensified insulin therapy.

Analytical methods

Plasma glucose was measured in duplicate using a Beckman Glucose Analyser II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured by a commercially available radioimmunoassay (RIA) (Pharmacia, Uppsala, Sweden).

Statistical methods

Plasma glucose excursion (PG_{exc}) was defined as the area under the curve (AUC) from –15–240 min of the absolute values of the glucose concentrations after subtraction of the initial value

(t = –15 min). The AUCs were calculated by the trapezoidal method. Maximum concentration of plasma glucose (PG_{max}) and time to maximum concentration of plasma glucose (tPG_{max}) were derived from the profiles of plasma glucose concentrations. PG_{exc} and PG_{max} were log-transformed in the analyses and the results were transformed back to the original scale. All variables were analysed by two-way ANOVA with subject and treatment as factors. Means and 95% confidence intervals (CI) were based on the ANOVA. Significance testing was performed by the Student–Newman–Keuls method thereby adjusting for multiple comparisons. In some experiments, intravenous administration of glucose was necessary to prevent a fall of plasma glucose concentration below 2.8 mmol/l in the post-prandial phase. In these experiments all values of plasma glucose after the intervention were set to equal to the last value prior to the intervention. In none of the cases was glucose infused earlier than 2 h after the test meal.

Results

The mean profiles of plasma glucose values following the different treatments are shown in Fig. 1 and Table 1. As shown in Fig. 2a and Table 2 plasma glucose excursions from baseline levels (PG_{exc}) after the test meal were highest with $HI_{(0min)}$ (17.9 mmol.l^{-1}.h; $P < 0.05$ vs. other treatments). PG_{exc} were not statistically different for $HI_{(-15min)}$, $IAsp_{(0min)}$ and $IAsp_{(+15min)}$ (13.6, 11.9 and 14.2 mmol.l^{-1}.h, respectively). Figure 2b demonstrates the mean (95% CI) maximum concentration of plasma glucose (PG_{max}) following the different treatments. PG_{max} was lowest with $IAsp_{(0min)}$ (11.2 mmol/l; $P < 0.05$ vs. other treatments) and was comparable with $HI_{(-15min)}$, $HI_{(0min)}$ and $IAsp_{(+15min)}$ (13.3, 14.1 and 13.2 mmol/l, respectively). No differences among the treatment groups were observed in terms of plasma glucose and plasma insulin levels at baseline (Table 2).

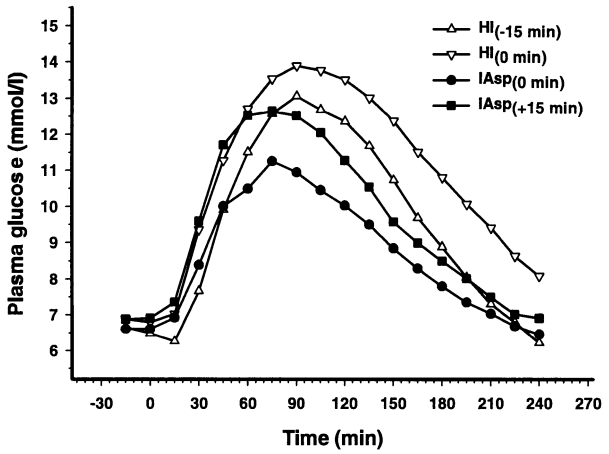

Figure 1 Mean profiles (n = 20) of plasma glucose following the different treatments. Start of the test meal at 0 min.

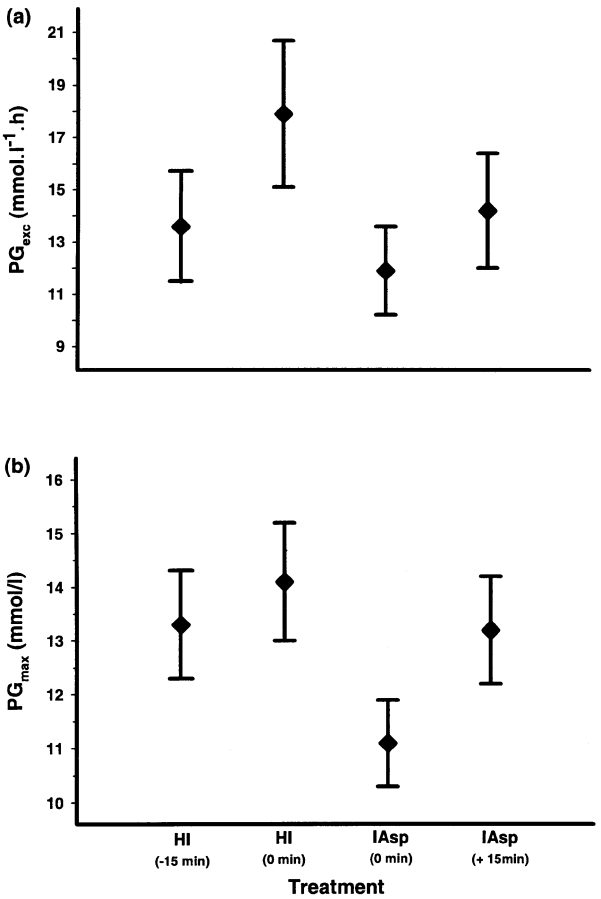

Figure 2 (a) Plasma glucose excursions during a 4-h-period (PG_{exc}) after the test meal following the different treatments (mean ± 95% confidence interval, n = 20). (b) Maximum concentration of plasma glucose (PG_{max}) following the different treatments (mean ± 95% confidence interval, n = 20).

Table 1 Mean post-prandial plasma glucose

	Treatment			
Time	$HI_{(-15\ min)}$	$HI_{(0\ min)}$	$IAsp_{(0\ min)}$	$IAsp_{(+15\ min)}$
60 min	11.4 (7.1–14.8)	12.5 (3.9–16.4)	10.4 (4.1–14.8)	12.4 (8.2–16.2)
120 min	12.3 (6.5–17.4)	13.4 (3.7–18.0)	9.9 (3.8–16.0)	11.2 (4.3–19.1)
180 min	8.8 (3.3–15.8)	10.8 (4.0–15.9)	8.0 (3.2–15.8)	8.7 (2.9–17.0)
240 min	6.2 (3.0–13.2)	8.1 (3.1–12.0)	6.7 (3.1–14.2)	7.3 (3.8–14.4)

Data are mean (range) in mmol/l; n = 20.
HI, soluble human insulin; IAsp, insulin analogue insulin aspart.

Table 2 Plasma insulin and glucose dynamics for the four treatments

	Treatment			
	$HI_{(-15min)}$	$HI_{(0\ min)}$	$IAsp_{(0\ min)}$	$IAsp_{(+15\ min)}$
Plasma insulin concentration at baseline (pmol/l)	78 (66–90)	72 (60–84)	66 (54–78)	78 (66–96)
Plasma glucose concentration at baseline (mmo/l)	6.6 (6.3–6.9)	6.8 (6.4–7.1)	6.6 (6.3–6.9)	6.8 (6.5–7.1)
Maximum concentration of plasma glucose (mmol/l)	13.3 (12.3–14.3)	14.1 (13.1–15.2)	11.2 (10.4–12.0)*	13.2 (12.3–14.2)
Time to maximum concentration of plasma glucose (min)	99 (87–111)*	94 (82–106)	75 (63–87)*	80 (68–92)
Plasma glucose excursion (–15–240 min) ($mmol.l^{-1}.h$)	13.6 (11.7–15.8)	17.9 (15.4–20.9)*	11.9 (10.3–13.9)	14.2 (12.2–16.5)

Data are mean (95% confidence interval); $n = 20$; $^*P < 0.05$ vs. at least one of the other treatments (which are not significantly different from each other).
HI, soluble human insulin; IAsp, insulin analogue insulin aspart.

In order to avoid hypoglycaemia (plasma glucose < 2.8 mmol/l) during the post-prandial phase, intravenous administration of glucose was necessary in 17 experiments (21%) in nine patients ($HI_{(-15min)}$ $n = 2$; $HI_{(0min)}$ $n = 3$; $IAsp_{(0min)}$ $n = 6$; $IAsp_{(+15min)}$ $n = 6$; P = NS). In these cases, the average amount of infused glucose for a single patient was 20 ± 10 g (mean ± SD). The mean time of the intervention was 181 min after the start of the meal (range 135–225 min). With regard to intravenous glucose administration no statistically significant differences were observed between the treatment groups for the type of insulin or the injection–meal interval.

Discussion

Several studies have investigated the influence of different injection–meal intervals on metabolic control [9,13,14] but the literature is inconsistent and there is still a lack of a generally accepted recommendation. In 1999, the ADA recommended the injection of short-acting insulin 15–30 min before the meal [15]. However, the ADA have not yet published recommendations about injection–meal intervals with regard to short-acting insulin analogues. Moreover, in contrast to the recommendations of the ADA, it is well-known that patients themselves prefer to inject their prandial insulin just before the meal [2,16] for reasons of flexibility and quality-of-life. Pharmacokinetics indicate that short injection–meal intervals might worsen metabolic control with soluble human insulin as a result of its late onset of action. Nevertheless, to our knowledge, this has not yet been investigated in a long-term clinical trial. Furthermore, several studies [8,9,17] have demonstrated that excessive intervals between injection and the start of the meal may increase early hypoglycaemic events, especially for patients who achieve pre-prandial near-normoglycaemia. In the present study, plasma glucose values prior to the test meal ranged between 5.6 and 7.8 mmol/l and with intervals between injection and start of the meal of no longer than 15 min there were no early hypoglycaemic events. However, late hypoglycaemia (mean onset 181 min after the start of the meal) occurred in 21% of the experiments. Neither the type of insulin nor the injection–meal interval was associated with these hypoglycaemic events. The most likely explanation for these late hypoglycaemic events seems to be the amount of prandial insulin that was injected. Furthermore, the imposition of pre-prandial near-normoglycaemia and the optimized basal insulin substitution by an intravenous infusion might also have contributed to this phenomenon. This finding of late-onset hypoglycaemia in the present study highlights the need for optimal adjustment of basal and prandial insulin dosage in order to avoid any hypoglycaemia in every-day practice.

With regard to prandial glycaemia in the present study, $IAsp_{(0min)}$ showed the best performance whereas metabolic control was obviously impaired with $HI_{(0min)}$ compared to the other treatments. Moreover, these results suggest that metabolic control with the post-prandial injection of insulin aspart ($IAsp_{(0min)}$) is comparable to that with injection of soluble human insulin 15 min before the start of the meal. This new therapeutic option of post-prandial administration of a short-acting insulin has recently been investigated with another short-acting insulin analogue [9]. That study investigated the effect of different injection times of soluble human insulin (–40 min, –20 min, 0 min) and the insulin analogue lispro (–20 min, 0 min, +15 min) on post-prandial plasma glucose excursions. The authors concluded that injection of lispro immediately after a meal provided post-prandial blood glucose control at least as good as injection of soluble human insulin from 40 to 0 min before the meal. However, the large variation of preprandial values of plasma glucose (3.3–11.1 mmol/l) in this study makes it difficult to interpret these data. Gastric emptying and consequently post-prandial glycaemia is influenced by pre-prandial metabolic control (i.e. accelerated emptying during hypoglycaemia and delayed emptying during hyperglycaemia [18–20]). To prevent this in the present study, pre-prandial values of plasma glucose were kept within a well-defined range (5.6–7.8 mmol/l) by intravenous infusion of insulin [11]. Moreover, the infusion rate that maintained plasma glucose values in this range during the last 90 min before the test meal was kept

constant until the end of the experiment, thus providing an idealized basal rate. This prevented the influence of varying kinetics and dynamics of subcutaneously injected long-acting insulin [12] on prandial glycaemia. It should be emphasized that the present study has been performed under standardized conditions and the question remains open whether the results can be confirmed under conditions of every-day practice. To evaluate these issues further, clinical trials investigating the endpoints HbA_{1c} level, incidence of hypoglycaemic events and quality-of-life are required [21].

In conclusion, these results demonstrate that those attempting intensified insulin therapy should take into consideration not only the dose of prandial insulin but also the type of short-acting insulin and the meal–injection interval. Injection of soluble human insulin immediately before the start of the meal leads to less satisfactory glycaemia compared to other treatment regimens and should therefore not be performed. The best time for the administration of insulin aspart seems to be immediately before the meal. However, injection of insulin aspart 15 min post-prandially provides metabolic control that is comparable to the injection of soluble human insulin 15 min before the start of the meal. The post-prandial administration of the insulin analogue insulin aspart offers an attractive and feasible therapeutic option for well-controlled patients with Type 1 diabetes mellitus.

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