Prandial Glycaemia After a Carbohydrate-rich Meal in Type I Diabetic Patients: Using the Rapid Acting Insulin Analogue [Lys(B28), Pro(B29)] Human Insulin

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The time–action profile of the insulin analogue insulin lispro ([Lys(B28), Pro(B29)] human insulin) with its rapid onset and short duration of action might be more suitable to limit hyperglycaemic excursions after a meal rich in rapidly absorbable carbohydrates in comparison to regular human insulin. A randomized, double-blind study was performed in 10 Type I diabetic patients with good metabolic control (HbA_{1c} 7.0 ± 0.5 %). After a baseline period of 3 h (blood glucose clamped at 6.7 mmol l^{-1}, i.v. insulin infusion of 0.2 mU kg^{-1} min^{-1} throughout the study), the patients ate a pizza, drank a cola and had a carbohydrate-rich dessert (total carbohydrate content 140 g). Immediately before the meal 15.4 ± 3.5 U of either insulin preparation were injected subcutaneously. Blood glucose concentrations were monitored continuously thereafter. Following the injection of insulin lispro the area under the blood glucose curve after the meal was 78 % of that of regular insulin (1.76 ± 0.34 vs 2.26 ± 0.68 mol l^{-1} *240 min^{-1}; $p < 0.01$). Maximal blood glucose excursions were higher and were reached later after regular insulin as compared to insulin lispro (11.9 ± 2.8 vs 9.9 ± 1.4 mmol l^{-1}; $p < 0.05$; 66 ± 37 vs 41 ± 7 min; $p < 0.05$). Maximal individual differences in the blood glucose excursions (regular human insulin minus insulin lispro) were 4.8 ± 2.2 mmol l^{-1} ($p < 0.0001$ against zero) after 110 ± 37 min. In Type I diabetic patients prandial blood glucose excursions after a carbohydrate rich meal were reduced after preprandial injection of insulin lispro in comparison to human regular insulin.

KEY WORDS **Insulin analogues Fast absorbable carbohydrates Prandial glycaemia Insulin-dependent diabetic patients**

Introduction

Intensified insulin therapy is now widely used to achieve near-normoglycaemia in Type I (insulin-dependent) diabetic patients.[1] Ideally, preprandial administration of short-acting insulin should also allow the patient a variable and liberalized carbohydrate intake. However, diabetic patients are still advised to avoid meals with a high content of rapidly absorbable carbohydrates because the prandial increase in glycaemia cannot be adequately controlled with s.c. regular insulin and the risk of late postprandial hypoglycaemia when using high doses of regular insulin is considerable. This is because the time–action profile of available regular insulin preparations show a slow onset and a long duration of action and thus are far from mimicking the physiological insulin profile in response to a meal.

Inversion of the natural proline–lysine amino acid sequence in the B-chain of the insulin molecule at position B28 and B29, results in the insulin analogue [Lys(B28), Pro(B29)] human insulin (insulin lispro) with a more rapid onset and a shorter duration of action in comparison to regular human insulin.[2,3] The aim of our study was to investigate whether the use of insulin lispro results in an improved prandial glycaemic response to a meal rich in rapidly absorbable carbohydrates when compared to regular human insulin. In order to concentrate on prandial blood glucose responses after a meal including pizza, cola and a carbohydrate rich desssert, a model was developed in which other impacting factors were excluded, such as differences in preprandial glucose levels and the influence of long acting insulin preparations. Thus, we decided to test the efficacy of the rapid acting insulin analogue insulin lispro in an extreme—although not so rare—situation, in order to

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investigate the potency of insulin lispro in comparison to that of regular insulin.

Patients and Methods

Ten C-peptide negative Type I diabetic patients in good metabolic control (HbA_{1c} 7.0 ± 0.5 (6.2–7.5) % (DIAMAT, Biorad, München, Germany; reference range 4.2–6.1 %), age 29 ± 3 (25–33) years; duration of diabetes 11 ± 3 (5–15) years; BMI 24.2 ± 2.0 (20.1–26.3) kg m^{-2}; mean ± SD (range)) participated in this double-blind randomized clinical trial after giving written informed consent. The study was approved by the local ethical committee following the principles of the declaration of Helsinki.

On each of the two study days the patients arrived at 8.30 in our test room and were connected to a Biostator (Life Science Instruments, Elkhart, Indiana, USA). The study procedure has been described in detail elsewhere.[4] Patients were advised to inject their last short acting and NPH-insulin on the previous evening or to stop their insulin pump at 6 am on the study day (all patients were on intensified insulin therapy: 5 used multiple insulin injections, the others were on continuous subcutaneous insulin infusion therapy). To get a comparable preprandial metabolic situation on both study days a 3 h baseline period was established. During this period blood glucose was held constant at 6.7 mmol l^{-1} by means of a glucose clamp and a continuous i.v. insulin infusion of 0.2 mU kg^{-1} min^{-1} was maintained throughout the study to simulate an idealized basal insulin substitution.

After the baseline period the subject ate a meal composed of a pizza, cola and an Italian dessert (Tirami-su, mainly consisting of soft cheese and cookie crust). The pizza contained 94 g carbohydrates (22.4 g protein, 15 g fat), the cola (330 ml, Coca-Cola AG, Hamburg, Germany) 23.8 g carbohydrates and the Tirami-su (100 g Zott KG, Mertingen, Germany) 22.2 g carbohydrates (5.4 g protein, 19.5 g fat). Altogether, the carbohydrate content of the meal was 140 g (total energy content 4254 kJ). Patients were instructed to eat the pizza within 10 min, to drink the cola within 5 min afterwards and finally to eat the Tirami-su within 5 min. Blood glucose excursions were monitored continuously by the Biostator thereafter. Glucose infusion was terminated by the Biostator when blood glucose increased above the clamp level. The patients did not consume any more food until the end of the experiment.

Immediately before the meal the patients received a subcutaneous insulin injection into the abdominal wall of the periumbilical region by means of a syringe (micro-fine IV, U100; Becton Dickinson, Heidelberg, Germany). The insulin dose (15.4 ± 3.5 (12–22) U) was self-selected by the patients according to their own experience. The same dose was used on both study days. In randomized order the patients received the human insulin analogue [Lys(B28), Pro(B29)] (LY275585; Eli Lilly, Indianapolis, USA) on one of the two study days and regular insulin (Humulin R, U100) on the other day.

The accuracy of the continuous blood glucose measurement of the Biostator was checked in 30 min intervals by measurements of venous blood samples (Glucose Analyser II, Beckman Instruments, München, Germany). The polyethyleneglycol extraction for free plasma insulin was performed immediately after blood withdrawal and insulin concentrations were estimated with a commercial radioimmunoassay kit (Pharmacia RIA, Uppsala, Sweden).[5]

Results given in the text were prepared by obtaining the data from each individual to produce a *group* mean and SD for each set of variables. The figures were prepared by averaging the data of the sampling times across all subjects for each treatment and are presented as *treatment* means and SEM. Paired *t*-tests or Wilcoxon tests (for not normally distributed values) were used for intraindividual comparisons.

Results

On both study days blood glucose concentrations were kept constant at the target level (insulin lispro vs regular insulin: 6.7 ± 0.2 vs 6.7 ± 0.2 mmol l^{-1}; coefficient of variation 2.6 vs 3.5 %) with similar glucose infusion rates during the baseline period (2.2 ± 0.8 vs 1.6 ± 1.1 mg kg^{-1} min^{-1}; NS). After the meal, blood glucose increased within 41 ± 7 min to maximal values of 9.9 ± 1.4 mmol l^{-1} with insulin lispro and within 66 ± 37 min to 11.9 ± 2.8 mmol l^{-1} with regular insulin (Figure 1; both $p < 0.05$). On the day with insulin lispro, blood glucose returned within 108 ± 70 min to baseline values, whereas this level was reached again after 218 ± 112 min on the day with regular insulin ($p < 0.05$). Maximal differences (regular insulin minus insulin lispro) in the blood glucose excursions after the meal were 4.8 ± 2.2 mmol l^{-1} after 110 ± 37 min. In the 240 min after insulin injection blood glucose did not decline below 3.3 mmol l^{-1} in a single patient. With insulin lispro the area under the blood glucose profile after the meal was 78 % of that of regular insulin (1.76 ± 0.34 vs 2.26 ± 0.68 mol l^{-1} *240 min^{-1}; $p < 0.01$).

Mean free plasma insulin concentrations during the baseline period were comparable (86 ± 20 vs 80 ± 33 pmol l^{-1}; NS). After the s.c. injection of insulin lispro free plasma insulin concentrations rose to maximal values of 369 ± 73 within 68 ± 18 min (Figure 2). In contrast to the rapid increase and decrease in free plasma insulin concentration seen after insulin lispro, s.c. injection of regular human insulin resulted in the well-known insulin profile with maximal values of 263 ± 59 pmol l^{-1} ($p < 0.01$) reached after 116 ± 27 min ($p < 0.01$). However, areas under insulin profiles were not significantly different (52.9 ± 3.2 vs 48.8 ± 3.3 μmol l^{-1} * 240 min^{-1}; NS).

Discussion

This study shows that subcutaneous injection of the rapid acting insulin analogue insulin lispro results in

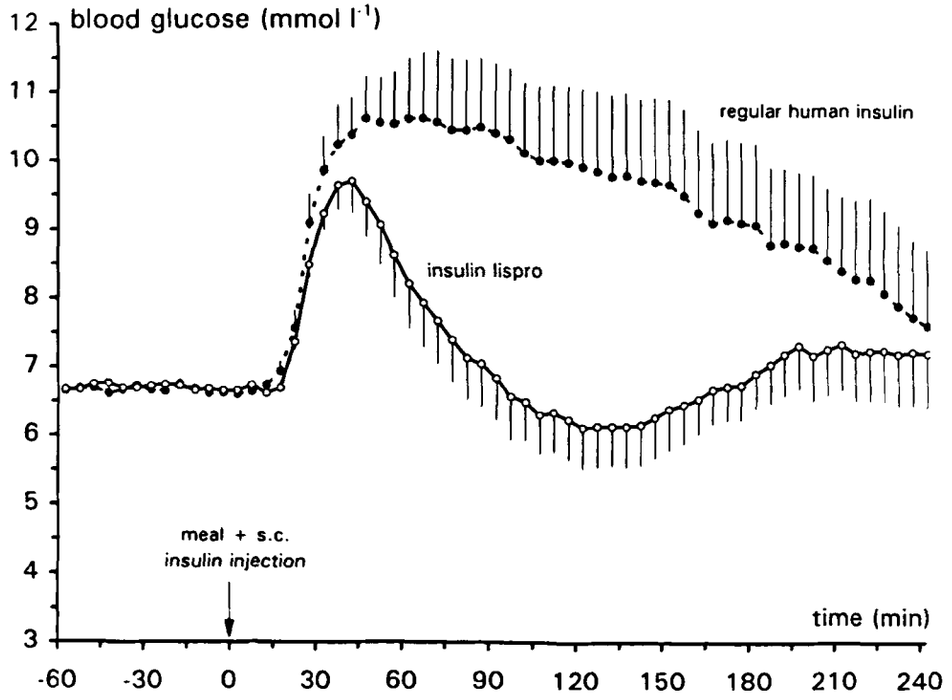

Figure 1. Blood glucose excursions of 10 Type I diabetic patients in good metabolic control after consumption of a meal rich in rapidly absorbable carbohydrates (pizza, cola, and Tirami-su). After a subcutaneous insulin injection of 15.4 ± 3.5 U at $t = 0$ min the meal was eaten within 20 min. On one of the two study days the insulin analogue insulin lispro (continuous line, mean – SEM) was injected, on the other regular human insulin (broken line, mean + SEM). Blood glucose was kept constant at 6.7 mmol l^{-1} in the 3 h prior to the meal by means of a glucose clamp. SEMs were given for 10-min intervals only

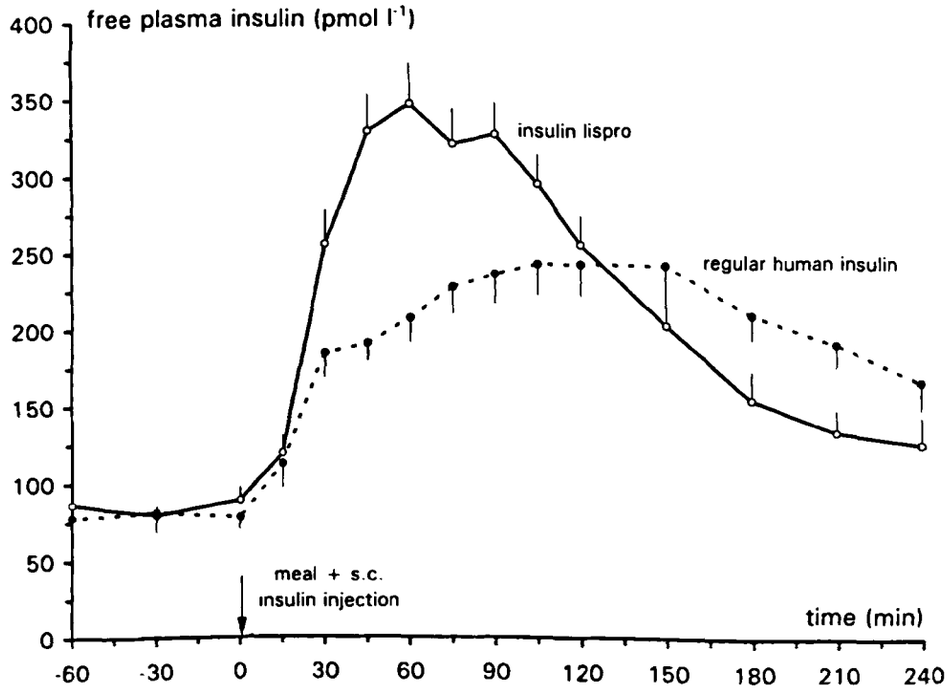

Figure 2. Free plasma insulin concentrations of 10 Type I diabetic patients induced by an i.v. insulin infusion of 0.2 mU kg^{-1} min^{-1} (maintained throughout the study) and a s.c. insulin injection immediately prior to the meal at $t = 0$ min. On one of the two study days the insulin analogue insulin lispro (continuous line, mean + SEM) was injected, on the other regular human insulin (broken line, mean – SEM)

lower prandial blood glucose excursions in comparison to regular insulin after consumption of a meal rich in rapidly absorbable carbohydrates.

This study design might tend to render favourable results for insulin lispro as the differences in post prandial blood glucose excursions between insulin lispro and regular insulin would have been smaller if regular insulin had been injected 30 min before the meal. From the pharmacokinetic point of view there may be a need for an injection–meal interval due to the slow absorption of regular insulin after subcutaneous injection. However, the suggestion of such an injection–meal interval to diabetic patients does not necessarily mean that patients follow through with it under daily life conditions. Our knowledge about the behaviour of diabetic patients is scarce, but the limited knowledge hints to the fact that most patients in reality do not use any or only a short interval.[6,7]

More importantly, it is contraindicated to keep fixed time intervals between the injection of regular insulin and a meal of more than 10 to 15 min in the context of intensified insulin therapy striving for (near-) normoglycaemia. In case a patient is preprandially near-normoglycaemic (according to therapeutic goals) the risk of preprandial hypoglycaemia when waiting between the injection of regular insulin and the meal for more than 10–15 min is prohibitive. We have demonstrated this phenomenon in pharmacokinetic studies on the absorption of regular insulin.[8,10] Consequently, for the last 15 years we and many other centres practising intensified insulin therapy have strongly advised our patients against keeping a time interval between the injection of regular insulin and a meal of more than 10–15 min at maximum.[1,11] To randomize Type I diabetic patients with preprandial normoglycaemia in the context of this study to a procedure which includes a time interval of 30 min between a considerable dose of regular insulin (approximately 15 U) and a standardized carbohydrate-rich meal would have been impractical, unethical, and contrary to our usual clinical practice.

It has been shown repeatedly that postprandial blood glucose excursions are critically dependent on preprandial glucose values. Thus, in order to achieve a reproducible experimental situation we established a baseline period with identical near-normoglycaemic blood glucose concentrations and free plasma insulin concentrations. Moreover, only C-peptide negative patients with preceding good metabolic control participated in our study, in order to avoid large interindividual differences in insulin sensitivity. In contrast, other studies investigating meal related blood glucose excursions and insulin concentrations of diabetic patients after insulin/insulin analogue administration did not meet such strict conditions.[12–14]

It is of note, however, that ingestion of such a carbohydrate-rich meal did not result in pronounced hyperglycaemia with either insulin preparation. In contrast, in the study of Ahern *et al.* a pizza with similar carbohydrate content (125 vs 140 g (= 89 %)) resulted in late postprandial hyperglycaemia after 4–9 h; however, the dose of regular insulin used was lower than in our study (8.8 vs 15.4 U (= 57 %)).[15] In our study the insulin dose injected to cover the meal was self-selected by the patients. All of them had participated in a structured diabetes treatment and teaching programme emphasizing self-adjustment of insulin doses based on regular home blood glucose measurements and carbohydrate intake and were in good metabolic control. The blood glucose profiles show that experienced patients can self-select appropriate insulin doses even for such an extraordinary meal, supporting the concept of liberalized carbohydrate intake with intensified insulin regimen:[1] Even if such a meal may not be regarded as appropriate for diabetic (and non-diabetic) man by some nutrition experts one cannot deny that patients do eat similar food in daily life and regard these meals as an important part of their quality of life.

In conclusion, in Type I diabetic patients prandial glycaemia after a meal rich in rapidly absorbable carbohydrates can be reduced by the use of a rapid acting insulin analogue. Although the use of such a rapid insulin analogue may cause some particular problems due to its particular pharmacokinetics, like the risks of early hypoglycemia[3] or with early exercise,[14] such an insulin analogue has the potential to further reduce dietary restrictions for diabetic patients on intensified insulin treatment. Whether there will be an overall clinical benefit of this and other insulin analogues remains to be elucidated.[16]

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References

1. Berger M, Mühlhauser I. Implementation of intensified insulin therapy: a European perspective. *Diabetic Med* 1995; **12**: 201–208.
2. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 1994; **43**: 396–402.
3. Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, *et al.* Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28, Pro(B29)] in IDDM. *Diabetologia* 1994; **37**: 713–720.
4. Heinemann L, Heise T, Jorgensen LN, Starke AAR. Action profile of the rapid acting insulin analogue B28Asp. *Diabetic Med* 1993, **10**: 535–539.
5. Hanning I, Home PD, Alberti KGMM. Measurement of free insulin concentrations: the influence of the timing of

extraction of insulin antibodies. *Diabetologia* 1985; **28**: 831–835.
6. Lean MEJ, Ng LL, Tennison BR. Interval between insulin injection and eating in relation to blood glucose control in adult diabetics. *Br Med J* 1985; **290**: 105–108.
7. Jorgensen LN, Nielsen FS. Timing of pre-meal insulins in diabetic patients on a multiple daily injection regimen. A questionaire study. *Diabetologia* 1990; **33** (suppl 1): A116.
8. Berger M, Cuppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 1982; **5**: 77–91.
9. Sonnenberg GE, Kemmer FW, Berger M. Exercise in type 1 (insulin-dependent) diabetic patients treated with continuous subcutaneous insulin infusion. Prevention of exercise induced hypoglycaemia. *Diabetologia* 1990, **33**: 696–703.
10. Heinemann L, Hohmann A, Starke AAR, Berger M. What is the correct timing of subcutaneous injections of regular insulin to cover carbohydrate rich meals? *Horm Metab Res* 1992; **26** (suppl): 137–139.
11. Berger M, Jörgens V. *Praxis der Insulintherapie*, 1st edn and 5th edn; Berlin, Springer-Verlag, 1982, 1995.
12. Kang S, Owens DR, Vora JP, Brange J. Comparison of insulin analogue B9AspB27Glu and soluble human insulin in insulin-treated diabetes. *Lancet* 1990; **335**: 303–306.
13. Kang S, Creagh FM, Peters JR, Brange J, Vølund Aa, Owens DR. Comparison of subcutaneous soluble human insulin and insulin analogues ($Asp^{B9}Glu^{B27}$; Asp^{B10}; Asp^{B28}) on meal-related plasma glucose excursions in type I diabetic subjects. *Diabetes Care* 1991; **14**: 571–577.
14. Tuominen JA, Karonen SL, Melamies L, Bolli G, Koivisto VA. Exercise induced hypoglycaemia in IDDM patients treated with a short acting insulin analogue. *Diabetologia* 1995; **38**: 106–111.
15. Ahern JA, Gatcomb PM, Held NA, Petit WA, Tamborlane WV. Exaggerated hyperglycemia after a pizza meal in well-controlled diabetes. *Diabetes Care* 1993, **16**: 578–580.
16. Berger M, Heinemann L. Are presently available insulin analogues clinically beneficial? *Diabetologia* **39** (suppl) 1996; (in press).