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Post-prandial insulin lispro vs. human regular insulin in prepubertal children with Type 1 diabetes mellitus

S. Tupola, J. Komulainen*, J. Jääskeläinen* and I. Sipilä

Hospital for Children and Adolescents, University of Helsinki, Helsinki, and *Kuopio University Hospital, Department of Paediatrics, Kuopio, Finland

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Abstract

Aims To study whether post-prandial insulin lispro (PL) could be used as a part of insulin therapy instead of premeal human regular insulin (HR) in prepubertal children with Type 1 diabetes mellitus (Type 1 DM).

Patients and methods In this open, randomized cross-over study patients used either PL or HR at breakfast and at dinner. After a 1-month screening period, patients were randomized to treatment with PL or HR for 3 months and then they crossed over to the other insulin for an additional 3 months. The patients were 24 prepubertal children with Type 1 DM (median age 6.2 years, duration of diabetes 37 months). Home monitoring of 1-day glucose profiles at meals (premeal, 1 h and 2 h after breakfast and after dinner) and HbA_{1c} were measured before randomization, before cross-over, and at the last visit. Data on hypoglycaemic episodes were collected at each of the seven visits. The variables were compared between the two treatments.

Results Of the patients 22/24 completed the study. There were no major differences in the glucose excursions between PL and HR after breakfast (mean ± SD: 1-h PL 3.7 ± 4.7 vs. HR 2.9 ± 3.9 mmol/l, $P = 0.3$; 2-h –0.9 ± 5.4 vs. 0.3 ± 4.5 mmol/l, $P = 0.2$, respectively) or after dinner (1-h PL –2.5 ± 4.8 vs. HR –0.4 ± 3.7 mmol/l, $P = 0.07$, 2-h –4.1 ± 5.2 vs. –0.7 ± 5.0 mmol/l, $P = 0.05$, respectively). Mean change of HbA_{1c} was similar in both treatment groups (PL 0.2 ± 0.8% vs. HR –0.4 ± 0.7%, $P = 0.1$). The frequency of hypoglycaemic episodes was 4.9 per patient per month during treatment with PL, and 4.4 during HR ($P = 0.3$).

Conclusion Treatment with post-prandial lispro as a meal insulin is as effective and safe as traditional treatment with regular insulin in young children.

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Keywords insulin lispro, children, Type 1 diabetes mellitus

Abbreviations PL, post-prandial insulin lispro; HR, human regular insulin; Type 1 DM, Type 1 diabetes mellitus; SBGM, self-blood glucose monitoring

Introduction

It is not always easy to predict whether young children wish to eat, and refusal of food is common. Adjustment of the preprandial insulin dose to the assumed nutrient intake is a

Correspondence to: Dr Sarimari Tupola, Hospital for Children and Adolescents, University of Helsinki, BO Box 281, 00290 HUS, Finland. E-mail: sarimari.tupola@hus.fi

recurrent problem in families with young children with Type 1 diabetes mellitus (Type 1 DM) [1].

Biosynthetic insulin analogue lispro is more rapidly absorbed following subcutaneous administration and has a quicker onset and shorter duration of action than human insulin [2,3]. Those properties make it possible to administer insulin lispro after meals [4,5]. For young children with Type 1 DM adjusting insulin post-prandially on the basis of true carbohydrate intake would be a tempting alternative.

In this study we investigated whether post-prandial insulin lispro (PL) could be used as a part of long-term insulin therapy in prepubertal children instead of premeal human regular insulin (HR). Hitherto, we have found no reports evaluating long-term diabetes care with insulin lispro in children.

Patients and methods

Patients

A total of 24 children (12 boys and 12 girls) participated in the study. Their median (range) age was 6.2 (3.9–9.9) years at the beginning of the study and duration of diabetes 3.1 (1.0–5.0) years. Their mean (± SD) HbA_{1c} was 8.1 (± 0.9)%, daily insulin dose 0.77 (± 0.28) U/kg, and weight for height (% of normal) 104 (± 8)%. The median (range) ratio of basal insulin to total daily insulin was 0.61 (0.46–0.77), and morning basal insulin to total daily basal insulin 0.68 (0.41–0.80). All of those contacted accepted the invitation to the study. Of the patients, 16 were attending the out-patient diabetes clinic in the Hospital for Children and Adolescents, Helsinki, and eight the out-patient diabetes clinic in the Kuopio University Hospital. The inclusion criteria were age < 10 years, no signs of puberty, a duration of Type 1 DM at least 1 year, and daily insulin dose of > 0.5 U/kg. Furthermore, the families had to be accustomed to performing daily self-blood glucose monitoring (SBGM) as well as to evaluating the carbohydrate content of meals. Exclusion criteria included presence of allergy to insulin or excipients contained in insulin products, other chronic diseases, and previous treatment with insulin lispro. Those who were unable to follow or complete the protocol were excluded from the final analysis.

The study protocol was approved by the ethical committee of the two participating centres. Patients, if possible, and their guardians gave informed consent prior to the study.

Study design

This 7-month prospective study was an open, randomized cross-over trial, using PL (Humalog®) or HR (Humulin Regular®) at breakfast and dinner (4–6 p.m.). Each treatment period was 3 months, and the trial was preceded by a 1-month screening period when the patients received Humulin Regular® before breakfast and dinner, and Humulin NPH® as a basal insulin. There were seven scheduled visits during the 7-month study period.

The basal insulin was administered during the whole 7-month period in two daily injections. Insulin doses were tailored individually, but a tentative recommendation for dose of PL was one unit to 8–10 g carbohydrates. The patients and their families were encouraged to adjust the PL dose according the true carbohydrate intake. Permission was given to the families to administer PL in more than two daily injections. PL was instructed to be taken no longer than 30 min from the start of the meal, and HR 20–30 min before the meal. All patients received PL and basal insulin, or HR and basal insulin mixed, when appropriate. During the HR period (as before the study), the meal plan included snacks at late morning and at afternoon. During the PL period, the snacks were allowed to be omitted if energy and carbohydrate content of the snacks had been added to the meals. However, only one patient and his family omitted the snacks during the PL period.

Patients and their families were given a standardized blood glucose meter (Accutrend® sensor; Boehringer Mannheim, Mannheim, Germany) for the study period. They measured seven-point glucose profiles (before breakfast, 1 h and 2 h after breakfast, before dinner, 1 h and 2 h after dinner, and at bedtime) at home 1 day during the week before each visit. HbA_{1c} (high pressure liquid chromatography, reference limit 4–6%) was measured, and patients' height, weight, and insulin dose were recorded at each visit. Data on glucose excursions and HbA_{1c} changes were used for analysis from three visits: just before randomization, just before cross-over, and at the end of the study. Pubertal status (Tanner stage 1–5) was examined before the study and at the last visit. All hypoglycaemic episodes were recorded throughout the study with the aid of a diary and by analysis of glucose monitor printouts. Data on hypoglycaemic episodes were collected at each visit. Hypoglycaemia was defined as any situation where the patient had hypoglycaemic signs or symptoms, or the measured blood glucose value was < 3 mmol/l. Dominant symptoms or signs were to be described in own words, no symptom lists were given. The most dominant symptoms (one per episode) were classified as (i) autonomic, adrenergic or cholinergic, (ii) neuroglycopenic, and (iii) non-specific [6]. Patients were asked to report adverse events at each visit, and data were confirmed by review of the patient's hospital record.

By the beginning of the study insulin lispro had been studied in clinical trials globally with > 5000 adult patients and with > 500 children. Study patients and their families were informed that in the registration trials there had been no differences in the type or frequency of adverse events between insulin lispro and human regular insulin. At the beginning of the study insulin lispro was registered in Finland for patients over 12 years, and it became available for children under 12 years during the study in April 1998.

Statistical analysis

For statistical analyses, the cross-over was broken and each patient served as his or her own control. Wilcoxon matched-pairs test and χ^2 test, where appropriate, were used to compare the data in the two treatment groups as well as the data of the within-treatment comparisons. A P-value of < 0.05 was considered significant. The sample size was estimated so that with

power 80% and two-sided significance level 5% we could detect a moderate clinical effect of 0.65 in standardized difference of the main efficacy measures.

Results

Of the 24 patients, 22 (92%) completed the study. One 5-year-old boy (duration of diabetes 3.1 years) dropped out due to a family crisis. One 6-year-old boy (duration of diabetes 3.9 years) was excluded from the analyses because his parents had changed the morning PL to HR without authorization. He had experienced recurrent symptomatic hypoglycaemia 2 h after breakfast for 2 weeks since starting PL treatment.

Blood glucose values and HbA_{1c}

There were no major differences in the mean 1- or 2-h glucose excursions between the PL and HR treatment groups after breakfast or after dinner (Fig. 1). Fasting blood glucose values before breakfast (mean ± SD) were higher in the PL group than in the HR group (11.5 ± 4.5 vs. 8.4 ± 3.8 mmol/l, $P = 0.02$). However, the blood glucose values were similar in the two treatment groups before dinner (PL 11.7 ± 6.0 vs. HR 9.6 ± 5.7 mmol/l, $P = 0.4$), and at bedtime (PL 11.5 ± 5.0 vs. HR 10.6 ± 6.0 mmol/l, $P = 0.8$). The mean content of ingested carbohydrates did not differ in the two treatment groups either at breakfast or at dinner. Change in HbA_{1c} (mean ± SD) was similar in the PL period (0.2 ± 0.8%) and in the HR period (–0.4 ± 0.7%) ($P = 0.1$).

Hypoglycaemias

A total amount of 621 hypoglycaemic episodes was reported, giving a frequency of 4.9 per patient per month during treatment with PL and 4.4 with HR ($P = 0.3$). All episodes reported in the diary were confirmed by a SBGM, the highest blood glucose value being 4.1 mmol/l. Of all the episodes, 75 (12%) occurred during the night 11 p.m. to 6 a.m. (PL 34 vs. HR 41, $P = 0.6$). There were two severe hypoglycaemic episodes resulting in unconsciousness in both treatment groups (total frequency 21.7/100 patient years). Of all the episodes, 205 (33%) were asymptomatic (PL 109 vs. HR 96, $P = 0.9$). Of the symptoms, 44% were autonomic, 7% neuroglycopenic, and 16% non-specific. There were no significant differences in the symptom profiles between the two treatments.

Insulin regimen, insulin doses, weight for height, puberty

Four patients received PL regularly in three daily doses, i.e. also at lunch time, and the remaining 18 in two. Within-treatment comparisons revealed no differences in the total daily insulin dose, in the ratio of basal insulin to the total daily insulin, or in the ratio of morning basal insulin to total basal insulin. Nor were there differences in weight for height. All patients were prepubertal (Tanner stage 1) at the end of the study.

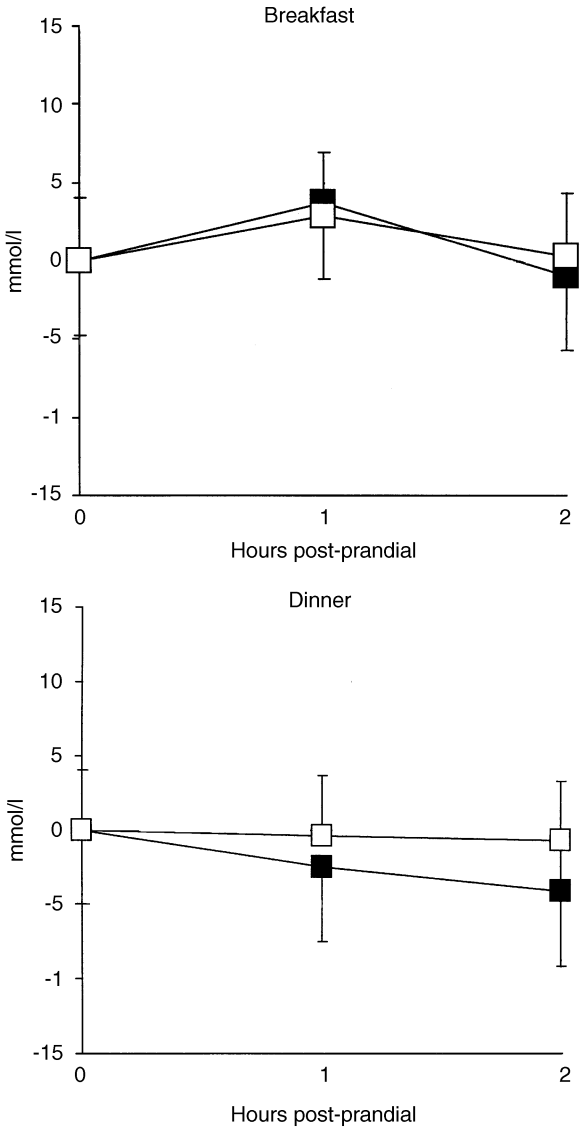

Figure 1 Post-prandial 1- and 2-h glucose excursions (mean ± SD) after breakfast and after dinner. ■, Post-prandial insulin lispro; □, human regular insulin.

Satisfaction of the patients and their families

After the study, 18/22 (82%) patients and their families wanted to continue treatment with pre- or post-prandial insulin lispro because of its convenience.

Discussion

Our study indicates that the use of post-prandial insulin lispro is possible and does not compromise glycaemic control in long-term conventional insulin treatment in young children. For families of young children with Type 1 DM adjusting the insulin dose after meals based on the amount of ingested carbohydrates is of great potential benefit, especially for children who have wholly unpredictable eating habits.

PL as a part of insulin therapy compared with HR resulted in quite similar post-prandial 1- and 2-h glucose excursions. Two studies in which glucose excursions were studied after standardized meals reported similar findings in children with Type 1 DM [5] as well as in adults [4]. It has also been shown that post-prandial injection of insulin aspart in adults leads to comparable post-prandial glycaemia to short-acting human insulin before meals [7]. Rutledge *et al*. [8] has demonstrated in five children that the post-prandial 2-h increase in serum glucose was less with post-prandial insulin lispro than after preprandial soluble insulin. The benefits of premeal insulin lispro in improving post-prandial glucose control compared with soluble insulin have been demonstrated clearly not only in adults with Type 1 and Type 2 DM [4,9–11] but also in children [5]. In our study standardized meals were not used because of the individual eating habits of young children. In our opinion, the fact that each child served as his/her own control was a more reliable design. However, the mean carbohydrate contents at meals did not differ between the two treatments. In addition, we should emphasize that the whole study design, including the freedom to give more than two daily PL injections, served the individual needs of the child and his/her family.

The fasting blood glucose values were significantly higher in treatment with PL than in HR. This finding was the only statistically significant difference between the two treatments and may be clinically important, although the higher fasting blood glucose levels in PL treatment did not result in higher HbA_{1c} levels. Mohn *et al*. [12] described higher glucose and lower insulin concentrations at night after use of insulin lispro compared with use of human soluble insulin. Our protocol did not include nocturnal blood glucose measurements. Perhaps we should have increased the basal insulin dose during the PL treatment to avoid higher fasting blood glucose levels.

Blood glucose data were collected prior to, and HbA_{1c} was measured at every seven visits, but only data from three visits (before randomization, before cross-over, and the final visit) were used in the analyses. This procedure was adopted owing to our lack of experience in the use of insulin lispro in young children. Prior to this study in 1998, none of the physicians had treated their patients below 10 years with insulin lispro, and only a few reports were available concerning use of insulin lispro in prepubertal children.

Our patients experienced hypoglycaemic episodes with equal frequency during the treatments with PL and HR. Previous studies in adults with Type 1 DM have reported both a decrease [9,10] and comparable rates [4,11] during treatment with preprandial insulin lispro compared with regular insulin. A meta-analysis of 2576 patients demonstrated a 30% reduction in severe hypoglycaemia during preprandial insulin lispro therapy [13]. Post-prandial insulin lispro has also been associated with a decreased rate of hypoglycaemic episodes [4] compared with regular insulin in adult patients. The question why the hypoglycaemia frequency in our patients was similar remains open.

Frequency, symptom profile and severity of the hypoglycaemic episodes during the two treatments were similar in our study. These findings are in accordance with experimental studies showing similar counterregulatory hormone responses to insulin lispro and human regular insulin in healthy adults [14] as well as in patients with Type 1 DM [15]. There are no comparable studies concerning children.

The change of HbA_{1c} in our study was similar during the use of both PL and HR. This is consistent with our results of similar post-prandial glucose excursions and rates of hypoglycaemia. Studies comparing the long-term glycaemic control with post-prandial insulin lispro and human regular insulin are lacking. However, many studies have shown that preprandial insulin lispro, when compared with human regular insulin, does not lead to better glycaemic control in patients with Type 1 DM [9–11]. We can therefore conclude that PL as a meal insulin could be used as an alternative to traditional insulin treatment in young children.

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