Pediatric Diabetes 2000: 1: 135–141
Printed in Ireland. All rights reserved

Pediatric Diabetes
ISSN 1399-543X

Original Article

Insulin lispro versus regular insulin in children with type 1 diabetes on twice daily insulin

Fairchild JM, Ambler GR, Genoud-Lawton CH, Westman EA, Chan A, Howard NJ, Crock PA, Nunn EA, Silink M. Insulin lispro versus regular insulin in children with type 1 diabetes on twice daily insulin. Pediatric Diabetes 2000: 1: 135–141. © Munksgaard, 2000

Abstract: Objective: The aim of this study was to compare the clinical efficacy and safety of insulin lispro with regular insulin in 5- to 10-yr-old prepubertal children on twice daily insulin.
Research design and methods: Thirty-five children (16 M, 19 F) completed an open-label randomised crossover study, with each child receiving insulin lispro for 3 months and regular insulin for 3 months in addition to their intermediate-acting insulin. Families were instructed to give regular insulin 30 min before meals and insulin lispro immediately before meals. Glycaemic control was monitored by eight-point blood glucose profiles and six weekly hemoglobin A1cs (HbA1cs) and the frequency and severity of hypoglycaemia was documented.
Results: The endpoint HbA1c after 3 months on insulin lispro (8.33%, SD $\pm$ 0.89) was not significantly different to that on regular insulin (8.14%, SD $\pm$ 0.77). No significant differences were found in blood glucose levels before or after meals, 2-h postprandial glucose excursions or in blood glucose levels before bed between the treatments. However, blood glucose levels at 3 am were significantly lower on regular insulin than on insulin lispro (mean difference -2.35 mmol/L (95%CI: -3.98, -0.72, $p = 0.01$). There was no significant difference in the frequency of hypoglycaemic episodes between the groups.
Conclusions: The main advantage of insulin lispro in children on twice daily insulin was found to be its greater convenience, this being achieved without a deterioration in glycaemic control. The higher 3 am blood glucose levels in those on insulin lispro could translate to reduced nocturnal hypoglycaemia in some individuals.

Jan M Fairchild[a], Geoffrey R Ambler[a], Christine H Genoud-Lawton[a], Elizabeth A Westman[a], Albert Chan[a], Neville J Howard[a], Patricia A Crock[b], Elizabeth A Nunn[b] and Martin Silink[a]

[a] The Ray Williams Institute of Paediatric Endocrinology, Diabetes and Metabolism, The New Children's Hospital, Westmead, NSW, Australia, [b] The Department of Endocrinology and Diabetes, John Hunter Children's Hospital, Newcastle, NSW, Australia

Key words: child – insulin analogue – type 1 diabetes mellitus

Corresponding author: Dr Jan M Fairchild, The Ray Williams Institute of Paediatric Endocrinology, Diabetes and Metabolism, The New Children's Hospital, PO Box 3515 Parramatta, NSW 2124, Australia. Tel.: + 61 2 9845 3169; fax: + 61 2 9845 3170; e-mail: janf@nch.edu.au

Submitted 1 December 1999. Accepted for publication 17 March 2000

The limitations of conventional short-acting insulin are its slow onset and prolonged duration of action. Conventional short-acting insulin (regular insulin) reaches its peak about 2 h after injection, making it advisable to inject at least 30 min before meals if the postprandial rise in blood glucose concentration is to be limited (1, 2). Many people find this practice inconvenient and the injection is given closer to mealtime, resulting in significant postprandial hyperglycaemia. The prolonged duration of action of regular insulin may in turn lead to late postprandial hypoglycaemia.

To overcome these problems, the short-acting insulin analogue insulin lispro (Lys(B28), Pro(B29)) was developed. Insulin lispro is a human insulin analogue in which the natural amino acid sequence of the B-chain at positions 28 and 29 is reversed. These changes result in an insulin molecule with a greatly reduced capacity for self-association and faster absorption from subcutaneous injection sites. Pharmacokinetic studies of this new analogue in adults have shown a more rapid onset of action (10–15 min), an earlier peak effect (60 min) and a more consistent duration of

action (4 h) (3, 4). The length of time to peak activity after subcutaneous injection of insulin lispro has also been shown to be independent of dose, unlike regular insulin where the length of time to peak activity increases with increasing doses (5).

Large-scale clinical trials have been conducted in recent years to assess the clinical efficacy and safety of insulin lispro in the treatment of adult patients with type 1 and type 2 diabetes. These trials have shown that postprandial increases in blood glucose concentrations were lower in subjects using insulin lispro than in those using regular insulin, however, the fasting and pre-meal blood glucose concentrations tended to be higher (6–9). Most studies showed little or no improvement in glycated haemoglobin values during therapy with insulin lispro. In the one adult study sufficiently powered to detect differences in hypoglycaemia, there was a significant reduction in the total number of hypoglycaemic episodes in patients with type 1 diabetes using insulin lispro (6). No differences have been reported between insulin lispro and regular insulin with respect to adverse events, allergic reactions or abnormal laboratory values.

There are no published data on the pharmacokinetics of insulin lispro in 5–10-yr-old children and the clinical advantages of insulin lispro demonstrated for adults, usually on multiple injection regimens, may not be conferred to children. Many young children are managed on twice daily combined insulin regimens (10) and require a smaller proportion of short-acting insulin than adults (11). The limited data available on the use of insulin lispro in adults on twice daily insulin, have shown reduced blood glucose excursions after breakfast and the evening meal but no change in glycaemic control (12, 13). In the one abstract on the use of insulin lispro in children, similar blood glucose profiles were reported, however, glycated haemoglobin values were not provided (14). The aim of this study was to compare the clinical efficacy and safety of insulin lispro with regular insulin, in prepubertal children, aged 5–10 yrs on a twice daily insulin regimen.

Research design and methods

All 5–10-yr-old children with type 1 diabetes and on twice daily insulin, attending the Diabetes Clinics at The New Children's Hospital, Westmead and The John Hunter Children's Hospital, Newcastle were invited to participate in the study. An open-label randomised crossover design was used, with each child receiving insulin lispro (Humalog, AZA-Eli Lilly) for 3 months and regular insulin (Humulin R, AZA-Eli Lilly) for 3 months in addition to their intermediate-acting insulin. Children were included if they were prepubertal (< Tanner stage 2 breast development in girls, < 4 mL testicular volume in boys) and had had diabetes for at least 12 months. Children with poor compliance or glycaemic control (hemoglobin A1c (HbA1c) > 10%) and those with language or social difficulties were excluded from the study. The hospital's ethics committee approved the study and informed consent was obtained.

Of the 43 children with type 1 diabetes originally enrolled, eight children withdrew from the study prior to commencing insulin lispro. Four withdrew for personal reasons unrelated to the study, three found Humulin L unsuitable (preferring to return to their previous insulin, not compatible with the protocol) and one developed lipoatrophy during the lead-in period. Thirty-five children (16 M, 19 F) completed the study. Their baseline characteristics are shown in Table 1. Enrolments were spread over the 12 months from 21 April 1997 to 2 March 1998. All children were prepubertal at enrolment, however, six girls had commenced puberty by the end of the study (five had stage 2 and one had stage 3 breast development). Six children used lente insulin (Humulin L, AZA-Eli Lilly) and 29 used isophane insulin (Humulin NPH, AZA Eli

Table 1. Patient characteristics at baseline

	Total group	Seq A = regular/lispro	Seq B = lispro/regular
Number	35	17	18
Gender	16 M, 19 F	9 M, 8 F	7 M, 11 F
Age (yrs)	8.05 ± 1.39	7.60 ± 1.27	8.47 ± 1.39
Diabetes duration (yrs)	3.10 [1.59 – 5.18]	2.16 [1.40 – 4.31]	3.89 [1.83 – 5.18]
HbA1c (%)	8.21 ± 0.73	8.25 ± 0.67	8.18 ± 0.81
Total insulin (units/kg/d)	0.83 ± 0.12	0.80 ± 0.12	0.86 ± 0.12
BMI (kg/m^2)*	17.50 [16.93 – 18.38]	18.11 [17.30 – 18.36]	17.10 [16.33 – 18.38]

Summary statistics shown as mean ± SD or median [interquartile range].

* Australian Health and Fitness Survey Body Mass Index (BMI) Centiles (22). 8-yr-old males: 85th centile = 18.3, 95th centile is 20.6. 8-yr-old females: 85th centile = 18.5, 95th centile = 20.3.

Lilly) as their intermediate-acting insulin. Two children were known to have coeliac disease and were on a gluten free diet throughout the study.

At enrolment, children on an alternative brand of insulin, were changed to Humulin R with Humulin NPH or L, prior to a lead-in period of 6 wks. They had their blood glucose meter and their blood glucose testing method checked and corrected if necessary. Baseline physical examination, HbA1c and screening blood tests were performed (to assess eligibility and screen for the associated conditions, autoimmune thyroiditis and coeliac disease). During the lead-in period there was no patient contact other than that initiated by the family.

Following the lead-in period, patients were randomised into one of two treatment sequences. In sequence A, children received regular insulin with Humulin NPH or L for 3 months followed by insulin lispro with Humulin NPH or L for 3 months. In sequence B, children received insulin lispro with Humulin NPH or L for 3 months, followed by regular insulin with Humulin NPH and L for 3 months. Families were asked to give regular insulin 30 min before meals and to give insulin lispro immediately before meals. The starting dosage for insulin lispro was the same as their current regular insulin dosage. Glycaemic goals and the timing and content of meals remained the same throughout the study. Food was distributed as three main meals and three snacks, with insulin given before breakfast and the evening meal. Written instructions for dosage adjustment, sick day management and exercise were provided for both insulin lispro and regular insulin users. Glycaemic goals were a HbA1c between 6–8% and preprandial blood glucose levels between 4–10 mmol/L. Families were asked to increase their insulin dosage when blood glucose levels were >10 mmol/L at the same time of the day for 3 d in a row and to decrease their dosage when blood glucose levels were <4 mmol/L at the same time of day for 2 d in a row. In general, insulin dosage was adjusted in increments of 10% of the relevant dose or one unit, whichever was greater.

Clinic visits were 3 monthly. At each clinic visit a physical examination including height, weight and Tanner pubertal staging was performed (15). HbA1c measurements were made 6 weekly throughout the study. Telephone contact with the coordinating diabetes educator or endocrinologist was twice weekly for the first week, then weekly for the first month of each treatment sequence. During the second and third months telephone contact was every 2 wks. These telephone calls enabled assistance to be given with insulin adjustment and regular central documentation of insulin dosages, blood glucose profiles and hypoglycaemic episodes. The criteria for insulin dosage adjustment was the same as that recommended to families in response to blood glucose profiles and hypoglycaemia. Blood glucose profiles obtained at seven timepoints (before and 2 h after each main meal and before bed) were performed weekly for the first month and every 2 wks for the second and third months of each treatment sequence, prior to the arranged telephone contact. In addition, an eighth timepoint (3 am) blood glucose level was recorded monthly throughout the study.

A 3 Day Food Record (3DFR), was completed by the families prior to each clinic visit. Dietary data obtained using these records were used to ensure that any significant changes in diet during the study were quantitated (16). The total energy intake and the percentage of fat, protein and carbohydrate were calculated as a mean over 3 d, at baseline and at the end of the 3 months on insulin lispro and regular insulin.

All hypoglycaemic episodes were recorded by the family and confirmed by blood glucose testing where possible. A hypoglycaemic episode was defined as any time a patient felt (or another person observed) that he or she was experiencing a sign/symptom that would be associated with hypoglycaemia (where possible confirmed by a blood glucose level <4.0 mmol/L) or any asymptomatic blood glucose measurement less than 3.0 mmol/L. Hypoglycaemic episodes were then classified as follows: total hypoglycaemic episodes included all recorded episodes, including those not confirmed by blood glucose testing, hypoglycaemic episodes with a blood glucose level <3 mmol/L and severe hypoglycaemic episodes associated with convulsion or coma.

At the conclusion of the study a patient/parent preference questionnaire was administered.

Laboratory methods

HbA1c was measured at a central laboratory using the Bio-Rad Diamat analyser, (Hercules, CA). This is a high pressure liquid chromatography (HPLC) method for measuring HbA1c as a proportion of total haemoglobin. The non-diabetic range established for this method is 4–6% (mean HbA1c: $4.99 \pm 0.36\%$). Comparison with the Diabetes Control and Complications Trial (DCCT) HbA1c values may be made using the following regression equation: DCCT HbA1c = (Diamat HbA1c + 0.0972) ÷ 1.0627. This was calculated by comparison with the Bio-Rad Variant HPLC method (Hercules, CA) used in our laboratory,

which has National Glycohemaglobin Standardisation Program Level II laboratory certification. The Diamat values were therefore 2–6% higher than the DCCT values (17). John Hunter Children's Hospital patients also had a simultaneous HbA1c measured by the DCA 2000 method (Bayer Diagnostics Division, Barcelona). On four occasions in 3 patients from this hospital, blood samples were lost en route to the central laboratory. On two of these occasions the patients were using insulin lispro and on the other two occasions regular insulin. Their corrected DCA 2000 results were substituted on these four occasions. The correction formula used was derived in our own laboratory following a comparative study of 81 consecutive simultaneous samples using the two methods ($R^2 = 0.88$). The formula is: Diamat HbA1c = (1.02 × DCA 2000 HbA1c) + 0.34 (17). Re-analysis excluding the 3 patients with missing data did not alter our results.

Statistical analysis

To estimate the number of children required for the study, we used HbA1c as the variable of interest with a change of 0.5% representing a clinically significant change. The estimation of standard deviation in HbA1c was made using the most recent HbA1c result of 244 patients with type 1 diabetes between 5 and 10 yrs of age, in the 12 months prior to 1 October 1996. The mean HbA1c of this group was 8.39% and the SD was 0.98%. Using a 0.05 level of significance and a power of 0.80, a sample size of 33 was required to detect a clinically significant change in HbA1c.

The paired t-test was used to compare the mean differences in HbA1c, blood glucose levels, insulin dosage and frequency of hypoglycaemic episodes from baseline and between the treatments. If the data were not normally distributed, the signed rank test was used. All paired differences were obtained by subtracting the values for insulin lispro from regular insulin (regular − lispro).

The nutrient analysis on the data obtained from the 3DFRs was analysed using the Diet 3 software program. This program utilises the Australian 'Nutrient Data Table' (NUTTAB) 1995 food composition database (18). A standardised nutrient analysis data sheet was set up for the 3DFR. Average daily intake was calculated by multiplying the frequency of consumption by the weight of the standard serving size or estimated serving size. Any vitamin or mineral supplements taken by the subjects were not included in the nutrient analysis. Means and SDs were calculated for energy (kcals), protein (g), fat (g) and carbohydrate (g), and paired t-test was used to analyse if these were different between the two insulins. Macronutrients were also expressed as a percentage of the total energy intake.

Table 2. Mean (± SD) blood glucose values at each timepoint and 2-h postprandial blood glucose excursions for each treatment period (mmol/L)

Timepoint	Humulin R	Lispro
Pre breakfast	8.83 ± 0.51	9.44 ± 0.63
After breakfast	11.73 ± 1.04	12.14 ± 2.62
Excursion	2.87 ± 1.34	2.70 ± 2.38
Before lunch	8.54 ± 0.87	8.55 ± 0.37
After lunch	11.59 ± 0.63	11.72 ± 0.98
Excursion	3.07 ± 0.85	3.35 ± 1.11
Before dinner	11.38 ± 1.18	11.59 ± 1.03
After dinner	10.12 ± 0.71	9.66 ± 0.74
Excursion	−1.23 ± 1.12	−1.71 ± 0.92
Before bed	10.93 ± 1.11	11.06 ± 0.44
3 am	9.02 ± 0.46	10.57 ± 0.26

Results

Thirty-five children completed the study (26 from The New Children's Hospital and 9 from John Hunter Children's Hospital). There were no significant differences in age, gender, diabetes duration or HbA1c at baseline between those children assigned to sequence A and those assigned to sequence B (Table 1).

The endpoint HbA1c after 3 months on insulin lispro (8.33 ± 0.89%) was not significantly different from that after 3 months on regular insulin (8.14 ± 0.77%) (mean difference: −0.19 ± 0.63%). No significant differences were found in blood glucose levels before or after meals, 2-h postprandial glucose excursions or in blood glucose levels before bed between the treatments. However, the 3 am blood glucose levels were significantly lower when using regular insulin than when using insulin lispro. The mean blood glucose levels at 3 am in those on Humulin R was 9.02 ± 0.46 mmol/L and in those on insulin lispro was 10.57 ± 0.26 mmol/L (Table 2). The mean difference in 3 am blood glucose between the treatments was −2.35 mmol/L (95% confidence interval: −3.98, −0.72, p = 0.01; Fig. 1). All blood glucose data collected in each 3 month treatment period were used in the analysis. Re-analysis excluding the first month's blood glucose data from each treatment period was performed but did not alter the results.

The mean total insulin dose at baseline was 0.83 ± 0.12 units/kg/d (mean short-acting dose: 0.15 ± 0.09 units/kg/d, mean intermediate-acting dose: 0.68 ± 0.11 units/kg/d). There was a small but significant increase in total insulin dosage when using insulin lispro (mean difference:

0.047 ± 0.11 units/kg/d, $p = 0.02$). This was due to a relative increase in the morning intermediate-acting insulin requirements. The mean difference in intermediate-acting insulin dosage from baseline in those using insulin lispro was 0.05 ± 0.1 units/kg/d, or a 5.7% increase ($p = 0.005$). There was no significant difference in the short-acting insulin requirements.

Twenty-seven children had documented hypoglycaemic episodes. There was no significant difference in the frequency of total hypoglycaemic episodes or hypoglycaemic episodes with a blood glucose of < 3 mmol/L between those on regular insulin and those on insulin lispro. When the data were analysed according to time of occurrence throughout the day, the total recorded hypoglycaemic episodes between 06:00 and 12:00 h was significantly higher in those on insulin lispro (mean difference: 2.4 ± 5.1 episodes/person/3 months). However, there was no difference in the number of hypoglycaemic episodes with blood glucose < 3 mmol/L during this time period (Table 3). Three of the 27 children had a severe nocturnal hypoglycaemic episode during the study, two when using regular insulin with Humulin L at 04:00 h (Wk12, SeqA, HbA1c 7.7%) and 05:30 h (Wk13, SeqB, HbA1c 7.8%), respectively, and one when using insulin lispro with Humulin NPH at 06:00 h (Wk3, SeqB, HbA1c 8.7%). No other adverse events could be attributed to insulin lispro, however, one boy, with a past history of lipoatrophy on other insulins, developed lipoatrophy at the end of his 3 months on insulin lispro.

3DFRs were collected at baseline and at the end of each treatment sequence in 25 children. No differences in total energy intake or percentages of protein, carbohydrate or fat were detected between the two treatment groups. The 2 patients with coeliac disease were strictly compliant with their gluten free diets, as assessed by their 3DFRs.

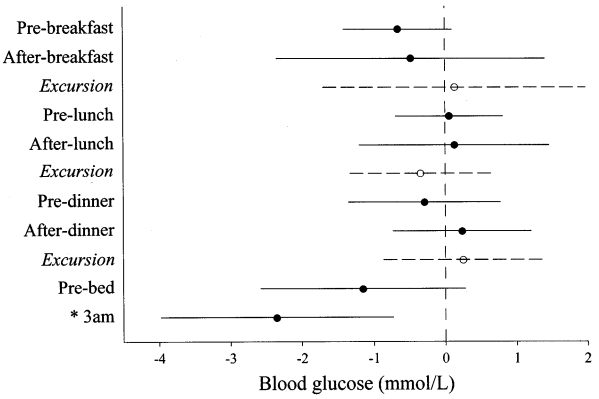

Fig. 1. Mean differences (regular – lispro) for blood glucose levels at eight timepoints (solid dots) and for 2-h postprandial glucose excursions after each main meal (open dots). 95% confidence intervals are shown in solid lines for blood glucose levels and in broken lines for glucose excursions. *$p = 0.01$.

Table 3. Hypoglycaemia rate (episodes per person per 3 months) by therapy

	Regular	Lispro
Total recorded hypos	10.77	13.47
Total hypos per time period		
24:00–06:00 h	0.93	1.03
06:00–12:00 h*	3.31	5.69
12:00–18:00 h	4.66	4.48
18:00–24:00 h	2.21	2.69
Hypos with BGL < 3 mmol/L	6.83	6.55
Hypos <3 mmol/L per time period		
24:00–06:00 h	0.62	0.62
06:00–12:00 h	1.79	2.31
12:00–18:00 h	2.83	2.48
18:00–24:00 h	1.340	1.38
Severe hypos	0.065	0.032

* Significant (paired) difference, $p = 0.02$.

The majority of families (28/35) preferred using insulin lispro because of its greater convenience, with 25 (71%) continuing on insulin lispro after the study. The seven children whose families chose to use regular insulin after the study were doing so because of better glycaemic control or the perception that their blood glucose profile was more stable.

Conclusions

This study provides much needed data on the use of insulin lispro in young children on twice daily insulin. Unlike adults, many young children are managed on twice daily combined insulin regimens and require a smaller proportion of short-acting insulin (10, 11). Our study showed no significant differences in fasting blood glucose levels, postprandial blood glucose levels or HbA1c between the treatments. Our results are similar to those from the parallel study by Garg et al., comparing insulin lispro with regular insulin in 39 adolescents and young adults on multiple injection regimens (7). They found no difference in HbA1c, fasting blood glucose or 2-h postprandial blood glucose levels at any time. They reported a significantly lower 2-h glucose excursion in those on insulin lispro only after 12 months. This was largely due to a higher glucose excursion in those on regular insulin, possibly the result of reduced compliance with the timing of injections. This contrasts with the findings of most adult studies, including the limited data on adults using twice daily insulin regimens, which have shown a reduction in post-

prandial blood glucose levels, an increase in fasting blood glucose levels but no change in HbA1c with insulin lispro. It may be that the relatively small proportion of short-acting insulin used in children contributes to these differences in blood glucose profiles.

The only other study comparing insulin lispro with regular insulin in children reported significantly reduced glucose excursions after breakfast and the evening meal when insulin lispro was given before meals (14). There were no significant differences in preprandial levels between the treatments and HbA1c data were not provided. They found larger glucose excursions when using regular insulin and smaller glucose excursions when using insulin lispro than in our study. These differences in postprandial glucose excursions could be explained by variation in timing of injections, insulin dose or dietary adjustments. Insulin dosages and dietary information were not provided.

In our study, patients were asked to maintain the same timing and carbohydrate content of meals and snacks on both treatments. A recently published study in adults on multiple injection regimens, has suggested that HbA1c can be improved by transferring $> 50\%$ of the snack carbohydrate to the preceding meal when on insulin lispro (19). As experience with insulin lispro in children increases, manipulation of dietary intake may enable glycaemic control to be improved.

We found no difference in the overall frequency of hypoglycaemic episodes between the treatment groups, however, when the data were analysed according to time of occurrence throughout the day, the total recorded hypoglycaemic episodes between 06:00 and 12:00 h was significantly higher in those on insulin lispro. There was no difference in the number of hypoglycaemic episodes with blood glucose < 3 mmol/L during this time period and a number of these episodes were not confirmed by blood glucose levels as they occurred at school. The relatively high mean 3 am blood glucose levels on both treatments may explain why a difference in hypoglycaemia rate was not seen between 24:00 and 06:00 h in this study. Fear of hypoglycaemia, especially at night, is one of the main barriers to improving glycaemic control and preventing complications at all ages. In the largest crossover comparative study in adults, there was a 12% decrease in the total number of hypoglycaemic episodes in those using insulin lispro, with the largest relative improvement being at night (6). Another study of 199 patients with well-controlled type-1 diabetes found that despite a similar overall frequency of hypoglycaemia, the number of severe hypoglycaemic episodes was lower in those on insulin lispro (20). Our study was not sufficiently powered to detect a difference in the frequency of severe hypoglycaemic episodes between the groups, however, no severe hypoglycaemic episodes occurred in our study that could be attributed to insulin lispro. Much larger collaborative studies over a longer time period would be required to definitively demonstrate a difference in rates of severe hypoglycaemia in children.

The reliability of quality of life data is limited in open-labelled studies, however, most studies have demonstrated that treatment satisfaction improved significantly when using insulin lispro (8, 9). This difference was attributed to the convenience offered by the time–action profile of insulin lispro. In our study, families also cited the convenience of insulin lispro as the biggest advantage. Interestingly, despite instructions to inject regular insulin 30 min before the meal when questioned at the end of the study, 10% gave their injection < 10 min before the meal, 29% 10–20 min, 58% 20–30 min and 3% waited more than 30 min. Given that those participating in a study would generally be more motivated, this is probably a better performance than that which occurs in the total population and concurs with the findings of other studies which have shown that a majority of patients receiving regular insulin did not follow the instructions to inject at least 30 min before meals (1, 9, 21).

In conclusion, this study shows the main advantage of insulin lispro in young children on twice daily insulin to be its greater convenience, this being achieved without a deterioration in glycaemic control. As with most insulins, insulin lispro appeared to suit some children better than others and treatment needs to be individualized. A small increase in the morning intermediate-acting insulin dosage was often required when using insulin lispro, but the dosage of insulin lispro was equivalent to regular insulin. Higher 3 am blood glucose levels and an increased rate of hypoglycaemic episodes between 06:00 and 12:00 h occurred in those on insulin lispro, consistent with the known action profiles. Higher 3 am blood glucose levels could translate to reduced nocturnal hypoglycaemia in some individuals. The observed difference in blood glucose levels at 3 am needs confirmation in a larger study. Further studies are also required to examine the usefulness of insulin lispro in other dosage regimens in this age group.

Acknowledgements

The authors would like to acknowledge the assistance of Dr Don Anderson, Dr Christopher Cowell and Dr Christopher Poon in the recruitment of subjects for the study and AZA Research who provided the insulins for the study.

Preliminary data from this study have been published in the Proceedings of the Australasian Paediatric Endocrine Group ASM 1998: Fairchild JM et al. 'Insulin Lispro versus Humulin R in Children with IDDM on a Twice Daily Insulin Regimen: Preliminary Results'. Co-author Dr Patricia Crock is a consultant for The University of Newcastle Novo-Nordisk Diabetes Academy.

References

1. 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.
2. Dimitriadis GD, Gerich JE. Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. Diabetes Care 1983: 6: 374–377.
3. Torlone E, Fanelli C, Rambotti AM 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. Holleman F, van den Brand JJG, Hoven RARA et al. Comparison of LysB28,ProB29-human insulin analog and regular human insulin in the correction of incidental hyperglycaemia. Diabetes Care 1996: 19: 1426–1429.
5. Woodworth J, Howey D, Bowsher R, Lutz S, Santa P, Brady P. [Lys(B28), Pro(B29)] human insulin(K): dose ranging vs. Humulin R(H) (Abstract). Diabetes 1993: 42 (Suppl 1): 54A.
6. Anderson JH, Brunelle RL, Koivisto VA, et al. and The Multicenter Insulin Lispro Study Group. Reduction of postprandial hyperglycaemia and frequency of hypoglycaemia in IDDM patients on insulin analog treatment. Diabetes 1997: 46: 265–270.
7. Garg SK, Carmain JA, Braddy KC et al. Premeal insulin analogue insulin lispro vs Humulin R insulin treatment in young subjects with type 1 diabetes. Diabet Med 1996: 13: 47–52.
8. Pfutzner A, Kustner E, Frost T, et al. on behalf of the German Insulin Lispro/IDDM study group. Intensive therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycaemic episodes. Exp Clin Endocrinol 1996: 104: 25–30.
9. Schmitt H, Symanowski SM, Holleman F, Rees A, Rottiers R, Anderson JH. Comparison of premeal therapy with insulin lispro and regular insulin in patients with IDDM (Abstract). Diabetologia 1996: 39 (Suppl 1): A221.
10. Mortensen HB, Hougaard P for the Hvidore Study Group on Childhood Diabetes. Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. Diabetes Care 1997: 20 (5) 714–720.
11. Mortensen HB, Robertson KJ, Aanstoot HJ et al. Insulin management and metabolic control of type 1 diabetes mellitus in childhood and adolescence in 18 countries. Hvidore Study Group on Childhood Diabetes. Diabet Med 1998: 15 (9): 752–759.
12. Pieber TR, Feinbock C, Rabensteiner D, Weitgasser R, Ristic S. Lispro insulin analog in twice a day insulin treatment (Abstract). Diabetologia 1995: 38 (Suppl 1): A3.
13. Vignati L, Anderson JH, Szwast S, Symanowski S. Twice daily lispro results in less glucose variability compared to human regular insulin (Abstract). Diabetologia 1995: 38 (Suppl 1): A191.
14. Holcombe JH, Brunelle R, Zalani S, Deeb LC. Comparative study of insulin lispro and regular insulin in prepubertal children with type 1 diabetes (Abstract). Diabetes 1998: 47: A96.
15. Tanner JM. Growth at Adolescence, 2nd Edition. Oxford: Blackwell, 1962.
16. Black AE, Prentice AM, Goldberg GR et al. Measurements of total energy expenditure provide insights into the validity of dietary measurements of energy intake. J Am Diet Assoc 1993: 93: 572–579.
17. Dr Barbara Blades, Head of the Endocrine Laboratory, The New Children's Hospital, Westmead NSW. Personal communication, February 2000.
18. Lewis J, Milligan G, Hunt A. NUTTAB 1995 Nutrient Data Table for Use in Australia. Australian Government Publishing Service, 1995: 1995.
19. Ronnemaa T, Viikari J. Reducing snacks when switching from conventional soluble to lispro insulin treatment: effects on glycaemic control and hypoglycaemia. Diabet Med 1998: 15 (7): 601–607.
20. Holleman F, Schmitt H, Rottiers R, et al. and the Benelux-UK Insulin Lispro Study Group. Reduced frequency of severe hypoglycaemia and coma in well-controlled IDDM patients treated with insulin lispro. Diabet Care 1997: 20:1827–1832.
21. Jorgensen LN, Nielsen FS. Timing of pre-meal insulins in diabetic patients on a multiple daily injection regimen: a questionnaire study (Abstract). Diabetologia 1990: 33 (Suppl): A116.
22. Lazarus R, Baur L, Webb K et al. Recommended body mass index cutoff values for overweight screening programmes in Australian children and adolescents: Comparisons with North American values. J Paediatr Child Health 1995: 31: 143–147.