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RESEARCH ARTICLE

Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin

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Abstract

Objective To assess the potential of insulin lispro to limit the frequency of severe hypoglycaemia without compromising glycaemic control in a cohort of patients with type 1 diabetes who are at a high risk of severe hypoglycemia.

Research design and methods An open-label, randomised, 12-month comparative crossover study of insulin lispro and regular human insulin was performed in 33 patients with type 1 diabetes with impaired hypoglycaemia awareness. The efficacy of each treatment was evaluated by glycaemic control (HbA_{1c}), eight-point home blood glucose profiles, and the frequency and severity of hypoglycaemic episodes and quality of life.

Results Eighteen (55%) patients experienced one or more episodes of severe hypoglycaemia in the 48 weeks of study. There was a trend to a lower incidence of severe hypoglycaemia during treatment with insulin lispro in comparison with regular human insulin (55 vs 84 episodes, $p = 0.087$). This resulted principally from a 47% lower incidence of nocturnal severe hypoglycaemia with insulin lispro (25 vs 47 episodes, $p = 0.11$). The lower frequency of severe hypoglycaemia associated with insulin lispro was not explained by differences in glycated haemoglobin between insulin treatments (HbA_{1c} 9.1% insulin lispro vs 9.3% regular human insulin).

Conclusions In individuals with type 1 diabetes, who have impaired awareness of hypoglycaemia, treatment with insulin lispro may be associated with a lower incidence of severe hypoglycaemia manifested predominantly through less frequent nocturnal episodes. Insulin lispro may have a beneficial role in the management of patients with diabetes at risk of severe hypoglycaemia, although a larger study is required to confirm these findings.

Keywords type 1 diabetes; insulin lispro; hypoglycaemia unawareness; hypoglycaemia

Introduction

Impaired awareness of hypoglycaemia, defined as a reduced ability to perceive the onset of hypoglycaemia, is common in type 1 diabetes, affecting around 25% of patients [1–4], with its prevalence increasing with duration of diabetes [1]. It is associated with diminished symptoms of hypoglycaemia, an altered symptom profile, in which neuroglycopenic symptoms predominate

[3,5], and a rate of severe hypoglycaemia six-fold higher than that observed in patients who have normal awareness [2–5]. Because of the high incidence of severe hypoglycaemia in patients with diabetes with impaired awareness of hypoglycaemia, novel insulin preparations can be tested in this important subgroup to examine whether a therapeutic benefit may be conferred through a lower frequency of severe hypoglycaemia.

The insulin analogue, insulin lispro, is rapidly absorbed following subcutaneous injection and, when compared to regular human insulin, achieves higher post-injection peak insulin concentrations, a more rapid onset of biological activity, and a shorter duration of action [6]. Insulin lispro treatment, within a multiple injection regimen, was associated with a lower incidence of mild symptomatic and biochemical hypoglycaemia particularly at night, in individuals with type 1 diabetes [7–9] and a lower incidence of severe hypoglycaemia in patients with normal awareness of hypoglycaemia [8]. However, a metanalysis of 24 studies assessing the effect of insulin lispro treatment in those with normal awareness of hypoglycaemia concluded that there was no substantive reduction in the overall rate of hypoglycaemia [10]. To our knowledge patients with diabetes and impaired awareness of hypoglycaemia have not been included previously in trials with insulin lispro.

The aim of the present study was to compare treatment with insulin lispro and regular human insulin in a cohort of patients with type 1 diabetes who had impaired awareness of hypoglycaemia and a history of frequent severe hypoglycaemia. The two insulins were compared with respect to the frequency of mild and severe hypoglycaemia, glycaemic control, and quality of life measures.

Research design and methods

The trial was performed according to the principles of the Declaration of Helsinki and was approved by the local medical ethics advisory committee. Written informed consent was obtained from all individuals before their enrolment into the study.

Patients

A total of 40 patients (19 male, 21 female) with type 1 diabetes, aged between 19 and 65 years, all of whom had diabetes for more than 5 years, were recruited from the outpatient clinic of the Department of Diabetes, Royal Infirmary of Edinburgh. Participants were included only if they had reported a reduction in their warning symptoms of hypoglycaemia for at least 2 years, had experienced two or more episodes of severe hypoglycaemia in the 2 years preceding participation, and had a glycated haemoglobin of less than double the local non-diabetic reference range (HbA_{1c}: 5.0–6.5%). Patients with systemic, renal or hepatic disease were excluded, and pregnant patients were not studied. Of the 39 patients randomised for study, four patients withdrew for personal or employment reasons and one patient was withdrawn after a positive pregnancy test was obtained after completing the first treatment period with insulin lispro. Of the remaining 34 patients who completed the study protocol, the data from one participant was not analysed because of observed inconsistencies between the home glucose monitoring diary, HbA_{1c} results and the contents of the glucose meter memory. The demographic characteristics of the 33 participants who completed the study protocol are shown in Table 1.

Definition of impaired awareness of hypoglycaemia

Diminished intensity of hypoglycaemia warning symptoms was elicited by clinical history and the ability of individuals to detect the onset of hypoglycaemia, which was quantified using the method described by Gold and colleagues [4]. Patients were considered to have impaired awareness of hypoglycaemia if they described a reduction in their hypoglycaemia warning symptoms for at least 2 years, during which they had experienced severe hypoglycaemia at least twice, and self-scored an impaired ability to detect the onset of hypoglycaemia on a Likert scale [5].

Hypoglycaemia symptomatology was further evaluated using an established scoring system, the Edinburgh Hypoglycaemia Score, which uses a validated questionnaire [11]. This questionnaire lists individual hypoglycaemia symptoms which participants are required to score from 1 to 7, depending on symptom intensity. Total scores for autonomic, neuroglycopenic and non-specific symptoms of hypoglycaemia were derived using this system [11]. Participants completed the questionnaire with respect to their existing profile and intensity of symptoms and retrospectively assessed the nature and intensity of the symptoms they had experienced before the development of impaired awareness of hypoglycaemia. Data from the symptoms questionnaire, summarised in Table 2, confirmed that the cohort had noted a subjective reduction in the intensity of (mainly) autonomic warning symptoms since commencing insulin

Table 1. Characteristics of patients with type 1 diabetes completing the study ($n = 33$)

Category	
Men	18 (54.5%)
Women	15 (45.5%)
Age (years)	46 ± 11 (19–65)
BMI (kg m^{-2})	25.4 ± 2.6 (19.6–30.0)
Duration of diabetes (years)	25.8 ± 9.8 (10–45)
HbA_{1c} (%) (non-diabetic range 5.0–6.5%)	9.0 ± 1.1 (6.5–11.7)
Insulin regimen	
Twice daily free-mixed insulin	11 (33.3%)
Multiple injection regimen	22 (66.7%)
U/kg	0.67 ± 0.20 (0.42–1.23)
Duration of impaired awareness (years)	8.0 ± 5.8 (2–27 years)

Data are means ± SD, with the range or percentage given in parentheses.

Table 2. Symptoms of hypoglycaemia based on Edinburgh Hypoglycaemia Score [11]

	Present	Previous	*p* value
Autonomic symptoms	21.1 ± 9.9	25.8 ± 12.2	0.002*
Neuroglycopenic symptoms	30.6 ± 13.2	28.8 ± 12.2	0.37
Non-specific symptoms	4.8 ± 2.9	4.9 ± 3.2	0.78
Percentage autonomic (%)	37.3	43.4	–
Percentage neuroglycopenic (%)	54.2	48.4	–

*$p < 0.01$. Data are means ± SD.

therapy and that predominantly neuroglycopenic symptoms were being experienced during hypoglycaemia. The cohort of patients recruited, therefore, had demonstrable evidence of impaired hypoglycaemia awareness.

The ability of an individual to detect the onset of hypoglycaemia was evaluated on a scale of 1 to 7, a score of 1 indicating that the individual always detected hypoglycaemia and a score of 7 indicating that the individual could never detect the onset of hypoglycaemia. In a previous study in our department utilising an identical scoring system, it was demonstrated that individuals who scored ≥4 on this scale had impaired awareness of hypoglycaemia [5]. The present cohort had a mean score of 4.6 (±1.8), congruent with the findings of the hypoglycaemia symptoms questionnaire.

Study design

The study was designed and powered to compare the effects of two insulin therapies, insulin lispro and regular human insulin, with respect to the incidence of severe hypoglycaemia in a cohort of patients with type 1 diabetes who had a history of impaired hypoglycaemia awareness. An open-label, randomised, crossover design was used. Following enrolment, all individuals were treated with regular human insulin (Humulin® S; Eli Lilly, Basingstoke, UK) in combination with NPH insulin (Humulin® I; Eli Lilly) for a run-in period of 4 weeks. During the run-in period and the treatment phases no alterations were made to the number of injections of insulin that individuals were receiving, so that each participant maintained the same regimen throughout the study. The term 'twice daily' regimen refers to those administering a mixture of soluble and isophane (NPH) insulins before breakfast and the main evening meal. 'Multiple injection' regimen refers to those injecting soluble insulin before meals and isophane (NPH) insulin before bed. Participants were allowed to adjust their own insulin dose on a daily basis although advice regarding dose adjustments was offered around the beginning of each treatment phase. No formal blood glucose targets were requested nor advised. Participants were randomised to receive treatment either with insulin lispro and human NPH insulin, or alternatively with regular human insulin and NPH insulin, for two treatment periods each lasting 24 weeks. On completion of the first treatment period, participants were changed to the alternative treatment for a further 24 weeks. In view of the different pharmacokinetics of insulin lispro and regular human insulin the study was open-label. Participants were advised to inject insulin lispro immediately before meals and regular human insulin 30 min before meals and were requested to use the anterior abdominal wall as the sole injection site throughout the study [12].

Glycated haemoglobin (HbA_{1c}) was estimated using high-performance liquid chromatography (HPLC) (Hi Auto A1c HA 8121), performed at randomisation and at the termination of each treatment period. The participants used a home blood glucose meter with a memory facility (Accutrend®; Boehringer Mannheim, Livingston, UK) to measure capillary blood glucose concentrations. Participants were asked to perform an eight-point home capillary blood glucose profile every 4 weeks to ascertain the quality of within-day control and were advised to continue self-monitoring of blood glucose as per their normal routine. Values of ≤3.5 mmol/l (65 mg/dl) were recorded as evidence of biochemical hypoglycaemia. Capillary blood glucose concentrations in this range, irrespective of whether accompanied by symptoms of hypoglycaemia, were recorded as hypoglycaemic episodes, to ensure that all biochemical and symptomatic episodes of hypoglycaemia were documented. Symptomatic episodes of hypoglycaemia were recorded whether or not capillary blood glucose had been measured. Severe hypoglycaemia was defined as any episode of hypoglycaemia for which an individual required external (third party) assistance to facilitate recovery.

The time of occurrence of hypoglycaemia, whether during the day or night, the relationship to meals, snacks and insulin injections, the presence or absence of symptoms, the ability to self-treat, method of treatment and the outcome of each hypoglycaemic episode were recorded in study diaries issued at 4-weekly study visits. At each 4-week review during the active treatment phases of the study, the entries in the completed study diary were validated against the memory in the blood glucose meter. Discrepancies between the meter memory and the diary record were discussed with participants. The primary outcome measures were the frequency of episodes of severe hypoglycaemia and the quality of glycaemic control.

Quality of life questionnaires were completed at randomisation and at the end of each treatment period. These included the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [13] and the Hypoglycaemia Fear Survey (HFS) [14].

Statistical analysis

Statistical analysis was performed using SPSS© v8.0 (SPSS Inc., Chicago, IL, USA). Severe hypoglycaemia data were analysed using the Mann-Whitney U-test to determine crossover effects and the effect of treatment. Glycated haemoglobin concentrations were compared using paired *t*-tests, and home capillary blood glucose profile and questionnaire data were compared using ANOVA.

Results

Because of the crossover design of the study a crossover analysis was performed to assess the effects of periodicity, treatment-period interactions and treatment itself. No significant effects of periodicity ($p = 0.26$) or treatment-period interactions ($p = 0.87$) were observed concerning the incidence of severe hypoglycaemia. No significant difference was identified in the duration of treatment between either insulin studied, although on average insulin lispro was administered for 8 days more to each patient ($p =$ NS).

The results of HbA_{1c} measurements and the monthly eight-point home capillary glucose profiles are summarised in Table 3, with glucose profile data subdivided according to insulin regimen. No difference was observed in overall glycaemic control between the two insulin treatments, as determined by mean HbA_{1c} measurements taken at the end of each treatment period (insulin lispro 9.1%, regular human insulin 9.3%, $p = 0.14$, paired *t*-test). The home capillary blood glucose profiles were generally consistent with those that would be expected with the insulin regimens of individual patients. The mean capillary blood glucose concentrations during the night (which were sampled between 0200 h and 0300 h) were consistently higher during insulin lispro treatment, achieving statistical significance when compared with both free-mixed regular and NPH insulins administered twice daily ($p = 0.028$, ANOVA), and for multiple injection regimens ($p = 0.002$, ANOVA).

Table 3. Home blood glucose values and HbA_{1c} concentrations on regular human insulin and insulin lispro by type of insulin regimen

	Regular human insulin	Insulin lispro	*p* value
HbA_{1c} (local range 5.0–6.5%)	9.3 ± 1.0	9.1 ± 0.83	NS
Twice daily ($n = 11$)	9.2 ± 0.89	9.2 ± 0.75	NS
Multiple injection ($n = 22$)	9.4 ± 1.1	9.1 ± 0.90	NS
Fasting glucose (mmol l^{-1})			
Twice daily ($n = 11$)	8.9 ± 4.5	10.3 ± 4.2	0.067
Multiple injection ($n = 22$)	8.3 ± 3.9	8.8 ± 4.3	NS
2 h post-breakfast (mmol l^{-1})			
Twice daily	10.4 ± 5.4	9.6 ± 5.0	NS
Multiple injection	9.9 ± 4.4	8.7 ± 5.0	0.051
Pre-lunch (mmol l^{-1})			
Twice daily	6.3 ± 3.5	6.3 ± 3.5	NS
Multiple injection	7.6 ± 4.1	7.4 ± 3.9	NS
2 h post-lunch (mmol l^{-1})			
Twice daily	9.3 ± 3.6	9.9 ± 4.1	NS
Multiple injection	8.8 ± 4.2	9.0 ± 4.7	NS
Pre-dinner (mmol l^{-1})			
Twice daily	8.0 ± 4.1	7.8 ± 4.1	NS
Multiple injection	8.1 ± 4.6	8.7 ± 4.6	NS
2 h post-dinner (mmol l^{-1})			
Twice daily	8.8 ± 4.3	8.1 ± 4.0	NS
Multiple injection	9.3 ± 4.1	9.2 ± 4.5	NS
Bedtime (mmol l^{-1})			
Twice daily	8.4 ± 4.4	9.0 ± 4.1	NS
Multiple injection	8.8 ± 4.2	10.6 ± 5.3	0.003**
Nocturnal (mmol l^{-1})			
Twice daily	7.8 ± 4.1	9.4 ± 3.7	0.028*
Multiple injection	8.0 ± 4.4	9.9 ± 4.1	0.001†

Twice daily indicates insulin lispro or regular human insulin free-mixed with NPH and administered twice daily. Multiple injection indicates three or more injections of insulin per day.
*$p < 0.05$, ** $p < 0.01$; NS, not significant. Data are means ± SD.

Hypoglycaemic events

The data on hypoglycaemic episodes are summarised in Table 4. No difference was noted between the two treatment regimens in the total incidence of hypoglycaemia (self-treated plus severe episodes). However, a trend towards a difference was observed in the incidence of severe hypoglycaemia between insulin lispro and regular human insulin, with a lower incidence of severe hypoglycaemia being recorded during treatment with insulin lispro (55 vs 84 episodes, $p = 0.087$). Although fewer episodes of severe hypoglycaemia were recorded during insulin lispro treatment, 18/33 participants (55%) experienced severe hypoglycaemia with each insulin under evaluation.

The times of day at which episodes of severe hypoglycaemia occurred are summarised in Table 4. The day was subdivided according to the times at which insulin was administered before meals and at bedtime. Fewer episodes of severe hypoglycaemia occurred during the night in the insulin lispro treatment phase of the study (25 vs 47 episodes, $p = 0.11$), which principally accounted for the difference in the incidence of severe hypoglycaemia observed between the study insulins. A lower incidence of nocturnal severe hypoglycaemia with insulin lispro was observed during both the early (0000–0400 h) and later (0400–0800 h) parts of the night (Figure 1), and is consistent with the blood glucose profile data which demonstrated moderate hyperglycaemia during the night with insulin lispro treatment (Table 4). Fewer episodes of hypoglycaemic coma and emergency treatments with glucagon were recorded during the insulin lispro treatment arm but the frequency was too low to detect a statistical difference between the treatments. The data for the times of day during which mild hypoglycaemia occurred are not displayed, as no significant differences were observed. No difference was detected in the blood glucose threshold at which

Table 4. Hypoglycaemic episodes during each treatment period

	Total	Regular insulin	Insulin lispro	*p* value
Total	2271	1115	1156	NS
Non-severe	2132	1031	1101	NS
Severe				
Total	139	84	55	0.087
Glucagon therapy	24	18	6	NS
Coma	27	19	8	NS
Severe–clock time				
0000–0800 h	72	47	25	0.11
0800–1300 h	24	11	13	NS
1300–1800 h	13	9	4	NS
1800–0000 h	30	17	13	NS
Percentage with severe hypoglycaemia	18/33 (54.5%)	18/33 (54.5%)	18/33 (54.5%)	NS

The day was divided according to the time at which insulin injections were administered.
NS, Not significant.

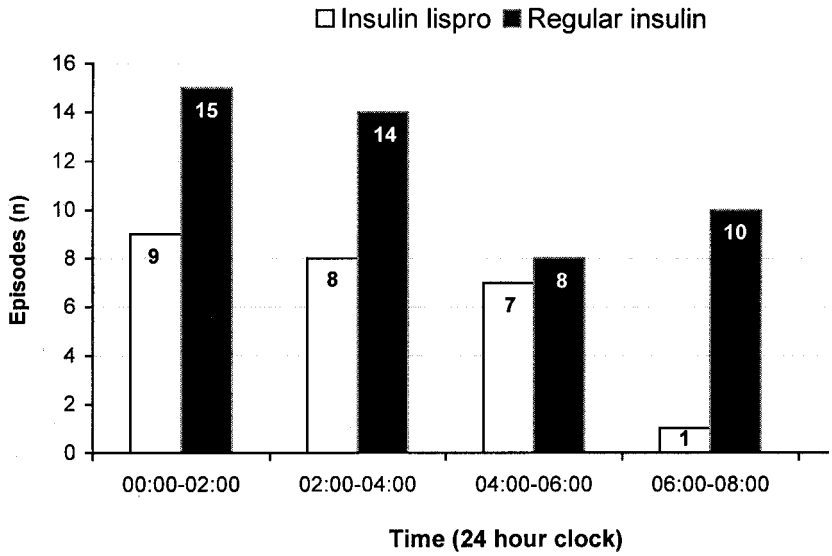

Figure 1. Time of occurrence of episodes of nocturnal severe hypoglycaemia with each insulin treatment

hypoglycaemia initiated the perception of symptoms (2.6 mmol/l insulin lispro vs 2.5 mmol/l regular human insulin, p = NS).

The severe hypoglycaemia data were analysed with respect to insulin regimen to determine whether the lower rate of nocturnal severe hypoglycaemia with insulin lispro applied equally to patients using conventional twice daily regular and NPH insulins and multiple injection insulin regimens. Of the 139 episodes of severe hypoglycaemia recorded, only 18 episodes occurred in patients on a twice daily insulin regimen, of which four episodes were nocturnal (one insulin lispro vs three regular human insulin). Despite fewer episodes of severe hypoglycaemia being recorded during insulin lispro treatment (6 vs 12 episodes, $p = 0.11$) in those patients administering insulin twice daily, no statistically significant reduction was observed.

Quality of life questionnaires

No differences were observed between regular human insulin and insulin lispro in the scores obtained on the DTSQ [13] or the HFS [14]. However, scores on the DTSQ and the HFS were influenced by exposure to severe hypoglycaemia during the period of study. The 55% of participants who experienced severe hypoglycaemia during the 48 weeks of follow-up scored significantly higher on the worry ($p = 0.049$) and behaviour ($p = 0.015$) categories of the HFS and had significantly lower DTSQ scores ($p = 0.040$). The HFS scores suggest that those individuals who had experienced previous severe hypoglycaemia may have altered their behaviour to minimise their future risk of severe hypoglycaemia, but that this modification had either been unsuccessful or inadequate.

Exposure to recurrent severe hypoglycaemia over the study period exhibited a negative correlation with many quality of life outcomes. An increase in exposure to severe hypoglycaemia correlated with greater anxiety ($r = 0.55$, $p = 0.001$) and worry ($r = 0.58$, $p = 0.001$), depression ($r = 0.45$, $p = 0.010$) and lower levels of energy ($r = -0.52$, $p = 0.002$). No significant improvements in quality of life measures were associated with insulin lispro treatment despite the lower incidence of severe hypoglycaemia.

Discussion

The present study suggests that in individuals with type 1 diabetes at high risk of developing severe hypoglycaemia, treatment with insulin lispro may be associated with a lower incidence of severe hypoglycaemia compared with regular human insulin, without causing any deterioration in glycaemic control. The frequency of severe hypoglycaemia observed in this prospective study is concordant with estimates in previous prospective surveys of very similar cohorts of patients who had impaired awareness of hypoglycaemia [2,3,5]. The lower incidence of severe hypoglycaemia observed during treatment with insulin lispro was associated principally with significantly fewer nocturnal events (Figure 1). Sleep, per se, is a risk factor for severe hypoglycaemia [15,16] because the premonitory symptoms of hypoglycaemia are blunted or absent during sleep, which usually takes place at night. The results of the present study are consistent with this premise as 56% and 45% of severe hypoglycaemic episodes with regular human insulin and insulin lispro, respectively, occurred at night. Insulin lispro did not appear to confer any benefit at other times of the day in this group of patients.

The lower incidence of nocturnal severe hypoglycaemia associated with insulin lispro is consistent with the home capillary blood glucose profiles which demonstrated moderate elevation of bedtime and nocturnal blood glucose concentrations when insulin lispro was being

used, irrespective of insulin regimen. The modest elevation of nocturnal blood glucose associated with insulin lispro treatment did not adversely affect overall glycaemic control, as measured by HbA_{1c}. No difference was observed in fasting blood glucose between insulin lispro and regular human insulin, implying that the moderate nocturnal hyperglycemia was limited to the first part of the night. This observation is consistent with the shorter duration of biological activity of insulin lispro and with the time of night at which severe hypoglycaemia was observed most commonly (Figure 1). The excess of severe hypoglycaemia that occurred between 0600–0800 h during regular human insulin treatment probably relates to the bedtime dose of intermediate-acting insulin (NPH) which has a much longer duration of action. One individual who was receiving insulin replacement by a multiple injection regimen experienced the majority of the severe hypoglycaemic episodes that occurred in the fasting state (pre-breakfast). This individual did not experience severe hypoglycaemia at this time of day during treatment with insulin lispro.

The distribution of severe hypoglycaemia with respect to insulin regimen was not anticipated but may be a consequence of the local treatment policy for the management of patients who have a history of recurrent severe hypoglycaemia. In our centre, patients who have given a history of recurrent severe hypoglycaemia and/or have developed impaired awareness of hypoglycaemia have been advised to use a multiple injection insulin regimen, as this had been perceived to limit the frequency of severe hypoglycaemia. Patients with impaired awareness of hypoglycaemia who were not using a multiple injection insulin regimen had either experienced recurrent severe hypoglycaemia less frequently or simply had preferred to continue with a twice daily insulin regimen. In the pre-study assessment of hypoglycaemia history, those patients on a twice daily insulin regimen self-estimated that they experienced severe hypoglycaemia less frequently than those patients taking a multiple injection regimen, and this was confirmed by partners and spouses of the subjects. It is therefore possible that the patients in the present study who were administering insulin twice daily represented a self-selected group at lower risk of severe hypoglycaemia, and who were therefore less likely to derive any tangible benefit with insulin lispro in terms of lower frequency of severe hypoglycaemia.

The incidence of mild and biochemical hypoglycaemia recorded with each insulin type did not differ at any time of day. The absence of any significant difference in the incidence of mild and biochemical nocturnal hypoglycaemia with insulin lispro was unexpected in view of previous studies performed in patients with type 1 diabetes who had normal awareness of hypoglycaemia [7–9], but is consistent with the conclusions of a recent metanalysis [10]. Previous clinical studies that reported a reduction in the incidence of nocturnal mild hypoglycaemia with treatment with insulin lispro have studied large numbers of patients (presumed to have normal hypoglycaemia awareness) and have identified up to a 44% lower incidence [8]. In the present study a much smaller number of patients was studied, the participants all had impaired awareness of hypoglycaemia, and the magnitude of the difference in the frequency of nocturnal mild hypoglycaemia was considerably less (12%). However, a lower incidence of nocturnal severe hypoglycaemia and higher nocturnal concentrations of capillary blood glucose were observed during the treatment period with insulin lispro.

The open-label nature of the present study may have introduced bias, in that the patients knew which type of insulin they were using in each treatment arm. However, an open-label design was necessary in view of the different pharmacokinetics of the two insulin treatments under comparison. To have blinded patients to insulin type could have introduced a bias toward insulin lispro, as it would have been necessary for both insulins to have been administered immediately before meals, which could have had a detrimental effect on post-meal glycaemic excursions during treatment with regular human insulin [17].

In conclusion, people with type 1 diabetes who have impaired awareness of hypoglycaemia, may benefit from the use of insulin lispro, particularly with respect to the risk of severe hypoglycaemia occurring overnight. However, severe hypoglycaemia is common in all patients with type 1 diabetes, with almost one-third experiencing one or more episodes each year [18,19]. The lower frequency of nocturnal severe hypoglycaemia observed with insulin lispro implies that its use as a pre-evening meal insulin may incur a similar benefit to all patients treated with insulin. This possible beneficial effect of insulin lispro treatment requires a further larger study for confirmation.

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