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A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy

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Abstract

Aims Despite considerable experience with insulin lispro, few blinded comparisons with soluble insulin are available. This study compared insulin lispro with human soluble insulin in patients with Type 1 diabetes mellitus on multiple injection therapy who inject shortly before meals.

Methods Glucose control, frequency of hypoglycaemia and patient preference were examined in the course of a prospective, randomized, double-blind, crossover comparison, with a 6-week run-in period and 12 weeks on each therapy. Ninety-three patients took part, all on multiple daily doses of insulin, with soluble insulin before meals and NPH (isophane) insulin at night. The main outcome measures were self-monitored blood glucose profiles, glycated haemoglobin, frequency of hypoglycaemic episodes, patient satisfaction and well-being and patient preference.

Results Blood glucose levels were significantly lower after breakfast and lunch, but higher before breakfast, lunch and supper, in patients taking insulin lispro. Levels of HbA_{1c} were 7.4 ± 1.1% on Humulin S and 7.5 ± 1.1% on insulin lispro (P = 0.807). The overall frequency of symptomatic hypoglycaemia did not differ, but patients on insulin lispro were less likely to experience hypoglycaemia between midnight and 6 a.m., and more likely to experience episodes from 6 a.m. to midday. Questionnaires completed by 84/87 patients at the end of the study showed that 43 (51%) were able to identify each insulin correctly, nine (11%) were incorrect, and 32 (38%) were unable to tell the insulins apart. No significant preference emerged: 35 (42%) opted for insulin lispro, 24 (29%) opted for Humulin S, while the remainder had no clear preference.

Conclusions Substitution of insulin lispro for soluble insulin in a multiple injection regimen improved post-prandial glucose control at the expense of an increase in fasting and pre-prandial glucose levels. Patients who already injected shortly before meals expressed no clear preference for the fast-acting analogue, and did not improve their overall control as a result of using it. Nocturnal hypoglycaemia was however, less frequent on insulin lispro, and may emerge as a robust indication for its use.

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Keywords hypoglycaemia, insulin analogues, insulin therapy, randomized controlled trial, Type 1 diabetes mellitus

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Introduction

Soluble insulin is formulated as hexamers that dissociate following subcutaneous injection to form dimers and monomers which then diffuse rapidly into the circulation. Dissociation of hexamers is the rate-limiting step in insulin absorption [1]. Insulin lispro [Lys(B28), Pro(B29) human insulin molecule], in which the positions of the amino acids lysine and proline are reversed on the B chain of insulin, self-associates much more weakly than human soluble insulin. The result of this minor modification, which appears to affect none of the other biological properties of insulin, is that insulin lispro dissociates more readily following injection, reaches the circulation more rapidly and has a shorter duration of action [2]. These characteristics offer the potential for better control of post-prandial hyperglycaemia and reduced risk of hypoglycaemia.

A double-blind comparison of insulin lispro and soluble insulin has been performed in patients on continuous subcutaneous insulin therapy [3], and basal insulins have been compared in a blinded fashion in patients taking lispro [4]. No direct comparison of lispro and soluble insulin has been reported in patients on injection therapy. Open-label comparisons have generally been employed, on the reasoning that soluble insulin should ideally be injected some 30 min before food in order to optimize its effect [5], whereas lispro is designed for injection within 10–15 min of eating. This difference in timing would entail a risk of pre-meal hypoglycaemia if lispro were injected 30 min before a meal, or sub-optimal use of soluble insulin if given closer to food. However, many patients – at least one in three – do not follow the recommendation to inject 30 min before meals [6] and could therefore participate without disadvantage in a double-blind trial in which all injections are given shortly before meals. Selection of patients in this category on multiple injection therapy allowed glucose control, hypoglycaemia and patient preference on soluble and lispro insulins to be compared using a double-blind trial design.

Patients and methods

Patients

Patients were recruited from 10 diabetic clinics in the UK. Eligible patients had developed Type 1 diabetes before the age of 40 years, had suffered from diabetes for more than 1 year and had no evidence of major complications. The trial set out to recruit well-motivated individuals in good to moderate control (HbA_{1c} value < 1.5-times the upper limit of the non-diabetic range) who took four daily injections of insulin, and injected within 15 min of meals on more than 50% of occasions. Ethical approval was obtained for the study at each centre, and written, informed consent was obtained from all participants. Of 114 patients enrolled, 20 were excluded because their HbA_{1c} was > 1.5 times the upper limit of the non-diabetic range when checked in the reference laboratory and one decided not to participate, so that 93 (44 women and 49 men) were randomized to treatment. The median age was 35 years (range 18–63 years), the median duration of diabetes 13.1 years (range 1–51 years), and the median body mass index 25.2 kg/m^2 (range 20.0–33.7 kg/m^2). At study entry all patients were on multiple injection therapy, and those not using using Humulin S (soluble) as their short-acting insulin and Humulin I (isophane) as their basal insulin were converted to this regimen before entering the study. The majority injected Humulin S three times daily before meals and Humulin I with their bed-time snack, and injections were given via pen devices (Becton Dickinson).

Trial design

Following a run-in period of 6 weeks during which control was optimized on the above regimen, patients were randomly allocated to treatment with Humulin S or insulin lispro before meals, with unchanged basal insulin. A crossover design was employed, such that each patient received 3 months' treatment with Humulin S and 3 months' treatment with insulin lispro, in random order. Insulin for injection was supplied in double-blind fashion as 1.5 ml cartridges for use in the pen devices. Patients and investigators were instructed to adjust insulin doses in the light of home blood glucose tests, with target blood glucose levels < 7.0 mmol/l fasting and < 10 mmol/l post-prandially.

Efficacy measures

Patients were asked to perform weekly 7-point glucose profiles before and 2-h after meals using a memory glucose meter and to record the results in their patient diary for at least 1 day a week throughout the study. Post-prandial glucose excursions were calculated by subtracting the pre-prandial glucose level from the 2-h post-prandial glucose value. Other events including experience of hypoglycaemia were recorded at the same time. A hypoglycaemic episode was defined in terms of symptoms experienced by the patient, signs noted by an observer, or a blood glucose recorded below 2.5 mmol/l. Severe hypoglycaemia was defined as coma and/or a requirement for intramuscular glucagon or intravenous glucose. HbA_{1c} was measured at a central reference laboratory (upper limit of non-diabetic range 6.3%). Patients and physicians were asked to adjust insulin doses during each phase of the study to achieve fasting blood glucose levels of 7 mmol/l or below and post-prandial blood glucose levels below 10 mmol/l.

End points

The main end-points for analysis were weekly self-monitored blood glucose readings, glycated haemoglobin levels, experience of hypoglycaemia and quality of life.

Quality-of-life measures

Two widely used quality-of-life measures including patient preference, treatment satisfaction and well-being developed for people with diabetes were used: the Diabetes Treatment Satisfaction Questionnaire, and the Well-Being Questionnaire

[7]. A further questionnaire known as the Global Impression Questionnaire was designed for use in this study and was given to the patients on completion of both limbs of therapy. This assessed the ability of the patients to identify which insulin had been used at each stage, and their degree of confidence in their choice. Finally, patients were asked to express a preference for one or the other insulin.

Statistical analyses

The study had power at the 80% level to detect a difference in HbA_{1c} of 0.27%, with an anticipated standard deviation of 0.95%. The Student's *t*-test was used for comparisons between treatments except where otherwise stated. For the efficacy and safety measurements an analysis for a crossover design was used to test for both the treatment and carryover effects. The crossover analyses for the numerical variables were performed using methods described by Koch [8] and Taulbee [9] for the numerical data and for the categorical variables using a crossover technique reported by Nagelkerke *et al*. [10]. No indication of a carryover effect was observed. An intention-to-treat analysis using the last observation for each patient within each of the crossover periods was employed. A sign test was used in analysis of the Global Impression Questionnaire.

Results

Of the 93 patients randomized to treatment, six dropped out in the course of the study. Two patients were withdrawn because of potential serious adverse events – hypoglycaemic coma and increasing emotional lability. Both these patients proved to be taking Humulin S at the time. One patient was withdrawn at the discretion of the local physician owing to difficulties in compliance with the requirements of the study. One patient withdrew because of personal problems, and two (both on insulin lispro) withdrew because of difficulties with glucose control.

Blood glucose

Glucose profiles are presented as means for each treatment period. Fasting blood glucose (mean ± 1SD) was 9.1 ± 3.5 mmol/l (lispro) vs. 8.4 ± 3.1 mmol/l (Humulin S), $P = 0.02$. Two hours after breakfast, blood glucose was 8.3 ± 2.9 mmol/l (lispro) vs. 9.3 ± 3.0 mmol/l (Humulin S), $P = 0.006$. Before lunch, blood glucose was 7.6 ± 2.3 mmol/l (lispro) vs. 7.2 ± 2.5 mmol/l (Humulin S), $P = 0.03$. Blood glucose 2-h after lunch was 7.4 ± 2.5 mmol/l (lispro) vs. 8.8 ± 2.8 mmol/l (Humulin S), $P < 0.001$. Before the evening meal, blood glucose was 9.1 ± 3.0 mmol/l (lispro) vs. 7.9 ± 2.8 mmol/l (Humulin S), $P = 0.002$. Two hours after supper, blood glucose was 9.1 ± 2.6 mmol/l (lispro) vs. 9.4 ± 2.6 (Humulin S), $P = 0.433$. At bedtime, blood glucose was 10.1 ± 2.8 mmol/l (lispro) vs. 9.4 ± 3.1 mmol/l (Humulin S), $P = 0.079$. Fasting and pre-prandial levels were significantly lower on Humulin S, whereas postprandial levels after breakfast and lunch were significantly lower on lispro (Fig. 1).

Post-prandial glucose excursions

The mean (± SD) morning post-prandial glucose excursion was – 0.9 ± 3.0 mmol/l (lispro) vs. + 0.9 ± 3.3 mmol/l (Humulin S), $P < 0.001$. The mean blood glucose excursion following lunch was – 0.1 ± 2.5 mmol/l (lispro) vs. 1.6 ± 2.4 mol/l (Humulin S), $P < 0.001$. After the evening meal, the blood glucose excursion was 0.2 ± 2.6 mmol/l (lispro) vs. 1.4 ± 2.6 mmol/l (Humulin S), $P = 0.002$. Mean post-prandial glucose excursions were thus 1.8, 1.7 and 1.2 mmol/l less in patients taking lispro than in those taking Humulin S after each of the three main meals.

Haemoglobin A_{1c}

Levels of HbA_{1c} were almost identical at the end of each treatment period, at 7.4 ± 1.1% on Humulin S and 7.5 ± 1.1% on insulin lispro, $P = 0.807$.

Hypoglycaemia

The overall hypoglycaemic rate per 30 days was 3.1 ± 4.4 episodes on Humulin S and 2.6 ± 3.0 on lispro ($P = 0.96$). When compared according to time of day, however, a reduced frequency of nocturnal hypoglycaemia was observed on lispro between midnight and 6 a.m. (0.7 ± 1.6 vs. 1.8 ± 3.1 episodes/month, $P < 0.001$), balanced by an increased frequency between 6 a.m. and mid-day (2.8 ± 3.7 vs. 2.2 ± 3.0 episodes/month, $P = 0.029$). The overall frequency of symptomatic and/or biochemical hypoglycaemia was similar on the two insulin regimens, and 88% of episodes were self-treated in each group. Asymptomatic hypoglycaemia was reported by nine patients whilst on Humulin S and 12 whilst on lispro ($P = 0.357$), and overall 67% of patients on Humulin S always experienced symptoms during hypoglycaemia as against 61% during treatment with lispro ($P = 0.077$). There were three episodes of severe hypoglycaemia (coma and/or a requirement for parenteral glucagon or glucose) in two of 92 patients completing the lispro arm, as against 10 episodes in six of 89 patients completing the Humulin S arm ($P = 0.135$, Chi-square analysis).

Insulin doses

The daily dose of short-acting insulin (expressed as $units.kg^{-1}.day^{-1}$) was similar for the two insulin preparations, with 0.45 ± 0.15 for lispro and 0.43 ± 0.14 for Humulin S ($P = 0.065$). The total dose of basal insulin was almost identical (0.26 ± 0.11 vs. 0.27 ± 0.11).

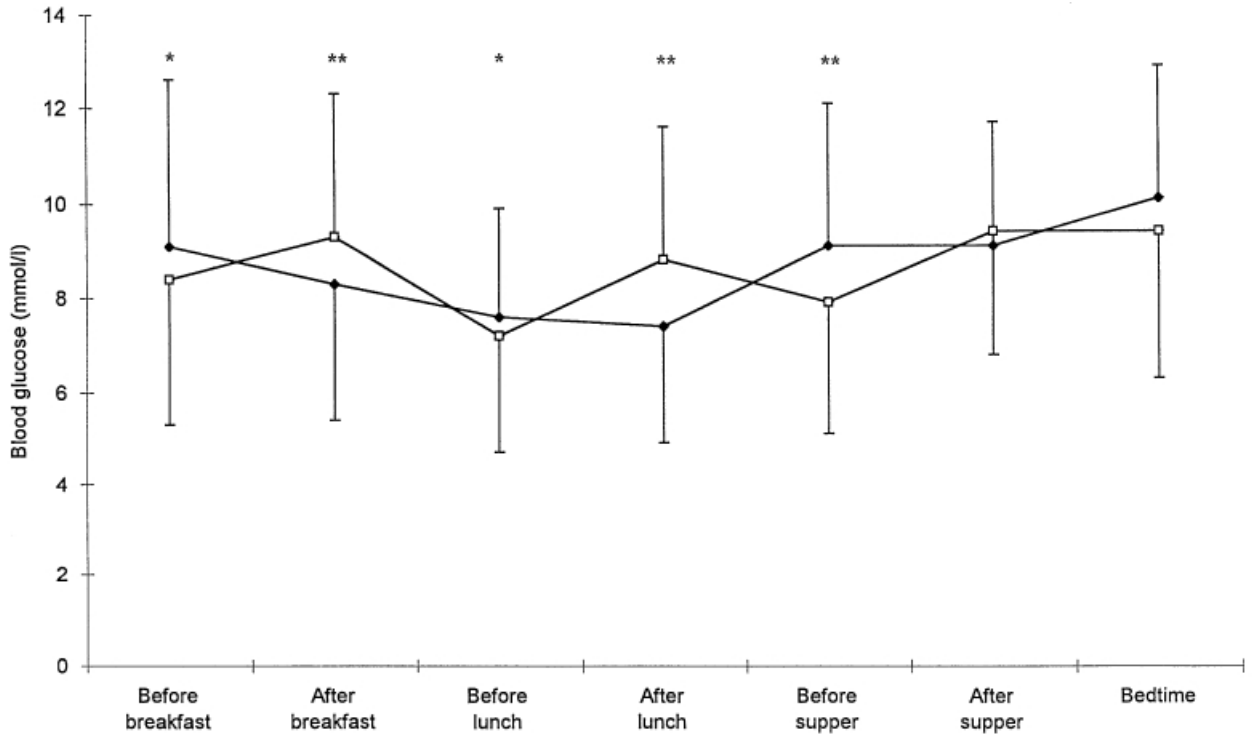

Figure 1 Self monitored blood glucose levels (± 1SD) on treatment with human soluble insulin (open squares) and insulin lispro (solid diamonds): $*P < 0.05$; $**P < 0.01$.

Diet and weight

The number of snacks taken during treatment with lispro was slightly lower than with Humulin S, but this reached statistical significance ($P = 0.038$) only for the period after supper. The mean weight after the period on lispro insulin was 77.0 kg vs. 77.2 kg after treatment with Humulin S ($P = 0.305$).

Quality of life

There were no differences between the two treatment arms for any of the scores obtained from the the Diabetes Treatment Satisfaction Questionnaire, or the Well-Being Questionnaire. The Global Impression Questionnaire was completed by 84 patients at the end of the study. Of these, 43 (51%) were able to identify the insulin correctly, nine (11%) were incorrect, and 32 (38%) were unable to tell the insulins apart. When asked to express a preference, 35 (42%) opted for insulin lispro, 24 (29%) opted for Humulin S, while the remainder had no clear preference.

Discussion

Lispro has been the first insulin analogue to reach the market. Its properties of rapid absorption and shorter duration of action have been shown to result in better control of post-prandial blood glucose levels, but most studies have shown no improvement in overall glycaemic control, as reflected in measurements of HbA_{1c} [11]. Evaluation has been based almost exclusively on open comparisons, and the only previous blinded, cross-over comparison was in patients on continuous subcutaneous insulin infusion therapy. This showed that substitution of lispro for soluble insulin in the infusion device produced better post-prandial glucose control, unchanged pre-prandial control, and a reduction in HbA_{1c} levels of 0.34% [3]. In the present study, in which basal insulin levels were not regulated by continuous infusion, post-prandial glucose levels were 1.2–1.8 mmol/l lower after meals in patients on insulin lispro, whereas fasting and pre-prandial glucose levels were increased and HbA_{1c} was unchanged. It can be noted that patient inclusion criteria biased the comparison in favour of insulin lispro, since post-prandial control is less good when soluble insulin is given shortly before meals [5]. The small but significant elevation in fasting blood glucose levels in patients taking lispro, despite similar overnight doses of NPH insulin, implies that soluble insulin taken before supper on the previous day exerted a carry-over effect some 12 h later. Equally, pre-prandial blood glucose levels were higher before lunch and supper on insulin lispro, indicating that its more rapid onset of action is matched by more rapid dissipation of effect.

Although the overall frequency of symptomatic or biochemical hypoglycaemia was similar in each treatment

arm, the pattern was different. Insulin lispro produced fewer episodes of nocturnal hypoglycaemia – almost certainly as a result of the loss of the carry-over effect of soluble insulin taken before the evening meal – but more episodes in the second half of the morning. It could be argued that comparison of the rates of nocturnal hypoglycaemia on the two regimens is misleading, since fasting glucose levels were higher on insulin lispro and overnight glucose control was therefore not equivalent. For practical purposes, however, the study showed that a useful reduction in the risk of nocturnal hypoglycaemia could be achieved at the cost of an increase in fasting glucose of 0.7 mmol/l. Open studies have shown a similar reduction in nocturnal hypoglycaemia [12], and a blinded comparison of overnight control in patients given soluble vs. lispro insulins before the evening meal showed that blood glucose levels were higher from midnight to 4 a.m. on lispro insulin [13]. There was no difference in the number of asymptomatic episodes of hypoglycaemia on each insulin in our study, although these were slightly more frequent in patients treated with lispro. Severe hypoglycaemia did not differ between the treatments, with 10 episodes in six patients on soluble insulin and three episodes in two patients on lispro. No single study with lispro has reported a reduction in the frequency of severe hypoglycaemia, but meta-analysis of eight major trials (including the present study) suggests that the frequency of severe hypoglycaemia is reduced by around 30% [14]. This may be related to differences in the overnight profile, since some 40% of episodes of severe hypoglycaemia occurred during the night in the Diabetes Control and Complications Trial [15].

Measures of treatment satisfaction and well-being did not differ between the treatments. The blinded design allowed an evaluation of the ability of patients to tell the insulins apart, showing that 51% were able to identify the two insulins correctly, 11% were incorrect and 38% uncertain. When asked to express a preference, 35 opted for insulin lispro, 24 for Humulin S and 25 were undecided. Patients in open trials had a much clearer preference for insulin lispro, mainly on the grounds of injection timing, which was not an issue in the patients selected for this study.

In conclusion, better post-prandial blood glucose levels were achieved with insulin lispro, but rapid dissipation of effect resulted in higher fasting and preprandial glucose levels, and HbA_{1c} levels were unchanged. Similar results have been reported by Home *et al*. [16] from a double-blind cross-over study of another rapid acting analogue, insulin aspart. This suggests that straight substitution of one formulation for another in multiple injection regimens is unlikely to benefit overall control, and occasional patients (two in this study) may find that their control is destabilized. Nocturnal hypoglycaemia was however, less frequent on insulin lispro, at the cost of a small increase in fasting glucose levels. Insulin lispro is a safe and effective alternative to soluble insulin, but it is still necessary to learn how best to take advantage of its altered pharmacokinetics. Daytime basal insulin supplementation is a logical strategy [4], and resulted in improved control in selected patients participating in an uncontrolled feasibility study [17]. Patient convenience may have been over-emphasized as an indication for use of rapidly absorbed insulin analogues, since this study suggests that patients could achieve equivalent overall control simply by injecting soluble insulin shortly before meals. Risk of hypoglycaemia – especially at night – may prove the more robust indication.

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