Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes
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Authors' objectives
To compare the frequency of severe hypoglycaemia during insulin lispro and human regular insulin in type 1 diabetic patients.

Searching
The Eli Lilly database was searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing the incidence of severe hypoglycaemia in type 1 diabetics during insulin lispro therapy and during soluble insulin therapy. The trials were included if they measured hypoglycaemia using a standard hypoglycaemia questionnaire, they enrolled at least 50 patients, and were of at least 2 months' duration. Both parallel and crossover trial designs were included. The duration of the studies was 1 year for the parallel group, and ranged from 4 to 8 months for the crossover studies. Double-blind and open trials were also included. Acute pharmacokinetic trials, case reports, and smaller studies with different objectives or the lack of a control group treated with human soluble insulin, were excluded. The included studies had a formal protocol and each used standardised case report forms. The case report forms, and methods for the collection and storage of the data, were similar across the trials.

Specific interventions included in the review
Insulin lispro and regular human insulin, including Humulin Regular (Eli Lilly) and Actrapid (Novo Nordisk). Basal insulin included isophane insulin NPH or ultralente (Eli Lilly). Rapid acting insulin (insulin lispro or human soluble insulin) was injected into the subcutaneous tissue of the abdomen from 45 to 15 minutes before each meal. The insulin doses and dietary instructions were adjusted, based on glucose self-monitoring and the metabolic needs of the patient. The glycaemic targets were fasting blood glucose values of less than 7.8 mmol/L without hypoglycaemia, and maintenance of 2-hour post-prandial glucose values of less than 10 mmol/L.

Participants included in the review
Type I diabetes. The participants included adults, newly diagnosed adults, and adolescents with type I diabetes. Patients with a history of recurrent severe hypoglycaemia were excluded.

Outcomes assessed in the review
The primary outcome was the number of hypoglycaemic episodes defined as coma or requiring glucagon or intravenous glucose. The haemoglobin (Hb)A1c level at the end point of the study was also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Validity was assessed by reviewing the designs and implementation of each study. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
No details were given of the methods used to extract the data. The following data were extracted: study design; type of treatment; study duration; date when study was completed; patients' characteristics; basal insulin; and sample size. The crossover data were split such that the crossover and parallel data could be combined and thus represent patient exposures. A chi-squared test was used to compare the number of patients experiencing at least one severe hypoglycaemic event between the two study groups for each of the individual studies.

Methods of synthesis

How were the studies combined?
The Mantel-Haenszel test, as modified by Cochran (see Other Publications of Related Interest no.1), was used to compare the incidence of severe hypoglycaemic events between the treatment groups. The overall relative risk (RR) and 95% confidence intervals (CIs) were calculated. The number of severe hypoglycaemic episodes per 100 patient years was computed by dividing the number of severe hypoglycaemic episodes by the years of exposure, and then multiplying by 100.

How were differences between studies investigated?
A cumulative meta-analysis process was conducted in chronological order on completion of each study, as described by Lau et al. (see Other Publications of Related Interest no.2). This was used to combine the studies to examine the effects of the various studies on the overall outcome. An additional analysis was undertaken, examining only the crossover trials using McNemer's test, to show that the results were consistent when the data were combined with the data from the parallel studies. The odds ratios and 95% CIs of severe hypoglycaemic episodes were presented graphically for the individual studies.

Results of the review

Eight multicentre RCTs (N=2,576) were included: 3 parallel group (N=434) and 5 crossover (N=2,142) studies. A meta-analysis was undertaken on these 8 trials using 4,666 patient exposures, where the crossover trials contributed the patient exposures.

None of the individual trials showed a statistically-significant difference between the effects of treatment with lispro and human regular insulin.

The overall proportion of patients who experienced at least one episode of severe hypoglycaemia was 3.1% with lispro insulin and 4.4% with soluble insulin (P=0.024). The RR of severe hypoglycaemia was 0.703 (95% CI: 0.518, 0.956).

Diurnal variation: the proportion of severe hypoglycaemic episodes occurring between midnight and 6 am was 31% with lispro 31% and 34% with regular insulin.

Crossover studies: the number of patients with at least one episode of severe hypoglycaemia was lower with lispro than with regular insulin (P=0.019).

The mean level of HbA1c at end point was 8.15 (standard deviation 1.50%) with lispro insulin and 8.14 (standard deviation 1.52%) with regular insulin (P=0.370).

Authors' conclusions

The frequency of severe hypoglycaemia can be reduced by taking insulin lispro rather than regular human insulin. A smaller risk of severe hypoglycaemia should help to improve the quality of life, compliance with insulin therapy and long-term prognosis of patients with type 1 diabetes.

CRD commentary

The aims and the inclusion criteria were clearly stated. The authors considered that the meta-analysis included 90% of the type 1 diabetic patients using insulin lispro published to date. They also acknowledged that by excluding patients with a history of recurrent hypoglycaemia, the risks reported in the review may under represent the general population of type 1 diabetics.
There were several potential sources of bias in the review: the literature search was limited to the database held by Eli Lilly; all the authors acknowledge a financial relationship with Eli Lilly; one study (reference 15 in the review) was entered in the meta-analysis as two separate trials, and the reasons for this were not stated; seven of the eight included studies had a common author, who was an employee of Eli Lilly; no mention was made of ensuring the exclusion of duplicated patients; no details were given of the methods used to select the primary studies or to extract the data, such as the number of reviewers involved and whether decisions were made independently. Validity was said to have been assessed by reviewing study design and implementation, but no further comment was made concerning the quality of the implementation of trials. More comprehensive details of the participants' characteristics would have been welcome.

The results from the review would be strengthened by clarification of the potential sources of bias highlighted.

**Implications of the review for practice and research**

Practice: The authors suggest that the use of lispro insulin in reducing the incidence of severe hypoglycaemia can reduce risks during intensive insulin therapy, restore the counter regulatory response to hypoglycaemia, improve hypoglycaemic awareness among type 1 diabetics, and reduce both somatic morbidity and psychological anxiety associated with hypoglycaemia.

Research: The authors did not state any implications for further research.

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