Clinical outcomes with insulin lispro compared with human regular insulin: a meta-analysis
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Authors' objectives
To compare insulin lispro and human regular insulin across a range of outcomes common in modern diabetes management, to establish a basis for subsequent economic evaluation.

Searching
Reports of all phase III trials conducted by Eli Lilly and Company were obtained from the New Drug Application package. MEDLINE via SilverPlatter was searched using the following keywords: 'Lys Pro' or 'lispro', 'lyspro', 'LY 275585', 'LY-275585', 'Humulin R', 'Humulin regular', 'Humulin (short acting or short-acting)', 'insulin regular', and 'Actrapid'. Dial-up searches of MEDLINE (from 1966 to 1996) and EMBASE (from 1974 to 1996) were conducted using similar search terms.

Study selection
Study designs of evaluations included in the review
Trials had to have more than 30 patients. Randomised controlled trials (RCTs), both parallel-group design and crossover studies, were assessed for inclusion. Only parallel-group design studies were included in the analysis. The trials had to be of at least 6 months' duration.

Specific interventions included in the review
Insulin lispro compared with human regular insulin. The insulin dose and duration of the trials were not reported.

Participants included in the review
Patients with type I (insulin-dependent) or type II (non-insulin dependent) diabetes who had previously been managed on insulin therapy.

Outcomes assessed in the review
The primary outcome was the number of patients achieving at least one therapeutic success. This was defined as one of the following three measures: decrease in postprandial blood glucose levels to less than or equal to 8 mmol/L; a 2-hour postprandial blood glucose level within 20% of the pre-meal level; or at least a 50% decrease from baseline in 2-hour postprandial glucose excursion. Trials that focused on the measurement of short-term pharmacokinetic and glucose responses were excluded.

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
The quality of the studies was assessed according to published guidelines for the pharmaceutical industry (see Other Publications of Related Interest no. 1), which apparently cover the main areas of concern in terms of quality. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were combined quantitatively using both fixed-effect and random-effects methods for dichotomous variables. The random-effects odds ratios (ORs) and risk differences were derived using the method of DerSimonian and Laird (see Other Publications of Related Interest no.2). For the fixed-effect OR, the method of Yusuf et al. (see Other Publications of Related Interest no.3) was used, and also the weighted least-squares pooled estimate, with weighting by study precision. For continuous variables, a weighted least-squares estimation with weighting by study precision was used to obtain a pooled fixed-effect estimate of the mean difference in response.

A meta-analysis was conducted using only six of the eight trials. The other two were excluded because the patients were new to insulin.

How were differences between studies investigated?
The chi-squared statistic was used to test for lack of homogeneity. Studies were analysed together and separately for type I and type II diabetics who were new to therapy. The analysis was performed both including and excluding the second phase of the two crossover studies.

Results of the review
Eight phase III open-label trials with a total of 2,361 participants were identified, although only six were included in the main analysis. Three of these trials enrolled patients with type I diabetes (n=1,344), whilst the other 3 enrolled patients with type II diabetes (n=1,017). The other two trials were of a crossover design, one in type I diabetics and one in type II diabetics.

Pooled studies (patients with type I and type II diabetes; 6 studies).
Using a fixed-effect model, one outcome (a decrease in postprandial blood glucose levels to less than or equal to 8 mmol/L) showed a statistically-significant difference in favour of insulin lispro (p<0.00001). Using a random-effects model, a significantly higher proportion of patients receiving lispro achieved at least one therapeutic success (59.4 versus 49.3%; OR 1.68, 95% confidence interval, CI: 1.34, 2.12). No significant differences were found for the other two variables (a 2-hour postprandial blood glucose level within 20% of the pre-meal level or at least a 50% decrease from baseline in 2-hour postprandial glucose excursion).

Continuous variables (1- and 2-hour postprandial blood glucose, and 1- and 2-hour glucose excursion) showed statistically-significant differences in favour of insulin lispro (p<0.02, p<0.001, p<0.001 and p<0.001, respectively). The weighted mean differences for measures of long-term glycaemic control, fasting blood glucose, and hypoglycaemic rate per 30 days showed no distinctions between insulins.

Studies in patients with type I diabetes (3 studies).
Overall, a significantly higher proportion of patients receiving lispro achieved at least one therapeutic success (OR 1.35, 95% CI: 1.32, 1.83), although only one third of the individual measurements showed a statistically-significant benefit. Significantly more patients had a decrease in the postprandial blood glucose to less than or equal to 8 mmol/L with insulin lispro (OR 1.52, 95% CI: 1.27, 1.83, p<0.00001).

Studies in patients with type II diabetes (3 studies).
Overall, a significantly higher proportion of patients receiving lispro achieved at least one therapeutic success (OR 1.45, 95% CI: 1.20, 1.75), although only one third of the individual measurements showed a statistically-significant benefit (OR 1.79, 95% CI: 1.39, 2.32). Significantly more patients had a decrease in the postprandial blood glucose level to less than or equal to 8 mmol/L with insulin lispro (p<0.00001). Statistically-significant differences in the weighted mean differences were seen in the 1- and 2-hour glucose excursion (p<0.05 and p<0.02, respectively) but not in the 1- and 2-hour postprandial glucose levels.

The results obtained when using the random-effects model with all 8 studies reached similar conclusions to the fixed-effect model.
Authors' conclusions
The meta-analysis supported the existence of significant differences between insulin lispro and human regular insulin, in terms of important postprandial outcome measures in diabetes. The appropriate use of insulin lispro is likely to assist in the normalisation of blood glucose excursions, particularly in the postprandial period. In addition, there is a practical difference in injection timing relative to meals: human regular insulin should be administered 30 to 45 minutes before eating, whereas insulin lispro can be administered 15 minutes or less before eating. The differences should be the subject of an economic evaluation to help determine the place of insulin lispro in diabetes management.

CRD commentary
This was a well-written review with a description of the studies and an appropriate statistical analysis. The authors identified both published and unpublished trials. All of the published trials were excluded, however, because they focused on short-term pharmacokinetic and glucose response. Only unpublished trials undertaken by one pharmaceutical company (Eli Lilly) were, therefore, included in the analysis. Unfortunately the review failed to outline the process for assessing the quality and relevance of the primary studies. In addition, there was no discussion of the method for abstracting the data from the studies. The authors made suggestions relating to the timing of the administration in their conclusions, but these were not reported elsewhere in the review. The review was funded partly by Eli Lilly, the pharmaceutical company that makes both insulins, and the principal author was employed by a pharmaceutical company (M-TAG Pty Limited).

Implications of the review for practice and research
The authors suggest that further research is necessary to assess the benefit to the patients of the injection timing difference. Other areas to be considered include the lower risk of nocturnal hypoglycaemia and the possibility of achieving improved glycaemic control without increased hypoglycaemia. Further long-term research is also required to assess whether such tight control results in benefits in terms of a reduction in the likelihood or extent of end-organ damage.

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Other publications of related interest

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**Record Status**
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