Insulin aspart: an evidence-based medicine review
Haycox A

CRD summary
Evidence on the efficacy, safety and ease of administration of the rapid-acting insulin analogue insulin aspart in comparison with human insulin, in diabetes mellitus, was reviewed. The review concluded that there is evidence to support the efficacy, tolerability and ease of administration of insulin aspart. However, it is difficult to assess the reliability of this conclusion.

Authors' objectives
To review and evaluate the published evidence on the efficacy, safety and ease of administration of the rapid-acting insulin analogue insulin aspart in comparison with human insulin (HI), in diabetes mellitus.

Searching
The Cochrane Library, BIOSIS Previews, EMBASE-DP and MEDLINE were searched; the search period was not reported. The search was restricted to publications in the English language.

Study selection

Explicit inclusion criteria were not reported. Product-specific reviews without comparisons and general reviews of insulin analogues were excluded from the review.

Specific interventions included in the review
Studies that investigated the rapid-acting insulin analogue insulin aspart were eligible for inclusion. These could also include premixed formulations containing various ratios of soluble rapid-acting insulin aspart and protamine-crystallised intermediate-acting insulin aspart. The included studies stated that insulin aspart or biphasic insulin aspart, insulin aspart plus insulin detemir was used. The studies varied in their combination of soluble and protamine-bound insulin aspart use, the mode of presentation (including subcutaneous), the dose (up to three times daily), and administration before or after meals.

Participants included in the review
The review was restricted to studies with human participants; other than that no inclusion criteria were defined. The included studies enrolled patients with type 1 and/or type 2 diabetes mellitus, healthy volunteers, and/or those with diabetic ketoacidosis.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported on the assessment of post-prandial glycaemia, glycosylated haemoglobin levels and the corresponding effect on major hypoglycaemia, the incidence of major and nocturnal hypoglycaemia, the assessment of convenience and flexibility of administration before and after a meal, and the safety and efficacy in pump use.

How were decisions on the relevance of primary studies made?
Two independent reviewers determined the relevance of publications.

Assessment of study quality
The author used the Oxford grading system, but other than that did not assess validity. The author did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
The author did not state explicitly how the data were extracted for the review, or how many reviewers performed the data extraction.

One of the tables contained minimal data from the original studies, including the number of participants, the type of diabetes, how long the treatment lasted and what the study message was.

Methods of synthesis
How were the studies combined?
The studies were summarised in a narrative synthesis that presented evidence separately for adults, children/adolescents and insulin aspart in continuous subcutaneous insulin infusion. The evidence for adults was further grouped according to outcome: post-prandial glycaemic control and risk of hypoglycaemia, nocturnal hypoglycaemia, long-term efficacy and safety, and administration flexibility and convenience.

How were differences between studies investigated?
Individual study results were reported in the content structure.

Results of the review
Twenty-nine studies (n=6,592) met the inclusion criteria: 26 randomised controlled trials, 2 controlled trials and one crossover trial.

Twenty-seven studies showed better glycaemic control with insulin aspart than with HI, without an increased risk of hypoglycaemia. Three studies reported a lower incidence of major nocturnal hypoglycaemia. Insulin aspart was at least as effective as HI in 3 long-term trials, and was superior in 3 studies. Ten trials reported that insulin aspart showed improved convenience and flexibility in administration in comparison with HI.

Authors' conclusions
There is a good body of evidence supporting the efficacy, tolerability and ease of administration of insulin aspart in patients with type 1 and type 2 diabetes.

CRD commentary
The review reported only a few explicit inclusion criteria and appeared to be relatively inclusive with regard to the interventions, participants and study designs. The search covered several electronic databases, but the search period was not reported. Non-English language studies were excluded from the review and no explicit attempts to search for unpublished studies were reported; these issues leave the review open to language and publication bias. The data extraction was not described, and it was unclear whether any steps were undertaken to reduce errors and bias. The table contained only the study message of the results, which did not seem to have been extracted in a highly standardised way, and this made it difficult to follow the author's conclusions. The narrative synthesis was detailed, but it was unclear for all aspects exactly how many studies had reported on a particular outcome; only the number of positive results was explicitly stated.

The author stated that there appears to be a substantial body of evidence to support the efficacy, tolerability and ease of administration of insulin aspart but, given the limitations in the review methodology and/or reporting, it was unclear whether this is a complete and up-to-date summary of the existing literature.

Implications of the review for practice and research
Practice: The author stated that insulin aspart offers a useful addition to the therapeutic armamentarium in diabetes.

Research: The author stated that there is a need for more long-term follow-up studies to assess the benefit and safety of insulin aspart in more detail, and new potential dimensions to treatment with insulin (e.g. combination therapy with oral
antidiabetic agents) need to be considered in the future.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.