Biphasic insulin aspart 30: literature review of adverse events associated with treatment


CRD summary
This review assessed the safety of biphasic insulin aspart 30 (BIAsp 30) for patients with diabetes. The authors concluded that the safety profile is comparable to that of biphasic human insulin 30 (BHI 30) and neutral protamine Hagedorn (NPH) insulin, and that the risk of major and nocturnal hypoglycaemia is lower. Poor reporting and problems with review methodology mean that the reliability of these conclusions should be regarded with great caution.

Authors' objectives
To assess the safety of biphasic insulin aspart 30 (BIAsp 30), compared with alternative insulin products, in patients with type 1 or type 2 diabetes.

Searching
MEDLINE was searched to February 2005; the search terms were reported. The references of retrieved studies were checked. Proceedings of major diabetes conferences were reviewed, as were the authors’ reference files. Only studies published in peer-reviewed journals were eligible for inclusion.

Study selection
Studies that compared BIAsp 30 to comparator insulins in patients with type 1 or type 2 diabetes and reported safety results were eligible for inclusion. The majority of patients in the included studies had type 2 diabetes. The included studies examined BIAsp 30 as a monotherapy or in conjunction with an oral antidiabetic medication, and used a range of dosing schedules. The comparators were biphasic human insulin 30 (BHI 30), neutral protamine Hagedorn (NPH) insulin and Mix 25. Study duration ranged from a single dose to 2 years. The safety outcomes reported included hypoglycaemic events, major hypoglycaemia, nocturnal hypoglycaemia, minor hypoglycaemia, weight gain and other adverse events. No inclusion criteria for the study design were stated, although the criteria for intervention required the use of a controlled design. However, in addition to randomised controlled trials (RCTs), one uncontrolled trial was included. The mean age of the patients in the included studies ranged from 36 to 70 years (mean 58). The mean duration of type 2 diabetes was 11.8 years (range of means: 9 to 17 years) and the mean baseline glycated haemoglobin A\textsubscript{1c} was 8.4% (range of means: 7.2 to 10.4).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative, grouped by reported outcomes.

Results of the review
Seventeen studies (at least 2,700 participants) were included in the review, of which sixteen were RCTs.

Hypoglycaemia (11 studies): the incidence of hypoglycaemia was similar for patients taking BIAsp 30 and other types of insulin. Hypoglycaemia was reported by between 43% and 57% of patients in the BIAsp 30 groups compared with a range of 32 to 57% for patients given BHI 30 and 28% of those taking NPH insulin.

Major hypoglycaemia (9 studies): major hypoglycaemic episodes were less common in patients receiving BIAsp 30, being reported by between 2% and 8% of patients given BIAsp 30 compared with a range of 2 to 14% for patients in...
the BHI 30 groups.

Nocturnal hypoglycaemia (3 studies): one study found no significant difference between BIAsp 30 and BHI 30, one reported a significant reduction in nocturnal hypoglycaemia (p=0.02), and one reported no statistical results.

Minor hypoglycaemia (3 studies): the majority of the studies found no difference between the groups in the incidence of minor hypoglycaemia.

Weight gain (7 studies): all of the studies that assessed weight gain reported that patients gained weight while taking BIAsp 30. Where comparative statistics were reported, one trial reported a trend to a lower increase in the mean weight gain in the BIAsp 30 group than in the BHI 30 group (p=0.07), while another found patients given BIAsp 30 or BHI 30 gained significantly more weight than patients given NPH insulin (p=0.025).

Other adverse events (7 studies): adverse events were reported in between 36% and 90% of patients treated with BIAsp 30 compared with 38 to 88% of patients receiving BHI 30, 38% of patients taking NPH insulin, and 51% of patients taking Mix 25. Few patients in any study discontinued treatment as a result of adverse events associated with either BIAsp 30 or comparator insulins. Where cardiovascular events occurred, the rates were comparable in the BIAsp 30 and BHI 30 groups. No major biochemical changes were observed.

Authors' conclusions
BIAsp 30 has a safety profile comparable to that of BHI 30 and NPH insulin, and is associated with a lower risk of major and nocturnal hypoglycaemic events.

CRD commentary
The review question and inclusion criteria, with the exception of study design, were clear. While the inclusion criteria for the interventions required a comparative design, nonetheless one uncontrolled study was included in the review. The authors only searched one database and included only peer-reviewed published studies in the review. This makes it more likely that some relevant studies were not included in the review and the review may be subject to language and publication bias. The authors did not report using methods designed to reduce bias and error in the review process, nor did they report assessing the validity of the included studies. The decision to adopt a narrative synthesis was justifiable. However, the synthesis presented makes some statements for which statistical support is lacking in the reporting of the review. As a result of the methodological and reporting limitations described, the authors’ conclusions should probably be interpreted with great caution.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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