Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomised placebo-controlled trials

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Authors' objectives
To assess the efficacy of insulin and sulfonylurea combination therapy in type II diabetes mellitus.

Searching
MEDLINE was searched from January 1980 to March 1992 using the keywords 'sulfonylurea', 'insulin' and 'combination therapy in type II diabetes', and bibliographies of identified papers were examined. Citations reported in non-English language journals, without English translation, were excluded.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials of the same treatment, i.e. the same sulfonylurea agent throughout the study, and well-defined outcome measures (body weight, fasting serum or plasma glucose, fasting serum C peptide concentration, daily insulin dose).

Specific interventions included in the review
Insulin and sulfonylurea combination therapy (glibenclamide and tolazamide).

Participants included in the review
Patients with type II diabetes were included.

Outcomes assessed in the review
Body weight; values for fasting serum or plasma glucose, glycohaemoglobin, and fasting C peptide; daily insulin dosage; and lipid concentrations.

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
Specific qualitative subcriteria were used to assess the quality of the studies: clear inclusion or exclusion criteria, baseline similarity of patients, uniform manoeuvres, detailed description of ancillary treatments, and similar outcome measures. Two reviewers blinded to the source of the articles, assessed the methodology of the studies. Each study was awarded a score for each of the qualitative subcriteria. An overall quality score was computed according to the degree of satisfaction of these criteria with a maximum score of 6; only studies scoring 2 or greater were included. The two reviewers had to make a unanimous decision on whether to accept or reject articles.

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 data were pooled and analysed using Student's t test and Winer's combined test.
How were differences between studies investigated?
An omnibus test was used to determine the homogeneity between the studies' test for each outcome measure, to assess if the results should be pooled before quantitative analysis (see Other Publications of Related Interest no. 1). Subgroups of concurrent and crossover studies were assessed due to the distinct types of data collected with each method.

Results of the review
Sixteen studies with a total of 351 patients (Table 4 includes only 345 patients). Forty-four studies were identified by the search, of which 16 were found to be homogeneous using the omnibus test, and 28 were excluded from the analysis. One study was excluded due to its lack of homogeneity with the pooled glucose data, 13 because they were not placebo-controlled; 3 because metformin was used; 5 because only abstracts could be obtained; 4 for miscellaneous reasons such as use of proinsulin rather than insulin, no English language translation, no evaluation, and a comparison with the combination therapy and therapy with the oral therapy alone; and 2 because data reported were insufficient, or median rather than mean values were reported.

Analysis of the 16 included studies found improved metabolic control (up to at least 16 weeks) with the combination therapy, as reflected by a significant lowering of fasting serum glucose (difference in treatment group -2.5 plus or minus 0.4, compared with -0.6 plus or minus 0.7 in control, p<0.01) and glycohaemaglobin concentrations (difference in treatment group -1.1 plus or minus 0.2, compared with -0.25 plus or minus 0.25 in control, p<0.025). Moreover, improved metabolic control was achieved with a significantly-smaller daily insulin dose (difference in treatment group -12 plus or minus 6, compared with -1 plus or minus 2.5 in control, p<0.01) and without a significant reduction in body weight. Finally, the combination therapy enhanced the endogenous insulin secretion, as expressed by an increase in fasting serum C peptide concentration (difference in treatment group 0.15 plus or minus 0.06, compared with -0.01 plus or minus 0.80 in control, p<0.05). The effect on lipids could not be clearly assessed because data were either non-uniform or insufficient in the selected studies.

Euglycaemic concentrations were not achieved in all studies because the goal was to observe the change in metabolic concentration, rather than to achieve euglycaemia or normalisation of haemoglobin A1c levels. Significant improvements in metabolic control together with a decrease in insulin levels were observed in the concurrent trials, but not the crossover trials. The authors suggest that the lack of uniformity may be explained by the differences in the study designs, especially in terms of daily insulin dosage. Most of the studies lacked distinct guidelines for adjusting insulin regimens.

Cost information
The total cost for combination therapy is US$60 to $85, compared with US$20 for 2 daily injections of a total dose of 100 U of an intermediate-acting insulin. However, the costs are distinctly higher in patients using insulin monotherapy because of the requirement of multiple injections, a markedly-higher daily insulin dose, and supplies such as syringes. Patients requiring more injections and higher dosages may require more frequent out-patient visits (US$35 to $50 each), as well as emergency department visits (US$250 to $1000). Increased daily insulin dosages may result in circulating hyperinsulinaemia, probably a major risk factor for promoting hypertension, and atherosclerosis.

Authors' conclusions
Combination therapy with insulin and sulfonylurea may be more appropriate and a suitable alternative to insulin monotherapy in patients with non-insulin dependent diabetes.

CRD commentary
This is a well-conducted meta-analysis with clear inclusion and exclusion criteria. However, limiting the included studies to English language papers may introduce an element of bias.

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