

Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus

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Authors' objectives

To assess the efficacy and safety of glimepiride with and without insulin in the treatment of type 2 diabetes mellitus.

Searching

A MEDLINE database search (January 1985 to April 1997) was performed for English language studies, including reviews and abstracts. The author also contacted a manufacturer of glimepiride (Hoechst Marion Roussel) for unpublished study data.

Study selection

Study designs of evaluations included in the review

Large (but actual size unspecified) double-blind, randomised controlled trials (RCTs) were included in the review. Included trials had to be published as an individual study, as part of a review, or pending publication. Relatively small, nonrandomised, noncomparative, open-label trials were excluded.

Specific interventions included in the review

Glimepiride (1 to 16 mg total daily dose, usually given once daily for a period of 8 to 52 weeks), other sulfonylureas (glipizide and glyburide), insulin and placebo.

Participants included in the review

Male and female patients between the ages of 30 and 80 years with type 2 diabetes mellitus uncontrolled by diet and exercise which was confirmed during a single-blind, placebo-controlled washout period.

Outcomes assessed in the review

Fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG) and HbA1C.

How were decisions on the relevance of primary studies made?

The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality

The author does not state that they assessed quality.

Data extraction

The author do not state who, or how many of the reviewers, performed the data extraction. Data were extracted for study reference details, the number of patients enrolled, the study design, the drug regimen, and the results of the study.

Methods of synthesis

How were the studies combined?

The review listed the individual study results and summarised the outcome in a narrative review, however, two studies were statistically combined in the dose-finding studies.

How were differences between studies investigated?

There were no formal tests for homogeneity.

Results of the review

Eight RCTs were included in the review with 3,643 participants. Four RCTs were dose-finding studies, 3 RCTs compared glimepiride with other sulfonylureas, and 1 RCT added glimepiride or placebo to insulin therapy.

Glimepiride was as effective as second generation sulfonylureas.

In the dose-finding studies, two studies were combined statistically and reported that median changes from baseline to end point in FPG after 1, 4, and 8 mg of glimepiride exceeded those after placebo ($p < 0.001$) by 43, 70 and 74 mg/dL respectively. In the third study FPG decreased by 28% from a baseline of 212 mg/dL in the glimepiride group compared with 6% from a baseline of 205 mg/dL in the placebo group ($p < 0.001$). In the fourth study, glimepiride reduced plasma glucose throughout the 24-hour observation period regardless whether it was given in one or two divided doses.

In the first two studies, median HbA1C values at baseline for the placebo, 1-, 4- and 8-mg dose groups were 7.8%, 7.8%, 7.7%, and 7.8% respectively, and at end point were 9.5%, 8.0%, 7.7% and 7.5% respectively. The data from combining these two studies shows a dose response up to 4 mg, and the 4-mg dose appears to be nearly maximally effective. In the third study, the median baseline HbA1C in the glimepiride and placebo groups were 9.1% and 8.9% respectively, and at end point were 6.7% in the glimepiride group and 7.9% in the placebo group. In the active-controlled studies, in the two studies comparing glimepiride with glyburide, there were no statistically significant differences between the glimepiride and glyburide groups as measured by FPG, PPG or HbA1C. In the third study comparing glimepiride and glipizide, mean FPG concentrations were lower in the glimepiride group ($p < 0.05$) than in the glipizide group at every point during the titration phase except at week 12 ($p = 0.053$). Otherwise there were no statistically significant differences found between the two groups.

In the one study of adjunct therapy with insulin, glimepiride significantly lowered the requirement for exogenous insulin in patients with type 2 diabetes whose sulfonylurea therapy had failed. The mean daily insulin dose was significantly lower in the group that also received glimepiride than in the insulin-alone group (49 versus 78 units, $p < 0.001$).

Two thirds of patients achieved tight control (i.e. HbA1C less than or equal to 7.2%).

The most common adverse events were dizziness and headache, but no single adverse event occurred in more than 2% of patients.

In the U.S. the incidence of deaths, discontinuations due to adverse events, and other serious adverse events in the glimepiride group (10.3%) was approximately half that in the placebo group (21.4%) which was primarily attributable to the 17.0% incidence of hyperglycemia-related signs and symptoms in the placebo group. In Europe the slightly higher incidence of deaths, discontinuations due to adverse events, and other serious adverse events in the glimepiride group was attributable to the longer duration of treatment (i.e. less than or equal to 2.8 years).

Cost information

The daily cost of glimepiride 4 mg (\$1.05) is comparable to that of the second-generation sulfonylurea, glipizide 10 mg (\$1.03), and generic glyburide 5 mg (\$0.93). These costs are slightly less than branded glyburide 5 mg (\$1.46), approximately one-half that of metformin 850 mg twice daily (\$1.98) and acarbose 100 mg three times daily (\$1.77), and one-fifth that of troglitazone 400 mg daily (\$5.15).

Authors' conclusions

Glimepiride appears to be a useful option for patients with type 2 diabetes not controlled by diet and exercise and who want to achieve tight glucose control. Glimepiride can be used alone, in combination with antihyperglycemic agents, or in patients with secondary sulfonylurea failure, as an adjunct to insulin therapy.

CRD commentary

The author has clearly stated their research question and their inclusion and exclusion criteria. The literature search is limited (the search terms were not stated) but they have sought unpublished data from manufacturers of glimepiride. The author may have missed studies published outside the United States by focusing the search on only the MEDLINE database and by limiting their search to English language publications.

The data extraction is reported in tables and text and the narrative review was appropriate because of the small number of trials in each grouping. The quality of the included studies was not assessed and the author has not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction. The author has not tested for homogeneity.

Although the conclusions appear to follow from the results, because of the methodological limitations of the review, the conclusions should be viewed with caution.

Implications of the review for practice and research

Practice: The author states that the three available dosages make glimepiride easy to titrate and once-daily dosing may enhance patient compliance.

Research: The author states that further study and wider exposure should demonstrate whether glimepiride offers significant benefits compared with other sulfonylureas. An important area for further research is the pharmaco-economic profile of glimepiride compared with other sulfonylureas.

Bibliographic details

Campbell R K. Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. *Annals of Pharmacotherapy* 1998; 32(10): 1044-1052

PubMedID

[9793597](#)

Indexing Status

Subject indexing assigned by NLM

MeSH

Clinical Trials as Topic; Diabetes Mellitus, Type 2 /drug therapy; Humans; Hypoglycemic Agents /adverse effects /pharmacokinetics /therapeutic use; Sulfonylurea Compounds /adverse effects /pharmacokinetics /therapeutic use; Treatment Outcome

AccessionNumber

11998001850

Database entry date

31/05/2000

Record Status

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