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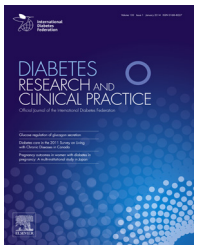

Systematic review and meta-analysis of the efficacy and hypoglycemic safety of gliclazide versus other insulinotropic agents☆

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ABSTRACT

Aims: Sulfonylureas are well positioned in treating type 2 diabetes, after lifestyle modification and metformin. The sulfonylurea gliclazide was given preference over glibenclamide in older people with type 2 diabetes in the World Health Organization model list of essential medicines. Consequently, a systematic review and meta-analysis of randomized controlled trials of the efficacy and safety of gliclazide versus other oral insulinotropic agents (sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glinides) was performed.

Methods: Two reviewers searched MEDLINE for studies of ≥12 weeks duration in adults with type 2 diabetes. The key search word was "gliclazide", filtered with "randomized controlled trial", "human" and "19+ years". Differences were explored in mean change in glycated hemoglobin (HbA_{1c}) from baseline (primary outcome) and risk of hypoglycemia (secondary outcome) between gliclazide and other oral insulinotropic agents; and other sulfonylureas.

Results: Nine out of 181 references reported primary outcomes, of which 7 reported secondary outcomes. Gliclazide lowered HbA_{1c} more than other oral insulinotropic agents, with a weighted mean difference of −0.11% (95%, CI −0.19 to −0.03%, $P = 0.008$, $I^2 = 60\%$), though not more than other sulfonylureas (−0.12%; 95%, CI −0.25 to 0.01%, $P = 0.07$, $I^2 = 77\%$). Risk of hypoglycemia with gliclazide was not different to other insulinotropic agents (RR 0.85; 95%, CI 0.66 to 1.09, $P = 0.20$, $I^2 = 61\%$) but significantly lower than other sulfonylureas (RR 0.47; 95%, CI 0.27 to 0.79, $P = 0.004$, $I^2 = 0\%$).

Conclusion: Compared with other oral insulinotropic agents, gliclazide significantly reduced HbA_{1c} with no difference regarding hypoglycemia risk. Compared with other sulfonylureas, HbA_{1c} reduction with gliclazide was not significantly different, but hypoglycemia risk was significantly lower.

1. Introduction

Sulfonylureas are a well-established and integral part of type 2 diabetes management because of their proven efficacy, good long-term safety, and low cost [1,2]. Several current diabetes guidelines advocate the use of sulfonylureas early in the treatment of type 2 diabetes, after lifestyle modification and treatment with the biguanide metformin [3–8]. Metformin has a range of benefits (blood glucose–lowering efficacy, little risk

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of hypoglycemia, weight neutrality, and cardiovascular safety) that make it the first-line oral antidiabetic therapy of choice, but on its own is unlikely to control severe hyperglycemia or hyperglycemia over the long term [4,9]. Second-line options remain essential, as therapeutic failure of metformin monotherapy often occurs within 2 years of treatment initiation [10]. Furthermore, some patients are unable to tolerate metformin due to gastrointestinal side effects [2], and its use is contraindicated in renal impairment.

The sulfonylurea gliclazide recently replaced glibenclamide in the diabetes section of the World Health Organization (WHO) list of essential medicines for people aged over 60 years. This list also includes metformin, glucagon, and two insulins (soluble and intermediate-acting) [11,12]. The decision of the WHO was based on evidence demonstrating that gliclazide is as effective as glibenclamide and glimepiride and more effective than glipizide in reducing glycated hemoglobin (HbA_{1c}), while causing less hypoglycemia than glibenclamide or glimepiride. The blood glucose–lowering efficacy of gliclazide was previously demonstrated in the first head-to-head trial of sulfonylureas (GUIDE) and its safety was demonstrated in the randomized controlled trial Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) [13,14]. One of the main adverse effects associated with sulfonylureas in general is hypoglycemia, although severe hypoglycemia is rare with gliclazide compared with other oral antidiabetic agents [14,15].

With these facts in mind, a systematic review and meta-analysis of randomized controlled trials of the efficacy and safety of gliclazide versus other oral insulinotropic agents (other sulfonylureas, dipeptidyl peptidase 4 [DPP-4] inhibitors, and glinides) and also versus other sulfonylureas were performed. Efficacy and safety were compared by assessing changes in HbA_{1c} from baseline and risk of hypoglycemia.

2. Methods

MEDLINE was searched electronically by two reviewers from the clinical research organization ClinSearch (Bagneux, France) to identify randomized controlled trials in adults (>18 years) with type 2 diabetes that compared gliclazide with other glucose-lowering drugs (in monotherapy or in combination with metformin or insulin). Appropriate references were identified using the key search word ''gliclazide'' and 3 filters: ''randomized controlled trial'', ''human'', and ''adult: 19+ years''. Treatment duration was ≥12 weeks. Efficacy, defined as change in HbA_{1c} from baseline, was reported in most trials and was chosen as the principle criterion for comparison. The primary efficacy outcome was between-arm difference in mean change in HbA_{1c} from baseline; and the secondary safety outcome was risk of hypoglycemia. Duplicate or irrelevant references were discarded, and the remaining references evaluated in greater detail. References with no reported primary outcome, a comparator that was not an insulinotropic agent, or a non-oral antidiabetic agent comparator were removed after this subsequent evaluation.

Following independent data extraction by the reviewers, items included were study duration, number of patients randomized, mean HbA_{1c} level, comparator drug, add-on antidiabetic therapy, gender, age, duration of diabetes, and outcomes. If standard deviation was not reported, this was calculated where possible from the standard error or 95% confidence intervals. Where data were missing, corresponding data were extracted from other sources (articles or meta-analyses) [16]. Studies that did not report hypoglycemic events were excluded from the safety meta-analysis. Further efficacy and safety analyses compared gliclazide with other sulfonylureas (glibenclamide/glyburide, glipizide and glimepiride). Study heterogeneity was assessed using a χ^2 test. The I^2 statistic was used to estimate the percentage of total variation between studies due to heterogeneity rather than chance, with $I^2 = 0\%$ indicating no heterogeneity and $I^2 = 100\%$ indicating all variation due to heterogeneity. Presentation of results was determined by the I^2 value (fixed effects model if $I^2 < 50\%$ or random effects model if $I^2 \geq 50\%$ [to reflect possible clinical diversity and methodological variation among the studies]). All P values were two sided. Review Manager version 5.1.2. (Cochrane Collaboration, Oxford, UK) and SAS version 9.2. (SAS Institute Inc., Cary, NC, USA) were used for the statistical analysis.

3. Results

From the 181 references identified in MEDLINE, 131 were discarded because of duplication or irrelevance (no reference to hypoglycemia or HbA_{1c}). Of the 50 remaining references, 28 did not report the difference in mean change in HbA_{1c} from baseline (primary outcome), 11 had a comparator that was not an insulinotropic agent, and 2 had a comparator that was not an oral antidiabetic agent. Data for the analysis of the primary and secondary outcomes were available in 9 and 7 studies, respectively. Study identification and selection are summarized in Fig. 1, while Table 1 summarizes characteristics of the 9 primary outcome studies [14,17–24].

The 9 studies, which included 3461 patients and had a median duration of 24 weeks, compared differences in mean change in HbA_{1c} from baseline in type 2 diabetes patients treated with gliclazide versus other oral insulinotropic agents. Analysis indicated that gliclazide lowered HbA_{1c} significantly more than other oral insulinotropic agents, alone or in combination, with a weighted mean difference of −0.11% (95% CI −0.19 to −0.03%, $P = 0.008$, $I^2 = 60\%$) (Fig. 2). Hypoglycemic events were not reported in two primary outcome studies [17,20], which were thus excluded from the meta-analysis of safety (Fig. 3). The risk of hypoglycemia with gliclazide was not significantly different to that of other insulinotropic agents (RR 0.85, 95% CI 0.66 to 1.09, $P = 0.20$, $I^2 = 61\%$).

Among the five studies comparing sulfonylureas, there was no significant difference in HbA_{1c} reduction with gliclazide compared with other sulfonylureas (glibenclamide and glimepiride), with a weighted mean difference of −0.12% (95% CI −0.25 to 0.01%, $P = 0.07$, $I^2 = 77\%$), favoring gliclazide (Fig. 4). However, the reduction in the risk of hypoglycemia was significantly diminished when treated with gliclazide in comparison with other sulfonylureas (RR 0.47, 95% CI 0.27 to 0.79, $P = 0.004$, $I^2 = 0\%$) (Fig. 5).