TITLE: Gliclazide MR versus Glyburide for Management of Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety

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CONTEXT AND POLICY ISSUES:

About 5% of the Canadian population has diabetes mellitus, an endocrine disorder that is characterized by hyperglycemia (high blood glucose) that results from defective insulin secretion, defective insulin action, or a combination of the two.\(^1\) Diabetes mellitus is further classified as type 1, type 2, or gestational diabetes. Type 2 diabetes accounts for the majority of diabetes cases and can be managed through lifestyle modification (e.g. diet and exercise), oral medications that lower blood glucose, and insulin.\(^1\) Canadian Diabetes Association Guidelines for the management of type 2 diabetes recommend the use of sulfonylureas (medications which increase the secretion of insulin from the pancreas to lower blood glucose) in individuals whose blood glucose is not adequately controlled with diet, exercise, and metformin, an oral medication that potentiates the effects of insulin.\(^1\)

There are a number of sulfonylureas available on the market in Canada, two of which are gliclazide and glyburide (also referred to as glibenclamide).\(^1\) Glyburide is administered orally at dosages of 5 mg to 20 mg daily.\(^2\) Depending on the dose, glyburide is administered once or twice daily.\(^2\) Gliclazide is available in a modified release (MR) preparation that allows the drug to be orally administered once daily at dosages of 30 mg to 120 mg.\(^3\) Gliclazide MR has a hydrophilic polymer matrix that creates a gel when it contacts gastrointestinal fluid.\(^4\) The gel progressively releases gliclazide over a 24 hour period and parallels the circadian glycemic profile in individuals with type 2 diabetes.\(^4\) Once daily administration of medication can potentially improve adherence to therapy, which is vital to achieving blood glucose targets and preventing complications of diabetes.\(^4\) Studies have demonstrated that gliclazide MR provides efficient glycemic control with relatively few hypoglycemic events and good acceptability from a patient perspective.\(^4\)
The safety profiles of sulfonylureas, as well as their relative effectiveness, are important considerations in the management of patients with type 2 diabetes. More broadly, these factors are important from the perspective of a publicly funded health care system when making decisions about which medications to include on a drug formulary. This report will review the evidence of clinical effectiveness and safety of gliclazide MR compared to glyburide, which could potentially help in individual patient management and decision-making at the level of the healthcare system.

**RESEARCH QUESTION:**

What is the clinical effectiveness and safety of gliclazide MR versus glyburide for the management of type 2 diabetes?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1999 and February 2009 and are limited to English language publications only. No filters were applied to limit the retrieval by study type. Internet links are provided, where available.

**SUMMARY OF FINDINGS:**

No health technology assessments, systematic reviews, meta-analyses, or observational studies were identified in which the clinical effectiveness of gliclazide MR was compared to glyburide. Three relevant randomized controlled trials (RCTs) were identified, but full-text of one study was available in Chinese only. Thus, information from the study's abstract was used in this report. Another study was published as a brief research letter.

**Randomized controlled trials**

Cao *et al.* (2008) conducted a randomized study in 58 individuals with type 2 diabetes to compare the effects of sustained-release gliclazide and glyburide on plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis that has been associated with coronary artery disease. Given that only the study abstract was available in English language it could not be ascertained with certainty whether the sustained release preparation used in this study was gliclazide MR. Patients were randomized to receive either sustained-release gliclazide (n = 30) or glyburide (n = 28). Blood glucose, glycated hemoglobin (A1c), serum lipid, and PAI-1 were measured at baseline and after three months of treatment, but only results for PAI-1 were presented in the abstract. PAI-1 was reduced by 9.3 ng/mL in the sustained-release gliclazide group (p < 0.01) and by 1.0 ng/mL in the glyburide group (p > 0.05). From this, the authors concluded that sustained-release gliclazide was more effective in reducing PAI-1 than glyburide which may be beneficial for protecting endothelial function, and preventing complications of diabetes. From the available information it is difficult to comment on the limitations or generalizability of the study.

Rakel *et al.* (2007) conducted a double-blind, double-dummy randomized trial to compare the effects of gliclazide MR and glyburide on carotid intima-media thickness (IMT), serum markers of endothelial activation, and low-grade inflammation in 46 individuals with type 2 diabetes. The study included individuals between 40 and 70 years of age, who had durations of diabetes between 1 and 12 years. As well, study participants had to have A1c (a measure of average
glycemic control over the previous three months) less than 9%, be treated with glyburide alone or in combination with metformin or acarbose and have carotid IMTs between 0.40 and 1.07 mm. Individuals with cardiac, renal, or hepatic insufficiency, evidence of macrovascular disease, uncontrolled blood pressure, and those who were treated with insulin or anti-oxidants were excluded. Carotid IMT, serum adhesion molecules (sE-selectin, sICAM-1 and sVCAM-1), and high-sensitivity C-reactive protein (hsCRP) were assessed at baseline, and after six, 12, and 18 months. These markers of endothelial activation and low-grade inflammation are potential risk factors for cardiovascular disease in diabetes.

At the end of the study, patients treated with gliclazide MR had decreases in sICAM-1 and hsCRP that were statistically significantly greater than those observed with patients treated with glyburide. Changes in carotid IMT, sVCAM-1 and sE-selectin did not differ between groups. The authors concluded that the effects of gliclazide MR on serum levels of endothelial activation and low-grade inflammation markers and carotid IMT differed from those of glyburide in individuals with well-controlled type 2 diabetes. This conclusion was reached despite changes in a number of the parameters measured not being statistically significant. The results of this study were published as a research letter, with limited information about the methodology, making it difficult to comment on the quality of the study. Details of the dosing regimens of the medications were not provided, nor were demographic characteristics of the study populations. It was, however, stated that the baseline characteristics of the groups were similar. The generalizability of this study may be limited by its exclusion of individuals with macrovascular complications and poorly controlled blood pressure, as well as by the exclusion of individuals with poorly controlled type 2 diabetes.

Kardas (2005) conducted an open-label RCT in order to assess the impact of different dosing regimens of glyburide and gliclazide MR on adherence to therapy and glycemic control in 105 individuals with type 2 diabetes. In order to be included, patients had to be between the ages of 40 and 75 years old, diagnosed with type 2 diabetes within the previous five years, treated with diet and glyburide at a dosage of 5 mg twice daily (alone or in combination with metformin), have body mass indices (BMIs) between 22 and 30, and A1c less than 9.0%. Patients were randomized to gliclazide MR 60mg once daily (n=55) or glyburide 5 mg twice daily (n=50) for 16 weeks. Those patients who were on metformin at baseline continued treatment throughout the study. Adherence to therapy was evaluated through pill counts and by using an electronic monitoring system, referred to as Medication Event Monitoring System (MEMS®). Fasting plasma glucose (FPG) and A1c were assessed at baseline and after 16 weeks. A total of 99 patients were included in the efficacy analysis and 97 were included in the adherence analysis. The average age of patients in the glyburide and gliclazide MR groups was 62.4 years and 60.9 years, respectively. In terms of overall adherence, according to data from the MEMS, individuals in the gliclazide MR group took an average of 93.5% of recommended dosages compared to 87.2% of the glyburide group (p<0.05). Fewer individuals in the gliclazide MR group had delayed or missed dosages and had a larger percentage of dosages taken in the correct time window, at the correct interdose interval, and within the period of therapeutic coverage. As well, 77.6% of gliclazide MR group took more than 90% of the recommended doses, compared with 56.3% of the glyburide group (p<0.05). Days with no dosages or extra dosages did not differ between groups. According to pill count data, adherence did not differ between groups. A larger mean decrease in FPG from baseline was observed in the gliclazide MR group (18.9±18.7 mg/dL) than in the glyburide group (3.0±18.6 mg/dL, between-group p=0.0001). A1c decreased by 0.5 ±1.3% in the gliclazide MR group, compared to a 0.4 ± 1.2% increase in the glyburide group (p<0.0001 between groups). No hypoglycemic adverse events occurred in either group. The authors concluded that adherence to therapy was significantly higher and glycemic control
was significantly better with gliclazide MR 60 mg once daily compared to glyburide 5mg twice daily, suggesting a therapeutic advantage with gliclazide MR.

This study had a number of limitations. Individuals in the glyburide group had a significantly longer duration of diabetes, which could impact the outcomes measured in the study. As well, the author selected half maximum dosages for the medications used in the study and the dosages of the medications were not titrated in order to achieve blood glucose and A1c targets. While the dosages used were considered clinically equivalent, it is not clear that gliclazide MR would be superior to glyburide if the dosages were titrated to achieve glycemic targets. Finally, the study was relatively short in duration and it is not clear if results would be sustained longer term. It is uncertain whether the results of the study are generalizable to the broader population with type 2 diabetes given that only nonobese (BMI < 30) patients were included. As well, individuals with heart failure, unstable angina pectoris, and symptomatic peripheral vascular disease were excluded, as were those on insulin. It is not clear if the results would be generalizable to the population with type 2 diabetes with these complications or who required insulin.

Limitations

No relevant systematic reviews, health technology assessments, meta-analyses or observational studies were identified by the literature search. The clinical effectiveness of gliclazide MR was compared to glyburide in a limited number of RCTs. These studies have included small numbers of patients and two of the three studies had relatively short durations of follow-up. Further, two of the three studies assessed mainly biochemical markers, and did not evaluate or present data about important endpoints such as measures of glycemic control or the development of complications of diabetes. Generalizability of the results of two of the studies may be limited by the exclusion of individuals with certain types of complications of diabetes and restricting the study populations to those who were not obese, did not take insulin, and were relatively well controlled. Further, the generalizability of the studies is not clear given that demographic characteristics of the included patients were not available for two studies. Finally, the dosages of medications were not reported in two of the three studies, making it difficult to assess the validity of conclusions about the relative effectiveness of the medications.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

This report included studies in which the clinical effectiveness of a particular dosage form of gliclazide (gliclazide MR) was compared to glyburide. Based on data from one small study of relatively short duration, it appeared that adherence to therapy with 60 mg of gliclazide MR administered once daily may be superior to 5mg of glyburide administered twice daily and that this may be associated with better glycemic control. Safety, the risk hypoglycemia in particular, is also an important consideration in choosing drug therapy in type 2 diabetes. No conclusions about the relative safety of gliclazide MR and glyburide could be drawn from the included literature.

PREPARED BY:
Ron Pohar, BScPharm, Clinical Pharmacist
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


