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Original Research

The Hypoglycemic Risk of Glyburide (Glibenclamide) Compared with Modified-Release Gliclazide

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ABSTRACT

Objectives: The risk for hypoglycemia when taking glyburide compared with modified-release gliclazide remains to be established in older adults in routine care. We investigated the risk of a hospital encounter with hypoglycemia following a new prescription for glyburide compared with modified-release gliclazide.
Methods: In 2 population-based matched retrospective cohort studies in Ontario, Canada, between 2002 and 2011, we examined older adults who were newly prescribed glyburide or gliclazide as monotherapy or in the presence of metformin. Our primary outcome was a hospital encounter with hypoglycemia assessed within 90 days.
Results: The baseline characteristics between matched groups were similar. Initiating glyburide vs. gliclazide as monotherapy was associated with a higher risk for a hospital encounter with hypoglycemia (69 patients of 4374 taking glyburide [1.58%] vs. 8 patients of 4374 taking gliclazide [0.18%], absolute risk increase 1.40% [95% CI 1.01% to 1.79%], number needed to harm 71 [55 to 99], odds ratio 8.63 [95% CI 4.15 to 17.93], $p<0.0001$). Similar findings were noted when glyburide vs. gliclazide was initiated in the presence of metformin (110 patients of 8038 taking glyburide [1.37%] vs. 19 patients of 8038 taking gliclazide [0.24%], absolute risk increase 1.13% [95% CI 0.86% to 1.40%], number needed to harm 77 [71 to 116], odds ratio 6.06 [95% CI 3.68 to 9.97], $p<0.0001$).
Conclusions: Glyburide was associated with a higher risk for hypoglycemia than modified-release gliclazide. The results of our studies may help to convince healthcare professionals who use glyburide to consider modified-release gliclazide as a safer alternative.

Mots clés :
diabète
personnes âgées
gliclazide
glyburide
hypoglycémie

RÉSUMÉ

Objectifs : Il reste à déterminer le risque d'hypoglycémie lors de la prise de glyburide comparativement à la prise de gliclazide à libération modifiée chez les aînés en soins courants. Nous avons étudié le risque d'une visite à l'hôpital liée à l'hypoglycémie à la suite d'une nouvelle ordonnance de glyburide par rapport au gliclazide à libération modifiée.
Méthodes : Dans 2 études rétrospectives, en population, de cohortes appariées en Ontario, au Canada, entre 2002 et 2011, nous avons examiné des aînés qui avaient nouvellement reçu une ordonnance de glyburide ou de gliclazide en monothérapie ou en présence de metformine. Notre critère d'évaluation principal était une visite à l'hôpital et l'hypoglycémie évaluées dans les 90 jours.
Résultats : Les caractéristiques initiales entre les groupes appariés étaient similaires. L'introduction du glyburide *vs* du gliclazide en monothérapie a été associée à un risque plus élevé d'une visite à l'hôpital liée à l'hypoglycémie (69 patients sur 4374 prenant du glyburide [1,58 %] *vs* 8 patients sur 4374 prenant du gliclazide [0,18 %], augmentation absolue du risque, 1,40 % [IC à 95 %, 1,01 % à 1,79 %], nombre de sujets à traiter pour observer un effet indésirable, 71 [55 à 99], ratio d'incidence approché, 8,63 [IC à 95 %, 4,15 à

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17,93], p < 0,0001). Des résultats similaires ont été notés lors de l'introduction du glyburide *vs* au gliclazide en présence de metformine (110 patients sur 8038 prenant du glyburide [1,37 %] *vs* 19 patients sur 8038 prenant du gliclazide [0,24 %], augmentation du risque absolu, 1,13 % [IC à 95 %, 0,86 % à 1,40 %], nombre de sujets à traiter pour observer un effet indésirable, 77 [71 à 116], ratio d'incidence approché, 6,06 [IC à 95 %, 3,68 à 9,97], p < 0,0001).

Conclusions : Le glyburide a été associé à un risque plus élevé d'hypoglycémie que le gliclazide à libération modifiée. Les résultats de nos études peuvent aider à convaincre les professionnels de la santé qui utilisent le glyburide à envisager le gliclazide à libération modifiée comme une alternative qui démontre une plus grande innocuité.

Introduction

Sulfonylureas are easy to administer, low in cost and, through their insulin-secreting mechanism, are among the most potent of all oral hypoglycemic agents (1,2) These drugs, however, must be used very carefully in older adults to avoid hypoglycemia because this population commonly has medical comorbidities, takes multiple medications and has altered drug metabolism.

In Canada, glyburide (glibenclamide) and gliclazide are 2 commonly prescribed sulfonylureas. Because of glyburide's high affinity for the sulfonylurea receptor (3), its long duration of action and its glucose-lowering metabolites (4), the risk for hypoglycemia with glyburide is anticipated to be higher than that with other sulfonylureas (5–7). Accordingly, diabetes guidelines have cautioned against the use of glyburide when treating older persons in favour of other oral hypoglycemic agents (8). However, to our knowledge, the risk for hypoglycemia when using glyburide compared with a long-acting alternative, modified-release gliclazide (9), has not been examined in a large representative population of older adults in routine practice. For this reason, we conducted 2 population-based cohort studies to examine the risk of hospital encounters with hypoglycemia after the initiation of glyburide vs. once-daily modified-release gliclazide in the outpatient setting.

Methods

Study design and setting

We conducted 2 population-based matched retrospective cohort studies of older adults using linked healthcare databases in Ontario, Canada. Ontario has approximately 1.8 million adults aged 65 years or older who have comprehensive universal healthcare, including coverage for outpatient prescription medications, physician services, hospitalizations and diagnostic testing (10). The reporting of these studies follows guidelines for observational studies (Appendix Table A1) (11).

The studies were conducted at the Institute for Clinical Evaluative Sciences (ICES) according to a prespecified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). Participants' informed consent was not required.

Data sources

We obtained patient characteristics, drug use, covariate information and outcome data using records from several databases. We ascertained vital statistics from the Registered Persons Database of Ontario, which contains demographic information on all Ontario residents who have been issued a health card. The Ontario Drug Benefit Program database was used to identify prescription drug use, and it contains accurate records of all formulary prescriptions dispensed to those 65 years of age or older, with an error rate of less than 1% (12). Diagnostic and procedural information about hospital admissions and emergency room visits was abstracted from the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System database, respectively. Covariate information was also derived from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We used the ICES Physician Database to abstract sulfonylurea prescriber information. In previous studies, we have used these databases to research adverse drug events and health outcomes (13–18). A subpopulation of patients had laboratory creatinine or glycated hemoglobin (A1C) values that were available in the year prior to the relevant sulfonylurea prescription (19,20).

With the exception of sulfonylurea-prescriber information (missing in approximately 13% of both studies) and income quintile (missing in approximately 0.5% of both studies), the databases were complete for all variables used. The International Classification of Diseases, 9th revision (ICD-9) (pre-2002); the International Classification of Diseases, 10th revision (ICD-10) (post-2002); the Canadian Classification of Health Interventions (CCI); the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) (pre-2002); and the Canadian Classification of Health Interventions (CCI) (post-2002) codes were utilized to assess baseline comorbidities and investigations in the 5 years prior to the relevant sulfonylurea prescription (Appendix Table A2). Physician visits in the year prior to the sulfonylurea prescription were assessed through provincial fee-for-service codes. Codes used to assess outcomes are detailed in Appendix Table A3, which lists only ICD-10 codes because all events would have occurred after the implementation of this coding system in Canada.

Patients

To mimic routine practice, we conducted 2 population-based studies of older adults newly prescribed glyburide or modified-release gliclazide between April 2002 and December 2011. In the first study we examined a sulfonylurea prescribed as monotherapy, and in the second study we examined a sulfonylurea prescribed in the presence of metformin. In both studies, the date of the sulfonylurea prescription served as the index date (cohort entry date).

Monotherapy study

In this study, we excluded the following patients from analysis: 1) those in their first year of eligibility for prescription drug coverage (65 years of age) so as to avoid incomplete medication records; 2) those who had insulin or any other oral hypoglycemic agent dispensed in the year prior to the index date so as to ensure new oral hypoglycemic agent use; 3) those who had received other medications commonly associated with hypoglycemia (i.e. pentamidine, quinine, glucagon, indomethacin) in the year prior to the index date (21); 4) those with a history of at least 1 hospital encounter (emergency department or hospitalization) with hypoglycemia in the 5 years prior to the index date because antecedent