The Effects of a Glipizide Formulary Conversion

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This retrospective review, assessing the changes in A1C, adverse effects, adherence rates, and difference in cost at the Oklahoma City VAMC, showed that a formulary conversion of glipizide sustained-release to glipizide immediate-release did not adversely affect patient care.

In 2011, the National Diabetes Information Clearinghouse reported an estimated 25.8 million Americans with diabetes, which accounted for an estimated $174 billion spent in total health care costs that year.[1] At the Oklahoma City Veteran Affairs Medical Center (VAMC) in Oklahoma, about 33% of the patient population is known to have diabetes with the majority of these patients having type 2 diabetes. Subsequent to a Veterans Integrated Service Network (VISN) directive, in June 2006, the Oklahoma City VAMC's Pharmacy and Therapeutics (P&T) Committee undertook an initiative to convert all patients receiving glipizide sustained-release (SA) to glipizide immediate-release (IR). With limited and contradictory evidence to support either formulation, evidence that this conversion did not adversely affect patient care was necessary.

Type 2 diabetes is characterized by progressive β-cell dysfunction with insulin deficiency resulting in hyperglycemia.[2] Persistent hyperglycemia contributes to life-altering microvascular and macrovascular complications. However, tight glucose control has been found to significantly delay and slow the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes mellitus.[3,4] It has been postulated that tight control would have the same effects in patients with type 2 diabetes.[5]

Sulfonylurea medications are part of the mainstay of therapy to achieve glycemic control when medications, nutritional therapy, and exercise are insufficient. One of the most commonly used sulfonylureas is glipizide due to its convenient dosing and safety in renal insufficiency. Glipizide is a well-established oral agent that works by stimulating insulin release from the pancreas in patients with type 2 diabetes. A relatively short-acting agent, glipizide is a second-generation sulfonylurea that is rapidly absorbed and has a half-life of about 2 to 5 hours. The dosage may be adjusted at intervals of several days from 2.5 mg to 5 mg daily, up to a maximum recommended daily dose of 40 mg, with use of the IR formulation, and a maximum recommended daily dose of 20 mg, with use of the SA formulation.[6]

One previous study demonstrated a significant improvement in A1C reduction when comparing glipizide SA to glipizide IR, perhaps attributed to the improved compliance observed with the SA product.[7] However, this study was admittedly insufficiently powered. Another study by Berelowitz and colleagues found no difference in A1C between glipizide IR and SA but noted that glipizide SA was more effective than IR in reducing fasting plasma glucose (FPG) levels.[8] Yet another study found no difference in A1C or FPG values at 23 weeks.[9] Whether one of these formulations is more cost-effective or therapeutically effective than the other remains a largely unanswered question.

The primary objective of this study was to determine the effect of the conversion from glipizide SA to glipizide IR in our veteran population by assessing the change in A1C, adverse effects (AEs), adherence rate, and difference in cost. In addition, we were to determine how formulary conversion affected the intensity of concomitant antidiabetic medications for those in the secondary analysis group.

This study was reviewed and approved with exempt status in accordance with the ethical standards of the Veteran Affairs Research and Development Committee as well as the University of Oklahoma Institutional Review Board.

METHODS

This retrospective review, where patients served as their own control, was performed at the Oklahoma City VAMC. This center is a tertiary care, teaching medical facility that provides services to eligible veterans in 48 Oklahoma counties and 2 counties in north central Texas with an estimated veteran population of 224,696. In 2010, the Oklahoma City VAMC had

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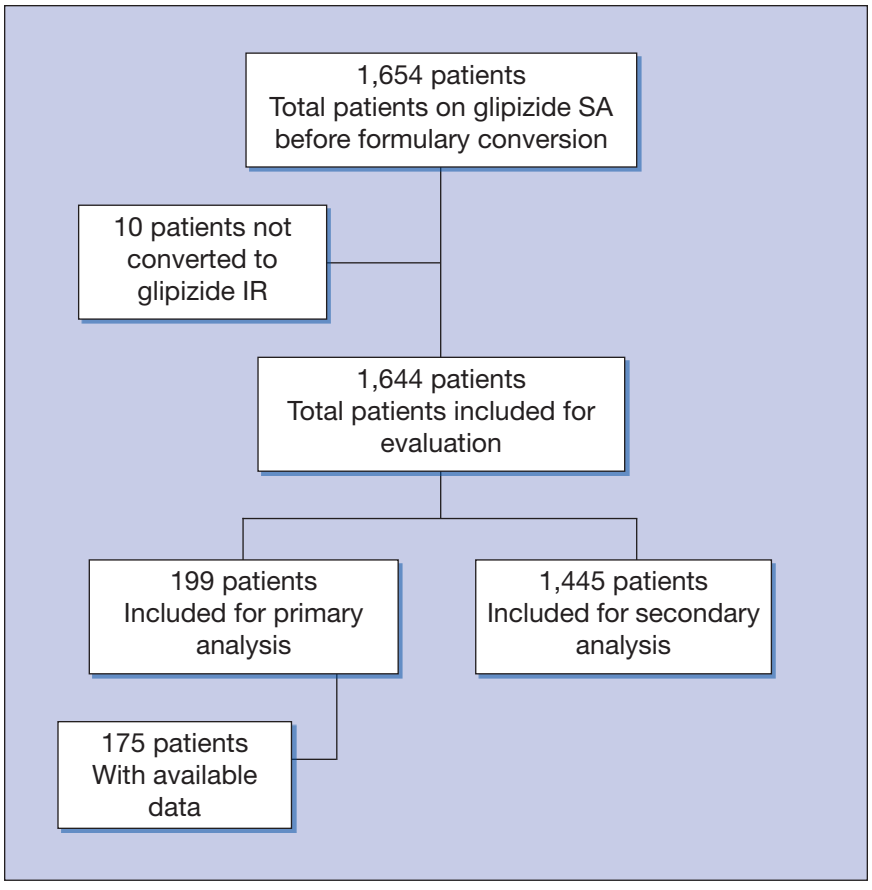

Figure 1. Trial profile.

503,420 outpatient visits and treated 6,871 patients on an inpatient basis.

The facility's computerized database was used to identify all patients converted from glipizide SA (≤ 20 mg daily) to an equivalent dose of glipizide IR given bid. All patients who were switched from glipizide SA to glipizide IR with an active prescription were included in the study. To be included in the primary analysis, patients were required to have 1 A1C determination within 180 days before formulation change (baseline) and 1 A1C value between 90 and 180 days after formulation change (follow-up). A stable diabetic regimen with no changes in concomitant antidiabetic medications during the evaluation period was also necessary for primary analysis. All patients who did not meet criteria for primary analysis were included in the secondary analysis.

The last A1C value before the conversion was compared with the first A1C value that was at least 90 days from the conversion to determine change in A1C. All prescriptions for glipizide SA filled within 180 days of the formulary conversion were analyzed for adherence rate and compared with prescriptions filled within 270 days of the conversion date, using the medication possession ratio (MPR).[10] The MPR was defined as the number of daily doses of glipizide dispensed by the pharmacy, divided by the total number of follow-up days since the first glipizide fill and A1C result. Antidiabetic medication expenses were also obtained from the institution for analysis. The number of Emergency Department (ED) visits and number of Telecare contacts were collected for patients eligible for primary analysis to assess the safety of the formulation change. For patients who met criteria for secondary analysis, medication changes were noted pre- and postformulary conversion.

STATISTICAL ANALYSIS

Continuous variables were compared using the Wilcoxon signed rank test, and categorical variables were analyzed using the chi-square test. All other data are descriptive, reporting trends and measures of central tendency as appropriate. A P value of $< .05$ was considered statistically significant.

Results

A total of 1,644 patients were switched from glipizide SA to glipizide IR. One hundred ninety-nine patients met criteria for primary analysis, and 1,445 patients met criteria for secondary analysis (Figure 1).

Primary Analysis Group

Complete data were available on 175 patients who met criteria for primary analysis. Average age was 68.9 years ± 16.2 years with all but 2 participants being male. Weight before formulation change was 224.6 lb ± 46.3 lb and 223.0 lb ± 43.9 lb postformulation conversion ($P = .88$). Average body mass index (BMI) was 32.7 kg/m^2 ± 9.9 kg/m^2 and 31.9 kg/m^2 ± 6.1 kg/m^2 pre- and postformulation change, respectively ($P = .85$).

Average A1C value was 6.84% ± 1.18% while on glipizide SA and 7.00% ± 1.16% while on glipizide IR ($P = .08$). Of the 175 patients, 149 had an adequate fill history in which adherence rate was found to be 94.1% ± 14.2% while on SA and 80.3% ± 18.7% while on the IR formulation ($P < .00001$) (Table 1).

A total of 27 Telecare calls were

made in the primary analysis group during the study period in which 33.33% of calls were made while patients were on glipizide SA and 66.67% of calls were made while on glipizide IR ($P = .07$). Only 2 of these calls were related to hypoglycemia, and both were made by the same patient; one occurred while the patient was on glipizide SA; the other occured in a patient on glipizide IR. All other Telecare calls were unrelated to diabetes.

A total of 42 ED visits occurred in these 175 patients during the study period, of which 52.4% came through while on glipizide SA and 47.6% while on glipizide IR ($P = .74$). No ED visits were related to diabetes.

Secondary Analysis Group

A total of 1,445 patients did not meet the criteria for primary analysis and were evaluated for secondary analysis. Of these patients, 538 had a stable diabetic regimen but did not have either baseline or follow-up A1C levels during the evaluation period. The other 907 patients had fluctuations in their diabetic regimens, such as the addition or reduction of other diabetes medications that could have affected glycemic control. Three hundred fifty-eight of these patients had medication changes while on glipizide SA, 354 patients had medication changes while on glipizide IR, and 195 patients had medication changes while on both formulations.

The average A1C for these 907 patients while on glipizide SA was 7.68% ± 1.67% and 7.84% ± 1.83% while on glipizide IR ($P = .058$). For those with an adequate fill history (827/907), average adherence rate was 91.8% ± 16.1% while on SA and 75.3% ± 23.4% while on the IR formulation ($P < .00001$) (Table 1).

Table 1. Changes in A1C and adherence

	Glipizide SA (%)	Glipizide IR (%)	*P* value
Primary analysis group			
Change in A1C (n = 175)	6.84 ± 1.18	7.00 ± 1.16	$P = .08$
Adherence rate (n = 149)	94.1 ± 14.2	80.3 ± 18.7	$P < .00001$
Secondary analysis group			
Change in A1C (n = 907)	7.68 ± 1.67	7.84 ± 1.83	$P = .058$
Adherence rate (n = 827)	91.8 ± 16.1	75.3 ± 23.4	$P < .00001$

COST ANALYSIS

Given the modest impact on both A1C and medication intensity noted, cost analysis was limited to medication acquisition costs (Figure 2). Total cost of all antidiabetic medications from January to June before the formulation change totaled $1,043,122 vs $983,061 after the formulation change from July to December. This was a decrease of 5.8% in total antidiabetic medication cost. Cost of only glipizide formulations during the same period was $189,948 and $71,503, respectively, which was a decrease of 62.4%. Quarterly evaluation of glipizide cost revealed $94,276 spent in the first quarter, $95,672 in the second, $59,104 in the third, and $12,399 in the fourth. The analysis revealed the occurrence of delays in the conversion process during the third quarter. Comparing the representative first and fourth quarters reveals an 86.8% decrease in glipizide cost. In the first quarter, glipizide products comprised 18.1% of the total antidiabetic medication cost, and by the end of the fourth quarter, glipizide products made up only 2.6% of the total antidiabetic medication costs.

DISCUSSION

Primary and secondary analysis revealed a slight, nonstatistically significant increase in A1C 3 to 6 months following formulation change from glipizide SA to glipizide IR despite that patients were significantly more compliant while on the SA formulation. The adherence difference was not unexpected and is consistent with other real-world situations in which increasing pill burden has been found to diminish patient adherence.[11-13] Historically, switching from once-daily to twice-daily drug administration attenuates adherence by approximately 22%,[14] similar to the reduction seen in this case. One may have expected the increase in A1C to be commensurate with the degree of attenuation in adherence, but this was not observed. One possible explanation for the observed A1C stability is that the second scheduled administration served as a reminder of the disease process, thus reinforcing dietary adherence in some, but this cannot be proven within the constraints of this evaluation. Of interest, the pre- and postchange variances in A1C (based on the coefficients of variation) were consistent in both groups, further suggesting that the interchange had no demonstrable effect on diabetic control. Whether improving adherence in the IR group would have improved diabetic control remains speculative.

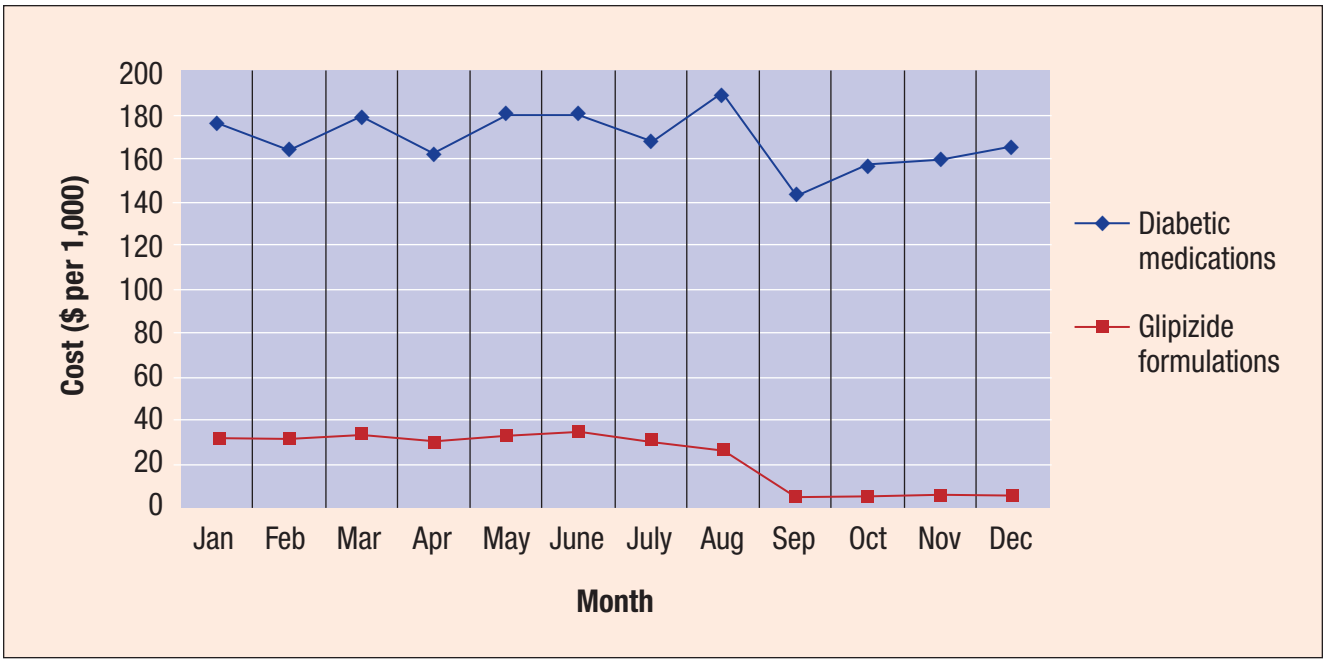

Figure 2. Drug acquisition cost in 2006.

Although these results were consistent with the findings of Berelowitz and colleagues and Hsieh and colleagues, who found both formulations of glipizide yielding similar mean A1C values, it is important to note that the mean A1C value was at American Diabetes Association (ADA) goal of < 7.0% while on glipizide SA (6.84%) and was no longer at goal (7.00%) following the switch to glipizide IR in the primary analysis group. This finding is likely a reflection of a low margin for variance rather than an inadequacy of the particular formulation. In spite of this finding, formulation change seems to have been appropriate given that both formulations were tolerable, where only 1 patient experienced hypoglycemia on both formulations.

Secondary analysis demonstrates that modification of antidiabetic medications while on either glipizide formulation (glipizide SA [n = 358] vs glipizide IR [n = 354]) was comparable; therefore, indicating that medication intensity, and thus medical need essentially remained the same. The burden of change in medications on physicians seemed to remain equivocal during the pre- and postformulation periods, and change in A1C was not statistically different; both also support the validity of the formulation change.

Noteworthy, the A1C at baseline and at follow-up in the secondary analysis group is much higher compared with the A1C levels in the primary analysis group, despite similar adherence values between the 2 groups. This could reflect more advanced disease in the secondary analysis group or a less intense therapeutic approach in these patients. A thorough review of the duration, complications, and follow-up of the disease process in these patients is beyond the scope of this study. It was noted, however, that 33% of patients converted from glipizide SA to glipizide IR did not qualify for primary analysis because A1C was not reassessed within 6 months of the formulary conversion. This observation identifies an area for quality improvement, since the ADA standard of care is to monitor A1C quarterly in patients whose therapy has changed. Given this standard of care measure, 6 months was at first thought to be able to maximize patient inclusion.

The anticipated drug acquisition cost reduction from the formulary conversion was confirmed. The authors acknowledge that the true cost impact of such changes would include any changes in resource use. We have attempted to assess this indirectly by monitoring antidiabetic medication intensity changes, which should reflect relative resource use. Given that the cost savings was significant and that the patients remained therapeutically stable, the conversion seems justifiable.

Since frequency of administration was a component of this therapeutic intervention, the ability to assess

adherence is a strength of the study. The limitations of this study include the retrospective nature of the analysis, small primary patient population, group rather than individual assessments, and no control of other possible confounding variables (eg, diet and exercise).

CONCLUSION

Patients were safely converted from glipizide SA to glipizide IR without a significant loss in efficacy or increase in complications, despite a significant difference in adherence. However, the modest observed increase in A1C resulted in this group of patients no longer being "controlled." Significant cost savings further support the appropriateness of the formulary conversion. Although intensity and burden of medication changes remained comparable while on both formulations, further studies comparing the difference in efficacy between the 2 glipizide formulations are warranted. In the era of fiscal medical responsibility, such therapeutic interchanges can play an important role in making health care more affordable and accessible to all.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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