Treatment and Treatment-Related Adverse Events of Type 2 Diabetes Mellitus in Residents of Long-Term Care Facilities: A Retrospective Study

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ABSTRACT

Background: In the United States, type 2 diabetes mellitus (DM) is most prevalent among adults aged >75 years. Judicious use of available therapies can improve plasma glucose concentration and reduce the risk for complications in elderly patients. However, selecting the appropriate medication for these patients is often challenging.

Objectives: The goals of this retrospective study were to determine whether 1 or 2 medications were needed for the treatment of type 2 DM in elderly patients and to identify treatment-related adverse events (AEs).

Methods: The charts of residents of long-term care (LTC) facilities in New Jersey and Pennsylvania with a diagnosis of type 2 DM and receiving metformin, a sulfonylurea, rosiglitazone, or pioglitazone, either alone or in combination with insulin or another drug, were included. Data for laboratory values (including fasting plasma glucose [FPG] and serum creatinine concentration), body weight, and AEs were analyzed.

Results: The charts of 182 patients (121 women, 61 men) were included. The mean (SD) age of the women was 80.2 (10.2) years; and of the men, 73.7 (12.0) years. Many patients were switched from monotherapy to combination therapy due to a high FPG concentration. Sixty treatment-related AEs occurred in 60 patients; the pioglitazone and metformin groups had the highest incidence of AEs (8/11 [72.7%] patients and 21/48 [43.8%] patients, respectively) and the rosiglitazone group had the lowest (2/13 [15.4%] patients), although the number of patients in the pioglitazone and rosiglitazone groups was extremely low.

Conclusions: In this study population of older patients, rosiglitazone monotherapy had favorable tolerability and appeared to be more effective than other therapies for type 2 DM. These results suggest that rosiglitazone monotherapy may be the safest and most effective of the 4 treatments for type 2 DM in older patients. The rosiglitazone group was the only group that did not have a second medication added to control plasma glucose. However, additional studies are suggested to determine whether larger groups of older patients residing in LTC

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facilities would demonstrate similar results. (*Curr Ther Res Clin Exp.* 2003;64: 1-9) Copyright © 2003 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, metformin, sulfonylurea, pioglitazone, rosiglitazone.

INTRODUCTION

In the United States, type 2 diabetes mellitus (DM) is most prevalent among adults aged >75 years. According to the most recent data, 17.5% of women and 21.1% of men aged >75 years have type 2 DM.¹ With the aging of the US population, the increasing incidence of obesity, and reduced physical activity, type 2 DM is expected to affect millions more in the coming years. Thus, the disease is commonly seen in long-term care (LTC) facilities. As many as 50% of people with type 2 DM are unaware that they have the condition, and in the LTC setting, many cases are not discovered until blood chemistry screening for other conditions.

Judicious use of available therapies can improve plasma glucose concentration and reduce the risk for complications in elderly patients. However, selecting the appropriate medication for elderly patients is often challenging. Aging is associated with increasing insulin resistance, that is, impairment of the efficient use of the body's own insulin. In a person with insulin resistance, the need for usable insulin provokes ever-increasing demands on the beta cells to produce insulin, resulting in hyperinsulinemia. Depending on other risk factors, such as lifestyle, genetic makeup, and obesity, insulin resistance may progress to impaired glucose tolerance and eventually to type 2 DM.

Various therapies, including lifestyle changes (diet and exercise), oral medications, and exogenous insulin, have been used to treat type 2 DM in older patients. Patients often are started on sulfonylurea therapy, which stimulates the beta cells to produce insulin and thus decreases plasma glucose concentration. However, the effectiveness of sulfonylureas decreases over time as the beta cells become exhausted. At this point, other agents often are added. Metformin is called an *antihyperglycemic agent* because it decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.² However, the gastrointestinal side effects of metformin can be problematic for older people. Also, when metformin is combined with a hypoglycemic agent, such as a sulfonylurea, the risk for hypoglycemia increases.

The 2 thiazolidinediones, pioglitazone and rosiglitazone, are also insulin sensitizers; however, unlike metformin, pioglitazone and rosiglitazone work mainly by increasing peripheral glucose uptake. Their mechanism of action involves modulating insulin-responsive genes at the cellular level; thus, they directly affect insulin resistance rather than treating a symptom (hyperglycemia). In addition to monotherapy for type 2 DM, the thiazolidinediones may be beneficial

in reducing insulin requirements. Serum aminotransferase activities should be monitored periodically during the first year of therapy with a thiazolidinedione.²

The goals of this retrospective study were to determine whether 1 or 2 medications were needed for the treatment of type 2 DM in elderly patients and to identify treatment-related adverse events (AEs).

MATERIALS AND METHODS

Patients' charts were selected from among the charts of 7000 LTC-facility residents in New Jersey and Pennsylvania who had a diagnosis of type 2 DM and who were prescribed metformin, a sulfonylurea, rosiglitazone, or pioglitazone, either alone or in combination with insulin.

Verbal approval for access to numbered patient charts, devoid of names or initials, was obtained from administrators and the director of nurses at each LTC facility. Patients were not identified, and no additional procedure or therapy was administered to any patient before, during, or after the analysis. All data were accessed and recorded by one of several consulting pharmacists.

Patient data, recorded in January 2001, were collected for all included patients, beginning with their date of admission to the LTC facility. Patients' actual body weight, compared with ideal body weight (IBW) (from dietitians' notes), was recorded initially, when medications were adjusted, and at the final data collection. Other data recorded included concomitant illnesses and fasting plasma glucose (FPG) concentration (normal, <110 mg/dL; normal preprandial range, 80–120 mg/dL; normal bedtime range, 100–140 mg/dL) on admission and when medications were adjusted; all prescribed medications; and AEs during the first week of therapy or when medications were increased, decreased, or changed. Hemoglobin A_{1c} was measured in some patients; however, FPG data were available for all patients and thus were used for statistical analysis. Attribution of AEs to the disease or medication was recorded from physicians' notes. All patients' diet orders included no concentrated sweets. Diet compliance was not measured.

Serum creatinine concentration (SCC) was recorded when available. It is important to observe SCC in elderly patients receiving antidiabetic medication because of the increased risk for declining renal function with age and because some medications are contraindicated in patients with a high SCC. Metformin is contraindicated if SCC is ≥ 1.4 mg/dL in women or ≥ 1.5 mg/dL in men because these patients may develop lactic acidosis.² Data on individual sulfonylurea drugs were not collected but were aggregated because the individual drugs have the same characteristics, mode of action, and side effects.

Statistical Analysis

SAS software (SAS Institute Inc., Cary, North Carolina) was used to calculate means, SDs, medians, odds ratios, and 95% CIs. Statistical significance was set at $P \leq 0.05$.

RESULTS

The records of 182 patients (121 women, 61 men) with type 2 DM were included in the study. The mean (SD) age of the women was 80.2 (10.2) years; of men, 73.7 (12.0) years. Increased age was significantly correlated with increased FPG concentration ($P = 0.04$).

All patients had at least 1 concomitant diagnosis, the most common of which were hypertension (45.6%) and dementia (23.1%) (Table I). On admission to the LTC facility, most (164/182 [90.1%]) patients were receiving monotherapy (109 [66.5%] sulfonylurea, 38 [23.2%] metformin, 9 [5.5%] rosiglitazone, and 8 [4.9%] pioglitazone). Eighteen (9.9%) patients were receiving dual therapy either with a combination of these drugs or with insulin or another drug (Table II).

On admission, 121 (66.5%) patients weighed more than IBW, 34 (18.7%) weighed less than IBW, and 27 (14.8%) were at IBW. During the study period, 86 (47.3%) patients gained body weight, 76 (41.8%) lost body weight, and 17 (9.3%) had no body weight change; body weight was not recorded for 3 (1.6%) patients. No significant correlation was found between body weight change and

Table I. Concomitant diagnosis in long-term care facility residents with type 2 diabetes mellitus (N=182).

Diagnosis	No. (%) of Patients*
Hypertension	83 (45.6)
Dementia	42 (23.1)
Stroke/TIA	37 (20.3)
ASHD/CAD/ASCVD	23 (12.6)
Depression	19 (10.4)
COPD	13 (7.1)
Osteoarthritis/degenerative joint disease	13 (7.1)
Seizures	11 (6.0)
CHF	11 (6.0)
GERD	11 (6.0)
Cancer	11 (6.0)
Anemia	10 (5.5)
Atrial fibrillation	9 (4.9)
Parkinson's disease	8 (4.4)
Schizophrenia	8 (4.4)
Bipolar disorder	7 (3.8)
Hypothyroidism	7 (3.8)
Glaucoma	6 (3.3)
Miscellaneous diagnoses	41 (22.5)

TIA = transient ischemic attack; ASHD = arteriosclerotic heart disease; CAD = coronary artery disease; ASCVD = arteriosclerotic cardiovascular disease; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; GERD = gastrointestinal reflux disease.

*Some residents had >1 concomitant diagnosis.

Table II. Diabetes medications and fasting plasma glucose (FPG) concentration of patients (N = 182) on admission to a long-term care facility.

Medications	No. (%) of Patients on Admission	Mean FPG on Admission, mg/dL
Monotherapy (n = 164 [90.1%])		
Sulfonylurea	109 (66.5)	130
Metformin	38 (23.2)	141
Rosiglitazone	9 (5.5)	144
Pioglitazone	8 (4.9)	157
Dual therapy (n = 18 [9.9%])		
Sulfonylurea + metformin	8 (44.4)	131
Rosiglitazone + repaglinide	2 (11.1)	154
Rosiglitazone + sulfonylurea	2 (11.1)	199
Pioglitazone + insulin injection	1 (5.6)	140
Pioglitazone + insulin suspension	1 (5.6)	103
Metformin + insulin injection	1 (5.6)	96
Metformin + pioglitazone	1 (5.6)	187
Sulfonylurea + insulin suspension	1 (5.6)	207
Sulfonylurea + insulin injection	1 (5.6)	159

FPG concentration. SCC data were available for 92 (50.5%) patients; the mean (SD) SCC was 1.17 (0.69) mg/dL.

On admission, only 43 (23.6%) patients were considered to have good plasma glucose control (as measured by FPG); after physicians adjusted diabetes medications, 73 (40.1%) patients had good plasma glucose control. Overall, FPG concentrations in patients treated with rosiglitazone alone or metformin alone were comparable.

Table III shows changes in FPG concentrations for patients initially receiving monotherapy. Fourteen of 79 (17.7%) patients who received initial monotherapy with a sulfonylurea were prescribed a second medication due to increased FPG concentration—9 (64.3%) were prescribed metformin, 2 (14.3%) insulin suspension, 2 (14.3%) rosiglitazone, and 1 (7.1%) pioglitazone. Ten of 21 (47.6%) patients who received metformin alone as initial therapy were prescribed a second medication—9 (90%) were prescribed sulfonylureas, and 1 (10%) insulin. Six of 8 (66.7%) patients receiving pioglitazone alone as initial therapy were prescribed a second medication due to high FPG concentration—2 (33.3%) were prescribed sulfonylureas; 2 (33.3%) metformin; and 2 (33.3%) insulin injection. None of the 9 patients initially receiving rosiglitazone monotherapy were prescribed a second medication.

The only potentially life-threatening AE reported was low FPG concentration (23/182 [12.6%] patients; Table IV).

Patients receiving pioglitazone alone or in combination with another drug had the highest incidence of treatment-related AEs (8/11 [72.7%] patients). Four

Table III. Mean (SD) fasting plasma glucose (FPG) concentrations (mg/dL) for patients initially receiving monotherapy.

Medication	On Admission		Remaining on Monotherapy		Before 2nd Medication Added		After 2nd Medication Added	
	No. of Patients	FPG	No. (%) of Patients	FPG	No. (%) of Patients	FPG	No. (%) of Patients	FPG
Sulfonylurea	79	186 (46.3)	65 (82.3)	125 (35.7)	14 (17.7)	205 (57.8)	14 (17.7)	148 (34.7)
Metformin	21	215 (68.6)	11 (52.4)	124 (25.0)	10 (47.6)	229 (45.1)	10 (47.6)	148 (34.7)
Rosiglitazone	9	195 (39.0)	8 (100)	118 (32.3)	0 (0.0)*	–	0 (0.0)*	–
Pioglitazone	8	155 (35.2)	3 (33.3)	170 –	6 (66.7)	228 (40.2)	6 (66.7)	107 (16.5)

*No patient required a second medication.

Table IV. Incidence (%) of treatment-related adverse events (AEs) occurring throughout the study (N = 182).

AE	Sulfonylurea* (n = 121)	Metformin [†] (n = 48)	Rosiglitazone (n = 13)	Pioglitazone [‡] (n = 11)
Low FPG level	18 (14.9)	2 (4.2)	2 (15.4)	1 (9.1)
Headache	4 (3.3)	3 (6.3)	0 (0.0)	1 (9.1)
Edema	3 (2.5)	2 (4.2)	0 (0.0)	1 (9.1)
Nausea and vomiting	2 (1.7)	5 (10.4)	0 (0.0)	4 (36.4)
Body weight loss	1 (0.8)	1 (2.1)	0 (0.0)	0 (0.0)
Diarrhea	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
High FPG level	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Low vitamin B ₁₂ level	0 (0.0)	7 (14.6)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Total (%) AEs	29 (24.0)	21 (43.8)	2 (15.4)	8 (72.7)
Odds ratio	0.21	0.49	1 [§]	0.80
95% CI	0.13–0.28	0.34–0.64	1 [§]	0.55–1.00

FPG = fasting plasma glucose.

*Six (5%) of these patients had doses decreased due to AEs.

[†]Six (12.5%) of these patients had doses decreased due to AEs, and 6 (12.5%) patients discontinued treatment for the following reasons: high serum creatinine concentration (2 [4.2%] patients; not a treatment-related AE), and high FPG level, body weight loss, and nausea and vomiting (1 [2.1%] patient for each).

[‡]One (9.1%) of these patients had dose decreased due to an AE.

[§]Reference group.

(36.4%) had nausea and vomiting, 1 (9.1%) had low FPG concentration, and 1 (9.1%) had edema. These AEs are common with thiazolidinedione therapy.²

Patients receiving metformin alone or in combination with other medications experienced the next-highest incidence of AEs (21/48 [43.8%] patients). In this group, 7 (14.6%) patients had a low vitamin B₁₂ level, which may be due to interference with B₁₂ absorption from the B₁₂ intrinsic factor complex.² In addition, 5 (10.4%) patients had nausea and vomiting, and 2 (4.2%) had low FPG concentration. In addition, in the metformin group, 6 (12.5%) patients discontinued treatment for the following reasons: high SCC (2 [4.2%] patients; not a treatment-related AE) and high FPG concentration, body weight loss, and nausea and vomiting (1 [2.1%] patient for each). The metformin group was also the only group in which treatment was discontinued due to AEs.

Patients receiving sulfonylurea drugs had the next-highest incidence of AEs (29/121 [24%] patients), including 18 (14.9%) with low FPG concentration. In contrast, patients receiving rosiglitazone experienced the lowest incidence of AEs (2/13 [15.4%] patients, both of whom had a low FPG concentration).

Although abnormal values on liver function tests and fluid retention, which may exacerbate or lead to heart failure,² are known complications of treatment with pioglitazone or rosiglitazone, no patients receiving these drugs experienced

these AEs. No patients in the rosiglitazone group had their doses decreased due to AEs, whereas doses were decreased in the other treatment groups, as follows: sulfonylurea, 6 (5%) patients; metformin, 6 (12.5%) patients; pioglitazone, 1 (9.1%) patient.

DISCUSSION

Type 2 DM is highly prevalent in older individuals, particularly women. In the population in this retrospective study, 66.5% of the patients were women. Other risk factors for type 2 DM were body weight in excess of IBW, which was seen in 66.5% of this patient population, and, perhaps, a lack of exercise. Diet plans in LTC facilities tend to be pragmatic; often, the diet order reflects sufficient calories to maintain a resident's body weight, regardless of whether it reflects his or her IBW. Thus, drug therapy is a mainstay of DM management. A goal for the treatment of residents in LTC facilities is to maximize the efficacy of antidiabetic medications while minimizing treatment-related AEs. In this retrospective study of LTC-facility residents with type 2 DM, the most favorable efficacy was demonstrated for rosiglitazone therapy, which also manifested the fewest AEs (15.4%). Patients receiving pioglitazone experienced the highest incidence of AEs (72.7%), followed by metformin (43.8%). The majority of patients treated with pioglitazone also were receiving concomitant therapy with a second medication, which may have resulted in more AEs.

Monotherapy for type 2 DM is often insufficient in the LTC-facility setting due to the advancing age of the residents and possible decreased insulin production. In this study, rosiglitazone monotherapy achieved comparable or better plasma glucose control compared with metformin, with a lower incidence of AEs. Previous studies have demonstrated equivalent FPG results in patients both younger and older than 65 years.³ The absorption and elimination of sulfonylureas is impaired in elderly patients, and insulin responses may be enhanced, a combination that can promote more frequent and more severe hypoglycemia.⁴ Also, the effectiveness of sulfonylureas decreases with time as beta cells become exhausted.⁵ Metformin often is used for obese diabetic patients, but it is important to observe SCC, especially in patients with a creatinine clearance rate <60 mL/min or an SCC ≥ 1.4 mg/dL. Also, patients with congestive heart failure, chronic obstructive pulmonary disease, or a history of liver disease or alcohol abuse may be at greater risk for metformin-induced lactic acidosis.²

Because the number of patients receiving rosiglitazone or pioglitazone was small, the study does not have sufficient power to allow comment on these findings in any definitive manner, and the results obtained may have been due to chance. In addition, other potential confounders, such as patient selection, past AEs, past therapy, and concomitant therapy, may have clouded the results. Therefore, additional studies are suggested to determine whether larger groups of older patients residing in LTC facilities would demonstrate similar results.

CONCLUSIONS

In this study population of older patients, rosiglitazone monotherapy had favorable tolerability and appeared to be more effective than other therapies for type 2 DM. These results suggest that rosiglitazone monotherapy may be the safest and most effective of the 4 treatments for type 2 DM in older patients. The rosiglitazone group was the only group that did not have a second medication added to control plasma glucose. However, additional studies are suggested to determine whether larger groups of older patients residing in LTC facilities would demonstrate similar results.

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