ORIGINAL ARTICLE

Effect of Glyburide–Metformin Combination Tablet in Patients with Type 2 Diabetes

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Background: To evaluate the efficacy and safety of glyburide/metformin combined tablet compared to glyburide or metformin alone in patients with type 2 diabetes.

Methods: In this 16-week, multicenter, randomized, double-blind, 4-arm and parallel clinical trial study, 100 patients with type 2 diabetes mellitus were recruited and 76 patients were available for statistical analysis at the end of the study. After 1 week of placebo washout period, eligible patients were randomly assigned into 1 of 4 treatment groups: glyburide 5 mg b.i.d.; metformin 500 mg b.i.d.; glyburide/metformin 2.5 mg/500 mg b.i.d.; or glyburide/metformin 5.0 mg/500 mg b.i.d. The doses were titrated every 2 weeks to a maximum of 4 tablets per day if the patient's fasting plasma glucose (FPG) still exceeded 140 mg/dL. Efficacy was evaluated by the changes from baseline in glycosylated hemoglobin (HbA1c) and FPG at week 16. Adverse events were recorded and summarized by treatment group.

Results: At week 16, patients who received glyburide/metformin 2.5 mg/500 mg or 5.0 mg/500 mg tablets had greater reductions in FPG (all $p < 0.001$) compared with glyburide or metformin monotherapy. Patients who took glyburide/metformin 2.5 mg/500 mg tablet and glyburide/metformin 5.0 mg/500 mg tablet had significant decreases in HbA1c (both $p < 0.0125$). Furthermore, treatment with glyburide/metformin 2.5 mg/500 mg resulted in significantly greater reduction in HbA1c compared to glyburide or metformin (-1.77%, $p < 0.001$ and -1.34%, $p = 0.002$), and treatment with glyburide/metformin 5.0 mg/500 mg resulted in significant lowering of HbA1c compared to glyburide or metformin alone (-1.73%, $p < 0.001$ and -1.30%, $p = 0.005$). Both the glyburide/metformin 2.5 mg/500 mg and glyburide/metformin 5.0 mg/500 mg combination therapy groups experienced fewer gastrointestinal adverse events than the metformin monotherapy group.

Conclusion: Both glyburide/metformin 2.5 mg/500 mg and glyburide/metformin 5.0 mg/500 mg combination therapy were efficacious and well tolerated in the treatment of Chinese patients with type 2 diabetes mellitus. [*J Chin Med Assoc* 2007;70(11):473–480]

Key Words: diabetes mellitus, glyburide, metformin

Introduction

Diabetes mellitus is a chronic disease that is growing in prevalence worldwide, and the burden of this disease will continue to grow.[1] Type 2 diabetes mellitus is a metabolic disorder that results from complex interactions of multiple factors and is characterized by 2 major defects in insulin action (insulin resistance) and a relative insulin deficiency (progressive beta cell failure). Aggressive glycemic control has been demonstrated

to decrease the risk of long-term microvascular and macrovascular complications such as neuropathy, retinopathy and myocardial infarction.[2] Therefore, effective treatment often requires therapy directed at both abnormalities. There is evidence to show that glycemic control can be improved by early use of combinations of agents to simultaneously improve insulin secretion and reduce insulin resistance.[3,4] The most commonly used combination is that of a sulfonylurea and biguanide, which has been proven to effectively control glycemia in patients with type 2 diabetes.[3–6] In this context, clinical studies have demonstrated that glyburide/metformin combinations led to a significantly greater reduction in fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) than monotherapy or the co-administration of glyburide and metformin in type 2 diabetes.[7–12] In addition, single-tablet combination therapies offered the opportunity for simplifying oral antidiabetic regimens, reducing inconvenience and improving compliance.[13–17] This study was designed to investigate the efficacy and safety of glyburide/metformin single-tablet compared to glyburide or metformin alone in Chinese patients with type 2 diabetes.

Methods

Study population

This was a randomized, double-blind, 4-arm parallel clinical trial of patients with type 2 diabetes and inadequate glycemic control (HbA1c >7%) previously. The study protocol was reviewed and approved by institutional review boards in Taiwan, and patients gave written informed consent before participation.

The inclusion criteria were: age 30–75 years, type 2 diabetes, body mass index (BMI) 18.5–35 kg/m^2, FPG 140–250 mg/dL and HbA1c 7–12% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use. Doses of sulfonylurea were at least equal to or exceeded 1 of the following doses: glimepiride 4 mg/day, glyburide or glipizide 10 mg/day, gliclazide 160 mg/day. In the case of concomitant use of metformin, the dose was not more than 1,000 mg/day.

Exclusion criteria included: liver disease, renal disease, renal impairment, heart failure, current significant gastrointestinal disorder or other conditions which may interfere with absorption of the study drugs, history of drug or alcohol abuse, history of diabetic ketoacidosis, hyperglycemic hyperosmolar non-ketotic coma, known hypersensitivity to glyburide or metformin, history of stroke, myocardial infarction, coronary

revascularization, or arrhythmia that required medical treatment within the past 6 months, proliferative retinopathy, current infection, had been treated with insulin during the past 6 months, seriously dehydrated, or took other investigation drug, had undergone an operation within 4 weeks prior to entering the study or a history of cancer within 5 years, received concomitant medication known to affect glucose tolerance, hypoglycemic action, or to interfere with the metabolism of the study drugs during the past 1 month.

Study design

After 1 week of placebo washout period, eligible patients were randomly assigned into 1 of 4 treatment groups: glyburide 5 mg b.i.d.; metformin 500 mg b.i.d.; glyburide/metformin 2.5 mg/500 mg b.i.d.; or glyburide/metformin 5.0 mg/500 mg b.i.d. The doses were titrated every 2 weeks to a maximum of 4 tablets per day if the patient's FPG still exceeded 140 mg/dL. The investigational drugs and the matching placebo were prepared by Orient Europharma (OEP) Co. Ltd., Taiwan. For active drug, each tablet contained either glyburide/metformin 2.5 mg/500 mg or 5.0 mg/500 mg. Euglucon® 5 mg (glyburide) was manufactured by Roche Diagnostics, and Glucophage® 500 mg (metformin) was manufactured by LIPHA S.A., France. All study medications were supplied by OEP, Taiwan. At the end of week 4, down-titration (t.i.d. to b.i.d. or double dose b.i.d. to t.i.d.) was permitted. The investigators were allowed to reduce the dose of study medication to the previous level if the patient's FPG was <70 mg/dL. If FPG was between 70 and 100 mg/dL and the patient experienced 1 episode of hypoglycemia, the investigator could decide whether to reduce the medication dose based on the patient's clinical condition. All patients were maintained at the dose level of week 4 until the end of the study at week 16.

Efficacy and safety evaluations

The primary efficacy endpoint was the change in HbA1c from baseline to week 16. The secondary endpoint was the change in FPG at week 16. Adverse drug events were recorded and rated by the study investigators and included any illness, sign, symptom, or clinically significant laboratory test abnormality that appeared or worsened during the course of the clinical trial. Hypoglycemia was defined in 2 ways. Symptomatic hypoglycemia was defined by the presence of at least 1 symptom of hypoglycemia and judged by the investigator to be a possible hypoglycemic event. Laboratory-confirmed hypoglycemia was defined as a plasma glucose concentration <60 mg/dL. Gastrointestinal reactions were defined as symptoms of gastrointestinal side effects

(diarrhea, nausea/vomiting, abdominal pain). Serious adverse events were defined as any adverse experience occurring at any dose that resulted in death, a life-threatening adverse experience, inpatient hospitalization, congenital anomaly, permanent or severe disabling or other important medical condition that required medical or surgical intervention to prevent permanent impairment/damage.

Statistical methods

All patients who completed the entire treatment period were included in the final analysis. Patients who took at least 1 study medication were included in the safety analysis. All statistical assessments were 2-sided and evaluated at the 0.05 level of significance. Categorical variables were analyzed using χ^2 test or Fisher's exact test. Continuous variables were analyzed using t test, ANOVA, or the Kruskal–Wallis test. The 0.0125 significance level applied when performing the Bonferroni procedure to compare glyburide/metformin with glyburide or metformin alone.

Results

A total of 166 patients with type 2 diabetes mellitus were screened from 5 medical centers in Taiwan. Sixty-six of them were unqualified due to fluctuation in fasting glucose values ($n = 36$), unstable A1c levels ($n = 7$) and patients' refusal to join the study ($n = 13$). One hundred

patients were randomly assigned into this study with a total of 76 patients at the end for final analysis (19 terminated prematurely and 5 violated protocol). The baseline demographic and diabetes characteristics for all patients randomized are shown in Table 1. There were no statistically significant differences in terms of gender distribution, BMI, age, weight, height and history of diabetes mellitus among the 4 treatment groups ($p > 0.05$). Also, no significant differences in terms of systolic blood pressure, diastolic blood pressure, pulse, HbA1c and FPG were observed among the treatment groups ($p > 0.05$).

The final doses achieved in each group were glyburide 19 mg, metformin 1,910 mg, glyburide 2.5 mg/metformin 500 mg: 8.4/1,680 mg, glyburide 5.0 mg/metformin 500 mg: 17.2/1,723 mg. The mean changes in body weight from baseline were −0.24 kg, −2.07 kg, 0.71 kg, −0.16 kg in the glyburide, metformin, glyburide/metformin 2.5/500 mg and glyburide/metformin 5.0/500 mg groups, respectively. This was statistically significantly different in terms of body weight among treatment groups ($p < 0.001$).
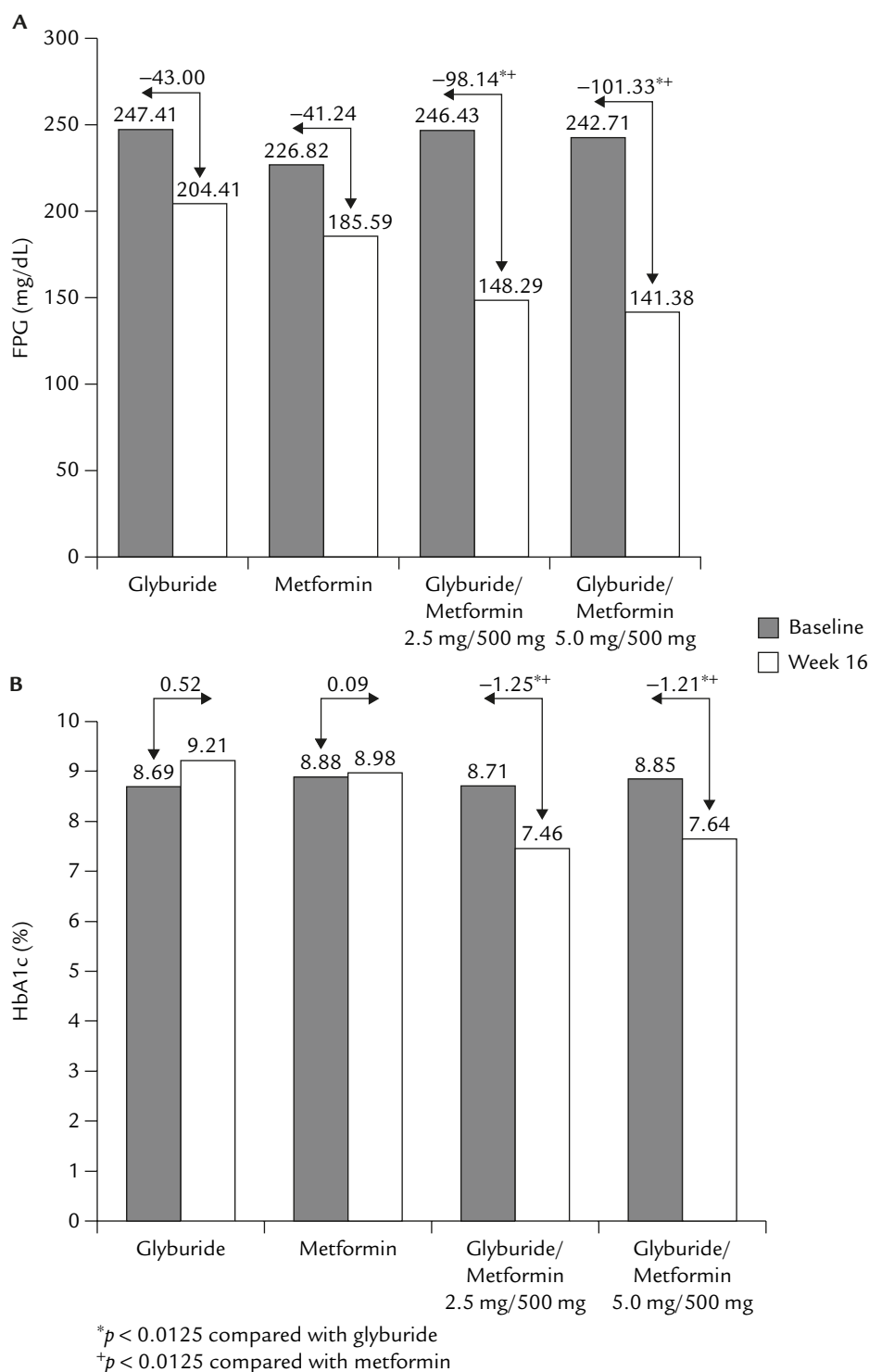
FPG concentrations

Figure 1A shows the mean changes in FPG from baseline. They were −43 ± 11 mg/dL in the glyburide group, −41 ± 13 mg/dL in the metformin group, −98 ± 11 mg/dL in the glyburide/metformin 2.5 mg/500 mg group and −101 ± 10 mg/dL in the glyburide/metformin 5.0 mg/500 mg group, with only the latter 2 groups

Table 1. Baseline clinical characteristics of all study subjects*

| | Glyburide (n = 17) | Metformin (n = 17) | Glyburide/metformin | |
			2.5 mg/500 mg (n = 21)	5 mg/500 mg (n = 21)
Age, yr	63 ± 7	59 ± 9	60 ± 7	57 ± 8
Gender				
Male	9 (53)	7 (41)	15 (71)	13 (62)
Female	8 (47)	10 (59)	6 (23)	8 (38)
BMI, kg/m^2	25.3 ± 34	25.7 ± 3.2	24.2 ± 3.2	24.2 ± 2.7
Weight, kg	63.7 ± 9.6	65.6 ± 11.4	63.8 ± 9.0	61.3 ± 8.8
Duration of DM, yr	8.6 ± 5.9	6.4 ± 4.8	9.0 ± 5.6	6.6 ± 5.6
Baseline HbA1c, %	8.69 ± 0.94	8.88 ± 1.08	8.71 ± 1.10	8.85 ± 1.21
Baseline FPG, mg/dL	247 ± 46	227 ± 43	246 ± 38	243 ± 50
Diabetes medication used before enrolment				
Sulfonylurea	17 (100)	17 (100)	21 (100)	21 (100)
Metformin	14 (82)	15 (88)	14 (67)	15 (71)

*Data are presented as mean ± standard deviation or n (%). BMI = body mass index; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; FPG = fasting plasma glucose.

A

B

*$p < 0.0125$ compared with glyburide
+$p < 0.0125$ compared with metformin

Figure 1. (A) Changes in fasting plasma glucose (FPG) levels from baseline to end of week 16. (B) Changes in glycosylated hemoglobin (HbA1c) concentrations from baseline to end of week 16.

reaching significant difference (both $p < 0.0125$ compared with glyburide and metformin, respectively). In addition, treatment with glyburide/metformin 2.5 mg/500 mg resulted in a 55 mg/dL reduction ($p = 0.001$) in FPG compared to glyburide and a 57 mg/dL lowering in FPG compared to metformin ($p = 0.001$). Glyburide/metformin 5.0 mg/500 mg resulted in a significant lowering of FPG compared to glyburide or metformin alone (−58 mg/dL, $p < 0.001$ and −60 mg/dL, $p = 0.001$).
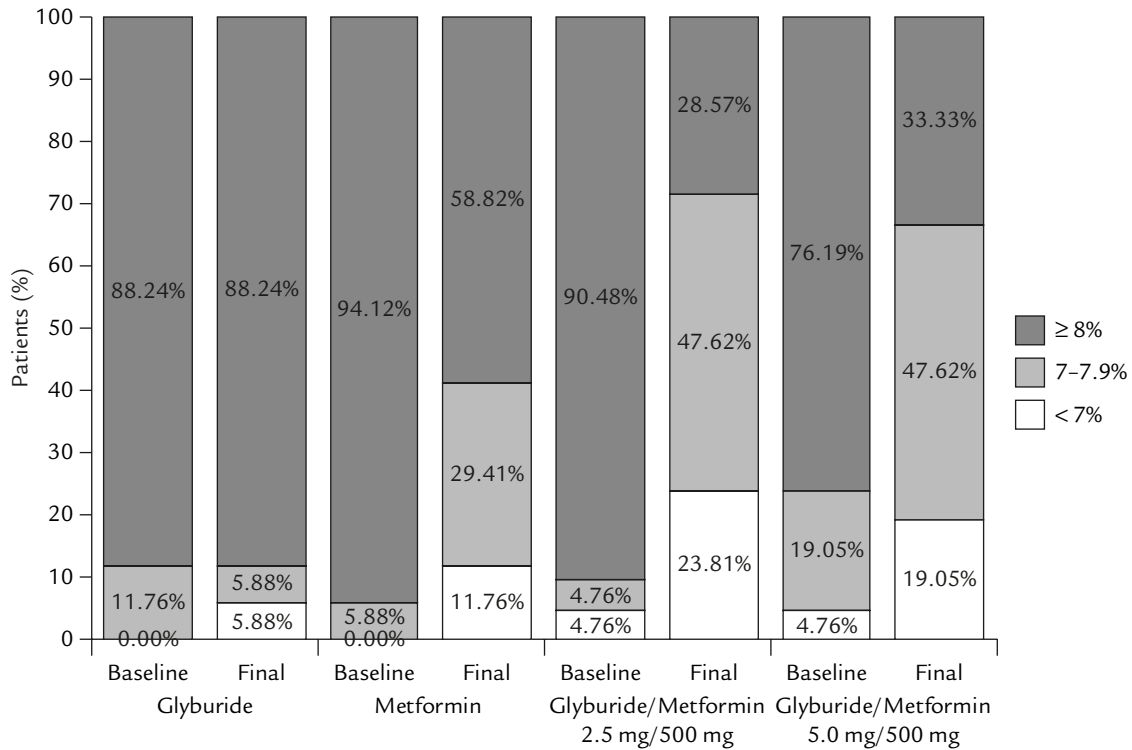
Figure 2. Baseline and final glycosylated hemoglobin (HbA1c) distribution by HbA1c values < 7%, 7–7.9% and ≥ 8%.

HbA1c levels

After 16 weeks of therapy (Figure 1B), statistically significant differences among the 4 treatment groups were observed ($p < 0.001$). Patients who took glyburide had a significant elevation of HbA1c at the end of treatment ($0.52 \pm 0.24\%$, $p = 0018$), while treatment with metformin resulted in no significant change in HbA1c ($0.09 \pm 0.37\%$, $p = NS$). Patients who received glyburide/metformin 2.5 mg/500 mg tablet and glyburide/metformin 5.0 mg/500 mg tablet had significant decreases in HbA1c compared with glyburide and metformin, respectively (both $p < 0.0125$). Furthermore, treatment with glyburide/metformin 2.5 mg/500 mg resulted in significantly greater reduction in HbA1c compared to glyburide or metformin (-1.77%, $p < 0.001$ and -1.34%, $p = 0.002$), and treatment with glyburide/metformin 5.0 mg/500 mg resulted in significant lowering of HbA1c compared to glyburide or metformin alone (-1.73, $p < 0.001$ and -1.30, $p = 0.005$). Respectively, 19% and 24% of patients in the glyburide/metformin groups had an A1c concentration less than 7% relative to 12% in the metformin monotherapy group and 6% in the glyburide monotherapy group (Figure 2). In order to understand the effect of baseline HbA1c on change in HbA1C, we divided baseline HbA1c into 3 groups ($\geq 8\%$, 7.0–7.9%, < 7.0%) (Figure 3). We found that

the higher the baseline HbA1c, the greater the reduction in HbA1c that was seen in the glyburide/metformin groups.

Safety and other effects

Patients who received at least 1 dose of the study drugs were eligible for the safety analysis. This included all 100 patients enrolled at pretreatment (screening) and randomly assigned into the 4 treatment groups.

Ninety-eight episodes of adverse events (categorized by body system and COSTART) were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5 mg/500 mg group, and 2 (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study.

There were statistically significant differences in terms of digestive system and nervous system reactions among the 4 treatment groups during the treatment period (Table 2). The highest incidence of digestive system side effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5 mg/500 mg group ($p = 0.021$). The highest incidence of nervous system side effects was 15.4% in patients who received glyburide/metformin 2.5 mg/500 mg, and
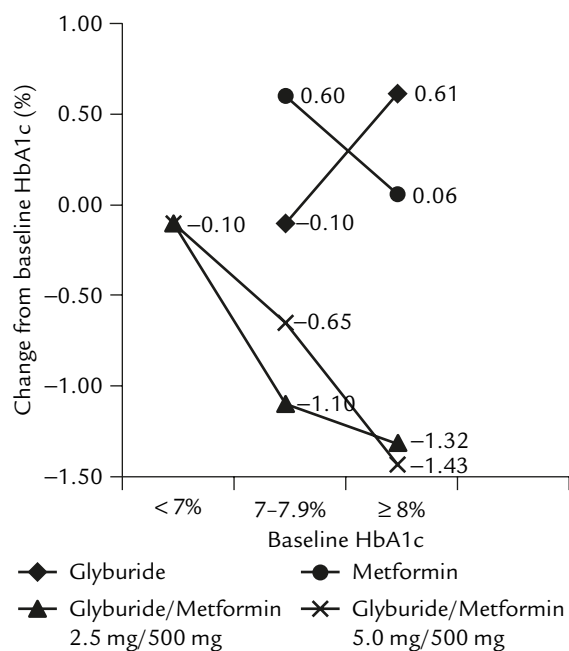
Figure 3. Changes in glycosylated hemoglobin (HbA1c) levels to week 16 stratified by baseline HbA1c levels.

the lowest was 4.0% in patients who took metformin ($p = 0.02$).

No death was reported during the study. Of the 4 serious adverse events (due to left hand cutting injury, right metacarpal bone fracture, hemorrhoid and duodenal ulcer, respectively), 1 was reported at the screening visit and the remainder were experienced by 3 glyburide-treated patients.

With regard to changes in blood pressure, serum biochemistry and urinary albumin values, there were no significant differences before and after treatment among the 4 groups (data not shown).

Discussion

Many patients with type 2 diabetes are unable to achieve or maintain the American Diabetes Association's (ADA) recommended treatment goal of HbA1c levels below 7%.[18] Difficulties in achieving adequate glycemic control may arise, in part, from the current stepwise treatment paradigm, which typically begins with

Table 2. Incidence of common adverse events during the treatment period*[†]

Body system/COSTART	Glyburide[†] (n = 23)	Metformin[†] (n = 25)	Glyburide/metformin 2.5/500 mg[†] (n = 26)	Glyburide/metformin 5.0/500 mg[†] (n = 26)	p
Body as a whole	3 (13.04)	1 (4.00)	5 (19.23)	3 (11.54)	0.329
Asthenia	1 (4.35)	0	1 (3.85)	2 (7.69)	0.719
Back pain	2 (8.70)	0	0	0	0.238
Digestive system	3 (13.04)	8 (32.00)	2 (7.69)	7 (26.92)	0.021
Diarrhea	1 (4.35)	2 (8.00)	1 (3.85)	5 (19.23)	0.133
Dry mouth	0	2 (8.00)	0	0	0.158
Gastrointestinal disease	0	2 (8.00)	0	0	0.158
Increased appetite	0	1 (4.00)	0	2 (7.69)	0.286
Metabolic and nutritional disorders	1 (4.35)	1 (4.00)	3 (11.54)	1 (3.85)	0.663
Musculoskeletal system	2 (8.70)	2 (8.00)	1 (3.85)	1 (3.85)	1.000
Nervous system	0	1 (4.00)	4 (15.38)	0	0.018
Dizziness	0	1 (4.00)	3 (11.54)	0	0.077
Respiratory system	6 (26.09)	6 (24.0)	3 (11.54)	2 (7.69)	0.314
Increased cough	0	2 (8.00)	1 (3.85)	0	0.286
Pharyngitis	3 (13.04)	3 (12.00)	1 (3.85)	1 (3.85)	0.604
Rhinitis	2 (8.70)	1 (4.00)	1 (3.85)	1 (3.85)	1.000
Skin and appendages	1 (4.35)	0	2 (7.69)	2 (7.69)	0.532
Rash	0	0	1 (3.85)	2 (7.69)	0.286
Urogenital system	5 (21.74)	2 (8.00)	1 (3.85)	0	0.115
Urinary tract infection	2 (8.70)	0	0	0	0.238

*Common was defined as when at least 5% of any of the treatment groups had the symptoms; [†]data are presented as n (%); [‡]columns are not additive—number represents the total number of subjects with at least 1 event.

monotherapy after diet and exercise failure, proceeds to oral combination therapy and, eventually, to insulin. The most obvious limitation of this approach is failure to swiftly address the dual pathophysiologic defects, insulin resistance and progressive beta-cell dysfunction, that are present at diagnosis in virtually all patients with type 2 diabetes. Because it is now appreciated that the use of a single antihyperglycemic agent corrects only 1 of these defects, initial monotherapy may be less than optimal for the management of type 2 diabetes. Sulfonylureas enhance insulin secretion, whereas metformin, among other actions, increases insulin sensitivity, resulting in reduced hepatic glucose output and increased glucose uptake in muscle, although serious side effects have been reported.[19] The current ADA practice guidelines recommend early metformin use and lifestyle changes followed by other oral hypoglycemic agents and/or insulin regimen in order to aim at A1c levels less than 7.0%.[18] In patients inadequately controlled by diet and exercise alone, initial therapy with glyburide/metformin tablets provided glycemic control superior to that of glyburide or metformin monotherapy.[5–9] Therefore, the present study was designed without placebo to examine the efficacy of initial therapy with traditional glyburide or metformin monotherapy in patients with more severe hyperglycemia.

Our study found that the single-tablet metformin–glyburide combinations were more effective than either component monotherapy in controlling hyperglycemia in inadequately controlled type 2 diabetes mellitus patients. Treatment with glyburide/metformin 2.5 mg/500 mg resulted in significantly greater reduction in HbA1c compared to glyburide or metformin alone (-1.77%, $p < 0.001$ and -1.34%, $p = 0.002$, respectively), and treatment with glyburide/metformin 5.0 mg/500 mg resulted in a significant lowering of HbA1c compared to glyburide or metformin alone (-1.73%, $p < 0.001$ and -1.30%, $p = 0.005$, respectively). Both combinations also showed statistically significant FPG reductions compared with glyburide or metformin monotherapy. Our findings therefore confirmed the potential of intensified therapy with the single-tablet metformin–glyburide treatment to improve the control of hyperglycemia in this population. The mean final HbA1c achieved in the lower-dose (glyburide/metformin 2.5 mg/500 mg) and higher-dose (glyburide/metformin 5.0 mg/500 mg) combination groups was similar. The slightly smaller change in HbA1c from baseline in the higher-dose (glyburide/metformin 5.0 mg/500 mg) combination group, compared with patients receiving the lower-dose (glyburide/metformin 2.5 mg/500 mg) combination tablet, may be explained by the slightly higher mean HbA1c at baseline in the higher-dose patients (8.9% and 8.7% at baseline, respectively). However, the modest changes in HbA1c in patients randomized to metformin or glyburide monotherapy in this study are consistent with the results of previous clinical studies[9–11] and showed that combination therapy is a more effective management strategy for type 2 diabetes than trying another monotherapy when patients are inadequately controlled by oral antidiabetic monotherapy.[14] A recent report indicated that treatment with glibenclamide–metformin combination tablets provided better insulin responses to oral glucose tolerance test in a group of type 2 diabetes patients, suggesting that combination therapy might confer more benefits on beta cell function compared with glibenclamide therapy.[20]

Although combination therapy was well tolerated, the duration of this study was too short (16 weeks) to provide information on long-term safety. While free combinations of metformin and a sulfonylurea are commonly used in clinical practice, the only available prospective long-term evaluation of such a combination was conducted as a substudy of the UKPDS.[2] This was carried out in 537 patients with hyperglycemia despite maximal sulfonylurea therapy, who were followed-up for an average of 6.6 years. The initial publication of that study revealed an apparent significant ($p = 0.039$) excess of diabetes-related mortality in the combination group compared with patients who received sulfonylurea alone. However, there was no associated increase in morbidity with the combination, and an analysis of the much larger overall UKPDS cohort showed that the apparent increase in mortality in the combination group arose due to an unexpectedly low mortality in the sulfonylurea monotherapy group of the substudy, rather than excess mortality in the combination group.[2] The single-tablet approach used in the present study differs importantly from the use of free combinations, however, as it involved switching from the previously used either high dose of monotherapy or two combined therapy to initial therapy with relatively low doses of metformin and glyburide. As a result, after optimization of the dose of each treatment, the superior antihyperglycemic efficacy of the single-tablet combination treatments was achieved with a lower average exposure of patients to metformin or glyburide compared with patients receiving these agents as monotherapy. We did not measure postprandial glucose levels, which have become more critical in predicting cardiovascular disease in individuals with diabetes.[21,22] Although the action of both sulfonylurea and metformin are not specific to postprandial glucose alterations, the effect of combination tablets on postprandial glucose control merits further evaluation.

Four (14.29%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5 mg/500 mg group. The slightly higher incidence of hypoglycemia in the combination therapy groups is consistent with the greater decreases in plasma glucose observed in these patients. The risk of hypoglycemia is highly dependent on study design, particularly with regard to the severity of hypoglycemia at baseline and the rate of intensification of oral antidiabetic therapy. However, available data from studies evaluating metformin in combination with insulinotropic agents in patients who previously received oral antidiabetic monotherapy suggest that the incidence of hypoglycemia with the combinations was relatively similar to the corresponding incidences with free combinations of metformin with glibenclamide (18%),[3] glimepiride (22%)[15] and repaglinide (33%).[16] Furthermore, the incidence of severe hypoglycemia was low in all of the treatment arms in our study, and no patient experienced hypoglycemia categorized as a serious adverse event.

In conclusion, combining glyburide and metformin in a fixed dose combination tablet may improve adherence by simplifying dosing and reducing the number of doses and/or tablets included in the patients' treatment regimens. Improved adherence may contribute further to improved glycemic control. Therefore, glyburide/metformin tablets are safe and effective in Chinese patients with type 2 diabetes.

Acknowledgments

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