Effect of the combination of mitiglinide and metformin on glycemic control in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Mitiglinide is the newest drug in the meglitinide family. It increases the early-phase insulin release through rapid association-dissociation kinetics in the pancreatic β cells. The efficacy and safety of adding meglitinide to metformin monotherapy in patients with type 2 diabetes are unknown.

Materials and Methods: We carried out a prospective, randomized, multicenter trial to assess the efficacy and safety of combined treatment with mitiglinide and metformin for patients with type 2 diabetes who showed inadequate glycemic control with metformin monotherapy. Subjects with glycated hemoglobin (HbA_{1c}) >7.0% after an 8-week metformin run-in phase were randomized to a 16-week trial phase with metformin plus mitiglinide (Met + Mit) or metformin plus placebo (Met + Pcb).

Results: Compared with the Met + Pcb group, the Met + Mit group showed a greater reduction in HbA_{1c} (−0.7 ± 0.6% *vs* −0.4 ± 0.7%, $P = 0.002$), fasting plasma glucose (−0.77 ± 1.76 mmol/L *vs* −0.05 ± 1.60 mmol/L, $P = 0.015$) and 2-h postprandial glucose (−3.76 ± 3.57 mmol/L *vs* −0.84 ± 3.07 mmol/L, $P < 0.0001$). The proportion of the patients who achieved the target HbA_{1c} value of <7% at the end of the study was also higher in the Met + Mit group than the Met + Pcb group (49.3% *vs* 28.8%, $P = 0.016$). There were no differences in the adverse event rates between groups.

Conclusions: Combination therapy with metformin and mitiglinide is effective and safe for the treatment of patients with type 2 diabetes who have inadequate glycemic control with metformin monotherapy. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00023.x, 2010)

KEY WORDS: Mitiglinide, Metformin, Type 2 diabetes

INTRODUCTION

The progressive nature of pancreatic β cell dysfunction is the key abnormality of type 2 diabetes mellitus, along with decreased insulin sensitivity. Therefore, both abnormalities should be adequately addressed when treating type 2 diabetic patients[1,2]. To this end, the combination of insulin secretogogues and insulin sensitizers would be a good treatment option.

Drugs in the meglitinide family are known to increase the early-phase insulin release without affecting total insulin release through faster association–dissociation kinetics in the pancreatic β cells, compared with sulfonylurea[3–6]. In addition, the inhibition of an ATP-sensitive potassium channel (K_{ATP}) current by repaglinide or nateglinide is enhanced under hyperglycemic conditions. This phenomenon could not be observed with glibenclamide[7]. Mitiglinide is the newest drug in the meglitinide family[8]. It also has a rapid mode of action[9,10] and shows a higher selectivity for pancreatic β cells than other meglitinides, including nateglinide and repaglinide, through a high affinity to SUR1, a subunit of the K_{ATP} in pancreatic β cells[11,12]. In addition, its calcium ionophoretic activity, which results in the stimulation of calcium influx and subsequent insulin secretion[9,10], is greater than that of nateglinide and repaglinide[13].

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The anti-hyperglycemic efficacy of mitiglinide has been shown in combination with basal insulin[14] or premixed insulin[15]. However, the efficacy and safety of the combination of mitiglinide and metformin are currently unknown. In the present study, we carried out a prospective, randomized, multicenter, therapeutic confirmatory clinical trial to assess the efficacy and safety of add-on mitiglinide to metformin in patients with type 2 diabetes who showed inadequate glycemic control with metformin monotherapy.

MATERIALS AND METHODS

Enrolled Subjects

Subjects with type 2 diabetes were screened and enrolled if they were aged 30–70 years, had a duration of diabetes of <10 years, body mass index (BMI) of 20–35 kg/m^2 and a plasma glycated hemoglobin (HbA_{1c}) level of 7.5–11% during the previous 4 weeks. We excluded subjects who were diagnosed with type 1 diabetes, gestational diabetes or diabetes with any specific causes. Subjects who had been treated with nateglinide, repaglinide, metformin (over 1000 mg/day), or sulfonylurea (over one-quarter of the maximum recommended dose) during the previous 8 weeks were also excluded. In addition, subjects with a fasting plasma glucose (FPG) level >13.9 mmol/L, a history of lactic acidosis or other contraindications for metformin, hepatic disease or an alanine aminotransferase (ALT) level ≥2.5-fold of the upper normal limit, impaired renal function with an elevated creatinine level >1.5 mg/dL in males or 1.4 mg/dL in females, severe complications of diabetes requiring additional treatment, uncontrolled hypertension with diastolic blood pressure >110 mmHg, cardiovascular or pulmonary diseases, a history of drug abuse or allergy, or anticipated changes in concomitant medication affecting glucose homeostasis were not eligible for the present study. The protocol was approved by local institutional review boards, and subjects provided written informed consent before the initiation of any trial-related activities.

Study Design and Methods

This was a 16-week, randomized, double-blind study for comparing metformin plus mitiglinide (Met + Mit) *vs* metformin plus placebo (Me t+ Pcb). The present study is registered with ClinicalTrials.gov, number NCT01037842. An 8-week metformin run-in phase (500 mg twice a day for the first 4 weeks and 500 mg three times a day for the following 4 weeks) was followed by a 16-week trial phase (mitiglinide 10 mg or placebo three times a day in addition to metformin 500 mg three times a day). The subjects with a HbA_{1c} level of >7.0% at the end of the metformin run-in phase were randomized to a Met + Mit group or a Met + Pcb group of the trial phase.

The primary end-point was the change in HbA_{1c} level at the end of the study. Secondary end-points were the proportion of subjects who attained a HbA_{1c} level of <7.0% and changes in FPG and 2-h postprandial glucose (PPG). The population used for analyzing efficacy evaluation – the intention-to-treat (ITT) population – was defined as those who had at least one measurement of any efficacy parameters among the randomized subjects. The trial subjects visited the clinic every 4 weeks and their plasma HbA_{1c} and FPG levels were measured at each visit. A standardized liquid meal challenge test (400 kcal in 400 mL; 58 g of carbohydrates, 12 g of fat, and 22 g of protein) was carried out at baseline and at the 16-week visit. Mitiglinide or placebo was given 10 min before the test meal.

Investigators measured bodyweight, blood pressure and heart rate, and assessed the presence of adverse events at each visit. Routine complete blood count, plasma creatinine, aspartate aminotransferase (AST), ALT and urinalysis were also carried out to monitor the safety. A hypoglycemic episode was defined as symptoms of hypoglycemia that resolved with oral carbohydrate intake or any symptomatic or asymptomatic blood glucose concentration <2.8 mmol/L. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring any assistance from other people that were associated with a blood glucose concentration <2.0 mmol/L, or recovery after glucagon or intravenous glucose administration. Safety was evaluated for all patients making at least one visit after starting study medication.

Statistical Analysis

The minimum clinically relevant treatment difference in HbA_{1c} between groups was assumed to be 0.5% and the standard deviation (SD) to be 1.0. With 80% power and 5% type I error rate, a sample size of 63 per treatment group was required to detect the specified difference between the two treatment groups. Assuming an overall dropout rate of 15% and a 1:1 randomization ratio, we enrolled 75 subjects in each treatment group.

Statistical analyses were carried out using SAS software version 9.1 (SAS Institute, Cary, NC, USA). Student's *t*-tests and χ^2-tests were carried out where appropriate. $P < 0.05$ was considered to be statistically significant.

RESULTS

Demographic Information of the Subjects

We carried out a prospective, randomized, multicenter trial to assess the efficacy and safety of combined treatment with mitiglinide and metformin for patients with type 2 diabetes who showed inadequate glycemic control with metformin monotherapy (Figure 1). We screened 270 subjects and finally included 138 subjects in the ITT population: 70 for the Met + Mit group and 68 for the Met + Pcb group. The total numbers of patients who did not complete the 16-week trial did not differ significantly between the Met + Mit group (n = 10, 14.3%) and the Met + Pcb group (n = 12, 17.6%; Figure 1). The mean (±SD) age was 51 ± 9 years, BMI was 25.2 ± 2.7 kg/m^2 and the duration of diabetes was 4 ± 3 years; there were no significant differences in these parameters between the two groups (Table 1). At the time of enrolment, 45 subjects in the Met + Mit group and 36 in the Met + Pcb group were taking oral antidiabetic drugs (OAD), where the most commonly prescribed OAD was metformin (48.6% in the Met + Mit group and 47.1% in the Met + Pcb group; Table 1). There were 19 subjects taking OAD

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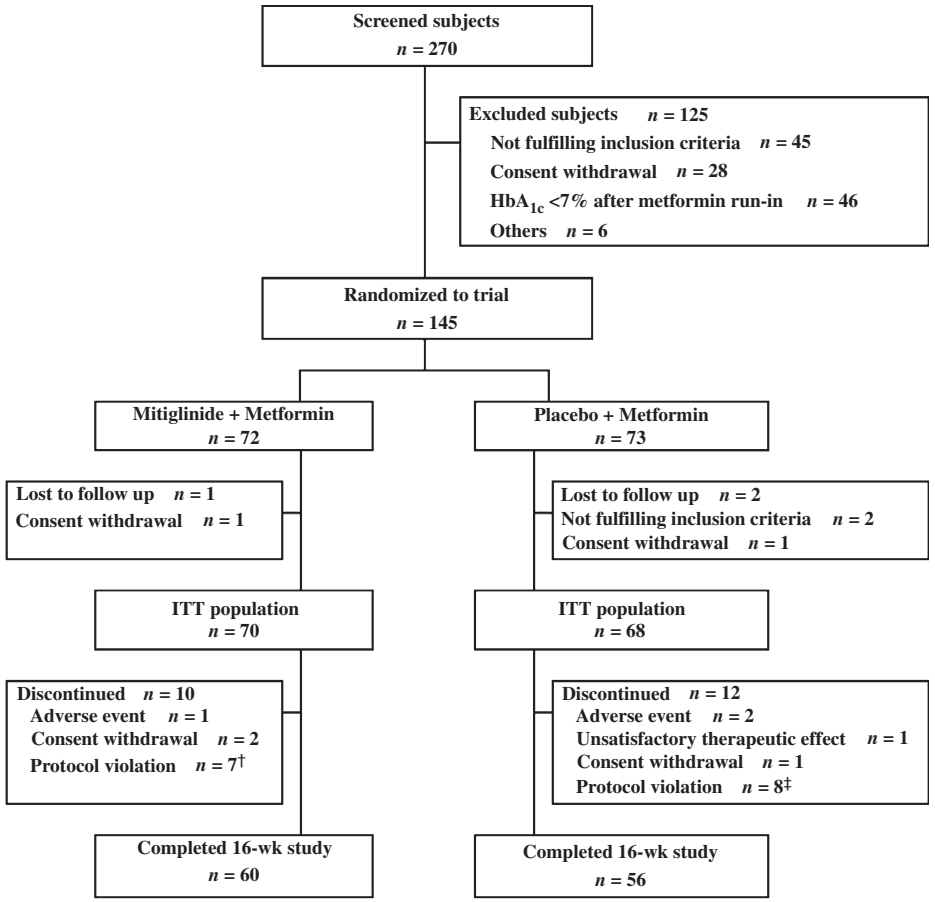

Figure 1 | Enrolment and outcomes. †Protocol violation included no-shows for scheduled visits (n = 6) and non-adherence to study medication (n = 1). ‡Protocol violation included no-shows for scheduled visits (n = 7) and non-adherence to study medication (n = 1). HbA_{1c}, glycated hemoglobin; ITT, intention-to-treat.

Table 1 | Demographic characteristics of the subjects in the intention-to-treat population

Characteristics	Met + Pcb	Met + Mit
n	68	70
Sex (male/female)	34/34	40/30
Age (years)	50.0 ± 8.9	52.1 ± 8.5
Bodyweight (kg)	68.4 ± 11.0	66.9 ± 9.8
BMI (kg/m^2)	25.7 ± 2.6	24.8 ± 2.6
Duration of diabetes (years)	4 ± 3	4 ± 3
Medication for glucose control		
None	32 (47.1)	25 (35.7)
Biguanide	32 (47.1)	34 (48.6)
Sulfonylureas	19 (27.9)	27 (38.6)
Thiazolidinediones	1 (1.5)	2 (2.9)
Alpha glucosidase inhibitors	5 (7.4)	5 (7.1)

Data are mean ± SD or *n* (%).
BMI, body mass index; Met + Mit, metformin plus mitiglinide; Met + Pcb, metformin plus placebo.

combination therapy in the Met + Mit group and 15 in the Met + Pcb group. There were no statistical differences in the frequencies of OAD prescription or the prevalence of chronic complications of diabetes at the time of randomization between groups (data not shown).

Efficacy

The mean decrease in HbA_{1c} at the end of the study (week 16) was significantly greater in the Met + Mit group than in the Met + Pcb group (−0.7 ± 0.6% and −0.4 ± 0.7%, respectively, P = 0.002; Figure 2). The proportion of patients who achieved the target HbA_{1c} value of <7.0% at the end of the study was also higher in the Met + Mit group than in the Met + Pcb group [49.3% (33/67) *vs* 28.8% (19/66), P = 0.016]. Compared with the Met + Pcb group, the Met + Mit group showed a greater reduction in FPG (−0.77 ± 1.76 mmol/L *vs* −0.05 ± 1.60 mmol/L, P = 0.015) and in 1-h and 2-h PPG values during the liquid meal challenge test (−2.10 ± 3.04 mmol/L *vs* −0.45 ± 2.40 mmol/L and −3.76 ± 3.57 mmol/L *vs* −0.84 ± 3.07 mmol/L, respectively;

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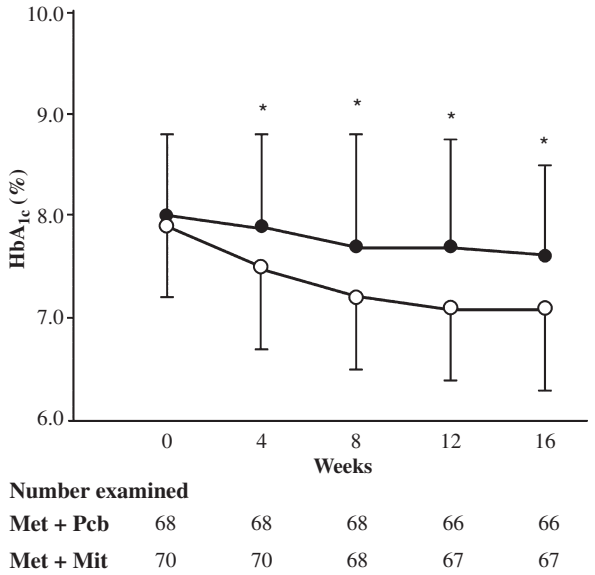

Figure 2 | The changes in plasma glycated hemoglobin (HbA_{1c}) level after randomization. Open circles denote the metformin plus mitiglinide group and closed circles denote the metformin plus placebo group. *$P < 0.05$. ITT, intention-to-treat.

Table 2 | Changes in glycemic control during 16 weeks of treatment

	Met + Pcb	Met + Mit
HbA_{1c} (%)		
Baseline	8.0 ± 0.8	7.9 ± 0.7
End of study	7.7 ± 1.0	7.1 ± 0.8
Change from baseline	−0.4 ± 0.7	−0.7 ± 0.6*
FPG (mmol/L)		
Baseline	8.03 ± 2.00	7.80 ± 2.09
End of study	8.00 ± 1.76	7.05 ± 1.52
Change from baseline	−0.05 ± 1.60	−0.77 ± 1.76*
1-h PPG (mmol/L)		
Baseline	14.79 ± 3.09	14.43 ± 2.54
End of study	14.30 ± 3.14	12.21 ± 2.29
Change from baseline	−0.45 ± 2.40	−2.10 ± 3.04*
2-h PPG (mmol/L)		
Baseline	12.74 ± 3.37	13.07 ± 2.86
End of study	11.91 ± 3.46	9.22 ± 3.02
Change from baseline	−0.84 ± 3.07	−3.76 ± 3.57**
Achievement of treatment goal		
Patients with HbA_{1c} <7.0% at the end of the study (%)	19/66 (28.8)	33/67 (49.3)*

Data are mean ± SD or *n* (%).
FPG, fasting plasma glucose; Met + Mit, metformin plus mitiglinide; Met + Pcb, metformin plus placebo; PPG, postprandial glucose after liquid meal challenge.
*$P < 0.05$ *vs* Met + Pcb; **$P < 0.0001$ *vs* Met + Pcb.

both $P < 0.001$; Table 2). At the end of the present study, the proportion of patients who had 2-h PPG values of <11.1 mmol/L was significantly higher in the Met + Mit group than the Met + Pcb group [76.6% (49/64) *vs* 45.3% (29/64), $P < 0.001$].

Table 3 | Safety results

	Met + Pcb (*n* = 71)	Met + Mit (*n* = 71)
Adverse events	22 (31.0)	21 (29.6)
Drug-related clinical adverse events	8 (11.3)	6 (8.5)
ALT/AST increase	3 (4.2)	0 (0.0)
Hypoglycemia	0 (0.0)	1 (1.4)
Abdominal discomfort or pain	2 (2.8)	2 (2.8)
Diarrhea	4 (5.6)	2 (2.8)
Loose stool	4 (5.6)	3 (4.2)
Anorexia	1 (1.4)	0 (0.0)
Serious adverse events	0 (0.0)	2 (2.8)
Herpes zoster	0 (0.0)	1 (1.4)
Transient ischemic attack	0 (0.0)	1 (1.4)

Data are *n* (%).
Met + Pcb, metformin plus placebo; Met + Mit, metformin plus mitiglinide; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Safety

Among 142 patients (71 in the Met + Mit group and 71 in the Met + Pcb group) who were treated with the trial medication at least once, there were no differences in the adverse event rates: 21 (29.6%) in the Met + Mit group and 22 (31.0%) in the Met + Pcb group (Table 3). There were no significant changes in the levels of plasma creatinine or AST. One case of herpes zoster and one case of transient ischemic attack were reported in the Met + Mit group, which were not regarded to be related to the study medication. One case of hypoglycemia with mild symptoms occurred in the Met + Mit group, whereas no hypoglycemia was reported in the Met + Pcb group. There was no weight change in either group over 16 weeks (−0.1 ± 1.7 kg in the Met + Mit group and −0.5 ± 1.7 kg in the Met + Pcb group, $P = 0.218$).

DISCUSSION

To our knowledge, the present study is the first prospective evaluation specifically examining the efficacy and safety of giving mitiglinide to patients with inadequate glycemic control with metformin monotherapy. Mitiglinide effectively decreased HbA_{1c} levels at the end of the study and showed a higher rate of achieving the target HbA_{1c} of <7.0%. In addition, mitiglinide improved both fasting and postprandial hyperglycemia, and did not increase adverse events compared with the placebo. Therefore, the efficacy and safety of mitiglinide in combination with metformin were comparable with those of other members of the meglitinide family (repaglinide and nateglinide)[16–18].

Type 2 diabetes is characterized by two major pathophysiological defects: pancreatic β cell dysfunction and insulin resistance in the skeletal muscle, fat and liver[19]. Metformin suppresses glucose production in the liver[20,21] and improves insulin resistance in the skeletal muscle through the activation of AMP-activated protein kinase and other yet unidentified

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mechanisms[20,22]. Metformin monotherapy is known to reduce FPG by approximately 2.0 mmol/L and HbA_{1c} by approximately 1.5%[23,24]. However, a gradual deterioration in glycemic control is commonly observed in subjects receiving metformin monotherapy, which is related to progressive β cell failure[25]. One of the earliest signs of pancreatic β cell dysfunction in type 2 diabetes is the loss of early phase insulin release[26–28]. In this regard, meglitinide can restore the early phase insulin release from pancreatic β cells more effectively than sulfonylureas[3–5,7]. This is particularly important in that the early phase insulin release after meal inhibits endogenous glucose production and thereby plays a critical role in the maintenance of postprandial glucose homeostasis[29–31]. Therefore, the combination of meglitinide and metformin would be a good treatment option for better glycemic control[16,17], which was well shown in the current study. In this regard, mitiglinide added to pioglitazone, another insulin sensitizer, also showed successful glucose control in Japanese subject[32], which further indicates the usefulness of the combination of mitiglinide and insulin sensitizer.

In the present study, the absolute HbA_{1c} difference between Met + Mit and Met + Pcb groups at week 6 was 0.3%, which is a rather modest effect compared with other studies examining the HbA_{1c} lowering effect of glinide drugs in combination with metformin (ΔHbA_{1c} was 1.08% with repaglinide[17] and 0.4–0.6% with nateglinide[18,33]). The differences in the HbA_{1c} lowering effect could be explained by differing potency. However, in the studies with repaglinide and nateglinide, the HbA_{1c} values achieved at the end of the study were similar to that of our current study, whereas the baseline HbA_{1c} values were higher than that of ours. Because the subjects of the previous studies[17,18] were Caucasians, and their BMI was higher than that of our study subjects, different demographic factors should be considered when comparing the glucose-lowering efficacy between drugs.

We showed that mitiglinide effectively controlled postprandial hyperglycemia, which is known as an independent risk factor of cardiovascular diseases[34–36]. Controlling postprandial hyperglycemia with mitiglinide was shown to improve the markers of both oxidative stress and inflammation, which are well-known pathophysiological mechanisms of cardiovascular diseases in diabetic patients[37]. In addition, mitiglinide was shown to have cardioprotective effects through a process called ischemic preconditioning regardless of hyperglycemia in an animal model[38], which implies that it might have a beneficial effect on myocardial ischemia in diabetic patients.

In conclusion, combination therapy with metformin and mitiglinide is effective and safe for the treatment of the type 2 diabetic patients, who show inadequate glycemic control with metformin monotherapy. Given that postprandial hyperglycemia is very important in the development of cardiovascular diseases, further clinical studies are needed to examine the effect of mitiglinide on cardiovascular outcomes in type 2 diabetic patients.

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