Effect of Mitiglinide on Glycemic Control over 52 Weeks in Japanese Type 2 Diabetic Patients Insufficiently Controlled with Pioglitazone Monotherapy

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Abstract. This study was performed to examine the efficacy and safety of the rapid- and short-acting insulinotropic SUR ligand mitiglinide given as add-on therapy for 52 weeks in type 2 diabetic patients whose blood glucose was insufficiently controlled by pioglitazone monotherapy. Type 2 diabetic patients aged ≥ 20 years with postprandial plasma glucose (PPG1 or 2) ≥ 200 mg/dL and glycated hemoglobin (HbA_{1c}) 6.5– $<9.0\%$ despite receiving pioglitazone 15–45 mg/day were additionally treated with concomitant mitiglinide 10 mg tid p.o. for a total treatment period of 52 weeks. In 171 patients recruited, HbA_{1c} was significantly reduced from $7.64 \pm 0.77\%$ at baseline to $6.84 \pm 0.73\%$, $6.64 \pm 0.64\%$, $6.67 \pm 0.57\%$ and $6.81 \pm 0.65\%$ at weeks 16, 28, 40, and 52, respectively. Over half the patients achieved HbA_{1c} target of $<7.0\%$, and one third $<6.5\%$. Significant reductions in fasting plasma glucose (FPG) and PPG 1 and 2 hours after a meal versus baseline were noted at all time-points evaluated. The most frequently noted adverse reactions were hypoglycemic symptoms, weight gain, and peripheral edema (all mild). In type 2 diabetic patients combination therapy with mitiglinide and pioglitazone exerted significant long-term improvements in HbA_{1c}, FPG, and PPG and was well tolerated. This drug combination therapy is a promising means of alleviating insufficient pancreatic insulin secretion and insulin resistance.

Key words: Type 2 diabetes, Mitiglinide, Pioglitazone, Combination therapy

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TYPE 2 diabetes mellitus is a syndrome involving insufficient insulin secretion from pancreatic β -cells and insulin resistance in peripheral tissues [1]. Patients with this disease often have postprandial hyperglycemia because rapid additional secretion of insulin after meals is insufficient, and a vicious circle of glucotoxicity leading to protracted and advanced hyperglycemia arises when this condition continues.

It has become clear from large-scale clinical studies that postprandial hyperglycemia is a risk factor for arteriosclerosis independent of hypertension and hy-

perlipidemia [2, 3]. In the STOP-NIDDM trial [4] it was shown that improvement in postprandial hyperglycemia exerted by α -glucosidase inhibitors in patients with impaired glucose tolerance (IGT) delays the onset of cardiovascular events, and the importance of correction of postprandial hyperglycemia on limiting the progression of diabetes as well as preventing the onset of macrovascular diseases was thus suggested.

At present, sulfonylurea (SU) agents and rapid- and short-acting insulinotropic SU receptor (SUR) ligands are used to supplement insufficient insulin secretion in type 2 diabetic patients. SU agents have strong hypoglycemic actions, but are ineffective at promoting additional secretion of insulin after meals. In addition, these agents are known to induce protracted hypoglycemia and obesity is a problem associated with their use. Mitiglinide is a new rapid- and short-acting insulinotropic SUR ligand, a benzylsuccinic acid deriva-

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tive developed in Japan, which features rapid hypoglycemic action unlike SU agents [5–7]. It alleviates postprandial hyperglycemia and as a result improves glycemic control as a whole [8]. Since the blood concentration rapidly rises after oral administration then quickly disappears, the drug is thought unlikely to exert hypoglycemic effects early in the morning and between meals. Moreover, mitiglinide shows potent affinity to and selective action on the K_{ATP} channel (Kir6.2/SUR1) [9], suggesting that it acts specifically on pancreatic β -cells to secrete insulin and has few unwanted effects on the cardiovascular system.

Pioglitazone, a thiazolidinedione derivative, is a hypoglycemic agent that improves insulin resistance and is widely used in the treatment of type 2 diabetes. In postmarketing studies [10] and large-scale clinical studies [11] performed in recent years, it was reported that pioglitazone elicits safe glycemic control and inhibits the onset of cardiovascular disorders.

The present study was performed to examine the efficacy and safety of mitiglinide given as add-on therapy for 52 weeks in type 2 diabetic patients who were insufficiently controlled by pioglitazone monotherapy.

Materials and Methods

Patients

Included in this study were Japanese type 2 diabetic patients aged ≥ 20 years who did not show adequate glycemic control defined as having a 1- or 2-hour postprandial glucose (PPG1 or PPG2) value ≥ 200 mg/dL with a meal of 400 kcal despite receiving treatment for ≥ 8 weeks (56 days) with pioglitazone monotherapy at a fixed dose (15, 30, or 45 mg/day) in addition to diet therapy and whose glycated hemoglobin (HbA_{1C}) at screening visit (week –4) was $6.5\text{--}9.0\%$. Patients with a history of treatment with pioglitazone and high-dose SU agents within 24 weeks (168 days) before screening and those requiring insulin therapy were excluded, as were patients with severe diabetic complications (neuropathy, retinopathy, and nephropathy), severe liver disease, renal dysfunction, hypertension, and heart disease.

This study was performed in compliance with GCP; all subjects provided written informed consent to participate prior to its commencement. Appropriate institutional review boards approved the study.

Study design

This was an open label study that consisted of a pretreatment observation period lasting 4 weeks and a 52-week treatment period. During the 4-week observation period, a fixed dose of pioglitazone (15, 30, or 45 mg/day) was administered orally before or after breakfast. Eligible patients who met the inclusion criteria during the observation period then continued pioglitazone monotherapy at the same dosage and additionally received mitiglinide 10 mg tid po immediately (within 5 min) before each meal. Thereafter, if HbA_{1C} after 12 weeks of continuous administration did not reach the target value ($<7.0\%$ if $\geq 7.0\%$ at start of administration [week 0] or $<6.5\%$ if $<7.0\%$ at week 0), the dosage of mitiglinide could be increased to 20 mg tid from week 16 so as to attempt further improvement. On the other hand, if the physician judged that mitiglinide 10 mg tid presented a safety problem, it could be reduced to 5 mg tid.

During both the observation and treatment periods concomitant use of oral hypoglycemic agents other than the test agents and insulin products was prohibited whereas administration and dosage of drugs used from before the study for treatment of complications was not changed whenever possible.

Patient characteristics were examined at screening (week –4). HbA_{1C} , FPG, hematology, blood chemistry and urinalysis values, body weight, and blood pressure were assessed every 4 weeks from week –4 to week 52. PPG1 and PPG2 were measured at weeks –4, 16, 28, and 52. The meal tolerance test at screening was performed by administration of pioglitazone and from after week 16 by that of pioglitazone plus mitiglinide.

Study evaluations

Efficacy endpoints were HbA_{1C} , change in HbA_{1C} at each evaluation point from that measured at week 4 after addition of mitiglinide, therapeutic achievement rate of HbA_{1C} target, and measured values of and changes in FPG, PPG1, and PPG2.

Safety endpoints were incidence rates of adverse events including hypoglycemic episodes and adverse drug reactions.

Statistical analysis

Summary statistics were calculated for efficacy and

Fig. 1. Patients' disposition

safety endpoints. Intragroup comparisons of HbA_{1c} were performed by one-sample t-test with week 0 values as control. Therapeutic achievement rate of HbA_{1c} target was assessed by calculating two-sided 95%CI. Summary statistics of measured values of FPG, PPG1, and PPG2 from week -4 were calculated, and changes in these parameters from week 4 were also compiled as summary statistics. Intragroup comparison was performed by one-sample t-test with week -4 (PPG1 and PPG2) or week 0 (FPG) values as control.

Results

Patients

Figure 1 shows the disposition of patients in this study. A total of 171 patients were eligible for enrollment in this study and received test medication; they included 103 patients who maintained a mitiglinide dosage of 10 mg tid until completion of the study, 8 patients whose dosage was decreased to 5 mg tid, and 60 patients who were increased to 20 mg tid. Ten patients discontinued due to insufficient effects; 9 discontinued because HbA_{1c} was >8.0% at 2 consecutive measurements after week 28 despite a dose increase to 20 mg (one of the study withdrawal criterions), and 1 withdrew after mitiglinide 10 mg did not achieve target HbA_{1c} level, but was not then increased to 20 mg

Table 1. Patient baseline characteristics

Parameter	n (or mean $\pm$ SD)
No. of patients	170
Sex, Male/Female	120/50
Age, years	60.1 $\pm$ 10.1
Pioglitazone dosage, mg/day	
15	79
30	91
45	—
BMI, kg/m ²	25.33 $\pm$ 4.33
Duration of diabetes, years	6.6 $\pm$ 5.8
HbA _{1c} , %	7.64 $\pm$ 0.77
FPG, mg/dL	160.1 $\pm$ 27.4
PPG1, mg/dL	269.0 $\pm$ 40.7
PPG2, mg/dL	253.5 $\pm$ 56.8
Fasting serum insulin, μ U/mL	7.807 $\pm$ 5.934
Adiponectin, μ g/mL	16.13 $\pm$ 9.88

BMI, body mass index; FPG, fasting plasma glucose; PPG1, postprandial plasma glucose at 1 hour after a meal; PPG2, postprandial plasma glucose at 2 hours after a meal.

as specified in the study protocol because of hypoglycemic symptoms during administration of mitiglinide 10 mg. One patient who maintained a dose of 10 mg tid was excluded from the full analysis set (FAS) because evaluable HbA_{1c} data were missing. In the FAS, 142 patients completed 52 weeks of treatment.

Table 1 shows the patient characteristics as demographic statistics in the FAS, the main population for the efficacy analysis.

Fig. 2. Time-course of changes in HbA_{1c}. * $p < 0.001$.

Fig. 3. Achievement rate of HbA_{1c} targets <7.0% and <6.5%.

Efficacy

Figure 2 shows the time-course of HbA_{1c} in the FAS. At screening (week -4) and baseline (week 0), HbA_{1c} was $7.61 \pm 0.61\%$ and $7.64 \pm 0.77\%$, respectively, whereas at weeks 16, 28, 40, and 52 HbA_{1c} was reduced to $6.84 \pm 0.73\%$, $6.64 \pm 0.64\%$, $6.67 \pm 0.66\%$, and $6.81 \pm 0.65\%$, respectively. Addition of mitiglinide to pioglitazone therapy exerted significant reductions in this parameter starting from week 4 and persistently thereafter until the end of the 52-week

treatment period.

The percentage of patients whose HbA_{1c} reached therapeutic target levels at each evaluation is shown in Figure 3. Throughout the study, achievement rate of HbA_{1c} <7.0% ranged from 53.6–69.8% whereas that of the <6.5% target was 27.1–38.6%.

Change in HbA_{1c} in patients stratified by their final dose of mitiglinide is shown in Figure 4. In the 104 patients who were maintained at the 10-mg dose throughout the study (baseline HbA_{1c}, 7.42 ± 0.65) reduction in HbA_{1c} at weeks 16, 28, 40, and 52 was

Table 2. Baseline and mean change in fasting plasma glucose (FPG) and postprandial plasma glucose at 1 hour (PPG1) and 2 hour (PPG2) after a meal at weeks 16, 28, and 52 and final evaluation

	FPG, mg/dL		PPG1, mg/dL		PPG2, mg/dL	
	Change	<i>p</i> value	Change	<i>p</i> value	Change	<i>p</i> value
Week 16	-20.0 ± 24.0	<0.001	-58.5 ± 38.0	<0.001	-57.8 ± 48.4	<0.001
Week 28	-23.5 ± 24.5	<0.001	-64.2 ± 42.3	<0.001	-63.6 ± 50.4	<0.001
Week 52	-16.9 ± 27.2	<0.001	-57.8 ± 43.9	<0.001	-54.9 ± 54.8	<0.001
Final evaluation	-17.2 ± 29.0	<0.001	-57.5 ± 45.9	<0.001	-54.3 ± 54.7	<0.001

Fig. 4. Subgroup analysis of change in HbA_{1c} in patients who were maintained at mitiglinide 10 mg tid (A) and who did not achieve target levels and whose dosage was increased to 20 mg tid at 16 weeks (B). **p*<0.001.

$-0.92 \pm 0.61\%$, $-1.01 \pm 0.58\%$, $-0.91 \pm 0.65\%$, and $-0.75 \pm 0.62\%$, respectively (all $p < 0.001$; Fig. 4A). Whereas, in those whose dose was up-titrated to the 20-mg dose ($n = 58$; baseline $\text{HbA}_{1\text{C}}$, $8.13 \pm 0.76\%$), although the change in $\text{HbA}_{1\text{C}}$ at week 16 ($-0.63 \pm 0.62\%$) was lower than that observed in patients whose dose was maintained at 10 mg, significant ($p < 0.001$) changes in $\text{HbA}_{1\text{C}}$ were noted following dose increase ($-1.02 \pm 0.74\%$, $-1.03 \pm 0.79\%$, and $-0.87 \pm 0.91\%$ at weeks 28, 40, and 52, respectively; Fig. 4B).

As shown in Table 2, significant reductions in FPG, PPG1, and PPG2 versus baseline were noted at all time-points evaluated.

Safety

In this study a total of 15 patients discontinued due to adverse events. Of these patients, 9 experienced adverse drug reactions of which a causal relation to mitiglinide could not be ruled out. Among them, 6 patients discontinued before week 16 of mitiglinide treatment and 3 at week 16 or later. Adverse drug reactions that caused discontinuation were "edema" in 3 patients; "increased AST" and "increased ALT"; "pancreatic carcinoma" ("metastases to liver"); "palpitations" and "thirst"; "pain"; "constipation," "insomnia," and "dry tongue"; and "edema," "weight gain," and "increased BNP" in 1 patient each.

The overall incidence of adverse drug reactions was 57.3%, with clinical symptoms and abnormal laboratory findings noted in 41.5% and 33.9%, respectively. Adverse clinical symptoms with an incidence of $\geq 3.0\%$ included hypoglycemic symptoms such as dizziness, cold sweats and feeling abnormal, weight gain, and peripheral edema; abnormal laboratory findings occurring in $\geq 3.0\%$ included elevated brain natriuretic peptide (BNP), creatine kinase (CK), and urine occult blood. Sixty-two of 68 hypoglycemic symptoms were judged mild, as were most weight gain (15/16 events) and eyelid, face, and peripheral edema (21/23 events). Mean body weight increased by approximately 1.3 kg from 67.2 ± 13.3 kg at baseline to 68.5 ± 13.3 kg at 52 weeks, and no severe edema was reported.

Increased BNP (15.4%) and increased CK (5.9%) although relatively frequent were not in the range that would cause clinical problems.

Discussion

The aim of treatment in most patients with type 2 diabetes mellitus is to improve both insufficient insulin secretion and insulin resistance and thereby achieve glycemic control. Based on encouraging data we obtained in a previous 16-week, double blind study (manuscript in preparation) this study was performed to investigate the efficacy and safety of adding mitiglinide 10 mg/day to the regimens of patients on pioglitazone monotherapy over a long treatment period.

We observed significant improvement in $\text{HbA}_{1\text{C}}$, the main efficacy endpoint, starting from week 4 of administration through to study end. Change in $\text{HbA}_{1\text{C}}$ at weeks 28 and 52 was $-1.01 \pm 0.65\%$ and $-0.78 \pm 0.73\%$, respectively; thus long-term improvement of this parameter was confirmed. It was also possible to achieve American Diabetes Association [12]-recommended $\text{HbA}_{1\text{C}}$ target of $<7.0\%$ in over half our patients and $<6.5\%$ in about one third.

With the addition of mitiglinide to pioglitazone, not only improvement in $\text{HbA}_{1\text{C}}$ but also amelioration of postprandial hyperglycemia was confirmed and this beneficial effect continued for 52 weeks. It has been reported that intermittent hyperglycemia (glucose spikes) induces apoptosis of vascular endothelial cells when compared with persistent hyperglycemia [13] and that mitiglinide inhibits markers of oxidative stress and inflammation caused by postprandial hyperglycemia [14]. Continuous improvement in postprandial hyperglycemia over the long term as confirmed in this study is considered highly significant clinically. Postprandial hyperglycemia has also been reported as a primary factor affecting glycemic control in mild-to-moderate type 2 diabetic patients [15]; therefore its alleviation from an early stage of the disease is considered important in preventing progression to more severe diabetes.

In the safety evaluation in this study, the hypoglycemic symptoms in this study were mostly mild (62/68 incidents) and presented no clinical problems. Furthermore, the appearance of hypoglycemic symptoms did not increase along with the period of administration of mitiglinide.

Weight gain, which often presents a problem associated with glitazone and SU agents, was about 1.3 kg over 52 weeks of combination therapy, which is mild compared with published reports of weight gain amounting to 2–6 kg associated with combinations of

a rapid- and short-acting insulinotropic SUR ligand and thiazolidinedione derivative to improve insulin resistance [16–18]. Edema observed in this study was mostly mild (21/23 incidents) and did not present any clinical problem. Since no dose-dependent increase in edema was found in a previous study of mitiglinide, there appears almost no risk that adding this agent to pioglitazone regimens will cause this unwanted event.

The above findings indicate that in type 2 diabetic patients with insufficient pancreatic insulin secretion and insulin resistance as main presenting features,

combination therapy with mitiglinide and pioglitazone aimed at alleviating both of these pathologies is a promising therapeutic strategy that evokes long-term improvement in HbA_{1c}, PPG, and FPG.

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