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Therapeutic Efficacy of Mitiglinide Combined with Once Daily Insulin Glargine after Switching from Multiple Daily Insulin Regimen of Aspart Insulin and Glargine in Patients with Type 2 Diabetes Mellitus

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Abstract. Mitiglinide is novel class of rapid-acting insulin secretagogues, which have been widely used alone or in combination with other oral hypoglycemic drugs to improve postprandial hyperglycemia in early type 2 diabetes. While mitiglinide enhances postprandial requirement of insulin, the efficacy of mitiglinide combined with insulin has yet to be established. We investigated the efficacy of mitiglinide combined with insulin glargine, the first soluble insulin analog that has a flat and prolonged effect. After control with the intensive regimen (daily aspart insulin and glargine), 30 inpatients with type 2 diabetes were switched to premeal mitiglinide combined with once daily insulin glargine (mitiglinide regimen), and daily profiles of blood glucose level were compared under each regimen. Fifteen patients showed similar control of hyperglycemia with mitiglinide regimen and intensive insulin regimen, assessed by M value (<32), while the remaining 15 showed worsening under the mitiglinide regimen. The patients who were well controlled with mitiglinide regimen were significantly younger (51.9 ± 16.0 years, $p<0.005$) and heavier (body mass index: 25.7 ± 3.3 kg/m^2, $p<0.05$) than those who were not (67.9 ± 8.7 and 23.0 ± 3.1, respectively). Moreover, insulin doses of aspart per body weight were significantly fewer in effective group than in ineffective group. Duration of diabetes was shorter in the effective group, albeit insignificantly. Previous treatment before starting intensive insulin regimen, such as insulin and sulfonylurea, was not different between the two groups. Our results suggest that mitiglinide plus insulin glargine combination therapy is useful for lowering both fasting and postprandial hyperglycemia in a subpopulation of type 2 diabetes. The long-term effects of such treatment need to be established in future studies.

Key words: Oral antidiabetic drugs, Combination therapy, Postprandial hyperglycemia

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POSTPRANDIAL hyperglycemia is a major risk factor for arteriosclerosis and cardiovascular death. Several studies reported that fasting glucose concentrations alone do not identify individuals at increased risk of hyperglycemia-associated death and that mealtime glycemia significantly contributes to overall glycemic control and coronary artery disease mortality [1–4]. It has been believed that the earliest determinant of progression to type 2 diabetes is a loss of early insulin secretion, a defect which results in postprandial hyperglycemia and is often believed to reflect insulin resistance in particular in Japanese population [5]. In this regard, mitiglinide, a novel class of rapid-acting insulin secretagogues, selectively enhances early meal-induced insulin secretion and thus improves mealtime glucose control [6–9]. Consistent with the physiological nature of this category of the drug, the overall insulin exposure is relatively lower than that produced by

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sulfonylurea compounds in type 2 diabetes [10]. However, mitiglinide is not necessarily effective for all diabetic patients. These drugs may be less effective for the patients with advanced diabetes in particular those with persistently elevated fasting plasma glucose concentrations. In such patients, many physicians select sulfonylurea as the next line antidiabetic agent, but these drugs do not effectively improve postmeal glycemic excursion. In this regard, the combined use of nateglinide or mitiglinide with insulin glargine, which has a 24-h time-action profile with no pronounced peak [11, 12], may be a potent regimen to lower both postprandial hyperglycemia and fasting plasma glucose concentrations, before switching to sulfonylurea or intensive insulin therapy using insulin injections.

The present study was designed to determine the short-term therapeutic efficacy of mitiglinide combined with once daily insulin glargine, switching from a multiple daily insulin regimen using three times daily aspart insulin and once daily glargine.

Subjects and Methods

This study was planned prospectively and we randomly chose 30 hospitalized patients with type 2 diabetes mellitus who received intensive insulin therapy in Juntendo University School of Medicine from June 2004 to March 2005 and were under good glycemic condition at least for more than two weeks. Selection criterion were based on M value from the daily profile of blood glucose concentration (seven daily estimations: before each meal, 2 hours after each meal, and bedtime), which has been used as an index of blood sugar control (M value <32) [13, 14]. We excluded the patients who had apparent liver or renal dysfunction, those who showed inflammatory status, and those in other seriously ill condition. All of them were on appropriate diet therapy and intensive insulin regimen using three times daily aspart insulin and once daily insulin glargine during hospitalization. The characteristics of the 30 patients were described in Table 1. Other laboratory tests which were not shown in Table 1 were within normal limit or very slight abnormality. Among 30 patients, 19 were males. Their mean age was 59.9 ± 15.0 years old, and body mass index (BMI) was 24.3 ± 3.5 kg/m^2 (mean ± SD). After improvement of glycemic control with intensive insulin regimen (M value <32), the regimen was switched to premeal administration of mitiglinide (20 mg for each meal) combined with once daily insulin glargine (same doses as the ones used in the intensive insulin regimen) (termed mitiglinide regimen). The M values were calculated from seven daily estimations of blood glucose as described previously [13] and compared with those of the intensive insulin regimen. Effectively switched patients were defined as those with M values of <32 after switching to mitiglinide regimen. M values less than 32 were defined as good to fair glycemic control as in Schlichtkrull *et al.* [13]. Several clinical characteristics were compared between the patients effectively switched and those not. All data were expressed as mean ± SD. Differences between groups were examined for statistical significance using the Student's *t*-test. A *P* value less than 0.05 was regarded as statistically significant.

Table 1. Baseline clinical characteristics of patients

n	30 (M19, F11)
Age (years)	59.9 ± 15.0
Body mass index	24.3 ± 3.5
Duration of diabetes (years)	12.8 ± 7.1
HbA_{1c} (on admission) (%)	9.1 ± 2.7
Total cholesterol (mg/dl)	183.3 ± 32.4
HDL cholesterol (mg/dl)	45.5 ± 16.3
Triglyceride (mg/dl)	127.5 ± 59.6
History of sulfonylurea	yes 18, no 12
History of insulin	yes 13, no 17
Aspart insulin used (units)	21.5 ± 9.9
Glargine insulin used (units)	9.0 ± 0.8

Data are expressed as n or mean ± SD.

Results

Thirty type 2 diabetic patients hospitalized for glycemic control (mean HbA_{1c}, 9.1 ± 2.7%) received appropriate diet therapy and intensive insulin regimen including three times daily premeal aspart insulin and once daily glargine. More than two weeks after improvement of glycemic control, their three times daily aspart insulin injections were switched to premeal 20 mg of mitiglinide administration. Seven-time blood glucose monitoring was performed under both intensive insulin regimen and mitiglinide regimen on two continuous days. Table 1 summarizes the clinical characteristics of type 2 diabetic inpatients before admission or switching from intensive insulin regimen to

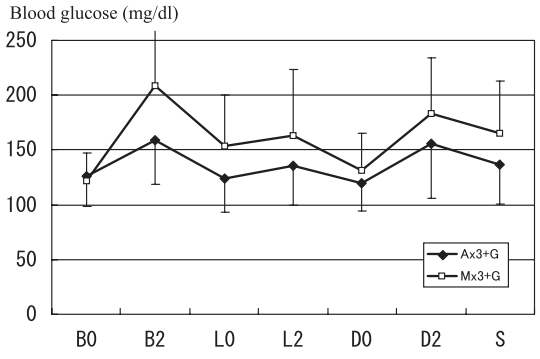

Fig. 1. Average daily profiles of blood glucose (BG) in patients treated with intensive insulin regimen and mitiglinide regimen.
Daily profile of BG concentration (seven daily estimations: before each meal, 2 hours after each meal, and bedtime) was determined in 30 inpatients who were well-controlled with three times daily insulin aspart and once daily glargine during hospitalization (Ax3 + G). The next day, insulin aspart was switched to 20 mg of mitiglinide three times a day (Mx3 + G). Daily profiles of BG level were compared between patients on Mx3 + G and those on Ax3 + G. B0 and B2: BG level before and 2 hours after breakfast, L0 and L2: BG level before and 2 hours after lunch, D0 and D2: BG level before and 2 hours after dinner, S: BG level at bed time.

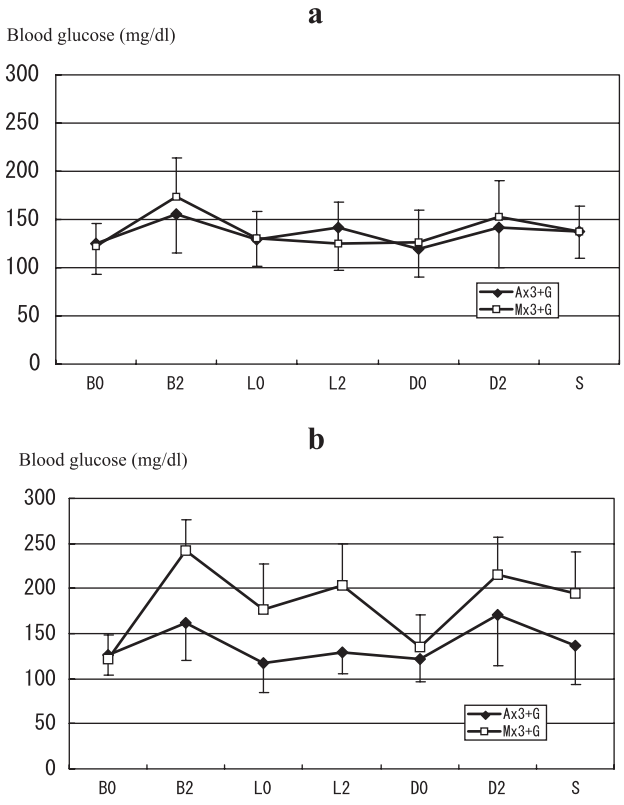

Fig. 2. Average daily profiles of blood glucose (BG) in patients treated with intensive insulin regimen and mitiglinide regimen.
a. Daily profile of BG concentration (seven daily estimations: before each meal, 2 hours after each meal, and bedtime) during insulin aspart and glargine (Ax3 + G) and during mitiglinide (Mx3 + G) in patients with M values of <32 after switching to mitiglinide regimen (a), and those with M values ≥32 after switching to mitiglinide regimen (b).

mitiglinide regimen. Eighteen of the 30 patients had used sulfonylurea and 13 of 30 patients had used insulin before admission and enrolement in the present study.

At the time just before switching from intensive insulin regimen to mitiglinide regimen, the average dose of aspart insulin was 21.5 ± 9.9 units per day and average dose of insulin glargine was 9.0 ± 0.8 units per day. As shown in Fig. 1, the mean daily blood glucose concentration for the whole group of 30 patients deteriorated after switching from aspart to mitiglinide regimen. We then divided the patients into two groups: the effective group (defined as those patients with M value of <32 after switching) and ineffective group (defined as those with M value of ≥32 after switching). Fifteen patients showed effective response (M value; 20.6 ± 12.4, average blood glucose: 138.7 ± 18.7 mg/dl) while the other 15 patients formed the ineffective group (M value: 94.1 ± 46.8; average blood glucose: 184.1 ± 56.1 mg/dl). Fig. 2 shows the daily profiles of blood glucose concentration before and after therapy regimen switching for the effective (Fig. 2a) and ineffective groups (Fig. 2b). For the effective group, blood glucose levels at all of the points with mitiglinide regimen were almost equal to the ones with intensive insulin regimen. Comparisons of the M value and baseline glucose concentration between each regimen in patients of the effective group did not show significant differences (intensive insulin regimen vs mitiglinide regimen; average blood glucose: 135.9 ± 16.4 vs 138.7 ± 18.7 mg/dl ($p = 0.67$), M value: 18.9 ± 13.7 vs 20.6 ± 12.4 ($p = 0.73$)).

Table 2 compares the clinical characteristics of patients of the effective and ineffective groups. The age of patients of the effective group was significantly younger than those of the ineffective group. Body mass index and body weight under mitiglinide regimen were significantly higher in effective than in ineffective group ($p<0.05$, each). Daily urine excretion of C-

Table 2. Comparison of baseline demographics and clinical characteristics between patients who responded well to mitiglinide + glargine regimen and those who did not

	Effective	Ineffective	*p*
n	15	15	
Gender (M/F)	9/6	10/5	
Age (years)	51.9 ± 16.0	67.9 ± 8.7	0.0044
Body weight (kg)	69.1 ± 13.3	57.6 ± 11.6	0.013
Body mass index (kg/m^2)	25.7 ± 3.3	23.0 ± 3.1	0.022
Maximum BMI (kg/m^2)	28.7 ± 3.2	27.6 ± 4.7	0.37
Duration of diabetes (years)	11.5 ± 7.9	13.6 ± 9.0	0.48
Fasting plasma glucose (mg/dl)	125.1 ± 31.6	126.1 ± 22.3	0.93
Urinary C-peptide (mg/day)	49.8 ± 39.1	30.1 ± 31.7	0.18
Fasting serum C-peptide (ng/ml)	1.93 ± 0.78	1.89 ± 1.17	0.94
Average blood glucose concentration (mg/dl)	135.9 ± 16.4	138.7 ± 18.7	0.67
Total cholesterol	174.0 ± 36.6	195.6 ± 26.0	0.09
Triglyceride (mg/dl)	130.3 ± 62.0	131.9 ± 66.0	0.95
HDL cholesterol (mg/dl)	40.6 ± 11.0	50.4 ± 21.2	0.17
Duration of admission (day)	33.8 ± 29.3	29.4 ± 16.5	0.72
HbA_{1c} before intensive insulin therapy (%)	10.0 ± 2.6	8.4 ± 2.9	0.13
M values	18.9 ± 13.7	24.7 ± 15.8	0.30
Total insulin aspart (units/day)	19.6 ± 10.6	23.3 ± 8.5	0.32
Insulin glargine (units/day)	10.1 ± 4.6	7.5 ± 4.0	0.14
Total insulin aspart per body weight (units/day/kg)	0.27 ± 0.13	0.42 ± 0.14	0.0098
Insulin glargine per body weight (units/day/kg)	0.15 ± 0.07	0.14 ± 0.07	0.72

Data are mean ± SD.

peptide tended to be larger and duration of diabetes tended to be shorter in the effective group than ineffective group but the differences were not statistically significant. Baseline treatment before starting intensive insulin regimen including insulin and sulfonylurea, did not show any difference between effective and ineffective groups (data not shown). The insulin doses, including aspart insulin, glargine, and total insulin, were not different between the two groups. On the other hand, insulin doses of aspart per body weight were significantly fewer in effective group than in ineffective group (effective group vs ineffective group; average doses of aspart insulin: 0.27 ± 0.14 vs 0.42 ± 0.14 units per body weight ($p = 0.0098$); average doses of insulin glargine: 0.15 ± 0.07 vs 0.14 ± 0.07 ($p = 0.72$); average doses of total insulin: 0.42 ± 0.19 vs 0.56 ± 0.17 ($p = 0.056$)).

Discussion

In the present study, we investigated the short-term efficacy of mitiglinide, a novel class of rapid-acting insulin secretagogue, combined with insulin glargine, in type 2 diabetes. The rapid-acting insulin secretagogues, *e.g.*, mitiglinide and nateglinide, selectively enhance early meal-induced insulin secretion and improve mealtime glucose control when given alone or in combination with oral hypoglycemic drugs. We previously described that nateglinide improved glycemic response after oral glucose load in obese individuals with impaired glucose tolerance or early type 2 diabetes by improvement of early phase insulin secretion without increasing the total amount of insulin (*i.e.*, area under the curve) [15, 16]. While we compared the effects of a small dose of gliclazide (20 mg) with nateglinide (270 mg), the hypoglycemic effects of glicalzide are stronger though it elicited more frequent hypoglycemic episodes [17]. Even when administered at a single high dose (3420 mg), the hypoglycemic effect of nateglinide appeared immediately and did not last more than 6 hours [18].

Importance of treatment of postprandial hyperglycemia has been established [1–4] and mitiglinide has been reported to improve it effectively. Consistent with the physiological nature of this category of drugs, the overall insulin exposure is relatively lower than that produced by sulfonylurea medication in type 2 diabetes [10]. Based on these limited effects of insulin stimu-

lation by mitiglinide and nateglinide, it is likely that monotherapy with one of these drugs cannot improve postprandial hyperglycemia effectively in patients with high fasting plasma glucose concentrations [19]. In such a case, we would use sulfonylurea medication or intensive insulin therapy. However, sulfonylurea does not effectively improve postmeal glycemic excursion. Intensive insulin therapy is effective for glycemic control but is not easy to use for all diabetic patients. Some patients show adverse reaction to multiple insulin injection. In this study, we investigated the possible effectiveness of mitiglinide with insulin glargine to improve both fasting and postprandial glucose level. More patients could receive benefit from this combination therapy.

To our knowledge, there has been no report of the effects of combination therapies of insulin and mitiglinide or nateglinide in patients with type 2 diabetes mellitus. In daily clinical practice we sometimes experience that type 2 diabetic patients can maintain good glycemic control with or without sulfonylurea after short-term intensive insulin therapy but even these reports are very few [20, 21]. The results of our study indicated the effectiveness of short-term combination therapy of mitiglinide and insulin glargine. Fifteen of 30 patients were successfully switched from intensive daily insulin regimen using aspart insulin and glargine to premeal administration of mitiglinide combined with once daily insulin glargine based on the record of M values over two consecutive days. Clinical comparisons showed that patients who responded to mitiglinide plus insulin glargine were younger, heavier, and had a larger body mass index, than those who did not respond well to this therapy. Our results also showed that 24-hour urinary C-peptide secretion just before the switching tended to be higher in the effective group than the ineffective group, though the difference was not statistically significant. These characteristics suggest that patients with potentially higher capacity of endogenous insulin secretion were more responsive to mitiglinide regimen. We also showed that in effective group the dose of aspart insulin per body weight was lower than that of ineffective group. The patients with low dose of insulin aspart per body weight can be good candidates in switching from intensive daily insulin regimen to premeal administration of mitiglinide combined with once daily insulin glargine. Our study also showed that the baseline treatment (*e.g.*, insulin and sulfonylurea) before starting the intensive insulin regimen was not different between the two groups.

In the present study, we examined the efficacy of combination therapy of mitiglinide and insulin glargine over two continuous days, but did not evaluate the long-term efficacy of the combination therapy. Our preliminary data showed that some patients were continuously well-controlled using the same regimen while others showed deterioration after discharge from the hospital. Further studies are needed to examine the efficacy of long-term combination therapy.

In conclusion, combination therapy of mitiglinide and insulin glargine could be potentially useful for type 2 diabetes, with the aim of lowering both fasting and postprandial hyperglycemia in at least some patients with type 2 diabetes mellitus.

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