

Efficacy and safety of repaglinide vs nateglinide for treatment of Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Repaglinide is a short-acting insulin secretagogue. We assessed the efficacy and safety of repaglinide in comparison with nateglinide in Japanese patients with type 2 diabetes previously treated with diet and exercise.

Materials and Methods: In this 16-week randomized, multicenter, double-blind, parallel-group, active-controlled superiority trial, Japanese patients with type 2 diabetes and glycated hemoglobin (HbA_{1c}) of ≥ 6.9 and $\leq 9.4\%$ were enrolled. Patients were randomly assigned to receive 0.5 mg repaglinide ($n = 64$) or 90 mg nateglinide ($n = 66$) three times a day. The primary end-point was changes in HbA_{1c} from baseline to the end of treatment.

Results: Mean reductions of HbA_{1c} were significantly greater for the repaglinide group than the nateglinide group (-1.17 ± 0.62 vs $-0.81 \pm 0.39\%$, $P < 0.001$). The target HbA_{1c} values of $< 6.9\%$ were achieved by 75.0% of the repaglinide group vs 59.1% for nateglinide. Mean changes in fasting plasma glucose also showed significantly greater efficacy for repaglinide than nateglinide (-26.0 ± 20.9 vs -18.3 ± 17.8 mg/dL, $P < 0.001$). There were no differences in the adverse event rates between the repaglinide and the nateglinide group, by 57.8% (37/64) and 60.6% (40/66), respectively. Incidences of hypoglycemic symptoms were 17.2% (11/64, 28 events) in the repaglinide group and 6.1% (4/66, 20 events) in the nateglinide group, respectively.

Conclusions: In type 2 diabetic patients treated with diet and exercise, repaglinide monotherapy gives greater glycemic improvement than nateglinide monotherapy in reducing HbA_{1c} and fasting plasma glucose values after 16 weeks. This trial was registered with JapicCTI (no. JapicCTI-080521). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00188.x, 2012)

KEY WORDS: Nateglinide, Repaglinide, Type 2 diabetes

INTRODUCTION

Diabetes is a syndrome presenting with chronic hyperglycemia (arising from insufficiency of insulin activity) as a primary sign, accompanied by diverse characteristic abnormalities of metabolism¹. Chronic hyperglycemia is a risk factor for microangiopathy, such as retinopathy, nephropathy, neuropathy; and macroangiopathy, such as ischemic heart disease and cerebrovascular disease²⁻⁶. It has been reported that intensive control of blood glucose level in patients with type 2 diabetes can prevent the onset and progression of these complications, and improve the prognosis as to the survival of patients². Therefore, it seems essential to treat diabetes appropriately.

Repaglinide is a short-acting insulin secretagogue and, like sulfonylureas (SU), repaglinide exerts its efficacy by inhibiting

adenosine triphosphate (ATP)-sensitive potassium channels (K_{ATP} channel) in pancreatic β -cells, thus inducing depolarization of β -cell membrane and inflow of Ca²⁺ ion into cells to stimulate insulin secretion⁷⁻⁹. However, unlike SU, repaglinide can be characterized by short duration of action and the early disappearance of efficacy. In the study of clinical pharmacology in patients with type 2 diabetes carried out before the present study, a single dose of repaglinide (0.5 or 1 mg) immediately before a meal resulted in rapid absorption of repaglinide, with C_{max} being recorded in approximately 30 min and the half-life being approximately 1 h¹⁰. Furthermore, after a dose of repaglinide, plasma repaglinide concentration rose quickly and insulin secretion was stimulated soon after a meal, followed by a gradual decrease in insulin level (returning to a level approximately equal to the predose baseline by the next meal)¹⁰. In addition, postprandial blood glucose elevation was suppressed as insulin secretion increased after a dose of repaglinide¹⁰. These results suggest that, like existing short-acting insulin secretagogues, repaglinide stimulates insulin secretion soon after a meal and ceases to exert this activity in a short time.

In a placebo-controlled double-blind comparative study in patients with type 2 diabetes treated with diet and exercise¹⁰, we

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confirmed the efficacy and safety of repaglinide given three times daily, immediately (within 10 min) before each meal, for a period of 12 weeks at a dose of 0.25, 0.5 or 1 mg.

Under these circumstances, we undertook the present study to evaluate the efficacy and safety of repaglinide in comparison with nateglinide (an existing short-acting insulin secretagogue with established efficacy and safety) in patients with type 2 diabetes treated with diet and exercise. Glycated hemoglobin (HbA_{1c}) was analyzed as the primary end-point to confirm the superiority of repaglinide over nateglinide.

MATERIALS AND METHODS

Enrolled Participants

Patients with type 2 diabetes were screened and enrolled if they were aged over 20 years, had received treatment with diet and exercise in the previous 8 weeks, and had HbA_{1c} of 6.9–9.4% accompanied either by fasting plasma glucose (FPG) over 120 mg/dL or postprandial plasma glucose at 1 or 2 h over 200 mg/dL. Patients who had been treated with insulin, nateglinide or SU during the previous 24 weeks, or other oral-dose hypoglycemic agents or corticosteroids (oral-dose preparation, suppository or injection) during the previous 12 weeks were also excluded. In addition, the following were also excluded: patients with heart diseases (heart failure [NYHA class III or IV], unstable angina, myocardial infarction having developed during the previous 12 months), diabetic complications (diabetic proliferative retinopathy or preproliferative retinopathy, serious diabetic neuropathy requiring treatment), aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase (ALP) over 2.5-times the upper normal limit, serum creatinine over 2 mg/dL and malignant tumors, as well as pregnant women, possibly pregnant women or lactating women. The study was examined and approved at the institutional review board (IRB) of each participating facility and subsequently implemented in accordance with Good Clinical Practice. At each participating facility, the investigator or subinvestigator informed each candidate patient of the study design using the leaflet and consent form authorized by the IRB before the patient was enrolled in the study, and the patient's consent to the study was obtained in writing.

Study Design and Methods

The present study was a randomized, multicenter, double-blind, parallel-group, active-controlled superiority study. Nateglinide served as a reference drug for comparison.

The repaglinide group received treatment with repaglinide tablets and placebo nateglinide tablets, whereas the nateglinide group received treatment with nateglinide tablets and placebo repaglinide tablets. For allocation of the participants, a computer-generated list of random numbers was used. In each group, oral medication was given three times daily, immediately (within 10 min) before each meal, for a period of 16 weeks. In the repaglinide group, repaglinide was given at a dose of 0.75 mg/day for the first 2 weeks and 1.5 mg/day for the follow-

ing 14 weeks. In the nateglinide group, nateglinide was given at a dose of 270 mg/day for 16 weeks.

The primary end-point was the change in HbA_{1c} at the end of the study. Secondary end-points were the proportion of patients who achieved the target HbA_{1c} value of <6.9%, postprandial blood glucose (PPG [the area under the curve (AUC)_{0–3 h} at 30 min, 1, 2 and 3 h]), glycoalbumin (GA), FPG, postprandial serum insulin (AUC_{0–3 h} at 30 min, 1, 2 and 3 h).

The value for HbA_{1c} (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society [JDS]; %) + 0.4%, considering the relational expression of HbA_{1c} (JDS; %) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)¹¹. Another end-point was the proportion of patients who achieved the target HbA_{1c} value of <6.2%. The population used for analyzing efficacy evaluation – the full analysis set (FAS) – was defined as those who had at least one measurement of any efficacy parameters among the randomized patients. Their plasma HbA_{1c} was measured every 4 weeks. The meal tolerance test (the retort pouch food and rice whose energy unit was adjusted to approximately 400 kcal; carbohydrate 73.6 g, protein 14.9 g, and lipid 5.7 g) was carried out at breakfast time at baseline and at the 16-week visit. For the meal tolerance test, breakfast was started within 30 min after collection of blood during fasting, and blood glucose level and serum insulin level were measured at five points of time (30, 60, 90, 120 and 180 min after the start of breakfast). Repaglinide or nateglinide was given 10 min before the meal.

Adverse events were counted as adverse drug reactions if their causal relationship to the test drug was not ruled out by the investigator or subinvestigator. As a means of monitoring the safety after the start of test drug treatment, a subject diary and an instrument for self-monitoring of blood glucose were provided to each patient. On appearance of any symptom suggesting hypoglycemia, its features and situation (time of appearance, time of disappearance, time of latest meal and way of dealing with the symptom) were investigated. In cases where blood glucose was measured on appearance of symptoms, the blood glucose data (date and time of measurement and measurement) were investigated as well.

Laboratory tests (hematology, biochemistry and urinalysis) and measurement of vital signs were carried out before and 2, 4, 8, 12 and 16 weeks after the start of treatment (or on discontinuation of treatment). A central laboratory institute measured the data of laboratory tests. Twelve-lead electrocardiography (12-lead ECG) was carried out before registration with the present study and 16 weeks after the start of treatment (or on discontinuation of treatment).

Statistical Analysis

The present study was aimed at confirming the superiority of repaglinide (1.5 mg/day) over nateglinide (270 mg/day) in Japanese patients with type 2 diabetes through analysis of

change in HbA_{1c}. On the basis of previous results of clinical studies of repaglinide¹⁰ and nateglinide^{12,13}, the difference in the magnitude of change in HbA_{1c} relative to the pretreatment baseline between the repaglinide treatment group and the nateglinide treatment group was assumed to be 0.4–0.5%. The number of subjects needed for superiority testing at a detective power of 90% and a common standard deviation of 0.7% (the lower bound of the two-tailed 95% confidence interval for intergroup difference: >0) is 65 per group if the difference is 0.4% and 42 per group if the difference is 0.5%. In this way, the targeted number of subjects was set at 60 per group.

Statistical analyses were carried out using SAS software version 9.1.3. Analysis of covariance (ANCOVA) and Fisher's exact test were carried out where appropriate. In ANCOVA, we used treatment group as the fixed effect, and the baseline value as a covariate for the intergroup difference of the change from baseline. A *P*-value of < 0.05 was considered to be statistically significant.

RESULTS

Demographic Information of Patients

A total of 138 patients were screened and 130 patients were finally included in FAS: 64 for the repaglinide group and 66 for the nateglinide group (Figure 1). The total numbers of patients who did not complete the 16-week trial did not differ significantly between the repaglinide group (*n* = 4) and the nateglinide group (*n* = 4). The reasons for discontinuation were adverse events (four cases from the repaglinide group and three cases from the nateglinide group) and difficulty in complying with the protocol (one case from the nateglinide group). Demographic and baseline characteristics of the 130 randomized subjects are summarized in Table 1. The repaglinide and nateglinide groups were very comparable in age, sex, body mass index values, duration of diagnosed diabetes and baseline characteristics. None of these variables differed significantly by treatment group.

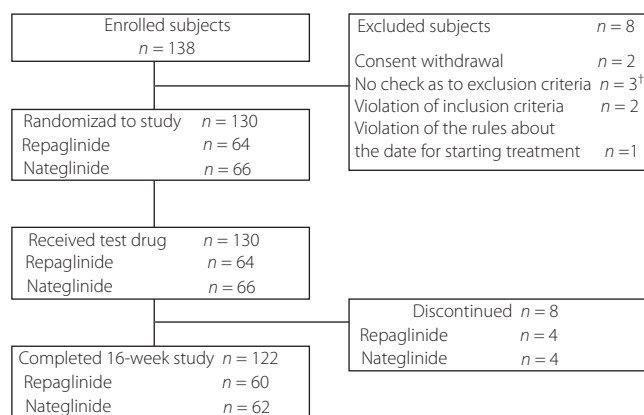


Figure 1 | Enrolment and outcomes. †These patients were unregistered once and re-enrolled after necessary examinations for registration.

Efficacy

The mean decrease in HbA_{1c} at the end of the study (week 16 or at the time of discontinuation) was $-1.17 \pm 0.62\%$ in the repaglinide group and $-0.81 \pm 0.39\%$ in the nateglinide group (Figure 2, Table 2). In ANCOVA of the inter-group difference, the magnitude of change was significantly greater in the repaglinide group than the nateglinide group, showing the superiority of repaglinide over nateglinide in the primary end-point (*P* < 0.001). The proportion of patients who achieved the target HbA_{1c} value of <6.9% at the end of the study was higher in the repaglinide group than in the nateglinide group (75.0% [48/64] vs 59.1% [39/66]). In addition, the proportion with a HbA_{1c} value of <6.2% was also higher in the repaglinide group than in the nateglinide group (29.7% [19/64] vs 9.1% [6/66]). There was no marked difference in the magnitude of change in HbA_{1c} level of all groups in the subgroups analysis based on the baseline body mass index. The magnitude of change in HbA_{1c} level tended to be greater the higher the baseline HbA_{1c} became in the subgroups analysis based on the baseline HbA_{1c}. The mean

Table 1 | Demographic characteristics of the subjects in the full analysis set

	Repaglinide	Nateglinide
<i>n</i>	64	66
Sex (male/female)	42/22	46/20
Age (years)	60.9 ± 9.9	63.9 ± 8.9
Body mass index (kg/m ²)	24.98 ± 4.33	24.09 ± 3.15
Duration of diabetes (years)	5.7 ± 6.0	5.5 ± 4.7
HbA _{1c} (%)	7.72 ± 0.74	7.59 ± 0.52
FPG (mg/dL)	150.3 ± 23.9	147.9 ± 20.9
2-h PPG (mg/dL)	238.8 ± 51.8	245.4 ± 50.7*

Data are mean ± SD. **n* = 65. FPG, fasting plasma glucose; PPG, postprandial plasma glucose.

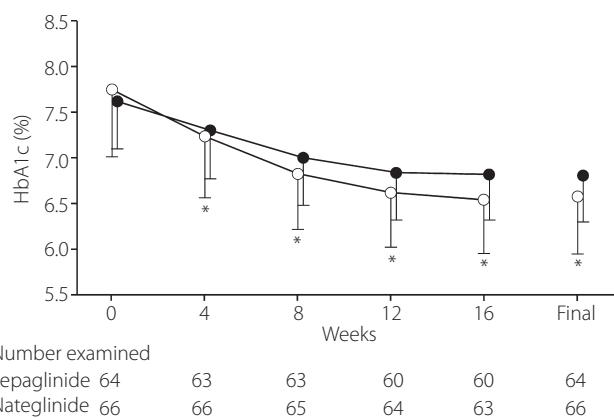


Figure 2 | The change in mean (±SD) HbA_{1c} level after randomization. Open circles denote the repaglinide group and closed circles denote the nateglinide group. *Raw *P*-value < 0.05 vs nateglinide (*t*-test for intergroup difference of the change from baseline).

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

	Repaglinide				Nateglinide			
	n	Baseline	End of study	Change from baseline	n	Baseline	End of study	Change from baseline
HbA _{1c} (%)	64	7.72 ± 0.74	6.55 ± 0.63	-1.17 ± 0.62**	66	7.59 ± 0.52	6.78 ± 0.51	-0.81 ± 0.39
According to the baseline HbA _{1c}								
<7	26	6.67 ± 0.20	5.75 ± 0.20	-0.93 ± 0.20	26	6.73 ± 0.14	6.13 ± 0.14	-0.61 ± 0.14
7 to ≤8	26	7.38 ± 0.25	6.28 ± 0.25	-1.10 ± 0.25	35	7.35 ± 0.30	6.46 ± 0.30	-0.90 ± 0.30
8≤	12	8.61 ± 0.36	6.77 ± 0.36	-1.84 ± 0.36	5	8.38 ± 0.41	7.18 ± 0.41	-1.20 ± 0.41
According to the baseline body mass index								
<22	16	7.14 ± 0.60	6.02 ± 0.66	-1.12 ± 0.42	17	7.15 ± 0.49	6.35 ± 0.49	-0.80 ± 0.48
22 to ≤25	22	7.48 ± 0.88	6.12 ± 0.62	-1.36 ± 0.66	25	7.12 ± 0.41	6.36 ± 0.44	-0.75 ± 0.29
25≤	26	7.30 ± 0.69	6.27 ± 0.61	-1.03 ± 0.68	24	7.29 ± 0.63	6.42 ± 0.61	-0.87 ± 0.41
PPG-AUC _{0-3 h} (mg h/dL)	60	684 ± 116	552 ± 110	-132 ± 109	61	701 ± 106	548 ± 103	-153 ± 81
FPG (mg/dL)	64	150.3 ± 23.9	124.2 ± 19.3	-26.0 ± 20.9*	66	147.9 ± 20.9	129.6 ± 17.8	-18.3 ± 17.8
GA (%)	64	21.25 ± 3.19	17.32 ± 2.50	-3.93 ± 2.25**	66	21.38 ± 2.86	18.67 ± 2.34	-2.72 ± 1.58
30-min PPG (mg/dL)	60	222.3 ± 33.2	197.5 ± 32.7	-25.7 ± 32.9	61	220.7 ± 28.8	188.5 ± 27.1	-32.2 ± 28.5
1-h PPG (mg/dL)	59	265.2 ± 39.1	223.2 ± 41.3	-42.0 ± 34.9	61	271.6 ± 32.8	213.1 ± 41.2	-58.5 ± 34.6*
2-h PPG (mg/dL)	60	236.9 ± 51.2	183.6 ± 50.9	-53.4 ± 52.6	61	247.0 ± 50.8	186.9 ± 47.8	-60.1 ± 40.3
3-h PPG (mg/dL)	60	199.4 ± 46.6	143.1 ± 41.3	-56.3 ± 46.2	60	205.8 ± 49.5	149.1 ± 38.8	-56.7 ± 36.5
Postprandial serum insulin								
AUC _{0-3 h} (μU h/mL)	58	76.9 ± 59.3	102.7 ± 72.7	25.8 ± 33.8	56	72.3 ± 46.5	101.7 ± 57.0	29.4 ± 28.9
30-min (μU/mL)	60	20.50 ± 19.48	29.18 ± 17.59	8.68 ± 9.09	61	16.86 ± 9.11	38.22 ± 20.60	21.36 ± 14.63**
1-h (μU/mL)	59	28.70 ± 21.53	41.79 ± 29.84	13.08 ± 14.98	61	27.64 ± 17.61	41.60 ± 23.34	13.95 ± 12.55
2-h (μU/mL)	60	31.11 ± 23.68	39.84 ± 31.07	8.73 ± 18.26	61	30.94 ± 20.73	38.70 ± 24.03	7.76 ± 17.16
3-h (μU/mL)	60	23.16 ± 19.04	29.07 ± 23.02	5.91 ± 12.10*	60	22.00 ± 18.09	22.65 ± 17.90	0.65 ± 11.70
Achievement of treatment goal at the end of the study Patient with HbA _{1c}								
HbA _{1c} < 6.9%	64	-	48 (75.0)	-	66	-	39 (59.1)	-
HbA _{1c} < 6.2%	64	-	19 (29.7)	-	66	-	6 (9.1)	-

Data are mean ± SD. **P* < 0.05, ***P* < 0.001 (ANCOVA for intergroup difference of the change from baseline). FPG, fasting plasma glucose; GA, glycoalbumin; PPG, postprandial plasma glucose.

decrease in PPG-AUC_{0-3 h} was not significantly different for repaglinide and nateglinide (-132 ± 109 vs -153 ± 81 mg h/dL, *P* = 0.363). Compared with the nateglinide group, the repaglinide group showed a greater reduction in FPG (-26.0 ± 20.9 vs -18.3 ± 17.8 mg/dL, *P* = 0.018) and GA (-3.93 ± 2.25 vs -2.72 ± 1.58%, *P* < 0.001). Though the mean decrease in 1-h PPG was significantly greater in the nateglinide group than in the repaglinide group, there was no significant difference in 30-min PPG, 2-h PPG or 3-h PPG. The mean increase in postprandial serum insulin AUC_{0-3 h} was not significantly different for repaglinide and nateglinide. The postprandial serum insulin in 30-min was significantly greater in the nateglinide group than in the repaglinide group. In contrast, that in 3-h was significantly greater in the repaglinide group than in the nateglinide group.

Safety

Among 130 patients (64 in the repaglinide group and 66 in the nateglinide group) treated with the trial medication at least once, there were no differences in the adverse event rates: 57.8% (37/64) in the repaglinide group and 60.6% (40/66) in

the nateglinide group (Table 3). The most common adverse events (the frequency of adverse events over 5% in at least 1 group) in the repaglinide group and the nateglinide group were hypoglycemia (15.6 [10/64] vs 6.1%, [4/66]), nasopharyngitis (12.5 [8/64] vs 16.7% [11/66]) and diarrhea (6.3 [4/64] vs 3.0% [2/66]). In the repaglinide group, all of the most common adverse events were mild, and there was no severe or moderate

Table 3 | Adverse events and drug-related adverse events in any treatment group

	Repaglinide (n = 64)	Nateglinide (n = 66)
Adverse events	37 (57.8)	40 (60.6)
Deaths	0	0
Serious adverse events	1 (1.6)	1 (1.5)
Discontinuation	3 (4.7)	3 (4.5)
Hypoglycemia	11 (17.2)	4 (6.1)
Drug-related adverse events	18 (28.1)	12 (18.2)

Data are n (%).

adverse event. In the nateglinide group, one patients had moderate hypoglycemia, but the other adverse events were mild, with no severe adverse event noted. During the present study, no patients died. As serious adverse events, cerebral infarction (the repaglinide group) and colonic adenoma (the nateglinide group) were seen in each patients (one event each), the causal relationships to the test drug was rated as unknown and ruled out, respectively. Adverse events requiring discontinuation of treatment were seen in three patients (three events; psychosomatic disease, Parkinsonism and cerebral infarction) from the repaglinide group and three patients (five events; muscle cramp, dysgeusia, rash, hypoglycemia and colonic adenoma) from the nateglinide group.

When adverse events arising from hypoglycemia were counted as hypoglycemic symptoms, their incidence was 17.2% (11/64, 28 events) in the repaglinide group and 6.1% (4/66, 20 events) in the nateglinide group. Measurement of blood glucose level with a blood glucose self-checking device was carried out on appearance of hypoglycemic symptoms in seven patients (20 events) from the repaglinide group and two patients (16 events) from the nateglinide group, yielding the results of blood glucose level ≤ 60 mg/dL in five patients (seven events) from the repaglinide group and one patient (14 events) from the nateglinide group. Many of the hypoglycemic episodes in the repaglinide group were developed from 10.00 to 13.00 h (42.8%, 12/28 events), considered as before lunch, and from 16.00 to 19.00 h (32.1%, 9/28 events), considered as before dinner. In contrast, many of the hypoglycemic episodes in the nateglinide group were developed from 04.00 to 07.00 h (35.0%, 7/20 events), considered as before breakfast, and from 19.00 to 22.00 h (30.0%, 7/20 events), considered as before dinner. More than half of these episodes in both groups disappeared within 60 min. The hypoglycemic episodes did not include any significant central nervous system symptoms, such as loss of consciousness. Blood glucose level measurement was not carried out on appearance of hypoglycemic symptoms in one patient (one event) from the nateglinide group. In this case, dizziness, chest distress, cold sweat and vomiting were noted, and they were rated as moderate, disturbing the patient's daily life. All of the other hypoglycemic episodes were rated as mild, not disturbing the patient's daily life. None of the events required intervention by any other individual and subsided after measures taken at the patient's own discretion (intake of glucose, meal, etc.) or without any particular measure. There was no clinically significant abnormal change in any laboratory parameter, any vital sign or 12-lead ECG.

DISCUSSION

The present study examined the efficacy and safety of repaglinide compared with nateglinide for 16 weeks in Japanese patients with type 2 diabetes. The change from baseline in HbA_{1c} was significantly greater in the repaglinide group than in the nateglinide group, thus showing the superiority of repaglinide over nateglinide. In addition, both the percentage of

patients achieving the treatment goals (HbA_{1c} < 6.9 and 6.2%)^{14–16} were higher in the repaglinide group than in the nateglinide group. Compared with the previous results of repaglinide¹⁰ and nateglinide^{12,13}, clinical efficacy of these drugs in patients with type 2 diabetes was reproducible even in Japanese subjects.

The reduction in PPG-AUC_{0–3 h} was not significantly different between both groups, although the mean decrease in 1-h PPG was significantly greater in the nateglinide group than in the repaglinide group. The change in FPG was significantly greater in the repaglinide group than in the nateglinide group. These results suggest that repaglinide improves postprandial hyperglycemia to a degree not significantly different from nateglinide and lowers FPG level more powerfully than nateglinide, resulting in the manifestation of potent HbA_{1c}-lowering activity. The difference between these drugs in the effect of lowering FPG level seems to be attributed to the insulinotropic effects of repaglinide that lasts longer than nateglinide, although not in a continuous manner as seen with SU, and repaglinide is rapidly absorbed and disappears pharmacokinetically^{10,17}. This would result in reduction of the blood glucose level recorded immediately before the next meal (a change not seen after a nateglinide dose) and probably explains the difference of FPG reduction between repaglinide and nateglinide.

After a dose of repaglinide, plasma repaglinide concentration reached a peak at approximately 30 min and disappeared rapidly thereafter, with the half-life being approximately 1 h¹⁰. The pharmacokinetic parameters of repaglinide differed little from those of nateglinide¹⁸. Regarding insulin secretion stimulating drugs, which close the K_{ATP} channel by binding to the SU receptor, it has been reported that the time until disappearance of their action on the K_{ATP} channel (the time for recovery from K_{ATP} channel closure) after elimination of the drugs from pancreatic β -cells varied markedly among different drugs¹⁹. This suggests that the duration of the drug's effect in stimulating insulin secretion is determined not only by the drug's pharmacokinetics and potential of binding to the SU receptor, but also by the time for recovery from K_{ATP} channel closure. The time for recovery from K_{ATP} channel closure is approximately 30 min with nateglinide and approximately 3 h with repaglinide¹⁹. The results from the present study and those reported in previous papers^{9,19} suggest that nateglinide stimulates insulin secretion for approximately 2–3 h. After a dose of repaglinide, insulin secretion remained stimulated even at 3 h, but the insulin level had returned to the pretreatment baseline level by 5 h after a dose in clinical pharmacological studies¹⁰. From these results, it might be suggested that the longer duration of the effect of repaglinide on insulin secretion is attributable to longer recovery time from K_{ATP} channel closure and to longer duration of activity of repaglinide, despite the absence of a marked difference in pharmacokinetic parameters between these two drugs.

The incidence of adverse events or adverse drug reactions differed little between the two groups. The incidence of hypoglycemic symptoms was approximately 10% higher in the

repaglinide group (17.2%) than in the nateglinide group (6.1%). No severe symptom of hypoglycemia was noted in any group. Based on these safety data, it could be suggested that repaglinide is well tolerated by Japanese patients with type 2 diabetes. Because all symptoms of hypoglycemia were mild, although the incidence in the repaglinide group was higher than in the nateglinide group, none of these symptoms were clinically significant as they subsided after measures taken at the patient's own discretion (intake of a meal, glucose or the like) or without any particular measure.

The JDS recommends setting a treatment goal of achieving 'excellent or good' ($HbA_{1c} < 6.9\%$) in 'blood glucose control indicators and assessment' when intervention is made for the purpose of preventing the onset or suppression of the progression of microangiopathy (retinopathy, nephropathy, neuropathy etc.)^{14–16}. The results from the present study show that repaglinide reduced HbA_{1c} level and improved blood glucose control favorably, without posing any safety problem. Furthermore, the treatment goal 'excellent or good' was achieved by 75% of the patients treated with repaglinide. These results suggest that treatment with repaglinide is expected to suppress the onset and progression of diabetic complications classified as microangiopathy.

As aforementioned, treatment with repaglinide resulted not only in the alleviation of postprandial hyperglycemia, but also in significantly greater improvement in FPG level, thus leading to a significant reduction in HbA_{1c} level compared with nateglinide. Because of these features, repaglinide can be viewed as a short-acting insulin secretagogue applicable not only to patients for whom existing short-acting insulin secretagogues are indicated, but also to patients in whom adequate responses to existing short-acting insulin secretagogues are unlikely because of disease progression. Thus, repaglinide can provide a new alternative treatment to an extensive range of patients with type 2 diabetes in Japan.

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