Endocrine Journal 2007, **54** (6), 1009–1014

Divided-Dose Administration of Miglitol just before and 15 Minutes after the Start of a Meal Smoothes Postprandial Plasma Glucose Excursions and Serum Insulin Responses in Healthy Men

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Abstract. We recently demonstrated that administration of miglitol at 15 min after the start of a meal decreased the area under the curve (AUC) of plasma glucose, similar to the observation following its administration just before a meal. This finding prompted us to examine whether a divided-dose regimen of miglitol might attenuate postprandial glucose excursions even more effectively. We, therefore, examined several schedules of miglitol administration in 15 healthy men. Miglitol was administered by four different schedules in each subject (control: no miglitol, intake 1: drug administered just before a meal (50 mg); intake 2: drug administered at 15 min after the start of a meal (50 mg); intake 3: drug administered in two divided doses: just before a meal (25 mg) and at 15 min after the start of a meal (25 mg). The AUC of glucose excursions, defined as increment above the fasting glucose level, ($AUC_{0-180\ min}$ of glucose excursions) was significantly reduced as compared with that in the control condition after miglitol administration by intake schedule 3, while this parameter showed a tendency towards decrease after the drug administration by intake schedules 1 and 2. The $AUC_{0-180\ min}$ of the serum insulin level was also significantly decreased for all the intake schedules of miglitol, as compared with that in the control condition. Thus, administration of miglitol in two divided doses appeared to be the most suitable for obtaining effective regulation of postprandial glucose excursions in healthy men. This result may suggest that the divided-dose administration regimen may also be effective in diabetic patients.

Key words: αGI, Miglitol, Postprandial, Glucose, Insulin

(*Endocrine Journal* **54**: 1009–1014, 2007)

THE clinical significance of regulation of postprandial hyperglycemia in relation to the risk of microvascular and macrovascular complications has been revealed by numerous studies over the last several years [1–5]. Pharmacological agents are now used that primarily modify the postprandial plasma glucose levels, and alpha-glucosidase inhibitors (αGIs) represent one such class of agents, whose intake to achieve this purpose is recommended just before a meal [6–8]. Miglitol is the first pseudomonosaccharide αGI to become available in the market and the drug has been reported to be more effective at reducing the blood glucose levels at 30 and 60 min after a meal than voglibose [9]. This can be explained by the fact that, unlike acarbose or voglibose, miglitol is also partially absorbed from the upper portion of the small intestine, and can, therefore, be administered in large doses [10].

We hypothesized that administration of miglitol even after the start of a meal instead of just before a meal might be effective in reducing the postprandial blood glucose level, and examined the effect of miglitol administered after the start of a meal in type 2 diabetic patients. In fact, administration of miglitol at 15 min after the start of a meal decreased the area under the curve (AUC) of plasma glucose to a degree

Received: January 25, 2007
Accepted: October 2, 2007
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equivalent to that observed following the administration of the drug just before a meal [11]. This finding prompted us to examine whether a divided-dose regimen of miglitol, namely, administration of the drug just before and at 15 minutes after the start of a meal, might attenuate postprandial excursions of plasma glucose and serum insulin even more effectively. We, therefore, examined several schedules of miglitol administration in order to determine the most suitable regimen to obtain optimal regulation of the postprandial plasma glucose and serum insulin concentrations in 15 healthy men.

Materials and Methods

Subjects

After obtaining approval from the Institutional Ethics Review Committee, 15 healthy men aged 38.7 ± 1.3 years, with a height of 170.5 ± 1.4 cm, weight of 66.1 ± 1.3 kg, and BMI of 22.8 ± 0.4 kg/m^2, who had never been diagnosed to have diabetes or IGT, were enrolled for the study (the mean fasting plasma glucose and serum insulin were 89.9 ± 0.8 mg/dL and 7.2 ± 0.4 μU/mL, respectively). Informed consent was obtained from each of the subjects prior to the start of the study.

Methods

Miglitol was administered by four different intake schedules in each subject (control: no miglitol; intake schedule 1: drug administered just before a meal (50 mg); intake schedule 2: drug administered at15 min after the start of a meal (50 mg); intake schedule 3: drug administered in two divided doses: just before a meal (25 mg) and at 15 min after the start of a meal (25 mg). Subjects were randomized to one of the four interventions in a crossover design; *e.g.*, 1st day: control; 2nd day: intake schedule 1; 3rd day: intake schedule 2; 4th day: intake schedule 3. All received a standard breakfast (515 Kcal; protein: 22.0 gram; fat: 7.9 gram; carbohydrate: 84.6 gram). For the study, the subjects were requested to fast for at least 12 hours prior to breakfast on the following morning, and to finish their breakfast within 15 min. Blood samples were collected at 0, 30, 60, 120 and 180 min after the start of breakfast. Plasma glucose was measured by the glucose dehydrogenase method and serum insulin was measured by the enzyme immunoassay method at SRL, Inc. (Tokyo, Japan).

Statistical analysis

Data were expressed as mean ± SE. Profiles of the plasma glucose concentrations were also expressed as the glucose increment above fasting plasma glucose (glucose excursions). Analyses of the time-profiles of the plasma glucose and serum insulin levels were performed by Dunnett's test. The areas under the curve from just before a meal to 180 min after the start of a meal ($AUC_{0-180\ min}$) of plasma glucose excursions and serum insulin levels were calculated by the trapezoid method, and two-way layout analysis of variance (ANOVA) with Bonferroni's test was performed. Differences with P values of less than 0.05 were considered to be significant.

Results

Effects of miglitol administered by different schedules on the plasma glucose levels

As shown in Figure 1, the plasma glucose levels following miglitol administration by intake schedules 1 and 3 at 30 min after the start of a meal were significantly decreased as compared with that in the control condition (95.9 ± 3.7, 101.2 ± 3.1 vs. 126.3 ± 4.0 mg/dl). This result was consistent with a previous report [9]. The most significant decrease in the plasma glucose levels as compared with that in the control condition was observed at 60 min after a meal following miglitol administration by intake schedule 2, again consistent with our previous report (87.1 ± 4.8 vs. 115.7 ± 5.3 mg/dl) [11]. The plasma glucose levels in intake schedules 3 at 180 min after a meal were slightly increased as compared with the level in the control condition (97.6 ± 2.7 vs. 87.8 ± 2.5 mg/dl). However, there were no significant differences in the $AUC_{0-180\ min}$ of plasma glucose between the control condition and any of the three intake schedules (data not shown). We assumed that since healthy subjects show smaller increases in the postprandial blood glucose levels than diabetic patients, the $AUC_{0-180\ min}$ of plasma glucose predominantly reflects basal glucose levels rather than increments of the glucose levels after a meal. We therefore calculated the increments of the blood glu-

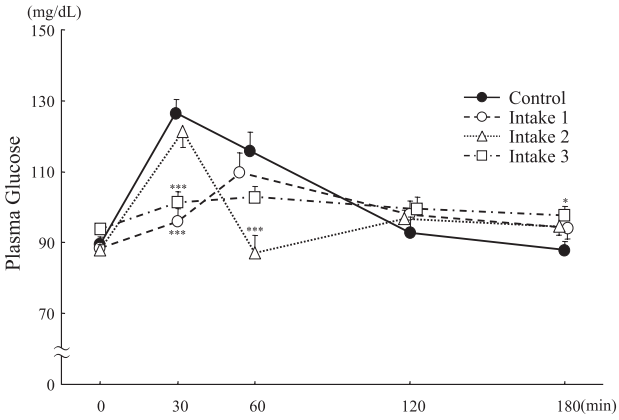

Fig. 1. Time-profiles of the plasma glucose levels for each intake schedule of miglitol.
Data are expressed as means ± SEM. *p<0.05, ***p< 0.001 vs. control. Control: filled circles; Intake 1: clear circles; Intake 2: triangles; Intake 3: squares.

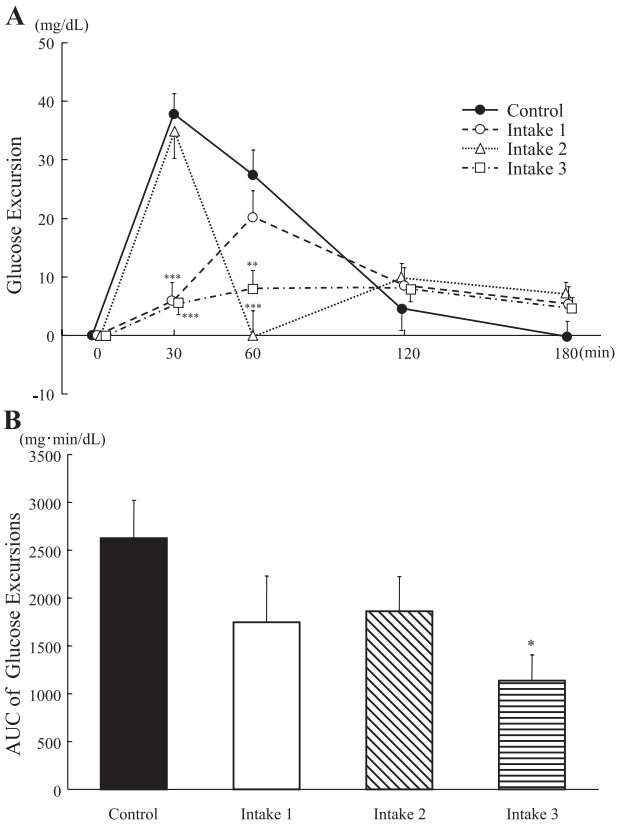

Fig. 2. Glucose excursions in the control condition and for the three intake schedules of miglitol.
A: Time-profiles of the plasma glucose excursions, defined as increments of plasma glucose above the fasting plasma glucose, for each intake schedule of miglitol. B: The $AUC_{0-180\ min}$ of the plasma glucose excursions for each intake schedule of miglitol. Data are expressed as means ± SEM. *p<0.05, ***p<0.001 vs. control. Control: filled circles; Intake 1: clear circles; Intake 2: triangles; Intake 3: squares.

cose levels after a meal (glucose excursions). Figure 2A shows the time-profiles of the plasma glucose excursions in the control condition and following miglitol administration by each of the intake schedules. The plasma glucose excursions at 30 min after a meal were significantly decreased following miglitol administration by intake schedules 1 and 3 as compared with that in the control condition (5.8 ± 3.1, 5.5 ± 2.3 vs. 37.8 ± 3.3 mg/dl). The plasma glucose excursions up to 60 min after a meal following miglitol administration by schedules 2 and 3 were also significantly decreased as compared with that in the control condition (0.0 ± 4.2, 8.0 ± 3.0 vs. 27.3 ± 4.2 mg/dl). Consequently, the $AUC_{0-180\ min}$ of the postprandial glucose excursions was significantly reduced as compared with that in the control condition only following miglitol administration by intake schedule 3 (Fig. 2B).

Effects of miglitol administered by different schedules on the serum insulin levels

As shown in Figure 3A, the serum insulin levels were significantly decreased, as compared with that in the control condition, at 30 min after a meal following miglitol administration by intake schedules 1 and 3 (17.3 ± 2.3, 14.5 ± 1.7 vs. 62.1 ± 11.2 μU/ml). This result was consistent with previous reports of miglitol significantly decreasing the postprandial insulin levels [9–14]. Serum insulin levels at 60 min after a meal were significantly decreased as compared with that in the control condition following miglitol administraton by intake schedules 1, 2 and 3 (42.0 ± 5.1, 26.7 ± 4.9, 21.0 ± 3.4 vs. 87.4 ± 11.3 μU/ml). Serum insulin levels at 120 min after a meal were significantly decreased as compared with that in the control condition following miglitol administration by intake schedules 2 and 3 (21.9 ± 2.9, 25.8 ± 4.3 vs. 53.1 ± 11.6 μU/ml). The $AUC_{0-180\ min}$ of the serum insulin levels was significantly decreased as compared with that in the control condition following miglitol administration by any of the three intake schedules (Fig. 3B). The $AUC_{0-180\ min}$ of the serum insulin levels following miglitol administration by intake schedule 3 was significantly decreased as compared with that following the drug administration by intake schedule 1.

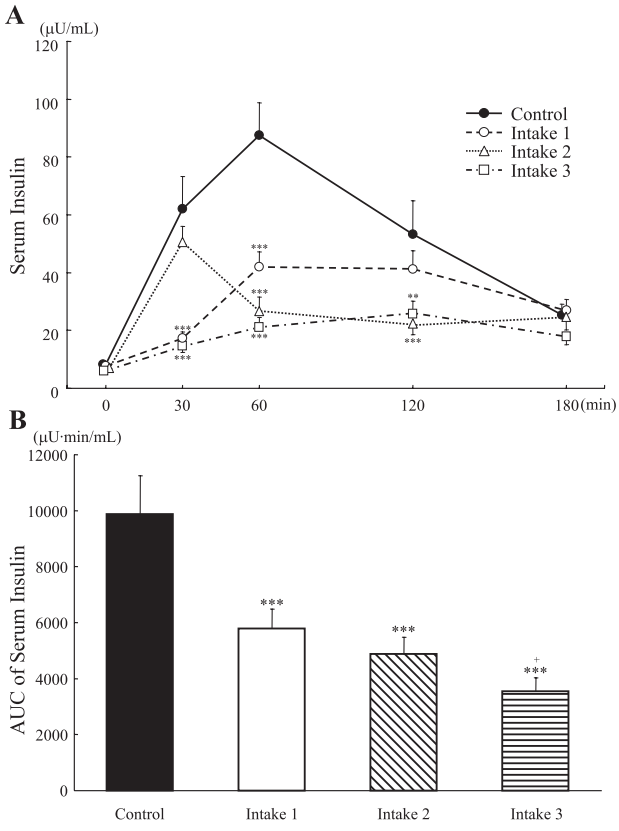

Fig. 3. Serum insulin levels in the control condition and for the three intake schedules of miglitol. A: Time-profiles of the serum insulin levels for each intake schedule of miglitol. B: The $AUC_{0-180\ min}$ of the serum insulin levels for each intake schedule of miglitol. Data are expressed as means ± SEM. *p<0.05, **p<0.01, ***p<0.001 vs. control. $^{+}$p<0.05 vs. intake 1.
Control: filled circles; Intake 1: clear circles; Intake 2: triangles; Intake 3: squares.

Adverse events

No adverse events were noted following the administration of miglitol by any of the intake schedules in the present study.

Discussion

We recently demonstrated that miglitol administered even 30 min after the start of a meal significantly decreased the postprandial glucose levels in Japanese type 2 diabetic patients [11]. In the present study, we examined whether a divided-dose regimen of miglitol, namely, administration of the drug just before a meal and at 15 minutes after the start of a meal, would attenuate postprandial excursions of the plasma glucose and serum insulin levels even more effectively. The most important finding of our study was that the $AUC_{0-180\ min}$ of glucose excursions was significantly decreased only by following administration of miglitol by intake schedule 3, although intake schedules 1 and 2 were also associated with a tendency towards decrease of this parameter as compared with that in the control condition (Fig. 2B). We interpret these results as indicating that the drug administered by intake schedule 3 exerts additive effects as compared with that following its administration by intake schedules 1 and 2, despite the total drug dose being the same in all the three intake schedules (50 mg).

Miglitol has been reported to be more effective at reducing the blood glucose levels at 30 and 60 min after a meal than voglibose [9]. Consistent with this report, we have recently shown that miglitol administered at 15 min after the start of a meal significantly decreased the postprandial glucose levels at 60 and 120 min in Japanese type 2 diabetic patients [11]. Based on these findings, we hypothesized that administration of miglitol in divided doses pre- and post-meal (divided-dose regimen) might attenuate the postprandial plasma glucose excursions more effectively than either pre-meal or post-meal administration.

As shown in Figures 2A and 3A, the effect of divided-dose (25 mg each) administration of miglitol (intake schedule 3) of reducing the plasma glucose excursions and serum insulin levels at 30 and 60 min after a meal was observed even at the usual dose (50 mg) of the drug , the same as that used for intake schedules 1 and 2. It is, therefore, conceivable that 25 mg of miglitol is sufficient for attenuating the rapid rise of blood glucose in the early postprandial phase in healthy men.

Then, are the major observations in this report common to all α-glucosidase inhibitors or only unique to miglitol? It has been reported that miglitol, as well as acarbose and voglibose, increase glucagon-like peptide-1 (GLP-1) secretion in type 2 diabetic patients [15–17]. The faster plasma glucose lowering effect of miglitol may be attributable to its greater absorption as well as its effect of activating GLP-1. To test whether the results obtained with the divided-dose regimen could be extrapolated to all α-glucosidase inhibitors, we propose to examine the effects of other αGIs, such as acarbose and voglibose, administered just before and 15 min after the start of a meal, and their effect of acti-

vating GLP-1.

Our results clearly demonstrate that administration of miglitol in divided doses is more effective for reducing the rise of the plasma glucose levels after a meal than its administration as a single dose either just before or at 15 min after the start of a meal. In this connection, Rosak *et al.* reported that the maximum glucose-lowering effect of acarbose was obtained when the drug was administered at the start of a meal or within 15 min after the start of a meal in type 2 diabetic patients [18]. Asakura *et al.* reported that acarbose was effective when administered within 30 min after the start of a meal in healthy subjects or subjects with IGT [19]. To the best of our knowledge, however, there have been no reports until now of the efficacy of αGIs administered in divided doses, which appears, as shown in this study, to be the most effective for postprandial glucose regulation.

In this study, no significant decrease of the $AUC_{0-180\ min}$ of the plasma glucose excursions was observed following administration of the drug by intake schedules 1 or 2 (Fig. 2B). In contrast, in type 2 diabetic patients, administration of miglitol at 15 min after the start of a meal as well as that just before the meal decreased the AUC of plasma glucose [11]. This apparent discrepancy may possibly be explained by the relatively smaller increases of the postprandial plasma glucose levels in healthy subjects than in diabetic patients.

Attenuation of the postprandial insulin secretion is crucial in type 2 diabetic patients, because excess insulin secretion may lead to obesity. In this connection, administration of acarbose at 15 min after the start of a meal reduced postprandial increase of the serum insulin levels in type 2 diabetic patients [18]. Our corresponding (intake schedule 2) results for miglitol in healthy subjects was consistent with those reported in the literature. Until now, however, there has been no evaluation of the effect of αGI administration in divided doses on the postprandial increase of insulin secretion. In this connection, our results clearly demonstrated that administration of miglitol in two divided doses was effective for attenuation of the postprandial increase of the insulin levels in healthy subjects. The effect of the timing of administration of miglitol in relation to meals on the postprandial insulin secretion in type 2 diabetic patients is an important issue and should be investigated thoroughly.

Although the divided-dose regimen may be more effective than the single-dose regimen, it is quite difficult to ensure compliance with thrice-daily intake of the divided-dose regimen. Thus, it remains to be solved how patients take the medication to achieve the best glycemic control. Dissolving miglitol tablets in drinking water (or tea) or the drug containing rapid-acting and slow-acting components of miglitol may be helpful.

Gastrointestinal adverse effects may occur with discontinuation of treatment with αGIs [20, 21]. Because none of the subjects complained of gastrointestinal symptoms in this study, we propose to examine whether the occurrence of gastrointestinal adverse effects may be associated with the intake patterns of αGIs.

In conclusion, administration of miglitol in two divided doses, that is, just before and 15 minutes after the start of a meal, appeared to be the most suitable for obtaining effective regulation of postprandial plasma glucose excursions in healthy men. Based on these results, it is considered that the divided-dose administration regimen may also be the most effective for regulation of postprandial hyperglycemia in type 2 diabetic patients. We therefore propose to systemically evaluate the long-term effects of administration of miglitol in divided doses on the glycemic control, incidence of adverse events and patient adherence to αGIs.

Acknowledgments

This work was supported in part by the Yokohama City University Center of Excellence Program and a grant for the 2006 Strategic Research Project (K18005) of Yokohama City University.

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