Mosapride citrate, a 5-HT$_4$ receptor agonist, increased the plasma active and total glucagon-like peptide-1 levels in non-diabetic men

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Abstract. Mosapride citrate, a selective agonist of the 5-hydroxytryptamine (5-HT)$_4$ receptor, is typically used to treat heartburn, nausea, and vomiting associated with chronic gastritis or to prepare for a barium enema X-ray examination. Mosapride citrate reportedly improves insulin sensitivity in patients with type 2 diabetes. As mosapride citrate activates the motility of the gastrointestinal tract, we hypothesized that mosapride citrate affects incretin secretion. We examined the effect of the administration of mosapride citrate on plasma glucose, serum insulin, plasma glucagon, and plasma incretin levels before breakfast and at 60, 120, and 180 min after breakfast in men with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) to exclude gastropathy. Mosapride citrate was administered according to two different intake schedules (C: control (no drug), M: mosapride citrate 20 mg) in each of the subject groups. The area under the curve (AUC) of the plasma glucose levels was smaller in the M group than in the C group. The time profiles for the serum insulin levels at 60 and 120 min after treatment with mosapride citrate tended to be higher, although the difference was not statistically significant. The AUCs of the plasma active and total glucagon-like peptide-1 (GLP-1) levels were significantly larger in the M group than in the C group. No significant difference in the AUC of the plasma glucose-dependent insulitropic polypeptide (GIP) level was observed between the two groups. Our results suggest that mosapride citrate may have an antidiabetic effect by increasing GLP-1 secretion.

Key words: glucagon-like peptide-1 (GLP-1), glucose-dependent insulitropic polypeptide (GIP), Mosapride citrate

RECENTLY, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogue have been widely used to treat patients with type 2 diabetes. Accordingly, many studies on incretin have been published. The alpha glucosidase inhibitor miglitol protects against carbohydrate absorption in the upper portion of the small intestine; therefore, a relatively higher amount of carbohydrate is absorbed in the lower portion of the small intestine, and this change increases GLP-1 secretion while decreasing the overall secretion of glucose-dependent insulitropic polypeptide (GIP) [1-3]. We previously reported that combined therapy with miglitol and sitagliptin further increases the active plasma GLP-1 levels, compared with miglitol or sitagliptin monotherapy [4-6].

The 5-hydroxytryptamine (5-HT) receptor subtypes have been identified as 5-HT$_1$ to 5-HT$_7$. The 5-HT$_4$ receptor is abundant in the stomach and intestine [7-9]. A 5-HT$_4$ receptor agonist accelerated gastric emptying and motility [10]. Mosapride citrate, a selective agonist of the 5-HT$_4$ receptor, is typically used to treat heartburn, nausea, and vomiting associated with chronic gastritis (5 mg, three times a day) or to prepare for a barium enema X-ray examination before (20 mg) and after (20 mg) the oral intake of gastrointestinal lavage solution. Mosapride has no dopamine D$_2$ receptor antagonist activity, unlike other gastrokinetic agents such as metoclopramide [11]. Mosapride citrate reportedly improves glycemic control in patients with type 2 diabetes [12] and in patients with gastropathy arising from diabetes [13]. By contrast, cisapride, which is another selective agonist of the 5-HT$_4$ receptor but is presently prohibited because of its effect on the QT interval, has no effect on glycemic control [14,
15]. Thus, the mechanisms responsible for the effect of mosapride citrate on the amelioration of hyperglycemia remain unknown. Metoclopramide, which antagonizes the dopamine D2 and 5-HT3 receptors and stimulates 5-HT4 receptors, reportedly increases GLP-1 and GIP release after the intraduodenal infusion of glucose [16]. As mosapride citrate activates the motility of the gastrointestinal tract, we hypothesized that mosapride citrate might also affect incretin secretion. Therefore, we examined the effect of the administration of mosapride on the plasma glucose, serum insulin, plasma glucagon, and plasma incretin levels in men with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) to exclude gastropathy.

Materials and Methods

Subjects and measurements

After obtaining approval from the Institutional Ethics Review Committee of Yokohama City University, 12 men (3 IGT men and 9 NGT men) were enrolled, as shown in Table 1. Informed consent was obtained from each of the subjects prior to the start of the study. The protocol was registered in the UMIN Clinical Trial Registry as UMIN000007292. This trial was performed over the course of two days in each subject (Day 1: no mosapride, Day 2: mosapride alone [20 mg] administered 2 hours before breakfast). These two trials were conducted within 2 weeks for each subject. Three men enrolled in this study received the same standard breakfast on day 1 and day 2 (849 Kcal; protein: 25.3 grams; fat: 27.5 grams; carbohydrate: 125 grams), and nine men received a different standard breakfast on day 1 and day 2 (674 Kcal; protein: 20.4 grams; fat: 22.4 grams; carbohydrate: 97.8 grams).

Blood samples were collected before the start of breakfast and at 60, 120, and 180 min after the start of breakfast. The plasma glucose, serum insulin, plasma glucagon, plasma active and total GLP-1, and plasma total GIP levels were measured. The plasma active GLP-1 and plasma total GIP levels were measured using an ELISA kit (Millipore Corporation, MA, USA) at SRL, Inc. (Tokyo, Japan). The plasma total GLP-1 levels were measured using an ELISA kit (Millipore Corporation, MA, USA) at our laboratory. The plasma active GLP-1 level was measured using a direct method according to our recent report [17]. We measured the total GIP level in this study because we could not obtain a commercially available kit capable of measuring active GIP accurately.

Statistical analysis

The data were expressed as the means ± SE. The analyses of the time profiles were performed using a two-way analysis of variance (ANOVA) with Bonferroni-type multiple comparisons. The area under the curve (AUC) from after the start of the meal until 180 min was calculated using the trapezoid method, and the results were analyzed using a paired t-test.

Results

The time profiles and the AUCs for the plasma glucose levels are shown in Fig. 1. The plasma glucose levels at 120 and 180 min after the start of the meal were significantly lower in the mosapride citrate-treated group than in the control group (Fig. 1A). As a result, the AUC of the plasma glucose levels was smaller in the mosapride citrate-treated group than in the control group (Table 2).

The serum insulin levels at 60 and 120 min after treatment with mosapride citrate tended to be elevated, but the differences were not statistically significant (Fig. 2A). No significant differences in the AUCs for serum insulin were observed between the two groups (Table 2). Also, no significant differences in the time profiles or the AUCs for the plasma glucagon levels were observed between the two groups (Fig. 3A and Table 2).

The plasma active GLP-1 levels at 60 and 120 min after the meal were significantly higher in the mosapride citrate-treated group than in the control group (Fig. 4A). As a result, the AUC of the plasma active GLP-1 levels was significantly larger in the mosapride citrate-treated group than in the control group (Table 2). The plasma

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of 12 men</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Body height (m)</td>
</tr>
<tr>
<td>37.0±1.9</td>
<td>1.75±0.01</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SE.
The HbA1c value was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated using the following formula: HbA1c (%%) = HbA1c (Japan Diabetes Society [JDS]) (%%) +0.4%.
Effect of mosapride on plasma GLP-1 level

Table 2 Comparison of each AUCs between control and mosapride citrate group

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Mosapride group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/min/L)</td>
<td>1179 ± 57</td>
<td>1125 ± 58</td>
<td>0.0050</td>
</tr>
<tr>
<td>Serum insulin (pmol/min/L)</td>
<td>64218 ± 9985</td>
<td>79629 ± 17360</td>
<td>0.2187</td>
</tr>
<tr>
<td>Plasma glucagon (ng/min/L)</td>
<td>15035 ± 845</td>
<td>15492 ± 833</td>
<td>0.3481</td>
</tr>
<tr>
<td>Plasma active GLP-1 (pmol/min/L)</td>
<td>952 ± 175</td>
<td>1548 ± 224</td>
<td>0.0021</td>
</tr>
<tr>
<td>Plasma total GLP-1 (pmol/min/L)</td>
<td>1666 ± 226</td>
<td>2608 ± 275</td>
<td>0.0001</td>
</tr>
<tr>
<td>Plasma total GIP (pmol/min/L)</td>
<td>14627 ± 1488</td>
<td>14847 ± 1306</td>
<td>0.8996</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SE. Differences in P values of less than 0.05 were considered significant.

Fig. 1 Plasma glucose levels in mosapride citrate (M) and control (C) groups. A: Time profiles of the plasma glucose levels. The control group is shown as the dotted line, and the mosapride group is shown as the solid line. The data are presented as the mean ± SE. *P < 0.05 and **P < 0.01 vs. control group. B: AUCs of the plasma glucose levels from the start of breakfast until 180 min after breakfast for each subject before and after the administration of mosapride citrate. The AUCs of the 3 IGT men are shown as the dotted lines, and the AUCs of the 9 NGT men are shown as the solid lines.

Fig. 2 Serum insulin levels in mosapride citrate (M) and control (C) groups. A: Time profiles of the serum insulin levels. The control group is shown as the dotted line, and the mosapride group is shown as the solid line. The data are presented as the mean ± SE. B: AUCs of the serum insulin levels from the start of breakfast until 180 min after breakfast for each subject before and after the administration of mosapride citrate. The AUCs of the 3 IGT men are shown as the dotted lines, and the AUCs of the 9 NGT men are shown as the solid lines.
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The AUCs for the plasma total GLP-1 levels were increased in 6 subjects whose insulin levels were also increased after mosapride administration (Fig. 5B). The values were also increased in all 5 subjects whose insulin levels were not increased after mosapride administration (Fig. 5B). Accordingly, differences in the active and total GLP-1 levels were not seen between the subjects with and those without an increase in their insulin levels after mosapride administration.

The AUCs for serum insulin were increased by the administration of mosapride in 7 subjects and decreased in 5 subjects (Fig. 2B). The AUCs for the plasma active GLP-1 levels were increased after the administration of mosapride in all the subjects (Fig. 4B). The AUCs for the plasma total GLP-1 levels were increased in 6 subjects whose insulin levels were also increased after mosapride administration (Fig. 5B). The values were also increased in all 5 subjects whose insulin levels were not increased after mosapride administration (Fig. 5B). Accordingly, differences in the active and total GLP-1 levels were not seen between the subjects with and those without an increase in their insulin levels after mosapride administration.
Effect of mosapride on plasma GLP-1 level

The present study investigated the effects of mosapride citrate on plasma GLP-1 levels. Mosapride citrate was found to exert an antidiabetic effect by increasing GLP-1 secretion. Ueno et al. reported that the administration of mosapride citrate for one week significantly improved glucose responses as evaluated using an intravenous glucose test [12]. They also reported that the administration of mosapride citrate significantly increased the number of autophosphorylation of insulin receptors.

No significant differences in the time profiles and the AUCs for the plasma total GIP levels were observed between the two groups (Fig. 6A and Table 2).

Discussion

The most important finding in this study is that the administration of mosapride citrate increased the AUC of the plasma active GLP-1 level and decreased the AUC of the plasma glucose level. Based on the results of the present study, mosapride citrate appears to exert an antidiabetic effect by increasing GLP-1 secretion.

Mosapride citrate reportedly has beneficial effects in patients with diabetes. Ueno et al. reported that the administration of mosapride citrate for one week significantly improved the glucose responses as evaluated using an intravenous glucose test [12]. They also reported that the administration of mosapride citrate significantly increased the number of autophosphorylation of insulin receptors as well as the
to elucidate the mechanism responsible for the increase in GLP-1 secretion and flow in the small intestine.

Given the fact that diabetes develops when the insulin secretion by beta cells is insufficient to compensate for insulin resistance [22, 23] and GLP-1 reportedly inhibits apoptosis in humans, the increase in the GLP-1 concentration may be important for improving beta cell function [24]. In addition, the increase in GLP-1 may protect against obesity because of the anti-obesity effect GLP-1 [25-28].

The standard dose for chronic gastritis is 5 mg three times daily (15 mg/day), while 20 mg of mosapride citrate is clinically used to prepare for a barium enema X-ray examination. We used 20 mg of mosapride in this study because the single administration of 5 mg of mosapride is considered to have a relatively weak effect on improving metabolic parameters during the meal tolerance test. We plan to evaluate the effect of the single administration of mosapride (5 mg dose) on glucose metabolism in the future.

In conclusion, the administration of mosapride citrate increased GLP-1 secretion and decreased the AUC of the plasma glucose level. In the future, we would like to evaluate the effectiveness of mosapride citrate on incretin levels in patients with type 2 diabetes.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research (B) 19390251 and (B) 21390282 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, a Medical Award from the Japan Medical Association, and the Suzuken Memorial Foundation.

Conflicts of Interest

No potential conflicts of interest relevant to this article were present.

References


