Improvement in Medication Compliance and Glycemic Control with Voglibose Oral Disintegrating Tablet

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Good compliance with hypoglycemic therapy is important for diabetes treatment, since positive relationship between medication compliance and glycemic control has been reported. To improve medication compliance, the oral disintegrating tablet technology that facilitates drug administration without water has been employed in various drugs, including voglibose, an alpha glucosidase inhibitor. In the present survey, we investigated safety profile of voglibose oral disintegrating tablet (VODT), and whether treatment with VODT results in improvement of medication compliance and glycemic control. Patients with diabetes received VODT 0.6 or 0.9 mg/day for 12 weeks. Among 2,930 eligible patients, adverse drug reactions were observed in 3.6%, with the most common being abdominal distension, flatulence, diarrhea, and increased alanine aminotransferase levels. In 1,067 patients who received conventional voglibose tablet (CVT) prior to VODT, 53.1% reported that taking VODT was easier than taking CVT. Medication compliance was improved after switching to VODT in 28.4% of patients who missed taking tablets more than one time a week during CVT treatment. A significant decrease in HbA₁C levels was observed in patients whose medication compliance was improved after switching to VODT ($P = 0.033$), but there was no significant reduction in HbA₁C levels in patients whose medication compliance did not change. In conclusion, the present survey suggests that the safety profile of VODT is comparable with that of CVT, and switching from CVT to VODT has positive impact on medication compliance which may lead to an improvement in glycemic control.

Diabetes; alpha-glucosidase inhibitor; voglibose; medication compliance; glycemic control.

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The alpha-glucosidase inhibitors (AGIs) represent a class of oral hypoglycemic agents that reduce postprandial glucose excursion by inhibiting alpha-glucosidase activities, thereby leading to delay the absorption of glucose in the small intestine (Matsumoto et al. 1998). Results from a survey have demonstrated that the prerequisite for AGIs to be taken just before each main meal had a negative impact on medication compliance (or adherence), particularly in individuals who frequently dined out (Yamaoka et al. 1999). Furthermore, medication compliance is potential-
Compliance with Voglibose Oral Disintegrating Tablet is compromised in patients who receive concomitant oral hypoglycemic agent with AGI because of difference in dose method. Since it has been reported that compliance with hypoglycemic treatment has a significant impact on blood glucose levels, better medication compliance is required to obtain better glycemic control (Rozenfeld et al. 2008).

Recently, the oral disintegrating tablet technology has been employed in various drugs (e.g. acid-suppressant drugs, antihypertensive drugs, or hypoglycemic drugs). The oral disintegrating tablet facilitates drug administration without water, and this may be useful for elderly patients (who sometimes have difficulty in swallowing) or patients in working age (who sometimes have difficulty in taking water). Also, this formulation is expected to improve medication compliance.

Voglibose is a potent AGI developed by Takeda Pharmaceutical Company Limited (Osaka, Japan) (Goto et al. 1992). A conventional voglibose tablet formulation (CVT) has been available for diabetes treatment since 1994, and voglibose oral disintegrating tablet (VODT) was launched in 2004 in Japan, and it is now widely used in various Asian countries. During its development, VODT was found to be equivalent to CVT with regards to hypoglycemic effects and safety in a clinical study involving 24 healthy volunteers. However, the safety of VODT in patients with diabetes requires clarification, and it is not well investigated whether switching from CVT to VODT results in improvement of medication compliance and glycemic control. Therefore, we investigated safety profile of VODT, and impact of VODT on medication compliance and glycemic control in a large cohort of Japanese patients with diabetes.

**PATIENTS AND METHODS**

**Patients and treatment**

This post-marketing survey was designed as an open-label, multicenter, observational evaluation of VODT in everyday clinical practice. Patients with type 1 or 2 diabetes were eligible including those who were currently receiving hypoglycemic agents. When patients had received CVT, drug was switched to VODT at enrollment to the survey. Patients were treated with VODT 0.6 or 0.9 mg/day for 12 weeks. The dose of VODT was left to the discretion of individual physician based on the usual care they would provide in day-to-day clinical practice. The use of additional drugs was not restricted during the survey with the exception of CVT.

This survey was performed in compliance with the Good Post-marketing Study Practice (GPSP), a ministerial ordinance concerning the standards of the implementation of post-marketing survey of drugs in Japan (Ministry of Health, Labor and Welfare 2004). Examination by institutional committee in each institution and patient’s written informed consent were not mandatory, because the GPSP does not require those for post-marketing survey.

**Adverse drug reactions**

Adverse events were monitored throughout the 12 weeks’ treatment period with VODT. Only those for which causal relationship with VODT could not be ruled out were considered as adverse drug reactions (ADRs) and these were classified according to the Medical Dictionary for Regulatory Activities version 9.1 (Brown et al. 1999).

**Convenience of VODT therapy**

After 12 weeks’ treatment, the convenience in terms of taking VODT was assessed by patients who previously received CVT with following 3 statements: “taking VODT was easier than taking CVT”, “there was no difference between VODT and CVT with regards easiness to take”, or “taking VODT was more difficult than taking CVT”.

**Medication compliance**

The medication compliance was assessed by patients who previously received CVT with following 4 statements: “I did not miss taking any tablets”, “I missed taking tablets 1 or 2 times a week”, “I missed taking tablets 3 or 4 times a week”, or “I missed taking tablets more than a half of the week”. Compliance with CVT was assessed at enrollment to the survey, and compliance with VODT was assessed after 12 weeks’ treatment with VODT.

Furthermore, compliance with VODT was compared with previous CVT therapy based on following 3 statements: improved (compliance with VODT was better than previous treatment with CVT), not changed (compliance with VODT was comparable with previous
Compliance with Voglibose Oral Disintegrating Tablet

Treatment with CVT excluding patients who rated their compliance as “I did not miss taking any tablets” in both VODT and CVT, or worse (compliance with VODT was worse than previous treatment with CVT).

HbA$_1C$

HbA$_1C$ levels were measured at enrolment to the survey (baseline) and following 12 weeks’ treatment with VODT.

Statistical analysis

Numerical data was expressed as mean ± standard deviation. Changes in HbA$_1C$ were analyzed for patients who measured both at baseline and 12 weeks' treatment. A subgroup analysis was performed for patients who switched from CVT to VODT at enrollment to the survey (Group 1) and those who had not received voglibose prior to the survey (Group 2).

Paired t-tests were used to compare HbA$_1C$ levels at baseline and 12 weeks’ treatment. Values of $P < 0.05$ (two-sided) were considered to be statistically significant.

**RESULTS**

Patient characteristics

Of the 2,975 patients enrolled in this survey, 2,930 were eligible for the analysis (45 patients were excluded with the main reasons being: did not receive VODT, did not return to the hospital for the follow-up visit, or were included twice in the enrolled patient list). The patient characteristics for all eligible patients and the 2 subgroups are summarized in Table 1. Prior to VODT administration, 36.4% of patients received CVT and 42.4% received sulfonylureas. The percentage of patients with dysphagia was 0.5% and those with a limitation of water intake was 1.2%.

Treatment after start of VODT administration

The initial dose of VODT was 0.6 mg/day in 58.1% of eligible patients. In terms of concomitant treatment, sulfonylureas were used most often with VODT (43.7% of patients), and 36.7% of patients did not receive any concomitant hypoglycemic agents (Table 2).

Safety

Among 2,930 eligible patients, ADRs were observed in 105 patients (3.6%) with the most common being abdominal distension (1.0%), flatulence (0.6%), diarrhea (0.5%), and increased alanine aminotransferase levels (0.5%).

Convenience of VODT therapy

Of 1,067 patients in Group 1, 53.1% reported that “taking VODT was easier than taking CVT”. This value was 57.0% in patients aged < 60 years which was higher than for patients aged ≥ 60 years (Table 3). More than 80% of patients with dysphagia or a limitation of water intake reported that “taking VODT was easier than taking CVT” (Table 3).

Medication compliance

Among 1,067 patients in Group 1, the percentage of patients who reported “I did not miss taking any tablets”. during treatment with CVT was 68.0%. Among 341 patients who reported “I missed taking tablets 1 or 2 times a week”, “I missed taking tablets 3 or 4 times a week”, or “I missed taking tablets more than a half of the week”, medication compliance was improved following switch to VODT in 28.4% of cases (Table 4).

To investigate whether concomitant oral hypoglycemic agents affected compliance with CVT or VODT, subgroup analysis was performed in patients who received any concomitant oral hypoglycemic agents during treatment with CVT and VODT ($n = 633$) and in those who did not receive these agents ($n = 363$) (Table 5). The percentage of patients who reported “I did not miss taking any tablets”. during treatment with CVT was 67.0% in patients receiving concomitant oral hypoglycemic agents and 72.7% in those not receiving these agents. The percentage of patients whose compliance was improved following treatment with VODT was 25.9% in patients receiving concomitant oral hypoglycemic agents and 30.8% in those not receiving these agents (Table 5).

Changes in HbA$_1C$

HbA$_1C$ levels at baseline and following 12 weeks’ treatment were 7.54 ± 1.50% and 7.12 ± 1.32% in all eligible patients, 7.21 ± 1.40% and 7.07 ± 1.32% in Group 1, and 7.72 ± 1.53% and
7.15 ± 1.31% in Group 2, respectively. Statistically significant decreases in HbA1c were observed in all groups after 12 weeks’ treatment compared with baseline: −0.42 ± 1.19% in all eligible patients (P < 0.001), −0.14 ± 1.05% in Group 1 (P < 0.001), and −0.57 ± 1.23% in Group 2 (P < 0.001).

Impact of changes in medication compliance on HbA1c was analyzed with patients in Group 1 excluding who changed concomitant hypoglycemic agents including insulin during the treatment with VODT (Fig. 1). The HbA1c change from baseline at 12 weeks’ treatment was −0.22 ± 0.88% in patients with improved medication compliance,
Compliance with Voglibose Oral Disintegrating Tablet

−0.07 ± 0.87% in those in whom medication compliance was not changed, and 0.14 ± 1.07% in those whose medication compliance was worse. A statistically significant decrease in HbA1c was observed only in patients with improved medication compliance ($P = 0.033$).

**DISCUSSION**

Good compliance with hypoglycemic therapy is very important for diabetes treatment since...
positive relationship between medication compliance and glycemic control has been reported (Rhee et al. 2005; Rozenfeld et al. 2008). Moreover, Sokol et al. reported that a high level of medication compliance was associated with lower disease related medical costs and hospitalization risk (Sokol et al. 2005). However, a systematic review revealed that many patients for whom diabetes medication was prescribed were poor compliers with treatment (Cramer 2004). To obtain better medication compliance, several methods including patient education have been recommended (Rubin 2005; Wens et al. 2005). Additionally, oral disintegrating tablet draws attention as an approach from drug formulation technology. In the present survey, improvement in medication compliance was observed in 28.4% of patients who switched from CVT to VODT at enrollment to the survey. This result was comparable with previous studies which reported a positive impact on medication compliance after switching from CVT to VODT (Koh 2005; Nakayama et al. 2006). A subgroup analysis of medication compliance was performed in patients who received concomitant oral hypoglycemic agents and those who did not, since we speculated that differences in dose method between voglibose and other agents might affect compliance with voglibose. Indeed, the percentage of patients who reported “I did not miss taking any tablets” during treatment with CVT was lower in patients who received concomitant oral hypoglycemic agents. The percentage of patients whose medication compliance was improved following VODT treatment was 25.9% in patients with concomitant oral hypoglycemic agents and 30.8% in those who did not receive these agents. In the Japanese Clinical Guidelines of Management of Diabetes, the benefit of AGI therapy is described as: “the hypoglycemic effect of AGI monotherapy is weaker than other hypoglycemic agents. However, AGI is suited for concomitant treatment with other agents because of its unique mechanism action”. (Japan Diabetes Society 2007). Since improvement in medication compliance after switching from CVT to VODT was observed even in patients who had concomitant oral hypoglycemic agents in the present survey, VODT may be beneficial for diabetes treatment which concomitant medication is common. However,

<table>
<thead>
<tr>
<th>Table 4. Medication compliance with CVT or VODT.</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
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<td><strong>Total</strong></td>
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</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Not missed</td>
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<tr>
<td>Missed 1 or 2 times a week</td>
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<tr>
<td>Missed 3 or 4 times a week</td>
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<tr>
<td>Missed more than a half of the week</td>
</tr>
</tbody>
</table>

\[ n (\%) \]

For VODT, voglibose oral disintegrating tablet; CVT, conventional voglibose tablet.
Table 5. Subgroup analysis of medication compliance with CVT or VODT.

1) Patients receiving concomitant oral hypoglycemic agents

<table>
<thead>
<tr>
<th></th>
<th>During VODT treatment</th>
<th>During CVT treatment</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Not missed</td>
</tr>
<tr>
<td>Total</td>
<td>633</td>
<td>424 (67.0)</td>
</tr>
<tr>
<td>Not missed</td>
<td>421</td>
<td>386 (91.7)</td>
</tr>
<tr>
<td>Missed 1 or 2 times a week</td>
<td>160</td>
<td>29 (18.1)</td>
</tr>
<tr>
<td>Missed 3 or 4 times a week</td>
<td>47</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>Missed more than a half of the week</td>
<td>5</td>
<td>1 (20.0)</td>
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</tbody>
</table>

n (%) Compliance improved 25.9% (55 / 212)

2) Patients not receiving concomitant oral hypoglycemic agents

<table>
<thead>
<tr>
<th></th>
<th>During VODT treatment</th>
<th>During CVT treatment</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Not missed</td>
</tr>
<tr>
<td>Total</td>
<td>363</td>
<td>264 (72.7)</td>
</tr>
<tr>
<td>Not missed</td>
<td>259</td>
<td>244 (94.2)</td>
</tr>
<tr>
<td>Missed 1 or 2 times a week</td>
<td>79</td>
<td>17 (21.5)</td>
</tr>
<tr>
<td>Missed 3 or 4 times a week</td>
<td>21</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Missed more than a half of the week</td>
<td>4</td>
<td>1 (25.0)</td>
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</tbody>
</table>

n (%) Compliance improved 30.8% (32 / 104)

VODT, voglibose oral disintegrating tablet; CVT, conventional voglibose tablet.

Our findings need to be interpreted with caution since we did not assess the condition of the instructions on drug administration given by physicians and pharmacists. The level of instruction could affect individual medication compliance. One of the aims of improving compliance...
Compliance with voglibose Oral Disintegrating Tablet with antidiabetic therapy is to obtain better glycemic control. In the present survey, significant improvement in HbA\(_1C\) (−0.22%) was observed only in patients whose medication compliance improved after switching from CVT to VODT, while there was no significant decrease in HbA\(_1C\) levels in patients whose medication compliance did not change. Nakayama et al. also reported that a significant decrease in HbA\(_1C\) levels was obtained only in patients whose medication compliance was improved after switching from CVT to VODT (Nakayama et al. 2006). In line with these reports, Rozenfeld et al. reported that each 10% increase in oral diabetes medication compliance was associated with a 0.1% HbA\(_1C\) decrease (Rozenfeld et al. 2008). Thus, it is reasonable to say that improvement in medication compliance is paralleled by a decrease in HbA\(_1C\) levels.

With regards to the convenience of taking VODT, 53.1% of patients who switched from CVT reported a preference for VODT. This value was 57.0% in patients aged < 60 years suggesting that VODT may be more beneficial in patients who are at working age. ADRs of VODT reported in this survey were similar to ADRs reported in previous post-marketing survey of CVT. Since no further concerns regarding the safety of VODT were observed, the results of this survey suggest that the safety profile of VODT is comparable with that of CVT.

In conclusion, the present survey suggests that switching from CVT to VODT has positive impact on medication compliance, and this may lead to an improvement in glycemic control.

**Fig. 1.** HbA\(_1C\) stratified according to the level of medication compliance
Acknowledgment

We thank the physicians at the 364 institutions that participated in this survey who made this work possible.

References


