Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, Decreases Systolic Blood Pressure in Japanese Hypertensive Patients with Type 2 Diabetes

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Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a newly developed oral hypoglycemic agent. Sitagliptin increases the level of glucagon-like polypeptide (GLP)-1 that increases insulin secretion. In addition, GLP-1 decreases salt intake and increases urinary salt excretion. Therefore, the sitagliptin treatment might lower blood pressure in hypertensive patients with type 2 diabetes. It also remains to be examined whether the reduction in blood pressure with sitagliptin treatment is related to the blood glucose improvement and the body weight decrease. To identify beneficial effects of sitagliptin treatment, we administered sitagliptin (50 mg) on alternate days to seventeen type 2 diabetes outpatients with insufficient blood glucose control (8 males and 9 females; mean age of 67.1 years). The patients were also treated with oral hypoglycemic agents and antihypertensive drugs for six months before and during the sitagliptin administration. We measured the level of hemoglobin (Hb) A1c, systolic blood pressure (SBP), and body mass index (BMI) for up to six months thereafter. Their BMIs remained unchanged. The levels of HbA1c were dropped from 6.5 ± 0.3% to 5.8 ± 0.3%, while SBP was also dropped from 130.0 ± 37.2 mmHg to 119.7 ± 9.4 mmHg. However, the degree of the decrease in HbA1c levels was not significantly correlated with that of SBP (r = 0.24). In conclusion, the present findings suggest that sitagliptin lowers SBP without reducing BMI, independent of the blood glucose reduction. The hypotensive effect is apparent with the alternate-day regimen of sitagliptin at a lower dose compared to the everyday medication.

Keywords: sitagliptin; dipeptidyl peptidase-4 inhibitor; hypertension; type 2 diabetes; glucagon-like polypeptide-1

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is an oral hypoglycemic drug originally released in 2009 in Japan. The inhibition of DPP-4 with sitagliptin increases the activity of glucagon-like polypeptide (GLP)-1, which was reported to decrease salt intake and increase urinary salt excretion (Gutzwiller et al. 2004, 2006). Sitagliptin may therefore lower blood pressure in salt-sensitive hypertension such as hypertensive type 2 diabetes. In fact, it has been reported that sitagliptin produced small but statistically significant reductions of 2 mmHg to 3 mmHg in 24-hour ambulatory blood pressure measurements in nondiabetic patients with mild to moderate hypertension (Mistry et al. 2008). However, these effects have not yet been confirmed in Japanese type 2 diabetes patients. Whether the reduction in blood pressure with sitagliptin treatment depends on the blood glucose improvement and the body weight decrease has not been investigated.

In view of sitagliptin’s long half-life, moreover, sufficient pharmacological effects may be obtained even if administered on alternate days (Herman et al. 2005). However, no such studies have been conducted. The aim of the present study was to determine whether a DPP-4 inhibitor reduces blood pressure and whether such effect is dependent on clinical changes of the glycemic control and body mass index (BMI).

Methods

We alternately administered 50 mg of sitagliptin to seventeen hypertensive Japanese type 2 diabetes patients with insufficient blood glucose control (Japan Diabetes Society value of HbA1c > 6.0%).

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The patients had shown no variation in blood pressure or did not have their hypotensive drugs changed over the previous six months. The definition of hypertension is the systolic BP $\geq$ 130 mmHg or the diastolic BP $\geq$ 80 mmHg. All subjects were outpatients who visited regularly to Iwate Prefectural Takata Hospital. Sitagliptin was taken after the breakfast. They had already taken many kinds of oral hypoglycemic agents (biguanides 16, pioglitazone 16, glinides 13, sulfonylureas 12 and $\alpha$-glucosidase inhibitors 6) and antihypertensive drugs (renin angiotensin system inhibitors 15, calcium channel blockers 11, diuretics 6 and others 7). We then evaluated their HbA1c, systolic blood pressure (SBP), and BMI for up to six months thereafter. The drugs they were administered had remained unchanged in the 6 months prior to the study as well as during the study period. The present study was conducted after obtaining informed consent from all subjects, and the study protocol was approved by the Ethics Committee of Iwate Prefectural Takata Hospital.

All statistical analyses were made using Statview 5.0 (SAS Institute, Cary, USA). Measurement values were noted in terms of mean ± s.d. To compare the numerical values such as BMI, HbA1c and SBP between the values at the baseline and after treatment, we used the ANOVA. Correlations were determined using Spearman’s rank correlation test. $P < 0.05$ was regarded as statistically significant.

Results

The clinical characteristics of the subjects prior to administration were shown in Table 1. BMI values at each month after administration were $25.3 \pm 2.6$, $25.3 \pm 2.6$, $25.3 \pm 2.5$, $25.2 \pm 2.6$, $25.2 \pm 2.6$, and $25.2 \pm 2.5$ kg/m$^2$, showing no significant changes during the six months. On the other hand, the levels of HbA1c were $6.3 \pm 0.2$, $6.1 \pm 0.3$, $6.0 \pm 0.3$, $5.9 \pm 0.3$, $5.8 \pm 0.4$, and $5.8 \pm 0.3\%$, dropping significantly from one month after administration, while SBPs were $124.7 \pm 17.2$, $123.7 \pm 12.6$, $121.0 \pm 14.1$, $122.6 \pm 14.3$, $120.4 \pm 12.2$, and $119.7 \pm 9.4$ mmHg, also dropping significantly from one month after administration (Fig. 1). Diastolic blood pressure was not significantly changed by treatment with sitagliptin. The degree of decrease in HbA1c after 6 months was not significantly correlated with that of SBP ($r = 0.24$, $p = 0.08$). None of the patients developed hypoglycemia and symptomatic hypotension.

Table 1. Baseline characteristics of the study subjects.

| number | 17 |
| age (years) | 67.1 ± 11.8 |
| male/female | 8 / 9 |
| duration (years) | 13.2 ± 5.9 |
| BMI (kg/m$^2$) | 25.4 ± 2.5 |
| BG (mg/dl) | 130.0 ± 37.2 |
| HbA1c (%) | 6.5 ± 0.3 |
| SBP (mmHg) | 130.4 ± 13.9 |
| DBP (mmHg) | 71.2 ± 5.6 |

Duration, diabetic duration; BMI, body mass index; BG, blood glucose concentration; HbA1c, glycated hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Discussion

Alternate-day administration of 50 mg/day of sitagliptin produced sufficient glycemic improvement effects in type 2 diabetes patients who were already being given numerous oral hypoglycemic drugs, because these subjects were moderate-degree hyperglycemics (median HbA1c of 6.4%, with a maximum of 7.3% and a minimum of 6.1%). Sitagliptin produced mostly significant changes in SBP on the order of +1 to −27 mmHg during the 6-month administration. Sitagliptin was also reported to have demonstrated significant hypotensive effects in a study of diabetic rats (Ferreira et al. 2010). Incretins regulate glucose homeostasis by increasing pancreatic insulin release. Insulin has been shown to have vasodilatory effects (Anderson et al. 1991), which may help explain the reduction in SBP in this study. On the other hand, hyperinsulinemia increases the salt re-absorption and sympathetic activity (Anderson et al. 1992). Unfortunately, insulin levels were not measured in the present study. It is difficult to explain the sitagliptin’s hypotensive effect with the action of insulin. As another explanation, a reduction in renal sodium reabsorption was suspected, due to a drop in blood glucose levels.

The degree of the decreases in HbA1c levels was not correlated with the changes in SBP, suggesting that the hypotensive action of sitagliptin was not directly mediated by glycemic reduction. The small sample size may account for the difficulty in detecting significant relationships. A recent report has shown that sitagliptin’s hypotensive actions can be related to its body weight reduction effects (Horton et al. 2010). In our study, however, there were no changes in BMI. In this connection, there were very few obese subjects in our study, and higher salt intakes are assumed to our subjects.
Jackson et al. (2008) have indicated that acute administration of a DPP-4 inhibitor increases blood pressure in spontaneously hypertensive rats via the vaso-constrictive effect of the neuropeptide Y (1) receptors. However, Pacheco et al. (2010) reported that that chronic administration of sitagliptin attenuated blood pressure rising in young prehypertensive adult spontaneously hypertensive rats, partially by inhibiting Na/H exchanger isofrom 3 (NHE3) activities in renal proximal tubule. Sitagliptin decreased blood pressure through its diuretic effect that increases the urinary sodium excretion. However, to our regret, we measured neither the change of urinary sodium excretion nor the inhibition of NHE3 revitalization in the present study.

Based on the previous findings of GLP-1 (Gutzwiller et al. 2004, 2006; Mistry et al. 2008), the reduction in SBP might have been caused by the increased levels of GLP-1 that would have resulted from sitagliptin treatment in these hypertensive patients with type 2 diabetes. However, the degree of the reduction in SBP with sitagliptin in our study is larger compared to the decreases in SBP noted with continuous infusion of GLP-1 during 48 hours in patients with type 2 diabetes (Toft-Nielsen et al. 1999) and with another DPP-4 inhibitor (Nathwani et al. 2006). In the present study, hypotensive effects were observed with sitagliptin therapy using smaller doses (50 mg/day, every other day) than usual (50 mg/day, every day). Interestingly, there is no difference in the SBP on the day when sitagliptin was taken and the day not taken in the subjects, as judged by measuring the home blood pressure. We hypothesized that the hypotensive effect of sitagliptin is obtained greater if the patients were administrated with sitagliptin every day. However, because their blood glucose levels had descended more than our expectation, we did not increase the dosage of sitagliptin.

The present study provides the important information, despite the small sample size and one arm study. The clinical benefit of sitagliptin on BP now needs to be established in a larger clinical randomized control trial in hypertensive patients with type 2 diabetes.

Conflicts of Interest

The Authors declare that there is no duality interest associated with this manuscript.

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