Effect of Cilostazol on Impaired Vasodilatory Response of the Brachial Artery to Ischemia in Smokers

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The vascular endothelial function of smokers is known to be impaired. This study investigated whether cilostazol could improve the vasodilatory response of the brachial artery to ischemia, an indicator of endothelial function, in ten male smokers. Endothelium-dependent vasodilatation and endothelium-independent vasodilatation of the brachial artery were measured in 11 male non-smokers and 20 male smokers with matching age and weight. The results showed that the vasodilatory response to reactive hyperemia was significantly smaller in the smokers (4.8 ± 1.6%) when compared to that in the non-smokers (7.6 ± 2.5%) (p = 0.0013). However, no significant difference in the vasodilatory response to isosorbide dinitrate was observed between the two groups. In addition, there were no significant differences in serum lipid, Lp (a), or blood homocysteine between the smokers and non-smokers. When 150 mg/day of cilostazol was administered for two weeks, the vasodilatory response to reactive hyperemia significantly improved (4.2 ± 1.2% to 7.8 ± 3.5%, p = 0.0032). The increased vasodilatory response to reactive hyperemia by cilostazol was reduced after cessation of the drug (4.5 ± 1.5%). These findings suggest that cilostazol improves vascular endothelial dysfunction in smokers. J Atheroscler Thromb, 2003; 10: 93–98.

Key words: Cilostazol, Smokers, Endothelial function, Nitric oxide

Introduction

Vascular endothelial cells play an important role in the regulation of vascular tone by releasing vasoactive substances, such as endothelin, prostaglandin and endothelium-derived relaxing factor (EDRF) (1). Endothelial cell injury is detectable from the early stages of the development of atherosclerosis, and the vasodilatory response to acetylcholine is impaired in damaged vessels (2).

In 1992, Celermajer et al. reported the usefulness of a non-invasive endothelial function test in which the vasodilatory response to reactive hyperemia, induced by releasing a tourniquet on the brachial artery, is measured (3). Since vasodilatation is partly dependent on EDRF (4–6), vasodilatory response is used as an indicator of endothelial function, particularly in nitric oxide (NO) production. The vasodilatory response to reactive hyperemia decreases with age and is smaller in individuals who are at risk of developing arteriosclerosis: men, smokers, or those with hyperlipidemia, hypertension or hyperhomocysteinemia (7–10).

Cilostazol, which was developed in Japan, is a potent inhibitor of platelet aggregation (11, 12) with vasodilatory effects (13, 14). This medication has been widely prescribed for more than 10 years for patients with peripheral arterial obstructive diseases. In 1999, this agent was approved by the United States Food and Drug Administration for the treatment of intermittent claudication. Cilostazol is a selective inhibitor of phosphodiesterase 3 (PDE3), an enzyme that breaks down cyclic AMP (cAMP). Large quantities of PDE3 are found in platelets and vascular smooth muscle cells, which are the target of arteriosclerosis therapy. Cilostazol relaxes vascular smooth muscle by raising cAMP levels in vitro (13). In patients
with peripheral arterial disease, cilostazol improves skin blood flow and clinical signs as a result of its vasodilating or antiplatelet effects (15). Cilostazol also suppresses the proliferation of vascular smooth muscle cells in vitro (16–19) and suppresses restenosis of the coronary artery following thrombolysis therapy using tPA, stenting, atherectomy or PTCA ex vivo. Cilostazol suppresses neointimal formation in animal models (20, 21) as well as carotid intima media thickness in patients with type 2 diabetes mellitus (22). Moreover, cilostazol enhances the activity of lipoprotein lipase, resulting in decreased serum triglyceride levels and increased serum HDL–cholesterol levels (23, 24). Hence, cilostazol is thought to be effective in treating arteriosclerosis (25).

This study investigated whether cilostazol could improve the vascular endothelial function of smokers.

Methods

Subjects
A vascular endothelial function test was performed on 11 male non-smokers and 20 male smokers with matching age and weight. These volunteers did not have a past or present history of coronary diseases, and the results of clinical laboratory tests showed no signs of hypertension, hyperlipidemia or diabetes. 150 mg/day of cilostazol, divided into morning, day and evening, was administered for two weeks to twelve smokers who gave informed consent, and the vasodilatory responses of these subjects were measured. Two of 12 smokers dropped out because of headaches. The level of smoking in these subjects remained constant during cilostazol administration.

Vascular endothelial function test
Endothelium-dependent vasodilatation and endothelium-independent vasodilatation were measured according to the method of Celermajer et al. (3). Each volunteer rested for 20 minutes, and an SSB2000–MultiView (Aloka Inc.) equipped with a 10-Mhz ultrasound probe (mechanical inline scanner) was used to measure the internal diameter of the brachial artery at a position several centimeters from the elbow, where the artery could easily be located. Next, a Manschette tourniquet was used to apply 200 mmHg of pressure for 5 minutes, and the internal diameter of the brachial artery was measured at the same location one minute after releasing the tourniquet in order to compare the rate of dilatation of the artery before and after reactive hyperemia (endothelium-dependent dilatation: EDD). Since any movement of the probe could have resulted in measurement errors, the probe was carefully monitored on a CRT display. The volunteer was then asked to rest for at least 20 minutes, and the internal diameter of the branchial artery was measured again at the same location. Next, 2.5 mg of isosorbide dinitrate was sprayed into the mouth, and the internal diameter of the branchial artery was measured at the same location 3 to 5 minutes following spraying in order to compare the rate of dilatation of the artery before and after spraying (endothelium-independent dilatation: EID). Vasodilatory responses to reactive hyperemia or isosorbide dinitrate spraying were measured 16–20 hours after the completion of cilostazol administration.

Statistical analysis
Data are expressed as the mean ± SD. An unpaired t-test was used to compare the test results between smokers and non-smokers. ANOVA and Scheffe’s post-hoc test were used to compare the test results before and after cilostazol administration. In this study, p values less than 0.01 were considered statistically significant.

Results
Table 1 shows the background of the volunteers. No significant differences were observed in blood pressure, weight, TC, TG, HDL-C, Lp (a) or homocysteine between

<table>
<thead>
<tr>
<th></th>
<th>non-smokers</th>
<th>smokers</th>
<th>significance</th>
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<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>40 ± 11.5</td>
<td>38 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23 ± 2.1</td>
<td>22 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>0 ± 0</td>
<td>478 ± 363</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>193 ± 50.8</td>
<td>186 ± 25.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>102 ± 64.9</td>
<td>136 ± 68.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>49 ± 8.3</td>
<td>53 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>15 ± 11.4</td>
<td>15 ± 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>5.6 ± 4.4</td>
<td>6.4 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>85 ± 7.3</td>
<td>92 ± 10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Homocysteine (mg/dl)</td>
<td>16.2 ± 9.7</td>
<td>17.9 ± 9.9</td>
<td>NS</td>
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Values are the mean ± SD, NS: not significant.
Cilostazol Improves Endothelial Dysfunction in Smokers

The smokers had smoked between 15 and 60 cigarettes a day (average: 26 ± 12 cigarettes) for 10 to 28 years (average: 17 ± 6 years), and the Brinkman index of the smokers was 478 ± 363. The EDD of the smokers was 4.8 ± 1.6%, which was clearly smaller than that of the non-smokers (7.6 ± 2.5%) (Fig. 1). No significant correlation was observed between the EDD and the Brinkman index among the smokers. In addition, no significant difference in the EID was observed between the smokers and the non-smokers (18.5 ± 6.2% and 17.5 ± 7.0%, respectively). Although 100mg of cilostazol was administered once to the smokers, their EDD 6 hours after administration showed no change. Therefore, 150 mg/day of cilostazol was administered for two weeks to ten smokers who gave informed consent and had no side effects throughout the study. The results showed that the EDD of these smokers significantly improved from 4.2 ± 1.2% to 7.8 ± 3.5% (p = 0.0032), a level comparable to the EDD of the non-smokers. There were no significant changes in the EID (Fig. 2). EDD and EID were re-measured more than 6 months after cilostazol cessation. The EDD had returned to the pretreatment level.

![Fig. 1. Comparison of endothelial-dependent dilatation (EDD, panel A) and endothelial-independent dilatation (EID, panel B) in non-smokers and smokers. Data are expressed as the mean ± SD. NS; not significant.](image)

![Fig. 2. Effects of cilostazol treatment on endothelial-dependent dilatation (EDD, panel A) and endothelial-independent dilatation (EID, panel B) in smokers. Cilostazol (150 mg/day) was administered for two weeks to ten smokers and the vasodilatory responses of these subjects were measured before and after treatment with cilostazol. They were re-measured more than 6 months after cilostazol cessation. A significant effect of cilostazol treatment on EDD but not on EID was observed. Data are expressed as the mean ± SD. NS; not significant.](image)
but not cGMP (13). An increased NO level in the endothelium induces the production of cGMP in smooth muscle cells. Therefore, the role of cGMP in the cilostazol-induced vasodilatory response remains to be clarified.

Cilostazol clearly improved EDD in six of ten smokers but not in the other four smokers. There was no difference in the clinical parameters between the responders and nonresponders in the limited number of subjects. In this study, the stable metabolites of NO were not measured in the subjects. At present, the reason for the different effects of cilostazol among individuals is unclear.

It has been shown that cilostazol has several other beneficial effects on vascular endothelial cells. Cilostazol attenuates the production of monocyte chemoattractant protein–1 in response to tumor necrosis factor–α in vascular endothelial cells (31), represses vascular cell adhesion molecule–1 gene transcription via the inhibition of NF–κB by binding to its recognition sequence (32), inhibits lipopolysaccharide-induced endothelial cell apoptosis (33) and enhances endothelial cell growth through the stimulation of hepatocyte growth factor (HGF) production by the cells (34). HGF has been tried for therapeutic angiogenesis in patients with ischemic diseases (35).

Cilostazol improved reactive hyperemia in smokers. At present, oxidative stress, such as that due to free radicals, is believed to play a pivotal role in the development of the smoke-induced impairment of endothelium-dependent vasodilatation (36). Since cilostazol is not an antioxidant, it is difficult to accept that this drug directly negates the effects of tobacco smoke.

NO is thought to play a very important role in the onset and prevention of arteriosclerosis by suppressing platelet aggregation, inhibiting monocytes from adhering to vascular walls, and suppressing the proliferation of smooth muscle cells (37). Cilostazol not only dilates blood vessels, but also suppresses platelet aggregation and smooth muscle cell proliferation. Therefore, cilostazol should improve endothelial dysfunction and suppress arteriosclerosis independent of whether the damage is caused by smoking. Clinical studies have shown that cilostazol suppresses reocclusion following coronary thrombolysis therapy using tPA and significantly suppresses restenosis following PTCA, stenting or atherectomy (25).

In conclusion, the administration of cilostazol (a PDE3 inhibitor) improves the vasodilatory response to reactive hyperemia in smokers.

References

(3) Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, and Deanfield
Cilostazol Improves Endothelial Dysfunction in Smokers


