Effects of a Single Oral Dose of Cilostazol on Epicardial Coronary Arteries and Hemodynamics in Humans

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Cilostazol, a novel cyclic adenosine monophosphate phosphodiesterase type III inhibitor, has been developed as an antiplatelet drug with a vasodilating action on peripheral arteries. The present study was designed to test, in humans, whether cilostazol can dilate the epicardial coronary arteries and what are its hemodynamic effects. Eight patients with chest pain syndrome were subjected to serial quantitative coronary arteriography immediately before and at 30, 60 and 150 min after a single oral dose of cilostazol (200 mg). Luminal cross-sectional areas (mm²) at the proximal and distal sites of major coronary arteries (6 segments at each sampling time) were significantly increased at 150 min after taking the drug. The percent increases relative to the baseline values were 25±7 (6.8±0.8 → 8.3±1.0) and 42±7% (2.1±0.3→3.0±0.4) in the right coronary artery, 24±5 (5.1±0.7→6.1±0.8) and 28±10% (1.6±0.3→1.9±0.3) in the left anterior descending artery, and 14±6 (5.9±0.9→6.6±0.6) and 24±10% (1.3±0.2→1.5±0.2) in the left circumflex artery, respectively (*p<0.05 vs baseline). This action, relative to that of nitroglycerine, was between 27% and 54%. Moreover, small but sustained decreases in systolic pulmonary pressure and stroke work index were observed. Thus, cilostazol has a mild coronary vasodilating action with minimal hemodynamic effects, thereby giving it a possible role in the treatment of coronary artery disease. (Circ J 2002; 66: 241–246)

Key Words: Antiplatelet agent; Cilostazol; Coronary artery disease; Coronary vasodilatation; Humans; Phosphodiesterase type III inhibitor

Recent studies have shown that antiplatelet therapy is beneficial in the treatment of coronary artery diseases such as acute myocardial infarction1-3 and unstable angina4 in terms of reducing cardiac mortality, preventing subsequent ischemic events and stabilizing anginal attacks. In addition, antiplatelet agents are commonly used as an adjunctive therapy to coronary vasodilators and anti-thrombotic drugs during or after coronary interventions such as thrombolytic therapy, coronary angioplasty or stenting. In this regard, a drug that possesses both antiplatelet and coronary vasodilation activity would be clinically useful.

Of particular interest over recent years in the treatment of cardiovascular disease is the advent of phosphodiesterase inhibitors, since they are capable of preferentially eliciting various pharmacological effects such as increases in cardiac contractility, reduction of pulmonary or systemic vascular resistance and inhibition of platelet aggregation, depending upon their tissue specificity. Cilostazol, a novel cyclic adenosine monophosphate (cAMP) phosphodiesterase type III inhibitor, was developed as an antiplatelet drug5 but in experimental animals it has been shown to possess a vasodilating action on the cerebral and peripheral resistance vessels. In fact, cilostazol is now used clinically for the treatment of arterial occlusive disease because significant improvement in the peripheral circulation6,7 and walking performance8,9 of such patients has been demonstrated. However, it has not been determined yet whether cilostazol can dilate human epicardial coronary arteries, partly because its limited aqueous solubility makes the use of parenteral formulations difficult.

Our objective in the present study was therefore to test in humans the effect of a single oral dose of cilostazol on both the luminal cross-sectional area (CSA) of the epicardial coronary arteries and various hemodynamic parameters.

Methods

Patients

The study group comprised 8 patients with atypical chest pain, ventricular arrhythmias or exercise-induced ST depression (Table 1) who underwent cardiac catheterization and were diagnosed as having chest pain syndrome with no significant coronary artery lesions. Informed consent was obtained from all patients at least 2 days before the study, and all vasoactive drugs were discontinued at least 48 h beforehand.

Protocol

Coronary arteriograms, hemodynamic measurements and blood sampling to determine the plasma concentration of cilostazol were performed immediately before, and at 30, 60 and 150 min after a single oral dose of cilostazol (200 mg). At the end of the study, 0.1 mg of nitroglycerine was infused into each coronary artery to obtain maximal coro-
Assisted videodensitometry is a quantitative coronary analyzing system with a computer (Vanguard Instruments Corp, Melville, NY, USA), which measured using a Vanguard XR-70 Coronary Analyzer segments (48 segments in total at each sampling point) was non-ionized contrast media, Omnipaque-350® (Daiichi technique (using 6Fr catheters) with manual injection of Assessment of the Coronary Artery Vascular Response Coronary angiography was performed by the Judkins technique (using 6Fr catheters) with manual injection of non-ionized contrast media, Omnipaque-350® (Daiichi Pharmaceutical Co, Tokyo, Japan): 5 ml of Omnipaque-350 was administered into the right coronary artery and 8 ml into the left. The study started with reference coronary arteriograms of the left coronary artery in the right anterior oblique projection, and of the right coronary artery in the left anterior oblique projection. Subsequent coronary arteriograms were carried out in the same projections as the reference images. Six segments, consisting of the proximal and distal segments of each coronary artery, were deliberately selected as the images for videodensitometric evaluation. The proximal segments were defined as segment 1 or 2 in the right coronary artery (RCA), segment 6 or 7 in the left anterior descending coronary artery (LAD) and segment 11 or 13 in the left circumflex coronary artery (LCx), according to the guidelines of the American Heart Association. Likewise, the distal segments were selected from segments 3 or 4 in the RCA, 8 or 9 in the LAD and 12 or 14 in the LCx. The luminal CSA (mm²) in the selected segments (48 segments in total at each sampling point) was measured using a Vanguard XR-70 Coronary Analyzer (Vanguard Instruments Corp, Melville, NY, USA), which is a quantitative coronary analyzing system with computer-assisted videodensitometry.

In brief, the method is based on the finding that the videodensity of cinefilm is linearly proportional to the concentration of intraluminal contrast medium and to the CSA of contrast-filled cylinders. The video image of the selected cine frame is analyzed by positioning the regions of interest (ROIs) on either side of the reference catheter shaft and the artery segment to be measured. Videodensity values for the pixels delineated by the lines connecting the pairs of ROIs are measured 5 times and averaged, and a video density profile curve representing the density values across the image of the catheter shaft or the coronary segment is generated. The width of the profile curve in pixels is determined for half of the peak height of the curve above background (full-width-at-half-maximum, FWHM). The diameter (d) of the artery is calculated by multiplying 2 mm (the ideal diameter of a 6Fr catheter) with a ratio of FWHM from the artery and that from the catheter. The CSA is then calculated from CSA=\(\pi(d/2)^2\), assuming the normal artery is circular in shape. This method has the advantage of being able to measure the diameter of smaller arteries because it assesses the width of cylindrical objects without requiring diameter measurements at the arterial margins, which are usually indistinct (see references 12, 13 for details).

All images used in the analysis were taken during end-diastole and great attention was paid to selection of the site so that it was identical to that determined in the reference image during the serial measurement of each coronary segment. The increase in luminal CSA, expressed as a percentage of the baseline values, was calculated, using the following formula, as the index of the vasodilatory effect of cilostazol or nitroglycerine: ∆CSA(%) = 100×(CSA after the administration of cilostazol or nitroglycerine – the baseline value (CSA before the administration))/the baseline value. All measurements were performed by the same cardiologist, and the error per 5 repeated determinations performed on the same portion was 1% or less.

Distances between the focal spot, the patient and the image tube were kept constant. Coronary cinearteriograms were recorded on 35-mm cine film (Fuji MI-CG) at 30 frames/s with an Arritechno camera, and the radiographic equipment consisted of a Toshiba CAS-UA/LA cinefluorography system with KXO-2050F generators. The image intensifier was operated in the 7-inch mode, and the X-ray exposure time was 3 ms at 15 kR per cine frame.

### Hemodynamic Measurements
A 7Fr thermodilution catheter was inserted through the femoral vein into the pulmonary artery for the determination of hemodynamic parameters: pulmonary capillary
Coronary Vasodilatation by Cilostazol

Wedge pressure, pulmonary artery pressure, right atrial pressure and cardiac output. Aortic pressure was also monitored by placing the 6Fr catheter used for coronary arteriography in the ascending aorta. Heart rate was derived from the electrocardiogram. The total pulmonary and systemic vascular resistances and the stroke work index were also calculated.

Plasma Concentration of Cilostazol

Blood samples collected at each sampling point were centrifuged to obtain plasma samples, which were frozen and kept at −80°C until high-performance liquid chromatography assays were performed (detection range: 25–2,000 ng/ml of plasma) using the procedure developed by Akiyama et al.14

Statistical Analysis

Data are expressed as mean±SEM. Changes of the variables over time, including luminal CSAs and hemodynamic parameters, were subjected to analysis of variance with repeated measurements. If a significant F ratio was obtained, further comparisons were made with the Bonferroni/Dunn post-hoc test. When required, Student’s t test was also utilized. A value of p<0.05 was considered significant.

Results

Serum Concentration of Cilostazol

The plasma concentrations of cilostazol were 231±59, 562±102 and 881±99 ng/ml at 30, 60 and 150 min, respectively (Fig 1).

Coronary Vascular Response to Cilostazol

There was a modest but substantial increase in the luminal CSA of the major coronary arteries at the proximal and distal sites, and in each coronary artery statistical significance was reached 150 min after drug administration (Fig 2). The maximal ∆CSAs (and the actual change in the absolute values in mm²), which occurred almost exclusively at 150 min after administration, were, in the proximal and distal sites, respectively, 25±7 (6.8±0.8→8.3±1.0*) and 42±7% (2.1±0.3→3.0±0.4*) in the RCA, 24±5 (5.1±0.7→6.1±0.8*) and 28±10% (1.6±0.3→1.9±0.3*) in the LAD, and 14±6 (5.9±0.9→7.6±0.9*) and 24±10% (1.3±0.2→1.5±0.2*) in the LCx, respectively (*p<0.05 vs baseline).

The corresponding values after intracoronary injection of 0.1 mg of nitroglycerine were 59±11 (6.8±0.8→10.8±1.5*) and 78±14% (2.1±0.3→3.8±0.7*) in the RCA, 56±28 (5.1±0.7→7.6±0.9*) and 79±14% (1.6±0.3→2.7±0.4*) in the LAD, and 51±9 (5.9±0.9→9.0±1.5*) and 66±14% (1.3±0.2→2.0±0.2*) in the LCx. These values are compared in
Table 2  Hemodynamic Responses to a Single Oral Dose of Cilostazol (200 mg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Time after administration (min)</th>
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<tbody>
<tr>
<td></td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>61±3</td>
<td>59±2</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>138±8</td>
<td>130±5</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9.1±1.2</td>
<td>7.9±1.0</td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>22.4±2.5</td>
<td>22.6±1.8</td>
</tr>
<tr>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>2.4±0.2</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>SWI (ARU/m²)</td>
<td>205±36</td>
<td>228±69</td>
</tr>
<tr>
<td>SVRI (ARU/m²)</td>
<td>3,347±406</td>
<td>3,168±242</td>
</tr>
</tbody>
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HR, heart rate; SAP, systolic aortic pressure; PCWP, pulmonary capillary wedge pressure; SPAP, systolic pulmonary artery pressure; RAP, right atrial pressure; CI, cardiac index; SWI, stroke work index; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index. Data are mean±SEM. *p<0.05 vs baseline (n=8).

Fig 3. Cilostazol increased the CSAs by approximately a third as much as nitroglycerine did. Although the vasodilator effect of cilostazol appeared to be greater in the RCA than in either the LAD or LCx, there was no significant difference in the response of the major coronary arteries.

Vasodilatory Effect vs Plasma Concentration of Cilostazol

Data were collected and averaged over 5 ranges of cilostazol concentration (0–199, 200–399, 400–599, 600–799, ≥800; in ng/ml) and the ∆CSAs were minimal at concentrations less than 400 ng/ml (Fig 4). However, there was a stepwise increase in ∆CSA in both the proximal and distal sites at concentrations ≥400 ng/ml, so the ∆CSA at these concentrations was significantly greater than those at lesser concentrations (8.7±1.5 vs 3.3±1.3% in the proximal sites, 13.5±2.0 vs 4.1±1.5% in the distal sites, respectively).

Hemodynamic Parameters

Table 2 shows the hemodynamic parameters before and after the administration of cilostazol. There was a small but significant decrease in systolic pulmonary pressure and stroke work index. Heart rate tended to increase, but the change was not significant. The other hemodynamic parameters did not change significantly throughout the study. There were no complications related to the procedures or the drug during or after the study.

Discussion

The present study is the first to demonstrate that cilostazol has a mild coronary vasodilating action without drastic changes in hemodynamic parameters. The extent of this action relative to that of nitroglycerine ranged between 27% and 54%, which may be beneficial, in addition to its established antiplatelet activity6,15–17 in the treatment of coronary artery disease.

Possible Anti-Ischemic Effect of Cilostazol

Although cilostazol has been released as an antiplatelet agent for arterial occlusive disease in Japan, its therapeutic implication(s) can be exploited in various ways because of its pharmacological versatility. Cilostazol inhibits type III phosphodiesterase (PDE) activity in platelets6-15 and in arterial10,18,19 and bronchial20 smooth muscle cells, thereby increasing the intracellular levels of cAMP through blocking its hydrolysis. Increased intracellular cAMP inhibits thromboxane A2 production and hence platelet aggregation by inhibiting phospholipase and cyclooxygenase in the platelets16,17 and it also blocks release of calcium ions from intracellular storage granules within the smooth muscle cells, thus inhibiting the contractile proteins.21 As for its cardiovascular relevance, cilostazol may exert an antiischemic action in the heart through the coronary vasorelaxant effect observed in the present study. That effect was significant at 150 min after drug administration, at a concentration of 881±99 ng/ml, which was within the range (500–1,000 ng/ml) that occurs when a dose of 100 mg twice daily is given for 7 days.22 The peak plasma concentration occurs at a mean of 2.4 h after administration;22 and the present study results were consistent with that finding. The coronary vasodilation was not accompanied by an increase in cardiac output or a decrease in systemic vascular resistance, suggesting that there is a direct action on the coronary arteries.

As noted earlier, an antiplatelet agent with a coronary vasorelaxant effect would be useful clinically under special circumstances where both activated platelets and the vasoactive substances released by them exacerbate myocardial ischemia by enhancing coronary vascular tone (such as may occur in acute coronary syndrome, and during or after coronary interventions). Indeed, clinical studies23–29 have shown that cilostazol can be safely used in patients who have undergone coronary angioplasty or stenting to prevent unfavorable postprocedural ischemic events. Furthermore, the restenosis rate was substantially reduced by cilostazol treatment in comparison with that following the use of aspirin23,24,26.

Despite the lack of significant change in systemic vascular resistance, a small but significant reduction in systolic pulmonary pressure and stroke work index was observed in this study. Cilostazol, at least when administered in a single oral dose, appears to reduce preload rather than afterload, which probably decreases myocardial oxygen consumption through the reduction of left ventricular wall tension. There are concerns that cilostazol can increase cardiac contractility when the cAMP level is elevated and aggravate myocardial ischemia by increasing oxygen consumption rather than decreasing it. Cone et al30 recently compared the effect of cilostazol and a positive inotropic PDE III inhibitor, milrinone, on intracellular cAMP levels and cellular function in rabbit platelets and cardiac cells. Both drugs exhibited similar potency in platelet aggregation with corresponding PDE III inhibition (reflected by a similar increase in cAMP level in platelets), but, cilostazol was significantly less effective in increasing left ventricular developed pressure and contractility in isolated hearts, which was consistent.
with the finding that an increase by cilostazol in cAMP level was significantly less than that by milrinone in isolated cardiomyocytes. Although the mechanism is unclear, this preferential action of cilostazol on the myocardium vs platelets may contribute to the lack of significant positive inotropic observed in the present study.

With regard to chronotropism, cilostazol tended to cause a slight increase in heart rate at 150 min after administration. Atarashi et al. reported that, if repeatedly administered orally, cilostazol can significantly increase heart rate in patients with bradycardia such as bradycardic chronic atrial fibrillation and sick sinus syndrome, which suggests a new clinical implication. This finding has been confirmed by Toyoma et al. and Tsutsui et al. also observed a positive chronotrophic effect of cilostazol from 1 to 6 months after the initiation of treatment without serious side effects. Therefore, it is certainly worth testing whether or not the drug has anti-ischemic effects in patients with coronary artery disease when given repeatedly.

Aside from its inhibition of platelet aggregation and its vasorelaxant effect, cilostazol has unique additional pharmacological actions that may be advantageous in treating coronary artery disease as well as peripheral arterial occlusive disease. First, it has inhibited the replication and growth of rat vascular smooth muscle cells in tissue culture through its increase of the levels of intracellular cAMP. Second, it reportedly decreases triglycerides, LDL, and total cholesterol, and increases HDL cholesterol via cAMP in hepatocytes, which enhances the activity of lipoprotein lipase and so resolves triglyceride and attenuates cholesterol synthesis. Third, in canine grafted veins, cilostazol suppresses the activity of angiotensin II-forming enzymes, both chymase and angiotensin-converting enzymes, with concomitant suppression of vascular proliferation. These effects may be anti-atherogenic and help explain cilostazol’s clinical benefits, including the reduction in the restenosis rate after coronary interventions.

Study Limitations

It may be argued that there was no contemporary control group to compare with the drug-treated group in order to exclude any time-related changes in the values obtained. However, it was impossible to include such a group for ethical reasons. In this regard, it is sensible to note that the coronary vasodilating effect of cilostazol became significant only when its plasma concentrations were close to or over the level reported for inhibition of platelet aggregation, and this occurred almost exclusively at approximately 120 min onward after drug administration.

This study was carried out in a small number of patients who did not have any significant coronary artery lesions. It remains to be determined whether or not the drug can also dilate atherosclerotic coronary sites with significant stenosis. Therefore, the current results should be interpreted with caution.

Conclusion

Cilostazol is an agent with versatile pharmacological actions. The coronary vasodilating action documented by the present study can be added to its reported pharmacological properties that are already considered advantageous in patients with coronary artery disease or peripheral arterial occlusive disease or both. As in the case of other anti-platelet agents, the drug’s real clinical value needs to be tested in a large-scale trial of various clinical parameters, most importantly that of its long-term prognosis.

References


