Cilostazol Has Beneficial Effects in Treatment of Intermittent Claudication

Results From a Multicenter, Randomized, Prospective, Double-blind Trial

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Background—Cilostazol is a new phosphodiesterase inhibitor that suppresses platelet aggregation and also acts as a direct arterial vasodilator. This prospective, randomized, placebo-controlled, parallel-group clinical trial evaluated the efficacy of cilostazol for treatment of stable, moderately severe intermittent claudication.

Methods and Results—Study inclusion criteria included age ≥40 years, initial claudication distance (ICD) on treadmill (12.5% incline, 3.2 km/h) between 30 and 200 m, and confirmation of diagnosis of chronic lower-extremity arterial occlusive disease. After stabilization and single-blind placebo lead-in, 81 subjects (62 male, 19 female) from 3 centers were randomized unequally (2:1) to 12 weeks of treatment with cilostazol 100 mg PO BID or placebo. Primary outcome measures included ICD and maximum distance walked (absolute claudication distance, or ACD). Secondary outcome measures included ankle pressures, subjective assessments of benefit by patients and physicians, and safety. Treatment and control groups were similar with respect to age, severity of symptoms, ankle pressures, and smoking status. Statistical analyses used intention-to-treat analyses for each of 77 subjects who had ≥1 treadmill test after initiation of therapy. Comparisons between groups were based on logarithms of ratios of ICD and ACD changes from baseline using ANOVA test at last treatment visit. The estimated treatment effect showed a 35% increase in ICD (P<0.01) and a 41% increase in ACD (P<0.01). There was no significant change in resting or postexercise ankle/brachial indexes. Patients’ and physicians’ subjective assessments corroborated the measured improvements in walking performance observed in the cilostazol-treated group.

Conclusions—Cilostazol improved walking distances, significantly increasing ICD and ACD. The data suggest cilostazol is safe and well tolerated for the treatment of intermittent claudication. (Circulation. 1998;98:678-686.)

Key Words: claudication ■ peripheral vascular disease ■ cilostazol ■ drugs

Although progress has been seen in surgical and interventional techniques for the management of arterial occlusive disease in recent years, these procedures are only appropriate for patients with intermittent claudication who have significant, lifestyle-limiting symptoms. Initially, nonoperative treatment is appropriate for patients with claudication, and for many this may suffice. Nonpharmacological interventions, such as smoking cessation, exercise, and weight loss, can improve walking performance1 and are fundamental in the management of patients with claudication. Pharmacological treatment also has a role. First, medical management of diabetes, hypertension, and hyperlipidemia may slow atherosclerosis progression. However, these interventions have not been shown to affect symptoms or cause regression of established peripheral arterial disease. Second, drug therapy may be used to provide symptomatic relief by improving pain-free and overall walking distances.

Many agents have been tried for the treatment of intermittent claudication, although few drugs have demonstrated efficacy in adequately designed, placebo-controlled trials. Classes of drugs that have been advocated or tested for treating claudication include rheological agents, vasodilators, antiplatelet agents, anticoagulants, prostaglandins and prostaglandin analogs, “metabolic enhancers,” and others.2 Generally, all these classes of drugs have been thought to increase skeletal muscle oxygen delivery or increase the efficiency of oxygen utilization.

Cilostazol (Otsuka Pharmaceutical Co Ltd, Tokushima, Japan), 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, is a new compound that may be useful for treating chronic arterial disease and symptoms of intermittent claudication. The principal mechanisms of its action include inhibition of platelet aggregation and vasodi-
lation. Early preclinical reports and small trials examining Japanese patients with lower-extremity arterial disease have suggested that cilostazol increases dermal blood flow, augments vasodilation with reactive hyperemia, and has utility in the treatment of cutaneous ulcers. Unpublished data from phase II studies in Germany suggested benefit in the treatment of patients with claudication, but very small sample sizes and poor follow-up severely limited those trials.

The present study was performed to test the efficacy and safety of cilostazol compared with placebo for amelioration of the symptoms of intermittent claudication. The primary outcome measures used to assess efficacy were pain-free walking distance (distance walked to the onset of symptoms, or the initial claudication distance [ICD]) and the maximum distance walked (absolute claudication distance [ACD]) on standardized treadmill testing. Secondary outcome measures examined included measurements of ankle pressures (at rest and after exercise), subjective assessments of symptoms by the patient and physician, and safety.

Methods

This study was designed according to the recommendations of the Society for Vascular Surgery Ad Hoc Committee on Clinical Research, which detail appropriate requirements for trials of medications for the treatment of intermittent claudication. Participating study centers included the University of Washington Medical Center, the University of Massachusetts Medical Center, and the Oregon Health Sciences Medical Center. The study was conducted with the approval of the Human Subjects Review committees of the respective institutions, and written informed consent was obtained from each participant before any study procedures were begun.

Patient Population

The study population included 81 patients with stable symptoms of intermittent claudication secondary to chronic occlusive arterial disease from atherosclerosis (symptoms present for ≥6 months and not significantly changed within the past 3 months). Clinical diagnoses of chronic occlusive arterial disease were supported with objective criteria from noninvasive vascular tests, including an ICD on the treadmill between 30 and 200 m and a minimum postexercise drop in Doppler-measured ankle systolic blood pressure of ≥20 mm Hg.

Patients with limb-threatening (grades II and III) chronic limb ischemia, manifested by ischemic rest pain, ulceration, or gangrene, were excluded. Other exclusion criteria were lower-extremity surgical or endovascular arterial reconstructions or sympathectomy in the preceding 6 months, uncontrolled hypertension, inability to complete the treadmill walking test for reasons other than claudication, recent myocardial infarction (within 6 months), recent deep vein thrombosis (within 3 months), severe concomitant diseases, substance abuse, and gross obesity.

Concomitant use of drugs known to have a significant effect on peripheral arteries was limited to antihypertensive agents, including ACE inhibitors, β-blockers, or calcium channel blockers, or the occasional use of nitroglycerin. Dosages of all concomitant medications were kept constant throughout the study when feasible.

Other classes of concomitant medications that were specifically disallowed included antiplatelet agents (including aspirin), anticoagulants, vasoactive agents (papaverine, isoxsuprine, nifedipine, cyanidolate, and niacin derivatives), hemorrhological agents (pentoxifylline), and nonsteroidal anti-inflammatory drugs (with the exceptions of acetaminophen and diclofenac sodium, which have minimal antiplatelet effects).

No specific counseling about diet, smoking cessation, or exercise was offered during the study period. These factors were not specifically controlled. Investigators neither encouraged nor discouraged lifestyle changes until patients completed the trial.

Study Methods

This study was a randomized, parallel, double-blind trial with the administration of either cilostazol 100 mg BID or placebo BID. After a 2-week baseline period for stabilization of concomitant medications and entry treadmill testing, there was a 2- to 4-week single-blind placebo lead-in phase, during which time each patient’s treadmill walking time (ICD) had to be within ±35% of the value at the previous visit. Patients with stable treadmill walking performance were then randomized 2:1 for treatment with cilostazol or placebo, respectively, for a period of 12 weeks. The active treatment group received cilostazol 100 mg PO BID. The control group received an identical placebo BID. Randomization was stratified by treatment center and patient’s use of calcium channel blocker. Subjects were then reevaluated 2, 4, 8, and 12 weeks after initiation of therapy.

Evaluation of walking performance was accomplished with standardized treadmill testing. A constant speed of 3.2 km/h (2 mile/h) and a fixed incline of 12.5% were used. The treadmill tests were considered valid only if claudication symptoms were the reason the subject had to stop walking. Brachial, anterior tibial, and posterior tibial artery systolic pressures were measured with continuous-wave Doppler ultrasound and cuff occlusion, and these pressures were used to calculate ankle/brachial indices (ABI) as follows:

\[
\text{ABI} = \frac{(\text{higher of the tibial artery pressures})}{(\text{higher of the arm pressures})}
\]

In addition to assessment of walking distances and ankle/brachial indices, patients were serially evaluated for new complaints, changes in symptoms, and functional status. ECGs were obtained, and laboratory testing, including hematologic studies, serum chemistries, and urinalyses, were routinely performed as part of the assessment of safety.

Statistical Analysis

All statistical tests were 2-sided, and differences were considered significant if the P value was <0.05. Using methods described by Porter et al. and Gillings et al., we also analyzed data for ICD and ACD in terms of logarithms of distance/baseline ratios. This transformation reduces the impact of extreme values. It also allows the results from each treatment group to be expressed in terms of percent change from baseline.

The relationship of percent change to the natural logarithm of the distance/baseline ratio is given by:

\[
\text{Percent change} = 100 \times \left\{ \text{antilog} \left[ \log \left( \frac{\text{distance}}{\text{baseline}} \right) \right] - 1 \right\}
\]

\[
= 100 \times \left( \frac{\text{distance}}{\text{baseline}} - 1 \right)
\]

\[
= 100 \times \left( \frac{\text{distance} - \text{baseline}}{\text{baseline}} \right)
\]

For analysis of the intention-to-treat population, log-rank scores were obtained separately for patients from each study center. Statistical comparisons of treatments for the combined centers were based on 3 methods: Mantel-Haenszel, Wei-Lachin, and Fisher tests.

Results

There were a total of 81 patients from the 3 study centers entered into the double-blind phase of the trial. All subjects had grade I chronic limb ischemia (according to reporting standards of the Society for Vascular Surgery/North Ameri-
can Chapter of the International Society for Cardiovascular Surgery). Claudication was characterized as “mild” (category 1) in 7 patients (8.6%), “moderate” (category 2) in 22 (27.3%), and “severe” (category 3) in 52 (64.2%). Before randomization, eligibility for inclusion was confirmed, and concomitant medical therapy was stabilized. All patients completed 2 to 4 weeks of single-blind placebo administration before randomization.

Characteristics of the subjects in these treatment groups are summarized in Table 1. The groups were similar with respect to demographic features and major cardiovascular risk factors. Eighty patients were white; there was 1 black patient. Of the 81 subjects randomized, 4 did not participate in the trial long enough to have \( n = 77 \) treadmill test after initiation of treatment. The remaining 77 were considered evaluable (by intention-to-treat analysis methods) and compose the principal subject of this report. A total of 27 patients were assigned to placebo, and 54 were assigned to treatment with cilostazol 100 mg PO BID. Sixty-six patients completed the trial, and analyses of this group were separately performed to better determine the actual treatment effect on walking performance when continued therapy was administered. The reasons for subjects’ withdrawal after randomization are summarized in Table 2.

**Efficacy**

The primary end point for the study was walking distance. Table 3 shows raw walking distances (ICD and ACD) for the treatment and control groups at each visit after the initiation of double-blind therapy. This table shows arithmetic mean data for all subjects who completed \( n = 77 \) treadmill test after randomization.

Table 3 shows there was a significant improvement in subjects’ treadmill walking distances after 12 weeks of
treatment, when mean ICD and ACD were compared with baseline performance, in the group treated with cilostazol. The mean ICD (arithmetic mean) improved by 58% in the subjects treated with cilostazol, compared with an increase of only 8.9% in the placebo group. These differences were highly significant. Cilostazol-treated subjects increased mean ACD by 63%, whereas there was a 9.8% decrease in mean ACD in the placebo group. These differences were also highly significant. No statistically significant differences were demonstrated between the treatment and control groups before week 12.

Geometric means were compared to detect differences between treatment groups with less impact of extreme values. When either intention-to-treat analysis was used or only those who completed 12 weeks of treatment were considered, the differences in log(distance/baseline) were significant (Table 4). As with the analysis of the raw walking distances, the differences demonstrated between the treatment and control groups were statistically significant after 12 weeks of treatment but not earlier. When patients were categorized by the magnitude of their response to treatment, there was a signifi-

**TABLE 3. Analysis of Raw Walking Distance Measurements, by Intention to Treat (Last Valid Observation Carried Forward)**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo (n=25)</th>
<th>Cilostazol (n=52)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD, m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>77.7±8.4</td>
<td>71.2±6.0</td>
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</tr>
<tr>
<td>2 wk</td>
<td>83.9±10.0</td>
<td>80.6±7.0</td>
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</tr>
<tr>
<td>4 wk</td>
<td>86.4±11.4</td>
<td>92.8±9.2</td>
<td>0.119</td>
</tr>
<tr>
<td>8 wk</td>
<td>93.2±14.4</td>
<td>102.1±11.8</td>
<td>0.292</td>
</tr>
<tr>
<td>12 wk</td>
<td>84.6±13.7</td>
<td>112.5±13.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.178</td>
</tr>
<tr>
<td>ACD, m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>168.6±33.1</td>
<td>141.9±21.0</td>
<td></td>
</tr>
<tr>
<td>2 wk</td>
<td>176.2±36.3</td>
<td>163.3±27.3</td>
<td>0.561</td>
</tr>
<tr>
<td>4 wk</td>
<td>185.0±40.7</td>
<td>196.4±30.8</td>
<td>0.061</td>
</tr>
<tr>
<td>8 wk</td>
<td>189.5±43.5</td>
<td>206.7±33.8</td>
<td>0.138</td>
</tr>
<tr>
<td>12 wk</td>
<td>152.1±23.9</td>
<td>231.7±36.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.114</td>
</tr>
</tbody>
</table>

*Wei-Lachin multivariate rank test.

**TABLE 4. Percent Change in Walking Distances From Baseline (Geometric Means)**

<table>
<thead>
<tr>
<th>Percent Change in Walking Distance*</th>
<th>Intention-to-Treat Analysis†</th>
<th>Analysis for Subjects Completing 12-wk Trial‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=25)</td>
<td>Placebo (n=22)</td>
</tr>
<tr>
<td>ICD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 wk</td>
<td>7.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td>4 wk</td>
<td>6.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>8 wk</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>12 wk</td>
<td>−2.5%</td>
<td>31.7%</td>
</tr>
<tr>
<td>ACD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 wk</td>
<td>0%</td>
<td>−0.4%</td>
</tr>
<tr>
<td>4 wk</td>
<td>1.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>8 wk</td>
<td>2.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>12 wk</td>
<td>−9.3%</td>
<td>30.5%</td>
</tr>
</tbody>
</table>

*Percent change (%ΔE) = 100*[(antilog[log(distance/baseline)] − 1)].
†Last observation carried forward for analysis.
‡Twelve weeks of double-blind therapy with placebo or cilostazol 100 mg PO BID.
§ANOVA, general linear model, overall P value for the model.
Cilostazol for Intermittent Claudication

Figure 1. Categorization of increase in raw ICD after 12 weeks of treatment.

Significantly more favorable response in the cilostazol-treated group (Figures 1 and 2).

There were no significant testing center or treatment-by-center interactions that affected the observed changes in ICD or ACD.

At each subject’s final study visit, both the subject and investigator were asked to subjectively assess the response to treatment, even if the subject withdrew early. These assessments are categorized in Table 5. Half of the patients treated with cilostazol judged their walking performance to be “better” or “much better”; none reported their symptoms to be worse. Sixty-three percent of placebo-treated patients reported their symptoms to be “unchanged,” with similar proportions (19%) reporting either improvement or worsening. Of note, patients’ positive subjective response rates were somewhat better when only the 44 patients who completed 12 weeks of therapy with cilostazol were considered; 11 such patients (25%) reported their symptoms to be “much better” and 14 (32%) said they were “better.” Physicians’ assessments were similar. Considering all randomized patients, 48% of the cilostazol-treated group were said to be “better” or “much better” versus 22% of the placebo-treated patients. Both the patients’ and physicians’ subjective assessments demonstrated a statistically significant improvement in claudication symptoms in the patients randomized to cilostazol.

Adverse Events

Reported serious adverse events include 1 death from myocardial infarction in the placebo group and 6 hospitalizations of cilostazol-treated patients (subclavian artery stenosis, unstable angina, pneumonia [2 patients], myocardial infarction, and transient ischemic attack). (The US Food and Drug Administration defines a serious adverse event as an occurrence that is fatal, life-threatening, disabling, or requires hospitalization; or a drug overdose, congenital anomaly, or cancer.) Gastrointestinal complaints were noted in 44% of the cilostazol-treated patients. The most commonly reported side effects included diarrhea, loose stools, flatulence, and nausea. Importantly, these symptoms were typically mild and often self-limited, although they persisted in some patients. Gastrointestinal complaints were recorded from 15% of the placebo group. Headaches were the next most common type of complaint, occurring in 20% of cilostazol-treated patients and 15% of placebo-treated patients. In general, the drug was well tolerated, and most of the reported side effects were managed symptomatically.

Laboratory Findings

Neither treatment group demonstrated clinically significant shifts in serum electrolytes, renal or liver function, coagulation profiles, or peripheral blood cell counts. There was no evidence of clinically significant changes in blood pressure, heart rate, or ECG alterations associated with cilostazol treatment. Review of the laboratory data seemed to indicate that the cilostazol-treated group had potentially beneficial alterations in plasma lipids (Table 6). However, this trial did not prospectively control for hyperlipidemia, concomitant use of lipid-lowering agents, poor diabetes control, diet, or other factors that might affect serum lipids.

Discussion

In this study, 12 weeks of cilostazol treatment resulted in a significant improvement in treadmill walking performance. Both ICD and ACD were significantly increased compared with baseline performance, and in this carefully designed study, there was essentially no change in walking performance observed in the placebo-treated group. Patient and physician assessments of treatment response suggested that the statistically significant measured improvement was clinically relevant as well. Although gastrointestinal side effects were common, these were typically mild and self-limited and did not interfere with continued therapy.

Cilostazol Pharmacology

Cilostazol has a number of actions that may be beneficial for the treatment of patients with arterial disease, including inhibition of platelet aggregation. Cilostazol inhibits type III phosphodiesterase activity in platelets, thereby increasing intracellular levels of cAMP by blocking its hydrolysis. Increased intraplatelet cAMP concentration inhibits thromboxane A2 production and platelet aggregation by inhibiting phospholipase and cyclooxygenase.

In a small, double-blind, crossover study, cilostazol was a better inhibitor of thromboxane-stimulated platelet aggregation than either aspirin or ticlopidine. This antiplatelet effect may be relevant, because previous clinical studies have suggested that ticlopipidine improves walking distances and ankle pressures in patients with claudication. Cilostazol is 10 to 30 times more potent than aspirin in inhibiting aggregation induced by ADP, collagen, epinephrine, or arachidonic acid. Unlike aspirin, cilostazol does not inhibit prostaglan-
Prostaglandin I₂ (prostacyclin) synthesis. This may be important, because endothelium-derived prostacyclin potentiates the effects of the inhibition of platelet aggregation by cilostazol. Prostaglandin I₂ has antithrombotic activity, inhibits platelet aggregation, and relaxes vascular smooth muscle.

In addition to its antiplatelet effects, cilostazol acts as an arterial vasodilator, probably through its direct action on vascular smooth muscle. Intracellular cAMP blocks release of calcium ions from intracellular storage granules within the smooth muscle cells, thus inhibiting the function of contractile proteins. It is unclear what role arterial or arteriolar vasodilation plays in any effect cilostazol has on patients with chronic occlusive arterial disease. Vasodilator drugs have typically been unsuccessful for the treatment of claudication. This is thought to be because resistance beds are already maximally vasodilated in ischemic limbs. Effects of cilostazol on regional blood flow and tissue oxygen delivery are unknown.

TABLE 5. Subjective Assessment of Effect of Study Drug on Ability to Walk

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Patient's Assessment</th>
<th>Physician's Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=27)</td>
<td>Cilostazol (n=54)</td>
</tr>
<tr>
<td>Much better</td>
<td>1 (4%)</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Better</td>
<td>4 (15%)</td>
<td>15 (28%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>17 (63%)</td>
<td>27 (50%)</td>
</tr>
<tr>
<td>Worse</td>
<td>4 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Much worse</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Includes responses from all randomized patients, asked at their final visit. Includes responses from those who withdrew, regardless of duration of therapy, as well as from those who completed some or all of the other study evaluation visits and procedures.

*Fisher’s exact test.

TABLE 6. Summary of Plasma Lipid Values

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mean ± SE</th>
<th>Mean Change From Baseline ± SE</th>
<th>Cilostazol</th>
<th>Mean ± SE</th>
<th>Mean Change From Baseline ± SE</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2 wk</td>
<td>25</td>
<td>245±34</td>
<td>13±21</td>
<td>52</td>
<td>189±14</td>
<td>-64±14</td>
</tr>
<tr>
<td>4 wk</td>
<td>25</td>
<td>247±41</td>
<td>16±24</td>
<td>50</td>
<td>173±12</td>
<td>-73±16</td>
</tr>
<tr>
<td>8 wk</td>
<td>24</td>
<td>227±43</td>
<td>-6±25</td>
<td>47</td>
<td>179±14</td>
<td>-73±14</td>
</tr>
<tr>
<td>12 wk</td>
<td>22</td>
<td>229±34</td>
<td>8±22</td>
<td>44</td>
<td>188±16</td>
<td>-69±16</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline*</td>
<td>27</td>
<td>225±8</td>
<td>. .</td>
<td>53</td>
<td>228±5</td>
<td>. .</td>
</tr>
<tr>
<td>2 wk</td>
<td>25</td>
<td>227±8</td>
<td>4±3</td>
<td>52</td>
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<td>-8±3</td>
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<tr>
<td>8 wk</td>
<td>24</td>
<td>232±10</td>
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<td>52</td>
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<td>-2±3</td>
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<tr>
<td>4 wk</td>
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<tr>
<td>8 wk</td>
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<tr>
<td>12 wk</td>
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<td>146±7</td>
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<td>HDL cholesterol, mg/dL</td>
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<td>Baseline*</td>
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<td>41±2</td>
<td>. .</td>
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<td>40±1</td>
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<td>46±3</td>
<td>3±2</td>
<td>44</td>
<td>47±2</td>
<td>7±1</td>
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</table>

*Four to 6 weeks before randomization to treatment with placebo or cilostazol 100 mg PO BID.
Cilostazol also affects smooth muscle cell proliferation. The drug inhibits replication and growth of rat vascular smooth muscle cells in tissue culture. This effect may also be mediated through increased levels of intracellular cAMP in smooth muscle cells.23

In the present study, cilostazol decreased triglycerides, LDL, and total cholesterol and increased HDL cholesterol, as previously described.24–27 Although the magnitude of the lipid-altering effect is small, it adds to the potential clinical utility of the drug. However, larger trials that control for other factors that may affect lipid metabolism are needed to confirm and better characterize any possible effect on plasma lipids.

Considerations in the Analysis of Efficacy
A typical feature of many follow-up studies is the occurrence of incomplete data for some of the subjects, either because some subjects withdraw before completion of the study or because they occasionally miss visits. An important consequence of such incomplete data is the introduction of variation in the patient population across visits. This can complicate interpretation across visits. One way to address this problem is to maintain the intention-to-treat population by assigning extended end-point values to missed visits, as was done in the current study. With this method, if a value for a visit is missing, it is replaced by the value from the nearest preceding visit. As a result, the value remains missing only if all preceding visits are missing or it corresponds to the first visit.

In the present study, outcome measures were examined both by analyses by intention-to-treat and by considering only those patients who completed 12 weeks of double-blind treatment. Analysis by intention-to-treat is a more rigorous comparison of alternate treatment regimens. Any subject completing ≥1 valid treadmill test after randomization was included in the intention-to-treat analysis. This was done by carrying the last valid observation forward and using that value for the analyses at later, missed visits. The disadvantage of this type of analysis is that it tends to mask treatment effects that increase over time.

For analysis of the intention-to-treat population, log-rank scores were obtained separately for the patients from each study center. Statistical comparisons of treatments for the combined centers were based on 3 methods: Mantel-Haenszel, Wei-Lachin, and Fisher.

The Mantel-Haenszel test for ordered contingency tables was used in categorical analyses. It is a nonparametric test that examines relationships among data in row-by-column tables. The Mantel-Haenszel test is directed at a weighted linear combination of differences between treatments in mean log-rank scores for the respective centers. It is particularly useful when the pattern of treatment differences is consistent across study centers. When the response to therapy was categorized, a statistically significant improvement was demonstrated in the cilostazol group.

Wei-Lachin is a 2-sample, nonparametric, multivariate analysis. It compares values at each visit as well as the change in walking distances over the course of the trial. Thus, it is a more stringent statistical challenge than ANOVA. The most rigorous analysis in any study of a therapeutic drug or procedure is by intention-to-treat (last observation carried forward) analysis. Because of this, the most pertinent analysis is at the last visit (week 12). Both ICD and ACD showed statistically significant increases at week 12 by Wei-Lachin analysis. The other comparisons at weeks 2, 4, and 8 do not show statistically significant changes. Because the early assessments do not show significance, the overall multivariate test is not significant.

The Fisher procedure is directed at the across-center sum of \((-\sum \log P_i)\), where \(\log\) denotes natural logarithm and \(P\) denotes the 1-sided \(P\) value for percent change with cilostazol compared with placebo for the \(i\)-th investigator. This method is sensitive to whether there are 1 or more \(P\) values that are sufficiently small to support the interpretation of the combined set as significant.

Limitations of Current Study
This trial was designed to be a pilot study; only a limited number of patients participated. There were 81 subjects enrolled; of these, 77 were evaluable (completing ≥1 treadmill test after randomization), and 66 completed the trial. There are some problems and limitations that are inescapable in a study with a relatively small sample population. There may be type II statistical errors. Given the inherent variability in the measurement of walking distances, we may have seen a significant treatment effect earlier if there had been more patients. Also, there is limited ability to perform analyses of selected subgroups because sample sizes would be decreased further. However, the fact that this trial demonstrated a positive effect despite the limited sample size suggests that improvement in claudication symptoms is clinically significant. Therapeutic responses that are statistically significant only when large numbers of patients are studied tend to be less important in clinical practice. Also, smaller studies are more subject to patient-selection biases.

This study was relatively short in duration. The mean ICD and ACD for the cilostazol-treated subjects increased at each testing visit during the 12-week double-blind treatment comparison in this study. This suggests that the therapeutic response may be gradual in onset and progressive. It is unknown whether treatment with a longer duration of cilostazol therapy would yield additional benefit.

The only direct comparison that this trial made was between cilostazol-treated patients and those treated with placebo. The relative benefit of cilostazol versus other claudication therapies was not examined as part of this trial. There was an effort to minimize the effects of other variables, however. No changes in activity or risk factor modification were recommended during the trial. The lack of change in the pain-free and maximal walking distances in the control group suggests that there were no significant confounding effects. The characteristics of the 2 treatment groups were similar, and the stratified randomization scheme made the treatment groups comparable with respect to use of calcium channel blockers.

Comparison of Results With Those Reported for Pentoxifylline
Although truly valid comparison awaits completion of trials that prospectively examine the efficacy of cilostazol com-
pared with other therapies, it may be useful to compare the results of the current study with the currently available medical therapy for intermittent claudication. Pentoxifylline has been the most extensively evaluated and most widely used drug for claudication, and it is the only agent in the United States with Food and Drug Administration–approved labeling for this indication.

Pentoxifylline efficacy has been tested in at least 10 randomized, placebo-controlled, blinded clinical trials,12,30–37 1 of which was performed in the United States.12 All but 1 of these studies33 demonstrated benefit with pentoxifylline. Meta-analysis is not possible because of significant differences in reporting, methodology, and outcome measures used in different reports.

The US study of Porter et al12 was one of the largest of the trials completed. Although 128 patients were randomized, 46 were withdrawn from that study and were not considered in the analysis of efficacy. An intention-to-treat analysis was not performed. During 24 weeks of treatment, there was a statistically significant difference between the pentoxifylline-treated and control groups, although the differences in percent change from baseline ICD and ACD when considered at week 24 were not statistically significant. In part, this reflects the pronounced placebo effect: 36% increase in ICD, 25% increase in ACD. Pentoxifylline-treated patients in the study had a 59% increase in ICD and a 38% increase in ACD.

In the present study, there was a mean 39% change from baseline for ICD and 45% for ACD in the patients who completed 12 weeks of treatment. Because the parallel, placebo-treated control group did not change from baseline (3% increase in ICD, 5% decrease in ACD), it appears that the treatment effect (relative to placebo) for cilostazol may be greater than that for pentoxifylline.

Pentoxifylline has failed to consistently demonstrate important clinical benefit in controlled clinical trials.2,24,33,38 Cameron et al38 reviewed the results of placebo-controlled trials with pentoxifylline and found a negative correlation between sample size and response. This may be because of a publication bias that favors pentoxifylline. Investigators may tend to withhold publication of negative results from small trials, but positive results are published. Findings from large studies tend to be published even with negative or less favorable results. Publication bias may explain why the largest trials of pentoxifylline efficacy12,39 demonstrated less of an increase in walking distances than seen in smaller studies. The studies that reported the most-favorable responses were small, often with 20 or fewer treated patients completing therapy.30,35 Seven of the 10 previous randomized, placebo-controlled trials of pentoxifylline had fewer than 20 patients in the treatment group.

The overall clinical utility of pentoxifylline is also limited by drug intolerance, costs of therapy,40 and inconsistent clinical response.23 Meta-analysis is most useful for patients with claudication that is moderately severe and that little symptomatic benefit is offered for patients with mild or severe disease.38,39,41,42 The cost-effectiveness of cilostazol therapy and the best target populations to treat are as yet unknown.

Problems Associated With Claudication Studies

Certainly patients in these trials undergo intensive surveillance, and there may be extensive physician attention and counseling regarding such factors as self-care, smoking cessation, and control of diabetes. Because of this, trials must be designed as placebo-controlled trials if useful conclusions are to be drawn. These factors can have a large effect on treadmill walking performance; as much as 149% improvement over baseline was seen in the placebo group in 1 pentoxifylline trial.24 Furthermore, treadmill testing has some inherent variability with repeated examinations.43

Of practical concern, there can be a difference between finding that a claudication treatment yields results that are statistically significant and finding that the effect is clinically significant, i.e., “is the patient better?” Given adequate sample size, a statistically significant improvement in walking distance may be demonstrated. However, if the patient’s subjective assessment of his or her symptoms is not affected, there is no reason to consider the effect to be beneficial. On the other hand, therapy does not have to completely eliminate symptoms to be considered useful. Claudication therapy is primarily directed at palliating symptoms and providing an improvement in patients’ overall functional status, and modest differences in walking ability may have little impact.

In the present study, participants’ subjective assessments corroborated the findings with treadmill testing. This suggests that measured improvement in walking distances translates into real functional benefit for some patients. However, although no patients found that cilostazol worsened their walking, half reported no change in performance. This suggests that there may be a subgroup of patients with claudication who derive a clinical benefit. Clinical features that might predict who would be expected to respond to therapy with cilostazol have yet to be identified.

Although a trend toward lowering triglycerides and increasing HDL cholesterol levels was observed in the cilostazol-treated group, it is premature to consider these to be therapeutic effects of cilostazol. Confirmation with additional clinical trials that control for potentially confounding effects on lipid metabolism is necessary. However, it is intriguing that an agent that effectively treats claudication symptoms may also have an effect that may slow progression of the underlying atherosclerotic arterial disease.

Conclusions

Cilostazol is an agent with pharmacological actions unlike other drugs used for the treatment of chronic occlusive arterial disease. This study represents a preliminary examination of its efficacy for treatment of the symptoms of intermittent claudication. Although this limited trial showed a statistically significant improvement in treadmill walking performance after 12 weeks of therapy with cilostazol 100 mg PO BID, and patients’ subjective assessment of symptoms corroborated this finding, additional studies with larger numbers of participating claudication patients are needed to confirm efficacy. The positive results of the current study are encouraging, and larger trials have been initiated to answer some of these questions.
Cilostazol for Intermittent Claudication

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Cilostazol Has Beneficial Effects in Treatment of Intermittent Claudication: Results From a Multicenter, Randomized, Prospective, Double-blind Trial
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