TREATING INTERMITTENT CLAUDICATION

CLOSE-UP ON CILOSTAZOL

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In the '80s and '90s, the only drug used to treat claudication was pentoxifylline. Then cilostazol was approved. See how this relative newcomer holds up under scrutiny.

Roughly one fifth of the older adult population in the United States has peripheral arterial disease (PAD)—and about 70% of them have intermittent claudication, the most debilitating PAD symptom.[1,2] Claudication, which occurs when blood flow to the legs is insufficient during periods of increased metabolic demand, is characterized by a painful aching, tightness, or burning sensation in the legs during walking.[3] The patient doesn't experience discomfort while at rest.[3] Claudication can reduce quality of life by impairing a person's ability to walk and perform activities of daily living.

Three different approaches are used to manage intermittent claudication: lifestyle and risk factor modification (including smoking cessation, weight reduction, exercise, and dietary changes to lower serum lipid levels), pharmacologic treatment (generally focused on managing diabetes, hypertension, and hyperlipidemia to slow the progression of atherosclerosis and to improve symptoms),[4] and vascular surgery (specifically, angioplasty and stenting of the narrowed artery or bypass surgery).

Smoking cessation has been shown to have a beneficial effect on walking performance.[5] Unfortunately, patients frequently fail to adhere to such lifestyle modifications as this, so symptoms don't abate and function continues to decline. Even when a patient makes positive lifestyle changes and manages comorbidities, symptoms may persist, necessitating pharmacotherapy. Referral to a vascular specialist is indicated when a patient fails to respond to exercise and pharmacotherapy or when there's evidence of critical limb ischemia, such as pain at rest or tissue loss (including ulcers or gangrene). Both vascular procedures carry the risks of infection and bleeding. Additionally, peripheral vascular bypass eliminates the possibility of using the harvested leg vein for a more serious surgery later on.

Until 1999, the only drug approved for treating intermittent claudication was pentoxifylline,[6] an agent that reduces blood viscosity and improves erythrocyte flexibility.[7] Unfortunately, pentoxifylline did not demonstrate consistency in relieving claudication.[5] Then, in 1999, the FDA gave providers another pharmacologic option with which to treat claudication: cilostazol, a phosphodiesterase III inhibitor with antiplatelet and vasodilatory properties.[1]

This article presents an overview of the performance of cilostazol in clinical studies. It reviews the six major clinical studies that have compared cilostazol to either placebo or pentoxifylline. Specifically, this article seeks to elucidate whether cilostazol has proven to be efficacious in increasing patients' pain free and maximum walking distances—the primary measures of exercise tolerance used to evaluate claudication symptoms (Table 1).[4]

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COMMON FEATURES OF THE STUDIES

The six clinical studies reviewed here all focused on the use of cilostazol in the treatment of intermittent claudication (Table 2).[1,2,4,6,8,9] All were randomized, controlled trials and all but one (study number 5) were double-blind, multicenter investigations. Participants for all six studies were predominantly white men in their mid to late 60s.

The studies used similar selection, inclusion, and exclusion criteria. For inclusion, subjects had to: (1) demonstrate reproducible walking distances on a treadmill kept at a constant speed of 2 mph and an incline of 12.5% and terminate such screening tests solely because of claudication pain; (2) have a resting ankle-brachial index of 0.9 or less and a reduction of 10 mm Hg or more in ankle arterial blood pressure at maximum walking distance compared with baseline; (3) demonstrate stable disease by walking between 30 and 200 m on two consecutive tests with no pain and with 25% or less variance between the two tests. Subjects were excluded if they had rest pain, hypertension, a current malignancy, or exercise-limiting cardiac disease; were grossly obese; had the potential to bear children; or used antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory drugs.

Baseline characteristics and characteristics of subjects who dropped out of the studies were, for the most part, evenly distributed among all treatment groups. Only statistically significant findings are described here.

CILOSTAZOL VERSUS PLACEBO

Three studies conducted since 1998 have compared cilostazol with placebo. The study by Beebe and colleagues (study 1), which was performed in 37 outpatient vascular clinics throughout the United States, evaluated cilostazol's efficacy and safety.[1] The subjects were men and women older than 40 who had at least a six-month history of intermittent claudication caused by PAD.

Of the 663 patients screened, 516 were randomly assigned to receive either cilostazol 100 mg twice daily (175), cilostazol 50 mg twice daily (171), or placebo (170). Evaluation, at baseline and weeks four, eight, 16, 20, and 24, included testing of pain free and maximum walking distances; quality of life and functional status (using questionnaires); and symptom improvement (using patient and physician assessment).

After 24 weeks, pain free walking distance had increased 59% in the 100-mg cilostazol group, 48% in the 50-mg cilostazol group, and only 20% in the placebo group. Maximum walking distances increased 51%, 38%, and 15% in the 100-mg, 50-mg, and placebo groups, respectively. Compared with the placebo group, both cilostazol groups demonstrated significant improvement in all outcomes, including functional status, pain, and quality-of-life issues (such as physical health and mental health concepts). Additionally, more patients receiving cilostazol than placebo judged themselves—and were judged by physicians—to be "better" or "much better" after treatment.[1] A total of 75 patients (14.5%) withdrew due to adverse events, and withdrawal was equally distributed among the treatment groups.

Table 1. Measures of walking tolerance in intermittent claudication[4]

- Pain free walking distance–Distance at which patient first reports onset of symptoms
- Maximum walking distance–Distance at which patient can no longer walk

In their comparison of cilostazol and placebo, Dawson and colleagues (study 2) used evaluation measures similar to those used in study 1, though Dawson didn't measure quality of life and functional status.[4] The 81 participants were assigned either to a placebo (27) or to cilostazol 100 mg twice daily (54). Investigators tested subjects at baseline and weeks two, four, eight, and 12.[4]

Compared with the placebo group, both cilostazol groups demonstrated significant improvement in all outcomes.

In the cilostazol group, pain free walking distance increased 58%, after 12 weeks of therapy, compared with 8.9% in the placebo group.[4] Maximum walking distance increased 63% in the cilostazol group—and actually decreased 9.8% in the placebo group.

Subjective physician and patient assessment confirmed significant improvement in symptoms: Of the

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Table 2. Evaluating cilostazol: What the studies show

Author (year)	Treatment groups (n)	Protocol	Findings
Study 1: Beebe et al (1999)[1]	Cilostazol 100 mg twice daily (175) Cilostazol 50 mg twice daily (171) Placebo (170)	Evaluated pain free walking distance, maximum walking distance, quality of life, functional status; patient and physician assessments	Both pain free and maximum walking distances increased significantly in cilostazol groups versus placebo group More patients receiving cilostazol than placebo judged themselves—and were judged by physicians—to be "better" or "much better"
Study 2: Dawson et al (1998)[4]	Cilostazol 100 mg twice daily (54) Placebo (27)	Evaluated pain free walking distance, maximum walking distance; patient and physician assessments	Significant increase in pain free and maximum walking distance in cilostazol group versus placebo group Patients and physicians reported that symptoms were "better" or "much better" in cilostazol group and unchanged or worse in placebo group
Study 3: Money et al (1998)[2]	Cilostazol 100 mg twice daily (119) Placebo (120)	Evaluated pain free walking distance, maximum walking distance, functional status, and walking impairment	Significant increase in pain free and maximum walking distances in cilostazol group versus placebo group Significant improvement in bodily pain, general health, walking speed, and walking difficulty in cilostazol group versus placebo group
Study 4: Dawson et al (2000)[6]	Cilostazol 100 mg twice daily (166) Pentoxifylline 400 mg three times daily (172) Placebo (201)	Evaluated pain free walking distance, maximum walking distance, functional status, and quality of life	Significant increase in pain free and maximum walking distances in cilostazol group versus pentoxifylline and placebo groups No significant differences in functional assessments and quality of life between the groups
Study 5: Lee et al (2001)[8]	Cilostazol 100 mg twice daily (17) Pentoxifylline 400 mg three times daily (17) Placebo (16)	Evaluated maximum walking distance and effect on VEGF*	Significant increase in maximum walking distance in both cilostazol and pentoxifylline groups versus placebo group Significant increase in VEGF in cilostazol group only
Study 6: Elam et al (1998)[9]	Cilostazol 100 mg twice daily (95) Placebo (94)	Evaluated maximum walking distance and effect on plasma lipoproteins	Significant increase in maximum walking distance in cilostazol group versus placebo group Significant decrease in triglycerides and significant increase in HDL† level in cilostazol group versus placebo group No correlation between maximum walking distance and change in lipoproteins

*VEGF = vascular endothelial growth factors. †HDL = high-density lipoprotein.

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patients receiving cilostazol, 22% described their postintervention ability to walk as "much better" and 28% described it as "better"; physicians judged this to be true in 13% and 35% of the group, respectively. The placebo group had very different results, with both patients and physicians reporting that ability to walk was "unchanged" by placebo administration in 63% of all cases. Patients and physicians considered ability to walk to be "worse" or "much worse" after placebo administration in 19% and 15% of cases, respectively.

In the trial by Money and colleagues (study 3), 239 patients from 17 centers, all of whom had intermittent claudication, were randomly assigned to receive either cilostazol 100 mg twice daily (119), or placebo (120).[2] Treadmill testing was performed at weeks eight, 12, and 16 and included evaluation of pain free walking distance, maximum walking distance. Questionnaires were used to assess functional status and walking impairment.

By the end of the study period, maximum walking distance and pain free walking distance had increased significantly in the cilostazol group—47% by week 16, compared with 12.9% in the placebo group.[2] Researchers also noted a significant overall increase in pain free walking distance in the cilostazol group, though the specifics weren't published. Bodily pain, general health, walking speed, and walking difficulty improved significantly in the cilostazol group compared with the placebo group. In addition, 55% of patients in the cilostazol group reported feeling "much better" and 35% reported feeling "better." Their physicians echoed these assessments, judging that 47% of patients who took cilostazol were "much better" and 32% were "better."

These three studies provide overwhelming evidence that cilostazol can increase walking distances dramatically for patients with intermittent claudication. Subjective measures also indicate that cilostazol is effective. Both patients and physicians noted improvement with cilostazol, and most patients who received cilostazol reported feeling either "better" or "much better."

Few subjects in these studies dropped out on account of adverse effects, indicating that cilostazol is well tolerated by most patients.

Unfortunately, like most drugs, cilostazol is associated with some adverse effects (Table 3).[1,2,5,6] Those reported most often in these three studies were headache, abnormal stools, diarrhea, nausea, flatulence, and dizziness. Nevertheless, few subjects in these studies dropped out on account of adverse effects, indicating that cilostazol is well tolerated by most patients.

It's worth noting that none of these investigations included more than a few African Americans or women. The effectiveness of cilostazol needs to be evaluated in these populations.

CILOSTAZOL VERSUS PENTOXIFYLLINE

In the comparison of cilostazol and pentoxifylline by Dawson and colleagues (study 4), the 539 subjects from 54 U.S. outpatient vascular clinics completed a 24-week therapy regimen, receiving either cilostazol 100 mg twice daily (166), pentoxifylline 400 mg three times daily (172), or placebo (201). Walking distances were measured every four weeks and functional and quality-of-life assessments were performed at weeks 12 and 24.[6]

From weeks four through 24, walking distances improved significantly in the cilostazol group compared with both the pentoxifylline and placebo groups. By the end of the study, pain free walking distances had increased over baseline by 75% in the cilostazol group, 59% in the pentoxifylline group, and 42% in the placebo group. In the cilostazol group, maximum walking distances increased about 54%, compared with 30% and 34% in the pentoxifylline and placebo groups, respectively.[6] No significant differences were found in functional status or walking impairment between the groups.

In addition to comparing the efficacy of cilostazol with pentoxifylline in terms of maximum walking distances, the study by Lee and colleagues (study 5) compared the effects of the drugs on vascular endothelial growth factors (VEGF).[8] The 50 participants received either cilostazol 100 mg twice daily (17), pentoxifylline 400 mg three times daily (17), or placebo (16). Patients were followed for eight weeks.

By the end of the study period, maximum walking distance increased 30% in the cilostazol group, 29% in the pentoxifylline

Table 3. Most common adverse effects of cilostazol[1,2,5,6]

- Headache
- Gastrointestinal disturbances (diarrhea, loose stools, abdominal cramps)
- Dizziness
- Palpitations
- Pain
- Pharyngitis

group, and 4% in the placebo group. VEGF increased significantly in the cilostazol group only.[8] This is an important finding because VEGF may increase the ability to form collateral circulation, increasing the amount of blood perfusion to the leg muscles.

CILOSTAZOL AND LIPOPROTEINS

In addition to increasing walking distances and improving quality of life, cilostazol may decrease lipoproteins. The study by Elam and colleagues (study 6) had the same inclusion and exclusion criteria as the other five studies, except that subjects weren't allowed to be taking any lipid modifying agents.[9] Walking distances were evaluated at weeks eight and 12, and blood levels were recorded at weeks two, four, six, eight, and 12. The 189 subjects received either cilostazol 100 mg twice daily (95) or placebo (94).

After 12 weeks, plasma triglycerides in the cilostazol group had decreased 15%, and high-density lipoprotein (HDL) levels had increased 10%. Both HDL and triglyceride levels remained unchanged in the placebo group. Cilostazol treatment did not affect low-density lipoprotein levels significantly. In this study, cilostazol increased maximum walking distance by 35%, compared with 24% in the placebo group. There was no correlation between maximum walking distance and change in lipoproteins.[9]

Cilostazol's apparent effect on triglycerides and HDL levels is an important benefit for people with PAD. High cholesterol levels lead to an increase in plaque formation in the peripheral vessels. This makes it more difficult for the blood to reach the leg muscles, contributing to claudication pain. If cilostazol can both decrease plasma lipoproteins and improve walking distances, then the drug moderates claudication in two ways. Furthermore, intermittent claudication suggests broader systemic arterial disease. In fact, 60% of patients with PAD also have arterial disease involving the cardiovascular and cerebrovascular systems.[3]

CLINICAL IMPLICATIONS

The six studies reviewed here offer overwhelming evidence that cilostazol is a beneficial pharmacologic option for managing intermittent claudication. In all six, cilostazol significantly improved both pain free and maximum walking distances compared with pentoxifylline, placebo, or both (Figure).[1,2,4,6,8,9]

Cilostazol's apparent effect on triglycerides and HDL levels is an important benefit for people with PAD.

Nonetheless, this pharmacologic treatment—dosed at 100 mg twice a day—should not be given to all patients with intermittent claudication. Because phosphodiesterase III inhibitors have been shown to increase mortality in patients with heart failure, cilostazol is contraindicated in such patients. Long-term effects of cilostazol use on morbidity and mortality in patients without heart failure aren't yet known. Moreover, cilostazol should not be viewed as a substitute for exercise programs or positive lifestyle changes but should be reserved for people who have not benefited sufficiently from such changes.[5] When treatment is discontinued, the drug's benefits stop and walking ability can worsen.

Keep in mind, too, that the drug's adverse effects may limit adherence to treatment, though studies suggest most patients find them tolerable.[1,2,5,6] The effects of cilostazol appear gradually, with improvement initially appearing about four weeks after therapy is begun. Consider discontinuing the drug if the patient hasn't experienced any beneficial effects after three to six months.

Patients taking cilostazol should avoid grapefruit juice, diltiazem, erythromycin, the ulcer medication omeprazole, and such antifungal agents as fluconazole and miconazole.[4,10] These substances increase absorption of cilostazol by inhibiting the drug's primary metabolizers, specifically cytochrome P450 3A4 or 2C19. Patients should take cilostazol

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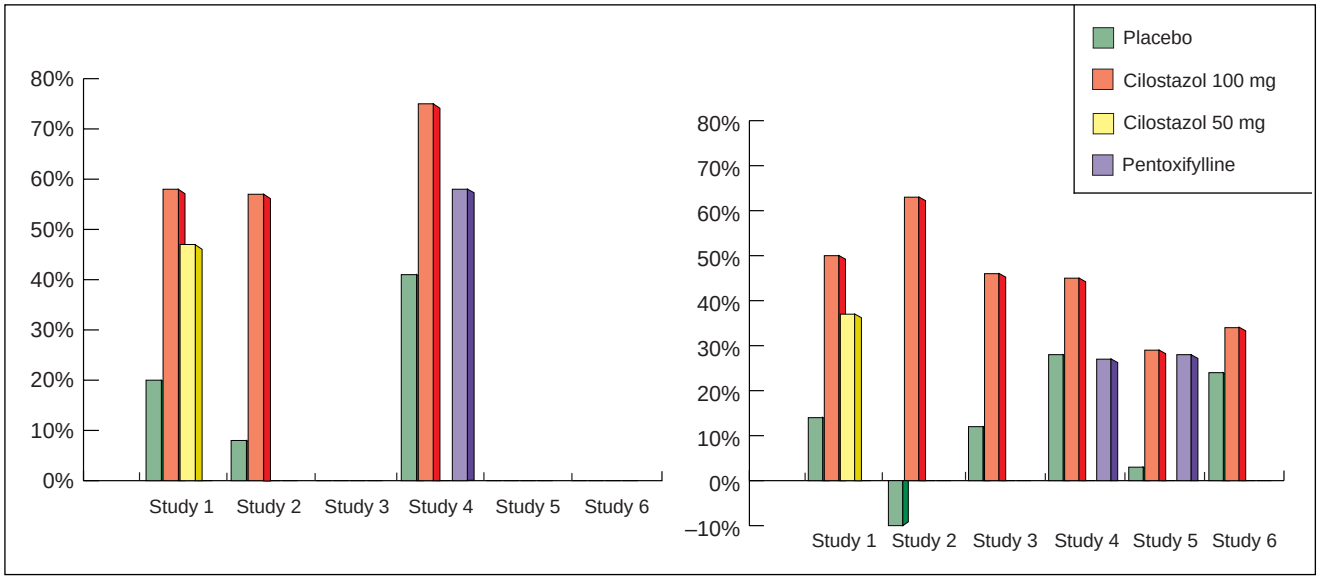

Figure. At left, mean percentage increase in pain free walking distance. (Studies 3,5, and 6 did not evaluate pain free walking distance.) At right, mean percentage increase in maximum walking distance. Created from: Beebe et al,[1] Dawson et al,[4] Money et al,[2] Dawson et al,[6] Lee et al,[8] Elam et al[9]—studies 1 through 6, respectively.

at least 30 minutes before or two hours after eating because high fat meals also can increase drug absorption.[11] Because cilostazol inhibits platelet activity, consider stopping the drug before surgery or other invasive procedures. The lack of information on the combined effects of cilostazol and clopidogrel—an agent commonly used in patients with arterial disease to reduce risk of stroke or heart attack—is a concern because both agents inhibit platelet function.

TYING IT TOGETHER

The six studies reviewed here show that cilostazol can increase walking tolerance in patients with intermittent claudication, thereby helping them continue performing activities of daily living. Two of the six also demonstrate that cilostazol has a beneficial effect on plasma VEGF[8] and lipoproteins.[9] These effects can contribute to an increase in functional ability and improved quality of life.

Of the four studies that measured functional status, only one failed to show a significant increase by the end of the study period. Notably, three studies found that cilostazol made subjects "feel better." All three of these studies included many people who had smoked or who still were smoking. Nonetheless, walking and functional status improved with cilostazol treatment. Although it is unknown if smoking cessation would enhance the benefits of cilostazol in these patients, practitioners should of course continue to advise patients to stop smoking in the interest of improving their overall health.

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