Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease

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Purpose: **This study evaluated the effects of cilostazol on walking distances in patients with intermittent claudication (IC) caused by peripheral arterial occlusive disease.**
Methods: **The study was a multicenter, randomized, double-blind, placebo-controlled trial. Two hundred thirty-nine patients with IC were randomly assigned to receive cilostazol (100 mg b.i.d.) or a placebo for 16 weeks. All patients underwent serial, variable-grade, constant-speed treadmill testing. Absolute claudication distance (ACD), assessed at the end of the 12-hour dosing interval (trough), was the primary end point. Secondary end points included ACD assessed 3 to 4 hours after dosing (peak) and initial claudication distances (trough and peak). Functional status measures, including the Medical Outcomes Scale (SF-36) and Walking Impairment Questionnaire, were used to assess subjective changes over the 16-week treatment period. Ankle-brachial indexes were calculated from Doppler-measured systolic pressures at every visit with treadmill testing.**
Results: **Patients treated with cilostazol demonstrated significant improvements over the placebo patients in ACD at all three time points tested after baseline (weeks 8, 12, and 16). Peak treadmill testing at weeks 8 and 12 also showed significant improvement in walking distances for cilostazol-treated patients over placebo-treated patients. At week 16, patients in the cilostazol group had a 96.4-meter (47%) increase in ACD compared with 31.4 meters (12.9%) for the placebo group ($p < 0.001$). In the SF-36, significant improvement was observed in the physical component subscale and the composite physical component score. In the Walking Impairment Questionnaire, improvements were significant in patient reports of walking speed and specific measures of walking difficulty. Ankle-brachial indexes improved in the cilostazol group (0.64 ± 0.02 to 0.70 ± 0.02) compared with the placebo group (0.68 ± 0.02 to 0.69 ± 0.02) ($p < 0.0125$). The most frequent adverse events were headache, abnormal stools (e.g. loose stools), diarrhea, and dizziness.**
Conclusions: **Cilostazol significantly increased ACD at all measured time points and initial claudication distances at most time points. This agent may represent a new treatment option for patients with intermittent claudication. (J Vasc Surg 1998;27:267-75.)**

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Peripheral arterial occlusive disease (PAOD) of the lower extremities has been attributed primarily to atherosclerotic changes and the risk factors associated with atherosclerotic disease, including smoking, male gender, hypercholesterolemia, and age.[1,2] The prevalence of PAOD in the general population increases with age.[3,4] Some estimates indicate that the prevalence of PAOD has an age adjusted rate of 12%.[5,6]

Intermittent claudication (IC) is the most common debilitating symptom of PAOD. In 1987, an estimated 4,234,000 people in the United States

Table I. Patient demographic characteristics

Parameter	*Cilostazol (100 mg b.i.d.)*		*Placebo*	
	Mean	*Percent*	*Mean*	*Percent*
Age (yr)				
Mean ± SD	64.8 ± 9.4		64.5 ± 8.8	
Range	45 to 91		41 to 88	
Gender				
Male	90	75.6	90	75.0
Female	29	24.4	30	25.0
Race				
White	106	89.1	102	85.0
Black	10	8.4	11	9.2
Hispanic	2	1.7	7	5.8
Asian	1	0.8	0	0.0
Weight (kg)				
Mean ± SD	82.5 ± 16.6		79.6 ± 14.9	
Range	42 to 130		49 to 127	
Diabetes				
Yes	30	25.2	37	30.8
No	89	74.8	83	69.2
Cigarettes				
Never	18	15.1	9	7.5
Previous	58	48.7	63	52.5
Current	43	36.1	48	40.0

had IC.[3] Patients with IC are severely impaired in their ability to perform daily activities.[7] Confirmation of impairment is reflected in lower quality-of-life scores on physical functioning scales and disease-specific scales measuring patients' perception of walking speed and distance.[8,9]

Established medical therapies available for IC include exercise programs, risk factor modifications, and surgical and endovascular procedures.[10] However, many of these are not applicable for many patients with IC.[11] Pharmacologic therapy for IC in the United States is limited to a single agent whose usefulness has been questioned.[12] Numerous drugs have been studied or are in development for the treatment of IC, including prostaglandins and prostaglandin analogs, vasodilating agents, calcium channel blockers, hemorrheologic agents, anticoagulants, and antiplatelet agents.[13]

Cilostazol has significantly more potent vasodilatory and antiplatelet activity than aspirin.[14] In addition, cilostazol has antiproliferative properties and enhances the effects of prostacyclin, the endogenous vessel-wall antiplatelet, and vasodilating substance.[15]

This study tested the hypothesis that treatment with cilostazol (100 mg b.i.d. for 16 weeks) would increase walking distances in patients with IC.

METHODS

Two hundred thirty-nine patients with IC caused by lower extremity PAOD were evaluated in a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-design study.

Study design. Patients were required to sign an informed consent form before undergoing screening procedures, beginning with a medical history and physical examination. The screening period lasted 2 weeks. After randomization to double-blind study medication, visits occurred at weeks 2, 4, 8, 12, and 16. At each visit the following safety assessments were made: serum chemistry, hematology, electrocardiogram, vital signs, concomitant medication changes, and adverse events.

Treadmill testing was performed at the two screening visits and at postrandomization weeks 8, 12, and 16. At baseline, week 8, and week 16, two treadmill tests were performed 3 to 4 hours apart. At weeks 8 and 16, study medication was administered immediately after the first treadmill tests.

At the completion of 16 weeks, another physical examination assessed potential changes, and both the physicians and the patients evaluated the effect of the study drug on claudication symptoms. In addition, at weeks 8 and 16, two functional status questionnaires, the Medical Outcome Scales Health Survey (SF-36) and the Walking Impairment Questionnaire (WIQ), were administered.

Inclusion criteria. Eligible patients were more than 40 years of age and had had PAOD for at least 6 months with no change in symptoms in the previous 3 months. The presence of PAOD was verified in patients by a Doppler-measured ankle-brachial index (ABI) of 0.90 or lower after 10 minutes of rest and by a reduction in the blood pressure of at least one ankle artery by a minimum of 10 mm Hg when measured 1 minute after claudication-limiting treadmill testing. If these criteria were not met, a decrease of at least one ankle artery blood pressure by a minimum of 20 mm Hg when measured 1 minute after treadmill testing was accepted for entry into the study. Eligible patients had a baseline initial claudication distance (ICD) of at least 54 meters (corresponding to 1 minute on the treadmill), a reproducible absolute claudication distance (ACD; variance no greater than 20% between the two screening visits), and a maximum allowable ACD of 805 meters (corresponding to 15 minutes).

Patients were excluded for the following reasons: limb-threatening PAOD, including gangrene or ischemic rest pain; surgical or endovascular procedures in the preceding 3 months; gross obesity; hypertension, >200 systolic or >100 diastolic (mm Hg); current malignancy (except basal cell carcino-

Table II. Absolute claudication distance and time (last observation carried forward)

	Cilostazol		*Placebo*	
	Meters ± SE	*Total seconds ± SE*	*Meters ± SE*	*Total seconds ± SE*
Baseline				
Trough	236.9 ± 13.6	265.0 ± 15.2	244.3 ± 13.7	273.3 ± 15.3
Peak	211.4 ± 12.4	236.5 ± 13.8	219.3 ± 12.9	245.2 ± 14.5
Week 8				
Trough	285.4 ± 16.8	319.2 ± 18.8	271.9 ± 17.2	254.5 ± 19.2
Peak	272.3 ± 15.5	304.6 ± 17.3	252.9 ± 17.0	282.9 ± 19.0
Week 12				
Trough	313.4 ± 19.9	350.5 ± 22.3	279.2 ± 18.3	257.0 ± 20.5
Week 16				
Trough	332.6 ± 20.0	372.0 ± 22.4	281.1 ± 19.2	255.0 ± 21.5
Peak	306.9 ± 19.1	343.3 ± 21.4	267.5 ± 18.5	299.3 ± 20.7

ma or in situ carcinoma); Buerger's disease or deep venous thrombosis in the previous 3 months; inability to complete treadmill testing for reasons unrelated to IC; or bleeding problems. Drugs with significant effects on peripheral vessels, bleeding, hemostasis, or platelet function were prohibited during the study. Among these were warfarin, heparin, and pentoxifylline. Antiplatelet agents, such as aspirin, persantine, and ticlopidine, and nonsteroidal antiinflammatory agents were also prohibited.

The patients were not given specific risk factor modification instructions about smoking cessation, lipid intake limitation, or exercise. All patients were free to follow any other medical care regimens.

Treadmill design. Testing was conducted with a variable-grade, constant-speed treadmill. This treadmill design begins at a 0% incline with a speed of 3.2 km/hr (2 miles/hr), and the incline increases by 3.5% every 3 minutes.

ABI. ABIs were calculated as the ratio of the lowest pressure from either the right or left posterior or anterior tibial (dorsalis pedis) arteries over the greatest brachial systolic pressure. This calculation allowed for patients' entry into the study. For analysis purposes, the highest pressure in each limb was used for determination of an "affected limb" (limb with the lower ABI at baseline), and the change in ABI was then assessed with this method of calculation.

Functional status assessments. The SF-36 is a general health questionnaire that measures the patient's perception of physical health, mental health, and combined physical and mental health. Four parameters (physical function, bodily pain, role-physical, and general health perception) compose the physical component scale. The WIQ assesses the patients' impressions of walking speed and distance and specific measures of walking difficulty because of pain or other problems.

Statistical methods. The primary variable analyzed for efficacy was ACD, as measured by standardized treadmill testing. Additional efficacy outcomes included ICD, ABI, and the functional status questionnaires. All statistical tests performed were two-sided. Values were significant if p was less than or equal to 0.05. The baseline comparability between the treatment group and the placebo group was assessed by comparing means, standard deviations, and proportions. Continuous efficacy measures were analyzed by variance or the Wilcoxon rank sum test. The data for claudication distances were analyzed in terms of logarithm ratios (walking distance at postbaseline/walking distance at baseline).[16-18] This analysis expresses results as a percent change from baseline and reduces the effects of extreme values. In addition, results were expressed as change from baseline in meters and as change in seconds walked. Estimated treatment effects were calculated with a ratio of the geometric means (cilostazol/placebo) to provide an estimate of the net drug effect. Subjective improvement of claudication, as assessed by the patient and the investigator at the end of treatment, were analyzed using the Cochran-Mantel-Haenszel test. In an attempt to use all data obtained throughout the period of study treatment rather than at selected time points, a repeated measure of analysis of variance was applied to walking distances, functional status questionnaires, and ABI results. For efficacy variables measured sequentially at time points, the following two types of analyses were performed: (a) a last visit-analysis and (b) a time-point-by-visit analysis.

RESULTS

This trial was performed at 17 centers in the United States after receiving approval from the Institutional Review Boards. Analysis of baseline demo-

Table III. Estimated treatment effects

Treatment comparison	*Week 8*		*Week 12*		*Week 16*	
	ICD	*ACD*	*ICD*	*ACD*	*ICD*	*ACD*
Cilostazol vs placebo (trough)						
Geometric mean	1.07	1.13*	1.15*	1.19*	1.20*	1.29*
Change (m)	13	27*	28*	46*	28*	62*
% Change	10	15*	19*	21*	27*	32*
Cilostazol vs placebo (peak)						
Geometric mean	1.10	1.16*	na	na	1.20*	1.21*
Change (m)	12	29*	na	na	26*	48*
% Change	19*	22*	na	na	32*	27*

*$p < 0.05$.

Table IV. Perception of patients and investigators after 16 weeks of treatment

	Cilostazol 100 mg b.i.d.				*Placebo*			
	*Patient**		*Investigator†*		*Patient*		*Investigator*	
	n	(%)	n	(%)	n	(%)	n	(%)
Judgment								
Much better	14	(11.8)	8	(6.7)	12	(10.0)	6	(5.0)
Better	52	(43.7)	48	(40.3)	30	(25.0)	33	(27.5)
Unchanged	44	(37.0)	54	(45.4)	64	(53.3)	72	(60.0)
Worse	5	(4.2)	3	(2.5)	8	(6.7)	4	(3.3)
Much worse	0	(0.0)	0	(0.0)	3	(2.5)	1	(0.8)
Unknown	4	(3.4)	6	(5.0)	3	(2.5)	4	(3.3)

*$p = 0.0043$.
†$p = 0.0408$.

graphics showed no significant or clinically relevant difference between the treatment groups (Table I). Two hundred ninety-eight patients were screened for inclusion in the trial. One hundred nineteen patients randomly received cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone)(Otsuka Pharmaceutical Company, Ltd., Tokushima, Japan) 100 mg b.i.d. One hundred twenty patients received matching placebo tablets. Randomized patients were primarily white (87%) men (75.3%), with an average age of 64.6 years and a range of 41 to 91 years.

Approximately one half of the randomized patients were previous cigarette smokers, and 38% were current smokers. Therefore 88.6% of the patients had a cigarette-smoking history (mean, 53.5 pack-years). The treatment groups had no apparent differences with respect to smoking or medical history. The most common medical histories were for previous myocardial infarction (18.8%) and previous attempts at distal revascularization (12.5%).

Trough and peak baseline ACD values were 236.9 and 211.4 meters, respectively, in the cilostazol group and 244.3 and 219.3 meters in the placebo group. No differences were noted in baseline ABI scores of 0.64 ± 0.02 and 0.68 ± 0.02, cilostazol and placebo, respectively.

Two hundred twelve patients (88.7%) completed the study, 104 in the cilostazol group and 108 in the placebo group. Fifty-nine patients failed to qualify for the study because of out-of-range treadmill testing, use of prohibited medications, or inability to return for follow-up visits. Patients included in the intent-to-treat analysis of the treadmill data had at least one postbaseline treadmill test. Intent-to-treat analysis of the safety population included all patients who ingested at least one dose of study medication.

Evaluation of efficacy. Cilostazol-treated patients walked significantly farther trough ACD distances than placebo-treated patients walked at all time points in therapy (Table II). The mean meter change from baseline after 16 weeks was 96.4 meters and 31.4 meters for the patients who received cilostazol and placebo, respectively. Improvement in trough ACD at week 8 was 49.1 meters for patients who received cilostazol versus 20.6 meters for patients who received placebo, and at week 12, the meter improvement was 77.1 for patients who received cilostazol compared with 29.5 for patients who received the placebo, at all time points ($p \leq 0.0013$; Fig.1).

The primary end point was ACD (trough) at week 16 versus baseline. The improvement for patients on cilostazol resulted in an estimated treatment effect of 1.29, a 29% improvement of the cilostazol-treated patients over the placebo-treated patients ($p = 0.0001$). The 95% confidence interval was 1.17 to 1.41.

Supplemental analysis showed similar improvement in the estimated treatment effects for trough ACD at weeks 8 and 12 of 1.13 and 1.19, respectively ($p \leq 0.001$) (Table III). The improvement in ACD in the cilostazol-treated patients over the placebo-treated patients was also noted in the second (peak) treadmill tests conducted at weeks 8 and 12, in which the estimated treatment effects were 1.16 and 1.21, respectively ($p \leq 0.0012$). No significant differences were noted between treadmill test 1 (trough) and treadmill test 2 (peak) ACD values (Tables I and III).

The number of patients in the cilostazol-treated group with an improvement in ACD greater than 50% was approximately double the number in the placebo group ($p < 0.003$).

All subgroups analyzed (age, smoking status, sex, race, and presence of diabetes) performed better on treadmill testing with cilostazol treatment. The small subgroup size precluded the derivation of inferential statistics.

Results similar to those for ACD were observed for the ICD at all measured time points, with the exception of week 8, in which no significant difference was noted between treatment groups (Table III).

The SF-36 physical component scale score improved significantly in cilostazol-treated patients after 16 weeks of therapy when compared with placebo-treated patients. The physical component scale score increased by 2.99 points in the cilostazol-treated patients and by 0.12 points in the placebo-treated patients ($p = 0.0059$). In evaluations of patients' perceptions of physical function at week 16, the cilostazol-treated group showed a mean positive change from baseline of 8.3 points versus 2.3 points in the placebo-treated group ($p = 0.0024$). Compared with placebo, the cilostazol-treated group also improved for the bodily pain ($p = 0.0772$), general health ($p = 0.436$), and role-physical ($p = 0.061$) parameters. No negative effects were noted in the mental components of the SF-36 in either treatment group.

In the WIQ, patients benefited from cilostazol after 16 weeks of treatment. Walking speed, assessed by this questionnaire, improved by 20% with cilostazol and did not change in the placebo-treated group

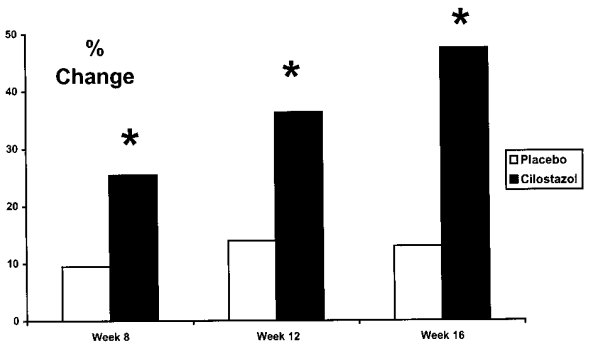

Fig. 1. Mean percent change from baseline ACD. $p < 0.05$.

($p = 0.0331$). Specific measures of walking difficulty, including "difficulty walking caused by pain or stiffness in joints," "difficulty walking caused by other problems," and "difficulty walking caused by pain or aching in calves," were improved in the cilostazol-treated patients. No changes in the walking distance score were noted.

Therapeutic assessment by both investigators and patients favored treatment with cilostazol over placebo (Table IV). In the cilostazol-treated group, 55.5% of the patients felt "much better" or "better" versus 35.0% of the patients in the placebo-treated group. The investigators felt that 47.0% of the patients were "much better" or "better" in the cilostazol-treated group as compared with 32.5% of the patients in the control group. Both the investigators' and patients' judgments were significant ($p < 0.05$).

Resting ABI increased from 0.64 ± 0.02 at baseline to 0.70 ± 0.02 after 16 weeks of treatment, representing a 9% increase. In the placebo group the mean ABI was 0.68 ± 0.02 at baseline and increased to 0.69 ± 0.02 at week 16 ($p = 0.0125$ cilostazol vs placebo).

Evaluation of safety. Generally, cilostazol was well tolerated. Patients in the cilostazol-treated group had higher incidences of headaches (30.3%), abnormal stools (16.0%) (generally described as "loose stools"), diarrhea (12.6%), and dizziness (12.6%) compared with the placebo group (9.2%, 5.0%, 6.7%, and 5.0%, respectively) ($p < 0.05$). Most of the headaches reported were mild and responded to nonprescription analgesic medication. Three patients, two in the cilostazol-treated group and one in the placebo-treated group, discontinued participation in this study because of headaches. No patients discontinued the study because of abnormal stools or diarrhea. One patient in the cilostazol-treated group discontinued because of dizziness.

Of the 27 patients (11.3%) who withdrew from the study, 21 withdrew because of adverse events. Total withdrawals and adverse-event withdrawals were similar between the cilostazol-treated and the placebo-treated groups (15 versus 12, and 12 versus 10, for cilostazol and placebo, respectively).

Similarly, the incidence of serious adverse events was similar between the two treatment groups. The incidence was 11.8% (13/119) in cilostazol-treated patients and 9.2% (11/120) in placebo-treated patients. A total of 12 patients, seven in the cilostazol-treated group and five in the placebo-treated group, discontinued participation in the study because of serious adverse events. One patient in the placebo-treated group died while on study medication, and one patient in the cilostazol-treated group died of a myocardial infarction 6 days after stopping study medication.

No significant differences between groups were noted in laboratory safety assessments, with the exception of triglyceride and plasma HDL levels. Mean triglyceride levels from baseline to end of treatment decreased by 48.8 ± 10.8 mg/dl (mean ± SE) in the cilostazol group and by 36.4 ± 20.0 mg/dl in the placebo group. In addition, mean HDL cholesterol from baseline to end of treatment increased from 47.6 ± 1.2 mg/dl to 52.8 ± 1.4 mg/dl (mean ± SE) in the cilostazol group and from 48.1 ± 1.1 mg/dl to 50.2 ± 1.2 mg/dl in the placebo group.

DISCUSSION

In this well-controlled, multicenter clinical trial, cilostazol-treated patients significantly increased the time to initial onset of symptoms, as well as their maximal walking distances, functional status measures, and ABIs. Striking, reproducible changes were observed in the end points of walking distances (ICD and ACD) in patients treated with cilostazol for 16 weeks. In variable-grade, constant-speed treadmill testing, the energy cost of walking is nonlinear because, as the patient progresses to longer distances (time) on the treadmill, the energy expenditure increases significantly as the incline increases. The walking changes and increased energy expenditure were coupled with significant corroborative improvements in functional status as noted in both the physical function scale and the physical component scale composite score of the SF-36, in the walking speed assessment of the WIQ, and in the judgments by patients and investigators at the end of treatment. The average patient had an increase in ACD values of approximately one-third to one-half at the end of the 16-week trial. When patients given cilostazol were asked to judge whether they had improved significantly relative to pretreatment, approximately one half of them felt they were "better" or "much better" versus one third in the placebo group.

The most common side effect was headache. More than one-quarter of the patients in the cilostazol-treated group had mild-to-moderate headaches. Four patients reported severe headaches, and two patients discontinued the study because of headaches. Most of the headaches responded to nonprescription analgesics. The second most common complaint was abnormal stools, primarily loose stools.

This study represented a scientifically rigorous examination of the effects of cilostazol on walking distances. All end points were defined a priori, and all analyses were carried out according to protocol, by an independent statistical group. Only one patient (on placebo) was unblinded during the course of the trial. The patient was unblinded to the investigator only after an abnormally high alkaline phosphatase level was detected. With careful monitoring according to Food and Drug Administration guidelines, no biases were noted.

Despite encouraging results from surgical and endovascular modalities, the initial treatment of claudication is usually a risk factor modification program. Changes include the cessation of smoking, dietary modification, and a routine exercise program. Patterson et al.[19] demonstrated that most patients with IC improve significantly with a walking program. However, compliance with supervised exercise programs has been questioned because of accessibility, cost, and patient dedication. An effective therapeutic agent for the amelioration of the symptoms of IC would be a welcome addition to clinicians' limited array of effective tools.

The action mechanisms of cilostazol are varied. The main known pharmacologic effects include antiplatelet, vasodilatory, and antithrombotic activities.[20] Additionally, cilostazol decreases triglycerides and increases HDL levels.[21] Smooth muscle cell proliferation has been inhibited by cilostazol in vitro.[22] It can be hypothesized that the mechanism by which cilostazol acts in claudication is multifactorial.

CONCLUSION

Cilostazol had a significant advantage over a placebo in improving ACD, ICD, ABI, and functional status measures. This trial showed statistically

significant improvement in treadmill walking performance after 16 weeks of therapy with cilostazol, 100 mg b.i.d. Cilostazol may represent a new option for the treatment of mild-to-moderate IC in patients with POAD.

REFERENCES

1. Balkau B, Vray M, Eschwege E. Epidemiology of peripheral arterial disease. J Cardiovasc Pharmacol 1994;23(suppl 3):8–16.
2. Barnes RW. Vascular holism: the epidemiology of vascular disease. Ann Vasc Surg 1995;9:576–82.
3. Porter JM, Friedman EI, Mills JL, Taylor LM Jr. Early recognition, evaluation and management of peripheral vascular diseases. Modern Medicine 1987;55:66–75.
4. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. Ann Vasc Surg 1989;3:273–7.
5. Hiatt WR, Marshall JA, Baxter J, Sandoval R, Hildebrandt W, Kahn LR. Diagnostic methods for peripheral arterial disease in the San Luis Valley Diabetes Study. J Clin Epidemiol 1990;43:597–606.
6. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation 1985; 71:510–5.
7. Regensteiner J, Stiener J, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. J Vasc Surg 1996;23:104–15.
8. Hiatt WR, Regensteiner JG, Steiner JF. Exercise training improves functional status in patients with peripheral arterial disease. J Vasc Surg 1996;23:104–15.
9. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 1990;81:602–9.
10. Darvin H, King T. Lower extremity arterial occlusive disease. Clin Podiatr Med Surg 1992;9:69–77.
11. Creasy T, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Eur J Vasc Surg 1990;4(2):135–40.
12. Isner J. Redefining intervention. Circulation 1993;88:1534–57.
13. De Felice M, Gallo P, Masotti G. Current therapy of peripheral obstructive arterial disease. The non-surgical approach. Angiology 1990;41:1–11.
14. Ikeda Y, Kikuchi M, Murakami H, Satoh K, Murata M, Watanabe K, et al. Comparison of the inhibitory effects of cilostazol, acetylsalicylic acid, and ticlopidine on platelet functions ex vivo. Randomized, double-blind cross-over study. Arzneimittelforschung 1987;37:563–6.
15. Nakagawa Y, Onuki Y, Orino H. Effect of cilostazol (10P-13013) on arachidonic acid metabolism. Japanese Journal of Pharmacology and Therapeutics 1986;14:6319–24.
16. Porter JM, Cutler BS, Lee BY, Reich T, Reichle FA, Scogin JT, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. Am Heart J 1982;104:66–72.
17. Dawson DL, Cutler BS, Meissner MH, Strandness DE. Effects of cilostazol on intermittent claudication: results from a multi-center, randomized, prospective, double-blind trial. Circulation. In press.
18. Gillings D, Koch G, Reich T, Stager WJ. Another look at the pentoxifylline efficacy data for intermittent claudication. J Clin Pharmacol 1987;27:601–9.
19. Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. J Vasc Surg 1997; 25:312–9.
20. Kimura Y, Tani T, Kanbe T, Watanabe K. Effect of cilostazol on platelet aggregation and experimental thrombosis. Arzneimittelforschung 1985;35:1144–9.
21. Elam MB, Heckman JR, Crouse JR, Hunninghake DB, Herd JA, Davidson M, et al. Effect of cilostazol on plasma lipoproteins in patients with intermittent claudication. J Am Coll Cardiol 1997;29:85A.
22. Matsumoto Y, Tani T, Watanabe K, Kimura Y. Effects of cilostazol, an antiplatelet drug, on smooth muscle cell proliferation after denudation in rats. Jpn J Pharmacol 1992;58:284P.

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APPENDIX.

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Los Angeles, CA

DISCUSSION

Dr. Robert B. Patterson (Providence, R.I.). Dr. Money and his colleagues have presented data from a double-blind, placebo-controlled, prospective trial investigating yet another candidate for the "holy grail" of pharmacologic management of IC. The choice of cilostazol, which inhibits type II phosphodiesterase activity in platelets, diminishes platelet aggregation, and acts secondarily as a vasodilator, has merit.

I have questions regarding the study design and the significance of the findings.

First, why did the authors choose not to include a placebo run-in period? A run-in period permits the initial placebo effect to be established, and selects patients for randomization who have stable claudication symptoms and have no early rapid improvement through treadmill training or placebo effect.

Second, why was ACD rather than ICD chosen as the prime end point? The authors state that ICD is subjective, and ACD is not. I disagree. ACD depends on the patient's motivation and tolerance of pain. ICD is more reproducible and less prone to errors of population enthusiasm.

How do you account for the change in ABI, particularly as no difference was found in treadmill walking between peak and trough dosing? Most authors agree there is no theoretic or experimental justification for the use of vasodilators in claudication.

Was the positive effect on resting ABI consistent at all 19 centers? Did you measure postexercise recovery times?

Finally, could the authors share the absolute values for the SF-36 scores and compare them with a nonclaudicant elderly population with chronic disease? Claudicants have worse responses to health questionnaires for a variety of reasons, and further demonstration that these patients match other claudicant populations may be useful.

Regarding the significance of the study, I am intrigued that most studies demonstrating efficacy for drug therapy of claudication have quite modest, although statistically significant, improvements in treadmill walking. Literature of exercise therapy alone, without institution of pharmacologic agents, reports in excess of 100% improvement in treadmill walking ability. Additionally, successful intervention approaches with angioplasty or surgery also demonstrate superior benefits of walking distance. Do the authors believe that cilostazol, with its expense, need for chronic administration, and moderate degree of side effects, is clinically relevant and not just statistically significant?

Rather than hailing cilostazol as the pentoxifylline of the 1990s, I suggest that efforts at pharmacologic management of arterial claudication turn to investigations of new classes of therapeutic agents, most notably those whose action mechanisms target the metabolic efficiency of skeletal muscle metabolism.

I enjoyed the presentation and encourage the authors to continue to seek answers to a vexing problem that is one of the more rapidly expanding clinical dilemmas facing our health care system.

Dr. Samuel R. Money. Thank you, Dr. Patterson, for your questions. You first asked why we did not include a placebo run-in period. A pilot study performed before this study demonstrated no real need for a placebo run-in. To limit expense and extra time, we decided not to use a placebo run-in period.

You next asked why ACD rather than ICD was chosen as the prime end point. The type of treadmill testing done determined the prime end point. The studies by Hiatt found less variability with the type of treadmill we used, with a constant speed and an increasing incline, and less variability with ACD rather than ICDs.

Your third question asked how we accounted for the change in ABI, and I really cannot tell you. The cilostazol has many different effects. The change may be simply caused by the platelet effect, or the vasodilating effect, or the reduction in smooth muscle proliferation.

Were the positive effects in resting ABI consistent at all 19 centers? No, they were not. In a multicenter study, nothing is consistent at all 19 centers.

Finally, you asked us to share some values for the SF-36 scores. For many patients, the values are well below what was expected. As you stated, these patients are elderly with chronic diseases, and, in general, they view their health as poor. For vitality and physical scores, their SF-36s, ranging from 0 to 100, averaged between 50 and 65. This is lower than the general population in this age group.

Finally, you asked whether the use of cilostazol, with its expense, is justifiable. I cannot answer that question. More extensive testing must be done, and time will define the usefulness of this drug.

Dr. John M. Porter (Portland, Ore.). This was a very nice presentation. I do have several questions.

Dr. William Hiatt from Colorado, who pioneered the use of the variable-load treadmill in claudication trials, always reported the results in terms of time walked. You have converted this to meters. I consider this a problematic exercise, because the more the patients walk, the more the incline increases, and the more metabolic energy is required. So the walking at the end of the trial is not comparable with the walking at the beginning of the trial. I believe the use of meters in your report is unique. I do not believe anybody has ever used meters before. I would like for you to justify the use of meters instead of time walked.

Also, you included patients who walked up to 875 meters. It is important to keep in mind that 875 meters is 18th-fairway claudication. Claudication trials should be limited to 200 to 300 meters. Thank you.

Dr. Money. Dr. Porter, I appreciate your comments, and I wholeheartedly expected more of you than just this, sir.

You first asked why we converted to meters rather than time walked. As a vascular surgeon, I think in terms of meters or distance walked. Your point that the longer the patients walk, the harder the walk becomes makes the results seem more striking because patients are walking further and harder for a longer distance, which translates to time. We used meters rather than feet, yards, or time for the same reason.

The study was limited to a person who could walk for 15 minutes. You asked why we did not limit the walk to 200 to 300 meters. If you look at the average ICD and ACD, they are well below this 800 level, with the average patient having an ACD of 236 meters.

Dr. Wesley S. Moore (Los Angeles, Calif.). I enjoyed your presentation. I would like to ask one question.

Your experimental group may have ended with a higher ABI because of a drug effect or because different population groups received the drug versus the placebo. Have you considered a crossover study making the placebo group the experimental group on a secondary trial and vice versa? If those two groups are comparable, then the new experimental group, that is, the old placebo group, may benefit from a switch to the drug.

Dr. Money. Dr. Moore, I cannot explain why the ABI was significantly increased. I agree with your point that a crossover study would more clearly demonstrate this statistically. It would be a great study; however, the expense incurred may not be worthwhile at this point.

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