

Cilostazol increased walking distance but had more adverse effects than did pentoxifylline in intermittent claudication

Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med.* 2000 Nov;109:523-30.

QUESTION

In patients with moderate-to-severe intermittent claudication, how do cilostazol, pentoxifylline, and placebo compare in terms of effectiveness and safety?

DESIGN

Randomized (allocation concealed*), blinded (patients and outcome assessors),* placebo-controlled trial with 24-week follow-up.

SETTING

54 outpatient U.S. vascular clinics.

PATIENTS

699 patients (mean age 66 y, 76% men) who had had stable moderate-to-severe intermittent claudication for at least 6 months, had peripheral artery disease, and had a baseline pain-free walking distance of ≥ 53.6 meters (1 min on treadmill protocol) and a baseline maximal walking distance of 537.6 meters (10 min). Exclusion criteria included exercise capacity limited by conditions other than intermittent claudication, previous use of cilostazol, and use of pentoxifylline within 30 days of study enrollment. 1 patient withdrew.

INTERVENTION

227 patients were allocated to receive cilostazol, 100 mg orally twice daily, 232 to receive pentoxifylline, 400 mg orally 3 times daily, and 239 to receive placebo.

COMMENTARY

Many drugs have been suggested for the treatment of intermittent claudication. Pentoxifylline has been the subject of previous randomized controlled trials. Results from a systematic review of studies that included 612 patients suggested a beneficial effect on walking distance but also highlighted the need for larger trials (1). This study by Dawson and colleagues does not support a benefit for pentoxifylline but does show an improvement in treadmill walking distance after treatment with cilostazol.

The link between treadmill walking distance and quality of life is not clear (2), and this study showed no significant effect on quality of life. The 30% improvement in walking distance that was seen for the placebo group is noteworthy. Conservative management of patients with stable intermittent claudication may result in substantive improvements. For example, studies of exercise, particularly supervised exercise programs, have shown benefits several times greater than those seen for cilostazol in this study (3).

Although cilostazol may result in a modest improvement in walking distance, exercise may result in greater improvements, with

MAIN OUTCOME MEASURES

The primary outcome was walking performance assessed by treadmill testing. Secondary outcomes included pain-free walking distance, quality of life, and safety.

MAIN RESULTS

643 patients (92%) were included in the intention-to-treat analysis. At 24 weeks, the mean increase from baseline in maximal walking distance was greater in patients in the cilostazol group than in those in the pentoxifylline or placebo groups ($P < 0.001$) (Table) with no difference between pentoxifylline and placebo ($P = 0.82$) (Table). Pain-free walking distance also increased more in patients in the cilostazol group than in those in the pentoxifylline or placebo groups ($P = 0.02$ and $P < 0.001$, respectively) with no difference between pentoxifylline and placebo ($P = 0.07$). Adverse effects were reported more often in the cilostazol group than in the pentoxifylline group, but withdrawal

rates caused by adverse effects were similar (16% vs 19%, $\{P = 0.45\}^\dagger$). No difference existed among the groups for quality of life.

CONCLUSION

In patients with moderate-to-severe intermittent claudication, cilostazol increased maximal and pain-free walking distance more than did pentoxifylline or placebo but was associated with more minor adverse effects.

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For correspondence: Dr. D.L. Dawson, Medical Sciences Division, NASA-Johnson Space Center, Mail Code SD, 2101 NASA Road 1, Houston, TX 77058-1406, USA. FAX 713-852-3906. ■

*See Glossary.

† P value calculated from data in article.

Comparison of cilostazol (C), pentoxifylline (P), and placebo (Pl) at 24 weeks in maximal walking distance on treadmill test in moderate-to-severe intermittent claudication

| Comparison | Difference in mean increase from baseline (95% CI) |
|------------|--|
| C vs Pl | 42 meters (14 to 70) |
| C vs P | 43 meters (15 to 71) |
| P vs Pl | 1 meter (-24 to -26) |

beneficial effects on general health rather than the potential adverse effects associated with drug treatments. A randomized trial comparing cilostazol with exercise is needed. Pharmacologic treatments should probably be reserved for patients for whom a small improvement in walking distance would probably result in a substantive benefit to quality of life and thus justify the cost and the risk for minor adverse effects.

*Jonathan A. Michaels, MChir
Sheffield Teaching Hospitals NHS Trust
Sheffield, England, UK*

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