Treatment of intermittent claudication: cilostazol

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Intermittent claudication is a potentially disabling disorder that impairs quality of life and is a marker of underlying cardiovascular disease. Treatment involves secondary prevention and measures to improve walking. Cilostazol significantly increases walking distance and quality of life in claudicants.

Intermittent claudication affects between 1.7 and 7.1% of the population over 55 years of age (Criqui et al, 1985; Leng et al, 1996). In these patients arterial narrowing caused by atherosclerosis leads to a reduction of blood flow to the lower limb during exercise. This results in the patient experiencing pain or cramp in the calf, thigh or buttock muscles on exercising, which is relieved by rest. The diagnosis is made on the basis of the history and the presence of an ankle brachial pressure index (ABPI) less than 0.9.

In terms of the limb, the condition is relatively benign, with less than 10% of claudicants requiring intervention to prevent limb loss and less than 1% per year requiring amputation (Dormandy, 1991). However, patients with intermittent claudication have a 3–4 times increased mortality from cardiovascular causes and are at as great a risk of dying from a heart attack as many patients who have survived their first myocardial infarction (Wood et al, 1998).

Patients with claudication have also been shown to have a significantly diminished quality of life compared to age- and sex-matched controls (Cassar et al, 2003a). Claudication is a subjective phenomenon and surgeons' assessments of patients' quality of life has been shown to be poor. However, studies have shown that claudicants have a quality of life comparable to patients with coronary heart disease (CHD) or patients with osteoarthritis or rheumatoid arthritis affecting the knee or hip joint (Cassar et al, 2003a).

TREATMENT TO PROLONG SURVIVAL IN CLAUDICANTS

Housley (1988), in an editorial, summarized the treatment of claudication as merely 'Stop smoking and keep walking'. Since then the major risk factors for both cardiac and peripheral arterial disease (PAD) have become well established, and treatment strategies devised. The joint British recommendations on prevention of CHD in clinical practice published in 1998 stated that patients with PAD should be managed in the same way as those with established CHD (Wood et al, 1998).

These guidelines state that patients with CHD or other major atherosclerotic disease, such as that present in claudicants, should receive lifestyle intervention measures aimed at discontinuing smoking and increasing aerobic exercise (*Table 1*). They should be prescribed aspirin and screened for the presence of diabetes. Rigorous control of blood pressure and lipids is recommended with the following targets: systolic less than 140 mmHg, diastolic less than 85 mmHg and total cholesterol less than 5 mmol/litre. The Heart Protection Study Collaborative Group (2002), however, has shown that the benefits of statins occur irrespective of the cholesterol level and thus all patients should be prescribed a statin providing their cholesterol level is above 3.5 mmol/litre.

Consideration should also be given to prescribing an angiotensin-converting enzyme inhibitor given the results of the Heart Outcomes Prevention Evaluation (HOPE) study (Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000). This secondary prevention or 'best medical' therapy is clearly designed to prevent cardiac events and prolong life, and has been the subject of a number of well-written reviews (Donnelly and Yeung, 2002). Unfortunately studies have shown that patients with PAD receive suboptimal therapy compared to patients with coronary artery disease and that there is scope for improvement in the management of secondary

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risk factors in claudicants both by primary care and vascular consultants (Cassar et al, 2003b,c). Best medical therapy is first-line management but generally does not improve walking distances and the limitations that restricted walking puts on the patient's quality of life. However, two studies have shown that statin therapy may improve walking function but not quality of life in claudicants (Mohler et al, 2003; Mondillo et al, 2003).

TREATMENT TO INCREASE WALKING DISTANCES IN CLAUDICANTS

Treatment of claudicants should extend beyond risk factor management to measures aimed at improving walking distance and quality of life. Treatment options include exercise therapy, pharmacotherapy, endovascular intervention and, in a minority of patients, surgery. A Cochrane review has found that supervised exercise therapy significantly improves walking time, with an overall improvement in walking ability of 150% (range 74–230%) (Leng et al, 2002). However, in the UK only 33% of consultant vascular surgeons have access to an exercise programme for their patients and patient compliance has been shown to be poor in some studies (Cassar et al, 2003c).

Before the advent of cilostazol pharmacological options were very limited and consisted of pentoxifylline and naftidrofuryl. A meta-analysis by Moher et al (2000) concluded that the amount and quality of data available were 'inadequate to support or refute the efficacy of pentoxifylline therapy and that there was a lack of consistency of effect of naftidrofuryl' in patients with intermittent claudication. Larger studies have shown a small benefit with naftidrofuryl on walking distances (Transatlantic Intersociety Consensus (TASC) Working Group, 2000) and a meta-analysis has shown that it can improve quality of life (Spengel et al, 2002). The efficacy of cilostazol is discussed below.

PHARMACOLOGICAL PROFILE OF CILOSTAZOL

Cilostazol (Pletal, Otsuka Pharmaceuticals Co Ltd, Tokushima, Japan) has vasodilating, antithrombotic and antiplatelet properties but its exact mechanism of action in patients with intermittent claudication is unknown. Cilostazol is a selective phosphodiesterase III inhibitor and thus suppresses cyclic adenosine monophosphate (cAMP) degradation. Increased intraplatelet cAMP inhibits thromboxane A2 production and platelet aggregation by inhibiting phospholipase and cyclooxygenase. Although it inhibits platelet aggregation it does not alter bleeding times. Cilostazol causes vasodilatation by inhibiting calcium-induced contractions of smooth muscle cells. It also has a beneficial effect on plasma lipids and in animal studies has been shown to inhibit proliferation of vascular smooth muscle cells (Chapman and Goa, 2003).

EFFICACY OF CILOSTAZOL IN CLINICAL TRIALS

To date there have been six published multicentre phase III trials involving 1751 patients with intermittent claudication (*Table 2*). In these studies the duration of treatment varied from 12 to 24 weeks, with cilostazol 100 mg or 50 mg twice daily. A meta-analysis by Thompson et al (2002) included data from a further two unpublished studies, bringing the total number of patients studied in phase III trials to 2702.

The patients included met the following criteria: age over 40 years, a greater than 6-month history of claudication with no change in symptom severity for a minimum of 3 months, an ABPI less than 0.9 and a greater than 10 mmHg drop in ankle pressure after exercise. Patients with rest pain or tissue loss were excluded. The treadmill protocols consisted of either a progressive workload or a constant workload format. Analysis was performed on an intention to treat basis. The primary outcome measure was change from baseline maximum walking distance. Secondary outcome measures were change in pain-free walking distance and quality of life as assessed via the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Study Short Form-36 (SF-36).

In six out of eight studies included in the meta-analysis by Thomson et al, when compared

TABLE 1.
Management of patients with intermittent claudication

Prolonging life (secondary cardiac risk factor prevention with best medical therapy)	Antiplatelets	Aspirin or clopidogrel
	Statins	Prescribe if cholesterol >3.5 mmol/litre
	Smoking cessation	Nicotine replacement therapy
	Blood pressure	Target: <140/85 mmHg
	Diabetes	Screen all and in diabetics aim for HbA_{1C} <7%
	Others	ACE inhibitor
Improving quality of life (measures to improve walking distance)	Exercise	Supervised exercise programme
	Medical therapy	Cilostazol, pentoxifylline, naftidrofuryl
	Endovascular	Angioplasty or stenting
	Surgery	If severe and none of above effective

ACE = angiotensin-converting enzyme; HbA_{1C} = glycosylated haemoglobin

to placebo cilostazol significantly increased walking distances and quality of life in patients with intermittent claudication. In the six published trials the increase in the mean maximal walking distance varied from 28 to 100% with cilostazol 100 mg twice daily compared to –10 to 28% for placebo (*Table 2*). In a meta-analysis of these trials, cilostazol 100 mg twice daily increased maximum walking distance (mean±standard deviation) on the graded treadmill protocol by 40% (100±143 m) compared with a 20% (50±127 m) increase for those taking placebo ($P<0.001$) (Regensteiner et al, 2002). For the constant load treadmill protocol cilostazol 100 mg twice daily resulted in a 76% (95±272 m) increase in maximal walking distance compared to 20% (27±113 m) in the placebo group ($P<0.001$). The increase in the 50 mg group was approximately 60% ($P<0.0011$) (Regensteiner et al, 2002).

Patients randomized to cilostazol had statistically significantly improved quality of life as assessed by both the WIQ and SF-36 in the six trials in which this was assessed. Cilostazol-treated patients reported significant improvement in all WIQ scores including walking distance, speed, stair climbing ability and calf pain severity compared to patients allocated to placebo ($P<0.001$) (Regensteiner et al, 2002). In the patients randomized to cilostazol there was a 5% improvement in the SF-36 physical summary score ($P<0.05$) but no change in the mental summary score compared to placebo (Regensteiner et al, 2002).

The effect of cilostazol on ABPI was assessed in two phase III trials (Elam et al, 1998; Money et al, 1998). There were statistically significant ($P<0.05$) increases of 9–11% following 12–16 weeks therapy, which just borders on clinical significance.

SUBGROUP ANALYSIS

Subgroup analysis has shown that cilostazol is equally beneficial in males and females, among older and younger patients, smokers and non-smokers and for differing severities of intermittent claudication (Regensteiner et al, 2002; Thompson et al, 2002; Chapman and Goa, 2003).

Rendell et al (2002) compared the efficacy (measured by absolute claudication distance) and safety of cilostazol in diabetic and non-diabetic patients from six placebo-controlled and two active-controlled randomized, double-blind trials. In diabetic and non-diabetic patients, cilostazol was superior to placebo (estimated treatment effect = 1.15, 95% confidence interval = 1.05–1.25, $P=0.001$, and estimated treatment effect = 1.24, 95% confidence interval = 1.18–1.31, $P<0.001$ respectively). There was no statistical difference in the response to cilostazol between diabetic and non-diabetic subjects. These findings were confirmed in a further subpopulation analysis of 436 patients with diabetes who were randomized in the phase III clinical trials to cilostazol (100 mg twice daily) or placebo (Hittel and Donnelly, 2002).

TABLE 2.
Cilostazol: effect on maximal walking distance in phase III trials

Study	Study duration (weeks)	Treadmill protocol	Numbers	Mean maximum walking distance		*P* value*
				Baseline (m)	Change at end point	
Money et al (1998)	16	Variable load	Placebo *n*=120	244.3	15%	
			Cilostazol 100 mg *n* =119	236.9	40%	*P*<0.05
Elam et al (1998)	12	Variable load	Placebo *n*=94	278.0	9%	
			Cilostazol 100 mg *n*=95	262.0	28%	*P*<0.01
Dawson et al (1998)	12	Variable load	Placebo *n*=35	168.6	–10%	
			Cilostazol 100 mg *n*=52	141.9	63%	*P*<0.01
Dawson et al (2000)	24	Variable load	Placebo *n*=239	234.0	28%	
			Cilostazol 100 mg *n*=227	241.0	45%	
			(Pentoxifylline *n*=239)	(234.0	28%)	*P*<0.005
Strandness et al (2002)	24	Constant load	Placebo *n*=129	120.1	18%	
			Cilostazol 50 mg *n*=132	122.7	36%	*P*>0.05
			Cilostazol 100 mg *n*=133	119.4	64%	*P*=0.0003
Beebe et al (1999)	24	Constant load	Placebo *n*=170	147.8	18%	
			Cilostazol 50 mg *n*=171	131.5	51%	*P*<0.01
			Cilostazol 100 mg *n*=175	129.7	100%	*P*<0.01

COMPARISON OF CILOSTAZOL AND PENTOXIFYLLINE

There have been two trials but only the study by Dawson et al (2000) has been published. In this phase III study 698 patients were randomized to cilostazol 100 mg twice daily (n=227), pentoxifylline 400 mg three times daily (n=232) or placebo (n=239). The primary endpoint was maximal walking distance on a standard treadmill test. The secondary endpoints were pain-free walking distance and resting ABPI. Assessments were made at 4, 8, 12, 16, 20 and 24 weeks. Patients randomized to cilostazol had significantly increased maximal walking distance at all time points compared with the two other groups. After 24 weeks there was a mean increase of 54% from baseline in the cilostazol group *vs* 30% in the pentoxifylline and 34% in the placebo group (P<0.05).

SIDE EFFECTS

To date, the largest randomized controlled trial has included 698 patients, 227 of whom were randomized to cilostazol 100 mg twice daily and the remainder to placebo or pentoxifylline. In this study by Dawson et al (2000) the overall withdrawal rate was 27% in the cilostazol group, compared to 16% in the placebo group (P=0.006). The withdrawal rate for the pentoxifylline group was similar to the cilostazol group. The following symptoms were significantly more common in the cilostazol than the placebo or pentoxifylline groups: headache (28%), palpitations (17%), diarrhoea (19%) and abnormal stool (15%). The frequency of these events in the placebo group was 12%, 3%, 5% and 7% respectively. Death and serious events were rare and similar in all groups.

Pooled data from the six published phase III trials has shown that cilostazol is generally well tolerated and that the adverse events were generally of mild to moderate intensity, transient or resolved after symptomatic treatment (Regensteiner et al, 2002; Chapman and Goa, 2003). The overall drug withdrawal rate is 12%. Safety data in patients with diabetes were in line with those seen in the group analysed as a whole and in particular there was no excess of ocular haemorrhage in the subgroup of cilostazol-treated patients (Hittel and Donnelly, 2002).

PRESCRIBING ISSUES

Cilostazol does not increase bleeding times and can be administered safely with aspirin and warfarin. However, it is recommended that the daily dosage of aspirin should not exceed 75 mg. There is no recognized interaction between cilostazol and clopidogrel. Cilostazol should not be prescribed to patients who are taking drugs which inhibit cytochrome P450 3A4 (e.g. erythromycin or diltiazem) or CYP2CI9 (e.g. omeprazole) (Chapman and Goa, 2003). The recommended dose is 100 mg twice daily administered orally half an hour before or 2 hours after meals. Cilostazol is contraindicated in patients with congestive cardiac failure, moderate or severe hepatic failure and severe renal failure.

The effect of withdrawing cilostazol has been studied in a single-blind crossover following on from a double-blind randomized controlled trial. There was a highly significant loss of treatment benefit in patients switched from 24 weeks of cilostazol therapy to placebo (Dawson et al, 1999).

CONCLUSIONS

Intermittent claudication is diagnosed on the basis of the history and the presence of a low ABPI. All patients should be prescribed secondary prevention or best medical therapy aimed at reducing future cardiac events, although this has not been shown to improve walking distance. Unfortunately, the management of these cardiac risk factors in claudicants is far from optimal both in primary and secondary care (Cassar et al, 2003b, c).

Cilostazol is the only effective pharmacotherapy that is reliably proven to increase walking distance (40–70% increase in maximal walking distances) and health-related quality of life in claudicants. While the benefits of cilostazol have clearly been shown in eight phase III studies there is debate as to whether it should be available to all claudicants or reserved for those with persisting unacceptable symptoms. If, as in the studies, patients present with a 6-month or more history of claudication and health-related quality of life is found to be significantly impaired then they should be given the opportunity to benefit from cilostazol therapy providing they are able to tolerate it. If these patients are not yet on best medical therapy, however, then there may be an understandable reluctance to start a considerable number of drugs, such as antiplatelets, statins, antihypertensives and nicotine replacement therapy, concurrently with cilostazol and this may be prescribed, if required, at a later visit.

Alternatives to pharmacotherapy include supervised exercise regimens which have clearly been shown to be beneficial. However, these are not readily available in the UK and compliance is poor. Angioplasty, especially of the iliac system, has been shown to be effective in improving walking distance and health-related quality of

life but has limited durability in the long term. The role of surgery is limited to those with severe disabling claudication in whom other therapies have been ineffective.

While the initial focus of management of these patients is secondary risk factor reduction, their impaired quality of life imposed by the reduction in walking distance should not be ignored, especially as effective pharmacotherapy now exists in the form of cilostazol. HM

Conflict of interest: Dr Brittenden has previously received consultant fees from Otsuka Pharmaceuticals.

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KEY POINTS

- Patients with intermittent claudication have a 3–4 times increased mortality as a result of underlying cardiovascular and cerebrovascular disease.
- Intermittent claudication is fairly benign in terms of limb outcome but significantly impairs quality of life.
- First-line management is secondary prevention or 'best medical therapy' which aims to reduce cardiovascular events.
- Results from eight phase III clinical trials, involving more than 2700 patients, show cilostazol significantly improves walking distance and health-related quality of life compared with placebo.
- Cilostazol is well tolerated but does have a higher incidence of headache, diarrhoea, abnormal stool and palpitations compared to placebo.
- Cilostazol (Pletal) is the only effective pharmacotherapy that results in a clinically significant increase in walking distance and health-related quality of life in patients with claudication.