Cilostazol

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Introduction

Peripheral arterial disease (PAD) affects around 14% of the population aged over 65 years. Patients with diabetes carry a two- to three-fold increased risk of PAD and have higher rates of complications, including gangrene and amputation. Intermittent claudication is a disabling symptom of PAD with limited effective therapeutic options. Cilostazol is a type 3 phosphodiesterase (PDE3) inhibitor licensed for use in intermittent claudication; it gained FDA approval in 1999.

Pharmacology

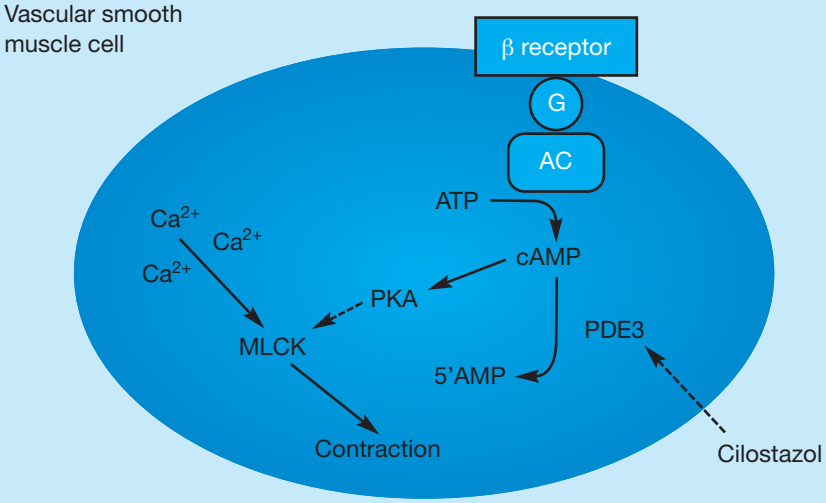
Cilostazol prevents the breakdown of cyclic adenosine monophosphate (cAMP) by inhibiting PDE3. (Figure 1.) Within vascular smooth muscle cAMP inhibits myosin light chain kinase, which is required for muscle contraction, and by increasing cAMP cilostazol promotes vasodilation. Within platelets cilostazol increases cAMP which inhibits platelet activation. The mechanism by which cilostazol improves walking distance is unclear.

Cilostazol is taken orally at a usual dose of 100mg twice daily; it is metabolised in the liver and the active metabolites travel bound to protein, usually albumin, and are excreted predominantly in the urine. The drug is metabolised via the cytochrome P450 system and should be discontinued if there is concomitant use of CYP3A4 inhibitors such as azole antifungals and macrolide antibiotics or CYP2C19 inhibitors such as omeprazole. There are limited long-term safety data regarding its use with aspirin, clopidogrel or warfarin.

Cilostazol is contraindicated in patients with congestive cardiac failure, previous ventricular arrhythmias and prolonged QT, and those with significant bleeding history. It should be avoided in moderate to severe hepatic dysfunction and renal dysfunction (eGFR less than 25ml/min/1.73m^2).

Frequently encountered adverse effects leading to discontinuation of the drug include headache, palpitations and diarrhoea. Other significant side effects include thrombocytopenia, agranulocytosis, cardiac disorders and allergic reactions.

Figure 1. Mechanism of action of cilostazol



NOTES. Cilostazol inhibits the breakdown of cAMP within the smooth muscle by type 3 phosphodiesterase (PDE3) leading to inhibition of myosin light chain kinase (MLCK) via protein kinase A (PKA) and therefore relaxation. Key: AC = adenylyl cyclase; ATP = adenosine-5'-triphosphate; cAMP = cyclic adenosine monophosphate; G = G-protein; 5'AMP = adenosine 5-monophosphate.

Trials of safety and efficacy

Since 1998 several randomised controlled trials have been published assessing the therapeutic use of cilostazol for intermittent claudication. One of the largest initial multicentre, randomised, double-blinded trials, conducted by Beebe *et al.*,[1] compared cilostazol with placebo. The study included 516 men and women aged over 40 years with moderately severe chronic intermittent claudication. Patients were randomised to receive cilostazol 100mg, cilostazol 50mg or placebo twice daily for 24 weeks. Outcome measures included walking distances using treadmill testing, quality of life measures and cardiovascular and all-cause mortality. Improved walking distances were observed as early as four weeks in both cilostazol groups compared with placebo. The cilostazol 100mg twice daily group (n=138) had the greatest benefit at 24 weeks; the pain-free walking distance increased from 70.4m to 137.9m, a 59% geometric mean improvement, compared to 20% in the placebo group ($p<0.001$) and the maximal walking distance increased from 129.7m to 258.8m.

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A meta-analysis[2] of eight randomised, placebo-controlled trials of cilostazol for intermittent claudication included 2702 patients with stable, moderate to severe intermittent claudication over 12 to 24 week trial periods. Similarly, cilostazol 100mg twice daily was found to significantly improve pain-free walking distance by 67% and maximal walking distance by 50% ($p<0.05$). Subgroup analysis for gender, age and diabetes found no differences. Two studies included comparison to another therapeutic agent available for intermittent claudication, pentoxifylline, and found it to be comparable to placebo. The same two studies also measured plasma lipids and found that cilostazol 100mg twice daily increased HDL cholesterol by 12.8% and decreased triglycerides by 15.8% at 24 weeks; this was significant when compared to placebo and pentoxifylline.

Specific evidence for use in diabetes

Initial studies were not powered to detect significant efficacy in the population with diabetes. Another meta-analysis[3] examined eight phase III trials looking specifically at the use of cilostazol 100mg twice daily compared to placebo in diabetic and non-diabetic patients. In the cilostazol group there were 216 diabetic patients and 599 non-diabetic patients, and in the placebo group there were 220 diabetic patients and 616 non-diabetic patients. Trial design was similar to that described above and lasted 12 to 24 weeks. Patients with diabetes showed a statistically significant mean percentage increase in walking distance (51.4%) when compared to placebo (32.6%). No statistical difference was found between the percentage change in maximal walking distance in the diabetic patients (51.4%) when compared to the non-diabetic patients (60.6%) treated with cilostazol. The authors examined the response to cilostazol based on baseline absolute claudication distance (ACD); they found that the response in non-diabetic patients was linear with greater response in those with better baseline function. However, this pattern was not seen in the diabetic cohort. Diabetic patients in the first quartile (ACD <96m) responded best to cilostazol with a 34.4% (95% CI 6.68–62.16%) improvement from baseline (n=59), in the second quartile (ACD 97–141m) 5.5% (95% CI -30.91–41.93%), in the third quartile (ACD 142–233m) 23% (95% CI -7.82–53.82%), and in the fourth quartile (ACD >233m) a 17.2% (95% CI -16.33–50.69%) change from baseline was seen. The adverse event profile was similar in the diabetic and non-diabetic patients.

A recent randomised, double-blinded trial assessed the vascular and biochemical effects of cilostazol compared to placebo in diabetic patients with peripheral arterial disease.[4] They recruited 26 patients between the ages of 30 and 90 years with type 2 diabetes and intermittent claudication. Twelve patients were randomised to receive cilostazol 100mg twice daily and 14 to placebo. The groups were assessed at baseline, six and 24 weeks. Walking assessment was matched at baseline and there was a non-significant trend for improvement in the cilostazol group at 24 weeks with the initial claudication distance improving by 21.1% compared to -4.4% in the placebo group. Lipid profiles were not significantly different between groups at baseline. However, in the cilostazol group there was a significant reduction in serum cholesterol ($p=0.007$) and triglycerides ($p=0.005$), and a significant increase in HDL cholesterol ($p=0.047$) at 24 weeks when compared to baseline. There was no significant difference between ankle-brachial indices, arterial compliance or HbA_{1c} in the cilostazol compared to the placebo group at baseline, six or 24 weeks.

Key points

- Cilostazol is a type 3 phosphodiesterase inhibitor with vasodilatory and antiplatelet properties
- A meta-analysis of 2702 patients showed a significant improvement in pain-free and maximal walking distance when cilostazol was used to treat intermittent claudication
- Patients with diabetes and intermittent claudication benefit similarly from cilostazol treatment, but the pattern of response may be slightly different from that of non-diabetic patients

Discussion

Cilostazol improves walking distance in patients with intermittent claudication and has desirable effects on lipid profiles. Diabetic patients with intermittent claudication have a higher risk of the complications of PAD and of cardiovascular events. The overall response to cilostazol in diabetic patients was not significantly different compared to non-diabetic patients but, interestingly, there appears to be a different pattern of response with the most severely affected diabetic patients gaining most benefit. Larger trials of its use in the diabetic population would be useful to further evaluate this finding.

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Conflict of interest statement

There are no conflicts of interest.

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