Treatment of Intermittent Claudication

B 4.2
Pharmacotherapy for Symptoms of Intermittent Claudication

B 4.2.1
Introduction

Patients with intermittent claudication mostly receive drug treatment for coexisting disease (eg, hypertension), risk factor modification (eg, hyperlipidaemia), and as prophylaxis against thrombotic events associated with atherosclerosis (eg, antiplatelet drugs). No pharmacological agent has proved efficacious enough in providing significant reduction or elimination of symptoms of claudication to gain widespread acceptance and use for improving walking. However, a number of types of drugs have been promoted for this indication, with varying evidential support, and these will be considered in this section. These drugs are frequently grouped together under the heading “vasoactive agents,” partly because of their multiplicity of potential mechanisms of action. Some of the drugs have been distinguished as “rheologic agents,” but for others such as prostanoids, the mode of action is still not well delineated. These drugs should not replace exercise programs and other lifestyle adjustments described in B 4.1.2, Basic Treatment (p 568). However, they have a place as adjunctive treatment where invasive therapy is not indicated, in those who cannot or will not follow exercise therapy or in those who have not sufficiently benefited from it (see D 4.13.5, Adjuvant Therapy, p S211). Table 16 and Figure 20 show results of randomised, placebo-controlled, double-blind trials of pharmacotherapy in IC.

B 4.2.2
Established Drugs With Proven but Small Benefit in Improving Claudication

Pentoxifylline

Pentoxifylline improves red cell deformability, lowers fibrinogen levels, decreases platelet aggregation, and has been shown to increase walking distance in patients with PAD. In early controlled trials, the drug produced a 22% improvement over placebo in ICD and a 12% improvement in the ACD.1 However, these percent improvements were expressed as the mean difference between week 2 and week 24. The actual improvement over placebo from entry to 6 months in ACD was 18%, but this difference was not statistically significant. A more recent study confirmed these results, with a 21% improvement over placebo (p = 0.09).2 The study showed that a subgroup of patients with symptoms for longer than a year and an ABPI < 0.80 responded better to the drug. Importantly, patient-based questionnaires to assess efficacy have not been employed in the clinical trials of pentoxifylline, so the actual clinical benefit of the drug has not been fully defined.

Naftidrofuryl

Naftidrofuryl has been available for treating IC for over 20 years. It is a SHT antagonist and may improve aerobic metabolism in oxygen-depleted tissues and possibly reduce erythrocyte and platelet aggregation.3 In four placebo-controlled studies, Naftidrofuryl was more effective than placebo in improving walking distance,4,5,6,7 and a further study showed no significant difference.8

Buflomedil

Buflomedil has an alpha-1 and -2 adrenolytic effect. It has been shown to decrease vasoconstriction. It has also been shown to have some effect on platelets, red cell deformability, and a weak calcium antagonist effect. Buflomedil has been available for the treatment of IC in some countries for over 10 years. Two relatively small studies, conducted more than 10 years ago, showed a significantly greater improvement in absolute walking distance with Buflomedil compared with placebo.9,10

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor with vasodilator and antiplatelet activity.11 The first published double-blind trial showed a 47% increase in ACD in the treatment group compared to 13% increase in the placebo group (Table 16).12 This trial also showed that all subgroups of patients (age, smoking status, gender, race, and diabetes) responded
### Table 16. Randomised, placebo-controlled, double-blind trials of pharmacotherapy in intermittent claudication

<table>
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<tr>
<th></th>
<th>N</th>
<th>Dose</th>
<th>Duration (weeks)</th>
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<th>p value</th>
<th>WIQ/SF-36*</th>
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<td>245</td>
<td>1-3 g/d</td>
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<td><strong>Bergprost:</strong></td>
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<td>Lievre et al, 1996</td>
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<td>Diehm et al, 1997</td>
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<td>8</td>
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<td>53</td>
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<td>Yes</td>
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</table>

**NOTE.** ACD=% change in absolute walking distance; NS, not significant.
*Functional assessment as defined by WIQ and SF-36.
‡Percentage of patients with ≥50% increase in baseline ACD.
¶Percentage of patients with 100% or greater increase in baseline ACD.

Equally well to cilostazol. Quality of life was assessed in this trial using the medical outcomes study SF-36 questionnaire. This showed that patients on cilostazol had significant improvement in their physical functioning relative to those on placebo. They reported improved physical performance in the community setting. Mental health scores were unaffected by treatment. Side effects included headache, diarrhoea, and dizziness. Further randomised multicentre studies have been published and also show consistent improvements in ICD and ACD in the cilostazol group as compared with placebo. Subjective functional
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- Thickness of bars indicates total number of patients in trial
- From Table 16. Studies with fewer than 50 patients are omitted.

![Diagram showing % difference in absolute claudication distance between drug and placebo groups.]

\[ \text{Statistical Significance} \]

- Propionyl-Carnitine

\[ \text{Statistical Significance} \]

- Beraprost

\[ \text{Statistical Significance} \]

- Ticloplide

\[ \text{Statistical Significance} \]

- Butilomedil

\[ \text{Statistical Significance} \]

- Naftidrofuryl

\[ \text{Statistical Significance} \]

- Pentoxifylline

\[ \text{Statistical Significance} \]

![Fig. 20. Randomised placebo-controlled, double-blind trials of pharmacotherapy in intermittent claudication.]

Assessment was not well assessed but did suggest that there was drug effect, as noted by both patients and physicians.\(^{15}\)

**B 4.2.3**

**Drugs With Minimal or No Benefit in Improving Claudication**

*Antiplatelet drugs*

As discussed previously, the use of aspirin and other antiplatelet agents are important in the long-term treatment of peripheral atherosclerosis assuming a significant degree of multisystem involvement, mainly to reduce the overall incidence of cardiovascular events (see Recommendation 28, p 71). However, no studies have shown a benefit of aspirin in the treatment of claudication per se, although there is one study that presented suggestive evidence that aspirin slowed progression of atherosclerosis assessed by serial angiography.\(^{16}\) In contrast, ticlopidine, a potent inhibitor of platelet aggregation that also has hemorheologic effects, was shown in two randomised, placebo-controlled trials to improve claudication symptoms and exercise performance\(^{17,18}\) (Table 16). However, only one of these studies, by Balsano et al, had evaluable data. In that trial, treadmill testing was performed on the flat, and therefore, the clinical bene-
fits of the drug may have been overestimated because of the very low treadmill workload.

**Vasodilators**

Arteriolar vasodilators were the first class of agents used to treat claudication. Examples include drugs that inhibit the sympathetic nervous system (alpha blockers), direct-acting vasodilators (papaverine), beta₂ agonists (nylidrin), calcium channel blockers (nifedipine), and angiotensin-converting enzyme inhibitors. These drugs have not been shown to have clinical efficacy in randomised, controlled trials.¹⁹,²⁰,²¹ There are several theoretical reasons why vasodilators may not be effective. Most importantly, in the exercising claudicant, vessels in ischaemic areas are already maximally dilated, so vasodilator drugs will only create a steal phenomena by dilating vessels in normally perfused tissues (primarily proximal muscles), thus shifting the distribution of blood flow away from muscles supplied by obstructed arteries.

**Ketanserin**

Ketanserin is a selective serotonin (S₂) antagonist that lowers blood viscosity and also has vasodilator and antiplatelet properties. Controlled trials of this drug have shown it not to be effective in treating claudication.²²

**Verapamil**

One study has looked at the possibility that the calcium antagonist verapamil may have a clinical benefit in patients with intermittent claudication. Although treatment was only for 2 weeks and the study design could be criticised, the ACD was statistically significantly greater in the treated than in the placebo group.²³

**Isovolaemic haemodilution**

Isovolaemic haemodilution has been advocated for the treatment of IC even in the absence of polycythaemia. No doubt, haemodilution lowers the viscosity of whole blood, but it is still uncertain whether the increase in blood flow compensates for the decrease in oxygen-carrying capacity of the blood. One double-blind, placebo controlled trial of dextran haemodilution showed efficacy in selected patients.²⁴

**Aminophylline**

Aminophylline inhibits adenosine receptors and thus may blunt the vasodilatation response during exercise. This effect would theoretically limit the steal of blood away from ischaemic skeletal muscle. One study has shown that intravenous aminophylline improves treadmill exercise performance in patients with claudication.²⁵

**Vitamin E**

Five randomised controlled trials have been published since 1953 regarding the use of vitamin E and the treatment of claudication. Although some results are encouraging, there is insufficient evidence to recommend the routine use of vitamin E in patients with IC.²⁶

**Defibrotide**

Defibrotide is a polydeoxyribonucleotide drug with antithrombotic and haemorrhheological properties. A meta-analysis was performed in 1994 on 10 placebo-controlled trials of defibrotide in patients with PAD stage II (406 patients on defibrotide, 337 patients on placebo). The drug was used at a dose of 400 to 800 mg daily, the treatment ranging from 60 to 180 days. There was a net gain in absolute walking distance over placebo of 73 m (95% confidence interval; range, 35-111 m).²⁷

**Other vasoactive drugs**

Other drugs that have been promoted include cinnarizine,²⁸,²⁹,³⁰ cyclandelate, nicotinic acid derivatives,³¹ Ginkgo biloba, and Isosuprine. However, there is no consistent scientific evidence of efficacy for any of these.

**Recommendation 30: Pharmacotherapy for symptoms of intermittent claudication**

Although some controlled clinical trials with pentoxifylline, naftidofuryl, buflomedil, and recently cilostazol, have shown statistically significant improvement in walking distance, the average benefit was small. Greater benefit, observed in a minority of patients, may warrant a short course of therapy with continued use of such agents if sufficient benefit is observed. Recent clinical trials have shown a greater benefit of cilostazol for both walking distance and quality of life, which may warrant more widespread use. However, currently there are insufficient data to recommend the routine use of pharmacotherapy in all patients with claudication.
B 4.2.4
Incompletely Studied Drugs With Potential Benefit in Improving Claudication

Carnitine

Patients with PAD not only have a limited arterial blood flow but also develop metabolic abnormalities in their skeletal muscle. An example of this is changes in carnitine metabolism. Patients with PAD have been shown to accumulate acylcarnitines (intermediates of oxidative metabolism) in their skeletal muscle. This abnormal accumulation of acylcarnitines is directly correlated with impaired exercise performance. It has thus been hypothesised that supplementation of patients with carnitine would improve ischaemic muscle metabolism. Carnitine, and an acyl form of carnitine (propionyl-L-carnitine), are drugs that have been shown to increase exercise performance and improve claudication symptoms in small phase II trials. Larger phase II trials have also shown benefit of propionyl-L-carnitine, with the optimal dose of 2 g/d (Table 16). Three multicentre, phase III trials are evaluating the efficacy and safety of propionyl-L-carnitine in the treatment of claudication.

Prostaglandins

Prostaglandins have been used in several studies in patients with CLI, with some success. In one open-label study of claudicants, 44 patients were treated either without an infusion (control group), with intravenous pentoxifylline, or with intravenous prostaglandin \( E_1 \) (PGE\(_1\)) for 4 weeks. All patients also underwent an exercise rehabilitation program. The exercise program alone resulted in a 99% increase in maximal walking distance; pentoxifylline, a 119% increase; and PGE\(_1\), a 51% increase. Because this trial was unblinded and not placebo controlled, and patients had a combined intervention of exercise training and drug, the results need to be confirmed with additional studies.

A prodrug of PGE\(_1\) (AS-013) was studied in a randomised, controlled, prospective study of 80 patients with IC, comparing placebo with three dosage regimens of the drug given intravenously for 5 days per week over 8 weeks. There was a significantly greater increase (\( p < 0.01 \)) in maximum walking distance in the combined active treatment group (53%) compared with the placebo group (-14%). There was also a dose-related improvement in the response to a quality-of-life questionnaire. In another recent study, intravenous PGE\(_1\) given for 5 days per week over 4 weeks and twice weekly per week for a further 4 weeks was compared with placebo in 213 claudicants. At the end of the 8 weeks of treatment, pain-free walking distance increased by 60% in the placebo group compared with 101% in the treated group (\( p < 0.05 \)). These improvements remained virtually unchanged over 3 months' follow-up without treatment. Intravenous administration may not be the most practical preparation. The recent development of an oral preparation may be more suitable in patients with IC. The experience with orally active prostaglandins in claudication is more limited, with only two published reports for evaluation. Beraprost is a PGI\(_2\) analog that is orally active. A single phase II dose-ranging study has been published in which 164 patients were randomised to placebo or three doses of drug. The improvement in absolute claudication distance over placebo was as follows: 60 \( \mu \)g/d produced a 48% increase, 120 \( \mu \)g/d a 51% increase, and 180 \( \mu \)g/d a 31% increase (Table 16). None of these changes was statistically significant. A concern was that at the highest dose, 62% of the patients reported side effects of headache, flushing, and gastrointestinal intolerance. Several phase III trials are evaluating the effectiveness of these drugs in claudication, and it is hoped that these studies will clarify the utility of this class of drug.

Critical Issue 8: Use of prostanoids for symptoms of intermittent claudication

There is a need to investigate the possibly greater efficacy of prostanoids in patients with intermittent claudication, because most randomised, open, or double-blind trials with intrarterial or intravenous prostanoids have been performed in patients with end-stage critical limb ischaemia. Predictors to select the most suitable patients for prostanoid treatment need to be determined.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are mitogenic agents for the development of new collateral channels in models of peripheral ischaemia. VEGF has been shown to augment collateral vessel development and increase capillary density in skeletal muscle in a rabbit model. This effect has been observed when the VEGF protein is administered by intraarterial infusion and when the DNA encoding for VEGF is given by intramuscular injection. Early phase I and phase II trials are now in progress to determine whether this novel therapy has a clinical application in patients with claudication and severe leg ischaemia.
L-arginine is an amino acid that has been shown to improve nitric oxide formation and endothelial-dependent vasodilatation in patients with atherosclerosis. A few small studies have been performed with this compound in patients with claudication. These studies have shown improvements in pain-free and maximal walking distance, but larger studies are necessary to determine the benefit of this treatment. Another new class of agent is drugs that open potassium channels in vascular smooth muscle. In animal studies, this unique vasodilating drug improves muscle blood flow and energy metabolism in experimental models of vascular disease. Other metabolic factors that may be addressed in PAD include modification of the balance between fatty acids versus carbohydrates as substrates for ischemic skeletal muscle. Although fatty acids are a plentiful source of energy, they require relatively more oxygen than carbohydrates for complete oxidation. The adenosine triphosphate (ATP)/oxygen ratio is 5.7 for fatty acids and 6.3 for glucose. Thus, when oxygen is limited, as during claudication, a shift toward carbohydrate metabolism would be favorable in terms of ATP production. Several agents are now under investigation that address these concepts.

**B 4.2.5**

**Summary: Pharmacotherapy for Symptoms of Intermittent Claudication**

In summary, patients with IC have cardiovascular risk factors that are critical to identify and modify to decrease the mortality risk of coronary and cerebrovascular disease. The pharmacological treatment of claudication itself is limited to a few drugs of uncertain efficacy. However, several new drugs are under investigation and may show marked benefit in the direct treatment of claudication symptoms.

**References**


Treatment of Intermittent Claudication

Intervention by endovascular procedure or surgery is only indicated in selected patients with IC in whom exercise treatment has failed. Imaging-guided catheter intervention for PAD was first described by Dotter and Judkins in 1964. Since that original report of PTA in femoropopliteal arteries using coaxial catheter techniques, more than 30 years have passed. The materials and methods have now been refined, practitioners have been and continue to be trained, and the application of percutaneous transluminal balloon angioplasty (PTA) and now stenting in PAD has become more widespread.

Endovascular interventions other than balloon and stent procedures may have a limited application in selected patients and are therefore not emphasised here. The following section considers the role of PTA and stenting in PAD patients with IC and aortoiliac disease, femoropopliteal disease, or both. Most trials cited were on claudicants only. Thrombolytic therapy has a role in some new claudicants and in previously stable claudicants whose symptoms worsen because of thrombosis superimposed on atherosclerotic stenosis (particularly those with thrombus-dominant rather than

B 4.3
Endovascular Procedures for Intermittent Claudication

B 4.3.1
General Concepts Regarding Catheter Intervention in PAD

Intervention by endovascular procedure or surgery is only indicated in selected patients with IC in whom exercise treatment has failed. Imaging-guided catheter intervention for PAD was first described by Dotter and Judkins in 1964. Since that original report of PTA in femoropopliteal arteries using coaxial catheter techniques, more than 30 years have passed. The materials and methods have now been refined, practitioners have been and continue to be trained, and the application of percutaneous transluminal balloon angioplasty (PTA) and now stenting in PAD has become more widespread.

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