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Drug Treatment of Intermittent Claudication

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Abstract

The US FDA has approved two drugs for the management of intermittent claudication: pentoxifylline and cilostazol. The mechanism of action that provides symptom relief with pentoxifylline is poorly understood but is thought to involve red blood cell deformability as well as a reduction in fibrinogen concentration, platelet adhesiveness and whole blood viscosity. The recommended dose of pentoxifylline is 400mg three times daily with meals. Cilostazol is a potent, reversible, phosphodiesterase III inhibitor. The inhibition of phosphodiesterase allows for the increased availability of cyclic adenosine monophosphate (cAMP). cAMP mediates many agonist-induced platelet inhibitory, vasodilatory and vascular antiproliferative responses. Cilostazol, at a dose of 100mg twice daily, is recommended to be taken 30 minutes before or 2 hours after breakfast and dinner.

In addition to pentoxifylline and cilostazol, clinical trials indicate many other drugs may relieve the symptoms of intermittent claudication. *Ginkgo biloba*, available as an over-the-counter extract, provides symptom relief comparable to pentoxifylline. Two European agents, naftidrofuryl and buflomedil, also have efficacy that is reported to be similar to pentoxifylline. Policosanol is a mixture of fatty alcohols derived from honeybee wax which, according to very limited data, reduces symptoms of claudication. Amino acids, certain peptides and prostaglandins may have a therapeutic role. Finally, novel approaches including angiogenesis mediated by growth factors, are currently under investigation.

Claudication, derived from the Latin word for 'to limp', describes discomfort in a particular muscle group brought on by exercise and relieved with rest, which is caused by an inadequate blood supply to

meet the metabolic demands of the particular muscle group. Peripheral arterial disease (PAD) caused by atherosclerosis is the most common cause of claudication in the lower extremities. A prospective study utilising the ankle-brachial index (ABI) as a diagnostic tool for identifying PAD indicates that close to 30% of individuals aged ≥70 years or aged 50 through 69 years with a history of diabetes mellitus or smoking, or both, have PAD.[1] It is estimated that there are 4 million patients in the US with PAD who experience claudication symptoms.[2] These symptoms typically correspond to the level of arterial obstruction and may severely limit lifestyle.

A relative minority of patients with PAD progress to the point of critical limb ischaemia (rest discomfort) that may require amputation.[3] The most common cause of death in individuals with PAD is a cardiovascular event, such as a heart attack or stroke.[4] The treatment of PAD and claudication involves prevention of progression of atherosclerosis and its associated cardiovascular events, as well as improvement in quality of life by improving ambulation. Revascularisation, exercise therapy and pharmacological treatment have all been shown to improve claudication symptoms. The 5-year patency rate for interventions to treat aortoiliac disease are 54–78% for percutaneous angioplasty and stenting, and 85–90% for aortofemoral bypass grafting. The patency rates for femoropopliteal disease are lower, with 38–70% patency for percutaneous angioplasty and stenting and 65–80% for bypass grafting.[4-7] While revascularisation eliminates the symptoms of claudication in many patients, these 5-year patency rates are the reason non-invasive approaches are frequently considered first-line therapy. Among non-invasive interventions, exercise therapy achieves increases in walking time that exceed those achieved by many pharmacological agents. Since exercise therapy has been extensively reviewed elsewhere, this review focuses on the treatment of claudication symptoms with drugs.

1. Drugs for Claudication

Two drugs have been approved by the US FDA for the management of intermittent claudication: pentoxifylline and cilostazol. The approval process for these agents primarily included evaluation of walking distance on a treadmill to determine if the pain-free and/or the maximum walking distance improved with the active compound.

2. Pentoxifylline

2.1 Mechanism of Action

The mechanism of action that provides symptom relief with pentoxifylline is poorly understood but is thought to involve red blood cell deformability as well as a reduction in fibrinogen concentration, platelet adhesiveness and whole blood viscosity.[8]

2.2 Clinical Trials

The recommended dose of this drug is 400mg three times daily with meals. The studies evaluating the effect of pentoxifylline on exercise performance have been inconsistent.[9-12] A meta-analysis of clinical trials investigating pentoxifylline indicates that pain-free walking time and maximal walking time can be improved by 29 and 48 metres, respectively.[13]

2.3 Adverse Effects

Pentoxifylline is contraindicated in individuals with hypersensitivity to xanthines as well as those with recent cerebral or retinal haemorrhage. Potential adverse reactions (1–10%) include dizziness, headache, dyspepsia, nausea and vomiting.[14] Caution is advised in patients with renal impairment as excretion is primarily in the urine. An increased effect may occur when pentoxifylline is taken with cimetidine, other histamine H_2 antagonists and warfarin.[14] Patients with cirrhosis should receive one-quarter the normal dose.[14]

3. Cilostazol

3.1 Platelet Effects

Cilostazol is a potent, reversible, phosphodiesterase III inhibitor. The inhibition of phosphodiesterase allows for the increased availability of cyclic adenosine monophosphate (cAMP).[15] cAMP mediates many agonist-induced platelet inhibitory, vasodilatory and vascular antiproliferative responses.[16] The result is inhibition of both primary and secondary phases of platelet aggregation induced by a variety of stimuli including adenosine diphosphate, collagen, epinephrine, arachidonic acid and thrombin. Prostacyclin, released from endothelial cells, enhances the anti-platelet activity of cilostazol *in vitro*.[17] This observation indicates that the increased sensitivity to adenylate cyclase stimuli may contribute to the anti-platelet effect of cilostazol at the level of the vessel-blood interface. Compared with aspirin (acetylsalicylic acid) and ticlopidine, cilostazol is a more potent inhibitor of adenosine diphosphate-, collagen- and arachidonic acid-induced platelet aggregation.[18] Interestingly, cilostazol, but not aspirin, inhibits high shear-stress-induced platelet aggregation both *in vitro* and *in vivo*.[19] This may have clinical ramifications as shear-stress during exercise is thought to be an important mechanism of platelet activation, especially at points of arterial bifurcation in patients with atherosclerotic plaques.

3.2 Vascular Effects

Cilostazol administration can result in vasodilatation through inhibition of smooth muscle phosphodiesterase III.[20] Cilostazol, via intravenous infusion to dogs, resulted in a 25% reduction in mean blood pressure at plasma concentrations similar to those in human clinical studies.[21] Long-term oral administration (6 months) of cilostazol resulted in a slight increase in the ABI, as well as a statistically significant improvement in recovery after exercise.[22] Other effects of cilostazol include attenuation of the prolific response to a variety of growth factors, including platelet-derived growth factor and insulin-like growth factor-I.[23,24] The increased availability of nitric oxide and inhibition of mitogen-activated protein kinase activity have also been reported with cilostazol.[24,25] Neo-intimal formation in a rat vascular injury model,[26] as well as several reports of inhibition of restenosis in humans,[27,28] indicate cilostazol may have important antiproliferative properties.

3.3 Lipid Effects

For unclear reasons, perhaps through enhancement of peripheral lipoprotein lipase activity or attenuation of hepatic triglyceride secretion, cilostazol results in approximately 15% reduction of plasma triglycerides and a 10% increase in high-density lipoprotein (HDL)-cholesterol.[29]

3.4 Clinical Trials

In the initial clinical studies conducted in Japan it was noted that cilostazol resulted in improved claudication symptoms, perhaps through an increase in dermal blood flow.[30] A series of multicentre clinical trials were conducted in the US which led to FDA approval of cilostazol for claudication symptoms in patients with PAD. These trials are summarised in table I.

Money et al.[34] conducted a 16-week trial and noted that absolute claudication distance (ACD) improved significantly in patients receiving cilostazol compared with placebo (47% vs 13%, respectively). A 24-week study conducted by Beebe et al.[31] found that an improvement in ACD and initial claudication distance (ICD) occurred as early as 4 weeks and remained improved throughout the rest of the study. Across eight clinical trials the maximum improvement in ACD and ICD was 100% and 45–96%, respectively.

Dawson et al.[31] compared the effects of cilostazol and pentoxifylline in a placebo-controlled study of 698 patients. The ACD and ICD improved significantly with cilostazol, but results for pentoxi-

Table I. Overview of randomised controlled trials (RCTs) of cilostazol (CLZ) in patients with intermittent claudication (modified from Reilly and Mohler,[15] with permission)

Study	Design	Drug (dose)	n	Duration (wk)	ICD (metres)				ACD (metres)				ABI			Functional status
					pre	post	Δ (%)	p-value[a]	pre	post	Δ (%)	p-value[a]	pre	post	p-value[a]	
Beebe et al.[31] (1999)	RCT	PLA	170	24	72.4	95.5	20		147.8	174.6	15%		NR			SF-36 +
		CLZ (100mg)	171		66.5	115.1	48	<0.001	131.5	198.8	38%	<0.001				WIQ +
		CLZ (200mg)	175		70.4	137.9	59	<0.001	129.7	258.8	51%	<0.001				COM +
																Pat/Phy +/+
Dawson et al.[32] (2000)	RCT	PLA	239	24			55.1				33.5%		NR			NR
		PTX (1200mg)	232				68.4	NS			30.4%	NS				
		CLZ (200mg)	227				98.3	<0.05			53.9%	<0.05				
Elam et al.[29] (1998)	RCT	PLA	94	12			NR		168	304	24.3%		0.65	0.65	NS	
		CLZ (200mg)	95						262	335	35.5%	<0.004	0.66	0.73	<0.001	NR
Dawson et al.[33] (1998)	RCT	PLA	25	12	77.7	84.6	−2.5	NS	168.6	152.1	−9.3%		NR			Pat/Phy +/+
		CLZ (200mg)	52		71.2	112.5	31.7	<0.01	141.9	231.7	30.5%	<0.005				
Money et al.[34] (1998)	RCT	PLA	120	16	NR				244.3	281.1	12.9%		0.68	0.69	NS	SF-36 +
		CLZ (200mg)	119						236.9	332.6	47%	<0.001	0.64	0.70	0.0125	WIQ +

a p-Value for comparison between active treatment and placebo.

ABI = ankle-brachial index; **ACD** = absolute claudication distance; **COM** = Claudication Outcome Measures; **ICD** = initial claudication distance; **n** = number of patients; **NR** = not reported; **NS** = not significant; **Pat/Phy** = subjective assessment of improvement by patient and physician; **PLA** = placebo; **post =** post-treatment; **pre** = pre-treatment; **PTX** = pentoxifylline; **SF-36** = Medical Outcomes Scale Short Form-36; **WIQ** = Walking Impairment Questionnaire; **wk** = weeks; Δ = percentage change in geometric means between baseline and follow-up; **+** indicates significant improvement in measure of functional status.

fylline did not differ from placebo over the course of 24 weeks. Figure 1 shows the maximal walking distance (MWD) comparing cilostazol, pentoxifylline and placebo for the duration of this trial.[32] The results of multiple trials have indicated that cilostazol 100mg twice daily is the most efficacious dosage.[35,36]

3.5 Adverse Effects

Over 1.5 million people worldwide have taken cilostazol, with safety profiles similar to the clinical trial data. All-cause mortality and cardiovascular morbidity were comparable with placebo, with a mortality of 0.8% in the cilostazol group and 0.7% in the placebo group.[35] Potential adverse reactions that occurred in >10% of patients in clinical studies include headache, abnormal stools and infection. Peripheral oedema, palpitations, tachycardia, dizziness, gastrointestinal discomfort, neuromuscular pain and respiratory irritation was experienced by 2–10% of patients. Since other phosphodiesterase III inhibitors have been associated with arrhythmias, cardiac safety was closely examined. There was no increase in cardiovascular morbidity or mortality, nor was there an increase in arrhythmias based on ECGs. There was a slight increase in the corrected QT interval of 3 milliseconds in patients receiving cilostazol.[35] A focus on heart failure did not reveal any increased adverse effects with cilostazol. Of 42 placebo-treated and 55 cilostazol-treated patients with a previous history of heart failure, 4.8% and 5.5%, respectively, developed worsening congestive heart failure.[37] However, despite any evidence that cilostazol is harmful in heart failure, it is still recommended that cilostazol be avoided in patients with heart failure. Table II summarises the adverse reactions encountered by patients in a randomised trial comparing cilostazol with pentoxifylline and placebo.[32] Postmarketing safety surveillance in the US continues to show an acceptable safety profile based on 70 430 patient-years. There have been 461 reported adverse events, of which 34 were considered serious. These events are summarised in table III.[37]

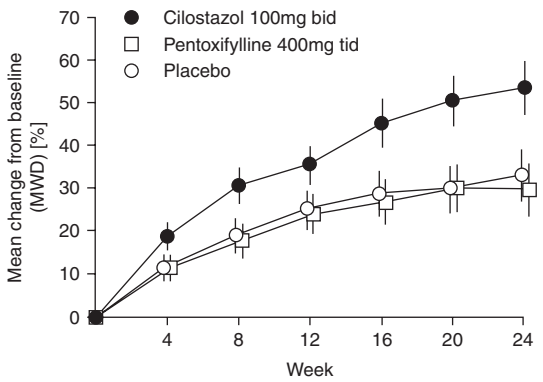

Fig. 1. Mean change from baseline in maximal walking distance (MWD) comparing cilostazol, pentoxifylline and placebo (reproduced from Dawson et al.,[32] with permission from Excerpta Medica, Inc.). **bid** = twice daily; **tid** = three times daily.

The pharmacokinetics of cilostazol are unchanged in elderly patients or in those with hepatic or renal disease. The peak concentration of cilostazol increases by 90% when taken with a high-fat meal and, thus, cilostazol is recommended taken 30 minutes before or 2 hours after breakfast and dinner. The concentration of cilostazol is increased with concomitant administration with omeprazole (a cytochrome P450 2C19 inhibitor), clarithromycin, fluconazole, itraconazole, microconazole, fluvoxamine, fluoxetine, nefazodone, sertraline and diltiazem. When administered with aspirin, platelet aggregation is further inhibited with cilostazol.[38]

4. *Ginkgo biloba*

4.1 Mechanism of Action

Ginkgo biloba is one of the world's oldest living tree species, existing for over 200 million years.[39] Extracts from *Ginkgo biloba* have vasoregulatory effects and prevent damage to membranes caused by free radicals.[40]

4.2 Clinical Trials

Ginkgo biloba extract is frequently administered at a dosage of 120 mg/day, with dosages ranging from 40mg three times daily to 320 mg/day. A meta-

Table II. Adverse reactions encountered by patients in a randomised clinical trial comparing cilostazol with pentoxifylline (reproduced from Dawson et al.,[32] with permission from Excerpta Medica, Inc.)

Adverse event	Number (%)		
	cilostazol (n = 227)	pentoxifylline (n = 232)	placebo (n = 239)
Patients with at least one event	201 (86)	200 (86)	188 (79)
Headache	63 (28)	26 (11)	28 (12)
Pain	30 (13)	38 (16)	33 (14)
Diarrhoea	43 (19)	18 (8)	13 (5)
Pharyngitis	22 (10)	32 (14)	17 (7)
Peripheral vascular disorder	13 (6)	22 (10)	26 (11)
Abnormal stools	33 (15)	12 (5)	7 (3)
Palpitation	39 (17)	5 (2)	3 (1)
Serious adverse events	27 (12)	31 (13)	31 (13)
Death	2 (0.8)	3 (1)	1 (0.4)

analysis of eight randomised, placebo-controlled trials of *Ginkgo biloba* showed improvement in pain-free walking distance (PFWD), with a mean difference of 34 metres; MWD also improved.[41,42] The investigators concluded that *Ginkgo biloba* was superior to placebo in treating intermittent claudication, but that the effect was modest making the clinical relevance uncertain. When compared with pentoxifylline, *Ginkgo biloba* has similar efficacy.[43,44]

4.3 Adverse Effects

In the meta-analysis,[40] adverse effects of *Ginkgo biloba* were rare, transient and mild in nature, with the most common adverse effect being gastrointestinal symptoms. Other adverse effects include dermatitis, headache and increased risk of bleeding.[39]

5. Policosanol

5.1 Mechanism of Action

Policosanol is a mixture of fatty alcohols derived from the wax of honeybees. Policosanol has both cholesterol-lowering effects and antiplatelet activity.[45]

5.2 Clinical Trials

A randomised controlled trial of 56 patients receiving policosanol 10mg twice daily showed improvement relative to placebo in ICD and ACD at 6 months and 2 years ($p < 0.0001$).[45] A recent randomised controlled trial of 28 patients with moderately severe intermittent claudication compared the effects of policosanol with lovastatin. Policosanol, but not lovastatin, increased both the ICD ($p < 0.01$) and ACD ($p < 0.001$) compared with baseline, with a significant difference between policosanol and lovastatin ($p < 0.01$). Similar results have been obtained comparing policosanol with fluvastatin.[46]

5.3 Adverse Effects

Mild adverse effects, to the same degree as with placebo, were experienced with policosanol and to a lesser degree than fluvastatin, with no patients withdrawing from the trials as a result of adverse effects.[46]

6. Naftidrofuryl

6.1 Mechanism of Action

Naftidrofuryl inhibits serotonin 5-HT_2 receptors, which may ameliorate symptoms of peripheral vascular disease through vasodilation and improved aerobic metabolism.[42,47]

6.2 Clinical Trials

Naftidrofuryl has been available in Europe for over 20 years, with standard dosage administration

Table III. Spontaneous cardiovascular adverse events reported with cilostazol in the US (reproduced from Pratt,[37] with permission from Excerpta Medica, Inc.)[a]

Adverse event	Events reported (no.)	Incidence/1000 PEY
Hypertension	11	0.156
Hypotension (mild)	3	0.043
Atrial fibrillation	1	0.014
Atrial flutter	1	0.014
Palpitation	23	0.327
Tachycardia	24	0.327
Angina pectoris	1	0.014
Myocardial infarction	1	0.014
Transient ischaemic attack	0	0
Stroke	0	0
Death	1	0.014

a Postmarketing surveillance data in the US, covering reports between 10 May 1999 and 15 January 2001.

PEY = patient-exposure years.

of 600 mg/day, often divided into 200mg three times daily. Early randomised controlled trials demonstrated that treatment with naftidrofuryl led to increase in mean PFWD as compared with placebo, with a 35% increase at 12 weeks ($p < 0.02$)[48,49] and a 32% increase at 6 months ($p < 0.02$).[50] Neither study showed an increase in MWD. Multiple later studies supported clinical benefit of naftidrofuryl, with a meta-analysis of 900 patients from eight randomised controlled trials finding improved PFWD at treatment courses ranging from 4 to 24 weeks.[40] A subsequent randomised, placebo-controlled study of 181 patients found a 92% improvement in PFWD at 6 months with naftidrofuryl compared with 17% improvement in the placebo group ($p < 0.001$), and an 83% improvement in MWD with naftidrofuryl compared with 14% in the placebo group ($p < 0.001$).[49] In addition to improving PFWD and MWD, patients taking naftidrofuryl have improved daily living, pain and social life compared with patients taking placebo ($p < 0.01$).[51]

6.3 Adverse Effects

Adverse reactions of naftidrofuryl are most commonly gastrointestinal in nature, with other adverse effects including headache, dizziness, insomnia and hepatitis. Intravenous administration of naftidrofuryl as a treatment of PAD was withdrawn worldwide as a result of concerns regarding cardiac and neurotoxicity. Acute renal failure due to calcium oxalate crystallisation has been reported, but this was more common with intravenous administration and is unlikely with oral therapy. Nonetheless, naftidrofuryl is contraindicated in patients with hyperoxaluria or recurrent calcium-containing kidney stones.[39]

7. Buflomedil

7.1 Mechanism of Action

Buflomedil has several properties that may benefit patients with claudication, including vasoactive effects with enhanced red blood cell deformability and muscle cell metabolism, in addition to platelet inhibition.[42]

7.2 Clinical Trials

Although buflomedil is not currently approved in the US it is available in Europe, and administered at a dosage of 600 mg/day, which may be given once daily or using divided doses.

A meta-analysis for the Cochrane Database of two trials (four trials were excluded because of quality evaluation and three unpublished trials were excluded as a result of an inability to obtain copies of the trials) found a moderate improvement in PFWD and MWD, but concluded that the results were not reliable because of publication bias.[52] A different meta-analysis of 744 patients receiving buflomedil in ten randomised controlled trials also found a moderate effect of buflomedil, with the average patient having a PFWD improvement greater than at least 60% of patients receiving placebo.[53]

When compared with other treatments for intermittent claudication, there has been no consistent difference in efficacy between buflomedil, naftidrofuryl and pentoxifylline. While naftidrofuryl

leads to a greater improvement in walking distance than buflomedil, buflomedil leads to a greater increase in the duration of ergometric testing.[54] In a study of 45 patients randomised to pentoxifylline 1200 mg/day, nifedipine 60 mg/day or buflomedil 600 mg/day, pentoxifylline was most effective in improving walking performance and ABI at 90 days.[55] In contrast, in 35 patients randomised to pentoxifylline 100mg three times daily or buflomedil 150mg three times daily, there was no difference between the agents in PFWD or MWD.[39,56]

7.3 Adverse Effects

Adverse effects of buflomedil include gastrointestinal symptoms, headache, dizziness, syncope, erythema and pruritus.[42]

8. Ticlopidine

8.1 Mechanism of Action

Ticlopidine blocks adenosine diphosphate receptors on platelets, thereby inhibiting their aggregation. This inhibition may reduce blood viscosity and may improve red blood cell deformability.[42,57]

8.2 Clinical Trials

The recommended dosage of ticlopidine is 500 mg/day or 250mg twice daily. A randomised controlled trial of 169 patients treated with ticlopidine for 6 months found improved PFWD (194 vs 124 metres; $p = 0.03$) and MWD (236 vs 170 metres; $p = 0.04$).[58] Another randomised controlled trial of 126 patients found improved MWD at 21 months.[59] However, no benefit of ticlopidine after 5 years of treatment was found in another trial.[60] According to a meta-analysis of four ticlopidine trials, short-term benefits were apparent but there was no longer-term benefit for symptoms of claudication when compared with placebo.[40]

8.3 Adverse Effects

The major adverse effect of ticlidopine that leads to cautious usage is potentially fatal bone marrow suppression, with a meta-analysis finding neutropenia in 2.4% of recipients.[61] Patients should be monitored for neutropenia every 2 weeks for 3 months.[39] The other more commonly experienced, but less severe, adverse effects are gastrointestinal symptoms, dizziness and rash.[39,58,59]

9. Levocarnitine

9.1 Mechanism of Action

Levocarnitine and its analogue propionyl carnitine are carrier molecules in the transport of long-chain fatty acids across the inner mitochondrial membrane, which provides substrates for energy production.[39]

9.2 Clinical Trials

When given intravenously at a dosage of 600–3000 mg/day, supplementation with propionyl carnitine has been shown to improve claudication and patients' walking capacities. In a randomised controlled trial of 214 patients lasting 6 months, propionyl carnitine increased MWD by 27% over placebo ($p = 0.03$), with a nonsignificant trend towards increased PFWD.[62] Another trial compared propionyl carnitine with placebo in 245 patients, finding increased walking capacity and quality of life in the propionyl carnitine group.[63] A trial of 485 patients with claudication found propionyl carnitine improved MWD and PFWD relative to placebo, but reached statistical significance only in patients with an MWD <250 metres.[64] In a 6-month double-blind, randomised controlled trial of 155 patients, patients experienced a 54% increase in MWD with propionyl carnitine as compared with a 25% increase with placebo ($p < 0.001$).[65] When compared with its analogue levocarnitine, propionyl carnitine was found to be superior.[65-67]

9.3 Adverse Effects

Gastrointestinal symptoms were occasionally experienced with levocarnitine, although this does not differ from placebo. Rarely, seizures have been reported.[39,40]

10. Arginine

10.1 Mechanism of Action

Arginine is an amino acid precursor of nitric oxide, which leads to vasodilation and improved endothelial function.[39,68]

10.2 Clinical Trials

Clinical trials with arginine are extremely limited. One small randomised controlled trial of 39 patients using two infusions of arginine 8g showed an improvement in PFWD by 230% and MWD by 144% after 3 weeks.[68] Flow-induced vasodilation of the femoral artery was assessed, with improved endothelium-dependent vasodilation. Thus, while arginine may provide a future therapy for intermittent claudication, additional studies and administration mechanisms will be necessary before arginine can be recommended.

10.3 Adverse Effects

No adverse effects were noted with arginine when studied for claudication. Adverse effects that have been noted with other indications include increased blood urea nitrogen and creatinine, as well as gastrointestinal effects.[39]

11. Glutathione

11.1 Mechanism of Action

Glutathione is an endogenous tripeptide of the amino acids cysteine, glycine and glutamic acid that has antioxidant properties. It serves an important role in modulating endothelium-derived nitric oxide, with increased intracellular glutathione resulting in increased nitric oxide activity and improved endothelial activity.[69]

11.2 Clinical Trials

Glutathione is administered at a dosage of 300–600mg once or twice daily.[41] A randomised controlled trial of 40 patients found that intravenous glutathione twice daily led to increases in PFWD ($p < 0.04$) as well as increased macrocirculatory flow measured with plethysmography ($p < 0.002$) and microcirculatory flow measured with laser Doppler flowmetry ($p < 0.005$).[69]

11.3 Adverse Effects

Oral glutathione has been reported to cause gastrointestinal adverse effects and, rarely, an urticarial rash.

12. Prostaglandins

12.1 Mechanism of Action

Prostaglandins (PGs) are naturally occurring lipids that have vasodilating and antiplatelet activity.[70]

12.2 Clinical Trials

A recent meta-analysis of 500 patients from eight randomised controlled trials of prostanoids found a 28% improvement in PFWD compared with placebo ($p = 0.008$), and a 30% improvement in mean MWD compared with placebo ($p = 0.002$).[71]

12.3 Adverse Effects

Adverse reactions occurred in 39% of patients receiving epoprostenol (prostacyclin) or its analogues, and in 14% of patients receiving PGE_1.[71] These adverse effects include flushing, bradycardia, tachycardia, hypotension and gastrointestinal adverse effects. PGs are contraindicated in New York Heart Association class 3 or 4 heart failure.

13. Sulodexide

13.1 Mechanism of Action

Sulodexide is a glycosaminoglycan that contains fast-moving heparin and dermatan sulfate. It may have antithrombotic, profibrinolytic and antiatherosclerotic properties.[39,72]

13.2 Clinical Trials

Sulodexide is frequently given intravenously or intramuscularly at dosages of 300–600 lipoprotein-lipase-releasing units (LRU) daily for 15–20 days, followed by oral dosage of 150 LRU three times daily or 250 LRU twice daily. A meta-analysis of 19 trials with sulodexide that averaged a duration of 2–6 months found a therapeutic effect in patients with diabetes and hyperlipidaemia, with an increase in PFWD of 36% compared with controls ($p < 0.001$).[73] In addition to ameliorating symptoms, sulodexide was also significantly associated with lowering triglycerides by 28% ($p = 0.0015$) and increasing HDL-cholesterol by 24.4% ($p = 0.0007$). A subsequent randomised controlled trial of 286 patients found that PFWD increased 83 metres with sulodexide, compared with 37 metres with placebo ($p = 0.001$), while MWD increased 142 metres with sulodexide and 55 metres with placebo ($p < 0.001$)[72]

13.3 Adverse Effects

Sulodexide is contraindicated in patients receiving heparin or oral anticoagulants. Although no adverse reactions were observed during the aforementioned clinical trials, reported adverse effects include gastrointestinal adverse effects and occasional skin rashes.[41]

14. Angiogenesis with Recombinant Fibroblast Growth Factor-2 and Vascular Endothelial Growth Factor

14.1 Mechanism of Action

Recombinant fibroblast growth factor (FGF)-2 (rFGF-2) and vascular endothelial growth factor (VEGF) stimulate angiogenesis, thereby improving perfusion.

14.2 Clinical Trials

A phase I trial of 51 patients with an ABI of <0.4 using intramuscular injection of naked plasmid DNA for FGF-1 found improved ABI at 2 and 3 months, but this was not sustained at 6 months. Nine patients experienced reduction in ischaemic ulcer size.[74] In the therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (TRAFFIC) study,[75] 190 patients were randomised to an infusion of placebo or one or two doses of rFGF-2 (30 μg/kg). An intention-to-treat analysis showed a significant increase in peak walking time with rFGF-2, although the double dose did not have any additional benefit.[75] In a small study using naked plasmid DNA encoding for VEGF, intramuscular injections to ten limbs with critical limb ischaemia resulted in improved ABI, improvement in ischaemic ulcers in four of seven limbs and limb salvage in three patients.[76] In a phase I trial of 13 patients with critical limb ischaemia, adenoviral-mediated gene transfer of VEGF appeared to be well tolerated, with further studies needed to establish efficacy.[77] A phase II trial of patients with chronic leg ischaemia who received VEGF by adenoviral vector or liposome/plasmid carrier after a percutaneous transluminal angioplasty found increased vascularity but no significant change in ABI relative to placebo.[78,79] Angiogenesis, especially using FGF and VEGF, appears to have significant promise in treating claudication and multiple phase III trials are currently in progress. These trials will need to establish the efficacy of different growth factors and

vectors in promoting angiogenesis and decreasing claudication.

14.3 Adverse Effects

Reported adverse effects with rFGF-2 and VEGF include irritability, headache and hyperactivity.[39]

15. Conclusion

Pentoxifylline and cilostazol are the only US FDA-approved drugs available for the treatment of claudication symptoms. Neither of these drugs is approved for the reduction of cardiovascular events in patients with PAD. In a meta-analysis of treatments for intermittent claudication, trials with cilostazol and vasodilators have shown the greatest efficacy.[40] Some agents, such as *Ginkgo biloba*, have consistently shown some benefit, though the lower magnitude of the benefit makes their clinical relevance uncertain. Almost all agents that demonstrated efficacy had a time-response relationship, with trials lasting longer than 16 weeks showing a greater effect on PFWD.[40] Multiple other agents that have been tried in the past appear to offer no or little benefit. Finally, many novel approaches to alleviate claudication, such as angiogenesis-promoting agents, may expand the medical options of patients with claudication in the future.

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