

DRUG TREATMENT OF INTERMITTENT CLAUDICATION

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Intermittent claudication is a major presenting manifestation of chronic obstructive peripheral arterial disease of the lower limbs. The goals of treatment in the absence of rest pain are relief of symptoms, improvement in walking distance and prevention of progression of disease. To achieve these goals, various treatment strategies are available which are influenced by the presence of any concurrent illnesses, health expectations and life expectancy. Initial treatment modalities are therefore conservative and are based on symptomatic relief through risk factor modification (such as the cessation of smoking), exercise and, in some cases, drug therapy. There is good clinical evidence that structured exercise programmes increase pain free walking distance. Smoking cessation may reduce the complications of peripheral arterial disease but is of greatest benefit in improving graft patency rates in patients undergoing by-pass surgery. The effectiveness of drug therapy for intermittent claudication, however, remains controversial and despite numerous clinical trials, many experts are not convinced of their value.

Which drugs? *Oxpentifylline* (Trental) and *naftidrofuryl oxalate* (Praxilene) are the most frequently used and most extensively studied. The *nicotinic acid* derivative *inositol nicotinate* (Hexopal) and anti-platelet drugs are also prescribed. What is their mode of action and how effective are they?

Oxpentifylline is thought to alter blood rheology by improving the deformability of red blood cells thereby increasing oxygen supply to ischaemic tissue; it also reduces plasma fibrinogen and decreases platelet adhesion and aggregation. The majority of published clinical trials of *oxpentifylline* show a beneficial effect of the drug on claudication distance. Placebo controlled studies report an average increase in claudication distance of 51% when compared with placebo. However, controversy exists over the magnitude of the effect and whether or not any effect observed is clinically important. Many trials included small numbers of patients and because of variations in study design, results cannot be pooled in any useful manner. Furthermore, progression of disease was not assessed.

Naftidrofuryl oxalate increases glucose consumption at the cellular level, leading to increased supply of ATP and decreased lactate levels in muscle. It also blocks serotonin induced vasoconstriction and platelet aggregation. A meta-analysis of several placebo controlled studies has shown that over a 3 month period, a daily dose of 600mg of *naftidrofuryl oxalate* increased the mean pain free walking distance by 55% compared to a 25% increase in the placebo group. Only one study, at a lower dose of 400mg daily, failed to show a difference between placebo and active treatment. In common with *oxpentifylline*, *naftidrofuryl oxalate* seems to produce a modest increase in walking distance but it is not possible to assess the degree of benefit. The effect of the drug on disease progression is also unknown.

There is less evidence to support the use of vasodilators in intermittent claudication. In a community based study, the *nicotinic acid* derivative *inositol nicotinate* failed to improve objective measurements of claudication, although subjective assessments were marginally improved. At present, no data is available to support the use of this drug in these patients.

Anti-platelet drugs such as aspirin are now routinely used in the secondary prevention of cerebrovascular and cardiovascular events in patients with a history of myocardial infarction, unstable angina, occlusive strokes or transient ischaemic attacks. Hence, there has been some interest in anti-platelet therapy in patients with peripheral arterial disease. To-date, there are no published data to determine whether anti-platelet drugs have a beneficial effect on claudication distance and disease progression in these patients. However, there is recent evidence

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which supports the use of low dose aspirin to reduce the incidence of cerebral and cardiac events in patients with peripheral vascular disease. At present aspirin is not licensed for such use.

In conclusion, the usefulness of drugs in intermittent claudication remains undetermined. The benefits seen with *oxpentifylline* and *naftidrofuryl oxalate* have been marginal and may not justify the cost of treatment with these drugs. The recent audit on prescribing habits in general practice commissioned by the department of health in the United Kingdom has classified these drugs as "drugs of limited clinical value". This suggests that financial savings can be made

in the health service by cutting their use without detriment to patients. This would direct scarce resources to more proven treatment modalities.

In the absence of any other pathology, the patient who initially presents with intermittent claudication without rest pain should first be advised to "stop smoking and keep walking". If there is progression of symptoms vascular assessment is required. The routine use of drugs to improve claudication cannot be recommended at present. Further, carefully designed placebo-controlled studies with large numbers of patients and more defined end points are required to establish their usefulness or otherwise.

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