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EDITORIAL COMMENT

Beraprost for the Treatment of Intermittent Claudication*

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Peripheral arterial disease (PAD), diagnosed by decreased ankle-brachial index (ABI), is a major clinical problem, affecting 8% of people 60 to 69 years old and at least 18% of people over age 70 (1). A substantial minority of patients with PAD report intermittent claudication (IC) (2). As the population ages, IC is an increasingly common cause of disability, particularly in elderly women (3). Patients with PAD have about a 30% rate of coronary artery disease (4) and a 44% to 52% rate of cerebrovascular disease (5). Thus, PAD is significant, not only because of disability, but also because patients with PAD have excess risk of myocardial infarction, stroke, and death.

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The best treatment for PAD is prevention, with risk-factor modification targeted at smoking cessation and treatment of diabetes, dyslipidemia, and hypertension. Aspirin or clopidrogel use decreases the risk of cardiovascular events for patients with PAD. Good foot care is essential because trauma can result in nonhealing ulceration and amputation.

Once symptoms of IC develop, treatment should then emphasize a structured walking program. Exercise rehabilitation with risk-factor modification improves pain-free treadmill walking distance up to threefold and absolute walking distance (AWD) up to fourfold (6).

PATHOPHYSIOLOGY OF "IC"

Development of novel therapeutic agents depends on an understanding of the complex pathophysiology of IC. Initial symptoms of exertional limb ischemia relate to a decrease in blood flow from proximal arterial atherosclerotic stenoses. At rest, the blood supply meets the tissue needs, but with exercise, a supply/demand mismatch occurs that presents as exertional pain that is relieved by rest. The observation that platelet activation is increased in patients with PAD led to the hypothesis that circulating platelet aggregates cause further microcirculatory obstruction in addition to the impaired flow from large-vessel atherosclerosis (7). The rationale for the use of epoprostenol (prostacyclin) and its derivatives in PAD come from their ability to vasodilate and impair platelet function. However, several studies suggest that calf blood flow is not the sole or even major determinant of maximal walking distance (8). Other factors, including altered carnitine metabolism (9) or atrophy of type II skeletal muscle nerve fibers, play a role in the symptoms of chronic IC (10).

CURRENT MEDICAL TREATMENT OF "IC"

The pharmacologic treatment of IC in the U.S. is limited to pentoxifylline (Trental) and cilostazol (Pletal) (11). Both drugs have been shown to increase pain-free walking time and total distance walked, although the data regarding pentoxifylline conflict. In a recent, randomized comparison of pentoxifylline and cilostazol, pentoxifylline had no significant effect on maximal walking distance or quality of life. In contract, cilostazol was associated with an improvement in functional status as assessed by the SF-36 and walking impairment questionnaire (12). Although cilostazol often results in modest improvement in IC, its use is contraindicated in patients with heart failure, and a sizable minority discontinue treatment due to gastrointestinal upset or palpitations. Two additional agents, nafidrofuryl, a serotonin (5-Hydroxytryptophan) antagonist, and buflomedil, an alpha-1 and -2 adrenolytic agent, are used outside the U.S. to a limited degree.

Although there is no evidence that antiplatelet agents improve walking distance, clopidrogel—or aspirin with or without dipyridamole—is indicated to reduce the risk of cardiovascular events. Among the 6,452 patients with PAD in the CAPRIE study, the risk of myocardial infarction, ischemic stroke, or vascular death was 3.71% in the clopidrogel-treated group compared with 4.86% in the aspirin-treated group, a 3.8% relative risk reduction ($p = 0.0028$). In a meta-analysis of 11 trials involving over 2,000 patients, the use of antiplatelet agents was associated with a reduced risk of vascular graft occlusion from 24% to 16% (13). Peripheral arterial bypass or percutaneous revascularization is often an excellent choice for claudicants with aortoiliac atherosclerosis who do not respond to an initial trial of conservative regimen.

THERAPEUTIC RATIONALE FOR PROSATNOIDS FOR THE TREATMENT OF "IC"

Prostaglandin (PGE_1) and prostacyclin (PGI_2) analogues have several biologic actions that suggest a possible therapeutic benefit in PAD. During treadmill exercise, platelet activation, aggregation, and release of mitogens is increased in PAD patients. In models of atherosclerosis, platelet granule products cause a proportion of vascular smooth muscle cells to activate and migrate into atherosclerotic plaques. These observations suggest that the balance of arterial vasodilation and constriction would lean toward constriction in patients with chronic PAD. Beraprost is an orally active PGI_2 analogue that inhibits platelet aggregation, suppresses smooth muscle proliferation, and promotes

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vasodilation. The convenience of oral administration and the possibility of three-times daily dosing suggested that beraprost could be useful in the treatment of chronic IC.

PREVIOUS STUDIES OF PROSTANOIDS FOR PERIPHERAL VASCULAR DISEASE

In the first randomized trial of epoprostenol (prostacyclin) for the treatment of rest ischemia, continuous intravenous (IV) infusion was associated with short-term improvement in pain (14). Recently, a multicenter trial of alprostadil-α-cyclodextrine (administered by 2 h infusion daily for 19 days) also demonstrated short-term improvement in critical limb ischemia (15). In a pooled analysis, a decrease in major amputation or death was sustained up to six months after treatment in patients with critical limb ischemia, suggesting that short-term or intermittent administration of prostanoids was not simply the result of vasodilatation and might result in sustained clinical efficacy (16).

Enthusiasm for the use of intravenous PGI_2 for IC treatment accelerated after a placebo-controlled trial demonstrated improved walking distance (17). In a study of 80 patients with IC, intravenous AS-103, a PGE_1 pro-drug with extended half-life, demonstrated modest improvement in maximal and pain-free walking distance (18). The advantage of AS-103 over prostacyclin is that a bolus injection can be used rather than continuous IV infusion.

Inconvenient IV dosing of prostaglandin and prostacyclin led to the development of more stable, orally active analogues. Beraprost sodium, the agent used in the study by Mohler et al. (19), decreases platelet aggregation in vivo with a half-life in serum of 30 to 54 min (20). Two multicenter, randomized, placebo-controlled trials of beraprost conducted in Europe demonstrated modest efficacy in improved pain-free walking distance. The BERCI dose-ranging study (21) and the BERCI-2 (22) are limited by relatively small size. The BERCI dose-ranging study enrolled 164 in four treatment groups, and the BERCI 2 study enrolled 422 patients in two treatment groups. The data from U.S. studies revealed no improvement in walking distance. The lack of efficacy had been attributed to the timing of beraprost dosing (with meals). In these studies, facial flushing, headache, and nausea were the most commonly reported side effects.

CONTRIBUTION OF THE PRESENT STUDY TO THE UNDERSTANDING OF "PAD" TREATMENT

The study by Mohler et al. (19), published in this issue of the *Journal*, is the largest well designed study of any prostanoid for the treatment of IC. Their results were remarkably consistent. There was no improvement in any of the pre-defined efficacy end points, including absolute and pain-free walking distance. The magnitude of increase in AWD was much lower than had been observed in BERCI-2. The AWD improved 16.7% and 14.6% in the treatment and placebo groups, compared with 60.1% and 35.0% in BERCI-2.

Why was the present study negative? Perhaps the study enrolled a population that differed significantly from those in the European studies. Ankle-brachial index were lower in the present study than in BERCI-2. However, this is not likely to be the case, because the subjects in BERCI-2 with the lower ABI had the greatest improvement in AWD. Perhaps the lack of efficacy was due to the greater rate of co-morbidities including diabetes, dyslipidemia, and hypertension in the present study. Possibly the dosing regimen may have left too great a window without significant drug levels to cause a lasting biologic effect in the vasculature. The half-life of beraprost is <1 h. Even with 100% compliance, there would be <3 h of drug exposure per day.

The more likely explanation for their negative efficacy results is that the underlying hypothesis that platelet microaggregates contribute to claudication is wrong. The size of microaggregates would probably be too small to occlude even a tightly stenosed iliac or superficial femoral artery. The vasodilatory effects of beraprost observed in animal models and volunteers would probably not add much flow in maximally vasodilated distal vascular beds.

A secondary and intriguing finding in the present study was a decrease in cardiovascular events in the beraprost treated patients. This is consistent with many observations of other platelet inhibitors and supports the established hypothesis that platelet thrombosis is important in most coronary events.

THE FUTURE OF MEDICAL THERAPY FOR CLAUDICATION

The study by Mohler et al. (19) was well designed and adds to our knowledge of IC treatment. Beraprost lacks efficacy and probably has too many side effects to be an effective treatment for IC in clinical practice. We know from previous clinical trials that IV prostanoid formulations may mildly increase walking distance, but the inconvenience and expense of IV administration of these agents is disproportionate to the benefits. Therefore, it is unlikely that prostanoids will be used clinically for IC caused by large-vessel atherosclerosis.

It is important to note that the present study did not evaluate limb ischemia resulting from other causes such as thromboangiitis obliterans (Buerger's disease) or atheroembolism. In these disorders, the level of arterial occlusion is in the smaller vessels in which platelet thrombi and microvascular occlusion may have a more substantial pathophysiologic role. Furthermore, the present study does not apply to critical limb ischemia or ischemic wound healing. Patients with more severe or diffuse atherosclerosis who are not candidates for revascularization may benefit from prostanoid therapy.

Future research is likely to focus on agents that favorably alter the metabolic state of skeletal muscle such as

L-arginine and propyl-L-carnitine. In the next two years, the results of major trials of statins, antiplatelet agents, recombinant growth factors, and immune modulators for IC will be available. The publication of the Mohler et al. (19) study in a high-profile cardiovascular journal such as the *Journal of the American College of Cardiology* is particularly warranted at this time because it emphasizes the importance of IC as a marker of cardiovascular morbidity and the need to establish interventions that improve clinically meaningful end points.

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