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Pentoxifylline for vascular health: a brief review of the literature

Mark F McCarty,[1] James H O'Keefe,[2] James J DiNicolantonio[2]

ABSTRACT

Pentoxifylline is a methylxanthine derivative that has been used for several decades in the symptomatic management of intermittent claudication. For reasons that remain fairly obscure, this drug benefits blood rheology in a number of complementary ways: decreasing blood and plasma viscosity, lowering plasma fibrinogen while promoting fibrinolysis, and improving blood filterability by enhancing erythrocyte distensibility and lessening neutrophil activation. Anti-inflammatory effects on neutrophils and macrophage/monocytes—some of them attributable to pentoxifylline metabolites—appear to play a mediating role in this regard. Although clinical trials with pentoxifylline have often been too small in size to reach statistically significant findings regarding impacts on hard end points, a review of the existing literature suggests that pentoxifylline may have potential for slowing the progression of atherosclerosis, stabilising plaque, reducing risk for vascular events, improving the outcome of vascular events, dampening the systemic inflammatory response following cardiopulmonary bypass, providing symptomatic benefit in angina and intermittent claudication, enhancing cerebral blood flow in patients with cerebrovascular disease while slowing progression of vascular dementia, improving prognosis in congestive heart failure, and aiding diabetes control. This safe and usually well-tolerated drug works in ways quite distinct from other drugs more commonly used for cardiovascular protection, and hence may confer complementary benefit when used in conjunction with them. Major clinical trials of adequate statistical power are now needed to confirm the scope of benefits that pentoxifylline can confer; studies evaluating hard end points in acute coronary syndrome, stroke/transient ischaemic attack and systolic heart failure might be particularly valuable.

[1]Catalytic Longevity, Encinitas, California, USA
[2]Saint Luke's Mid-America Heart Institute, Kansas City, Missouri, USA

Correspondence to
Dr Mark F McCarty;
markfmccarty@gmail.com

PENTOXIFYLLINE IMPROVES THE RHEOLOGICAL PROPERTIES OF BLOOD IN MULTIPLE WAYS

Pentoxifylline is a methylxanthine derivative used for the past three decades to treat intermittent claudication.[1–3] In clinical doses—typically 400 mg three times daily—it improves the rheological properties of blood in numerous ways: decreasing plasma and whole blood viscosity, in large measure owing to a reduction in plasma fibrinogen; increasing erythrocyte distensibility and suppressing erythrocyte aggregation; diminishing platelet aggregation; and increasing blood filterability by suppressing neutrophil activation.[4–8] The activation of neutrophils renders them less distensible owing to an increase in the intracellular actin scaffold; hence, pentoxifylline improves the efficiency with which neutrophils can flow through the microvasculature.[9–15] Such an effect is particularly valuable when the pressure gradient across a microvasculature is diminished owing to an upstream stenotic obstruction; hence, it may be a key reason why pentoxifylline is clinically useful in intermittent claudication. The cumulative effect of a reduction in plasma viscosity, an increase in erythrocyte flexibility, and a suppression of neutrophil activation is improvement in capillary blood flow, particularly in vascular beds downstream from an arterial stenosis.

Pentoxifylline also exerts anti-inflammatory and antioxidant effects. The antioxidant effects appear primarily attributable to decreased neutrophil activation, as activated neutrophils generate superoxide via NADPH oxidase.[16] [17] There are also numerous reports that, in at least some clinical circumstances, pentoxifylline therapy lowers plasma levels of proinflammatory cytokines such as tumour necrosis factor (TNF) α, interleukin (IL) 1 and IL-6.[18–22] Since the latter cytokine evokes fibrinogen synthesis in hepatocytes,[23] this may in part account for the decline in plasma fibrinogen levels also observed during pentoxifylline treatment.

HOW DOES PENTOXIFYLLINE WORK AT THE MOLECULAR LEVEL?

The molecular biology underlying these various effects remains rather murky. The standard explanation for pentoxifylline's utility is that it is a non-specific inhibitor of cAMP phosphodiesterases, and hence upregulates the effects of cAMP.[24] But this effect of pentoxifylline is only observed in vitro

when cells are exposed to near-millimolar concentrations of pentoxifylline, which are orders of magnitude higher than clinical plasma concentrations.[25–27] Regrettably, the bulk of cell culture studies with pentoxifylline employ the concentrations required for phosphodiesterase inhibition—typically low millimolar levels. At these levels, pentoxifylline does indeed exert a number of intriguing effects, but many and perhaps most of these lack clinical pertinence. Plasma levels of pentoxifylline per se during clinical dosing are in the neighbourhood of 1 μM.[17 28 29] Curiously, several metabolites of this drug achieve plasma levels several-fold higher.[30]

A cell culture study examining the impact of pentoxifylline and its metabolites on neutrophil activation in vitro is particularly illuminating.[17] This study is one of the few to examine the impact of clinically relevant concentrations of these agents. The researchers exposed neutrophils to agonists that provoke neutrophil activation (C5 Des Arg and formyl-methionylleucylphenylalanine) and measured the evoked increase in superoxide production. Whereas addition of pentoxifylline itself had no effect on superoxide production in concentrations ranging from 10 to 1000 ng/mL, the three pentoxifylline metabolites tested (M1, M4 and M5) significantly inhibited evoked superoxide production within this concentration range. The impact of M5 (3′-carboxypropyl-3, 7-dimethylxanthine) may be most clinically pertinent, as its plasma concentrations are nearly an order of magnitude higher than those of pentoxifylline itself during clinical administration, and higher than that of any other metabolite (Cmax near 10 μM, or 2560 ng/mL).

The ability of pentoxifylline therapy to lower plasma concentrations of inflammatory cytokines under certain circumstances seems likely to reflect an impact of this drug or its metabolites on monocyte/macrophage activity. One study enrolling eight healthy volunteers measured the response of their peripheral blood monocytes ex vivo to agents (titanium particles or lipopolysaccharide—LPS) that evoke TNF-α release; this assessment was repeated after the volunteers had ingested pentoxifylline (400 mg five times daily) for 1 week.[18] The pentoxifylline pretreatment was shown to significantly inhibit TNF-α release. Conceivably, pentoxifylline itself may be a mediator of this effect; in one study, the lowest concentration assessed, 10 μM, was found to suppress LPS-stimulated production of TNF-α and IL-6 by alveolar macrophages from patients with sarcoidosis.[31] A study evaluating a more clinically pertinent concentration—1 μM—would be warranted. The pentoxifylline metabolite M1, but not metabolites M4 and M5, appears to share this property.[32]

Pentoxifylline and its metabolite lisofylline (one of the isomers of its M1 metabolite) may act directly on erythrocytes to increase their distensibility and decrease their aggregability. In vitro, 10 μM of these agents modestly increase erythrocytes deformability; the same concentration of pentoxifylline, but not lisofylline, inhibits erythrocyte aggregation.[33]

PENTOXIFYLLINE: MYRIAD POTENTIAL BENEFITS FOR VASCULAR HEALTH

Whereas intermittent claudication is clearly the best-documented indication for pentoxifylline, a thin but provocative set of studies suggests that this drug may have a broader role to play in the promotion of cardiovascular health.

Prevention of atherosclerosis

When rabbits were fed a cholesterol-enriched diet to induce atherosclerotic plaque, a clinically relevant daily oral dose of pentoxifylline (40 mg/kg) was found to decrease the area of aortic atherosclerotic plaque by 38%.[16] The drug did not influence the rise in serum lipids, but plasma and aortic levels of malondialdehyde, a marker for oxidative stress, were 32% and 37% lower, respectively, in the pentoxifylline group. Since the neutrophil content of plaque tends to be low, it seems likely that anti-inflammatory effects on infiltrating monocytes and possibly on endothelial cells, mediated this benefit. Additionally, a 6-month controlled clinical trial enrolling adolescent type 1 diabetics has assessed the impact of pentoxifylline on common carotid intima-media thickness, an index of atheroma.[34] This index declined in those receiving the drug, while it rose slightly in those receiving placebo (p<0.001).

Prevention of cardiovascular events

It appears that very few studies with pentoxifylline have examined its long-term impact on hard end points. However, a 6-month randomised placebo-controlled trial, enrolling patients with acute coronary syndromes (ACS), did make such an assessment.[35] Patients received standard-dose pentoxifylline (400 mg three times a day) or placebo along with other appropriate medications. The predetermined composite end point assessed consisted of death, non-fatal infarction and urgent rehospitalisation for ACS. At the end of the trial, 4 (13%) of the patients in the pentoxifylline group and 11 (34%) of the patients in the placebo group had achieved this end point (p=0.04). The pentoxiflline-treated patients also experienced significant reductions in serum C reactive protein and TNF-α relative to the placebo group. While such a small trial evidently cannot yield any definitive conclusions, its encouraging results suggest that other larger trials examining pentoxifylline's impact on hard end points in at-risk patients should be conducted.

Although neutrophils are not prominent constituents of stable atherosclerotic plaque—and hence are not thought to play a direct role in the genesis of atheroma—they are found in unstable plaques of patients with ACS.[36 37] Furthermore, among patients with angina, an increase in serum myeloperoxidase levels, indicative of neutrophil activation, is an adverse marker associated with increased risk for myocardial infarction in patients with angina.[38 39] The emergence of neutrophil-lymphocyte ratio as an independent risk factor for coronary events in patients with diabetes or coronary

lesions might reflect a role for activated neutrophils in the precipitation of such events[40–42]—though this ratio may also be serving as a marker for inflammation.[43]

Control of stable angina

Clinical evidence regarding pentoxifylline's efficacy in this disorder is scarce, but mildly encouraging. An open trial enrolling only 11 patients reported significant (p<0.05) improvements in mean total exercise time (10.1 vs 7.7 min at baseline), time to onset of angina and heart rate at onset of angina after pentoxifylline therapy—albeit a strong placebo effect might have been involved.[44] In a modest sized, underpowered double-blind trial (21 participants), pentoxifylline therapy did not influence exercise time, but non-significant trends favouring pentoxifylline were seen in regard to angina attack rate (reduction of 1.5 attacks per week on drug vs 0.7 on placebo) and nitroglycerin use (reduction of 1.45 pills per week on drug vs 0.1 on placebo; p=0.10).[45] Further clinical assessment in stable angina appears indicated.

Prevention of stroke and transient ischaemic attacks

Spontaneously hypertensive stroke-prone rats are a commonly used model of spontaneous stroke and cerebral ischaemia. Researchers evaluated the impact of daily oral pentoxifylline (100 or 200 mg/kg—the former dose appears clinically relevant after adjusting by the three-fourth power of relative body mass) on development of brain ischaemia in these rats, as assessed by MRI.[46] In the control group, all rats had developed brain abnormalities after 42 days. In the lower dose pentoxifylline group, 80% had done so after 70 days. In the higher dose group, no abnormalities were detected at 84 days. Pentoxifylline did not influence the elevated blood pressure in these rats, but histological examination of the brains of these rats showed that drug treatment prevented activation of microglia and influx of T-lymphocytes and macrophages. A 6-month randomised clinical trial enrolling patients experiencing transient ischaemic attacks (TIAs) assigned 73 patients to asprin +dipyridamole and 65 patients to pentoxifylline.[47] During the trial, there were 80 TIAs in 19 patients in the aspirin/dipyridamole group, and 19 TIAs in 9 of those receiving pentoxifylline (p<0.05). There were four non-fatal strokes in the former group, 2 in the latter. A subsequent larger study by the same group, likewise of 6-month duration, observed recurrent TIAs in 14% of patients receiving pentoxifylline, and 24.1% of those receiving aspirin/dipyridamole.[48]

Treatment of acute ischaemic stroke

Four controlled trials, enrolling a total of 763 patients, have assessed the impact of intravenous pentoxifylline on early mortality following acute ischaemic stroke. The daily doses employed ranged from 600 to 1200 mg, and were administered for 3–5 days immediately following stroke onset; in the three studies in which intravenous

pentoxifylline was given for 3 days, this was followed up with oral pentoxifylline. A meta-analysis of these studies calculated a hazard rate of 0.65 (95% CI 0.41 to 1.04) for those receiving pentoxifylline.[49] Hence, there was a strong trend (just barely missing statistical significance) suggesting that poststroke pentoxifylline could reduce early mortality by about one-third.

Slowing of progression of vascular dementia

At least four controlled clinical trials have evaluated the impact of pentoxifylline on progression of vascular dementia. A trend towards slowed progression was noted in all trials, and three found statistically significant benefit with respect to cognitive function.[50–54] A likely mediator of this effect is increased perfusion of brain regions that are suboptimally perfused, owing to the drug's impact on blood viscosity and filterability. The ability of oral pentoxifylline in standard doses to enhance cerebral blood flow in patients with cerebrovascular disease has been demonstrated repeatedly.[55–61]

Preservation of tissues after thrombolytic therapy

Influx of activated neutrophils play a key role in the mediation of ischaemia-reperfusion tissue damage.[62] Not surprisingly, pentoxifylline treatment has been reported to lessen such damage in numerous rodent studies, including studies focusing on the heart or brain.[63–73]

Decreased inflammation and tissue damage following cardiopulmonary bypass

A systemic inflammatory response syndrome (SIRS) is commonly observed following cardiopulmonary bypass (CPB), and can be associated with impaired organ function, as well as increased postoperative morbidity and mortality.[74] Owing to its anti-inflammatory properties, preoperative or intraoperative administration of pentoxifylline has been evaluated in a number of small-sized or moderate-sized controlled studies as an adjuvant to CPB.[75–86] Pentoxifylline has been administered orally in standard clinical doses for several days prior to surgery, or has been given intravenously at the time of surgery in various dose schedules (eg, 5 mg/kg as a bolus, followed by 1.5 mg/kg/h continuous infusion until 3 h after cessation of CPB). Many of these studies concluded that pentoxifylline administration decreased SIRS after CPB, as assessed by serum levels of proinflammatory cytokines such as TNF-α and IL-6.[79 80 82–86] Decreased neutrophil activation (as assessed by serum polymorphonuclear leukocyte (PMN) elastase) and total leucocyte count was also reported in the pentoxifylline groups.[79 80] Markers for endothelial activation (soluble adhesion factors), and liver, lung and renal function (serum creatinine) were found to be favourably influenced by pentoxifylline.[75 77 78] In a study which enrolled patients with left ventricular dysfunction, pentoxifylline improved left ventricular ejection fraction (LVEF).[86] One study reported a reduction in haemolysis (serum haemoglobin) in the

pentoxifylline group.[81] Finally, two studies observed that patients receiving pentoxifylline benefited from a reduction in postoperative ventilation time and length of stay in the intensive care unit.[79 83] Inclusion of pentoxifylline in the cardioplegia solution attenuated cardiac inflammation.[66] Though these studies were not large or long enough to evaluate the impact of pentoxifylline on mortality risk following CPB, they do suggest that, as an adjuvant to CPB, this drug can rather notably dampen the postoperative inflammatory response that is thought to contribute to postoperative mortality.

Improved outcomes in congestive heart failure

The favourable effects of pentoxifylline on inflammation and blood rheology have prompted a number of relatively small controlled clinical trials examining pentoxifylline's long-term impact on outcomes in congestive heart failure (CHF). Uniformly, these trials failed to observe a statistically significant effect of the drug on mortality during the follow-up periods. However, also uniformly, these studies also noted a trend towards lower mortality in the pentoxifylline group. These considerations prompted a recent meta-analysis of randomised controlled trials that had enrolled patients with CHF with LVEF ≤40%, and assessed all-cause mortality.[87] Six studies were included, comprising a total of 221 patients, most of 6 months duration. Remarkably, it was found that the patients receiving pentoxifylline had experienced a nearly fourfold reduction in mortality relative to the placebo-treated patients, with high statistical significance: 5.45% vs 18.3% (OR 0.29; 95% CI 0.12 to 0.74; p<0.01).

Improved diabetic control

A very recent randomised controlled trial evaluated pentoxifylline (400 mg three times a day) in patients with type 2 diabetes over 6 months.[88] A reduction in proteinuria (23%) relative to that seen in the placebo group (4%) was statistically significant (p=0.012). In addition, modest improvements in fasting blood glucose (−10 mg/dL), glycated haemoglobin (−0.34) and homeostatic model assessment of insulin resistance (HOMA-IR) (−0.79) were seen in the pentoxifylline group that were significantly different relative to the small increases in these parameters observed in the placebo group. Since inflammation in adipose tissue can compromise systemic insulin sensitivity, the favourable impact of pentoxifylline on glycaemic control in this study may have reflected its anti-inflammatory actions.

A CALL FOR CLINICAL RESEARCH

At present, pentoxifylline is used primarily for relieving the symptoms of intermittent claudication. This brief overview suggests that it may have much broader potential for protecting vascular health and optimising tissue perfusion. Pentoxifylline combines a complementary array of effects that improve blood rheology—potentially beneficial in intermittent claudication, angina and vascular dementia—with anti-inflammatory effects that may oppose atherogenesis, ameliorate heart failure, aid diabetic control, lessen risk for plaque rupture and improve outcomes following vascular events or CPB. Because it works in ways that are entirely distinct from the drugs that are now in common use for cardiovascular protection—most notably statins, aspirin and angiotensin antagonists—it is likely to confer complementary benefit when used in conjunction with these well-established agents.

However, this exciting potential of pentoxifylline can only be realised if, at last, major multicentre trials are conducted to confirm or refute its utility for cardiovascular protection. Aside from its current accepted indication for intermittent claudication, other applications for pentoxifylline are currently supported by data that are too limited to permit definitive conclusions to be drawn. A trial in ACS would be particularly appropriate, as such patients are at high risk for vascular events, and a trial of moderate size and duration might be expected to observe significant benefit for hard end points, if the results of the pilot study in ACS are not a type I statistical error. Success with such a trial might then make it easier to get adequate funding support for larger trials evaluating pentoxifylline in coronary and cerebrovascular disease, heart failure, and diabetes.

Pentoxifylline lacks strong financial sponsorship, owing to the fact that its patent expired long ago. Our appreciation of the scope of pentoxifylline's utility for vascular protection may be constrained by the fact that the clinical trials assessing its various potential indications have been too small in size to reach definitive conclusions. It is instructive that, whereas every controlled trial of this drug in CHF failed to find a statistically significant impact on subsequent mortality, a meta-analysis of these trials found a large and highly significant protective effect in this regard. Larger studies are clearly indicated to evaluate pentoxifylline as an adjunct to current proven therapies.

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