REVIEW

Are the Protean Effects of Pentoxifylline in the Therapy of Diabetes and Its Complications Still Relevant?

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ABSTRACT

Pentoxifylline (Px) has protean effects that can be utilized in the therapy of diabetes and its complications. There have been well-documented but often inconclusive improvements in peripheral arterial disease, foot ulcers, peripheral neuropathy, nephropathy, retinopathy, ischemic heart disease and cerebrovascular disease. In addition, non-alcoholic steatosis and steatohepatitis, which are closely associated with insulin resistance and type 2 diabetes, have been shown to improve with pentoxifylline. Surprisingly, pentoxifylline modestly improves insulin resistance through improvements in capillary blood flow as well as beta cell function and decreased hepatic glucose production. The therapeutic effects of pentoxifylline are complementary to the effects of drugs such as blockers of the renin-angiotensin-aldosterone system when utilized in the therapy of diabetic nephropathy.

Keywords: Pentoxifylline; Diabetic neuropathy; Foot ulcers; Diabetic retinopathy; Diabetic nephropathy; Ischemic heart disease; Heart failure; Cerebrovascular disease; Peripheral vascular disease; Non-alcoholic steatosis and steatohepatitis

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Key Summary Points
Pentoxifylline's effects on diabetic complications are not modulated through improved rheolitic effect; rather it is mediated through its anti-inflammatory, anti-proliferative and anti-fibrotic effects, which occur through activation of the protein kinase system and inhibition of tumor necrosis factor-alpha (TNF-α) and other leukotrienes
Pentoxifylline has the potential to improve microvascular diabetic complications (particularly nephropathy)
Macrovascular complications such as multi-infarct dementia, transient ischemic attacks and heart failure may also benefit from pentoxifylline therapy
Due to improved endogenous insulin release, glycemic control may be improved with pentoxifylline
Insulin resistance is lowered with pentoxifylline as is hepatic steatosis, inflammation and perhaps fibrosis in non-alcoholic steatohepatitis

INTRODUCTION

Pentoxifylline (Px) is a methyl xanthine derivative that through non-specific competitive inhibition of phosphodiesterase raises intracellular cyclic AMP.

As a result, Px has rheotlytic activities which through decreasing erythrocyte rigidity result in decreased erythrocyte rigidity and increasing erythrocyte flexibility. This results in improved microvascular blood flow. Increased erythrocyte flexibility also results in decreased erythrocyte aggregation and Rouleaux formation as well as a decreased viscosity adding to an increase in tissue perfusion. In addition, effects on platelet aggregation and clotting affect the ability to improve tissue oxygenation [1].

Initially, the rheolytic effects of Px were thought to be the only benefit of this molecule. However, later studies showed that Px had anti-inflammatory, anti-proliferation and anti-fibrotic effects largely achieved through activation of protein kinase (PKA$_1$) system, inhibition of tumor necrosis factor alpha (TNFα) and leukotrienes and activity of the adenosine 2 receptor [2, 3].

Therefore, the benefits of Px in the diabetic patient can be due to improved tissue oxygenation, decreases in inflammation, cell proliferation and tissue fibrosis.

PERIPHERAL VASCULAR DISEASE AND INTERMITTENT CLAUDICATION

Px is only approved for the therapy of intermittent claudication [4]. However, an improvement in intermittent claudication is one of the lesser clinical benefits of Px. In fact, a Cochrane Database Systemic Review showed that any improvement in claudication was unproven since walking distance to the onset of claudication pain improved by 33.8% and total achieved walking distances by only 2% [5].

In the diabetic patient with peripheral vascular disease (PVD) [6], the usual site of lower limb arterial narrowing is at the trifurcation of the popliteal artery, an obstruction that is not associated with claudication pain [7]. However, with popliteal and more distant obstructions, foot ischemia as evidenced by delayed capillary filling, cyanosis and decreased foot temperature is present. Improvement in more distal arterial disease with Px is most easily documented by decreased toe pressures. The positive rheological effects of Px in the diabetic patient usually result in improvement in both signs of arterial insufficiency and improved toe pressure [8].

DIABETIC FOOT ULCERS

Foot ulcers in the diabetic patient are due to the combination of distal symmetrical polyneuropathy, infection and vascular insufficiency [9, 10]. Therefore, to achieve healing of foot ulcers, in addition to elimination of weight bearing, debridement and infection control, an improvement in blood flow is required [7]. Improved healing of diabetic foot ulcers has been shown to occur with Px in both type 1 and type 2 diabetes, which may not only be due to the improvement in blood flow but also to Px's anti-inflammatory effect.

In a small study (nine subjects) of diabetic foot ulcers that had not healed despite optimal care over 3 months, the following 3 months of therapy with Px induced complete healing of eight ulcers with one ulcer significantly decreasing in size. In addition, in all ulcers there was an improved blood flow to the ulcers as evidenced by an improvement in closing pressure of 11 mmHg [11]. In a randomized study of 40 subjects who were randomized to conservative therapy alone or conservative therapy plus Px, after 8 weeks healing was significantly greater and the need for "mutilating surgery" decreased in those randomized to Px [12]. Another foot ulcer study of 67 patients randomized to traditional therapy (bed rest with elevation, antibiotics, analgesics and dressings) or to traditional therapy plus Px, after 30 days blood flow at the edge of the ulcer had improved significantly ($p = 0.001$) with Px and non-significantly ($p = 0.21$) with traditional therapy. In addition, ulcer edge biopsies showed significant ($p = 0.05$) improvement, and the

presence of "slough" was also significantly decreased ($p = 0.03$) [13].

Improved blood flow may not be the only reason for the accelerated wound healing in diabetic humans treated with Px, as was shown in a study of streptozotocin-induced diabetic rats. In this study accelerated wound healing with Px occurred because of decreased expression of matrix metalloproteinases (MMPs) and increased TIMP-1 expression, both of which lead to decreases in inflammation [14]. Therefore, we can assume that diabetic foot ulcer healing occurs more rapidly with Px due to a combination of increased microcirculatory blood flow and decreased tissue damage caused by inflammation.

DIABETIC DISTAL SYMMETRICAL POLYNEUROPATHY

While the cause of diabetic neuropathy (DSP) in the type 1 diabetic patient is most likely due to metabolic change, in the type 2 diabetic and the prediabetic patient there is a vascular component [9]. For example, acute neuropathies such as cranial mononeuropathies or diabetic radiculopathy occur because of occlusion of the vasa nervorum, and with resolution of capillary obstruction the symptoms and signs of the acute neuropathies disappear, usually within 3 months [10]. Distal symmetrical polyneuropathy, especially when painful, occurs in the type 2 diabetic patient especially when symptomatic ischemia plays a prominent role. Sural nerve biopsies have shown that epineural arteriovenous shunting and neovascularization occur leading to neuronal ischemia and segmental demyelinization [15, 16]. Therefore, it can be hypothesized that with improved microvascular blood flow the symptoms of DSP should improve.

When Px first became available reports of dramatic improvement in DSP symptoms were reported in both single cases and unrandomized observational studies involving small numbers of subjects [17, 18]. Unfortunately, these results have not been repeated in the majority of randomized, placebo-controlled trials [19–21].

There is however one positive, randomized trial where 60 patients with painful distal symmetrical polyneuropathy, all of whom were receiving vitamin B_1 therapy, were randomized to the addition of placebo or Px. In this study utilizing the Michigan Neuropathy Screening Instrument the symptom score was significantly lowered with Px therapy ($p = 0.042$) [22].

From the above we can assume that in some patients, but not all, symptoms of DSP may respond dramatically to Px but that overall the drug is ineffective or only modestly effective in controlling the symptoms of distal symmetrical polyneuropathy. However, when standard therapies such as tricyclics and anti-epileptics are not effective in controlling neuropathic symptoms, a trial of Px therapy could be considered.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the leading cause of end-stage renal disease in industrialized nations. The presence of albuminuria is recognized as a major prognostic factor for progression to end stage renal disease and signifies early renal damage [23, 24]. While the major factor in the progression of diabetic nephropathy is increased intraglomerular pressure due to hyperglycemia, there is also an inflammatory oxidative stress and fibrotic component largely induced by cytokines, particularly tumor necrosis factor-alfa (TNF-α) [25]. A study of markers of inflammation (hsCRP, fibrinogen and TNF-α) in patients with chronic kidney disease showed that with Px, but not with placebo, these markers were decreased [26]. Px in open-label trials, presumably through its anti-inflammatory effects, has been shown to decrease the decline in renal function, in addition to decreasing albuminuria, especially when Px is utilized in combination with inhibitors of the renin-angiotensin-aldosterone system (RAAS).

A head-to-head study of Px 1200 mg daily versus the ACE inhibitor captopril 25 mg t.i.d. showed that Px was non-inferior to captopril in reducing proteinuria [26]. In a short-term 4-month randomized study of 61 patients with

diabetic nephropathy, who despite RAAS blockade still had residual proteinuria, were randomized for 4 months to the addition of Px or placebo. Over the 4 months with placebo, proteinuria increased by 5.5% while, with the addition of Px proteinuria, it decreased by 16.7% ($p = 0.001$), which was unrelated to glycemic control or to blood pressure lowering [27]. Furthermore, in a double-blind, placebo-controlled, randomized trial, Px at a daily dose of 1200 mg reduced both glomerular and tubular protein levels in type 2 normotensive diabetic subjects with microalbuminuria [28]. Conversely, in a randomized, placebo-controlled study with Px 1200 mg daily administered over 6 months, albuminuria was not reduced [29]. In contrast, a meta-analysis which showed a non-significant decline in proteinuria ($p = 0.1$) in those with microalbuminuria also showed a significant decline in macroalbuminuria (albumin > 300 mg/day) ($p = 0.001$) again without changes in blood pressure or the glomerular filtration rate [30]. In addition, a Cochrane Data Base Report concluded that Px offered beneficial effects in the therapy of kidney disease but on the basis of the available evidence a recommendation could not be made [31].

While the beneficial effect of Px in the reduction of the surrogate marker of macroalbuminuria has been proven with diabetic nephropathy, there is less evidence of an effect on the deceleration of renal function or delay in the onset of end-stage renal disease. An observational study of 609 subjects with stages 3 to 5 chronic kidney disease found that when added to RAAS inhibitors Px resulted in a deceleration in the decline in GFR but only in those whose proteinuria exceeded 1 g daily [32]. The risk of proceeding to dialysis has also been shown to be reduced with Px [33]. However, despite the decreased need for dialysis, mortality did not improve with Px, with or without the concomitant use of RAAS blockers [33]. Another randomized, double-blind study of 40 subjects with proteinuria > 1 g per day and treated with RAAS blockers showed that GFR decline was significantly less with Px (1.2 ± 7 versus 7.2 ± 8.2 ml/min, $p = 0.03$) than with placebo [34].

Therefore, in the presence of macroalbuminuria, and even at an advanced stage of diabetic nephropathy even when therapy with RAAS blockers is maximized, presumably through its anti-inflammatory, anti-oxidant and anti-fibrotic effects, Px decelerates the progression of diabetic nephropathy and should be considered as adjuvant therapy to RAAS blockers not only to decrease proteinuria but also to decelerate the progression to end-stage renal disease and dialysis [35].

DIABETIC RETINOPATHY

Angiogenesis, which occurs in response to retinal ischemia, is an important component of diabetic retinopathy. It is mediated by stimulation of adenosine receptors, which results in the release of angiogenic factors such as vascular endothelial growth factor. In animal studies Px downregulates the adenosine receptors and decreases angiogenic factors induced by hypoxia [36].

Retinal hypoxia occurs because of capillary occlusion; disaggregation caused by Px should decrease the severity and frequency of capillary occlusion, decrease hypoxia, decrease angiogenesis and therefore decelerate proliferative retinopathy and protect against visual loss [37]. Px is clearly under-investigated in the prevention and therapy of diabetic retinopathy. However, in a small number of human studies, Px has been shown to significantly improve retinal capillary blood flow velocity ($p = 0.02$) [38].

The most impressive study of Px's effect on retinal blood flow was in 56 children with type 1 diabetes who were randomized to either placebo or Px and in whom measures of retinal hemodynamics showed a significant improvement in retinal blood flow velocity with Px [39]. In addition, ten type 1 diabetic patients, four of whom had proliferative diabetic retinopathy, were compared to six non-diabetic control subjects for choroidal blood flow. After 9 months of Px therapy there was an increase in choroidal blood flow in the diabetic subjects to the extent that the previously significant difference in choroidal blood flow between the

non-diabetic control group and those with diabetic proliferative retinopathy was negated [40].

However, while surrogate measures have been shown to improve with Px, clinical measures of diabetic retinopathy have been negative. Indeed, a Cochrane Database Systemic Review concluded that the use of Px in diabetic retinopathy, through a lack of sound research, had not been shown to have a significant impact on the natural history of the condition [41].

Therefore, we can conclude that while surrogate measures of retinal blood flow improve in diabetic subjects with Px, there is no clinical evidence that Px is helpful in the therapy or prevention of diabetic retinopathy (Table 1).

CEREBROVASCULAR DISEASE

In a randomized trial preformed over 6 months, patients who had previously had a transient ischemic attack (TIA) were randomized to either aspirin/dipyridamole or Px. Of the 73 patients randomized to aspirin/dipyridamole therapy 80 TIAs occurred whereas in the 65 patients randomized to Px there were only 19 TIAs ($p = 0.05$). Furthermore, four strokes occurred in the aspirin/dipyridamole group compared with two in the Px group [42]. A subsequent larger randomized study over 6 months showed that recurrent TIAs occurred in 9% with Px and 20% with aspirin/dipyridamole, and the composite of TIA, strokes and death occurred in 14% on Px and 24.1% with aspirin/dipyridamole [43].

In the therapy of an acute stroke, Px has been used intravenously for up to 5 days followed by chronic oral Px. A meta-analysis of 763 subjects in four small studies that utilized this protocol showed a non-significant but impressive reduction in mortality (HR 0.65 95% CI 0.41 ± 1.04) of 35% [44].

Several randomized, placebo-controlled studies have also shown an improvement in cognitive function when Px was utilized in the therapy of vascular (multi-infarct) dementia. All studies showed a trend toward improved cognitive function but in three of the studies, which utilized a stricter definition of vascular dementia, there were significant differences between placebo and the Px treatment groups [45].

Reperfused cerebral tissue in most cases does not fully recover following ischemic injury, and Px has been shown to decrease this "ischemia-reperfusion damage," probably because of improved microvascular blood flow [46, 47].

Therefore, there is marginal evidence that Px may decrease the incidence of TIAs and multi-infarct dementia and that following a stroke therapy with Px may possibly decrease mortality. Thus, in the diabetic patient who has had a cerebrovascular event or has proven multi-infarct dementia Px therapy should be considered as a therapy or part of a regimen to improve outcomes.

Table 1 Efficacy of pentoxifylline on diabetic cardiovascular complications

Complication	Efficacy (0–3+)
Intermittent claudication	+
Microvascular peripheral blood flow	+
Transient ischemic attacks (TIAs)	+
Multi-infarct dementia	+
Stroke	±
Ischemic heart disease	±
Heart failure	+

CARDIOVASCULAR DISEASE

Through its anti-inflammatory effects, Px may well be anti-atherogenic. Rabbits fed a high cholesterol diet were found to decrease aortic plaque area by 38% with Px [48]. In humans a study measuring carotid intima-media thickness in adolescent type 1 diabetic subjects showed a significant deceleration in the progression of intima-media thickness ($p = 0.001$) when randomized to Px compared with placebo [49]. Therefore, by these surrogate measures Px seems to be anti-atherogenic but unfortunately this has not been shown to translate into a decrease in cardiovascular event.

In acute coronary syndrome a placebo-controlled, randomized trial has shown benefit with Px. This 6-month study enrolled patients with acute coronary syndrome and prospectively assessed the composite end point of death, non-fatal myocardial infarction and hospitalization for recurrence of acute coronary syndrome. After 6 months 34% of the placebo group had had an event whereas with Px an event occurred only in 13%, which was statistically significant ($p = 0.04$). That this outcome was likely due to Px's anti-inflammatory effect and not its rheolitic effect was suggested by the significant reductions in TNF-α ($p = 0.01$) and C-reactive protein ($p = 0.04$) that occurred [50].

Six small outcome studies of the use of Px in heart failure with a total enrollment of 221 patients individually showed a trend toward a lower mortality with Px only in patients with a low ejection fraction. However, a meta-analysis of these studies showed that over a 6-month period a major decrease (5.4% versus 18.3% (OR 0.29 95% CI 0.12–0.74, $p = 0.01$) occurred in mortality with Px [51].

Therefore, based on the sparse data that are available, Px has the potential to lower the atherosclerosis load and cardiovascular and cerebrovascular events as well as death from heart failure. Therefore, Px therapy in addition to other proven therapies for these conditions should be considered in the diabetic patient. However, clearly there is a need for further clinical studies to investigate the cardiovascular benefits of Px [52].

NON-ALCOHOLIC FATTY LIVER DISEASE AND NON-ALCOHOLIC STEATOHEPATITIS

Around 70% of obese patients with type 2 diabetes have non-alcoholic fatty liver disease (NAFLD) and as many as 40% have non-alcoholic steatohepatitis (NASH) [53]. Of those type 2 diabetic patients with NASH the prevalence of fibrosis is high, ranging from 17 to 55%. Liver fibrosis is the single best predictor of cirrhosis, and NASH is currently the second most common reason for liver transplant as well as the most common cause of hepatocellular carcinoma [54–56]. Therefore, any drug that will suppress the development of hepatic necrosis and/or fibrosis has a considerable prognostic value for the patient with fatty liver disease (Table 2).

Therapy for the prevention and therapy of NASH is weight loss, diet and exercise. Proven pharmacological therapies are pioglitazone and vitamin E, which clearly have an effect on hepatic inflammation but not on hepatic fibrosis [57]. Therefore, a drug that would complement the effect of other medications on hepatic inflammation and particularly decreases hepatic fibrosis has great potential in the therapy of NASH.

Px has been shown to improve steatosis, hepatocyte ballooning and reduce hepatic liver fat oxidation [58]. In a small, randomized, placebo-controlled study Px significantly lowered inflammation as evidenced by ALT and AST levels ($p = 0.05$) without any change in fibrosis [59]. However, in another placebo-controlled study a non-significant reduction in fibrosis (35% versus 15%) occurred as well as a significant decline in the fibrosis score ($p = 0.038$) [60]. A later study confirmed that Px improved steatosis (2.30 ± 0.68–0.95 ± 0.76, $p = 0.0001$) and inflammation (1.50 ± 0.51–1.30 ± 0.57, $p = 0.258$) but did not show any improvement in fibrosis over 1 year [60].

Since Px has been shown to be as efficacious as pioglitazone at the 30 mg dose, a combination of Px with pioglitazone and/or vitamin E could be a powerful combination in the therapy of NAFLD and NASH [61].

Table 2 Efficacy of pentoxifylline on diabetic microvascular complications

Complication	Efficacy
Distal symmetrical polyneuropathy	$\pm$
Foot ulcer healing	++
Diabetic nephropathy	+++
Diabetic retinopathy	$\pm$

Table 3 Metabolic efficacy of pentoxifylline in the diabetic patient

Diabetic factor	Efficacy (neg to 3+)
NAFLD/NASH (non-alcoholic fatty liver disease and steatohepatitis)	+++
Insulin resistance	±
Hepatic glucose production	+
Beta cell function	++
Glycemic control	+

METABOLIC SYNDROME

Px improves insulin resistance through its rheolitic effect, which increases the surface area for absorption of glucose and/or through its TNF-α activity, which lowers inflammation, by improved blood flow [62].

However, the improvement in glycemic control may not be only due to decreasing insulin resistance but also to improved pancreatic beta cell function. Like sulfonylureas, Px blocks the ATP-sensitive K+ channels, which increases insulin release [63]. Furthermore, in animal studies, Px has been shown to decrease cytokine levels within the beta cell resulting in improved insulin production [64].

In addition to the increased pancreatic beta cell production of insulin, which will result in decreased hepatic glucose production, Px has also been shown to independently decrease hepatic glucose production [65].

In human studies utilizing an artificial pancreas Px has been shown to decrease both glycemia and insulin needs and in the process improve fluctuations in glucose levels [66]. In a placebo-controlled randomized prospective study performed primarily to study diabetic nephropathy Px decreased fasting glucose by 18 mg/dl ($p = 0.009$) and HbA1c by 0.43% ($p = 0.002$) with a barely significant decrease in HOMA-IR ($p = 0.04$). Neither hs-CRP nor TNF-α in this study was significantly reduced ($p = 0.8$ and 0.3, respectively) [67].

From the above we can conclude that Px significantly improves glycemic control through increased insulin production rather than the lowering of insulin resistance. While the improvement in glycemic control is both statistically and clinically significant, it does not warrant the use of Px as an oral anti-diabetic agent. However, when utilized in the therapy of the complications of diabetes Px does provide added benefit by improving glycemic control (Table 3).

CONCLUSION

As outlined above, the current knowledge of the effects of Px is obviously limited and more research is needed. Px appears to have the potential to improve most diabetic complications. In particular, in the presence of macroalbuminuria, lowering of urinary protein and deceleration of the decline in renal function occur, and these effects are complementary to the effects of blockers of the RAAS. Improvement at least in the symptoms of diabetic neuropathy may occur in some individuals, and accelerated healing of diabetic foot ulcers has been well documented. Surprisingly, any evidence of improvement in diabetic retinopathy is sadly lacking. There is good but scanty evidence of improvement in macrovascular (coronary artery, cerebrovascular and peripheral vascular disease) as well as an improvement in mortality in those with heart failure. The co-morbidity of NAFLD and NASH, which occurs in 70% of type 2 diabetic subjects, has also been shown to improve with Px through lowering of inflammation without a reduction of fibrosis. In addition, pancreatic beta cell production may be improved.

Unfortunately, due to the choice of intermittent claudication, which has never been documented in diabetic subjects, as the end point used for the approval of Px, studies on other diseases were not performed before approval of Px or before the patent for Px expired. By the time efficacy of Px in other disease states was recognized, the funding for further research had evaporated. Therefore, funding for studies of Px in the therapy of diabetic complications need to be obtained and studies performed to document the effect of Px on diabetic complications through randomized, placebo-controlled, blinded trials.

ACKNOWLEDGEMENTS

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