The Renoprotective Potential of Pentoxifylline in Chronic Kidney Disease

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Current interventions with proven efficacy, such as glycemic and blood pressure control, dietary protein restriction, and angiotensin II blockade, slow the progression of chronic kidney disease (CKD); however, whether long-term cessation of CKD progression is possible remains unclear. Because of the pathogenetic complexity of this condition, multidrug interventions with the least adverse effects should be investigated as the next step in attempts to stop CKD progression. Pentoxifylline, a non-selective phosphodiesterase inhibitor with indiscernible toxicity, exerts potent inhibitory effects against cell proliferation, inflammation, and extracellular matrix accumulation, all of which play important roles in CKD progression. Pentoxifylline monotherapy markedly reduces proteinuria in patients with membranous nephropathy. Moreover, limited human studies have proven pentoxifylline efficacy in reducing proteinuria in patients with diabetes receiving angiotensin-converting enzyme inhibitors, and in patients with nephrotic syndrome secondary to lupus nephritis despite immunosuppressive therapy. Further clinical trials are necessary to examine whether pentoxifylline can improve renal outcomes in patients receiving interventions of proven efficacy. [*J Chin Med Assoc* 2005;68(3):99–105]

Key Words: angiotensin II, chronic kidney disease, pentoxifylline

Introduction

Pentoxifylline is a methylxanthine that improves perfusion in the impaired microcirculation of peripheral and cerebral vascular beds.[1] This hemorheologic activity mostly involves inhibition of cyclic-3',5'-phosphodiesterase (PDE), leading to raised intracellular cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). The superfamily of PDE isozymes consists of at least 11 gene families: PDE 1 to PDE 11.[2,3] The recent development of selective PDE isozyme inhibitors has advanced the identification of the specific role of PDE isozymes in several pathobiologic processes. Pentoxifylline inhibits PDE 1–5 with IC_{50} values ranging from 50–200 μM, thereby classifying it as a non-selective PDE inhibitor.[4,5] Notably, pentoxifylline is a safe drug that is usually well tolerated when administered as the conventional controlled-release formulation: gastrointestinal symptoms (i.e. nausea and dyspepsia) and dizziness are the most common

complaints and affect about 3% of patients.[1] Besides its hemorheologic activity, growing evidence has demonstrated that pentoxifylline has broad-spectrum effects to slow the progression of chronic kidney disease (CKD).[6–18] Although accumulation of the active metabolite of pentoxifylline has been documented in moderate and severe renal dysfunction during multi-dose pharmacokinetic studies, the clinical significance of this is unclear. Dosage reductions to 400 mg twice daily in patients with moderate renal dysfunction, and to 400 mg once daily in patients with severe renal dysfunction, are recommended.[19] This article reviews the rationale and evidence for the renoprotective effect of pentoxifylline, and raises some unanswered questions.

Rationale and Evidence for the Renoprotective Activity of Pentoxifylline

Whatever the initial injury to the kidney, the remaining

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nephrons undergo adaptive hypertrophy and hyper-filtration to minimize the functional consequences of progressive nephron loss.[20] However, such adaptation ultimately leads to a vicious cycle, in which hypertrophy and hyperfiltration of the remaining nephrons lead to glomerulosclerosis and glomerular barrier impairment, which in turn induce tubulointerstitial damage and the loss of more nephrons.[21,22] The adaptive hypertrophy and hyperfiltration of glomeruli result from increased expression of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF), and fibroblast growth factor-2 (FGF-2), and from activation of the renin-angiotensin-aldosterone system (RAAS).[20,23–26] Furthermore, after stimulation by pro-inflammatory cytokines, angiotensin II and urinary protein, various chemokines, such as monocyte chemo-attractant protein-1 (MCP-1), regulated on activation, normal T cell expressed and secreted (RANTES), and fractalkine, are secreted; these chemokines subsequently recruit inflammatory cells into the glomeruli and interstitium.[21,22,27–30] Thus, cell proliferation and inflammation result in further expression of growth factors, cytokines, and chemokines, leading to more and more inflammation, extracellular matrix (ECM) accumulation and, ultimately, renal fibrosis.

Examination of extracts from nephron segments and cultured renal cells has shown diverse expression of PDE isozymes.[2] Evidence shows that the PDE 3-linked cAMP-PKA pathway suppresses mitogenesis, whereas the PDE 4-linked pathway selectively modulates the generation of reactive oxygen species (ROS) in rat mesangial cells, which are considered to play a central role in the development of glomerulo-sclerosis.[31] Upon activation of the adjacent cAMP-PKA by selective inhibition of PDE 3, Raf-1 is phos-phorylated and 14-3-3 proteins bind, blocking Raf-1 recruitment to the plasma membrane and preventing its activation and downstream mitogenic signal.[31,32]

Conversely, inhibition of PDE 4 leads to an increase of another cAMP pool and activates adjacent PKA, which subsequently decreases nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase assembly and ROS generation via phosphorylating Rap-1a.[33] Inhibitors of PDE 3 and 4 have a suppressive effect in acute phases or relapses of experimental mesangial proliferative glomerulonephritis.[34] Besides a suppressive effect on cell proliferation and ROS generation in glomerulonephritis, PDE 4 inhibitors decrease *de novo* synthesis and tissue accumulation of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interferon-γ (IFN-γ), which all play

important roles in CKD progression.[35,36] Furthermore, inhibitors of PDE 3 and 4 inhibit fibroblast activation and fibrosis progression.[37,38] Therefore, various PDE inhibitors, alone or in combination, can target different pathogenetic mechanisms, including cell proliferation and inflammation, and ECM accumulation, and represent a novel "signal-transduction pharmaco-therapy" for CKD.

Laboratory evidence

As a non-selective PDE inhibitor, pentoxifylline has demonstrated potent inhibitory effects on cell pro-liferation, inflammation, and ECM accumulation. Pentoxifylline can suppress activation and prolifera-tion of mesangial cells, lymphocytes, and renal fibro-blasts, all of which play important roles in renal fibrosis.[9,12,15,16,39–41] Furthermore, pentoxifylline can downregulate the expression of various cytokines, including PDGF, FGF-2, TGF-β1, and CTGF, all of which are important growth factors for cell proliferation and ECM synthesis in glomerular mesangial cells and interstitial fibroblasts.[12,15,41] With indiscernible cytotoxicity, pentoxifylline potently inhibits mesangial cell proliferation by blocking multiple PDGF post-receptor signaling pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidyl-inositol 3-kinase/Akt (PI3K/Akt) pathways.[16] Although there is evidence that pentoxifylline can inhibit cell proliferation independent of PDE inhibi-tion,[42] we have demonstrated that pentoxifylline interferes with PDGF signaling to mesangial cell proliferation through PKA activation, a mechanism similar to that employed in vascular smooth muscle cells.[16,43]

In rats, we have demonstrated that pentoxifylline reduces the accumulation and proliferation of glomerular macrophages in mesangial proliferative glomerulonephritis, and the recruitment of macro-phages, lymphocytes, and major histocompatibility complex (MHC) class II antigen-positive cells into remnant kidney interstitium.[12,15] We further demon-strated that pentoxifylline suppresses the increased expression of TNF-α, intercellular adhesion molecule-1, MCP-1, RANTES, and osteopontin.[12,15,18] These anti-inflammatory actions are associated with such renoprotective effects as reduction of proteinuria and azotemia, and attenuation of glomerular crescents, sclerosis and interstitial fibrosis.[12,15,18] Besides its growth-inhibitory effect on lymphocytes themselves,[40] pentoxifylline potently downregulates MHC class II antigen expression, and inhibits peripheral mono-nuclear cell secretion of pro-inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, IFN-

γ, and MCP-1.[14,44–46]

In the local environment of the tubulointerstitium, urinary protein, angiotensin II and TNF-α stimulate proximal tubular epithelial cells to secrete chemokines, MCP-1, RANTES, and fractalkine, which are all important to the recruitment of inflammatory mononuclear cells into the interstitium.[15,28,47,48] Indeed, we have demonstrated that pentoxifylline reduces upregulation of MCP-1 in albumin-stimulated or angiotensin II-stimulated proximal tubular epithelial cells, a mechanism that is partly responsible for the attenuation of MCP-1 expression and interstitial inflammation.[15] Pentoxifylline and its metabolites are also reported to inhibit nuclear factor-κB (NF-κB) activation through PDE inhibition-dependent and -independent mechanisms.[29,46,49,50] In addition, we demonstrated that the TNF-α-induced activating protein-1 (AP-1) signal is the target by which pentoxifylline inhibits MCP-1 and fractalkine production.[29,50] Therefore, pentoxifylline is a potent anti-inflammatory agent capable of ameliorating kidney inflammation by acting on various targets, including the synthesis of pro-inflammatory cytokines and chemokines, and the growth and activation of inflammatory mononuclear cells.

Besides its growth-inhibitory effect on cultured mesangial cells and renal fibroblasts, pentoxifylline downregulates ECM gene expression and the synthesis of protein, including types I and III collagen and fibronectin, in these cells.[9,15,41] This downregulatory effect on ECM genes was accompanied by amelioration of glomerulosclerosis and interstitial fibrosis, as demonstrated in the kidneys of animals with experimental mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, and remnant kidney.[12,15,18]

Pentoxifylline also reduces overexpression of TGF-β1 and CTGF in the remnant kidney, but it has no direct inhibitory effect on angiotensin II-induction of TGF-β1 expression in both mesangial cells and fibroblasts.[15] We therefore suggest that TGF-β1 downregulation by pentoxifylline in the remnant kidney is due to reduced numbers of cells secreting this growth factor, including infiltrating inflammatory cells, glomerular mesangial cells, and interstitial fibroblasts. Indeed, we have demonstrated that pentoxifylline reduces angiotensin II-induced or TGF-β1-induced expression of CTGF in cultured mesangial cells and fibroblasts, and have suggested this as a possible mechanism for pentoxifylline effect on downregulation of CTGF expression and attenuation of fibrosis in remnant kidney.[15] Because TGF-β1 also plays important anti-inflammatory and anti-proliferative roles in mammalian systems, blockage of its downstream pro-fibrogenic mediators should be a better strategy for ameliorating renal fibrosis. CTGF plays a crucial role in ECM synthesis and epithelial-mesenchymal transdifferentiation of tubular epithelial cells induced by TGF-β1, suggesting that blockade of CTGF could be a selective therapeutic target against renal fibrosis. Therefore, pentoxifylline is not only an effective, but also a selective, drug to prevent renal fibrosis.

These beneficial effects of pentoxifylline on different cell types and animal models are summarized in Tables 1 and 2. In addition, Figure 1 outlines the possible renoprotective mechanisms of pentoxifylline in the treatment of CKD.

Clinical evidence

It is well known that pentoxifylline can reduce proteinuria in diabetic patients,[6–8,11] in part because of its hemorheologic action, but also because of its anti-TNF-α effect. In a recent study of early type 2 diabetic nephropathy, in patients receiving treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) when pentoxifylline was added, pentoxifylline further reduced urinary protein and N-acetyl-β-glucosaminidase excretion.[17] These findings provide clinical evidence that pentoxifylline, combined with RAAS blockade, may further

Table 1. The renoprotective potential of pentoxifylline in cellular models

Cell types	Inhibitory effects of pentoxifylline	References
Glomerular mesangial cells	Cell proliferation; ECM gene expression and protein synthesis; CTGF gene expression; cyclin D1	9,16
Renal interstitial fibroblasts	Cell proliferation; ECM gene expression and protein synthesis; CTGF gene expression; FGF-2 gene expression	15,41
Renal proximal tubular epithelial cells	MCP-1 gene expression	15
Macrophages/lymphocytes	Cell proliferation; MHC class II antigen expression; production of TNF-α, IL-1β, IL-6, IFN-γ, MCP-1	12,15,39,40

CTGF = connective tissue growth factor; ECM = extracellular matrix; FGF-2 = fibroblast growth factor-2; IFN-γ = interferon-γ; IL-1β = interleukin-1β; IL-6 = interleukin-6; MCP-1 = monocyte chemoattractant protein-1; MHC = major histocompatibility complex; TNF-α = tumor necrosis factor-α.

Table 2. The renoprotective effects of pentoxifylline in animal models

Animal models	Beneficial effects of pentoxifylline	References
Anti-thy1 GN of rats	Improves proteinuria and glomerulosclerosis; reduces the numbers of proliferating glomerular mesangial cells and macrophages; downregulates gene expression of glomerular MCP-1, ICAM-1, and ECM; reduces cyclin D1 expression of glomerular mesangial cells	12,16
Remnant nephropathy of rats	Attenuates proteinuria, azotemia, glomerulosclerosis, interstitial inflammation and fibrosis; reduces glomerular cellularity and the number of interstitial myofibroblasts; downregulates gene expression of cortical MCP-1, PDGF, FGF-2, TGF-β1, CTGF, and collagen	15
Crescentic GN of rats	Attenuates proteinuria and glomerular crescent formation; downregulates gene expression of cortical TNF-α, ICAM-1, RANTES, MCP-1, OPN, and ECM	18
SLE mice	Attenuates proteinuria and renal immune complex deposition; reduces the production of TNF-α and IL-1	14

CTGF = connective tissue growth factor; ECM = extracellular matrix; FGF-2 = fibroblast growth factor-2; GN = glomerulonephritis; ICAM-1 = intercellular adhesion molecule-1; IL-1 = interleukin-1; MCP-1 = monocyte chemoattractant protein-1; OPN = osteopontin; PDGF = platelet-derived growth factor; RANTES = regulated on activation, normal T cell expressed and secreted; SLE = systemic lupus erythematosus; TGF-β1 = transforming growth factor-β1; TNF-α = tumor necrosis factor-α.
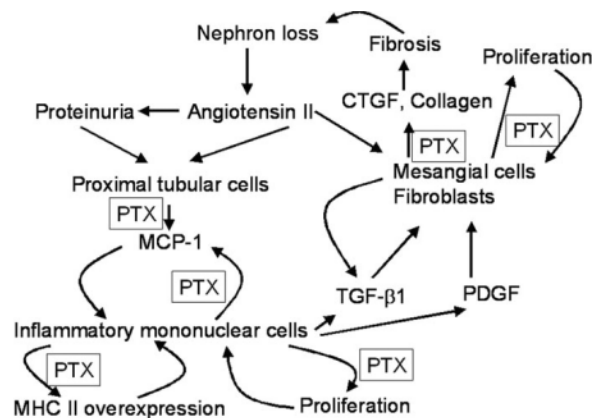

Figure 1. The renoprotective mechanisms of pentoxifylline in the treatment of chronic kidney disease. → indicates stimulation, secretion, or expression; PTX indicates that the pathway is inhibited by pentoxifylline. CTGF = connective tissue growth factor; MCP-1 = monocyte chemoattractant protein-1; MHC = major histocompatibility complex; PDGF = platelet-derived growth factor; TGF-β1 = transforming growth factor-β1.

protect the kidney.

Besides its beneficial effect against diabetic nephropathy, pentoxifylline also has anti-proteinuric activity in patients with refractory nephrotic syndrome due to membranous nephropathy or lupus nephritis:[13,51] remission of proteinuria was achieved and serum and urinary TNF-α levels were decreased. We also found that pentoxifylline significantly reduced urinary protein and TNF-α excretion in non-diabetic patients with non-nephrotic glomerular proteinuria (manuscript in preparation). Therefore, pentoxifylline has therapeutic potential in preventing the progression of most kidney diseases (Table 3).

The Next Treatments for CKD

Four principal interventions, including intensive glycemic control in diabetic patients, stringent blood pressure control, restriction of dietary protein intake,

Table 3. Clinical evidence for the renoprotective effects of pentoxifylline

Renal diseases	Beneficial effects of pentoxifylline	References
Diabetic nephropathy	Reduces proteinuria; reduces urinary N-acetyl-β-glucosaminidase excretion; improves glomerular filtration rate; reduces serum and urinary TNF-α	6–8,11,17
Membranous nephropathy	Reduces proteinuria; reduces plasma and urinary TNF-α	13
Lupus nephritis	Reduces proteinuria	51
Chronic glomerulonephritis	Reduces proteinuria; reduces urinary TNF-α	Manuscript in preparation

TNF-α = tumor necrosis factor-α.

and angiotensin II blockade, slow the progression of CKD.[52–60] Physicians can apply these interventions to actively prevent CKD progression in most cases. However, the ultimate intervention to prevent CKD progression in the long term remains unclear. Because of the pathogenetic complexity of CKD, multidrug interventions with the least adverse effects should be the next step towards potentially halting CKD progression.[15,61–67] Experimental and limited human studies have demonstrated the potential of added pentoxifylline to further improve existing CKD therapy (i.e. when used together with currently available interventions). However, recent trials of ARBs in patients with type 2 diabetic nephropathy required more than 1,500 participants to achieve a statistically meaningful result after about 3 years.[59,60] The efficacy of pentoxifylline may be hard to prove in large-scale clinical trials, against a background of ACE inhibitor or ARB therapy, and using conventional renal-progression endpoints such as death, end-stage renal disease, or halving of glomerular filtration rate. Therefore, before proteinuria or any other surrogate marker is proved to be a solid index of effective therapy, further studies should be performed to translate present evidence into established practice.

Because of high event rates, relatively few patients with a high risk of CKD progression need to be entered into clinical trials. Thus, we are conducting a clinical trial to determine whether pentoxifylline can prevent one of the conventional renal endpoints from being reached in high-risk individuals receiving background RAAS-blocking therapy. Results from this study will answer the question of whether pentoxifylline further improves renal outcomes in CKD patients already receiving interventions of proven efficacy.

In conclusion, the renoprotective potential of pentoxifylline has been uncovered in CKD patients. Further clinical trials are necessary to examine whether pentoxifylline can improve renal outcomes in patients already receiving interventions of proven efficacy. We believe that combining pentoxifylline with currently available interventions will be the next approach towards potentially halting the progression of CKD.

Acknowledgments

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