

## Pentoxifylline (PTF) and Kidney

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**Abstract:** Pentoxifylline (PTF), a phosphodiesterase inhibitor, activates cAMP-dependent protein kinase A and inhibits proliferation of macrophages and interstitial fibroblasts, extracellular matrix synthesis, and myofibroblast differentiation in the kidney. Pentoxifylline is a xanthine derivative that inhibits some inflammatory mediators and reduces interstitial renal fibrosis after partial ureteral obstruction in rats. PTF improves blood flow and reduce aching, cramping, and tiredness in the hands and feet, and it controls the symptoms of circulation problems, but it does not cure the diseases. PTF treatment ameliorates renal fibrosis and helps preserve filtration function of the kidney.

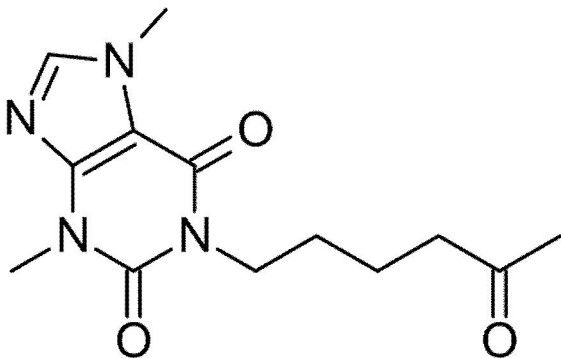
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**Keywords:** kidney; pentoxifylline (PTF); partial ureteral obstruction (PUO); interstitial fibroblast; phosphodiesterase inhibitor

### Introduction

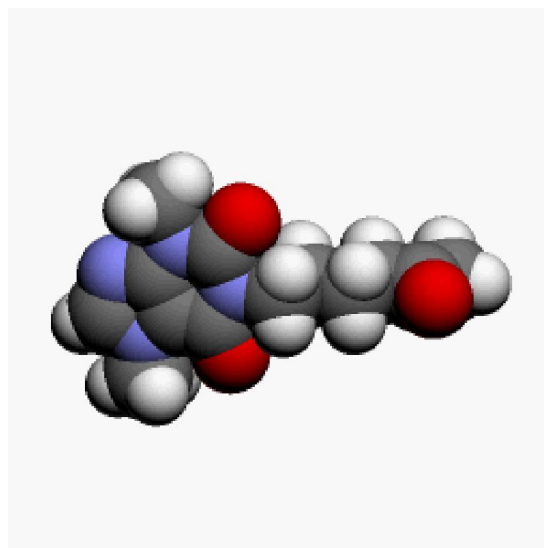
As the xanthine derivative, pentoxifylline (PTF) is a drug commonly sold by Sanofi under the brand name Trental. Its chemical name is 1-(5-oxohexyl)-3, 7-dimethylxanthine. Other brand names of PTF are Pentox, Pentoxil and Flexital, etc. Its primary use in medicine is in treating the symptoms of intermittent claudication resulting from peripheral artery disease. Pentoxifylline is also called oxpentifylline.

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base found in most human body tissues and fluids and in other organisms. A number of stimulants are derived from xanthine, including caffeine and theobromine. The PTF structure is shown in Figure 1 and Figure 2 (Wikipedia, 2014).



<http://upload.wikimedia.org/wikipedia/commons/5/52/Pentoxifylline2DACS.svg>

Figure 1. Chemical structure of pentoxifylline (PTF)



<http://en.wikipedia.org/wiki/File:Pentoxifylline3Dan2.gif>

Figure 2. Three demention structure of pentoxifylline (PTF)

Pentoxifylline is a xanthine derivative that inhibits some inflammatory mediators and reduces interstitial renal fibrosis after partial ureteral obstruction (PUO) in rats (Shirazi, et al, 2011). Acting as a phosphodiesterase inhibitor, PTF is used clinically to treat patients with peripheral arterial disease and claudication by improving blood rheology (Ward and Clissold, 1987). PTF inhibits the connective tissue growth factor (CTGF) and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) expression in normal rat kidney proximal tubular epithelial cells, and the proliferation of fibroblasts (Lin, et al, 2005). To the patients of diabetic or membranous nephropathy, PTF treatment

decreases proteinuria (Ducloux et al., 2001; Navarro et al., 2005) and renal fibrosis (Bohle et al., 1994; Bohle A. Strutz F; Chen et al.; Chen et al., 2004; Hewitson et al., 2000). Furthermore, PTF attenuated tubulointerstitial fibrosis, myofibroblast accumulation, and expression of CTGF in complete unilateral ureteral obstruction kidneys (Lin et al., 2005). PTF's ability to prevent acute renal failure may be a consequence of reduced vascular congestion and inhibition of nitric oxide release from activated macrophages (Vadiei et al., 1996).

Stem Cell is the original of life. All cells come from stem cells. Embryonic stem cells are derived from the inner cell mass of blastocyst stage embryos. Somatic stem cells differentiate into only the cells the specific tissue wherein they reside (Ma et al, 2014). PTF inhibits stem cell growth somehow and may have a role in treating peritoneal fibrosing syndrome.

Pentoxifylline improves blood flow and reduce aching, cramping, and tiredness in the hands and feet. It decreases the thickness (viscosity) of blood which allows the blood to flow more easily, especially in the small blood vessels of the hands and feet. Pentoxifylline is also used for leg ulcers, strokes, high-altitude sickness, eye and ear disorders, and sickle cell disease and to treat pain from diabetic neuropathy.

Pentoxifylline controls the symptoms of circulation problems, but it does not cure the diseases. Patients can continuously take the pentoxifylline even if they feel well.

As it was described by Doherty, et al in 1991: tumor necrosis factor- $\alpha$  (TNF) is secreted by macrophages in response to endotoxin and mediates some of the toxicity of endotoxin. Pentoxifylline decreases lung injury after intravenous endotoxin. Doherty's study investigated the effects of pentoxifylline on endotoxin-stimulated TNF production in vitro and in vivo. In Doherty's study, pentoxifylline concentrations of 100 and 1000 micrograms/ml inhibited TNF production by murine adherent peritoneal exudate cells incubated with endotoxin 1 microgram/ml, and pentoxifylline at 100 and 1000 micrograms/ml decreased the number of available TNF messenger RNA transcripts in peritoneal exudate cells assessed by Northern blot. Pentoxifylline had no effect on TNF mRNA stability, but appeared to act by inhibiting the rate of TNF mRNA production (transcription). In murine in vivo experiments at each dose of endotoxin administered from 0.01 to 30 mg/kg, pentoxifylline treatment significantly reduced serum TNF levels, suggesting a favorable shift of the endotoxin dose-response curve. Expression of murine TNF gene in the livers of these animals showed fewer TNF transcripts in the

pentoxifylline-treated animals compared to controls. Pentoxifylline inhibited endotoxin-induced TNF production both in vivo and in vitro and exerted this control by inhibiting endotoxin-induced transcription of the TNF gene. It suggested that pentoxifylline may ameliorate endotoxic shock by decreasing macrophage TNF production. (Doherty, et al, 1991).

Pentoxifylline is an orally active haemorheological drug for the treatment of peripheral vascular disease, cerebrovascular disease and some diseases involving a defective regional microcirculation. Pentoxifylline increases red blood cell deformability by reducing blood viscosity and decreasing platelet aggregation and thrombus formation. Pentoxifylline 600 to 1200 mg/day for 6 weeks improves in 60 to 100% of patients with peripheral vascular disease. And, PTF improves lower limb rest pain, paraesthesia, muscle blood flow, cramps and leg ulcers. Pentoxifylline has better treatment results than nyldrin, adenosine and naftidrofuryl, etc. At a dosage of 600 to 1200 mg/day PTF has an overall clinical improvement in about 85% of patients. Pentoxifylline appears to be useful in most types of cerebrovascular disease including transient ischemic attacks, sequelae of cerebral thrombosis and haemorrhage, and chronic ischaemic disorders. In patients with chronic cerebrovascular disease pentoxifylline 600 to 1200 mg/day conferred significant clinical benefit compared with placebo proved to be superior to drugs such as co-dergocrine mesylate, adenosine and pyridoxine.

Pentoxifylline also proves useful in vaso-occlusive crises of sickle cell disease, hearing disorders, disorders of eye circulation, high altitude sickness and asthenozoospermia. Pentoxifylline is tolerated when administered as the conventional controlled release formulation and gastrointestinal symptoms (about 3%). Pentoxifylline offers a well-tolerated and effective alternative to the treatment options available for patients with peripheral vascular disease. The primary pharmacodynamic effects of pentoxifylline are due to increased red blood cell deformability and to decreased blood viscosity. PTF increases erythrocyte ATP and other cyclic nucleotide levels and reduce whole blood viscosity and plasma viscosity by decreasing plasma fibrinogen concentrations. Pentoxifylline inhibits platelet aggregation and thrombosis via inhibition of membrane-bound phosphodiesterase and thromboxane synthesis, and increased prostacyclin (prostaglandin  $I_2$ ) synthesis. Pentoxifylline increases cerebral oxygen consumption and glucose utilisation, increased cerebral cyclic nucleotide levels and decreased oedema formation.

Pentoxifylline is rapidly absorbed from the gastrointestinal tract both in animals and in humans. It

is also rapidly metabolized systemically, with peak plasma concentrations of pentoxifylline (about 1100 µg/L) and one of its major metabolites (about 2000 µg/L) being reached at 1.05 and 1.8 hours, respectively, after administration of a 400mg capsule dose. Following administration of a 400mg sustained release dose (the commercially available dosage form), peak plasma concentrations of pentoxifylline and metabolite of about 300 and 343 µg/L were reached at 3.3 and 3.2 hours, respectively. Absolute bioavailability has been calculated as about 30 and 20% for the capsules and sustained release tablet formulations, respectively. Pentoxifylline usually at a dosage of 600 to 1200 mg/day for at least 6 weeks is effective in improving symptoms of peripheral vascular disease in 60 to 100% of patients. Pentoxifylline 1200 mg/day has produced significantly better results than nylidrin 9 mg/day and adenosine 7.2 mg/day, while a lower dose of 300 to 600 mg/day was as effective as pyridinolcarbamate 1500 mg/day and was superior to naftidrofuryl. Patients treated with pentoxifylline 1200 mg/day or dipyridamole 150 mg/day plus acetylsalicylic acid 1050 mg/day after vascular surgery, reocclusion of vessels occurred in 10% *versus* 20%, respectively. The usual adult oral dosage of pentoxifylline in the treatment of peripheral vascular disease is 1200mg daily in 3 divided doses with meals. Therapy should be maintained for at least 8 weeks. In cerebrovascular diseases the most often used dosage in clinical trials has been 300 to 600mg daily, although the currently recommended dosage is 600 to 1200mg daily. (Ward and Clissold 1987).

UUO caused ipsilateral renal hypofunction and contralateral hyperfunction, and PTX markedly decreased free radical activity in the ipsilateral kidney. While PTX showed a placebo effect. (Adnan Aslan, et al, 2003). PTF has multi-functions in the clinical application. It supposes that treatment with PTF, an agent with anti-inflammatory properties, decreases renal fibrosis and protects renal function in rats with chronic partial ureteral obstruction.

A rodent model of PUO allowed chronic studies of morphological and histological changes of the partially obstructed kidney and demonstrated progressive tubulointerstitial fibrosis and a decline in filtration function. PTF treatment ameliorated renal fibrosis and helped preserve filtration function of the kidney. Kidneys that progress to end-stage renal failure are almost invariably characterized by the presence of tubulointerstitial fibrosis. Therapeutic interventions to halt the progressive deterioration of renal function are still limited. PTF and gamma-interferon have shown a potential benefit in the treatment of fibrotic processes in the skin and lung (Strutz et al., 2000).

Progressive renal disease is associated with the development of fibrosing lesions not only in the glomerulus, but also in the interstitial and vascular compartments of the kidney. A growing body of work suggests that the mechanisms involved in this process are to a large extent shared by the glomerular mesangial cell, tubulointerstitial fibroblast and vascular smooth muscle cell (Becker et al., 2001). In a report in 2002, PTF reduced the upregulation of monocyte chemoattractant protein-1 gene by 60% in the cortex of remnant kidney, as well as in a dose-dependent manner in the albumin- or angiotensin II-stimulated proximal tubular cells. It also reduced the upregulation of mitogenic and profibrogenic genes by 50%, including platelet-derived growth factor, fibroblast growth factor-2, transforming growth factor-β1, connective tissue growth factor, and types I and III collagen in the cortex of remnant kidney. Furthermore, pentoxifylline was found to decrease the numbers of interstitial myofibroblasts by 60% in the cortex of remnant kidney and suppress the proliferation of cultured interstitial fibroblasts. It also reduced the angiotensin II-induced or TGF-β1-induced expression of connective tissue growth factor gene in cultured fibroblasts and mesangial cells. Combining PTF with an angiotensin-converting enzyme inhibitor, cilazapril, almost completely attenuated the renal disease progression in rats with remnant kidney. In conclusion, PTF alone can attenuate the chronic renal disease progression. Its combination with cilazapril has the potential to prevent the renal disease progression almost completely (Lin et al., 2002).

The principle application of PTF is to improve blood flow in patients with circulation problems to reduce aching, cramping, and tiredness in the hands and feet. It works by decreasing the thickness (viscosity) of blood (U.S. National Library of Medicine, 2008). This change allows the blood to flow more easily, especially in the small blood vessels of the hands and feet. Our results show that PTF has the function to preserve GFR forgot 30-day PUO rats, which indicates that PTF treatment may be related to improve blood floor then the GFR preserved until 30 days treatment, but not 15 days. 30 days PTF treatment reduces α-SMA expression in kidney indicates the gene expression is changed in kidney through 30 days PTF treatment.

Like other methylated xanthine derivatives, pentoxifylline is a competitive nonselective phosphodiesterase inhibitor, which raises intracellular cAMP, activates PKA, inhibits TNF and leukotriene synthesis, and reduces inflammation and innate immunity. In addition, pentoxifylline improves red blood cell deformability (known as a haemorrhologic effect), reduces blood viscosity and decreases the

potential for platelet aggregation and thrombus formation. Pentoxifylline is also an antagonist at adenosine 2 receptors.

Obstructive nephropathy is a serious problem for many patients in the chronic kidney disease. The kidney function decline in obstructive nephropathy is associated with structural derangements, which is reparative in an attempt to overcome the kidney injury caused by the obstruction of urine flow. With sustained obstruction, a permanent loss of renal function may occur. In this problem, renal fibrosis becomes a reactive process. Partial ureteral obstruction (PUO) produces a well documented triphasic response in the renal hemodynamics. This is characterized by an early increase in renal blood flow, followed by a decrease toward baseline, and later progressive profound renal ischemia. A lot studies have been performed in rodent models of unilateral urinary tract obstruction (Ma, et al, 2001).

Interstitial fibrosis is a complex process involving inflammatory cell infiltration, fibroblast proliferation, epithelial-mesenchymal transition, excessive extracellular matrix accumulation, and reduced matrix degradation (Bohle et al., 1994). This process is a saline feature of progressive renal disease and its extent correlates with renal function deterioration in either glomerular or tubulointerstitial diseases (Bohle et al., 1994; Nath, 1992). In obstructive nephropathy, inflammatory cells appear in the interstitial space shortly after urinary tract obstruction, releasing cytokines and growth factors which stimulate the fibrotic process (Fern et al., 1999; Klahr and Morrissey, 1998). Many studies have shown that inhibition of the renin-angiotensin system or transforming growth factor- $\beta$  (TGF- $\beta$ ) ameliorates obstruction-induced tubulointerstitial fibrosis, suggesting that angiotensin II and TGF-beta are involved in the development of fibrosis (Guo et al., 2001; Isaka et al., 2000; Klahr and Morrissey, 1998; Miyajima et al., 2000).

In a mouse model of complete UUO, the angiotensin system regulates about half of the renal interstitial fibrotic response in the obstructed kidney (Fern et al., 1999). At some stage of obstructive nephropathy, pharmacological inhibition of the angiotensin system may not be effective to reduce renal fibrosis and irreversible renal damage would ensue (Klahr and Morrissey, 1998; Fern et al., 1999; Klahr and Morrissey, 2002).

Other indications for which the literature supports its use include: Multi-infarct dementia, Peyronie's disease, Sarcoidosis, Peripheral neuropathy, Sickle cell disease, Alcoholic and non-alcoholic steatohepatitis, Endometriosis.

Multi-infarct dementia (MID) is a dementia caused by problems in the supply of blood to the

brain, typically by a series of minor strokes. MID is thought to be an irreversible form of dementia, and its onset is caused by a number of small strokes or, sometimes, one large stroke preceded or followed by other smaller strokes. The term refers to a group of syndromes caused by different mechanisms all resulting in vascular lesions in the brain. Early detection and accurate diagnosis are important, as vascular dementia is at least partially preventable. The main subtypes of this disease are: mild cognitive impairment, multi-infarct dementia, vascular dementia due to a strategic single infarct (affecting the thalamus, the anterior cerebral artery, the parietal lobes or the cingulate gyrus), vascular dementia due to hemorrhagic lesions, and mixed Alzheimer's and vascular dementia. Vascular lesions can be the result of diffuse cerebrovascular disease, such as small vessel disease, or focal lesions; usually both. Mixed dementia is diagnosed when patients have evidence of AD and cerebrovascular disease, either clinically or based on neuroimaging evidence of ischemic lesions. In fact vascular dementia and Alzheimer's disease often coexist, especially in older patients with dementia. MID is sometimes triggered by cerebral amyloid angiopathy, which involves accumulation of beta amyloid plaques in the walls of the cerebral arteries, leading to breakdown and rupture of the vessels. Since amyloid plaques are a characteristic feature of AD, vascular dementia may occur as a side effect of it. However, cerebral amyloid angiopathy can also appear in people with no prior dementia condition and a small amount of beta amyloid plaques are often present in cognitively normal older persons.

Sarcoidosis, also called sarcoid, is a disease involving abnormal collections of inflammatory cells that can form as nodules in multiple organs. The granulomas are most often located in the lungs or its associated lymph nodes, but any organ can be affected. Sarcoidosis seems to be caused by an immune reaction to an infection or some other trigger (called an antigen, which may be from one's environment) that continues even after the initial infection or other antigen is cleared from the body. In most cases it clears up by itself without any medical intervention, despite this some cases do go on to affect the person long-term or become life-threatening and require medical intervention, most often with medications. With an average mortality rate of less than 5% in untreated cases. Treatment is usually designed to help relieve the symptoms and hence do not directly alter the course of the disease. This treatment usually consists of drugs like ibuprofen or aspirin. In cases where the condition develops on a progressive and/or life-threatening course the treatment is most often steroid treatment with prednisone or prednisolone. Alternatively, drugs that

are most commonly used to treat cancer and suppress the immune system, such as methotrexate, azathioprine and leflunomide may be used. Cancer is a disease of abnormal cell growth possibly spreading to other parts of the body in animal including human being. Benign tumors are not cancer that do not spread to other parts of the body (Ma, et al, 2014).

In the United States it most commonly affects people of Northern European or African ancestry between the ages of 20 and 29, although any race or age group can be affected. Japan has a lower rate of sarcoidosis than the United States, although in these people the disease is usually more aggressive in its course with the heart often affected. Japanese individuals also have a different peak age for sarcoidosis, namely 25–40 years of age. It occurs more commonly in women too, with the female-to-male being roughly 2:1, it also usually takes a more aggressive course in women. In developing countries it often goes misdiagnosed as tuberculosis (TB) as its symptoms often resemble those of TB.

Pentoxifylline cannot be used under the following condition: (1) Allergic to any ingredient in pentoxifylline or to methylxanthines (eg, theophylline, caffeine, theobromine); (2) Have recent bleeding in the brain or eye. PTF affects human peritoneal mesothelial cell (HPMC) growth and collagen synthesis.

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