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The Uses Of Pentoxifylline In Nephrology

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Abstract

Pentoxifylline is a nonselective non-toxic phosphodiesterase inhibitor pentoxifylline with anti-inflammatory, anti-proliferative and anti-fibrotic activities in vitro and in vivo. It also inhibits extracellular matrix accumulation. There has been accumulating research evidence suggesting a renoprotective effect of pentoxifylline and a therapeutic potential for use in renal disorders. The aim of this paper is to review the relevant of pentoxifylline research to the field of nephrology.

Conclusion:

Proteinuria (albuminuria) in a variety of chronic renal disorders is correlated with dysfunction of the glomerular permeability barrier which is mostly caused by inflammatory cytokines. Angiotensin-converting-enzyme inhibitors have been increasingly used to reduce albuminuria with less than the desired benefit. There has been convincing research evidence suggesting that pentoxifylline can also be useful for reducing albuminuria and thus preventing the progression of a variety of chronic renal disorders including diabetic nephropathy and primary glomerulonephritis, and lupus nephritis.

Keywords: Pentoxifylline; uses; renal diseases.

Introduction

Pentoxifylline [3, 7-dimethyl-1-(5-oxo-hexyl)-xanthine], a xanthine derivative introduced during the 1970s, and is a nonselective non-toxic phosphodiesterase inhibitor pentoxifylline with anti-inflammatory, anti-proliferative and anti-fibrotic activities in vitro and in vivo. It also inhibits extracellular matrix accumulation [1, 2, 3].

Blagosklonnaia et al (1982) reported a study which included eleven diabetic patients with, seven of them had diabetic nephropathy. Pentoxifylline was given by intravenous drip in a dose of 300 mg daily for three weeks. Treatment was associated with a significant improvement of renal function with increased glomerular filtration, reduction of proteinuria, and also improvement in hyperglycemia. Treatment was not associated with side effects [2].

Shoĭkhet et al (1986) reported the use of pentoxifylline in 53 patients with a variety of chronic glomerulonephritis. Pentoxifylline monotherapy had a beneficial effect in latent and hypertonic variants of chronic glomerulonephritis. In chronic glomerulonephritis with nephrosis, pentoxifylline was more effective when used with heparin and prednisolone. In chronic glomerulonephritis with renal failure, pentoxifylline was more effective when used with heparin. [3].

Solerte et al (1986) reported a controlled study which included 82 patients with type I and type II diabetes with microproteinuria. Treatment group were treated with pentoxifylline 400 mg, while the control group included patients with more strict hypoglycemic control. Pentoxifylline treatment was associated with a significant reduction of albuminuria and proteinuria hypoglycemic control [4].

Gordeev et al (1991) reported 18 patients with senile pyelonephritis and renal hypertension whom were treated with pentoxifylline 600 daily for3 weeks to 6 months. Treatment was associated with a considerable improvement in medullary blood flow, increase in the excretion of natriuretic PGE and lowering of diurnal excretion of PGF2 alpha, which was associated with increased natriuresis and diuresis [5].

Guerrero-Romero et al (1995), Gorson et al (1998), and Navarro and Mora (1999)

reported reduction of albuminuria with pentoxifylline in diabetic patients [6, 7, 8].

Berens et al (1998) reported an experimental controlled study on rats with chemically induced nephrotic syndrome that were treated with pentoxifylline 45 mg/kg i.p. twice daily. Pentoxifylline treatment was associated with 3- and 6-fold reductions in proteinuria at 7 and 14 days, respectively, compared with the control rats ($p < .01$). Treatment was also associated with marked reductions in glomerular neutrophil and macro-phage counts, but not T-cells (OX19+) or suppressor/cytotoxic T-cells (0X8+), in rats' kidneys [9].

Chen et al (1999) emphasized that the accumulation of glomerular macrophages, proliferation of mesangial cells, and deposition of extracellular matrix proteins are pathological hallmarks of glomerulonephritis. They studied in vivo effects of pentoxifylline on rat anti-Thy1 disease, a model of mesangial proliferative nephritis.

Sprague-Dawley rats that had nephritis induced in by Anti-Thy1 and treated with pentoxifylline excreted less urinary protein on the fifth day of nephritis than control rats. Treatment also resulted in:

1-Reduction of glomerular cellularity accumulation and proliferation of glomerular macrophages

2- Reduction of glomerular sclerosis.

3-Suppression of the activation and proliferation of mesangial cells [10].

Vázquez García et al (2000) reported that treating pediatric patients with grade IV (OMS) lupus in nephritis with pentoxifilina resulted in reduction of proteinuria and hematuria and slowed the deterioration in renal function [11].

Ducloux and colleagues (2001) reported the use of pentoxifylline 1200 mg daily in the treatment of ten patients with idiopathic membranous nephropathy for 6 months. Treatment was associated with a significant reduction of proteinuria from 11 g/day [range 4.6-27] to 1.8 (0-10.9); p=0.001). Ducloux and colleagues suggested that pentoxifylline can be safely used as an adjunct therapy to steroids and immunosuppressant therapy in membranous nephropathy [12].

Lin et al (2000) reported an experimental study on rats that developed progressively elevated proteinuria and plasma creatinine, glomerulosclerosis, interstitial inflammation, and fibrosis after 5/6 subtotal nephrectomy. All the pathological features were reduced by 40-60% with use of pentoxifylline [13].

Yagmurlu et al (2003) reported an experimental study on rat model of pyelonephritis which showed that pentoxifylline was effective in preventing renal scar formation in pyelonephritis delayed antimicrobial [14].

Harmankaya and colleagues (2003) reported a study which included 50 hypertensive patients (31 males and 19 females, aged between 47-73 years) with type 2 diabetic who had persistent microalbuminuria with normal renal function. 25 patients were treated with lisinopril 10 mg daily, 25 patients were treated with lisinopril 10 mg daily + pentoxifylline 600 mg/day for nine months. The combined use of pentoxifylline with an angiotensin converting enzyme inhibitor was associated with a marked reduction in albuminuria regardless of the glycemic control [15].

Galindo-Rodríguez et al (2003) reported a study which included eleven patients with refractory nephrotic syndrome secondary to lupus nephritis whom were treated with corticosteroids and immunosuppressive therapy for at least six months. The use of pentoxifylline resulted in reduction of proteinuria concentrations after from a median of 5.5 to 2.0 ($p = 0.003$) in all patients [16].

Chen et al (2004) reported an experimental study on a Wistar rat model of anti-glomerular basement membrane crescentic glomerulonephritis. The study showed that pentoxifylline has an effective anti-inflammatory and immunomodulatory effects that can suppress rat crescentic glomerulonephritis [17].

Dávila-Esqueda and Martínez-Morales (2004) suggested that the renoprotective effects of pentoxifylline are possibly attributed to its antioxidant actions. They reported an experimental study on rats with streptozotocin-induced diabetic nephropathy. Treatment with pentoxifylline eight weeks showed renoprotective effects resulting in a significant reduction in lipoperoxide levels in the diabetic kidney ($P < 0.05$), compared to control rats [18].

Navarro et al (2005) reported a controlled study which included 61 patients with diabetic nephropathy and albuminuria despite treatment with angiotensin II receptor blockers for more than one year. Thirty patients were additionally treated with pentoxifylline 1200 mg daily. After four months, albuminuria was markedly reduced in the patients treated with pentoxifylline, while no significant reduction occurred in patients who didn't receive pentoxifylline. The additive antiproteinuric effect of pentoxifylline was associated with a reduction of urinary tumor necrosis factor (TNF)-alpha excretion [19].

Navarro et al (2006) reported an experimental study on streptozotocin-induced diabetic rats which showed that the renal expression of the chief pro-inflammatory cytokines TNF-alpha, interleukin (IL)-1 and IL-6 increased in diabetic nephropathy association with albuminuria. Enalapril and pentoxifylline treatment prevented the enhanced expression, and urinary cytokine and albumin excretion [20].

Chen et al (2006) reported a study which included patients with 17 patients with primary glomerulonephritis with a persistent spot proteinuria more than 1.5 g/g creatinine and a glomerular filtration rate between 24 and 115 ml/min/1.73 m (2). They were treated with pentoxifylline 400 mg twice daily for six months. Treatment was associated with marked reduction in proteinuria with elevation of serum albumin. Treatment was not associated with a significant change in blood pressure. This beneficial effect was correlated with reduction of urinary monocyte chemoattractant protein -1 excretion [21].

Lin et al (2008) reported a randomized controlled study which included patients with estimated glomerular filtration rate (eGFR) of 10 to 60 mL/min/1.73 m (2) and urinary protein more than 500 mg/g of creatinine. In the first year of the study, 27 patients were initially treated with losartan, 100 mg/daily, while the remaining 29 patients served as control. During the next 6 months of the study, all patients were treated with pentoxifylline in a dose of 400 mg twice daily for patients with eGFR of 30 to 60 mL/min/1.73 m(2) and once daily for patients with eGFR of 10 to 29 mL/min/1.73 m(2). During the first year of the study, pentoxifylline treatment was associated with reduction in median proteinuria from 1,140 to 800 mg/g (median change, -23.9%) compared with 1,410 to 1,810 mg/g (median change, 13.8%) in the control patients. Lin et al found that the addition of pentoxifylline to losartan reduced proteinuria in patients with chronic kidney disease stages 3 to 5 [22].

Zhou and colleagues (2009) reported an experimental study on a rat model of obstructive nephropathy which showed that pentoxifyllin can inhibit tubulointerstitial fibrosis and prevent loss

of vascular endothelial growth factor by up-regulating the expression of its mRNA through stabilizing it in cultured renal tubular epithelial cells [23].Ng et al (20090 reported a controlled experimental study on rat model of accelerated anti-glomerular basement membrane glomerulonephritis which showed that pentoxifylline had anti-fibrosis effect [24].

Goicoechea et al (2012) reported a randomized study which included 91 patients with estimated glomerular filtration rate (eGFR) less 60 ml/minutes. Forty-six patients were treated with pentoxifylline 800 mg in two divided doses for 12 months. Pentoxifylline treatment was associated with marked reduction of high-sensitivity C-reactive protein, serum fibrinogen and TNF-alpha. Pentoxifylline treatment also stabilized renal function and prevented worsening of eGFR in patients who didn't receive pentoxifylline [25].

Badri et al (2013) reported a double-blind, placebo-controlled study which included non-diabetic patients with membranous nephropathy and urinary protein excretion more than 500 mg/24 hours. The patients treated with pentoxifylline 400 mg two or three times a day for six months experienced a significant reduction of mean urinary protein excretion ($p < 0.001$) [26].

Conclusion:

Proteinuria (albuminuria) in a variety of chronic renal disorders is correlated with dysfunction of the glomerular permeability barrier which is mostly caused by inflammatory cytokines. Angiotensin-converting-enzyme inhibitors have been increasingly used to reduce albuminuria with less than the desired benefit. There has been convincing research evidence suggesting that pentoxifylline can also be useful for reducing albuminuria and thus preventing the progression of a variety of chronic renal disorders including diabetic nephropathy and primary glomerulonephritis, and lupus nephritis.

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