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The Uses Of Pentoxifylline In Cardiology And Hypertension

Aamir Jalal Al-Mosawi

Advisor doctor The National Training and Development Center of the Iraqi Ministry of Health Baghdad, Iraq

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***Corresponding author:** Aamir Jalal Al-Mosawi, Advisor doctor The National Training and Development Center of the Iraqi Ministry of Health Baghdad, Iraq

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Abstract

Pentoxifylline is a xanthine derivative with vasodilatory properties and rheological properties on blood that made it useful in the treatment of intermittent claudication. Pentoxifylline also has an immunomodulatory effect which inhibits on the production inflammatory cytokines including tumor necrosis factor-alpha. The aim of this paper is to review the uses of pentoxifylline in cardiology and hypertensive conditions.

Conclusion: There is evidence suggesting that inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha) have important role in pathogenesis and development of symptom in ischemic, non-ischemic, and hypertensive cardiomyopathic heart dysfunction and heart failure through depression of contractile performance. The addition of pentoxifylline to the traditional therapies in variety of cardiac disorders and hypertensive condition was found to be beneficial in experimental and clinical studies.

Keywords: pentoxifylline; cardiology; hypertensive conditions

Pentoxifylline is a xanthine derivative with vasodilatory properties that made it useful in the treatment of intermittent claudication. Xanthines in general stimulate muscle and cardiac cells and neurons. The most important pharmacological effects xanthines include inhibition of tissue phosphodiesterases which increases cellular cyclic AMP levels by preventing its breakdown and metabolism. Xanthines are adenosine receptor antagonists. and have anti-inflammatory properties that are attributed to the release of anti-inflammatory cytokines or modulation of gene transcription or activation of histone dacetylase.

Heidrich et al (1976) studied the cardiac effects of 100 mg of intravenous pentoxifylline eight patients who had peripheral-arterial disease and having normal myocardial function or myocardial insufficiency. Pentoxifylline short, but statistically significant increase in cardiac output of +9.6% and a simultaneous reduction in total peripheral resistance of -7.6% only in patients with normal myocardial function [1].

Rafibekova et al (1985) reported their experience with the use of pentoxifylline in the treatment of essential hypertension [2]. Solerte et al (1985) reported the use of pentoxifylline as an antihypertensive drug alone or with other antihypertensive drugs in the treatment of diabetic patients. Treatment was associated with a considerable reduction of systolic and diastolic blood pressure, an improvement of erythrocyte filterability, and a reduction of proteinuria. Rafibekova et al suggested that pentoxifylline is a good pharmacological option in the treatment of diabetic hypertension and in the prevention of diabetic renal disease [3].

Maiti et al (2007) emphasized that inflammation and oxidative stress had been increasingly suspected to be important contributors for the development atherosclerosis in diabetes mellitus. They reported a controlled study which included sixty hypertensive type 2 diabetic patients aged 45 years ore more. Thirty patients were received oral pentoxifylline 800 daily in two divided doses with meals for one month. Pentoxifylline treatment resulted in 20.9% lowering ($p<0.001$) of C-reactive protein level, 18% lowering ($p<0.001$) of erythrocyte sedimentation rate, 11.1% lowering ($p<0.001$) of total leukocyte count and 5.8% elevation ($p=0.003$) of serum albumin. In addition, pentoxifylline treatment was associated with 20.2% reduction in plasma malondialdehyde and 4.6% rise in

in blood reduced glutathione level. In therapeutic dose range, Pentoxifylline treatment also showed considerable anti-aggregatory effect and a dose dependent lowering of clot retraction in-vitro, but without causing significant change in ex-vivo clot retraction. Control patients didn't show statistically significant change in these parameters. Accordingly, Maiti et al suggested that improving inflammatory markers, oxidative stress and platelet-aggregation by adding pentoxifylline to the traditional therapies can prevent the development of atherosclerosis in diabetes mellitus [4].

Azhar and El-Bassossy (2015) reported an experimental study on rats with metabolic syndrome induced by feeding a diet high in fructose, and salt diet for 12 weeks. Pentoxifylline treatment in a daily dose of 30 mg kg/ body weight during the last 4 weeks of the study, prevented excessive weight gain but had no effect on hyperinsulinemia or hypertriglyceridemia that was associated with the metabolic syndrome.
Pentoxifylline also prevented the increase mean blood pressure associated with metabolic syndrome. In addition, pentoxifylline intake lessened low-grade inflammation, and markedly reduced serum tumor necrosis factor-α. Pentoxifylline also inhibited elevated expression of angiotensin receptor-1 in aortic tissue [5].

Mayyas and colleagues (2015) reported an experimental study on young adult Sprague Dawley which showed that pentoxifylline can have a favorable effect on the changes in blood pressure and myocardial oxidative activities associated with the intake of western diet [6].

Zhang et al (2016) reported an experimental study on angiotensin II-induced hypertensive Sprague-Dawley rats which showed that the anti-inflammatory property of pentoxifylline can reduce cardiac fibrosis and hypertrophy, and improve cardiac dysfunction. The observed therapeutic benefits associate with pentoxifylline occurred independently of the blood pressure lowering effect [7].

Plotnikov et al (2017) emphasized that isolated diastolic hypertension is the most common form of hypertension in young adults, and it is correlate with total peripheral resistance a, vascular hindrance, and blood viscosity. They reported a controlled experimental study on young spontaneously hypertensive rats which showed treatment with oral pentoxifylline 100 mg/kg/day for 6 week, had a favorable effects on the hemodynamic, hemorheological, and microcirculatory parameters during the development of arterial hypertension. Treatment resulted in marked lowering of systolic, diastolic, and mean BP (by 24%, 26%, and 15%, respectively) [8].

Plotnikov et al (2017) suggested that the rheological properties of blood have an important contribution to the development and progression of arterial hypertension. They reported a an experimental study on in spontaneously hypertensive rats which showed that combining captopril (angiotensin-converting enzyme inhibitor) and pentoxifylline is associated with a synergistic preventive effect on various systems on the development of arterial hypertension. The addition of pentoxifylline, improved the antihypertensive effect of captopril through a favorable effect on blood viscosity and erythrocyte deformability index [9].

Heublein et al (1988) reported a study which included 18 patients (15 males, 3 females, aged 51.3 +/- 9.0 years,) with stable angina pectoris and positive exercise-ECG in NYHA class I or II and LVWM greater than 160 g in 9 patients and less than or equal to 160 g in 9 patients. Treatment with intravenous pentoxifylline 200 mg was associated with considerable improvement in left ventricular diastolic function and considerable improvement of pump function particularly in patients with LVWM more than 160 g [10].

Insel and colleagues (1988) reported a study which included eleven patients with myocardial ischemia presented as stable angina with angiographic evidence of coronary artery disease. The patients were treated with 1200 mg of pentoxifylline daily for six weeks. Symptoms improved in 9 [82%] of patients without the occurrence of side effects. The mean total exercise time , time to onset of anginal symptom , heart rate at onset of angina and rate at onset of ST depression were increased considerably (p less than 0.05) after treatment. Mean maximum ST segment depression was slightly reduced. Insel and colleagues emphasized that pentoxifylline can improve exercise performance and capacity in patients with angina pectoris [11].

Azhar and El-Bassossy (2014) reported an experimental study on rats with cardiac ischemia and dysfunction occurring in experimental angina in insulin resistance which was induced by feeding the rats a high-fructose, high-fat diet which resulted in hyperinsulinemia, hyperglycemia, and increased inflammatory cytokine TNF-α. Treatment with pentoxifylline improved cardiac ischemia and dysfunction, and completely prevented the development of excessive ST height depression. In addition, treatment raised serum level anti-inflammatory cytokine adiponectin [12].

Nordhus and colleagues (1986) reported a study which included ten patients with congestive heart failure caused by aortic or mitral valve disease, mainly in NYHA group III or IV. The patients were treated with intravenous infusion of pentoxifylline in a dose of 4 mg/kg body weight during a stable hemodynamic situation after valve replacement. Treatment was associated with considerable increase in cardiac output and cardiac index occurring in association with lowering of the systemic vascular resistance. The heart rate and stroke volume were considerably increased after 5-10 minutes. Treatment was not associated with adverse effects [13].

Kochmański and Zochowski (1990) reported a study which included 21 patients with congestive heart failure (NYHA classes II-IV) whom were treated with digoxin and furosemide for at least 14 days. Thereafter, the patients received a 200 mg intravenous dosage of pentoxifylline followed by or pentoxifylline for at least 14 days. Digoxin-furosemide treatment was associated with a considerable increase in physical efficiency and an improvement in left ventricular functions, but considerable increase in blood viscosity was also observed. The addition of pentoxifylline was associated with reduction of increased blood viscosity and resulted in much better hemodynamic condition of the patients [14].

Sliwa et al (1998) emphasized the research evidence suggesting important contribution of elevated levels of inflammatory

cytokines including tumor necrosis factor alpha (TNF-alpha) to the pathogenesis and severity of symptoms of heart failure. They reported a double-blind, randomized, placebo-controlled study which included 28 patients with idiopathic dilated cardiomyopathy whom were treated with either pentoxifylline 400 mg three times daily or placebo for 6 months. Four patients died during the study period, all if them were receiving in the placebo. Pentoxifylline treatment improved symptoms and left-ventricular systolic function, and was associated with a higher proportion of patients in NYHA functional class I or II than in the patients receiving placebo. Pentoxifylline treatment markedly lowered TNF-alpha [15].

Skudicky et al (2001) emphasized the research evidence suggesting a usefulness of the inhibitory effect of pentoxifylline on the production of tumor necrosis factor-alpha, in patients with idiopathic dilated cardiomyopathy. They reported a double-blind, placebo-controlled trial which included 39 patients with idiopathic dilated cardiomyopathy whom were treated digoxin, ACE inhibitors, and carvedilol. Twenty patients received pentoxifylline 400 mg6 months, while nineteen patients received placebo. Five patients died including three in the placebo group). Pentoxifylline treatment was associated with a considerable improvement in symptoms and left ventricular function, and in functional class compared with the placebo, with an increase in exercise time from 9.5+/-5 to 12.3+/-6 minutes. Pentoxifylline treatment also improved left ventricular ejection fraction from 24+/-9% to 31+/-13% .

Sliwa et al (2002) emphasized the research evidence suggesting that treatment of peripartum cardiomyopathy with angiotensin-converting enzyme inhibitors and beta blockers generally remained unsatisfactory. They also emphasized the known contribution of raised levels of tumor necrosis factor-alpha (TNF-alpha) various cardiac disorders including peripartum cardiomyopathy. They reported a study which included 59 women with peripartum cardiomyopathy. 29 patients were treated with diuretics, digoxin, enalapril and carvedilol for 6 months, and 30 patients additionally received pentoxifylline 400 mg three times daily. Nine patients died including eight patients who didn't receive pentoxifylline. Sliwa et al suggested that the addition of pentoxifylline to traditional therapies can improve outcome in patients with peripartum cardiomyopathy [17].

Sliwa, Woodiwiss et al (2002) emphasized the research evidence suggesting that patients with severe heart failure have plasma cytokine level more than twofold higher than patients with moderate heart failure. They also emphasized the previous research evidence suggesting that pentoxifylline as an immunomodulatory drug that inhibits tumor necrosis factor-alpha can improve pump function in mild-to-moderate heart failure. They reported a double-blind, controlled study which included eighteen patients with advanced heart failure. The 18 patients had New York Heart Association functional class IV heart failure, and were treated with intravenous inotropic agents for more than 72 hours at the start of the study, and also received diuretics, digoxin, and an angiotensin-converting enzyme inhibitor for month. All patients had significant elevations in TNF-alpha and Fas/Apo-1 levels. Nine patients were treated with pentoxifylline (400 mg 3 times daily) for one month and nine patients received placebo. The use of pentoxifylline was associated with lowering of TNF-alpha and Fas/Apo-1 levels, and an increase in ejection fraction at one month ($p < 0.05$ compared with baseline and with patients who received placebo) [18].

Sliwa et al (2004) reported a controlled trial which included 38 patients with ischemic cardiomyopathy whom were treated with traditional therapies. The study showed that the addition of pentoxifylline 400 mg three times daily for six months was associated with or placebo in addition to standard therapy an improvement in functional class ($P<0.005$) and an increase in systolic blood pressure ($P<0.05$) and left ventricular radionuclide ejection fraction ($P<0.05$) compared with the patients who received placebo. Treatment was also associated with lowering of plasma levels of markers of inflammation and apoptosis. Five patients died including four who didn't receive pentoxifylline.

Champion et al (2014) published a meta-analysis of placebo-controlled studies which included 221 patients with heart from six randomized controlled trials. Patients were treated with pentoxifylline 1200 mg per daily for 6 months in five studies, but one study involved treatment severe acute heart failure for one month. The collected data from this meta-analysis showed approximately fourfold reduction in mortality with use pentoxifylline when compared with placebo [21].

Conclusion

There is evidence suggesting that inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha) have important role in pathogenesis and development of symptom in ischemic, non-ischemic, and hypertensive cardiomyopathic heart dysfunction and heart failure through depression of contractile performance. The addition of pentoxifylline to the traditional therapies in variety of cardiac disorders and hypertensive condition was found to be beneficial in experimental and clinical studies.

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