Therapeutic potentials of pentoxifylline for treatment of cardiovascular diseases

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BACKGROUND: Cardiovascular diseases are life-threatening conditions and, thus, have received a great deal of attention over the years. Several mechanisms, including hemorheology changes and inflammatory effects, are considered to be involved in the pathogenesis of these diseases. Because cardiovascular dysfunction is also known to worsen hemorheology changes and influence vital symptoms, it has become critical to formulate effective therapeutic strategies to combat the deleterious effects of cardiovascular diseases. Although a wide variety of drugs have been developed for the treatment of cardiovascular diseases, the effectiveness of any agent for therapy of a given disease cannot be indicated with certainty.

OBJECTIVES AND OBSERVATIONS: Pentoxifylline (PTXF), a phosphodiesterase inhibitor, has been investigated for close to two decades because of its primary pharmacological actions on hemorheology and other anti-inflammatory effects. Several studies have been conducted to investigate the effects and mechanisms of PTXF in ischemic injury, peripheral vascular disease and heart failure. The present article is intended to emphasize the therapeutic potentials of PTXF in different types of cardiovascular diseases, focusing on the mechanisms of its pharmacological actions.

Key Words: *Blood viscosity; Ischemia reperfusion injury; Pentoxifylline; Peripheral vascular disease; Platelet function*

Pentoxifylline (PTXF), a synthetic methylxanthine, was approved in 1984 for the prevention of intermittent claudication in chronic occlusive arterial disease (1,2). Like other methylxanthine derivatives, PTXF is not only prescribed for peripheral vascular and cerebrovascular diseases, but is also indicated for the treatment of asthma (3). Additionally, PTXF is used to improve the effectiveness of microcirculation, increase red blood cell (RBC) deformability, decrease platelet aggregation and lower plasma viscosity (3-5). PTXF has also been shown to modify the immune system. For instance, this drug improves leukocyte deformability and chemotaxis, depresses neutrophil degranulation, decreases endothelial leukocyte adhesion and lowers the sensitivity of leukocytes to cytokines (6-13). Furthermore, it has been reported that PTXF can inhibit the production of inflammatory cytokines (14), and, thus, reduces neutrophil adhesiveness to endothelial cells, enhances chemotaxis and lowers the production of free radicals (15). In other studies, PTXF has been shown to augment the production of prostacyclins and a vasodilator, eicosanoid (16,17). PTXF is known to inhibit phosphodiesterase (PDE), an enzyme that breaks down cyclic AMP (cAMP), which elevates the level of intracellular cAMP and, thus, lowers platelet aggregation (18) and depresses the production of tumour necrosis factor-alpha (TNF-α) (19). Furthermore, PTXF has been reported to promote the oxygenation of ischemic areas and lower the amount of metabolic derangements associated with ischemia-reperfusion injury (20). Therefore, in view of the wide variety of effects and potent hemorheological properties of PTXF, the pharmacological actions of this agent and its analogues will be discussed for a clear understanding of its therapeutic potential for treatment of cardiovascular disease.

ANALOGUES AND METABOLITES OF PTXF

PTXF is a derivative of theobromine, a methylated xanthine. The most closely related methylated xanthines include caffeine, theophylline and aminophylline (Figure 1), which have been discovered in plants and have several similar pharmacological actions. All of these agents relax smooth muscle, particularly bronchial muscle, stimulate the central nervous system and act on the kidney to promote diuresis. Furthermore, caffeine and theophylline modify blood circulation activities in a similar manner. Although it is known that caffeine increases the capacity for muscular work in humans, three major actions of methylxanthines, namely translocation of intracellular calcium, accumulation of cyclic nucleotides and blockade of adenosine receptors, have received the most attention (1). Of the methylxanthines, the effects of caffeine on the cardiovascular system have been studied since 1966. Caffeine is a widely consumed compound because it is present in many common beverages such as tea, coffee and soft drinks. It is also a frequently used pharmacological substance because it has an antagonist affect on the adenosine A_1 and $A_{2\alpha}$ receptors (21). However, caffeine has toxic effects at high doses (22), and chronic caffeine intake is a risk factor for cardiovascular disease because it causes an increase in blood pressure, heart rate and aortic stiffness (23). Sardao et al (22) have reported that caffeine produced an increase in mitochondria state 4 respiration and a decrease in state 3 respiration, in addition to Ca^{2+} accumulation. Okafor et al (24) demonstrated that the administration of caffeine influenced the alteration of myofilament Ca^{2+} responsiveness and contractile activation.

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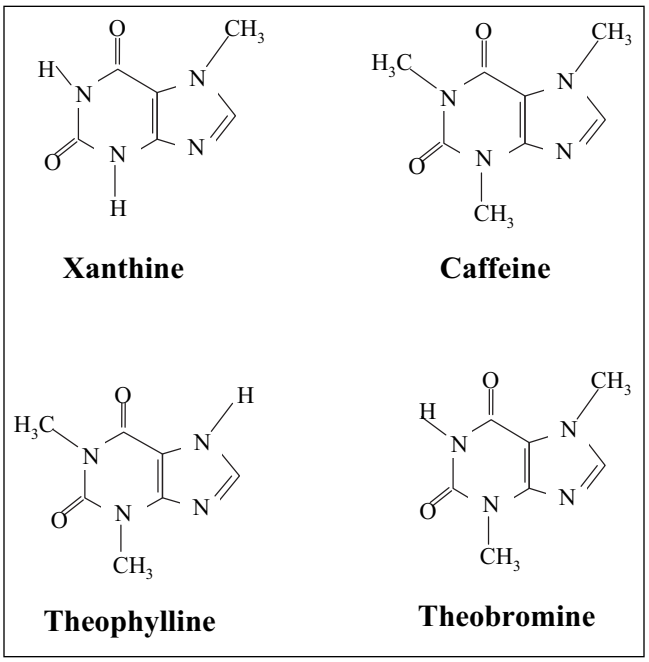

Figure 1) *Chemical structure of xanthine and its derivatives*

Theophylline, another antagonist of adenosine, has been reported to stabilize breathing in patients with brain damage (25). Other studies have demonstrated that theophylline has therapeutic effects with respect to arrhythmias and symptomatic bradycardia, which are secondary to atrioventricular nodal block and the sick sinus syndrome (26,27). Although some investigators (28) have indicated that theophylline lowers increased hemoglobin and hematocrit levels in the renal transplant recipient, Trivedi and Lal (29) reported that theophylline was ineffective in this condition. While the effects of theophylline on cardiovascular disease remain to be carefully examined, aminophylline has been shown to have beneficial effects on exercise-induced chest pain in humans due to vasodilation and inhibition of the myocardial steal phenomenon associated with transmural myocardial maldistribution of blood flow (30). In addition, Altun et al (31) have also indicated that aminophylline has a potential therapeutic effect on advanced atrioventricular block during acute inferior myocardial infarction. Because PTXF has fewer side effects and a larger therapeutic range than theobromine, most studies investigating treatments for cardiovascular diseases have focused on PTXF. In addition to PTXF, some PTXF analogues, including HWA-138 (albifylline), HWA-448 and A-802715, have been examined. HWA-138 has been considered a potential drug for treating cardiovascular disease because it has been shown to reduce cytokine production and inhibit coagulation disturbances (32). It has also been reported to protect the liver from shock-induced injury in rats by blocking leukocyte adhesion to the endothelium (32). Furthermore, HWA-138 was used to alleviate symptoms of endotoxin-induced acute lung injury in pigs (33). PTXF has been prescribed to increase blood flow to various organs such as the brain, skeletal muscle, kidney and lung. HWA-138 and HWA-448 have been demonstrated to impede the progression of renal damage associated with septic shock in rats (34) and were shown to induce prostocyclin synthesis in the endothelial cell (35). Another analogue, A-802715, has been reported to inhibit the production of TNF-α caused by

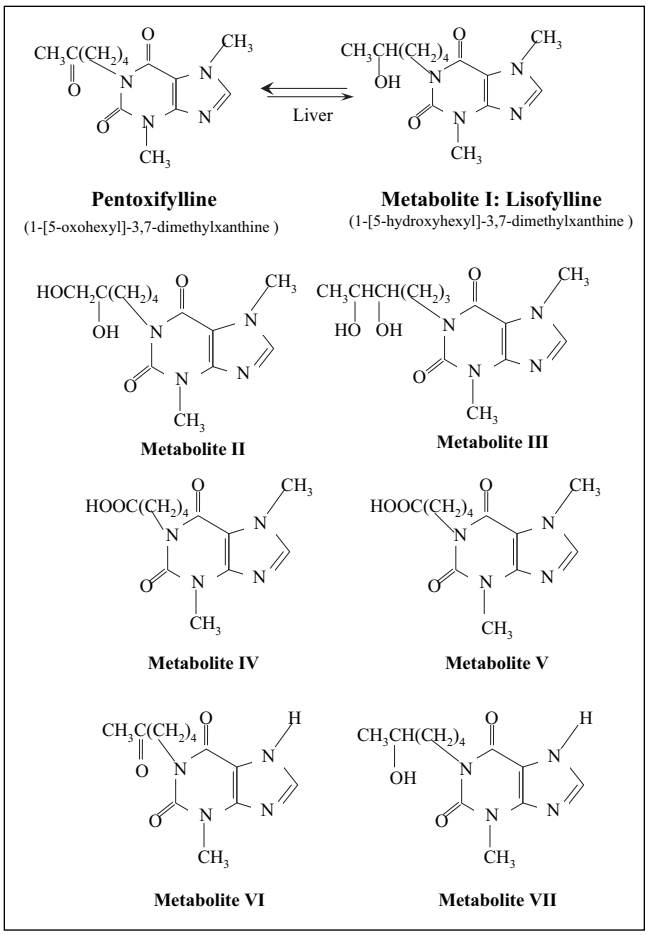

Figure 2) *Pentoxifylline and its metabolites*

lipopolysaccharides in serum (36). A-802715 was shown to be more potent than PTXF as an immunosupressant because it has been documented to suppress the cyclosporine-resistant signal-dependent pathway in T cell proliferation under both in vitro and in vivo conditions (37,38).

Thus, there are many analogues of PTXF which have been examined in both experimental and clinical settings. Some of these agents, such as A-802715, HWA-138 and HWA-448, have shown more potential therapeutic benefits than PTXF in treating cardiovascular disease.

Because PTXF has received much attention for its pharmacological effects on hemorheology and immune response, its metabolism has been examined extensively. This drug is clinically effective when administered either orally or intravenously. It is metabolized by erythrocytes and the liver, and is excreted by the kidney with a half-life of 3.4 h (3,39). Miller et al (40) have reported that the maximum plasma concentration of PTXF was achieved within 5 min following its injection. There are seven metabolites of PTXF (Figure 2); metabolite V is considered to be the major urinary metabolite of PTXF in humans (40). Honess et al (41) demonstrated no significant amount of metabolite I or PTXF detected in urine (3). Although the effects of these metabolites on cardiovascular disease have not been fully examined, some investigations of metabolites I and V indicate that these have hemorheological properties similar to those of PTXF (42). Moreover, metabolite I, known as lisofylline or BL149, was found to be the most active metabolite of PTXF for the treatment of

intermittent claudication in humans (42). Additionally, lisofylline was found to depress TNF-α synthesis, decrease transforming growth factor-beta (TGF-β) activity and inhibit macrophage inflammatory protein 1-alpha production in mice (43). Hasegawa et al (44) reported that lisofylline treatment decreased pulmonary hypertension, hypoxemia and neutropenia due to sepsis. The mechanism of its effect on cardiovascular disease was suggested to involve antiphosphatidic acid signalling (42) due to inhibition of lysophosphatidic acid acyl transferase activity; the inhibition of this enzyme blocks the conversion of lysophosphatidic acid to phosphatidic acid (45). Although, lysofylline can be useful in the treatment of cardiovascular disease, PTXF is required clinically due to its diverse effects on hemorheology and inflammation with fewer side effects.

EFFECT OF PTXF ON ISCHEMIC BRAIN

Stroke is a major global health concern because it is the third leading cause of death in North America (46-50) and is one of the primary factors that disable the elderly. Therefore, searching for an effective pharmacological intervention of ischemic cerebral disease has become important (46). Cerebral blood flow (CBF) is a major point of focus in treating stroke because it is necessary to maintain normal mental condition and consciousness. Reduced CBF is a significant symptom that leads to the death of brain cells as a consequence of cerebral ischemia. Other factors such as arteriosclerosis, thrombosis, and a number of vascular and hematolytic changes can also decrease CBF and, thus, may produce cerebral ischemia (47-50).

Deformation of RBCs is one example of a vascular event that results in marked abnormalities in patients with cerebral ischemia; this alteration in RBCs is both a consequence and a cause of this ischemia (50,51). There are three factors that determine the deformability of RBCs: the shape of the RBC, the viscoelastic properties of the membrane, and internal viscosity of the cell content (51). In addition, the flexibility of RBC membranes is determined by intracellular ATP and Ca^{2+} ion concentrations (50,52). An increase in plasma osmolarity and a lowered blood pH can also result in a rigid erythrocyte membrane (53-55). Because treatment of cell deformability with PTXF improves capillary perfusion and regional CBF (56), this reduces the damage that occurs due to cerebral ischemia. Thus, the increase in capillary perfusion and regional CBF are primarily due to the hemorheological properties of PTXF, which reduce blood viscosity, improve RBC flexibility and inhibit platelet aggregation (56,57).

Studies in rats also demonstrated that PTXF enhances the elasticity in RBCs by increasing the amount of ATP (3). Similar findings have been reported in humans (58). Bowton et al (59) found that this change in ATP level with oral administration of a single sustained release capsule of PTXF increased global and regional CBF in patients with cerebrovascular disease. Furthermore, studies have indicated that PTXF exerts beneficial effects in cerebrovascular disease by inhibiting brain edema, reducing disturbances of brain cell membrane permeability and removing mechanical obstacles in microcirculation (11,60,61). Thus, it can be seen that PTXF has a broad range of therapeutic effects in patients with cerebrovascular disorders. This drug has been used to treat transient ischemic attacks, cerebral thrombosis and hemorrhage, and chronic cerebrovascular insufficiency (3). As well, PTXF is useful in treating ischemic brain lesions, mainly by inhibiting membrane permeability of brain cells and preventing an increase in blood viscosity.

EFFECT OF PTXF ON ISCHEMIC HEART

Ischemic heart injury has become a major economic and health care concern. Almost 45% of all deaths in northern European countries in the past decade have been reported to result from this cardiovascular disease (62). A similar situation exists in Canada where more than 58% of cardiovascular deaths were attributed to ischemic cardiac lesions (63). There are a number of factors to consider before we can successfully treat ischemic injury in the heart. Cytokines, for example, are important mediators of cardiovascular diseases. A myocardial ischemic event prompts the release of cytokines and other inflammatory mediators that cause coronary vascular injury. The specific target of such mediators appears to be the endothelium and neutrophils. Inflammatory cytokines, including TNF-α and interleukin-1 (IL-1), act on neutrophils and adhere to the vascular endothelium. This induces the obstruction of capillary beds and causes the no-reflow phenomenon during reperfusion. Moreover, the accumulation of TNF-α and IL-1 within ischemic tissue directly injures the tissue and leads to the release of oxygen free radicals, which results in further damage to the endothelium (14). Other studies have demonstrated that TNF-α directly decreases contractile function in hamsters, dogs and humans (64,65). This acute negative inotropic effect of TNF-α is due to interference in Ca^{2+} homeostasis and, thus, TNF-α is considered to disrupt excitation-contraction coupling and desensitize the beta-adrenal receptors (66). The early contractile depression induced by TNF-α is mediated by sphingosine, an endogenous second messenger (67). In addition, TNF-α induces the production of nitric oxide and, thus, desensitizes myofilament sensitivity to Ca^{2+} leading to contractile dysfunction (68). Another mechanism of cardiac depression provoked by TNF-α is the induction of apoptosis in cardiomyocytes; this process appears to be mediated by sphingosine and nitric oxide (69-71). These studies indicate that anti-TNF-α therapy may be useful in ischemic injury.

Various pharmacodynamic investigations have demonstrated the beneficial effect of PTXF on ischemic myocardial and vascular disorders (15,72-77). In one study (3), 40 ischemic heart disease patients treated with PTXF 600 mg/day for 25 days to 30 days, showed a lowered level of glyceryl trinitrate consumption, greater ability to exercise and reduced tachycardia. Reduction in TNF-α production has been shown to be an important mechanism by which PTXF protects against ischemic injury; this has been shown to occur both in vitro and in vivo. PTXF decreases TNF-α synthesis via two mechanisms. First, one of its metabolites, lisofylline, inhibits the activity of lysophosphatidic acid acyl transferase that converts lysophosphatidic acid to phosphatidic acid (45). This induces a rise in Ca^{2+} concentration and a decrease in the synthesis of TNF-α (78). Second, PTXF acts as an inhibitor of PDE and induces prolonged cAMP levels resulting in the activation of protein kinase A, which blocks the nuclear factor kappa-B-induced TNF-α messenger RNA transcription (79). This indicates that PTXF, by inhibiting the PDE activity, blocks TNF-α gene transcription and protein synthesis (80) (Figure 3).

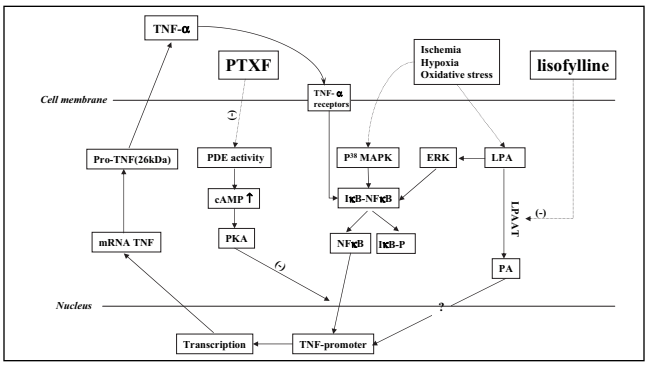

Figure 3) *Tumour necrosis factor-alpha (TNF-α) synthesis induced by ischemia reperfusion and hypoxia in cardiomyocytes, and the mechanism of pentoxifylline's (PTXF's) anti-TNF-α effect. (–) Inhibit; ? Controversial; cAMP Cyclic AMP; ERK Extracellular signal-regulated kinases; IκB-NFκB Inhibit kappa B-nuclear factor kappa B; LPA Lysophosphatidic acid; LPAAT Lysophosphatidic acid acyl transferase; P38 MAPK P38 mitogen-activated protein kinase; PA Phosphatidic acid; PDE Phosphodiesterase; PKA Protein kinase A; TACE TNF-α converting enzyme*

The primary pharmacodynamic effects of PTXF, such as increased RBC deformability and decreased blood viscosity. are also considered to be important mechanisms for protection of ischemic heart (3). Dauber et al (73) demonstrated that PTXF attenuates coronary microvascular protein leak and decreases endothelium-dependent relaxation in coronary epicardial arteries after ischemia and reperfusion. In addition, the increase in neutrophil cAMP induced by PTXF diminished superoxide anion production, adherence of neutrophils to vascular endothelium, and reduced the response of neutrophils to platelet-activating factor (PAF) and cytokines such as TNF-α and IL-1 (81-83). PTXF was also reported to decrease myeloperoxidase, an index of tissue leukocyte accumulation, and, thus, reduce leukocyte adhesion in ischemic myocardium (74,84). In addition, PTXF is an effective hydroxyl radical scavenger, preventing endothelial injury by reactive oxygen species (15). Studies from our laboratory have demonstrated that PTXF has a protective effect on both ischemic heart injury and Ca^{2+} paradox heart injury (85,86). Thus, PTXF, with its limited side effects and favorable hemorheological properties, may be considered to possess great potential for beneficial effects in ischemic heart disease.

EFFECT OF PTXF ON ISCHEMIC SKELETAL MUSCLE

Ischemia-reperfusion injury in skeletal muscle is a clinical disease that exhibits effects at the molecular and cellular levels (87). For instance, swelling of endothelial cells, leukocyte endothelial adhesion, modification of monocyte/neutrophil function, vascular thrombosis and even cell death have been identified in ischemic skeletal muscle (88-91). Finding a method to diminish the extent of endothelial injury and inhibit neutrophil adhesion in ischemic skeletal muscle are topics that have received considerable attention (20,88-90). It has been noted that neutrophils contain primary and secondary granules that consist of a variety of glycoproteins. Complement receptor-3 is one of the glycoproteins released by neutrophils that causes neutrophil adhesion when stimulated by a variety of cytokines (11). Because neutrophil adhesion plays a key role in ischemia-reperfusion injury, finding a way to block this adhesion is considered an important step in establishing a treatment for injuries to skeletal muscle (88,90).

Incidentally, it has been discovered that PTXF inhibits neutrophil adhesion by blocking the effects of complement receptor-3 up-modulation, preventing degranulation of myeloperoxidase and lysozyme, which are found in the granules of neutrophils, and modulating the cytoskeletal interactions at the adenosine A_2 receptor (11,92). PTXF also prevents the adherence of neutrophils stimulated by TNF-α (10). Furthermore, it has been shown that PTXF interferes with the leukocyte-signalling pathway by activating phosphatidylinositol-3-kinase and phospholipase D via a number of different agonists, which eventually inhibits actin polymerization and superoxide anion production (93). Moreover, PAF in venous blood is subsequently decreased; this potent lipid mediator, which is produced by ischemic skeletal muscle during periods of reperfusion, would otherwise result in increased binding of neutrophils to endothelial cells (20,91,94). PTXF also blocks the response of granulocytes to PAF (20,95).

Administration of PTXF at a high dose was found to decrease the degree of skeletal muscle necrosis (91). Adams et al (20) reported that using PTXF (25 mg/kg) immediately before reperfusion extensively diminished the degree of muscle necrosis and PAF levels in the venous effluents of the isolated canine gracilis. As well, Hanazawa et al (96) reported that PTXF treatment prevented leukocyte adhesion after reperfusion in the rat cremaster muscle. The administration of PTXF has also been reported to decrease PAF levels and neutrophil adhesion in ischemic skeletal muscle (10,20,96). In summary, both in vitro and in vivo studies have revealed that the hemorheological and anti-inflammatory activities of PTXF were responsible for the therapeutic effects of PTXF. PTXF can immensely increase recovery in a variety of organs, including the brain, heart, intestines, testes and skeletal muscle, during ischemia-reperfusion injury (4,73,74,84,87,97-101). Thus, PTXF has great potential as a therapeutic intervention for helping patients recover from clinically common ischemia-reperfusion injuries.

EFFECT OF PTXF ON VASCULAR DISEASE

An effective treatment for peripheral arterial disease is necessary because this life-threatening condition affects eight to 10 million people in the United States (102). Furthermore, increased incidence of this disease is correlated with the development of arteriosclerosis and the hypercoagulable state (103-105). It is also well known that a decrease in peripheral blood flow and pathological hemorheological changes are involved in the development of peripheral arterial disease (56). The abnormal proliferation of vascular smooth muscle cells (VSMC) and the accumulation of extracellular matrix components, such as collagen and fibronectin, are major contributing factors for arteriosclerotic vascular disease (106). Moreover, TNF-α, which is an important cytokine that promotes leukocyte adhesion to a vessel wall due to an increase in cell adhesion receptors, is released by the endothelium (107,108). Considering all of these factors, treatment of peripheral arterial disease should focus on lowering blood coagulation that induces arteriosclerosis, affecting blood flow in the injured vessels (109).

As well, it has been uncovered that oral and/or intravenous administration of PTXF can decrease the level of fibrinogen by increasing fibrinolytic activity or reducing fibrinogen production in patients with peripheral vascular disease (3,110,111). It can also improve rest and exercise blood flow in patients with vascular diseases (3). Furthermore, the anti-TNF-α effects of PTXF may provide another way to treat the hypercoagulable state of circulatory failure that worsens arteriosclerosis (11,112).

It has been revealed by a number of studies that PTXF may impede the development of arteriosclerosis by inhibiting the production of the platelet-derived growth factor, which then prevents the proliferation of VSMC (103,113). This drug also reduces the amount of TGF-β produced, thereby, lowering the extent of collagen synthesis in VSMC (113). These antimitogenic and anticollagenic effects of PTXF are mainly associated with the cAMP-protein kinase A effector pathway, thus, decreasing the messenger RNA level of TGF-β_1-stimulated collagen 24 h following PTXF administration (106). In addition, most in vitro and in vivo experiments show that PTXF induces vasodilation in both the skeletal muscle vascular bed and human forearm vascular bed (114-118). Consequently, perfusion in the microcirculatory vascular bed is improved (114-118). These PTXF-induced vasodilation effects may result from PDE activity inhibition, which causes an increase in cAMP levels. cAMP interacts with the adenosine receptor to induce the inhibition of adenosine uptake by blood cells and the endothelium (119-121). Although PTXF was proven to be therapeutically effective for peripheral arterial disease, it has been documented that PTXF does not have any greater beneficial effects over a placebo in treating the vasospastic peripheral vascular disorder known as Raynaud's phenomenon (122). On the other hand, several investigations have suggested that the effectiveness of PTXF stems from its hemorheological property and other pharmacological actions, such as the reduction of blood viscosity, enhancement of fibrinolytic activity, depression of the production of TNF-α and vasodilation action (106,112,119). Thus, PTXF is considered to be of great potential for treating various circulatory disorders clinically (123).

EFFECT OF PTXF ON PLATELET FUNCTION

Platelets are fragments from giant bone marrow megakaryocytes, which are disk-shaped in structure. These fragments have a diameter close to one-third of an RBC's width and they participate in various body functions including maintenance of vascular integrity, arterial thrombosis, activation of plasma coagulation and atherogenesis (52). A number of factors, such as the interactions between cAMP and Ca^{2+}, as well as the formation of prostaglandin, are known to stimulate platelets (52). The cAMP content of platelets regulates the activation of cyclo-oxygenase, which converts arachidonic acid of platelet lipids to end peroxides, and prostaglandin G_1 and H_2; this subsequently leads to the production of thromboxane A_2. As a result, the excessive thromboxane activity causes intravascular platelet aggregation. Prostacyclin, which is synthesized in vascular walls, activates adenylate cyclase to cause an increase in cAMP levels that inhibits prostaglandin-cyclo-oxygenase (52,124) (Figure 4). Thromboxane production is then reduced (5,125).

Platelets release platelet factor 3 that can initiate the coagulation system and stimulate the activation of thrombin, via cleavage of prothrombin, to cause platelet aggregation and disintegration (52,124,125). Alteration of platelet functions impairs

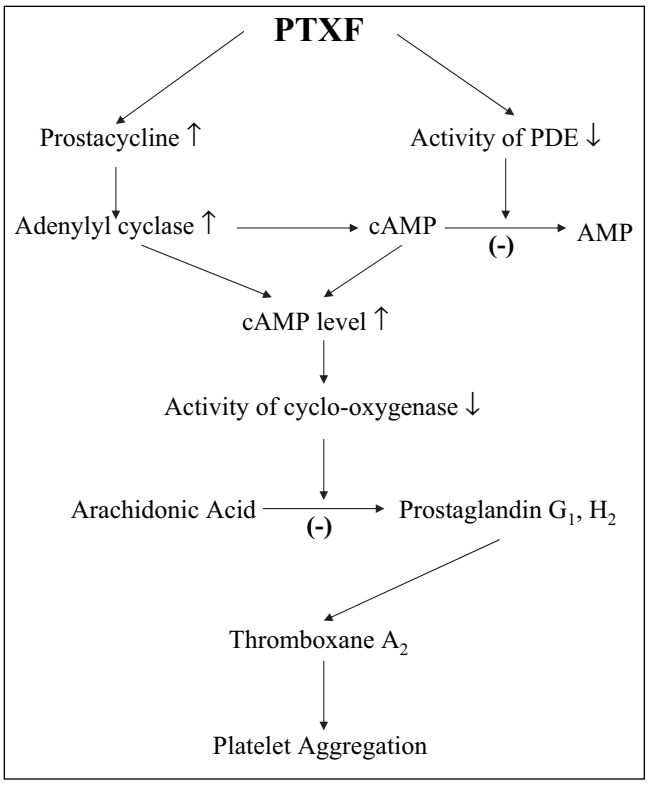

Figure 4) *The mechanism of pentoxifylline (PTXF) on antiplatelet aggregation. ↓ Decrease; ↑ Increase; (–) Inhibit; cAMP Cyclic AMP; PDE Phosphodiesterase*

microcirculation and plays an important role in the development of cardiovascular diseases. Additionally, platelets are highly reactive due to their greater tendency to aggregate and release platelet factor 3 during a stage of cardiovascular dysfunction (125). There is an observed positive feedback phenomenon where platelet dysfunction induces cardiovascular diseases, which further worsens platelet function. Therefore, pharmacological improvement of platelet function is considered to be important for the treatment of all kinds of vascular diseases.

Various research groups have reported that PTXF produces a marked decrease in platelet adhesion and aggregation to the vessel wall in experimental animal models and patients with severe peripheral vascular disorder, cerebrovascular disorders or diabetes (3,105). It is believed that platelet aggregation is prevented through a variety of mechanisms. For instance, platelet membrane PDE activity that converts cAMP to AMP is inhibited by PTXF (11). PTXF also has the added benefit of decreasing platelet aggregation and thrombocytes by decreasing platelet pseudopodia formation, thus, depressing the release of platelet factor 3 (125,126). Following intravenous administration of PTXF, vasodilation is enhanced as serum prostacyclin levels become elevated (3,16,17,20). PTXF can also increase the level of cAMP via prostacyclin-activating adenylate cyclase (125) (Figure 4). Based on all of these findings, it was suggested that PTXF effectively prevents platelet aggregation and adhesion, which lends more credit to the notion that PTXF has a number of therapeutic effects for treating various vascular diseases.

EFFECT OF PTXF ON BLOOD VISCOSITY

Blood viscosity is another major contributing factor for the development of vascular disease. Greater blood viscosity

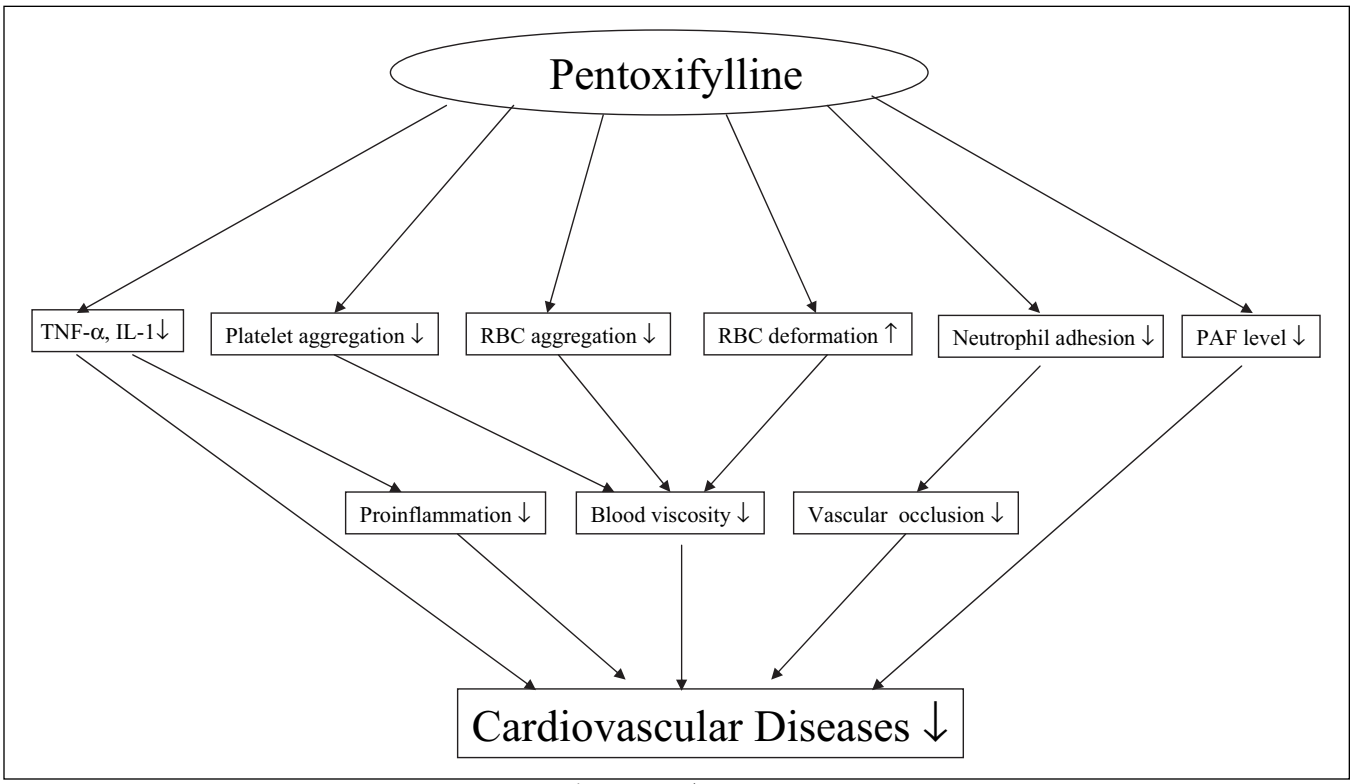

Figure 5) *The role of pentoxifylline in cardiovascular disease. ↓ Decrease; ↑ Increase; IL-1 Interleukin-1; PAF Platelet-activating factor; RBC Red blood cell; TNF-α Tumour necrosis factor-alpha*

induces vascular occlusion, which can occur in a wide variety of diseases such as heart disease, cerebrovascular disease, hypertension and diabetes (127-130). Furthermore, blood viscosity is a variable which changes along a vessel due to the combinatorial effects of many factors such as vascular geometry, flow separation and local blood composition (127). The flexibility of the RBC membrane, fibrinogen levels, shear stress and platelet aggregation are also close determinants of blood viscosity (105,131,132).

Rheology factors can differ greatly among various individuals and diseases. Such variations may influence oxygen supply in the blood (133). Therefore, counteracting an increase in blood viscosity may help treat many vascular diseases (129). A number of methods to decrease blood viscosity have been recognized. A prospective study (134), for instance, demonstrated that fibrinolytic therapy reduces fibrinogen in blood plasma and, in turn, reduces blood viscosity, which results in increased blood flow. Increasing RBC deformability is also another important way of improving blood flow (135,136). According to some studies, it has been found that PTXF decreases blood viscosity by increasing RBC flexibility, decreasing erythrocyte aggregation and stimulating fibrinolysis to reduce plasma fibrinogen concentration (46,137,138). Moreover, Schneider et al (139) reported that therapy with PTXF could decrease shear stress. Consequently, the flow properties of blood and microcirculation can be enhanced with PTXF treatment (128).

SUMMARY AND CONCLUDING REMARKS

Cardiovascular diseases are life-threatening conditions and, thus, have received a great deal of attention over the years. So, it is not surprising that various treatments to cure these diseases, by the use of drugs such as heparin and acetylsalicylic acid, have been approved (140-142). PTXF, however, is another drug now being used to treat various vascular diseases because this methylxanthine derivative has less severe side effects, as well as many potent hemorheological properties, which make it an effective drug for combating vascular disorders (3,57). PTXF may be used to treat ischemic heart disease because it can improve RBC deformability, decrease RBC aggregation (3), increase blood flow to the heart (59), and inhibit neutrophil adhesion and the production of some cytokines, such as TNF-α and IL-1 (14). This drug is also capable of decreasing PAF levels, reducing the effect of PAF during ischemia-reperfusion injury (20), depressing the proliferation of the VSMC (106), inhibiting platelet aggregation and improving blood flow (59). All these properties of PTXF are interrelated and originate from the inhibition of cAMP PDE (19,81,93). The mechanisms of PTXF action are shown in Figure 5. In addition, many studies have shown that PTXF can be therapeutically beneficial in treating liver fibrosis and cirrhosis due to its antifibrogenic action (143,144). Based on the cumulative action of all of these effects, PTXF has been recognized as an effective therapeutic strategy for treating various cardiovascular diseases. However, its mechanism for alleviating cardiovascular dysfunction and the optimum dosage for therapy have not been clearly identified. Hence, a great deal of research and appropriate clinical trials still need to be conducted.

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