Pentoxifylline and its applications in dermatology

Iffat Hassan, Konchok Dorjay, Parvaiz Anwar

Department of Dermatology, STD and Leprosy, Government Medical College Srinagar, University of Kashmir, Jammu and Kashmir, India

ABSTRACT

Pentoxifylline is a methyl-xanthine derivative with many anti inflammatory effects. Pentoxifylline has been found to be effective for many dermatological as well as non-dermatological conditions. It has been used both as primary drug as well as adjuvant and is a safe and relatively cost-effective alternative drug. In this article, we review the literature and highlight various important aspects of pentoxifylline.

Key words: Cost effective, methyl xanthine, pentoxifylline, safe

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Address for correspondence:
Prof. Iffat Hassan, Department of Dermatology, STD and Leprosy, Government Medical College Srinagar, University of Kashmir, Jammu and Kashmir, India.
E-mail: hassaniffat@gmail.com

INTRODUCTION

Pentoxifylline is a methyl-xanthine derivative with a variety of anti-inflammatory effects. Though, use and efficacy of pentoxifylline for a variety of dermatological conditions has been proved in various studies over a long period, yet United States Food and Drug Administration(FDA) has approved its use only for intermittent claudication.

CHEMICAL STRUCTURE

Systematic International Union of Pure and Applied Chemistry name of pentoxifylline is 3,7-dimethyl-1- (5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione and its chemical formula is $C_{13}H_{18}N_4O_3$. The structure is shown in Figure 1.

PHARMACOKINETICS AND METABOLISM

After oral administration, the aqueous solution of pentoxifylline is almost completely absorbed. It undergoes first pass metabolism and various metabolites appear in plasma very soon after administration; peak plasma levels reach within 2 hours. The major metabolites are metabolite I [1-(5-hydroxyhexyl)-3,7-dimethylxanthine] and metabolite V [1-(3-carboxypropyl) -3,7-dimethylxanthine]. The plasma levels of these metabolites are respectively 5 and 8 times greater than pentoxifylline. Excretion is almost totally through urine, main bio transformation product being metabolite V and essentially no parent drug is found in urine. Despite variations in the levels of the parent compound and its metabolites in plasma, urinary recovery of metabolite V is consistent and dose proportional. Less than 4% of the administered dose is recovered in feces.[1,2]

MECHANISMS OF ACTION

There are many hypotheses regarding the mechanism of action of pentoxifylline and its cellular and molecular effects, based on human and animal studies. This includes effects on immune modulation, anti-tumor necrosis factor-α (TNF-α) effects, hemorheological effects, anti fibrinolytic effects, along with effects on endothelial cells and adhesion molecules. These will be described briefly below.

Immune modulation

Pentoxifylline affects immune modulation by means of increased leukocyte deformability and chemotaxis, decreased endothelial leukocyte adhesion, decreased neutrophil degranulation and release of superoxides, decreased production of monocyte-derived TNF, decreased leukocyte responsiveness to interleukin 1 (IL-1) and TNF, inhibition of T and B lymphocyte activation and decreased natural killer cell activity.[3]

Anti-TNF-α effects

Pentoxifylline is known to inhibit the production of TNF-α, which is an important inflammatory

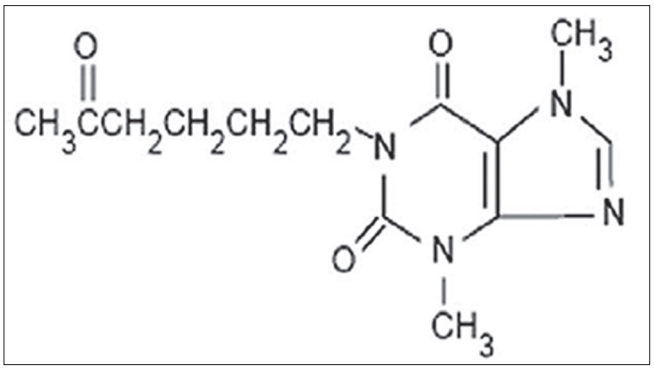

Figure 1: Molecular structure of pentoxifylline

mediator with a wide spectrum of activity, predominantly produced by mononuclear cells. Pentoxifylline is also an active inhibitor of already formed TNF. There is also evidence that pentoxifylline may influence other inflammatory cytokines, such as inhibition of IL-1 and IL-6.[4,5]

Hemorheological effects

Pentoxifylline affects almost all factors responsible for blood viscosity and is among the first known hemorheologically active drug.[6] The primary hemorheological effects of pentoxifylline are caused by increased red blood cell deformability and decreased blood viscosity. The possible mechanism by which this is achieved involves increased erythrocyte adenosine triphosphate and other cyclic nucleotide levels.[7] Pentoxifylline leads to the inhibition of thromboxane and increase of prostacyclin synthesis. Hypercoagulability states improve because of decreased platelet aggregation and adhesion; increased plasminogen activator, plasmin and anti-thrombin III; decreased fibrinogen, alpha 2-antiplasmin, alpha-1 antitrypsin and alpha-2 macroglobulin.[3] Furthermore, pentoxifylline increases leukocyte deformability, inferring the possibility of a greater role of polymorphonuclear leukocytes in whole blood viscosity.[8,9] Thus, it can be considered as an almost complete rheological drug.[10]

Anti-fibrinolytic effects

Pentoxifylline increases fibroblast collagenases and decreases the production of collagen, fibronectin and glycosaminoglycan.[11] These effects could be attributed to its anti TNF-α properties or separate mechanisms as suggested by various studies.[12]

Other effects

Pentoxifylline is a non-selective inhibitor of cyclic-3', 5'-phospho-diesterase (PDE), leading to a broad-spectrum effect against cell proliferation and inflammation. It also reduces the expression of adhesion molecules such as intercellular adhesion molecule-I (ICAM-I) on keratinocytes and E-selectin expression on endothelial cells.[13]

CLINICAL APPLICATIONS IN DERMATOLOGY

Pentoxifylline has found a place in the management of a variety of dermatological conditions. The most common ones are described below.

Peripheral vascular diseases

Pentoxifylline has been used world-wide for the treatment of intermittent claudication and in 1984 United States FDA approved its use for intermittent claudication in the United States. Various studies have shown the therapeutic efficacy of pentoxifylline in a significant percentage of patients with peripheral vascular disease.[14-16] However, use in intermittent claudication still remains the main indication.[17] Intravenous pentoxifylline may be of benefit in acute ischemic lesions in systemic sclerosis,[18] when used as 1200 mg/day for 21 days. However, further studies are required to confirm these initial findings.[18]

Vasculopathies and vasculitides

Due to its multiple effects on various blood cells and also through anti-inflammatory effects, pentoxifylline could be a useful drug in treating vasculopathies as described in various studies.[19-21]

Venous leg diseases and ulcers

Pentoxifylline is also used in the treatment of venous leg disease[22] and venous ulcers, especially in patients unable to tolerate compression therapy.[23,24]

Pigmented purpuric dermatoses

Successful treatment with pentoxifylline causes decrease in expression of ICAM-I on endothelial cells in and around PPD lesions,[13] resulting in decreased exudation of inflammatory cells from capillaries into the surrounding perivascular tissue and also reduced TNF mediated extravasations.[25] Pentoxifylline being economical, easily available and devoid of serious side-effects should be considered for use in Schamberg's disease, a type of PPD; some advocate it as first line therapy.[13,26-28]

Aphthosis and Behçet disease

Pentoxifylline has been found effective in recurrent oral and genital aphthosis.[29-32] These beneficial effects may be due to anti-TNF-α properties of pentoxifylline as well as correction of impaired erythrocyte deformability, which has been shown to be decreased in active Behçet disease patients in comparison with healthy control subjects.[33]

Leprosy

Various studies have documented that pentoxifylline rapidly ameliorates the systemic symptoms of type II leprosy reaction

and it could be an alternative (though less effective) to thalidomide[34-37] and a good option for patients with human immunodeficiency virus (HIV) co-infection, where steroids are contraindicated.[38]

Acquired immunodeficiency syndrome and pruritic papular eruption of HIV/AIDS

Pentoxifylline may be considered as safe and efficacious treatment for pruritus in HIV-infected patients. More controlled studies are however needed to authenticate it.[39] This could be because of the inhibitory effect of pentoxifylline on TNF-α, which increases in many patients with AIDS.[40] It also decreases HIV replication.[41]

Leishmaniasis

Pentoxifylline suppresses TNF-α gene transcription, potentiates the expression of inducible nitric oxide (NO) synthetase leading to NO production and decreases leukocyte migration and adhesion.[42,43] TNF-α seems to play a great role in the pathogenesis of mucosal leishmaniasis[42-44] and pentoxifylline has been proposed for the treatment of cutaneous[42] and mucocutaneous leishmaniasis[43] as adjuvant to pentavalent antimony, which reduces the healing time significantly and prevents the need for further courses of pentavalent antimony.[42,45,46] The combined therapy with glucantime and pentoxifylline has been found to be more effective than glucantime alone.[46]

Psoriasis

Besides its use as an adjuvant therapy in psoriasis, it has been suggested that pentoxifylline counteracts many of the unwanted effects of cyclosporine on red blood cells, platelets and coagulation factors.[6,47] Abnormal metabolism of triglyceride is common in psoriatic patients[48,49] and is exaggerated after cyclosporine therapy.[50] Pentoxifylline possibly reduces serum triglycerides, so it seems sensible to use pentoxifylline in combination with cyclosporine to reduce the side-effects of the later. Thus, pentoxifylline seems to be a promising well-tolerated and safe adjuvant drug for use in psoriasis.[51]

Graft-versus-host disease

Cytotoxic T lymphocyte mediated tissue injury and inflammatory cytokines including TNF-α play important roles in the pathogenesis of GVHD. Use of pentoxifylline in combination with other treatments could result in lower relapse rates and improved overall event free survival.[52] However, prophylactic role of pentoxifylline in GVHD is conflicting.[53]

Sarcoidosis

Although, specific inciting antigen for sarcoidosis has not yet been identified, it appears to be Th1 mediated disease and TNF-α likely plays a critical role in the granuloma formation.[54] Pentoxifylline can almost completely inhibit spontaneous TNF-α production from alveolar macrophages of sarcoidosis patients;[55] thus, a potential role in the treatment of pulmonary sarcoidosis,[56] but there is little evidence as yet, about its role in cutaneous sarcoidosis.

Peyronie's disease

Pentoxifylline is a non-specific PDE inhibitor, which downregulates transforming growth factor beta (TGF-β1), increases fibrinolytic activity[57] and increases NO levels, so possible role of pentoxifylline to prevent progression of Peyronie's disease, reverse fibrosis,[58] improve penile curvature and ultrasonographic appearance of the plaque[58] and stabilize or reduce calcium content in penile plaques.[59]

Radiation induced fibrosis and burns

Radiation induced fibrosis is mediated by TGF-β,[60] besides its central role in scleroderma.[61] TGF-beta induced collagen biosynthesis is reduced by pentoxifylline.[3,18,62] In addition, fibroblast collagenases are also activated.[3] Hence, the treatment of radiation induced fibrosis with pentoxifylline and vitamin E can be a practicable and cost-effective regimen, especially for inoperable patients.[63] Pentoxifylline has been found to have a direct effect on inhibiting burn scar fibroblasts and it can be potentially useful for reducing burn scar contractures in future.[64]

Keloids, scleroderma and morphoea

Because of inhibitory effects of pentoxifylline on the proliferation and certain biosynthetic activities of fibroblasts derived from human skin, it has a potential adjuvant role for keloids, hypertrophic scars, morphea, scleroderma and other fibrosing conditions.[65]

Oral sub-mucous fibrosis

Oral sub-mucous fibrosis is a common premalignant condition in the Indian subcontinent, caused by chewing areca nut and other irritants in various forms. The efficacy of pentoxifylline in oral sub mucous fibrosis, singly and as adjuvant therapy has been demonstrated in various studies.[66,67]

Pseudoxanthoma elasticum

The use of pentoxifylline for ischemic pain in pseudoxanthoma elasticum and other micro vascular disorders has been encouraging.[6]

Actinic prurigo

Induction of complete or partial remission of lesions of actinic prurigo with the use of pentoxifylline allows for reduction in the use of topical corticosteroids.[68]

Irritant and allergic hypersensitivity reactions

Various studies conducted on animals suggest a potential role of pharmacologic intervention with pentoxifylline as a means to treat contact dermatitis.[69]

Lipodermatosclerosis

Use of pentoxifylline along with hydroxychloroquine leads to better improvement in lipodermatosclerosis.[70]

Ulcerating necrobiosis lipoidica

The efficacy of pentoxifylline for necrobiosis lipoidica has been documented in various studies,[71,72] probably because it inhibits platelet aggregation and decreases blood viscosity.

Kasabach-Merritt syndrome, pretibial myxedema

Because of its anti-fibrinolytic effect, pentoxifylline could be useful in treating fibroblast mediated diseases such as pretibial myxedema, resulting in reduction of thickness of skin lesions, when used in combination with topical or intralesional steroids.[73,74]

Stevens-Johnson syndrome and toxic epidermal necrolysis

Pentoxifylline has been used as a miscellaneous drug for SJS and TEN, especially in children.[75,76]

Other uses

Pentoxifylline may also be beneficial in other diseases such as Kimura's disease with oral ulcers, generalized granuloma annulare, sweet syndrome, pemphigus vulgaris and other bullous disorders.[77-79]

DOSAGE

Adult dose is 400-800 mg twice to thrice-a-day.

NON-DERMATOLOGICAL USES

In addition to intermittent claudication, pentoxifylline has found application in varied disease processes; although, the mechanism is not fully elucidated in every case. The drug is gaining acceptance for conservative treatment of neuropathic injuries; prevention of thromboembolic strokes and septic shock;[80] management of sickle cell disease; nausea and headaches in high altitude mountain sickness; acute alcoholic and non-alcoholic steatohepatitis and alcoholic liver disease, presumably through its ability to inhibit TNF; treatment of endometriosis;[81] stimulation of various sperm motion parameters and cervical mucus penetrability in patients with asthenozoospermia,[82] to mention just a few.

CHECKLIST BEFORE PRESCRIBING PENTOXIFYLLINE

While prescribing pentoxifylline, following parameters should be specifically considered:

- Allergic to caffeine containing products (coffee, tea, colas), pentoxifylline, theobromine, theophylline or any other drugs
- Prior medications, especially anticoagulants ("blood thinners") such as warfarin (Coumadin) and vitamins
- Kidney disease
- Pregnant, planning pregnancy or lactating
- Any surgery in the near future
- Advice to avoid driving a car or operating machinery.

ADVERSE EFFECTS

Overall, pentoxifylline is a very safe drug and is usually well tolerated. The side-effects are dose-related and the most common are those of the gastrointestinal tract and central nervous system. The main central nervous system side effects are dizziness, headache, anxiety and confusion. Side effect profile of pentoxifylline is summarized in Table 1.

CONTRAINDICATIONS

- Pregnancy: Pregnancy category C
- Lactation: Pentoxifylline is excreted in breast milk and may cause adverse effects in the infant
- Children: Safety and efficacy not established
- Geriatric: Use with caution, usually starting at the lower dosage range, because of the greater frequency of

Table 1: Side-effect profile of pentoxifylline

Most common	Miscellaneous	Rare	Potentially fatal
Digestive: Dry mouth or dehydration, constipation, anorexia, cholecystitis	Excessive salivation, malaise, leukopenia, bad taste, weight gain or loss, sore throat, nausea, headache	Digestive: Jaundice, hepatitis, increase in liver enzymes	Fatal hemorrhage (cerebral and gastrointestinal tract)
Neurologic: Aseptic meningitis, seizures, confusion, depression, anxiety		Cardiovascular: Anaphylactoid reactions, angina, tachycardia, arrhythmia	Anaphylactoid reaction
Cardiovascular: Hypotension, edema, dyspnea		Hematologic and lymphatic: Aplastic anemia, purpura, leukemia, decrease in fibrinogen, thrombocytopenia, pancytopenia	
Respiratory: Nasal congestion, nosebleed, breathing difficulty			
Dermatological (skin related): Rash, angioedema, urticaria, pruritus, brittle nails			
Visual/aural: Earache, scotoma, conjunctivitis, blurred vision			

decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy
- Other contraindications include previous hypersensitivity reactions to xanthine related products, e.g. caffeine, theophylline and theobromine; recent cerebral and/or retinal hemorrhage; porphyria.

CONCLUSION

Pentoxifylline has been found to be a relatively safe and cost effective therapeutic drug with proven as well as potential uses in a number of dermatological diseases. It may be of use to dermatologists both singly (primary) and as an adjuvant drug, thus providing an alternative to other treatment options and sparing the adverse effects of various therapeutic modalities such as corticosteroids. Although a number of studies have been conducted in order to prove the beneficial effects of pentoxifylline, there is paucity of data to determine its role in various dermatological diseases. More studies are needed to fully establish its therapeutic efficacy.

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