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REVIEW ARTICLE

PENTOXIFYLLINE: APPLICATIONS IN DENTISTRY

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ABSTRACT

Pentoxifylline is a methylxanthine imitative with a range of anti-inflammatory effects presently pentoxifylline is permitted by the Food and Drug Administration for the management of intermittent claudication, but studies have revealed that it has a diversity of physiological effects at the cellular level which may be significant in treating a different group of diseases. Clinical

applications of pentoxifylline in dentistry have been reviewed Effects of PTX on different cellules and molecules Anti-TNF-α effects ,tumor Necrosis Factor-α is a cytokine with a wide spectrum of activity which is predominantly produced by mononuclear cells. Increasing evidence has implicated TNF-α as a pivotal molecule involved in the pathogenensis of a wide variety of acute and chronic inflammatory disease states including many skin diseases such as psoriasis, graft-versus-host-disease (GVHD), contact dermatitis , leprosy reactions, OSMF, AIDS..

INTRODUCTION

Pentoxifylline (PTX) is a methylxanthine derivative and is indeed the first known hemorheologically active drug [1]. The primary hemorheological effects of PTX are caused by increased red blood cell deformability and decreased blood viscosity. The mechanism by which this is achieved has been shown to involve increased erythrocyte adenosine triphosphate (ATP) and other cyclic nucleotide levels [2].

Hemorheological properties of PTX are not completely confined to its effects on red blood cells; by increasing intracellular cAMP levels,PTX leads to the inhibition of thromboxane synthesis and an increase of prostacyclin synthesis. Therefore, platelet aggregation and adhesion to vessel walls is also inhibited. In addition, it increases tissue plasminogen activator and plasmin and this complex of effects makes PTX a valuable drug for improving hypercoagulable states. Interestingly, PTX causes platelet disaggregation only in conditions in which the platelets are

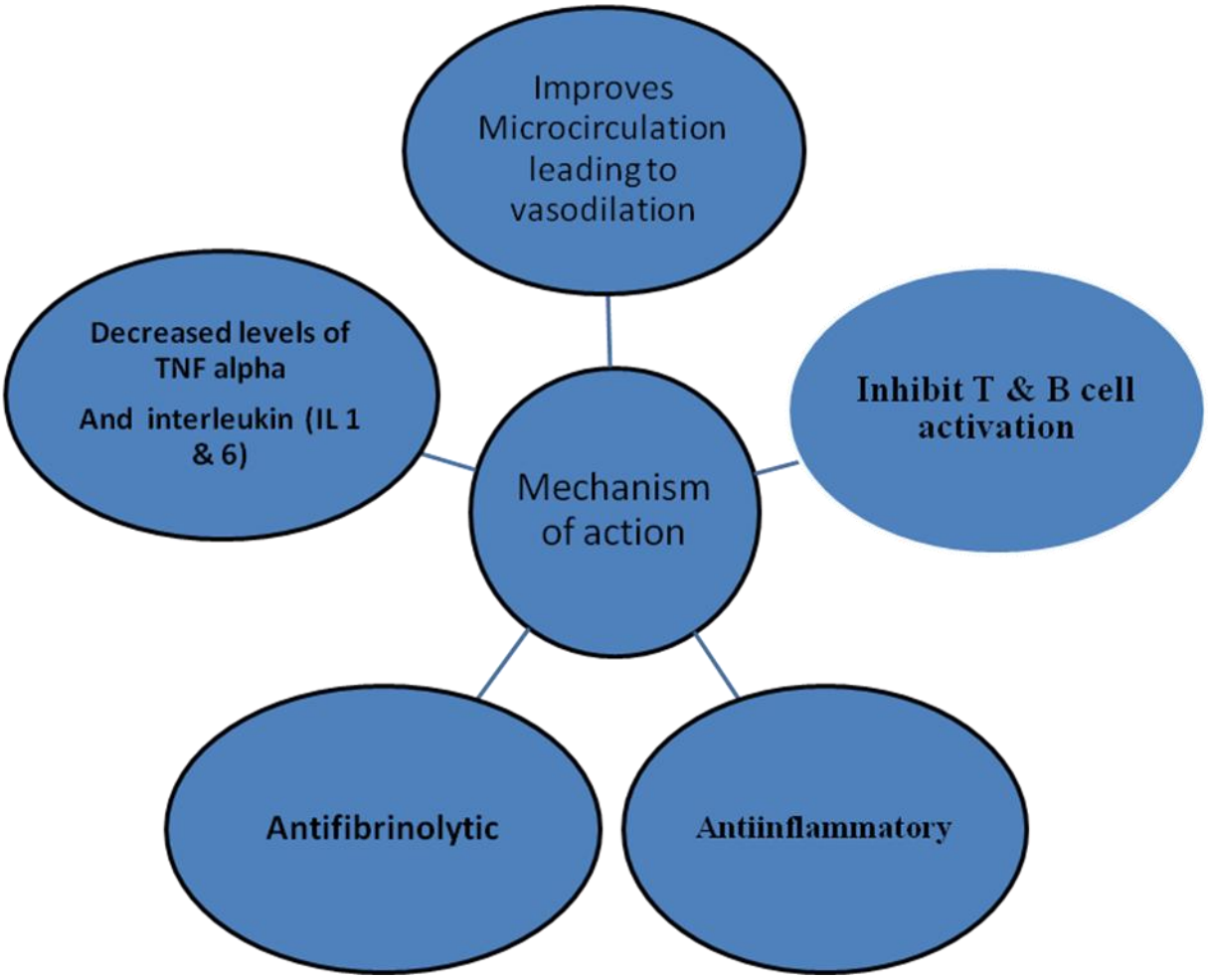
hyperaggregable, but does not cause prolonged bleeding or any platelet abnormalities in normal persons [1,3].

Pentoxifylline was first registered (in Germany) 20 years ago. Its main action seemed to be vasodilatation.It obtained marketing authorization in Germany 1972 and in USA 1984 for the treatment of intermittent claudication on the basis of chronic occlusive arterial disease of the limbs.Furthermore, PTX increases leucocyte deformability and regarding this new concept that polymorphonuclear leukocytes may play even a greater role in whole blood viscosity [4,5], it can be considered as an almost complete rheologic drug.

Antifibinolytic effects Pentoxifylline increases fibroblast collagenases and decreases collagen, fibronectin and glycosaminoglycan production [6]. Although, these effects could be due to anti TNF-α properties of PTX, studies have revealed that this inhibitory activities of PTX on

fibroblasts are mediated by a separate mechanism [7].It also have effects including a non-selective inhibitor of cyclic-3', 5'-phosphodiesterase (PDE), which leads to a broad-spectrum effects against cell proliferation and inflammation.Pentoxifylline is an inhibitor of production of IL-1 and IL-6, an inhibitor of T and B cell activation, and a suppressor of neutrophil degranulation. Furthermore, it has been shown that it reduces the expression of adhesion molecules such as ICAM-1, on keratinocytes and E-selectin expression on endothelial cells [8].

MECHANISM OF ACTION:



PHARMACOKINETICS, DOSAGE AND SIDE EFFECTS:

Pentoxifylline is readily absorbed from the gastrointestinal tract and its peak plasma level is achieved within 2 hours, but it undergoes firstpass hepatic metabolism [9,10]. The usual adult dosage of PTX is 400 mg TID after meals. However, in patients with renal insufficiency

the dose has to be adjusted. Overall, PTX is a very safe drug and is usually well tolerated. Its most common side effects are those of the gastrointestinal tract and central nervous system which appear in approximately 3 percent of patients [11]. The main central nervous system side effects are dizziness, headache, anxiety, and confusion. These side effects are dose-related and can be minimized by reduction of the dose.

CLINICAL APPLICATIONS IN DENTISTRY:

1) APHTHOUS ULCER AND BEHCET DISEASE:

There are some reports that have shown the efficacy of PTX in treating recurrent oral and genital aphthosis [12,13,14]. Furthermore, PTX has been used by many rheumatologists for the treatment of Behcet disease (BD).. Although these beneficial effects may be due to the anti-TNF-α properties of PTX, a recent study has shown that erythrocyte deformability is decreased in active BD patients in comparison with healthy control subjects. Hence, the therapeutic mechanism underlying the beneficial effect of PTX in BD is possibly the correction of impaired erythrocyte deformability [15]. PTX can be also regarded as a preventive modality for thrombotic events, which are among the other characteristics of BD.

2) AIDS:

Increased levels of TNF-α have been demonstrated in many patients with AIDS [16]; Pentoxifylline has been shown to decrease TNF-α expression, serum fasting triglycerides, and HIV replication in these patients [17]. Also, it has been documented that PTX is a safe and efficacious treatment for the pruritic papular eruption of HIV/AIDS, a common and usually recalcitrant manifestation of HIV infection [18].

3) GRAFT-VERSUS-HOST DISEASE (GVHD):

Cytotoxic T-lymphocyte mediated tissue injury and inflammatory cytokines including TNF-α play important roles in the pathogenesis of

GVHD. Therefore, theoretically PTX could be a useful drug in reducing the incidence of this disease.Theoretically, through its antifibfinolytic activities, PTX could be useful in treating fibroblast-mediated diseases such as pretibial myxedema. [11]

4) PERIPHERAL VASCULAR DISEASES:

Pentoxifylline is effective in peripheral vascular diseases.It act by inflammatory reactions which may lead to fibrosclerotic remodeling of the skin and then to ulceration. The leukocyte activation is accompanied by the expression of integrins and by synthesis and release of many inflammatory molecules, including proteolytic enzymes, leukotrienes, prostaglandin, bradykinin, free oxygen radicals, cytokines, and possibly other classes of inflammatory mediators [19]. As leukocytes become activated, they become rigid and immobile; this leads to further occlusion of small vessels and trophic changes in the overlying skin [5].

5) VASCULOPATHIES AND VASCULITIDES:

Due to its multiple effects on various blood cell types and probably through its anti-inflammatory effects, PTX could be a useful drug in treating vasculopathies. Indeed, several studies have shown the beneficial effects of PTX in idiopathic livedoid vasculopathies and some authors suggest it as a drug of choice for this condition [20, 21, 22].Cutaneous vasculitides are usually managed primarily with colchicine, dapsone, and prednisone. Theoretically, PTX can act as a

sparing agent in different kinds of vasculitides, both through its extensive hemorheologic effects and also by neutralizing proinflammatory cytokines. Specifically, it seems that PTX works synergistically with dapsone in treating hypocomplementemic urticarial vasculitis [23, 24].

6) PIGMENTED PURPURIC ERUPTIONS:

Although there is limited evidence, one study of three cases of Schamberg's disease revealed showed successful treatment with PTX. The authors suggested that PTX acts through its effects on adhesion molecules in this disease [8].

7) PSORIASIS:

Perhaps the prototype of TNF-α mediated diseases in dermatology is psoriasis. Indeed, some of the new biologic drugs for psoriasis act by inhibition of this cytokine. The beneficial effects of PTX in psoriasis have been shown in nude mice in both in vivo and in vitro studies [25], but there is a lack of sufficient studies in humans.Pentoxifylline can be used also as an adjuvant therapy in psoriasis. Because a possible beneficial of PTX is in reducing serum triglycerides, it seems that a combination of PTX and cyclosporine is a very sensible choice.

8) LEPROSY:

An increase in TNF-α has been implicated in type II leprosy reaction.Several studies have been documented that PTX rapidly ameliorates the systemic symptoms of type II leprosy reaction and could be an ideal alternative for thalidomide [26,27].These data suggest that PTX inhibits TNF-α production in erythema nodosum leprosum (ENL) patients both in vivo and in vitro; thus it may be useful in the treatment of this type of leprosy reaction [28].

9) LEISHMANIASIS:

Tumor Necrosis Factor-α has been also implicated in the immunopathogenesis of cutaneous leishmaniasis. It is expressed in lesions of patients with American cutaneous leishmaniasis and has been shown to be elevated in the serum of patients with mucocutaneous leishmaniasis [29].

Several studies have shown that PTX, as an adjuvant to pentavalent antimonials could be regarded as an effective tool in treating both mucosal and cutaneous leishmaniasis [29, 30, 31].

10) SARCOIDOSIS:

Although a specific inciting antigen has not yet been identified for sarcoidosis, it appears to be a Th1-mediated disease; TNF-α likely plays a critical role in granuloma formation in this disease [32]. Pentoxifylline can almost completely inhibit spontaneous TNF-α production from alveolar macrophages of sarcoidosis patients [33].Clinically, in an open-label trial, Zabel et al. have documented that PTX is an effective drug in the treatment of pulmonary sarcoidosis [34], but

specific studies addressing the treatment of cutaneous sarcoidosis haveyet to be done.

11) OSMF:

Pentoxifylline is effective in OSMF as its reduces the burning sensation and improves mouth opening It has the mechanism of action as follows in OSMF by improving microcirculation ,decreases platelet aggregation ,decrease granulocyte adhesion. Increases leukocyte deformability, Inhibits neutrophil adhesion,Fibrinolytic activity, Degranulation of neutrophils, inhibits T-cell, B-cell activation(35,36)

12) OSTEORADIONECROSIS:

Pentoxifylline is effective in treating cases with osteoradionecrosis .It is effective by the following action Inhibits dermal fibroblasts, and increases collagenase activity, Decreased levels of TNF, reduced production of interleukin-12 and improves microcirculation(37)

CONCLUSION

In conclusion, it seems that PTX is able to help dentist in a wide spectrum of diseases. However, the paucity of the clinical trials makes it difficult to draw definite conclusions about the degree of benefit of PTX in various clinical settings.

When using PTX therapy it should be kept in mind that in most cutaneous diseases the beneficial effects may not be evident until after several weeks or even months of treatment. For some diseases the full improvement may take several years. Some reports of treatment failure

may be due to inadequate therapy duration [57, 58]. Furthermore, it should be stressed that in most conditions PTX should be regarded as a valuable therapeutic adjuvant rather than a primary treatment.

REFERENCES

1.Ely H. Pentoxifylline therapy in dermatology: a review of localized hyperviscosity and its effect on the skin. Dermatol Clin 1988;6:585-608 PubMed

2. Porsche E, Stefanovich V. The influence of pentoxifylline on ATPase activity of human erythrocyte membranes. IRCS J Med Sci 1978;6:285

3. Ely H. Is pentoxifylline the drug of the decade? J Am Acad Dermatol 1994;30:639-42 PubMed

4. Nees S, Schonharting M. On the role of different blood cell types in the rheological behavior of whole blood. Clin Hemorheol 1987;7:417

5. Ely H. White blood cells as mediators of hyperviscosity-induced tissue damage in neutrophilic vascular reactions: therapy with pentoxifylline. J Am Acad Dermatol 1989;20:677-80 PubMed

6. Berman B, Duncan MR. Pentoxifylline inhibits normal human dermal fibroblast in vitro proliferation, collagen, glycosaminoglycan, and

1/30/2014 Pentoxifylline: A drug with wide spectrum applications in dermatology http://anagen.ucdavis.edu/1411/reviews/pentoxy/zargari.html 8/12

fibroblast in vitro proliferation, collagen, glycosaminoglycan, and fibronectin production, and increases collagenase activity. J Invest Dermatol 1989;92:605-10 PubMed

7. Berman B, Wietzerbin J, Sanceau J, Merlin G, Duncan MR. Pentoxifylline inhibits certain constitutive and tumor necrosis factor-α induced activities of human normal dermal fibroblasts. J Invest Dermatol 1992;98;706-12 PubMed

8. Kano Y, Hirayama K, Orihara M, Shiohara T. Successful treatment of Schamberg's disease with pentoxifylline. J Am Acad Dermatol 1997; 36: 827-30 PubMed

9. Smith RV, Waller ES, Doluisio JT, Bauza MT, Puri SK, Ho I, Lassman HB. Pharmacokinetics of orally administered pentoxifylline in humans. J Pharm Sci 1986;75:47-52 PubMed

10. Dettelbach HR, Aviado DM. Clinical pharmacology of pentoxifylline with special reference to its hemorrheologic effect for the treatment of intermittent caludication. J Clin Pharmacol 1985;25:8-26 PubMed

11. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs 1987; 34:50-97 PubMed.

12. Pizarro A, Herranz P, Ferrer M, Casado M. Recurrent oral aphthosis: treatment with pentoxifylline. Med Clin (Barc). 1993; 101:237 PubMed

13. Pizarro A, Herranz P, Garcia-Tobaruelaa A, Casado M. Pentoxifylline in the treatment of orogenital aphthosis and Behcet's syndrome. Med Clin (Barc). 2000; 115:678 PubMed

14. Thornhill MH, Baccaglini L, Theaker E, Pemberton MN. A randomized, double-blind, placebo-controlled trial of pentoxifylline for

the treatment of recurrent aphthous stomatitis. Arch Dermatol
2007;143:463-70 PubMed
15. Uskudar O, Erdem A, Demiroglu H, Dikmenoglu N. Decreased
erythrocyte deformability in Behcet's disease. Clin Hemorheol Microcirc
2005; 33:89-94 PubMed
16. Lahdevirta J, Maury CPJ, Teppo A-M, Repo H. Elevated levels of
circulating cachectin tumor necrosis factor in patients with acquired
immunodeficiency syndrome. Am J Med. 1988; 85:289-291 PubMed
17. Dezube BJ, Pardee AB, Chapman B, Beckett LA, Korvick JA,
Novick WJ, et al. Pentoxifylline decreases tumor necrosis factor
expression and serum triglycerides in people with AIDS. J Acquir
Immun Defic Syndr. 1993;6:787-794 PubMed
18. Berman B, Flores F, Burke G. Efficacy of pentoxifylline in the
treatment of pruritic papular eruption of HIV-infected persons. J Am
Acad Dermatol 1998; 38: 955-9 PubMed
19. Pascarella L, Schonbein GW, Bergen JJ. Microcirculation and
venous ulcers: a review. Ann Vasc Surg 2005; 19:921-7 PubMed
20. Sams WM. Livedo vasculitis: therapy with pentoxifylline. Arch
Dermatol 1988;124:684-7 PubMed
21. Marzano AV, Vanotti M, Alessi E. Widespread livedoid
vasculopathy. Acta Derm Venereol 2003; 83:457-60 PubMed
22. Ely H, Bard JW. Therapy of livedo vasculitis with pentoxifylline.
Cutis 1988;42:448-53 PubMed
1/30/2014 Pentoxifylline: A drug with wide spectrum applications in dermatology
http://anagen.ucdavis.edu/1411/reviews/pentoxy/zargari.html 9/12
Cutis 1988;42:448-53 PubMed
23. Nurnberg W, Grabbe J, Czarnetzki BM. Urticarial vasculitis
syndrome effectively treated with dapsone and pentoxifylline. Acta
Derm Venereol 1995; 75:54-6 PubMed
24. Nurnberg W, Grabbe J, Czarnetzki BM. Synergistic effects of
pentoxifylline and dapsone in leucocytoclastic vasculitis. Lancet
1994;343:491 PubMed
25. Gilhar A, Grossman N, Kahanovicz S, Reuveni H, Cohen S, Eitan
A. Antiproliferative effect of pentoxifylline on psoriatic and normal
epidermis. In vitro and in vivo studies. Acta Derm Venereol 1996
;76:437-41 PubMed
26. Welsh O, Gomez M, Mancias C, Ibarra-Leal S, Millikan LE. A
new therapeutic approach to type II leprosy reaction. Int J Dermatol
1999; 38:931-3 PubMed
27. Nery JA, Perisse AR, Sales AM, Vieira LM, Souza RV, Sampaio
EP, Sarno EN.
The use of pentoxifylline in the treatment of type 2 reactional episodes in
leprosy. Indian J Lepr 2000; 72: 457-67 PubMed
28. Sampaio EP, Moraes MO, Nery JA, Santos AR, Matos HC,
Sarno EN. Pentoxifylline decreases in vivo and in vitro tumour necrosis
factor-alpha (TNF-α) production in lepromatous leprosy patients with
1/30/2014 Pentoxifylline: A drug with wide spectrum applications in dermatology
http://anagen.ucdavis.edu/1411/reviews/pentoxy/zargari.html 10/12
erythema nodosum leprosum (ENL). Clin Exp Immunol 1998;111: 300-
8 PubMed
29. Báfica A, Oliveira F, Freitas LA, Nascimento EG, Barral A.
American cutaneous leishmaniasis unresponsive to antimonial drugs:

successful treatment using combination of N-methilglucamine
antimoniate plus pentoxifylline. Int J Dermatol. 2003; 42:203-7 PubMed
30. Sadeghian G, Nilforoushzadeh MA. Effect of combination therapy
with systemic glucantime and pentoxifylline in the treatment of cutaneous
leishmaniasis. Int J Dermatol. 2006 ;45:819-21 PubMed
31. Machado PR, Lessa H, Lessa M, Guimarães LH, Bang H, Ho JL,
et al. Oral pentoxifylline combined with pentavalent antimony: a
randomized trial for mucosal leishmaniasis. Clin Infect Dis.
2007;44:788-93 PubMed
32. Moller DR. Involvement of T-cells and alterations in T-cell
receptors in sarcoidosis. Semin Respir Infect 1998;13:174-83 PubMed
33. Marques LJ, Zheng L, Poulakis N, Guzman J, Costabel U.
Pentoxifylline inhibits TNF-alpha production from human alveolar
macrophages. Am J Respir Crit Care Med. 1999;159:508-11 PubMed
34. Zabel P, Entzian P, Dalhoff K, Schlaak M. Pentoxifylline in
treatment of sarcoidosis. Am J Respir Crit Care Med. 1997;155:1665-
9
35
Pentoxifylline Therapy in the Management Of OralSubmucousFibrosis
Asian Pacific J Cancer Prev, 12, 971-974
36) **Pentoxifylline therapy : A new adjunct in the treatment of oral submucous fibrosis**
Indian Journal of Dental Research, 2006; 17 (4):190—198
37). Haddad P, Kalaghchi B, Amouzegar-Hashemi F. Pentoxifylline and
vitamin E combination for superficial radiation-induced fibrosis: a phase
II clinical trial. Radiother Oncol 2005; 77:324-6 PubMed