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Research 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 pathogenesis 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.

Keywords: Pentoxifylline, TNF, GVHD, AIDS, OSMF.

INTRODUCTION

Pentoxifylline (PTX) is a methylxanthine derivative and is indeed the first known hemorheologically active drug. 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 [1].

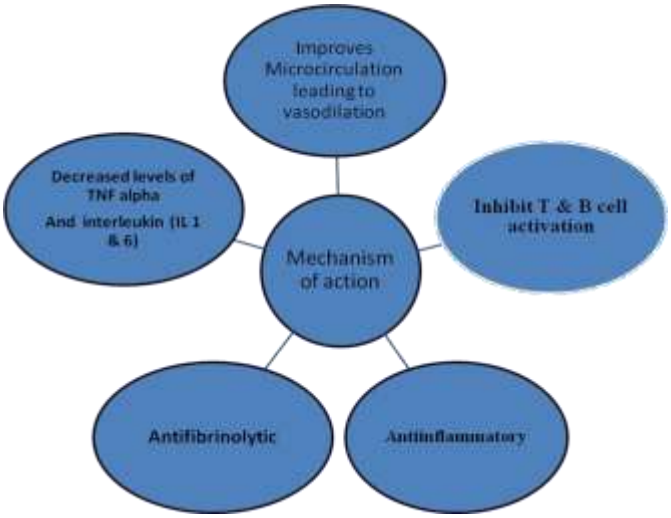
Hemorheological properties of PTX are not completely confined to its effects on red blood cells; by increasing intracellular cAMP levels, PTX leads to the inhibition of thromboxane synthesis and an increase of prostacyclin synthesis. Therefore, platelet aggregation and adhesion to vessel walls are also 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.

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, it can be considered as an almost complete rheologic drug [2].

Antifibrinolytic effects Pentoxifylline increases fibroblast collagenases and decreases collagen, fibronectin and glycosaminoglycan production. Although these effects could be due to anti-TNF-α properties of PTX, studies have revealed that the inhibitory activities of PTX on fibroblasts are mediated by a separate mechanism. It also has effects, including a non-selective inhibitor of cyclic-3', 5'-phosphodiesterase (PDE), which leads to broad-spectrum effects against cell proliferation and inflammation. Pentoxifylline is an inhibitor of the 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 [3].

MATERIALS AND METHODLOGY



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. 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. 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 [4].

Clinical applications in dentistry

Aphthous ulcer and behcet disease

There are some reports that have shown the efficacy of PTX in treating recurrent oral and genital aphthosis. 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. PTX can be also regarded as a preventive modality for thrombotic events, which are among the other characteristics of BD.

AIDS

Increased levels of TNF-α have been demonstrated in many patients with AIDS; Pentoxifylline has been shown to decrease TNF-α expression, serum fasting triglycerides, and HIV replication in these patients. 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 [5].

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.

Peripheral vascular diseases

Pentoxifylline is effective in peripheral vascular diseases.It acts by inflammatory reactions which may lead to fibrosclerotic remodelling of the skin and then to ulceration. The leukocyte activation is accompanied by the expression of integrins and by the synthesis and release of many inflammatory molecules, including proteolytic enzymes, leukotrienes, prostaglandin, bradykinin, free oxygen radicals, cytokines, and possibly other classes of inflammatory mediators. As leukocytes become activated, they become rigid and immobile; this leads to further occlusion of small vessels and trophic changes in the overlying skin [6].

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. 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.

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.

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, 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 [7].

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. 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.

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.

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 [8].

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. Pentoxifylline can almost completely inhibit spontaneous TNF-α production from alveolar macrophages of sarcoidosis patients. Clinically, in an open- label trial, Zabel et al. have documented that PTX is an effective drug in the treatment of pulmonary sarcoidosis, but specific studies addressing the treatment of cutaneous sarcoidosis haveyet to be done.

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.

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 [9].

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

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