CHAPTER 31

PENTOXIFYLLINE

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Pentoxifylline (PTX) is a methyl-xanthine derivative which inhibits phosphodiesterase. PTX was introduced as a vasoactive drug in 1972 and it has long been used to ameliorate symptoms of claudication.[1, 2] But soon after, it was discovered that PTX had a strong effect on inflammatory process. Both hemorrhagic and anti-inflammatory effects render this drug important in the field of dermatology.[3]

After oral administration, PTX is almost completely absorbed, undergoes a first-pass effect and various metabolites appear in plasma very soon after dosing. Plasma peak concentrations of the parent compound and its metabolites are reached within 2-4 hours after oral administration. Pentoxifylline is bound to erythrocyte membrane and is reduced to 5-hydroxy metabolite (metabolite 1). In addition to this compound, pentoxifyllin has 6 metabolites which are formed by hepatic oxidation and demethylation. The major metabolites are Metabolite l and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than PTX. Excretion of this agent happens mostly via urine.

Mechanism of action

PTX is a nonselective phosphodiesterase inhibitor. Phosphodiesterases are important enzymes that regulate breakdown of intracellular cyclic nucleotides. Inhibition of phosphodiesterases causes elevation of intracellular cyclic nucleotide concentration. PTX has hemorrhagic, antiinflammatory and immunomodulatory effects.

Hemorrhagic effects; PTX increases erythrocyte flexibility and reduces blood viscosity. Although its main mechanism of action but not the only factor that determines vascular perfusion. Vasoconstriction, red cell aggregation, platelet aggregation, thrombosis, increased fibrinogen levels and leukocyte hyperreactivity can promote vascular resistance or occlusion.[4] PTX inhibits aggregation of platelets, red and white cells and adhesion to vessel walls via inhibition of thromboxane synthesis and increasing prostacyclin level.

It also reduces plasma fibrinogen concentrations and increases fibrinolytic activity. PTX and its metabolites cause improvement during hypercoagulable states by the effect of decreased platelet aggregation and adhesion, increased plasminogen activator, increased plasmin, increased antithrombin III, decreased fibrinogen, decreased alpha 2-antiplasmin, decreased alpha 1-antitrypsin, and decreased alpha 2-macroglobulin.[4, 5]

Anti-inflammatory and immunomodulatory effects

PTX can affect several steps of skin inflammation. Antiinflammatory effects of PTX are related with cell adhesion and production of proinflammatory cytokines, chemokines. Studies demonstrated that PTX inhibited liberation of TNF alfa, IL-1 and IL-6 from keratinocytes and IFN gamma, IL-1, IL-6 and IL-8 from leukocytes.[6] PTX also increases liberation of an antiinflammatory cytokine, IL-10, from monocytes. Inhibition of TNF alfa, IL-1 and IFN gamma production results with blockade of extravasation of inflammatory cells via inhibiting upregulatory effect of these cytokines on adhesive molecules on endothelial cells.[3] PTX induces activation of fibroblast collegenases and reduces collagen, fibronectin and glycosaminoglicans.[4]

Dermatological uses

Owing to PTX's hemorrhagic, anti-inflammatory and immunomodulatory effects it can be used in several dermatological diseases. Although there are placebo-controlled trials for some of these diseases, many of them are limited with case reports.

Venous ulcer

Venous ulcer is a disease for which PTX is mostly used in dermatology. In a Cochrane review on PTX used to treat venous ulcers, 11 trials compared PTX with placebo or no treatment (with or without compression). It was demonstrated that PTX was more effective than placebo in terms of complete ulcer healing or significant improvement.[8]

Recurrent oral ulcers

Owing to affects of PTX on immune system (inhibiting TNF-α production, proinflammatory cytokines, such as IL-1β, inhibiting neutrophil functions, chemotaxis and expression of adhesion molecule, leading to reduced

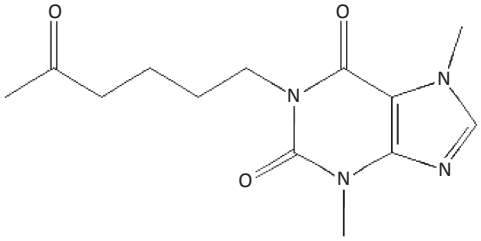


Figure 1. Chemical structure of pentoxifylline

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Adverse effects

Pentoxyfilline is a well tolerated drug, most seen side effects are related to gastrointestinal tract and central nervous system both of which are dose related and are therefore minimized by dose reduction. Cardiovascular complications are minimal with sustained-release oral pentoxyfilline and are higher after intravenous or capsule administration.[4] See table 1.

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