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REVIEW ARTICLE **OPEN ACCESS**

A Review Article on Pentoxifylline

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ABSTRACT
Studies have been proving that PTF is a compound derived from methyl xanthine that has been extensively researched due to its wide range of anti-inflammatory properties. Research has also established the beneficial impact of PTF on red blood cells, blood viscosity, and platelet aggregation, which helps decrease the likelihood of thrombus formation.Thus, in our review, we were evaluating and discussing PTF pharmacology, phramacokinetics, indiction, property, adverse effects, contraindications, precautions, and monitoring.
Key words: *PTF, Pharmacology, Phramacokinetics, Indiction, Property, Adverse Effects, Contraindications, Precautions, Monitoring.*

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INTRODUCTION

Many studies say that this drug, which is also called "pentoxifylline (PTF) 1 (oxpentifylline), is taken by mouth to treat peripheral vascular disease, cerebrovascular disease, and other conditions that affect the regional microcirculation".[1] Studies also confirmed that "PTF mainly makes red blood cells more flexible, lowers the viscosity of blood, and lowers the risk of platelets sticking together and thrombus formation".[1] Furthermore, multiple studies, which were conducted in a rigorous and controlled manner, have demonstrated that the administration of PTF at a dosage range of 600 to 1200 mg per day for a minimum duration of 6 weeks leads to noticeable improvements in both the subjective and objective measures of patients suffering from peripheral vascular disease. [1] Thus, in our review, we were evaluating and discussing PTF.

PHARMACOLOGY

Studies have been proving that when PTF is ingested as an aqueous solution, it is almost completely absorbed by the body. Plasma levels reach their peak approximately 2 hours after ingestion, and the process of first-pass metabolism leads to the appearance of several metabolites in the plasma shortly after taking the dose. The two most abundant metabolites are metabolite I, 1-(5-hydroxyhexyl)-3,7-dimethylxanthine, and metabolite V, 1-(3-carboxypropyl)-3,7-dimethylxanthine. The plasma concentrations of these metabolites are significantly higher than pentoxifylline, with a five-fold and eight-fold increase, respectively. The excretion process primarily occurs through urine, with the main metabolite being V. Studies have also shown that no traces of the drug are yet found in urine. Still, there are fluctuations in the concentrations of the original compound and its byproducts in the bloodstream, and the recovery of metabolite V in urine remains consistent and directly proportional to the dosage.[2]

INDICATION [3,4,5,6,7]

1. Systomatic treatment of claudication.
2. Supervised exercise
3. Venous ulcer (VU)
4. Severe alcoholic hepatitis
5. Fatal hepatorenal syndrome

PROPERTY [3,4,5,6,7]

1. Improves flow of blood by reducing viscosity

2. Effective in treating VU with or without compression therapy.
3. It is a tumor necrosis factor –α (TNF- α) inhibitor.

PHARAMACOKINETIC [8,9,10]
Studies have shown that PTF is rapidly and completely absorbed in the gastrointestinal system after oral administration. Furthermore, according to studies, it is recommended to take it with food or milk to minimize the risk of stomach upset. Also, studies have concluded that the bioavailability ranges from 20% to 30% due to a significant first-pass clearance. 28 29. Studies also showed that the liver and erythrocytes are the main places where pentoxifylline's active metabolites (M1) are made. Studies have also shown that the kidneys get rid of pentoxifylline and its metabolites more efficiently than the digestive tract as only a small amount is passed through that route. On the other hand, studies have also shown that , breast milk contains its main metabolites. Thus, the half-life of PTF according to many studies is approximately 0.4 to 0.8 hours, whereas its metabolites have a duration of about 1 to 1.5 hours.

ADVERSE EFFECTS [11]
1. Nausea
2. Vomiting
3. Abdominal discomfort
4. Bledding
5. Diarrhea
6. Dizziness
7. Headache
8. Flushing
9. Chest pain
10. Arrhytmias
11. Hypertension
12. Dyspnea,Tachcardia
13. Hypotension

CONTRAINDICATION [11]
1. Bledding
2. Increased risk of retinal bleeding
3. Peptic ulcer
4. Preoperative patients
5. Creatinine clearance less than 30ml/min
6. Allergy to xanthine derivative eg. Caffeine, theophylline, theobromine.
7. Acute myocardial infarction
8. Severe coronary disease
9. Severe liver disease
10. Cirrhosis

PRECAUTION [11]
1. Patients with below 18 years of age
2. Elderly patients (high plasma level)
3. Not recommended in pregnant women unles the benefits outweigh the risk
4. Ptients with renal impaiement (side effect risk is more)

MONITOR [11]
According to studies, patients of advanced age may experience an increased susceptibility to potential side effects associated with pentoxifylline. Additionally, patients revealed that it is important to closely monitor blood pressure and glucose levels when giving pentoxifylline to patients who are taking antihypertensive and antidiabetic medications. Furthermore, patients also concluded that they face a significant risk of experiencing low blood pressure, falls, and low blood sugar levels. Studies have also concluded that it is important for patients with liver disease to undergo regular laboratory monitoring to ensure their condition is closely monitored. In addition to this, studies concluded that it is important to inform patients who are at a higher risk of bleeding about the possible signs and symptoms of bleeding. Additionally, studies alos concluded that ,regular monitoring of laboratory data, such as hematocrit and hemoglobin levels, is also recommended. Finally, adding to this , according to studies, it is also important

for clinicians to be cautious when dealing with patients who have cardiac arrhythmias and low blood pressure.

THERAPEUTIC TRIALS

Studies have also shown that the findings of a "significant number of open and controlled studies show that PTF is beneficial in alleviating the symptoms of peripheral vascular disease in between sixty and one hundred percent of patients when it is provided at a dosage ranging from one thousand to one thousand and two hundred milligrams (mg) per day for a period of at least six weeks. The overall success rates with pentoxifylline in controlled studies ranged from 59 to 74%, which was much higher than the success rates with placebo, which ranged from 5% to 29%. The difference between the two was significant. Subjective symptoms, such as increased walking distance, decreased pain while resting, paraesthesia, cramping, healing of ulcers, oedema, and cyanosis, are improved in the majority of patients. Objective measures, including reactive hyperaemia, as well as oscillographic, thermographic, plethysmographic, scintigraphic, and ultrasound tests, have been greatly improved in recent years. On the other hand, open studies have often shown increases that are close to or even more than 100%. The improvements in walking distance have shown a large amount of variation from one study to the next. Clinical trials that were controlled with a placebo have shown, to a significant degree, the beneficial effect that PTF has on walking distances. These trials have shown that PTF increases walking distances.Studies have also shown that treating trophic leg ulcers with PTF is helpful, with a lot of patients either fully healing or getting a lot better after the treatment. In fact, one study found that PTF was superior to a placebo. In addition to this, pentoxifylline seems to yield more positive outcomes in severely injured limbs in studies where patients were stratified depending on the initial degree of sickness. These studies were conducted on humans. Comparing the results of other studies does not, however, give robust evidence to support these findings.

It was shown that PTF performed better than the majority of other drugs (with respect to traditional subjective and objective measures of disease activity) than the majority of the other treatments in a small number of comparative studies with patients who had peripheral vascular disease. These studies were done with patients who had the condition peripheral vascular disease. It was shown that a lower dosage of pentoxifylline, between 300 and 600 mg/day, was just as effective as pyridinolcarbamate 1500 mg/day, and that this lower dosage was more successful than the (recommended doses of) naftidrofuryl. When contrasted with the results acquired from a dosage of nylidrin that was 9 mg/day and the results received from a dosage of adenosine that was 7.2 mg/day, the results obtained from a dosage of PTF that was 1200 mg/day were considerably superior. Poor responses were seen to both PTF and buflomedil in two studies that compared doses of the drugs that were lower than those recommended by the manufacturers. The lower doses of PTF were 800 mg/day and 300 mg/day, respectively, while the lower doses of bufomedil were 600 mg/day and 450 mg/day. Comparable results were seen when PTF (1200 mg) and flunarizine (15 mg) were compared. Also, PTF has been tested in a few small studies on diabetic patients with vascular problems and has been shown to help ease the symptoms of peripheral disease in the lower limbs. Other secondary disorders, such as retinopathy, may be improved, despite the fact that further studies are required in this area. In patients like these, the concentrations of glucose in the blood and the metabolism of lipids are often unaffected or even improved. This is because glucose does not cross the blood-brain barrier. One study found that patients who had undergone vascular surgery and been treated with either pentoxifylline 1200 mg/day or dipyridamole 150 mg/day in conjunction with acetylsalicylic acid 1050 mg/day had a reocclusion of their vessels at a rate of either 10% or 20%, respectively. These patients were given the medications in combination with acetylsalicylic acid (1050 mg/day). These patients also received acetylsalicylic acid at 1050 mg/day in addition to the medications that were given to them. This adverse effect was produced as a direct result of taking both of these medications simultaneously. These patients were also given acetylsalicylic acid medications at the same time as their medications were administered to them. Studies have also concluded that in patients who were all suffering from cerebrovascular diseases, pentoxifylline has been shown to have therapeutic efficacy. The fact that there have been so few studies that have been well controlled makes it difficult to evaluate the relative efficacy of pentoxifylline in this particular therapeutic area. This is because there have been so few studies conducted. A total of around 13,000 patients took part in the research study, which was conducted over the course of an eight-week treatment with pentoxifylline at doses ranging from 300 to 600 mg per day. As the treatment proceeded, 86% of those patients showed clinical improvements. Significant improvements were seen in psychometric symptoms including disorientation, hypomnesia, loss of spontaneity, depression, and sleepiness (observed in 64 to 78% of patients), as well as improvements in speech problems (observed in 65% of patients), and improvements in subjective symptoms including tinnitus, cold extremities, headache, and vertigo (observed in 76 to 87% of patients). The condition that improved the most was the one involving speech difficulties. Patients who suffered

from cerebral arteriosclerosis (93%), transient ischemic episodes (85%), and cerebral infarction or thrombosis (93%), all showed improvements after being stratified according to their type of cerebrovascular disease.
Studies have also concluded that a 12-month follow-up revealed incidences of new ischaemic attacks to be 10 to 13% and 28 to 31%, respectively, and stroke incidences to be less than 5% with both treatments in a comparative study of PTF 1200 mg/day and dipyridamole 150 mg/day plus treatment with acetylsalicylic acid 1050 mg/day in patients with transient ischaemic attacks. Improved cerebral blood flow was linked to clinical improvements in men. Vascular therapy was shown to result in improvements in gross neuromotor and speech deficits, as well as overall rehabilitation, in patients with vascular conditions who had recently had acute cerebrovascular accidents. PTF and xanthinol nicotinate have both been shown in comparative studies to give significant improvements in motor deficits in patients with cerebral thrombosis. PTF has also been shown to enhance the memory of these patients when given intravenously. Studies have also concluded that it has been shown that the combination of hexobendine, ethamivan, and etofylline has a lower rate of rehabilitation in non-haemorrhagic stroke patients when compared to the rate of PTF that is seen with parenteral pentoxifylline 400 mg/day. Research that compared the two was essential in arriving at this conclusion. Open studies on chronic cerebrovascular disorders have shown improvements in approximately 60 to 90% of patients, and controlled vascular studies have shown significant benefits with PTF, with improvements (hemorheological as well as clinical) in over 90% of patients, compared to 15 to 20% of placebo patients, respectively. Open studies on chronic cerebrovascular disorders have shown improvements in approximately 60 to 90% of patients. These results show that PTF is more effective than placebo in the treatment of cerebrovascular diseases. It would seem that vertigo, headaches, and memory disturbances reacted particularly well to the treatment, although visual disturbances showed a lower level of reactivity to the treatment overall. Studies have also concluded that, once again, there was a connection between the clinical improvements and the increased blood flow to the area of the brain, which includes the cerebral region. A small group of patients with chronic cerebrovascular disorders were treated with PTF up to 1200 mg/day and compared it to codergocrine mesylate 6 mg/day (70% vs. 10% of patients) and adenosine 7.2 mg/day (10% vs. 37.5% of patients). The results showed that PTF treatment was more effective. Furthermore, studies have concluded that dipyridamole, administered at a dosage of 1200 mg per day, dipyridamole administered at a dosage of 300 mg per day, or a combination of the two, resulted in clinical improvements in 67%, 67%, and 83% of patients, respectively. A study very similar to this one, on the other hand, compared PTF 1200 mg/day with a sugar pill, piracetam 4800 mg/day, or a mix of PTF and piracetam. The combination therapy was the only one that showed significant clinical improvements. This was the case even though the study compared the three treatments to each other. Both piracetam and PTF were given at a daily dosage of 4800 milligrams (mg). It has also been found that PTF might be useful for treating a number of other conditions, such as the vaso-occlusive crises that come with sickle cell disease, high altitude sickness, asthenozoospermia (but not oligospermia), hearing disorders (both short-term and long-term), and retinal circulation disorders. In addition, PTF has shown some potential for use in the treatment of a number of other conditions. In addition to this, PTF has been shown to have some potent potential for use in the treatment of a variety of different disorders. However, before we can consider these places to be promising, we need to ensure that the preliminary results continue to hold true in each of them".[1]

LITERATURE REVIEW

Lyons et al., (2017)conducted a review of the use of PTF in patients with osteoradionecrosis. They have arrived at the conclusion that PTF has been used in the treatment of issues connected to fibrosis for more than 20 years. It was formerly used to treat those who had undergone radiotherapy for conditions such as osteoradionecrosis (ORN), but now it is being tried for medication-related osteonecrosis of the jaw (MRONJ), which can occur after prolonged use of bisphosphonates. Although no prospective randomized controlled trial has investigated the benefits of these agents in cases of ORN, the reported outcomes in many published case series are encouraging.[12]

González-Pacheco et al., (2020) conducted a thorough analysis of the potential efficacy of PTF in treating SARS-CoV-2. They come to the conclusion that PTF is a phosphodiesterase inhibitor that possesses various beneficial properties, including anti-inflammatory, anti-thrombotic, antioxidant, and anti-fibrogenic effects. According to their conclusion, PTF could potentially serve as a beneficial additional treatment for patients with COVID-19. Due to its various properties, it has the potential to mitigate the inflammatory response and thrombotic events, potentially leading to a reduction in multi-organ dysfunction and acute lung damage.[13]

Liang et al., (2022) conducted a original research article was written with the purpose of investigating the efficacy and safety of cilostazol, PTF, and beraprost in the treatment of intermittent claudication

brought on by lower extremity artery occlusive disease. The report focused on the assessment of the efficacy and safety of these three medications. They found that a total of 5352 patients were included in 29 different randomized controlled trials (RCTs), which were included in the study. Beraprost and pentoxifylline finished in second and third place, respectively, for the maximum walking distance that was achieved without experiencing any discomfort. For cilostazol, PTF, and beraprost, maximum walking distance increased by 62.93 95%CI (44.06, 81.79), 32.72 95%CI (13.51, 55.79), and 43.90 95%CI (2.10, 85.71) meters, respectively, relative to placebo, and pain-free walking distance increased by 23.92 95%CI (11.24, 36.61), 15.16 95%CI (2.33, 27.99), and 19.78 95%CI (3.07, 42.62) meters. Ankle-brachial index increased relative to placebo for beraprost, pentoxifylline, and cilostazol by 0.06 (95% CI: 0.04, 0.07), -0.01 (95% CI: -0.08, 0.05), 0.18 (95% CI: 0.12, 0.23), and 0.23 (95% CI: 0.18, 0.27). When compared to beraprost and cilostazol combined with beraprost, it was shown that the combination of PTF and cilostazol was related to a lower ratio of adverse events. They came to the conclusion that cilostazol, PTF, and beraprost were all effective treatments for intermittent claudication. They also came to the conclusion that cilostazol with good tolerance was likely to be the most effective treatment in terms of walking distance, whereas beraprost and cilostazol combined with beraprost were more prominent in the ankle-brachial index.[14]

CONCLUSION

The successful implementation of PTF treatment relies on the collective effort of a multidisciplinary healthcare team, comprising doctors, mid-level practitioners, nurses, and pharmacists. The expertise of a pharmacist is crucial when it comes to determining the safest and most effective dosage for a medicine. The roles of nurses and dieticians are vital in educating patients, promoting medication adherence, and mitigating risks related to atherosclerotic disease. Effective collaboration among healthcare professionals and seamless coordination of care are crucial to ensuring the best possible patient outcomes and minimizing any potential complications.

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