Is pentoxifylline an underused drug?

Review of the literature and a case study

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Abstract

Research supports the use of pentoxifylline to improve symptoms in people with peripheral arterial disease. It acts at the microcirculatory level, essentially improving the movement of blood cells in the smaller vessels. These actions would be useful in wound healing where poor microcirculation plays a significant inhibitory role. Here we present a short literature review and case study introducing the use of pentoxifylline in wound healing. We believe further investigation of pentoxifylline to ascertain its usefulness in the treatment of ulcers is warranted.

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Introduction

Some evidence suggests pentoxifylline (Trental®, also known as oxpentifylline) helps chronic leg ulcers. People with chronic venous leg ulcers have trophic changes to the skin. The microcirculation appears to be implicated in the pathophysiology of these ulcers [1]. Pentoxifylline acts at the microcirculatory level. It downregulates leukocyte activation, reduces leukocyte adhesion and has fibrinolytic effects, and thus may significantly improve wound healing.

Pentoxifylline chemically belongs to the methyl xanthine class of drugs and is related to caffeine, theophylline and theobromine [2]. In activity, it belongs to a class of drugs known as haemorrheologics – drugs that improve blood flow characteristics. In addition to down regulation of leukocyte activation, reduction in leukocyte adhesion and fibrinolytic activity, it also improves red blood cell (RBC) membrane flexibility and thus facilitates cell passage through microvessels and the supply of oxygen and nutrients to tissues [2, 3].

Ischaemia of any aetiology leads to the build up of anaerobic metabolites in the capillary bed, creating a hyperosmolar, acidotic environment. The energy reserve – adenosine triphosphate (ATP) – of RBCs is consumed which in turn decreases their membrane flexibility, reducing their ability to pass along capillaries and further reducing blood flow and exacerbating ischaemia [2]. Pentoxifylline may improve supply of oxygenated blood to ischaemic tissues to a clinically

significant degree [4, 5]. Pentoxifylline has also been reported to inhibit tumour necrosis factor alpha (TNF-α), a cytokine implicated in the pathogenesis of many microvascular disease states including the complications of diabetes, vasculitic syndromes and toxic epidermal necrolysis [2].

Pentoxifylline is used as a non-invasive therapy to reduce the symptom of intermittent claudication in those with peripheral arterial disease [4, 6]. Recently, its success in this area has been called to question, with placebo groups showing similar effects to pentoxifylline in patients with moderate to severe intermittent claudication [7]. Meta-analyses have also shown variable results, with average effects of treatment using pentoxifylline being small [8] or showing that more properly conducted clinical trials need to be undertaken to show effect [5]. In an effort to improve research in this area, recent work has been done to assess pentoxifylline use to treat intermittent claudication in groups with diabetes and those without [9-13]. Overall positive results have been shown, with pentoxifylline treatment compared to placebo.

Due to the effects on microcirculation, there has been some work to assess the effects of pentoxifylline on sensory nerve activity in people with peripheral neuropathy as a result of diabetes [14]. Studies have shown variable results, with some indicating little if any improvement using the drug [15, 16], whilst others showing an improvement [17, 18].

The effect of pentoxifylline in microvascular components such as retinopathy and nephropathy (although the microvascular component of neuropathy was not assessed), without a control group, are also positive [19]. The results are difficult to interpret in these trials due to the different doses of the drug used, the low number of participants in the trials and the short duration of the trials. Overall, there may well be benefits in the use of pentoxifylline on the microvascular effects of diabetes, but more clinical research is needed to confirm or refute this impression.

The Cochrane Wounds Group conducted a systematic review of pentoxifylline in wound healing [20]. The review shows that pentoxifylline appears to aid treatment of venous leg ulcers. A double-blind, randomised, placebo controlled prospective study of pentoxifylline showed healing in 64% of pentoxifylline treated cases, compared to only 34% of the placebo treated controls [21]. There was no significant difference in adverse events between the placebo and pentoxifylline groups. Other studies showed similar improvements [22, 23].

Diabetic foot ulcers were assessed to whether pentoxifylline could improve healing [24]. Unfortunately there was no control group. The authors enrolled patients that had non-healing ulcers for 3 months prior to taking the medication. Of those that completed the trial, 89% of ulcers healed, whilst the remaining ulceration reduced in size.

Evidence of the effectiveness of pentoxifylline for other types of ulcers is sparse. Its pharmacological actions suggest there may be benefit for a variety of wound types, especially those in which poor microcirculation is implicated. One reason for the lack of evidence of efficacy of pentoxifylline in other ulcer types may be that it has not been adequately studied for other ulcer types. In addition, the relatively high cost of this drug in Australia where it is not listed on the Pharmaceutical Benefits Scheme, may be curtailing its use. Hence there has been little opportunity for clinical impressions to form and for support for studies of efficacy to be carried out.

Here we describe the use of pentoxifylline in a patient of the Wound Management Service (WMS) of the Melbourne Extended Care and Rehabilitation Service (MECRS).

Case study

Mr B is a 56 year old married man, of Indian ethnicity, who works as a metallurgist. He had a left trans-tibial amputation in 1994 for ischaemic pain, and walks with the aid of a prosthesis.

History of presenting problem

The patient was referred to the WMS in June 2002 by his GP due to delayed healing of the right great toenail bed following nail avulsion. The problem began in January 2002 when he noted an ingrown toenail. This became cellulitic, with discharge of purulent exudate despite the use of antibiotics. He was reviewed in the vascular surgical clinic where no distal pulses were palpable but brisk flow was noted on Doppler examination in the dominant peroneal artery. The anterior and posterior arteries were occluded. The comment was made that this was consistent with a diabetic pattern of tibial occlusive disease.

In March 2002, the toenail was avulsed by the vascular surgical unit, and left to heal by secondary intention, using an antiseptic wash and foam dressing. A mixed growth of organisms was isolated from the nail, including *E. coli*, coagulase negative Staphlococcus and Streptococcus. He was prescribed cephalexin orally.

Previous medical history

- *1970:* sustained multiple fractures of right leg in a motor car accident.
- *December 1994:* Left trans-tibial (below knee) amputation due to resting ischaemic limb pain for 12 months. Angiography prior to amputation showed obliteration of distal arteries, reported as being consistent with embolus. He had smoked 12 cigarettes a day for 30 years. Exhaustive investigations revealed no source of emboli. He continued to smoke following the amputation, despite strong encouragement to quit.
- *January 1995:* A vascular physician was consulted. On the basis of the history and angiographic findings, and especially the absence of a source of arterial emboli, a diagnosis of Buerger's disease (*Thrombangitis obliterans*) was made. Having been informed of the high risk of losing both his remaining leg and even the upper limbs if he continued to smoke, he quit and has not smoked since.

Treatment

At the first WMS appointment (24 June 2002) significant pain was reported over the nail bed of the great toe which was severe at night, causing sleep disruption. Pain was relieved by hanging the foot over the edge of the bed. During the day, at work, the pain was not noticed. Mr B was still taking cephalexin and dressing the toe with foam. Blood tests at the time revealed a fasting blood glucose of 4.4, confirming the absence of diabetes mellitus, and other results were normal. His total cholesterol:HDL ratio was 4.4, above the desirable range of less than 3.4, although lower than the average ratio for the adult male population (4.5-6.4). No regular analgesics were being taken, as Mr B was concerned about tolerance and side effects.

On examination, the toe was inflamed and Mr B could not tolerate anyone touching the area. The toenail appeared thickened and discoloured. The clinicians recommended continuing with foam dressing and sent Mr B for radiography and blood tests.

At the second WMS appointment (8 July 2002) the pain in the toe had settled (Figure 1). X-rays of the right big toe revealed a focal area of radio lucency involving the posterior, lateral and anterior parts of the terminal tuft. These features suggested early bone infection. A nuclear scan had been performed and the result was inconclusive for infection. The area was still too painful to touch to allow debridement. Foam dressing was continued awaiting a vascular surgical consultation.

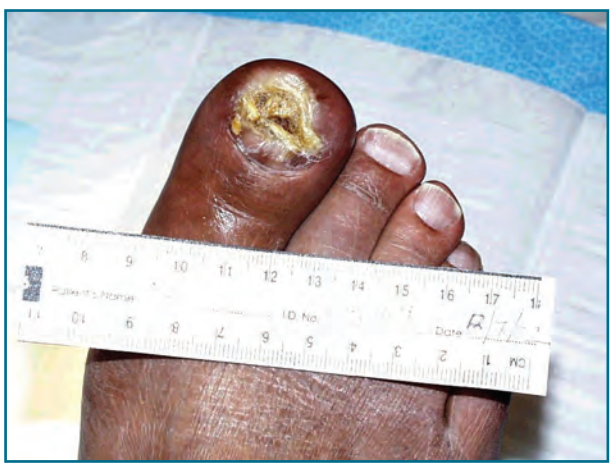
The vascular surgeon arranged digital subtraction angiography (DSA), which showed normal vessels down to and including the popliteal artery. Single vessel run off occurred through the peroneal artery, otherwise blood travelled through collateral arteries to the foot.

Upon his return to WMS on 5 August 2002, Mr B stated a wish to explore all options that may help in addition to or in place of surgery. At this point, pentoxifylline, hyperbaric oxygen and debridement of the nail/eschar were discussed. Emla® (Eutectic mixture of local anaesthetic) was applied and debridement was attempted. This was found to be too painful. Dressings were changed to cadexomer iodine paste (Iodosorb®) and foam (Lyofoam®) second daily, with the aim of reducing the surface bacterial load and thus reducing infection risk. Oral antibiotics (cephalexin 500 mg QID) were recommenced and continued for a period of 6-8 weeks, on the basis of surface swabs and clinical signs suggesting infection.

At his next WMS appointment (12 August 2002) Mr B stated that he had changed the dressings daily. The need to leave the dressings in place for 2-3 days for maximum cost effectiveness was reiterated. Enterococci and Gram negative bacillus were isolated from the wound swabs. At this point, using a local anaesthetic toe block, the eschar was debrided by the clinic podiatrist. The distal phalanx was exposed in the wound bed which measured 12x9mm. As bone was visible, the patient was considered to be at ongoing risk for osteomyelitis.

Oxygen tension was assessed; the great toe transcutaneous partial pressure of oxygen was just 23 mmHg (normal is greater than 30mmHg for adequate healing [25]). The management plan formulated at that time was to continue cephalexin 500mg QID and commence pentoxifylline 400mg

Figure 1. Mr B's ulcer at an early appointment at MECRS WMS.



TDS. The ulcer was to be dressed with cadexomer iodine and foam, and changed every third day.

Mr B was reviewed at the WMS every 2-4 weeks, with progress monitored by assessing pain, wound size and oxygen tension. The area was debrided at each appointment. Figure 2 shows the toe post-debridement. Wound size did not alter during this period.

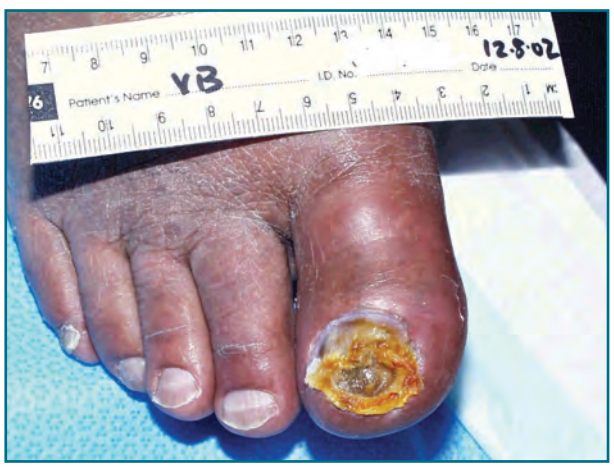
Upon pentoxifylline administration, pain reduced significantly and oxygen tension increased over time (Table 1). In late September pentoxifylline was unavailable for 3 weeks. The oxygen tension markedly deteriorated and pain increased somewhat. Once pentoxifylline became available again, pain reduced and oxygen tension improved. Wound dressings were changed to foam and hydrogel in December 2002 as cadexomer iodine had been used for 5 months. The manufacturer's recommendations are that a continuous period of 3 months use should not be exceeded, due to concern that there may be excessive systemic iodine absorption. Upon continued administration of pentoxifylline, the pain was maintained at low levels and oxygen tension readings improved.

Following further review by Mr B's vascular surgeon, the advice was that the wound bed should be left dry in order to minimise the risk of re-infection. Eschar was allowed to build up to provide some protection for the exposed phalanx. The surgeon was concerned that any intervention would run a risk of failing to heal at a distal level and require more proximal amputation.

Currently, Mr B is able to work without major interference from the toe wound, an important factor due to the physically demanding nature of his employment. Pain has remained at a low level. The long-term plan is to try to maintain foot function by improving tissue integrity of the right great toenail bed and avoiding amputation. At his last review he was given advice regarding the purchase of appropriate extra depth footwear.

Due to the ongoing infection risk, and in the interests of early detection and treatment, his symptoms and signs, as well as plain radiography and serological markers of inflammation, should be monitored. If there are progressive changes or a suspicion of active osteomyelitis, MRI and possibly bone biopsy may be useful establishing a diagnosis and guiding treatment.

Figure 2. Mr B's ulcer post debridement.



Discussion

The use of pentoxifylline in this case was commenced due to the microvascular impairment in Mr B's ulcerated extremity and the concern that the end result could lead to another amputation. Upon commencement of the treatment with pentoxifylline, pain was markedly attenuated. Pain in arterial ulcers is common [26], and is difficult to treat without the inherent side effects of the analgesics. The pain in many instances is the greatest concern in many ulcer patients and is often under-treated [27, 28]. The reduction of blood to the periphery is believed to stimulate the pain pathway.

Some pain in wound healing is necessary. However, too much pain stimulates the sympathetic nervous system which

Table 1. Assessment of Mr B right great toe wound over WMS appointments, assessing pain, oxygen tension and pentoxifylline.

WMS appointment date	Pain level	Oxygen tension	Taking pentoxifylline
24 Jun 2002	Very high	Not measured	No
8 Jul 2002	Moderate	Not measured	No
5 Aug 2002	High	Not measured	No
12 Aug 2002	High	23mmHg	No
26 Aug 2002	High	21mmHg	Yes
9 Sep 2002	Low	32mmHg	Yes
30 Sep 2002	Moderate	3mmHg	No
14 Oct 2002	Low	8mmHg	Yes
4 Nov 2002	Low	21mmHg	Yes
25 Nov 2002	Low	20mmHg	Yes
16 Dec 2002	Low	Not measured	Yes
7 Apr 2003	Low	28mmHg	Yes

increases vasoconstriction and may exacerbate the condition [29]. By encouraging blood flow to the periphery, as evidenced by improved oxygen tension readings, neurovascular components necessary to healing would be brought to the wound.

Mr B was unable to order the pentoxifylline for a few weeks; as a result, the oxygen tension readings reduced considerably. After pentoxifylline treatment resumed, there was a very slow improvement as compared to the relatively quick improvement shown after the initial administration.

Caution is required in interpreting the changes in the measured oxygen tension. The initial improvement was expected and seemed to parallel the patient's impression of benefit. The rapid decline on stopping treatment is not surprising given the current understanding of the mechanisms of action of pentoxifylline.

The increase to a higher level after several months of treatment could be due to a variety of causes. One possible explanation is that the result is due to measurement error. Another is that known and unknown physiological processes contributed to the measurement. Elsewhere we have published information describing the effect of autonomic nervous system tone on cutaneous oxygen tension and blood flow; decreased sympathetic alpha constriction might partly explain the increased oxygen tension [30]. Finally, it could be that some months of improved tissue oxygenation as a result of the rheologic effects of pentoxifylline cause structural changes at a microvascular level, with a resulting increase in perfusion. The research undertaken on pentoxifylline so far does not discuss this aspect of the drug. Further research would need to be undertaken to ascertain the cause.

Conclusion

It appears that pentoxifylline improved Mr B's overall quality of life, and he has said he would pay for pentoxifylline himself in the long term if it was not otherwise available. A placebo effect cannot be ruled out. We note that the improvement in pain began after the involvement of the clinic, but before the administration of pentoxifylline. However, the change in the measured oxygen tension supports a role for pentoxifylline in the symptomatic improvement.

Under the current treatment, there has been a significant improvement in Mr B's pain levels and overall condition of his right toe. Also his right foot and leg remain intact. There is some support from other researchers for the administration of pentoxifylline to improve ulcer healing and other impaired microvascular components. We believe this research and our case study show the need for further investigation of pentoxifylline to ascertain its usefulness in the treatment of ulcers.

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