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## Oral Pentoxifylline, Potentially Effective Additional Treatment for Calciphylaxis: Case Report

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### Abstract

Calciphylaxis is a rare condition, however it predicts poor outcomes among dialysis patients. Effective treatment options are limited and lack evidence for improved outcomes. Here, we describe the use of oral pentoxifylline in addition to conventional treatment of calciphylaxis, in a 73-year-old lady with end-stage kidney disease on haemodialysis. This case demonstrates the potential role of pentoxifylline in the management of calciphylaxis, as a relatively safe and inexpensive additional therapy. However, due to limited evidence, further studies are required to evaluate its efficacy and safety in the treatment of calciphylaxis.

**Keywords:** Calciphylaxis; Haemodialysis; Pentoxifylline; Treatment

### Introduction

Calciphylaxis, or calcific uremic arteriolopathy, affects 1-4% of haemodialysis patients, however it is associated with high morbidity and mortality, with a 6-month survival of approximately 50% [1]. Due to its low incidence and lack of large clinical trials, standardised treatment guidelines are lacking. The current mainstay of treatment comprises of: 1: Cessation of medications that may elevate calcium, including cholecalciferol, calcitriol, calcium supplements and calcium containing phosphate binders; 2: Cessation of coumarin anticoagulants; 3: Increased duration and frequency of dialysis; 4: Lower dialysate calcium (e.g. 1.0mmol/L); 5: Intravenous sodium thiosulfate; 6: Calcium lowering agents and interventions including bisphosphonates, parathyroidectomy, and cinacalcet; 7: Hyperbaric oxygen, and 8: Analgesia, wound care and infection prevention [1]. A meta-analysis by Udomkarnjananun in 2019 failed to demonstrate any significant clinical benefit in wound healing or mortality as a result of some of these interventions [2].

Here, we propose the addition of oral pentoxifylline as an affordable treatment with low side effect profile [3]. Pentoxifylline is a Food and Drug Administration approved treatment for claudication. It is a vasoactive agent that reduces blood viscosity and improves blood flow and peripheral tissue oxygenation [2]. It is also used off-label for treatment of venous ulcers, based on a Cochrane review demonstrating its efficacy compared to placebo [4].

## **Case Presentation**

We present a case of a 73-year-old woman with past medical history of end-stage kidney disease secondary to diabetes (on haemodialysis for two months), atrial fibrillation, psoriasis, and obesity. She was on regular secukinumab (IL-17a monoclonal antibody) for her psoriasis, colecalciferol and calcium supplements, and had been on warfarin prior to commencing haemodialysis. She presented to hospital with three weeks of painful skin lesions on her lower abdomen, which appeared as two inflamed areas of eschar (Figure 1A). Her inflammatory markers were elevated, white cell count  $15.4 \times 10^9/L$  and C-Reactive Protein 193mg/L, with borderline corrected calcium of 2.58mmol/L, normal phosphate level of 1.11mmol/L and increased parathyroid hormone level of 36pmol/L. Biopsy of the abdominal lesions did not demonstrate the typical presence of calcium thrombus in vessels, however the findings of fat necrosis and full epidermal ulceration/dermal fibrosis were suggestive of calciphylaxis. Management included commencement of sodium thiosulfate 25grams on haemodialysis 3 times per week, cessation of calcium and cholecalciferol, and broad-spectrum antibiotics for secondary bacterial infection. She improved and was discharged home, however represented two weeks later with wound re-infection (Figure 1B and C), requiring debridement and intravenous antibiotics for polymicrobial infection.

Interhospital transfer for hyperbaric oxygen therapy was unsuitable due to clinical instability. Upon review of the literature for alternative therapy, a decision was made to trial pentoxifylline 400mg orally daily which was commenced five weeks after initial presentation. Three weeks later, the wound showed improvement and a Vacuum-Assisted Closure dressing was applied to assist with healing. Figure 1E, F and G shows gradual improvement of the wound at 11 weeks and 18 weeks after commencing pentoxifylline. Unfortunately, the patient died six months after initial presentation, likely in the setting of sepsis secondary to wound infection.



**Figure 1(A):** Abdominal apron at presentation: 2 areas of eschar - dry necrosis with surrounding erythema, **B and C.** week 4: large necrotic wound with eschar with adjacent smaller wound that tunnels and connected medially. There was presence of wet adipose with necrosis and turbid fluid. **D.** Week 8, overall granulating tissue at the base of the wound, no signs of infection, some necrotic adipose tissues on the inferior edges of the larger wound. **E, F and G.** Week 16 and week 23 respectively, healthy granulation tissue at the base of the wound with no signs of infection.

## Discussion

Pentoxifylline is a methylxanthine derivative that improves blood flow and tissue oxygenation in the microcirculation, by increasing red cell deformability, as well as reducing blood viscosity, platelet aggregation and thrombus formation. It is rapidly absorbed and more than 90% is renally excreted. Side effects including gastrointestinal, cardiovascular, central nervous system, hepatic or dermatological, are overall uncommon. Additionally, it is relatively affordable with a monthly cost of AUD \$23-26 (private prescription at daily dose of 400mg).

There are a few case reports describing the use of pentoxifylline in renal transplantation [5], chronic kidney disease and peritoneal dialysis, and two retrospective chart reviews describe its use in haemodialysis patients. However, it is rarely used and there are no clinical trials supporting its use.

## **Conclusion**

Here we demonstrated that pentoxifylline can be considered as an inexpensive additional therapy for severe calciphylaxis, however we cannot report whether any benefit was derived in this case. Further investigation is warranted to support its future use.

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