

# Treatment of recurrent aphthous ulcers in an HIV patient – An emerging use for pentoxifylline

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KL Slayter, TJ Marrie. Treatment of recurrent aphthous ulcers in an HIV patient – An emerging use for pentoxifylline. *Can J Infect Dis* 1998;9(3):189-190.

Patients with human immunodeficiency virus (HIV) infection often suffer from persistent, painful ulcers that commonly occur on the soft palate, buccal mucosa, tonsillar area or tongue, which are referred to as aphthous ulcers. This paper reports the case in which pentoxifylline was successfully used to treat recurrent aphthous ulcers in an HIV patient.

**Key Words:** *Aphthous ulcers, HIV infection, Pentoxifylline*

## Traitement des ulcères aphteux récurrents chez un patient infecté au VIH –Nouveau rôle pour la pentoxifylline

**RÉSUMÉ :** Les patients infectés au virus de l'immunodéficience humaine (VIH) souffrent souvent d'ulcères persistants et douloureux qui affectent le palais mou, les muqueuses buccales et les amygdales ou la langue. On les appelle ulcères aphteux. Cet article fait état d'un cas où la pentoxifylline a été utilisée avec succès pour traiter les ulcères aphteux à répétition chez un patient infecté au VIH.

Patients with human immunodeficiency virus (HIV) infection often suffer from persistent, painful ulcers that commonly occur on the soft palate, buccal mucosa, tonsillar area or tongue, which are referred to as aphthous ulcers (1). Patients suffering from the lesions may experience a decreased quality of life secondary to severe pain, dysphagia and weight loss. Although viruses (such as herpes simplex), bacteria and fungi have been implicated as possible causes, there is little evidence that infection is the primary cause of recurrent aphthous ulcers (2,3). Because these ulcers may resemble other lesions, biopsy is often indicated to confirm the diagnosis or rule out iatrogenically induced ulcers secondary to pharmacotherapy, such as dideoxycytidine or foscarnet. Regimens employed to treat recurrent aphthous ulcers include topical or systemic steroids and more recently thalidomide (2-4). Pen-

toxifylline, a methylxanthine derivative with unique hemorheological properties, has been reported to induce dose-dependant suppression of tumour necrosis factor-alpha (TNF- $\alpha$ ) (5). It is postulated that this mechanism may be involved in the suppression of aphthous ulcers because TNF- $\alpha$  has been found to be elevated in patients with recurrent oral ulcerations (6).

We report a case in which pentoxifylline was successfully used to treat recurrent aphthous ulcers in an HIV patient.

### CASE PRESENTATION

A 37-year-old male who had known HIV for 3.5 years (CD4 count 6 cells/mm<sup>3</sup>) developed a chronic persistent painful mouth ulcer four months before admission to hospital. Despite repeated regimens of prednisone and discontinuation of

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Received for publication March 11, 1997. Accepted June 21, 1997

the antiretroviral didanosine, he was admitted to hospital for pain control and nutritional support. He was unable to tolerate anything by mouth because of the pain, which resulted in a 20 kg weight loss over the four months. Past medical history was unremarkable except for HIV-associated oral candidiasis and presumed *Mycobacterium avium* complex (MAC) infection of the right wrist. Medications at the time of admission were rifabutin 300 mg once daily, clarithromycin 500 mg bid, fluconazole 100 mg bid, cotrimoxazole one double strength tablet three times weekly, morphine sustained release 30 mg in the morning and 60 mg at bedtime, and morphine 5 mg every 3 to 4 h when needed for breakthrough pain.

Physical examination of the head and neck was remarkable for a 2 cm deep ulceration of the right anterior tip of the tongue, as well as a large right lateral tongue mass and ulcer. He also had several small plaques consistent with oral candidiasis in his mouth and pharynx. He had limited lingual range of motion accompanied by dysphagia without odynophagia.

He was treated with intravenous fluconazole for his oral candidiasis, and subsequently switched to oral fluconazole that allowed him to remain free of oral or esophageal candida infections throughout his hospital stay. A swab from the large anterior oral ulcer was negative for herpes simplex virus.

The preliminary biopsy of the anterior ulcer and lateral mass showed a noninfectious etiology. It was considered likely reactive in nature, with a rich vascular network within the skeletal muscle bulk of the tongue. The skeletal muscle fibre showed atrophic changes, and there were lymphocytes and eosinophils sprinkled throughout. A lymphoma or Kaposi's sarcoma, however, could not be ruled out; thus, the tissue was sent for further pathological review. Consultation with a pathologist at another centre confirmed the benign nature of the lesion. Other than adjusting his pain medications and inserting nasogastric feeds, he received no other specific therapy aimed at treating his oral ulcer during his 29-day hospital stay. When the biopsy results were obtained, the patient was started on pentoxifylline 400 mg, three times daily and naproxen 250 mg twice daily for pain. Two weeks after discharge there was a complete resolution of his oral mass and epithelization of the ulcer, and the patient was able to discontinue nasogastric feeds secondary to increased oral intake. The patient continued to gain weight (23 kg), and the mass lesion on his tongue failed to return. However, he briefly developed another painful ulcer on his right buccal mucosal while taking pentoxifylline. This ulcer was temporarily associated with a change in his antiretroviral therapy to indinavir and stavudine. He also complained of ankle edema. A drug interaction was suspected, and rifabutin and clarithromycin (which he had taken for three years) were replaced with 1250 mg of azithromycin once weekly. Within 10 days, the buccal ulcer had resolved. He remained well and symptom-free eight months later.

## DISCUSSION

Pentoxifylline is a methylxanthine derivative with hemorrheological and antithrombotic properties. Recent experimental and clinical observations have demonstrated that pentoxi-

fylline also has immunomodulating and anti-inflammatory activities that seem to be related at least in part to its inhibitory effect on TNF- $\alpha$  products (5). Thalidomide, one of the treatments of choice for severe recurrent aphthous stomatitis, also inhibits TNF- $\alpha$  production (4). The use of thalidomide has not as yet become the standard of care due to its teratogenic effects when used as an antiemetic for pregnant women.

In a small open trial, pentoxifylline was shown to be effective in the treatment of recurrent aphthous stomatitis in six non-HIV patients (7), and in one case report series of 22 patients (8) pentoxifylline was shown to be effective in treating oral and genital ulcers associated with Behçets Disease (9). To date, no case reports have been published in the English literature evaluating the use of pentoxifylline in aphthous stomatitis in HIV patients. This is of interest because preliminary studies have suggested that the use of pentoxifylline, in combination with antiretroviral compounds, may be useful in the treatment of patients with HIV-1 infection (10). It is noteworthy that pentoxifylline has immunomodulating and anti-inflammatory effects but does not have immunosuppressive properties. This could be related in part to the inhibitory effect of pentoxifylline on the production of the immunosuppressive cytotoxine interleukin-10. However, pentoxifylline could be detrimental in particular patient populations, including those with disseminated MAC infection (11). We conclude that pentoxifylline was effective in the treatment of severe aphthous ulcers in our HIV positive patient.

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