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Oxpentifylline is not effective for symptomatic oral lichen planus

Sasiwong Wongwatana[1], Jair C. Leao[1,2], Crispian Scully[1], Stephen Porter[1]

[1]*Oral Medicine, Division of Maxillofacial Diagnostic, Medical and Surgical Sciences, Eastman Dental Institute for Oral Health Care Sciences, UCL – University of London, London, UK;* [2]*Departamento de Clínica e Odontologia Preventiva, Universidade Federal de Pernambuco, Recife PE, Brazil*

BACKGROUND: There are no reliably effective therapies for oral lichen planus (OLP). The aim of the present work was to determine the potential efficacy of oxpentifylline in the management of OLP.
METHODS: Fifteen patients (six males, median age for the group 52 years, ranging from 33 to 72) with clinically and histopathologically confirmed OLP were treated with oxpentifylline at a dose of 400 mg three times daily.
RESULTS: Only 10 patients completed an 8 week course, the other five having to stop therapy because of adverse effects. Only three patients had any relief of their signs and symptoms of OLP.
CONCLUSION: The results indicate that oxpentifylline is unlikely to be of benefit for the treatment of OLP.
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Introduction

Oral lichen planus (OLP) typically has a chronic clinical course, symptoms and/or signs often remaining or recurring for 20 years or more (1). At present, there is no reliably effective safe therapy for the long-term management OLP (2). The mainstay of therapy remains topical corticosteroids, sometimes supplemented by a variety of other immunosuppressive agents (3–5), topical immunosuppressants such as tacrolimus may be of some benefit (5–7) but there remains a need to determine the efficacy of other immunosuppressive agents in the treatment of OLP.

Oxpentifylline is a theobromine derivative typically used in the management of arteriosclerosis, which also has a wide range of immunosuppressive actions, in particular an inhibitory action upon tumour necrosis factor (TNF)-α (8). It has therefore been suggested that oxpentifylline may be of benefit in the management of immunologically mediated disorders such as rheumatoid arthritis (9), Crohn's disease (10), Behcet's disease (11, 12), systemic sclerosis (13), and sarcoidosis (14). Two research groups have proposed that oxpentifylline may also be effective in the management of recurrent aphthous stomatitis (RAS), possibly resulting in a continued resolution of ulceration for several months following cessation of therapy (15–19). Tumour necrosis factor-α (TNF) appears to play a role in OLP (20) but there are no data on its potential efficacy in the management of OLP. Hence, the aim of the present study was to evaluate the potential clinical benefits of systemic oxpentifylline for the treatment of recalcitrant, symptomatic, OLP.

Correspondence: Prof. Stephen Porter, Oral Medicine, Division of Maxillofacial Diagnostic, Medical and Surgical Sciences, Eastman Dental Institute for Oral Health Care Sciences, University College London, London, UK. Tel.: +44 (0) 207 1197, Fax: +44 (0) 207 2341, E-mail: sporter@eastman.ucl.ac.uk
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Materials and methods

Patients

The study group comprised 15 adult patients with clinical and histopathological features of erosive or ulcerative OLP (six males; median age of group 52 years, range: 33–72). All patients had previously received topical and/or systemic corticosteroids for the treatment symptomatic erosive or ulcerative OLP. Patients were selected on the basis of the following criteria:

1 No treatment with topical and/or systemic corticosteroids or other immunosuppressive drugs in the past 4 weeks.
2 No history of cerebral haemorrhage and retinal haemorrhage.
3 No history of severe cardiac arrhythmias, ischaemic heart disease or myocardial infarction.
4 No history of present and past gastric or duodenal ulceration.
5 No history of present and past hepatic disease, including porphyria.
6 No present history of pregnancy or lactation.

Oxpentifylline therapy

Oxpentifylline (Trental 400, Hoechst, Kent, UK) was prescribed at a dose of 400 mg three times daily, to be taken with meals. The dosage was reduced to 400 mg two times daily if adverse effects were encountered. Each patient was clinically reviewed every 4 weeks, at which time the extent of oral lesions, associated discomfort or pain, and response to therapy were noted. The clinical signs of erosive or ulcerative OLP lesions were rated by an attending clinician according to the following scoring system: 3 = severe, 2 = moderate, 1 = mild, 0 = none. Improvement was recorded if the score was lower than that recorded at the initial visit. In addition, each patient was asked to record each week the severity of their oral pain on a scale of 0–3, with 0 indicating no pain and 3 representing severe pain.

Table 1 Patient reported adverse effects of oxpentifylline therapy

Adverse effect	*Frequency in 15 patients, n (%)*
Headache	3 (20)
Diarrhoea	3 (20)
Flushing	2 (13)
Ataxia	1 (6.5)
Gastric upset	1 (6.5)
Night sweats	1 (6.5)
Lethargy	1 (6.5)
Tremor	1 (6.5)
Flatulence	1 (6.5)
Metallic taste	1 (6.5)
Pruritus	1 (6.5)
Insomnia	1 (6.5)
Gingival bleeding	1 (6.5)

Results

Figure 1 summarizes the outcomes of oxpentifylline therapy. Ten of the 15 patients (66.6%) persisted with oxpentifylline therapy for more than 8 weeks. Three of these patients had symptomatic improvement but the remaining seven reported no notable changes. Of the three patients who had symptomatic improvement, only one had resolution of both signs and symptoms of erosive OLP. The remaining seven patients who were able to tolerate oxpentifylline had no notable clinical benefit, three had a worsening of painful symptoms while four reported no change in the oral discomfort associated with OLP.

Seven of the 15 patients (46.6%) had drug-related adverse effects, such that five were unable to continue oxpentifylline therapy (Table 1). Reported adverse effects included headache and diarrhoea (20% of 15 patients), flushing (13%), ataxia, gastric upset, night sweats, lethargy, tremor, flatulence, metallic taste, pruritus and insomnia (all 6.5%). One patient reported increased gingival bleeding.

Discussion

Oxpentifylline, used initially for the treatment of peripheral vascular disease (21) has important effects upon immune-mediated phenomena. It is able to inhibit cytokine production by macrophages/monocytes and whole blood cells, and the production of TNF-α relevant to any potential treatment of OLP (8, 22).

The TNF-α has been implicated in the immunopathogenesis of OLP (20, 22, 23), and thus oxpentifylline might be expected to be of some benefit in lessening the signs and symptoms, especially since thalidomide, which has strong anti-TNF-α properties (24) can reduce the severity of OLP in some patients (25). However, thalidomide may in contrast cause OLP (26) and most recently we have observed lichenoid dysplasia arising with the use of the anti-TNF-α agent adalimumab (27). Significantly, in the present study, oxpentifylline did not produce any real benefit in clinical symptoms or signs of OLP. It may be then that at least *in vivo* TNF-α agents have little role on the development or maintenance of OLP and therefore might explain why anti-TNF-α agents such as oxpentifylline are not of therapeutic benefit. Equally, it might be that the treatment period was too short (28). For example, topical tacrolimus (which does not have an anti-TNF-α action) does not cause reduction in symptoms or signs of erosive or ulcerative OLP until after 6 or more weeks of therapy (6). Of equal relevance, oxpentifylline was not tolerated by the majority of patients and thus even if the drug had been of benefit, its application would be limited to small number of patients.

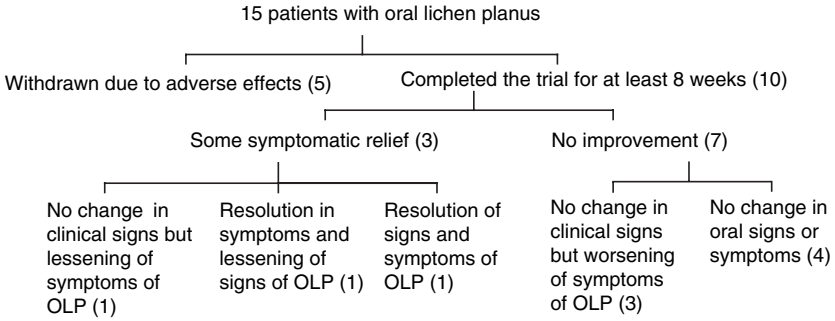

Figure 1 Summary of outcomes of oxpentifylline therapy of 15 patients with oral lichen planus.

Conclusion

It is concluded that oxpentifylline is unlikely to be an effective treatment for erosive or ulcerative OLP as it is poorly tolerated by patients and does not, at least in short-term, cause clinically significant reductions in signs nor painful symptoms.

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