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Efficacy of mometasone furoate microemulsion in the treatment of erosive-ulcerative oral lichen planus: pilot study

J. M. Aguirre[1], J. V. Bagán[2], C. Rodriguez[1], Y. Jimenez[2], R. Martínez-Conde[1], F. Díaz de Rojas[3], A. Ponte[3]

[1]*Medicina y Patología Bucal, Medicina Preventiva y Salud Pública, Facultad de Medicina y Odontología, Universidad del País Vasco/EHU, España;* [2]*Servicio de Estomatología, Hospital General Universitario, Facultad de Medicina y Odontología, Universidad de Valencia, España;* [3]*Departamento Médico, Schering-Plough SA, España, Spain*

BACKGROUND: Oral lichen planus (OLP) is a frequent immunological chronic disease, having different clinical forms: asymptomatic and symptomatic. Symptomatic OLP has been palliated with topical corticosteroids with different levels of efficacy and safety. The purpose of this pilot phase II clinical trial was to determine the efficacy of mometasone furoate microemulsion upon the symptoms and signs of erosive-ulcerative OLP.

METHODS: Forty-nine patients with clinical and histologically confirmed erosive-ulcerative OLP were enrolled in this study (36 women and 13 men). Their average age was 56.4 years (from 28 to 78). The treatment consisted of 0.1% mometasone furoate microemulsion mouthwash three times a day over 30 days. Pain, erythema and ulceration were assessed after 15 and 30 days of treatment. The data was processed and statistically analysed by student's *t*-test for paired samples.

RESULTS: Mometasone caused a statistically significant reduction in pain (3.58 vs. 0.65, $P = 0.0000$). Treatment significantly reduced the surface area of erythema (155.2 vs. 21.9 mm^2, $P = 0.0001$) and ulceration (30.7 vs. 7.3 mm^2, $P = 0.0000$). None of these patients suffered severe adverse effects.

CONCLUSIONS: Mometasone furoate microemulsion is a safe and effective therapy in the treatment of symptomatic erosive-ulcerative OLP.

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Correspondence: Prof. José M. Aguirre, Medicina Bucal, Departamento de Estomatologia, Universidad del País Vasco EHU, Leioa. 48940, Vizcaya, Spain. Tel.: (34)94 460 02924. Fax: (34)94 480 2551. E-mail: otpagurj@lg.ehu.es
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Introduction

Oral lichen planus (OLP) is a common chronic mucocutaneous disease with various clinical forms (reticular, papular, plaquelike, erosive-ulcerative, and bullous, that can occur separately or simultaneously). Erosive-ulcerative forms usually cause symptoms of pain and discomfort (1–4).

Although the cause of OLP is still unknown, it is documented that it represents a cell-mediated immune response with an inflammatory infiltrating cell population composed of T lymphocytes (3, 5).

Diagnosis of OLP is made by the clinical and histopathological characteristics. The treatment of OLP is often disappointing and controversial (3). Patients with symptomatic OLP often present significant management problems and the need to reduce morbidity perpetuates a continuing search for novel therapies (6). The most frequently described therapy for OLP has been the administration of topical or systemic corticosteroids (1, 3, 4, 7–12). The efficacy of corticosteroids in OLP is mainly attributed to the local anti-inflammatory effect and the anti-immunologic properties of suppressing T-cell function (3, 10–14).

Mometasone is a synthetic glucocorticoid 16 a-methyl analogue of beclomethasone which has been effective in the management of dermatological and mucosal conditions such as minor recurrent aphthous stomatitis (15–17).

Topical mometasone has been classified as a 'potent glucocorticoid' and it has demonstrated a greater anti-inflammatory activity and a longer duration of action than betamethasone. Mometasone has showed low adverse systemic effects such as suppression of the hypothalamic-pituitary-adrenal axis (16). One of the problems of the topical corticosteroids in oral treatments is the difficulty for application and the ability to reach posterior oral places and to cover extensive and multiple areas. To resolve these treatment challenges oral suspension is the most appropriate and efficacious form (14).

The purpose of this pilot phase II clinical trial was to establish the efficacy of mometasone furoate 0.1%, in it is new form as a liquid microemulsion, in the treatment of the erosive-ulcerative OLP.

Material and methods

Patient group

Participation in this pilot phase II study was limited to patients with clinical signs and symptoms of oral erosive-ulcerative lichen planus, in whom clinical diagnosis was confirmed by histopathology and immunofluorescence when the differential diagnosis with other mucocutaneous diseases were proposed. OLP was differentiated from mucocutaneous diseases as lupus erythematosus, mucous pemphigoid, erythema multiforme, and others (3, 5). Criteria for inclusion and exclusion for participation in this study appear in Table 1. Informed consent to participate in a research study was obtained from all patients.

Forty-nine patients with clinical and histologically confirmed erosive-ulcerative OLP were enrolled (36 women and 13 men). Their average age was 56.4 years (from 28 to 78).

Mometasone treatment

The treatment consisted of 0.1% mometasone furoate microemulsion mouthwash three times a day over a period of 30 days. Patients were instructed to rinse with 5 ml for 5 min and then to expectorate. Rinsing occurred at the same time each day, and no eating or drinking was permitted for 30 min after application. The microemulsion was composed by: transcutol (41.73%), plurol oleique (41.73%), Labrafil M 1944 (8.63%), demineralized water (6.47%), and fluorescence lemon (1.44%) (Gattefossé, s.a., Saint-Priest, France®) (Prof. A. Dominguez-Gil, University of Salamanca). Patients were evaluated prior to treatment and after 15 and 30 days of treatment.

Clinical evaluation

In the clinical analysis the three most important parameters evaluated in the patients were pain, erythema and ulceration. Pain, erythema and ulceration scores as well as a questionnaire documenting potential adverse effects were completed at each visit. Patients were asked to rank the severity of their pain and discomfort on a visual analogue scale from 0 (no pain) to 10 (extreme pain) (18). Intraoral areas of ulceration and erythema were measured in mm^2. These measurements were added at initial presentation and at each visit. Photographs were taken for visual documentation of changes in each case.

Laboratory evaluation

Initial and final baseline laboratory studies included a serial multiple analysis and a complete blood cell count with differential, was made. That included haemoglobin, glucose, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), alkaline phosphatase, total bilirrubin, creatinin, urea/BUN (blood urea nitrogen). Any patient who had *Candida* colony-forming units > 50 were excluded from the study; those with 50 colony-forming units and less were considered normal carriers (19).

Statistical analysis

This pilot study was designed following previous criteria (20). The data were processed and statistically analysed by student's *t*-test for paired samples.

Table 1 Clinical criteria

Criteria for inclusion
Older than 18 years
Clinical and histopathological diagnosis of erosive-ulcerative oral lichen planus
Criteria for exclusion
Treatment with corticosteroids during the previous month
Hypersensibility to corticosteroids
Liver or renal insufficiency
Diabetes or glaucoma
Oral candidosis or more than 50 CFU at the onset
Pregnancy or lactation
Notable abnormalities in full blood cell count and hepatic and renal biochemistry
Immunosuppresive disease
Social and personal reasons preventing regular and clinical review
Local or systemic pathologies likely to hinder accurate clinical examination

Results

Clinical data

Data showing the evolution of the three principal parameters (pain, erythema and ulceration) are displayed in Tables 2 and 3. We have observed an important reduction in pain with this treatment over 15 days. The average decrease in pain was 3.02 with a 95% confidence interval between 2.86 and 3.90. This decrease was statistically significant ($P < 0.0001$). We have observed an important disappearance of erythema. When we evaluated the severity of erythema over the treatment period starting at baseline, we found the greater improvement occurred during the first 2 weeks. The average size of the erythema decreased significantly in 15 days (155.2 vs. 46.3 mm^2, $P = 0.0000$) and continued at 30 days (155.2 vs. 21.9 mm^2, $P = 0.0001$; Fig. 1a,b).

Table 2 Clinicalresponse of patients treated with mometasone furoate microemulsion: pain (analogue visual scale 0–10), erythema (mm^2), ulceration (mm^2)

Day		*Pain*	*Erythema*	*Ulceration*
0	*N*	48	49	48
	Mean	3.583333	155.2653	30.77083
	SE (mean)	0.3914346	30.29015	4.630327
15	*N*	39	40	39
	Mean	0.7692308	46.35	8.035897
	SE (mean)	0.2365449	13.57215	2.114265
30	*N*	43	44	44
	Mean	0.6511628	21.93182	7.363636
	SE (mean)	0.2229464	6.749708	2.560492

SE, standard error.

Table 3 Statistical results with respect to clinical data

	Days	*N*	*Mean*	*SE*	*95% CI*
Pain	0	48	3.58	0.3914	2.79–4.37
	15	39	0.77	0.2365	0.29–1.25
	30	43	0.65	0.2229	0.20–1.10
Erythema	0	49	155.26	30.2901	94.36–216.17
	15	40	46.35	13.5722	18.89–73.80
	30	44	21.93	6.7497	8.32–35.54
Ulceration	0	48	30.77	4.6304	21.46–40.09
	15	39	8.03	2.1143	3.76–12.32
	30	44	7.36	2.5605	2.20–12.53

SE, standard error.
95% CI, 95% confidential interval.

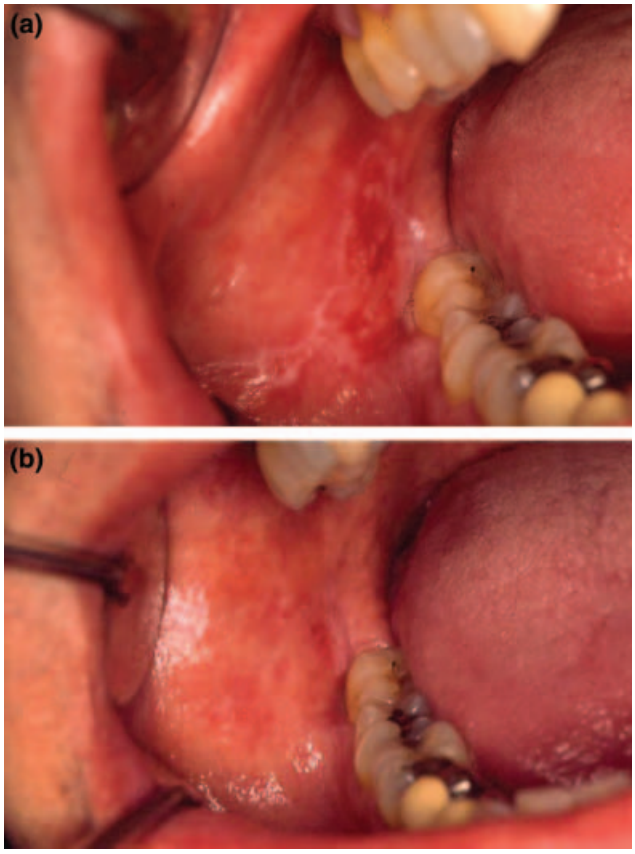

Figure 1 Clinical response: (a) reticular, atrophic and erosive lesions on right posterior buccal mucosa; (b) same patient after 30 days treatment with mometasone microemulsion.

The healing of the ulcerated lesions has been very quick, with a significant decrease in the first 2 weeks. The average size of the ulceration's decreased significantly in 15 days (30.7 vs. 8.03 mm^2, $P = 0.0000$) and continued but with minor intensity at 30 days (30.7 vs. 7.3 mm^2, $P = 0.0000$; Fig. 2a,b).

Laboratory investigations
There were no statistically significant differences between the initial and final laboratory analytical data. We have not observed any serious adverse effects in our patients. Six patients (12.2%) developed clinical oral candidosis, four pseudomembranous and two erythematous. These cases were confirmed by culture and treated with antifungals (fluconazole and/or nystatin).

Discussion

Oral lichen planus is a chronic mucocutaneous disease with no known cure at present. In this pilot phase II study, we explored the efficacy of a new potent glucocorticoid, mometasone furoate, in a new presentation as a liquid microemulsion, in the topical treatment of the erosive-ulcerative OLP. Our results showed that mometasone 0.1% used topically as microemulsion has a quick and significant beneficial effect in the control of the main symptoms and signs of erosive-ulcerative lichen planus with minimal adverse effects.

The management of OLP is not satisfactory in all cases and at present there is no definitive treatment. Amongst the many treatments available, high potency topical corticosteroids remain the most reliable and effective, though topical cyclosporin, topical tacrolimus, or systemic corticosteroids may be indicated in patients whose condition is unresponsive to topical corticosteroids (3, 6, 11). Often systemic corticosteroids are used in the treatment of OLP with erosive-ulcerative lesions but with the risk of severe adverse reactions. For this reason different authors have studied the efficacy of the topical corticosteroids such as triamcinolone, fluocinolone, clobetasol, fluticasone (3, 7, 11, 12, 14, 21). The most important features that should meet a topical corticosteroid in OLP treatment are the following: to be effective at minimal dose, to produce no or minor adverse effects, and to reach every part of the oral cavity and to remain in contact with the lesions for a time enough to act locally.

Mometasone furoate reduces the OLP pain quickly in the first 2 weeks of the treatment. These results are similar to those obtained with other potent corticoids such as clobetasol (7, 14). The great decrease in erythema in our patients during the first weeks of treatment may be because of vasoconstriction and reduction of the inflammatory response (22). It is important to underscore the fast ulcer healing in these patients including recalcitrant ulcerative lesions (Fig. 2a,b).

Our results show that 2 weeks is enough time for the initial treatment, except for erythema, which continues decreasing over the subsequent 2 weeks. For this reason, we think that this significant decrease in erythema warrants treatment for a period of 30 days. Similar to the findings of other studies we did not find any cases of severe adverse reactions associated with corticosteroid therapy, (7, 13, 14), although our duration of treatment was shorter.

Pharmacokinetics properties of mometasone are well established. Systemic absorption is minimal. With a single intranasal dose of mometasone furoate 400 μg, bioavailability was $< 0.1\%$ and peak plasma concentration was below to the limits of quantification (50 ng/l) of the assay used. Moreover, it undergoes extensive hepatic

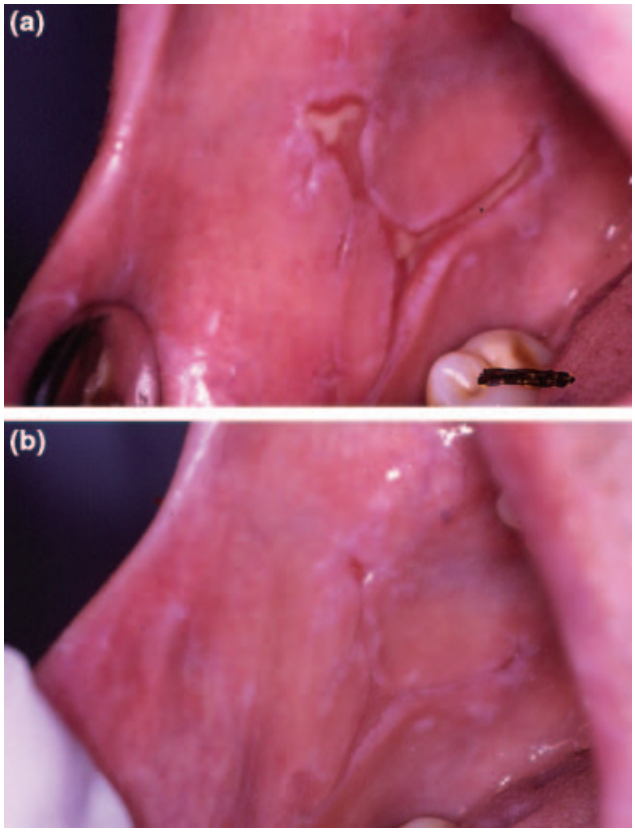

Figure 2 Clinical response: (a) large painful ulcer on right central buccal mucosa; (b) same patient after 30 days treatment with mometasone microemulsion.

metabolism. When is administered orally as a single dose or intranasally in a once-daily regimen for up to 1 year, mometasone did not suppress hypothalamic-pituitary-adrenal axis function in healthy volunteers, or in children or adults with allergic rhinitis (23). In this work we did not evaluate the adrenal function as the treatment period was only 30 days and the concentration of the corticosteroid used was 0.1%.

Only six (12.2%) of our patients developed oral candidosis during the treatment. In all of these cases, oral candidosis disappeared with antifungal treatment. For this reason we believe as other authors do (7), that a baseline culture is appropriate and necessary to identify high carriers of *Candida* (> 50 CFU) before starting topical treatment with a high potency corticosteroid such as mometasone furoate. As a preventive element adding 100 000 IU/cc of nystatin to prevent oral candidosis in these patients could be important, as proposed by Gonzalez-Moles et al. (14).

We think that the good results obtained in our study are because of the microemulsion used to transport the corticosteroid. The oleic microemulsion enabled us to reach parts of the oral cavity where were adhesive ointments cannot be applied. Also it allowed the corticosteroid to remain adhered to the lesions for a longer time. Recently Gonzalez-Moles et al. (14) have reported very good results with an aqueous solution of clobetasol in erosive oral diseases including OLP. However, the time of treatment was longer (48 vs. 4 weeks) and adverse reactions were evident.

In conclusion mometasone furoate microemulsion 0.1% is an effective topical therapy in the treatment of the erosive-ulcerative OLP. Wider studies are warranted with the following aims: to study the efficacy of other lower concentrations of mometasone (e.g. 0.05 or 0.025%); to compare the efficacy of mometasone with other high potency corticosteroids (e.g. clobetasol or fluocinonide) or immunosuppresive agents; to assess the evolution of mometasone-treated patients after total withdrawal of treatment. These results should be confirmed by double blind clinical studies in this pathology and in other oral ulcerative diseases.

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