The treatment of oral aphthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations: a clinical and pilot study on 54 patients

Lorenzo Lo Muzio[1]
Antonio della Valle[2]
Michele D. Mignogna[2]
Giuseppe Pannone[2]
Paolo Bucci[2]
Eduardo Bucci[2]
James Sciubba[3]

[1]*Institute of Dental Sciences, University of Ancona, Ancona,*
[2]*Division of Oral Pathology and Medicine, University of Naples Federico II, Naples, Italy and*
[3]*Department of Dental Medicine, Long Island Jewish Medical Center, New Hyde Park, New York, USA*

Abstract
Background: This study evaluated the clinical use of a corticosteroid in three preparations (topical clobetasol propionate ointment, clobetasol propionate in an oral analgesic base, and clobetasol propionate in an adhesive denture paste).
Methods: Fifty-four patients (34 males and 20 females) with a history of vesiculo-ulcero-erosive oral lesions were selected: 24 with oral erosive lichen planus and 30 with aphthae. The subjects enrolled were randomly divided into three groups, each of 18 patients (10 with aphthae and 8 with lichen planus): the first was treated with topical clobetasol propionate ointment (0.05%) directly on the lesion(s) three times a day; the second with clobetasol propionate in an adhesive denture paste in equal amounts (1:1) two times a day; the third with clobetasol propionate in an oral analgesic base (Orabase-B) in equal amounts (1:1) two times a day. Each subject scored his or her symptoms daily from most severe (7) to none (0) by verbal assessments using a categorical scale.
Results: In all cases, the administration of the corticosteroid was effective in producing remission of symptoms in each group of patients. Significant differences ($P<0.05$) between groups were determined by the Kruskal–Wallis test. The Dunn test was used in order to detect which group differs from the others; clobetasol and adhesive denture paste correlated with an early remission of pain in lichen and apthous lesions.
Conclusion: The results suggest that topical application of clobetasol in an adhesive denture paste is an effective drug for symptomatic oral vesiculo-erosive and/or ulcerative lesions.

Key words: adhesive paste; clobetasol propionate; vesiculo-ulcero-erosive oral lesions

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Correspondence to:
Lorenzo Lo Muzio
Via Carelli 28, 71100 Foggia, Italy
e-mail: llomuzio@tin.it

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The use of corticosteroids is indicated to reduce the symptoms and the local effects of autoimmune oral mucous membrane diseases (erosive lichen planus and aphthous stomatitis) (1–13). Topical corticosteroid drugs are often the mainstay in the treatment of oral inflammatory diseases. They are effective in that they help reduce inflammation (14–20) and, more specifically, to reduce exudation of

leukocytes and formation of soluble inflammatory mediators, while helping to maintain cellular membrane integrity, inhibit phagocytosis and release of lysozymes from granulocytes and stabilize the membranes of lysosomes that contain hydrolytic enzymes (15, 21–25).

The topical application of clobetasol propionate is promoted in clinical stomatological practice because it produces a high level of benefit with a minimal level of side effect when used properly.

Appropriate use does not cause hypothalamic-pituitary-adrenal axis suppression (26–28). Clobetasol propionate (0.05%) is a very potent corticosteroid based on vasoconstriction assay and, furthermore, has a low gastric absorption.

High-potency topical corticosteroids in an adhesive medium appear the safest and most effective treatment of oral lichen planus (for a review see Ref. 29). Topical corticosteroids are the mainstay of therapy also for aphtous ulcers (for a review see Ref. 13, 30).

Topical medications with mucosal adherence properties have been used effectively with variable results. Such preparations include Orabase (31), Zylactin (32), cyanoacrylate (33) and bioadhesive patches composed of a derivative of cellulose (34).

In this study, we evaluated the effects of topical corticosteroid therapy in association with agents that increased the adhesion of the active drug to the oral mucosal surface (35–36).

Furthermore, we evaluated the possibility of reducing the amount of drug necessary to achieve clinical improvement and the elapsed time to achieve oral mucosal healing.

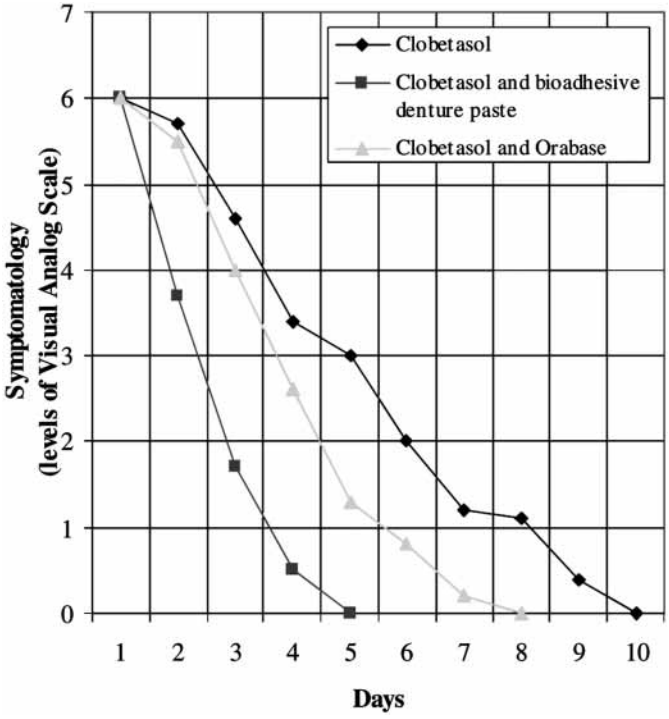

Fig. 1. Mean value scores for patients with aphthae using the verbal symptomatology scale. The group utilizing the bioadhesive system presented with clinical remission of recurrent aphthous ulcers (RAU) in 2–4 days, while the group utilizing clobetasol propionate ointment alone achieved the same clinical results in 6–9 days. In group three, where clobetasol propionate was applied in an oral analgesic base (Orabase-B), the absence of symptoms was achieved in 4–7 days.

Table 1. Site affected by oral lichen planus

Site	Lichen planus No. of cases	RAS No. of cases
Tongue	9	9
Cheek	15	
Floor		12
Alveolar mucosa		9

Table 2. Clinical data on oral lichen planus

	No. of cases
Atrophic/erosive	21
Reticular	3

Table 3. Clinical data on aphthous lesions

	Days
Healing time	7–10
Period of ulcer-free disease	15–40

Material and methods

Selection of cases

In the current study, we selected 54 patients (34 males and 20 females) with a stated history of vesiculo-ulcero-erosive oral lesions for at least 2 years (Tables 1–3). Their ages ranged between 15 and 60 (average age=38.7) years. Criteria for exclusion from the study were: hematological deficiencies, pregnancy, inflammatory bowel disease and immune dysfunction.

Twenty-four of the patients related a history of oral erosive lichen planus (Tables 1 & 2); criteria of inclusion in this study were: 1) the clinical diagnosis of OLP, 2) the confirmation of the diagnosis by oral biopsy; World Health Organization (WHO) criteria for the histological diagnosis of OLP were applied to hematoxylin and eosin (H&E) stained biopsy sections (37).

Thirty patients presented with a stated diagnosis of recurrent aphthous ulcers (Tables 3 & 4); criteria of inclusion in this study were the clinical features of the lesions as outlined by Lehner (38).

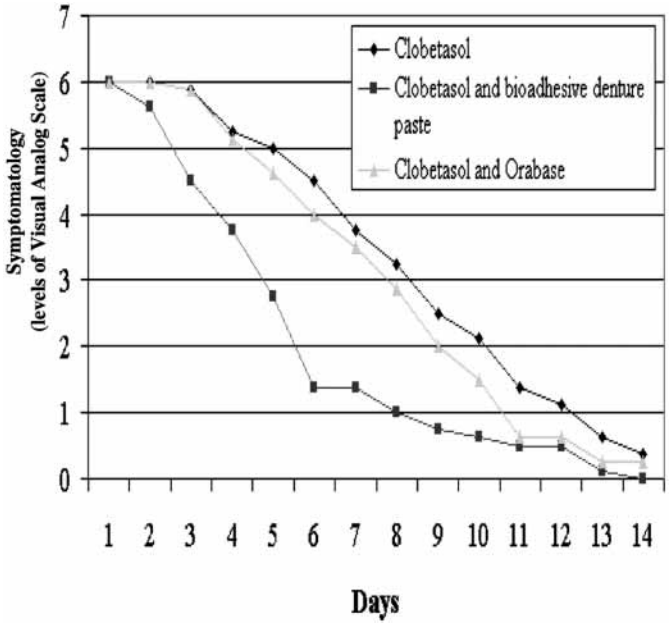

Fig. 2. Mean value scores for patients with oral lichen planus using the verbal symptomatology scale. Topical therapy in erosive lichen planus: the group utilizing the bioadhesive system presented a complete clinical remission in 6-13 days, while the group utilizing the clobetasol propionate ointment alone achieved the same clinical results in 10–14 days. In group three, where clobetasol propionate was applied in an oral analgesic base (Orabase-B), the absence of symptoms was achieved in 7–10 days.

No patient in this group had any hematological abnormality, such as deficiency of iron, vitamin B_{12} or folate.

All aphthous patients had active ulcers at the time of commencing their experimental therapy. In addition, in each case of lichen and aphthous lesions symptoms, location of lesions and clinical history were carefully recorded. A photograph of the lesion was also obtained.

The study design was approved by the Local Ethics Committee and all patients signed a written informed consent form.

Study design

The subjects enrolled in this study were randomly divided into three groups: The first group was treated with topical clobetasol propionate ointment (0.05%) directly on the lesion(s) three times per day. This group consisted of 18 patients, of which 8 had a working diagnosis of oral lichen planus, while the remainder (n=10) had a history of recurrent oral ulcerations of the aphthous type. The second group was treated with clobetasol propionate in an adhesive denture paste in equal amounts (1:1) with applications being done twice daily. Eighteen patients were assigned to this particular group, which was further characterized by 10 individuals with recurrent aphthous ulcers and 8 patients with erosive oral lichen planus. The third group (18 patients: 10 with aphthae and 8 with lichen planus) was treated with clobetasol propionate in an oral analgesic base (Orabase-B) in equal amounts (1:1), which was applied twice daily directly to the site of the lesion. The authors chose to use 0.05% clobetasol ointment in Orabase-B and an adhesive denture paste twice daily because it had been associated with an adhesive paste and to prevent the effects of overdosage.

The study was a double-blind trial; after use, the containers were weighed to limit the amount of each clobetasol preparation use (10 mg), in order to avoid a dose-related effect.

Patients affected by recurrent aphthous stomatitis (RAS) only applied the clobetasol at the start of a crop of new ulcers. All patients maintained daily records of their symptoms, from the lesions before and after starting the trial.

The adhesive denture paste contained inactive ingredients, including sodium carboxymethyl cellulose, copolymeric vinyl methyl ether and maleic anhydride calcium, as well as polyvinyl pyrrolidone, polyethylene oxide, microcrystalline cellulose and erythrocin lacquer and petrolatum. The Orabase-B, on the other hand, contained an active ingredient, benzocaine (20%), and an inactive component of a plasticized hydrocarbon gel, guar gum, cellulose gum, tragacanth gum, pectin, as well as preservatives and a flavoring agent.

Equal amounts of clobetasol propionate ointment and adhesive were mixed on a dry, smooth surface immediately prior to application. The mixture was applied with a cotton swab directly to the ulcer or painful mucosal site, in particular after meals.

Each of the three groups were examined each day when symptoms were present, and each subject was asked to score his or her symptoms from most severe (7) to none (0) by verbal assessments. To measure pain, subjects used a categorical scale to measure initial pain, with a subsequent evaluation denoting change in pain. A visual analog scale (VAS) (39) was used; it consisted of a 10 cm line containing equidistant subdivisions with the following associated notations: 7=aggravated pain, 6=pain before treatment, 5=marked, 4=moderate, 3=mild, 2=light, 1=very light and 0=no pain. There was no significant difference for severity of symptoms score and/or pain among the three groups of patients at entry.

Every morning serum and urine from all patients were analysed for electrolytes and glucose concentration. Blood pressure was measured twice daily.

Statistical analysis

The data were analysed using the Stanton A. Glantz statistical software (version 3.0 for MS-DOS), using the rank-based nonparametric tests of Kruskal–Wallis and Dunn.

Table 4. Mean and standard deviation (SD) of symptomatology score in 54 patients

Group 1: clobetasol		Group 2: clobetasol and adhesive paste		Group 3: clobetasol and Orabase	
	Average±SD		Average±SD		Average±SD
Case 1 lichen	3.93±1.94	Case 1 lichen	3.64±2.17	Case 1 lichen	3.86±1.88
Case 2 lichen	4.00±1.96	Case 2 lichen	1.29±2.02	Case 2 lichen	3.00±2.45
Case 3 lichen	2.43±2.24	Case 3 lichen	1.93±2.40	Case 3 lichen	3.00±2.45
Case 4 lichen	3.07±2.16	Case 4 lichen	1.93±2.40	Case 4 lichen	3.00±2.45
Case 5 lichen	2.71±2.43	Case 5 lichen	1.29±2.02	Case 5 lichen	1.93±2.40
Case 6 lichen	3.50±2.07	Case 6 lichen	1.29±2.02	Case 6 lichen	3.00±2.45
Case 7 lichen	3.43±2.03	Case 7 lichen	1.93±2.40	Case 7 lichen	3.07±2.16
Case 8 lichen	4.21±2.01	Case 8 lichen	3.79±2.01	Case 8 lichen	3.86±1.88
Case 9 RAS	2.00±2.35	Case 9 RAS	0.71±1.73	Case 9 RAS	1.71±2.43
Case 10 RAS	2.36±2.31	Case 10 RAS	0.64±1.65	Case 10 RAS	1.07±2.06
Case 11 RAS	2.71±2.55	Case 11 RAS	0.79±1.85	Case 11 RAS	1.07±2.06
Case 12 RAS	1.14±2.03	Case 12 RAS	0.93±1.86	Case 12 RAS	1.93±2.40
Case 13 RAS	1.14±2.03	Case 13 RAS	1.07±2.06	Case 13 RAS	1.71±2.43
Case 14 RAS	2.00±2.35	Case 14 RAS	0.71±1.73	Case 14 RAS	1.07±2.06
Case 15 RAS	2.36±2.31	Case 15 RAS	1.07±2.06	Case 15 RAS	1.29±2.02
Case 16 RAS	2.36±2.31	Case 16 RAS	0.93±1.86	Case 16 RAS	1.71±2.43
Case 17 RAS	2.00±2.35	Case 17 RAS	0.71±1.73	Case 17 RAS	1.93±2.40
Case 18 RAS	1.50±2.14	Case 18 RAS	0.93±1.86	Case 18 RAS	1.07±2.06

Results

The administration of the corticosteroid in all cases was effective in producing remission of symptoms in each group of patients. Every day no side effects at the systemic level were noted, including fluid and electrolyte disturbances, hyperglycemia, glycosuria or hypertension. No patient reported heartburn during treatment.

Using the VAS pain scores, an excellent response occurred in all patients with aphthous ulcers treated with the bioadhesive system: the healing times of this group (score=0) was 3.5±0.5 (range 2–4) days for clobetasol and adhesive paste (Fig. 1), 4.4±1.2 (range 4–7) days for clobetasol and Orabase-B and 6.6±1.6 (range 6–9) days for clobetasol ointment alone (Table 4).

In cases of erosive lichen planus, the group utilizing the bioadhesive system presented a complete clinical remission (score=0) in 8±2.8 (range 6–13) days (Fig. 2). In group one, where clobetasol propionate ointment alone was applied, the same clinical results were achieved in 12.5±1.6 (range 10–14) days. In group three, where clobetasol propionate was applied in an oral analgesic base (Orabase-B), the absence of symptomatology was achieved in 8±2.8 (range 7–14) days.

Before treatment subjects were asked to record daily the history of their symptoms and the usual time for healing of lesions and to compare this healing time with that using clobetasol and adhesive denture paste. The treatment with clobetasol reduced the healing times in most patients – more significantly in the group treated with the adhesive denture paste. The range varied from 5 to 7±3.4 days in patients treated with topical clobetasol and adhesive paste for erosive lichen planus and from 2 to 4±2.2 days for aphthous ulcers (Table 5). Use of clobetasol and Orabase-B resulted in healing times from 3 to 5±2.4 days for erosive lichen planus and from 1 to 3±2.2 days for aphthous ulcers (Table 5). The time for healing using clobetasol alone varied from 2 to 4±1.1 days for erosive lichen planus and from 1 to 2±1.1 days for aphthous ulcers (Table 5).

Ten cases (7 in the bioadhesive denture paste group) presented clinical features of an acute pseudomembranous candidiasis characterized by white, soft plaques along the surface of the mucosa that could be wiped off, revealing an erythematous base. The patients had minimal symptoms. This particular side effect was treated effectively with an antifungal (miconazole) used in conjunction with chlorhexidine (0.12%), which produced resolution quickly. In these cases, patients were monitored regularly thereafter for candidiasis or treated prophylactically with appropriate antifungal agents (40–42). Fungal hyphae were detected using periodic acid–Schiff (PAS) stain on smears prepared directly at chair side.

Significant differencies ($P<0.05$) between groups were determined by the rank-based Kruskal–Wallis test. Furthermore, the Dunn test was used in order to detect which group differed from

Table 5. Data on the average time of symptoms

	Before treatment Days for relief of symptoms	After treatment Days for relief of symptoms
Lichen		
Clobetasol alone	15.2±1.2	12.5±1.6
Clobetasol and Orabase	14.8±1.2	10.8±2.3
Clobetasol and adhesive denture paste	15.1±1.3	8±2.8
Aphthous ulcers		
Clobetasol alone	8.3±1.2	6.6±1.6
Clobetasol and Orabase	8.7±1.5	4.4±1.2
Clobetasol and adhesive denture paste	8.1±1.5	3.5±0.5

Table 6. Dunn's test in all cases

	Difference of rank averages	Standard error	Q*	$P<0.05$
Clobetasol alone vs clobetasol+adhesive paste	20.47	5.23	3.912	Yes
Clobetasol alone vs clobetasol+Orabase	7.44	5.23	1.423	No
Clobetasol+Orabase vs clobetasol+adhesive paste	13.03	5.23	2.490	Yes

*Q is the numerical result of Dunn's formula

Table 7. Dunn's test in cases of aphthous ulcers

	Difference of rank averages	Standard error	Q	$P<0.05$
Clobetasol alone vs clobetasol+paste	17.90	3.91	4.576	Yes
Clobetasol alone vs clobetasol+Orabase	7.00	3.91	1.789	No
Clobetasol+Orabase vs clobetasol+adhesive paste	10.90	3.91	2.786	Yes

Table 8. Dunn's test in cases of lichen planus

	Difference of rank averages	Standard error	Q	$P<0.05$
Clobetasol alone vs clobetasol+paste	9.25	3.52	2.631	Yes
Clobetasol alone vs clobetasol+Orabase	3.31	3.52	0.942	No
Clobetasol+Orabase vs clobetasol+adhesive paste	5.94	3.52	1.689	No

the others: clobetasol and adhesive denture paste correlated with an early remission of pain in lichen and apthous lesions (Tables 6–8).

Discussion

The primary aim of this paper was to show that a new formulation for topical application of glucocorticoids would be effective in managing common oral mucous membrane diseases, namely oral erosive lichen planus and recurrent aphthous stomatitis (RAS). The results of our study indicate the clear benefit of using adhesive systems – in particular, clobetasol combined with denture paste adhesive applied twice daily. Alternatively, the earlier phases of each episode produced resolution with an application three times per day for the first 2 days and once daily thereafter (2 days) with bioadhesive denture paste. This latter compound has excellent bioadhesive properties due to its high molecular weight (greater than 100,000), polymer chain flexibility, a great number of carboxylic groups and the ability to form hydrogen bonds at pH 4 and 5 (16, 24, 43–46).

The adhesive denture paste proved to have good stability and bioadhesive properties over a 12 h period of time, in particular over the buccal mucosa. It also provided a slow drug release over the local area during this time span.

Mean healing time of oral aphthous ulcers was 6.6 ± 1.6 days for clobetasol alone, 4.4 ± 1.2 days for clobetasol and Orabase, and only 3.5 ± 0.5 days for clobetasol and denture adhesive paste. The painful symptomatology of oral erosive lichen planus disappeared in 12.5 ± 1.6 days in patients treated with clobetasol alone, in 10.8 ± 2.3 days in patients treated with clobetasol and Orabase, and in 8 ± 2.8 days in patients treated with clobetasol and adhesive denture paste.

Patients reported the beneficial effect of this new mixture: it permitted accelerated healing of aphthous ulcers or erosive lesions; in fact, before treatment when subjects were asked about the usual time for healing and the anticipated or hoped for healing time using clobetasol and adhesive denture paste, their anticipated time was longer. The actual healing rate improvement was reduced to 5 days from 7 ± 3 days for erosive lichen planus and to 2 days from 4 ± 2 days for aphthous ulcers.

Several double-blind placebo-controlled studies showed the safety and efficacy of topical clobetasol propionate in the treatment of oral vesiculo-ulcero-erosive lesions. Clobetasol ointment (0.05%) in an adhesive base provided complete remission of signs and symptoms in 56–75% of patients with oral lichen planus (28, 47, 48). The most common local therapy for aphthous ulcers uses glucocorticoids, including hydrocortisone, triamcinolone, fluocinonide, beta-methasone, flumethasone, and clobetasol (6). Clobetasol ointment (0.05%) in an adhesive paste used two to three times daily provided

complete remission with no major side effects in five of seven patients with persistent major RAS (28).

Seven (36%) of the 18 patients (i.e., more than a third) treated with clobetasol in denture paste developed thrush and had to be treated with an antifungal. This is a common complication. There was a statistically significant difference for this complication, compared with that observed with the other two treatments. The persistent contact of corticosteroid in denture paste with oral mucosa probably causes local immunosuppression and leads to candidosis.

The results, therefore, show the greater level of effectiveness for the combined use of clobetasol ointment in association with a denture adhesive versus a topical steroid alone or in combination with benzocaine-containing Orabase ($P<0.05$). This study, however, was carried out on a small number of patients; studies on a larger series of subjects are needed to confirm these data.

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