Treatment of severe chronic oral erosive lesions with clobetasol propionate in aqueous solution

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Objective. We sought to analyze the results of topical treatment with a mouthwash of 0.05% clobetasol in aqueous solution in 30 patients with severe oral erosive lesions.
Study design. Over a 48-week period, we evaluated the evolution of pain, ulcerations, atrophy, and interference of the disease in the patient's daily life, classifying the response as *complete* (100% remission/recovery), *excellent* (75%), *good* (50%), *poor* (<50%), or *failed*.
Results. The pain and ulceration totally disappeared in 93.3% of cases and 90% reported a full recovery in their daily life activities. Atrophy response was complete in 28.5%, excellent in 60.7%, and good in 3.5%. Two patients showed no response to the treatment. Five patients suffered mild adverse effects (moon face and hirsutism) between week 4 and week 6 of treatment, which were speedily reversed by reducing the frequency of mouthwash.
Conclusions. Clobetasol mouthwash is a safe and efficacious option for the treatment of severe oral erosive lesions.
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Severe erosive disease of the oral mucosa is one of the main challenges facing oral medicine today. It is often chronic,[1] rarely spontaneously remits,[2-4] causes intense pain, and interferes with the usual daily activities of the patient (including eating, drinking, talking, and maintaining normal relationships).[5] Treatment of these lesions frequently involves the administration of systemic corticosteroids, which is often problematic because of its chronic nature and the associated risk of adverse effects.[6] Lozada-Nur and Zhong Huang[5] reported that an adhesive paste (Orabase) form of clobetasol propionate, the most potent topical corticosteroid,[7-9] is a safe and efficacious alternative to systemic therapy in erosive oral lesions. However, despite the evident benefits of this topical therapy, it may be difficult for patients with severe and extensive lesions to place the adhesive paste on the whole lesional surface and within deep erosive lesions, and a systemic approach is generally adopted in these cases. It has also been reported that the grainy texture of the paste is generally disliked, which may affect patient compliance.[5] Mouthwashes of clobetasol propionate in aqueous solution may offer an alternative topical approach to this patient population. The mouthwash solution provides ready access to all lesional areas, and there is excellent control over the contact time between drug and lesion.

The purpose of the present study was to evaluate the response of patients with severe erosive lesions of the oral cavity to treatment with a mouthwash of clobetasol propionate in aqueous solution, as well as to record any adverse effects.

MATERIAL AND METHODS

White Spanish patients with previously untreated severe erosive lesions of the oral mucosa were recruited from among patients referred to the oral medicine clinic at the University of Granada for the diagnosis and treatment of oral erosive lesions. The criteria for inclusion in the study were as follow: presence of severe pain; extensive and/or multiple ulcerations accompanied or not by painful and extensive atrophy localized in different areas of the oral mucosa; and interference by the disease in the daily life activities of the patient, reported as major difficulty to eat, drink, talk, and maintain normal relationships. The study group consisted of 30 patients, 19 women and 11 men between the ages of 34 and 79 years (mean, 55 years). Twenty-five patients presented with oral lichen planus, 3 presented with oral mucous membrane pemphigoid, and 2 had severe major recurrent aphthous stomatitis. In all patients, the diagnoses were based on medical history, clinical examination, and routine histopathology and direct immunofluorescence studies of a representative biopsy specimen.

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Table I. Response to treatment of the study sample

Pain	*Week 2* *n (%)*	*Week 4* *n (%)*	*Week 6* *n (%)*	*Week 8* *n (%)*	*Week 10* *n (%)*	*Week 12* *n (%)*	*Week 16* *n (%)*	*Week 20* *n (%)*	*Wk. 24* *n (%)*	*Week 48* *n (%)*
Complete	4 (13.3)	18 (60)	26 (86.6)	27 (90)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)
Excellent	14 (46.6)	8 (26.6)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Good	8 (26.6)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Poor	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed	4 (13.3)	3 (10)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)
Total	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)

Table II. Evolution of ulceration with treatment time

Ulceration	*Week 2* *n (%)*	*Week 4* *n (%)*	*Week 6* *n (%)*	*Week 8* *n (%)*	*Week 10* *n (%)*	*Week 12* *n (%)*	*Week 16* *n (%)*	*Week 20* *n (%)*	*Week 24* *n (%)*	*Week 48* *n (%)*
Complete	3 (10)	23 (76.6)	27 (90)	27 (90)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)	28 (93.3)
Excellent	20 (66.6)	4 (13.3)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Good	3 (10)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Poor	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed	4 (13.3)	3 (10)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)
Total	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)

Therapy schedule and evaluation

All patients received an aqueous solution containing 0.05% clobetasol propionate and 100 000 IU/cc nystatin to be used as a mouthwash. The schedule, partly based on published data on topical treatment with corticosteroids in adhesive paste (Orabase) form,[10] consisted of a 5-minute mouthwash with 10 cc of the solution 3 times daily (after breakfast, lunch, and the evening meal). The patients were instructed to not swallow the solution. Every variable (pain, atrophy, ulceration, and interference in daily life) was independently evaluated by the same experienced clinician (M.A.G.-M.) at 10 follow-up visits scheduled for weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 48 after the beginning of treatment. The response to treatment was assessed as *complete* (100% remission/recovery), *excellent* (75%), *good* (50%), *poor* (less than 50%), or *failed* (no response). When a complete or excellent response was recorded for pain, ulceration, and disturbance of daily life, the treatment was restricted to alternate days, similar to the approach recommended in the guidelines for systemic corticosteroid treatment.[1] At later visits, if the improvement continued, the frequency of mouthwashes was gradually reduced until the patient was on a maintenance dosage of one 5-minute mouthwash on alternate days. The patients were warned to not discontinue or modify the treatment on their own account, despite the disappearance of pain and lesions, because of the risk of recurrence. Professional oral prophylaxis was applied at the first visit or as soon as the gingival condition of the patient permitted, and was then repeated every 3 or 4 months.[11]

At every visit, the patients were examined for the presence of adverse effects related to prolonged clobetasol treatment. Glycemia and blood pressure were measured; patients were examined for clinical signs and symptoms of candidiasis (erythema and burning), as well as the presence of moon face, hirsutism, buffalo hump, liquid retention, and weight increase; and were interviewed regarding mood changes, gastrointestinal disorders, easy bruisability, and loss of the taste sensation.

RESULTS

Data on the posttreatment evolution of pain, ulceration, atrophy, and interference in daily activities are displayed in Tables I, II, III, and IV, respectively. At the end of the study period (48 weeks), the pain and ulceration had disappeared (complete response) in 93.3% of the sample (28/30 patients; Fig 1); daily life activities had completely rebounded in 90% (27/30), with another patient reporting an excellent response (3.3%). Atrophy of the oral mucosa completely disappeared in 28.5% (8/28) of the 28 patients who initially presented with atrophy, with an excellent response observed in 60.7% (17/28) and a good response in 3.5% (1/28). The 2 patients with major aphthous stomatitis never presented with atrophy. Two patients (6.6%) with hepatitis C–related oral lichen planus failed to respond or responded poorly to the treatment, which they discontinued at week 10. Fig 2 depicts the evolution of the percentage of patients with complete responses during the treatment period; most patients presented the complete response of pain, ulceration and daily

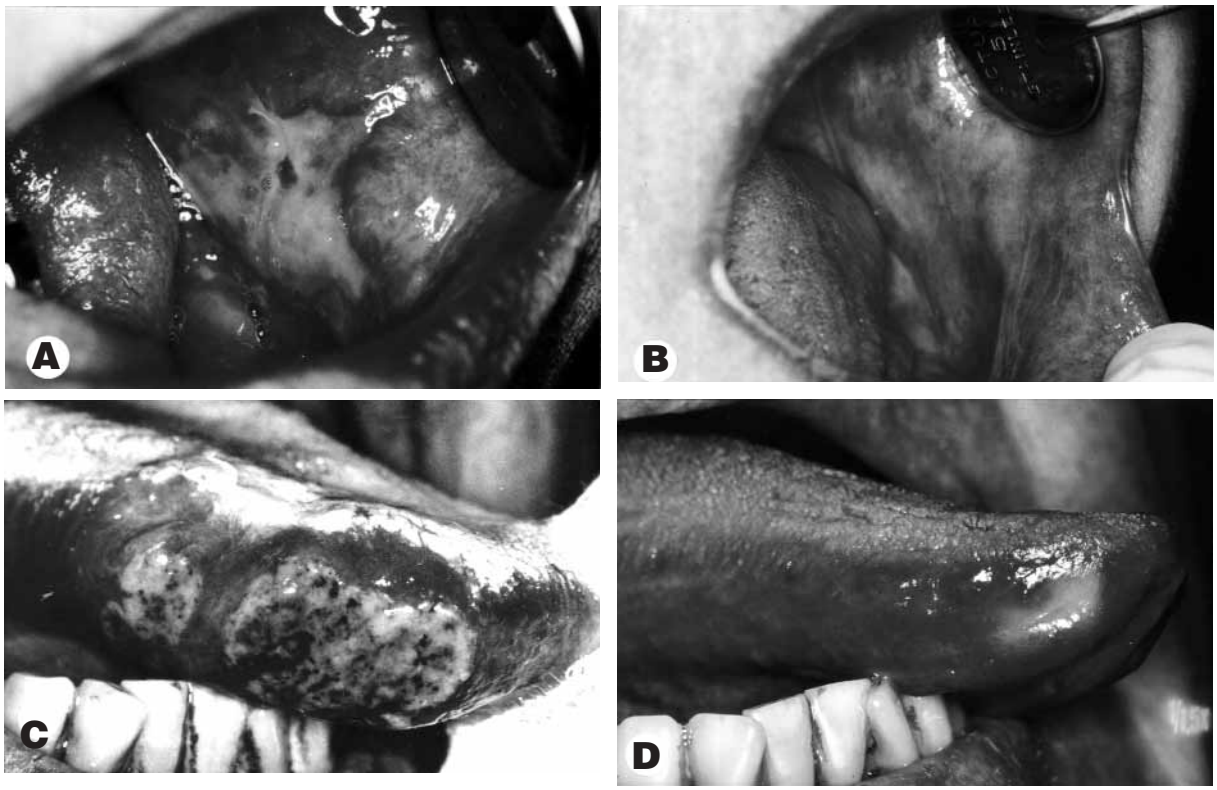

Fig 1. **A,** Female patient with oral lichen planus who presented with extensive erosive and atrophic lesion in left buccal mucosa. Other erosive and atrophic lesions were present at other locations. **B,** The same patient as in **A** after treatment with clobetasol propionate mouthwash. Although a certain degree of atrophy persists, the erosive lesion and pain have completely disappeared. **C,** Male patient with major ulcerous lesions of the lower right surface of the tongue. **D,** The same patient as in **C** after treatment with clobetasol propionate mouthwash. The ulcers have disappeared, leaving a small scar.

Table III. Evolution of atrophic lesions (total no. of cases with atrophy: 28)

Atrophy	*Week 2* *n (%)*	*Week 4* *n (%)*	*Week 6* *n (%)*	*Week 8* *N (%)*	*Week 10* *n (%)*	*Week 12* *n (%)*	*Week 16* *n (%)*	*Week 20* *n (%)*	*Week 24* *n (%)*	*Week 48* *n (%)*
Complete	0 (0.0)	3 (10.7)	8 (28.5)	8 (28.5)	8 (28.5)	8 (28.5)	8 (28.5)	8 (28.5)	8 (28.5)	8 (28.5)
Excellent	18 (64.2)	19 (67.8)	16 (57.1)	17 (60.7)	17 (60.7)	17 (60.7)	17 (60.7)	17 (60.7)	17 (60.7)	17 (60.7)
Good	6 (21.4)	3 (10.7)	2 (7.1)	1 (3.5)	1 (3.5)	1 (3.5)	1 (3.5)	1 (3.5)	1 (3.5)	1 (3.5)
Poor	1 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed	3 (10.7)	3 (10.7)	2 (7.1)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)	2 (7.1)	2 (7.1)	2 (7.1)	2 (7.1)	2 (7.1)
Total	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)	28 (100)

Table IV. Interference with daily life

Interference with daily life	*Week 2* *n (%)*	*Week 4* *n (%)*	*Week 6* *n (%)*	*Week 8* *n (%)*	*Week 10* *n (%)*	*Week 12* *n (%)*	*Week 16* *n (%)*	*Week 20* *n (%)*	*Week 24* *n (%)*	*Week 48* *n (%)*
Complete	11 (36.6)	24 (80)	25 (83.3)	26 (86.6)	27 (90)	27 (90)	27 (90)	27 (90)	27 (90)	27 (90)
Excellent	11 (36.6)	3 (10)	3 (10)	2 (6.6)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)
Good	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed	4 (13.3)	3 (10)	2 (6.6)	2 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)	2 (6.6)
Total	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)

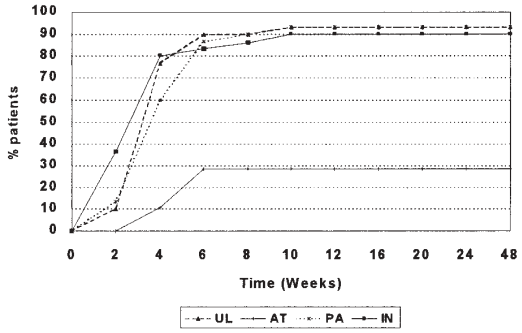

Fig 2. Evolution of the percentage of patients with complete response of signs and symptoms during the study period. *UL,* Ulcers; *AT,* atrophy, *PA,* pain; *IN,* interference with daily functions.

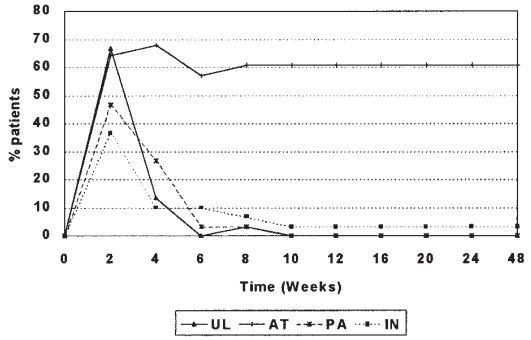

Fig 3. Evolution of the percentage of patients with an excellent response of signs and symptoms during the study period. *UL,* Ulcers; *AT,* atrophy, *PA,* pain; *IN,* interference with daily functions.

activities between week 4 and 6 of treatment. Fig 3 illustrates the evolution of the percentage of patients with an excellent response of signs and symptoms during the study period.

Because of the severity of their clinical manifestations, 2 of the patients were also started on adjuvant treatment with 40 mg oral prednisone once every morning. This treatment was discontinued in these patients after 1 week. Both patients continued with their mouthwash treatment until the end of the study period.

Five patients (16.6%) had adverse effects attributable to the use of corticosteroids. One of these patients also received systemic prednisone; therefore, these effects could only be exclusively attributed to the clobetasol treatment in 4 cases (13.3%). Three male patients diagnosed with oral lichen planus presented with moon face (Fig 4), including the patient taking prednisone. This condition, which was mild in all cases, was detected at week 4 in 2 patients and at week 6 in a third and completely resolved at week 8, 10, and 16, respectively, after a reduction in the frequency of mouthwash. Two female patients presented with growth of facial hair (Fig 5), which appeared at weeks 4 and 6 and was resolved with cosmetic depilation. All side effects were detected at a time when the control of signs/symptoms was already adequate to reduce the dosage.

DISCUSSION

We used a topical mouthwash containing 0.05% clobetasol propionate to treat patients with severe erosive lesions of the oral mucosa who would normally be selected for systemic corticosteroid therapy. Almost all of the patients (93.3%) showed a complete resolution of pain and ulceration at the end of the 48-week follow-up, and 90% had returned to complete normality in their daily activities, with another patient reporting excellent improvement. More than 85% of the patients had complete absence of pain and ulcerations and full recovery of daily activities by week 6 of treatment. With respect to the present study, this treatment with clobetasol propionate was found to be efficacious and relatively rapid to control severe erosive diseases of the oral mucosa. Lozada-Nur and Zhong Huang[5] and Lozada-Nur et al[6] treated patients with severe erosive disease by using clobetasol propionate mixed in an adhesive paste and reported a complete response in 62.5% of the series (15 patients), an excellent one in 29.7% (7 patients), and a failed response in 8.3% (2 patients). They concluded that their treatment was efficacious and safe. Our better outcomes are probably related to the improved access of the mouthwash to all lesional areas, to the higher concentration (0.05% vs 0.025%) administered, and to the control achieved over the contact time between drug and lesion (in our regimen, 15 minutes daily in the initial treatment phase). With the use of an adhesive paste form, the clinician cannot ensure that the patient will place the drug on all the lesions or that the desired contact time will be maintained. Although Orabase is an adherent vehicle, mouth movements can soon alter the initial placement of the paste. Nevertheless, we regard Orabase as a good vehicle for topical corticoids when it can be kept in contact with all the lesions for the prescribed time. It is of particular use when a dental tray can be used for the application, especially for lesions of the gingiva and palate. We previously reported our successful treatment of a large palatine ulcerous lesion with clobetasol propionate in adhesive paste form, when we used the prosthesis worn by the patient as a tray.[12]

In common with Lozada-Nur and Zhong Huang,[5] we observed a complete absence of response in 2 patients with oral lichen planus. According to their data[5] and ours, the efficacy of clobetasol propionate is good but not total and a failure to respond can be expected in a small

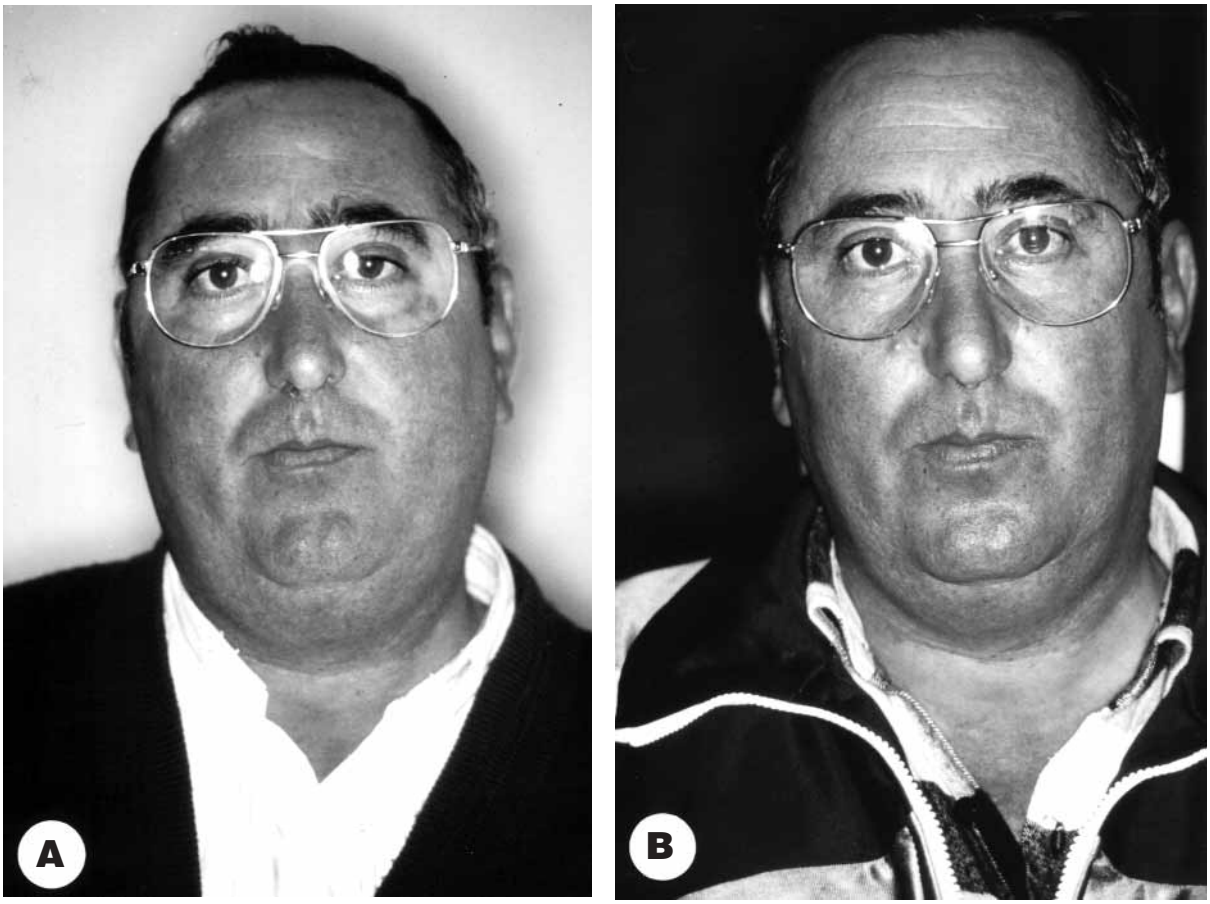

Fig 4. **A,** Male patient with mild moon face developed during clobetasol propionate mouthwash treatment. **B,** The same patient after reduction of frequency of mouthwashes. Improvement in the condition is revealed by the more pronounced groove below chin and reduction in thickness of soft tissues in lower third of face. Also note that the spectacles sit lower on the face, probably because of a reduction in the size of the cheeks.

percentage of cases. The 2 patients in our series who failed to respond had hepatitis C–associated oral lichen planus, confirming findings of previous reports[13-17] with respect to the difficulty of treating these patients, for whom systemic corticotherapy is contraindicated. Two patients had extremely severe lesions, which were quickly improved with a short course of adjuvant systemic prednisone therapy; the symptoms were then completely controlled by the mouthwash treatment until the end of the follow-up period.

Atrophy showed the worst response to our treatment, and most patients (60.7%; 17 patients) showed an excellent—rather than a complete—resolution of the atrophy. Nevertheless, the remaining atrophy was not painful and did not interfere with the daily life of the patients. In our view, this transformation of a severe erosive lesion to a painless atrophic lesion can be regarded as a successful outcome.

Five of our patients (16.6%) presented with adverse effects to corticosteroids, 4 of which (13.3%) could be exclusively attributed to the clobetasol propionate treatment. There were 3 cases of moon face and 2 of hirsutism, all of which presented between weeks 4 and 6 of treatment. Lozada-Nur and Zhong Huang[5] reported side effects in 20.8 % of their series (5 patients), of which pseudomembranous or erythematous candidiasis was the most frequent (12.5%; 3 patients). They observed no cases of moon face or other systemic adverse reactions. These authors[5,6] concluded that candidiasis could be prevented by antifungal treatment and that individuals at risk could be identified by means of pretreatment cultures and counts of colony-forming units. Lozada-Nur and Zhong Huang[5] attributed the low incidence of candidiasis in their study to the low doses of clobetasol (0.025%), the small surface area of application, and the wet environment. We included 100,000 IU/cc nystatin in our mouthwash because the greater surface area in

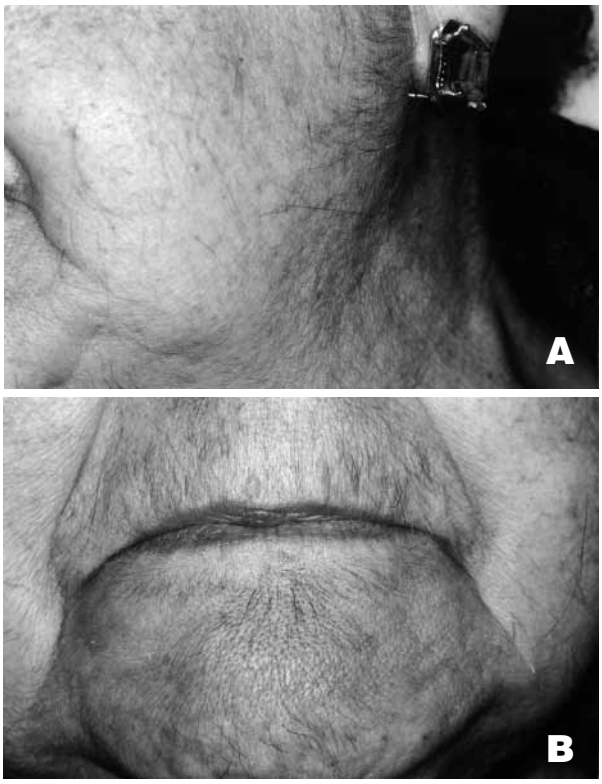

Fig 5. Female patient with development of hirsutism during the clobetasol propionate mouthwash treatment.

contact with the mouthwash and the higher concentration of clobetasol (0.05%) could have caused the appearance of candidiasis in many of our patients. The innocuous nature of nystatin, its low cost, and the fact that candidiasis symptoms (erythema and buccal pain or burning) may be confused with treatment failure indicate its use in patients receiving clobetasol mouthwash treatment. With our treatment regimen, no patient showed any signs of oral candidiasis during the 48-week period.

Lozada-Nur and Miranda[1] reported the appearance of moon face in a patient treated with a topical dexamethasone mouthwash. These effects (ie, moon face, hirsutism) suggest that clobetasol propionate and dexamethasone may be absorbed by extensive erosive areas of the oral mucosa when taken as a mouthwash. This phenomenon may be dictated by the aqueous vehicle used, by the presence of open blood vessels on the ulcerated surfaces, and by increased pressure of the drug against the ulcerated mucosa from intrabuccal movements during rinsing actions. Careful follow-up of clobetasol-treated patients is mandatory throughout the treatment, especially in the first phase, when the frequency of application is higher. Because adverse effects in our study appeared when the disease was already controlled, we did not have to address the question of the approach to side effects that appear at a time when dosage reduction cannot be justified by the clinical course of the disease.

In conclusion, the use of mouthwashes containing 0.05% clobetasol propionate plus 100,000 IU/cc nystatin in aqueous solution is a safe and efficacious alternative to systemic corticosteroid treatment in patients with severe erosive lesions of the oral mucosa, especially when there are doubts about the correct application of the drug in adhesive paste form. In our opinion, wider studies are warranted with the following aims: to compare the efficacy of clobetasol mouthwash with that of mouthwashes containing less potent corticoids (eg, fluocinonide); to determine whether the measurement of endogenous cortisol can identify patients prone to the development of adverse effects[18]; to define the correct approach for patients who develop adverse effects before their lesions are controlled; and to evaluate the evolution of clobetasol-treated patients after the complete withdrawal of treatment.

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