Response to Gonzalez-Moles, Morales-Garcia and Rodriguez-Archilla: The treatment of oral apthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations. A clinical study on 54 patients

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The authors' reply:

We are grateful to Gonzales and collaborators for their interest in and comments on our paper concerning the treatment of oral aphthous lesions and erosive oral lichen planus with three preparations of topical clobetasol propionate (1). As per the letter of Gonzales and colleagues, we will focus our response to the treatment of erosive oral lichen planus.

Firstly, we considered symptomatic responses to the adhesive-based preparation after establishing the diagnosis. We noted a reduced time of treatment to achieve symptomatic relief. Patients with severe chronic erosive lichen planus sometimes had a spontaneous clinical remission generally related to conversion of erosive lesions to plaque/reticular lesions. We treated recurrent and symptomatic lesions with the aim of reducing pain. In our study we treated chronic erosive forms of oral lichen planus with topical corticoids in order to reduce the symptoms, not to evaluate clinical conversion into painless, nonerosive lesions. Other studies obtained partial and complete absence of symptoms in oral lichen planus with topical use of clobetasol propionate (2) after the first clinical trial with this drug (3).

Secondly, topical clobetasol propionate in adhesive denture paste was shown to be more effective than other preparations without treatment-related adverse effects, e.g. moon face and hirsutism. Moreover the stability and adhesive properties of our preparation permitted contact with the mucosa for several hours with an effective response related to two daily applications.

We observed no steroid-related adverse effects. This is probably due to the relatively short time of administration of this formulation. In fact, Gonzales *et al.* report adverse effects (moon face and hirsutism) in a series of patients with severe oral lesions after 4–6 weeks of treatment with an aqueous solution of 0.05% clobetasol propionate. This may suggest enhanced absorption kinetics by way

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of the aqueous vehicle. Several reports suggested 50 g per week as a maximum suggested topical dose for the skin but an equivalent oral maximum recommended dose is unknown. Topical preparations are usually preferred because they limit the medication delivered to a specific area(s) thus reducing systemic side-effects. Mucosal/percutaneously absorbed steroids can exert systemic effects. When a potent steroid at a dose of 15/30 g/day is applied by occlusive dressing therapy, several systemic side-effect can occur, such as hypoadrenalism, peripheral eosinopenia, sodium and water retention and cushingoid signs. However, such side-effects resolve soon after the steroid is discontinued. It has been reported that hypoadrenalism can occur after simple topical application at a daily dose of less than 10 g. In fact inhibition of the pituitary-adrenal axis due to the application of moderately potent topical steroids, as well as more potent steroids (see clobetasol propionate), is well known. In adults, as a result of hypothalamo-pituitary-adrenal (HPA) axis suppression, a fall in plasma cortisol levels can generally be observed within the first days of treatment. Temporary suppression has been documented after administration of 49 g of superpotent steroids per week for two weeks in 8 out of 40 patients (4). This suppression is reversible, and patients with low morning plasma cortisol levels following 2–3 weeks of treatment return to normal within 1 week after cessation of therapy.

Such systemic effects are due to the penetration of a potent compound or of its active metabolite(s). Factors promoting systemic absorption include application over large areas, use of large amounts of material, and prolonged administration as well as the absorption kinetics of the active agent and its vehicle system.

Interesting and practical is the direct assessment of the effect on the HPA axis. In this respect, plasma cortisol determinations give more information than studies of cortisol metabolites in urine. So we monitored our patients daily, even if healing of damaged stratum corneum, which often occurs within eight days of treatment, produces a decrease in the systemic passage. However, we often used systemic corticoids in treatment of oral erosive diseases and have observed side-effects strictly connected to the time of administration (more then two weeks) rather than the dosage and the potency of the steroid (5).

Surely topical delivery would be indicated as treatment for small localized lesions or when they can be applied with the use of a tray (6), however, when this is not possible, our preparation can be used.

At this moment we are evaluating adhesive paste properties, but we can affirm our initial empirical results with final data concerning mucosal adhesion forthcoming. Our observation is that in spite of functional oral movements of chewing, swallowing and talking the paste was minimally displaced from its initial location. Our group of patients with medium and/or severe oral erosive lichen planus treated with topical 0.05% clobetasol propionate experienced a reduced level of symptoms and corresponding improvement of the clinical characteristics of the erosive lesions. Moreover we avoided chronic administration of the active drug and gained local persistence of clobetasol propionate by use of the bioadhesive system.

In our view, the use of an adhesive paste combined with clobetasol propionate provides specific control of the lesion and minimizes transmucosal absorption of the active drug.

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