Efficacy of a Mucoadhesive Patch Compared with an Oral Solution for Treatment of Aphthous Stomatitis

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Abstract

Objective: The purpose of this study was to evaluate the efficacy and tolerability of a mucoadhesive patch compared with a pain-relieving oral solution for the treatment of aphthous stomatitis.

Methods: Patients with active aphthous stomatitis were randomly treated either once a day with a mucoadhesive patch containing citrus oil and magnesium salts ($n = 26$) or three times a day with an oral solution containing benzocaine and compound benzoin tincture ($n = 22$). All patients were instructed to apply the medication until pain had resolved, and completed a questionnaire detailing multiple clinical parameters followed by an evaluation of the treatment.

Results: The mucoadhesive patch was found to be more effective than the oral solution in terms of healing time (mean $\pm$ SD: 36.0 ± 22.8 hours vs 134.7 ± 57.7 , $p < 0.001$) and pain intensity after 12 and 24 hours (3.7 ± 2.8 vs 6.3 ± 2.6 , $p = 0.003$, and 2.3 ± 2.7 vs 5.7 ± 2.5 , $p < 0.001$, respectively). Local adverse effects 1 hour after treatment were significantly ($p < 0.01$) less frequent among the mucoadhesive patch patients compared with the oral solution patients.

Conclusions: The mucoadhesive patch was found to be significantly more effective and better tolerated than the oral solution in the treatment of aphthous stomatitis.

Introduction

Aphthous stomatitis (canker sores) is an oral condition characterized by ulcers that affect mucous membranes in the mouth, which usually develop on the inner cheeks, gums, lips and occasionally the tongue. They may occur singly as aphthous stomatitis lesions or in groups in recurrent aphthous stomatitis (RAS), which is one of the most common oral ailments.^[1] The disease is typified by recurring pain-

ful ulcers of the mouth that are round or ovoid and have inflammatory halos. There are three main clinical types of RAS. Most common are minor aphthous ulcers, which account for 80% of all RAS. Some 10% of patients with RAS have major aphthous ulcers, and a further 10% have a herpetiform type of ulceration. The histopathology of the ulcerated lesions is similar to that which occurs under sites of acute inflammation of the skin.^[2]

The aetiology of RAS is unknown and thought to be multifactorial with various precipitating factors.^[3] It has been noted that oral trauma may contribute to the development of RAS in certain susceptible individuals.^[4] The trauma required to stimulate aphthous ulcer production could include biting the mucosa, tooth brushing, dental injection or certain sharp foods.^[5] Attempts have been made to implicate viral or bacterial infections as being involved in RAS,^[6] but there is no evidence based upon cultures, antibody titres, cytology or electron microscopy to support this theory.^[7] Genetic factors seem to play a major role in patients with RAS as its presence is increased in patients with a family history of the condition;^[7] approximately 50% of first-degree relatives of patients with RAS also experience RAS. Patients with a family history of the condition tend to develop RAS at an earlier age, and more severely than other patients.^[4] Vitamin deficiencies and stress^[5] have also been suggested as contributing to RAS development, usually a low serum iron or ferritin level, or a deficiency of folate or vitamin B. Pedersen^[8] found no association between psychological stress and recurrences of RAS, and concluded that more standardized investigation is needed for proving any such association. Physical irritation caused by certain irritants is associated with aphthous ulcers.^[9] Therefore, it is recommended that people experiencing RAS avoid acidic foods and certain preservatives that may irritate the mucosal tissue, as well as products containing sodium lauryl-sulfate,^[10] a common surfactant in toothpaste.

The pathogenesis is probably a cell-mediated immune response mechanism, involving generation of T cells and tumour necrosis factor- α (TNF α) by other leukocytes (macrophages and mast cells).^[11]

The aphthous ulcer is most painful during the first 3–4 days. The discomfort gradually diminishes and the sore heals in 10–14 days, usually without scarring.^[2,12] Before it becomes visible, the aphthous ulcer may produce a tingling or burning sensation. After 6–24 hours, the ulcer appears as a small round depression 3–9 mm in diameter, surrounded by a red area of inflammation.

Corticosteroids and other anti-inflammatory agents^[13] are used to treat the inflammation associated with aphthous ulcers. These medications, which are supplied in a gel, cream or paste formulation, are applied three to four times a day. Adhesive dosage forms for buccal administration of drugs have been reported for many years.^[4,14] Suitable adhesive carriers include linear and partially cross-linked polymers.^[15] An ideal buccal device should be elastic, soft and able to withstand breakage caused by stress from mouth activities. It must also possess bioadhesive properties to ensure that it is retained in the mouth for the required period of time.

The mucoadhesive patch used in this study has been found to adhere well to the mucosal tissue and to gradually erode for 8 hours while releasing magnesium salts and citrus oil in a zero-order pattern.^[16] The natural agents citrus oil and magnesium salt, which were incorporated into the adhesive patches, were examined for antibacterial and anti-inflammatory properties by using oral bacteria and an oral inflammation model.^[17,18] Citrus oil was found to have an antibacterial effect with a minimum inhibitory concentration (MIC) of 1 mg/mL, whereas the salt did not exhibit any antibacterial activity. However, the combination dramatically inhibited bacterial growth, suggesting that there was synergism between these two natural agents. The combination of magnesium salt and citrus oil resulted in lower levels of TNF α and leukocyte migration while maintaining the levels of the anti-inflammatory interleukin-10.

The oral solution used in this study is a 'gel-like' pharmaceutical product used primarily to treat aphthous ulcers. It is applied directly on the ulcer and works by numbing the local area (with benzocaine) to prevent discomfort and by forming a protective mucous barrier with a compound tincture that protects the ulcer from further irritation, allowing it to heal faster.^[19]

This study aimed to evaluate the efficacy and tolerability of once-a-day treatment with a mucoadhesive patch compared with three-times-a-day application of an oral solution of 20% benzo-

Table 1. Clinical data of the study population

Variable	Mucoadhesive patch (n = 26)	Oral solution (n = 22)	p-Value
Age (y) [mean $\pm$ SD]	40.5 $\pm$ 13.6	47.8 $\pm$ 14.7	NS
Gender (no. of patients)			
male	8	8	NS
female	18	14	
No. of RAS episodes per year (mean $\pm$ SD)	5.4 $\pm$ 3.4	7.1 $\pm$ 5.3	NS
Average aphthae area (mm ²) [mean $\pm$ SD] ^a	22.7 $\pm$ 8.6	21.2 $\pm$ 9.9	NS
Average time (days) for aphthae healing before the study (mean $\pm$ SD)	10.7 $\pm$ 3.0	11.2 $\pm$ 5.0	NS

a Measured by the clinician.

NS = non significant (statistical significance was defined as $p < 0.05$); RAS = recurrent aphthous stomatitis.

caine and compound benzoin tincture in patients with aphthous stomatitis.

Materials and Methods

Study Medications

1. Canker CoverTM patch (Quantum, Inc., Eugene, OR, USA)¹ is in a disc shape of 10 $\times$ 2 mm. The patches examined in this assay were described previously by Mizrahi et al.^[16] They were prepared by compression moulding of mixed powders of cross-linked polyacrylic acid and hydroxypropyl cellulose, absorbed with citrus oil, menthol, xylitol and carnallite (potassium magnesium chloride). One mucoadhesive patch lasts for 8–12 hours.

2. Kank-A[®] oral solution (Blistex[®] Inc., Oak Brook, IL, USA), which forms a protective coating over the wound. The active ingredients of the oral solution are benzocaine (20.0% w/v) and compound benzoin tincture. Other ingredients include benzyl alcohol, cetylpyridinium chloride, dimethyl isosorbide, ethylcellulose, flavour, octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer, oleth-10, PEG-6, propylene glycol, *Ricinus communis* (castor oil) seed oil, saccharin, alcohol (29.6% v/v) and tannic acid.

Subjects

A total of 48 patients with recurrent aphthous stomatitis were enrolled in the study. Further clinical data of the population are given in table I.

The protocol was reviewed and approved by the local ethics committee and oral consent to participate was obtained after providing written information about the trial.

Inclusion criteria were age ≥ 18 years, general good health and RAS. Excluded from the study were pregnant or lactating women, patients who used any investigational drug within 30 days prior to study entry, and patients receiving one or more of the following agents: systemic corticosteroids, topical or systemic retinoids, antineoplastic drugs and any systemic antidepressants or antipsychotic drugs. Also excluded from the study were individuals who had been treated with topical corticosteroid medications applied to the designated treatment area within 4 weeks prior to study entry, and patients with known hypersensitivity to one or more of the ingredients of the mucoadhesive patch or the oral solution.

Study Design

All participants were asked to complete a questionnaire regarding the average time that aphthae typically took to heal prior to the study. Patients were randomly divided according to sealed envelopes containing computer-generated random num-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

bers into two groups: group 1 was treated with one mucoadhesive patch applied directly on the aphthae once a day and group 2 was treated with the oral solution three times each day. The treatment was stopped by the patients in both groups when no pain remained at the aphthae site (defined as resolution for the purpose of this study).

Patients were instructed to avoid any other topical treatment, including cosmetic peeling, on the affected areas during the study period. Every patient was evaluated by the same physician before the treatment and 10 days afterwards. During the treatment phase the patient was asked to complete a questionnaire regarding the efficacy and adverse effects of the treatment, until either the aphthae were healed or 10 days had passed. Pain intensity was estimated on a 10-point visual analogue scale where no pain was defined as 0 and intolerable pain as 10. The safety, tolerability and adverse effects recorded included: redness, itching, pain, swelling, erythema, pruritus, paraesthesia and hyperaesthesia.

Statistical Analysis

Statistical comparisons of the findings were evaluated by Student's *t*-test. Data analysis was performed using a statistical software package (Instat,

GraphPad Software, San Diego, CA, USA). Statistical significance was defined as $p < 0.05$.

Results

Efficacy

Seven patients withdrew from the study because of personal reasons, leaving 41 patients for data analysis (18 patients were treated with the oral solution and 23 patients with the mucoadhesive patch). On average, the patients had 6.2 episodes of RAS in the year before the study, which lasted 10.9 days (range 3–30 days) without treatment, and had 1–5 aphthae (median 1 aphtha) at the time they were recruited into the study. The overall results of this study are summarized in table II.

For the purpose of this study, resolution was defined as the time the patients stopped feeling any pain from the aphthae site. Aphthous stomatitis lesions resolved (figure 1) after 1–96 hours (mean $\pm$ SD: 36.0 ± 22.8 hours, median 24 hours) in the patients treated with the mucoadhesive patch, while in the patients treated with the oral solution the lesions resolved after 72–240 hours (134.7 ± 57.7 hours, median 120 hours) [$p < 0.05$].

The patients' scores regarding pain intensity 1, 12 and 24 hours after treatment application are sum-

Table II. Pain intensity, adverse reactions and tolerability among patients receiving mucoadhesive patches and oral solution

Variable	Mucoadhesive patch (n = 23)	Oral solution (n = 18)	p-Value
Pain intensity after treatment (VAS) [mean $\pm$ SD]			
1 hour	6.2 $\pm$ 2.7	6.7 $\pm$ 2.6	<0.05
12 hours	3.7 $\pm$ 2.8	6.3 $\pm$ 2.6	<0.05
24 hours	2.3 $\pm$ 2.7	5.7 $\pm$ 2.5	<0.05
Time to aphthae resolution (h) [mean $\pm$ SD] ^a	36.0 $\pm$ 22.8	134.7 $\pm$ 57.7	<0.05
Ability to speak 1 h from beginning of treatment (% of patients)	52.2	57.9	<0.05
No difficulty in swallowing saliva 1 h from beginning of treatment (% of patients)	95.7	72.2	<0.05
Occurrence of adverse effects 1 h from beginning of treatment (% of patients)	43.5	100	<0.01
Patients who would use the treatment again (%)	87.0	55.6	<0.05
Patients who considered treatment easy to use (%)	73.9	85.0	NS

^a Resolution was defined as the time the patients stopped feeling any pain from the aphthae site.

NS = non significant (statistical significance was defined as $p < 0.05$); **VAS** = visual analogue scale where 0 equals no pain and 10 equals intolerable pain.

Fig. 1. Distribution of aphthae resolution time after treatment with (a) a mucoadhesive patch once a day and (b) an oral solution three times a day. Resolution was defined as the time the patients stopped feeling any pain from the aphthae.

marized in table II. There was no significant difference in pain intensity between the two treatments 1 hour after application (mean pain intensity 6.2 for the mucoadhesive patch and 6.7 for the oral solution). However, 12 and 24 hours after the first application the pain intensity in the mucoadhesive patch group was significantly lower than that in the oral solution group: 3.7 ± 2.8 vs 6.3 ± 2.6 ($p < 0.05$), and 2.3 ± 2.7 vs 5.7 ± 2.5 ($p < 0.05$), respectively.

Tolerability

With regard to adverse effects, all patients using the oral solution reported having one or more adverse effects (numbing, tingling, local pain or bad taste) 1 hour after application of the medication and throughout the healing process. Adverse effects (with the exception of bad taste, which was reported by four oral solution patients but not reported at all among mucoadhesive patch patients) were reported by only 43.5% of the patients using the mucoadhesive patch, and only at 1 hour after treatment application. After 1 hour, mucoadhesive patch users reported no adverse effects ($p < 0.01$ for the incidence of any adverse effect 1 hour post-treatment application).

There were no significant differences between the two treatments regarding overall ease of use of the treatment or the patient's ability to speak 1 hour after application of the medication. However, 22/23 of the mucoadhesive patch patients had no difficulty swallowing saliva 1 hour after application, com-

pared with 13/18 of the oral solution group ($p < 0.05$).

No patient in either group reported worsening of symptoms after applying the medication. However, 20/23 of the mucoadhesive patch patients reported their desire to use the treatment again, compared with 10/18 of the oral solution users.

Discussion

In this open-label study we evaluated the efficacy and tolerability of two topical medications for the treatment of aphthous stomatitis – a mucoadhesive patch and an oral solution. The mucoadhesive patch was found to be highly effective and well tolerated in the treatment of aphthous stomatitis. Lesions treated with this medication had a median resolution time of 24 hours versus 120 hours for the oral solution. Furthermore, more patients using the oral solution reported local adverse effects, had higher pain intensity 12 hours and 24 hours after treatment, and had more difficulty swallowing saliva 1 hour after treatment.

In a previous study^[16] conducted in 248 patients with aphthous ulcers, the efficacy of a similar patch releasing citrus oil and magnesium salt was compared with an mucoadhesive patch without releasable active ingredients (composed of mixed powders of cross-linked polyacrylic acid and hydroxypropylcellulose). The average time for pain disappearance (reported by the patients) was reduced from 134 hours for untreated patients to 48 hours for the group treated with plain patches, and to 5 hours for patients treated with the active patches. The time to healing (diagnosed by the dentist) was approximately 1.5, 6 and 10 days for patients treated with the medicated patch, the plain patch and untreated patients, respectively ($p < 0.05$). It was concluded that the effect gained by blocking the aphthous ulcer from the mouth environment was equal to the pharmacological effect of the active treatment in terms of pain reduction.

The effect of sealing and protecting the aphthous ulcer from irritating oral fluids and mouth activity is crucial for pain reduction and was demonstrated in 1985 by Nagai and Machida.^[20] Colgate Oral Phar-

maceuticals recently introduced a patient-applied topical medication, 2-octyl cyanoacrylate, which, on contact with oral soft tissue, polymerizes to form a protective barrier that lasts up to 6 hours.^[21] The purpose of this medication is to create a long-lasting barrier that will reduce or eliminate pain associated with oral ulcerative disease. Results from a recently concluded multicentre trial demonstrated that this barrier significantly reduced the pain associated with aphthous ulceration.^[21]

Because of the importance of mucoadhesive properties (also demonstrated in this study), much effort has been invested to improve the adhesiveness of polymers to the oral mucosa in recent years.^[22] Recently, thiolated chitosans, which are derived from polyglusam (chitosan), have demonstrated promising properties for a mucoadhesive substance. They form disulphide bonds with cysteine-rich domains of mucus glycoproteins.^[23] These products develop additional mucosal permeation-enhancing properties by a mechanism of glutathione (GSH) regeneration. Finally, they have potential antiprotease activity because of their ability to bind divalent cations such as Zn^{2+} or Mg^{2+} , which are cofactors of many proteases.^[24]

Reported studies on other materials topically applied to aphthous ulcers have demonstrated rather unremarkable results in accelerating healing.^[13] For example, in a study by Plemons et al.,^[5] mean healing times for commercially available Orabase® (Colgate-Palmolive, New York, USA) have been reported as 7.8 days; there were no significant differences in ulcer sizes throughout their study between the Orabase® group and the groups treated with acemannan hydrogel.^[5] The kenalog in Orabase® has been reported as being as effective as Orabase® alone.^[25] Although triamcinolone in Orabase® has been reported to result in some subjective improvement, Browne et al.^[26] reported that they were unable to demonstrate any significant benefit in healing, and stated that they “do not suggest that triamcinolone acetonide be prescribed for all subjects with aphthous ulcers.” These authors also concluded that “Orabase® alone is of no value at all in the treatment of recurrent aphthous ulcers.”

Dale et al.^[27] reported that ORA-5® decreased both pain and ulcer size, but mean ulcer duration in the treated group was >7 days, and the pain in the treated group actually increased between days 5 and 8.

While the benefit of using different pharmacological substances is controversial, the combination of mechanical protection of the aphthae surface together with the use of pharmacological ingredients is well established. Another major benefit of the mucoadhesive patch stems from its long-lasting action of about 8 hours. The oral solution has a very short residence time in contact with the aphthous ulcer since the solution easily washes away in the mouth.^[28] Therefore, the patch can be applied only once daily (compared with three times a day for the oral solution), thus increasing patient compliance. The fact that it does not have a bad taste and has overall fewer local adverse effects further increases patients' satisfaction with the product.

Conclusions

The mucoadhesive patch was significantly more effective and better tolerated than the oral solution in the management of aphthous stomatitis. These studies further support the notion that sealing and protecting the aphthae surface from mouth fluids and activities plays a crucial role in the treatment and pain relief of aphthous stomatitis.

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