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The efficacy of amelxanox OraDisc™ on the prevention of recurrent minor aphthous ulceration

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BACKGROUND: The study was designed to determine the efficacy of OraDisc™ (active component 2 mg amlexanox) on the prevention of aphthous ulcers treated at the prodromal stage.
METHODS: Thermographic imaging was used to confirm the presence of a prodromal ulcer. Fifty-two patients were randomized to receive OraDisc™ ($N = 26$) or vehicle patches ($N = 26$). Patches were applied four times a day for 72 h over the prodromal area. The percentage of subjects who developed an ulcer at 72 h was compared between groups using the Fisher's exact test.
RESULTS: About 50% of subjects in the OraDisc™ group developed an ulcer by day 4 compared with 69% in the vehicle group. Erythema score, ulcer size, pain scores and thermographically active area and temperature all showed trends towards healing in the OraDisc™ group.
CONCLUSION: The OraDisc™ prevents ulcers from developing when compared with the vehicle patch.
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Introduction

Recurrent aphthous ulceration affects between 15 and 20% of the population (1–5). Of the three clinical subtypes (minor, major and herpetiform), minor aphthous ulcers are the most common form, accounting for up to 87% of aphthous ulcers (6, 7). In the prodromal stage of minor aphthae, 24–48 h preceding overt ulcer development, sufferers may experience a pricking or burning sensation of the mucosa where the ulcer will develop and clinically the affected area may appear normal or slightly erythematous. The ulcers then develop as small, round or ovoid lesions which are usually < 10 mm in diameter on the non-keratinized, mucosa of the lips, cheeks, floor of mouth or tongue. The ulcers are shallow, covered within hours by a grey-white pseudomembrane of fibrin and surrounded by an erythematous margin. Usually less than five ulcers occur at any one time. Although individual ulcers heal in 1–2 weeks, occasionally new ulcers can develop as existing ones are healing (3, 5, 8–11).

A genetic predisposition, trauma, infective agents, allergic elements, hormonal factors, haematinic deficiency states, immunological abnormalities and psychological factors have all been implicated in the pathogenesis of minor aphthae (12). The most common treatment involves the use of topical agents to provide symptomatic relief and these include antibiotics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) to immunosuppressants (9, 13–18). Of the topical agents, the anti-inflammatory and antiallergic drug amlexanox (19) has been the most extensively studied in clinical trials (18).

The efficacy of 5% amlexanox paste in promoting ulcer healing and resolving pain has previously been demonstrated (20–22) and the drug is currently available as a 5% amlexanox paste in the United States for the treatment of recurrent aphthous ulceration (Aphthasol, Block). In the largest multicentre study undertaken, encompassing four vehicle-controlled, randomized, double-blind trials comprising 1335 patients, it was shown that after 6 days of treatment with 5% amlexanox paste there was complete resolution of ulcers in 74% of patients vs. 54% of those using the vehicle. This preparation was also found to significantly reduce the pain experienced by sufferers as complete resolution of pain was reported by 83% of patients using 5% amlexanox paste compared with 73% of those using the vehicle (22). Further studies this time in the United Kingdom have shown that if 5% amlexanox paste is applied at the prodromal stage of ulceration, then only 35% of subjects developed an ulcer by day 3 compared with 97% of subjects treated at the onset of ulceration. Furthermore, compared with no treatment, treatment at the prodromal stage reduced the maximum ulcer size by 84%, extent of ulceration by 88%, maximum pain score

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by 69% and extent of pain by 85% (23). These results indicate that although 5% amlexanox is an effective treatment for minor aphthae, greater therapeutic benefits can be obtained if it is used in the prodromal stage as opposed to when an ulcer has developed.

In addition to 5% amlexanox paste, a new formulation of amlexanox, OraDisc^{TM}, has recently been developed. OraDisc^{TM} is a bioerodible mucoadhesive patch which is designed to provide a more targeted release of the amlexanox to the affected mucosal site. The OraDisc^{TM} patches are made in the form of a thin, flexible film composed of a backing layer and an affixed mucoadhesive layer that contains the amlexanox. Each patch is approximately 1.5 cm in diameter and contains approximately 2 mg of amlexanox. The reason 2 mg of amlexanox was incorporated into the patches was it was estimated that a typical 'dab' of 5% amlexanox paste contained 2 mg of amlexanox. The active layer of the patches is applied to the oral mucosa to cover the affected site with complete dissolution of the patch occurring in <60 min. The final remaining pieces of the patch are washed away by normal saliva flow and swallowed.

The aim of the present study was firstly to determine the efficacy of OraDisc^{TM} in preventing minor aphthae development in subjects presenting at the prodromal stage of ulceration. In addition to the patient's own reports of experiencing prodromal symptoms of ulceration, infrared thermographic imaging was used to objectively confirm the prodromal event and site. This method has previously been reported by our research group to identify the sites of evolving minor aphthae (23) and prodromal herpes labialis lesions (24) and to assess the response of herpes labialis to acyclovir therapy (25). Secondly, the safety of OraDisc^{TM} was evaluated by determining the frequency of treatment-emergent adverse events.

Material and methods

Study design

The study was a single-centre, double-blind, randomized, vehicle-controlled, parallel group study with patients being treated at the prodromal stage of ulceration with either OraDisc^{TM} or vehicle patches. Ethical approval for the study was obtained from the Research Committee, Queen's University of Belfast and all patients gave their informed consent in accordance with the Declaration of Helsinki.

After screening to confirm that subjects suffered from recurrent aphthous ulceration, subjects returned to the study centre when they suspected that they were developing an ulcer, i.e. at the prodromal stage. The presence of a prodromal phase was clinically confirmed by infrared thermographic imaging using the Agema 900 Thermovision System (Agema, Danderyd, Sweden) (24). All patients were only randomized to receive OraDisc^{TM} or vehicle patches if a thermographically active area could be identified and a surface temperature difference of more than 0.5°C could be demonstrated between the reported prodromal site and the contralateral asymptomatic site. Thermographic measurements were repeated on day 4 (approximately 72 h after first application of the mucoadhesive patches). On days 1 and 4 the extent of erythema at the prodromal site was recorded by the investigator using a scale of 0–3, where 0 represented 'no erythema' and 3 represented 'clinically obvious erythema'. On day 4 the investigator also recorded the presence or absence of an ulcer at the prodromal site. If an ulcer had developed, the area of the ulcer was determined from measurement of the largest diameter of the ulcer and a second diameter measurement was taken perpendicularly to the first. The measurements were made using a calibrated dental probe. During the study, subjects were asked to record in diaries the severity of oral pain using a 100 mm visual analogue scale twice daily (morning and evening) in addition to at the times of application of the mucoadhesive patches.

Patch material

The OraDisc^{TM} patches contained 2 mg of amlexanox [2-amino-7-isopropyl-5-oxo-5H-(1)benzopyrano-(2,3-b)-pyridine-3-carboxylic acid]. These were supplied to the subjects in groups of four in a heat-sealed foil pouch with each patch being packaged in a separate compartment. The vehicle patches were almost identical to the OraDisc^{TM} patches except that the vehicle patches were slightly lighter in colour than the active patches. However, the subjects did not know which colour was associated with which product and in order to ensure that the investigator remained blinded, the person dispensing the drug and instructing subjects how to apply the patches was different from those individuals performing the efficacy measurements. Patients were instructed to apply slight pressure on the entire surface of the patch at the time of application either using their finger or tongue, to refrain from bringing their teeth into contact with the patch, to avoid chewing or excessive jaw movements and to avoid eating or drinking for at least 1 h following application of the patches. Patches were to be applied four times a day, after each meal and at night before sleep.

Subjects

Subjects for the study were recruited from patients referred to the Oral Medicine Clinic, Queen's University Belfast. For inclusion in the study subjects had to be over 18 years of age and capable of giving informed written consent. Patients had to have a history of recurrent aphthous ulceration and present with a prodromal ulcer, which could be thermographically confirmed in the anterior part of the mouth. Subjects were excluded from the study if they were experiencing oral pain other than from the prodromal ulcer or had any other type of mucosal disease, smoked or chewed tobacco, had abnormal haematological or biochemical values, were pregnant, planning a pregnancy or breast feeding or were wearing a denture or orthodontic appliance which would come in contact with the ulcer. Immune dysfunction related ulcers or systemic diseases that would interfere with the healing of a mucosal wound, known sensitivities to any of the study preparation ingredients, participation in a clinical trial within

30 days of enrolment in the study or an inability to communicate with the investigator also warranted exclusion. Patients who had not undergone a washout period of 3 months for steroid inhaler usage and 24 h for NSAIDs, had received systemic corticosteriods, oral retinoids or other immunomodulatory agents within 1 month prior to the study or who had applied a preparation or medication to the prodromal ulcer area were also excluded.

Criteria for evaluation

Efficacy

The primary efficacy parameter was the number of patients who developed an ulcer at 72 h. The secondary efficacy parameters analysed were ulcer diameter and degree of erythema – defined as the difference in thermographic temperature between the treated and contralateral asymptomatic area and the thermographically active area measured at 72 h and pain scores at 72 h and at end point. For end point analysis (applicable to pain assessment only), the end point value was defined as the last (non-missing) post-baseline observation carried forward for each subject.

Safety

A medical history, including all concomitant medications, and ulcer history was obtained at the screening visit. An oral examination was undertaken at the screening visit as well as measurement of vital signs. In addition, a venous blood sample was obtained for haematological parameters (full blood picture including haemoglobin, vitamin B_{12}, red cell folate and ferritin) and biochemical parameters [creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, total protein, uric acid, phosphorus, calcium, Na^+, K^+, Cl^-]. Pregnancy tests were carried out where appropriate prior to commencement of treatment.

Questions relating to adverse events were included in the subject diaries. The specific questions asked were 'Did you experience any change in your normal health today'? and 'Did you experience any change after applying the patch'? Subjects were also questioned about adverse events at their final visit by study personnel.

Statistical methods

Continuous variables were summarized using descriptive statistics and categorical variables by presenting the frequency and percentage of subjects in each category. The primary end point of the number of subjects who developed an ulcer at 72 h (day 4) was compared between the two groups using Fisher's exact test. An analysis of covariance using baseline value as covariates was performed on the secondary end points: the ulcer size, erythema score, difference in thermographic temperature, thermographic active area at 72 h and pain score at 72 h and at end point.

All statistical analyses were performed using two-sided tests at the 0.05 level of significance.

Results

Demographics and other baseline characteristics

In total 52 subjects were confirmed, using infrared thermographic imaging, as having an ulcer in the prodromal stage and were randomized to receive either OraDisc™ or vehicle patches. Of the 52 patients, 26 subjects (10 male,16 female: mean age 39.5 years, SD 10.4) received OraDisc™ patches and 26 received the vehicle patches (seven male, 19 females: mean age 32.0 years, SD 10.5). All patients were Caucasians except for one Asian subject and one subject from North Africa. Subjects in both groups were well matched in terms of the number of years for which they had suffered aphthous ulcers, the number of episodes per year, the number of ulcers per episode and the average duration of ulcers.

On entry to the trial no subject had significant medical or surgical histories or were taking any concomitant medication that may have interfered with the conduct or results of the study and no additional medications were commenced by any subjects during the course of the study. No clinically significant laboratory results were obtained (haematological or biochemical profiling) and vital signs were all within normal ranges. All oral examinations were normal except that one patient had dental caries but it was accepted that this would not interfere with the conduct or results of the study.

Compliance

No patient withdrew from the study prior to completing 4 days of treatment. All subjects used the study medication as directed and no patch applications were missed. Overall, subject compliance with data reporting were very good with 85% of patients not have any missing data: two subjects did not record the time of the pain score at one time point each and three patients did not record a pain score on day 4. However, 10 patients returned 1 day late (day 5) to the study centre for their final evaluations. Therefore, separate analyses of efficacy were performed considering all patients (intent-to-treat population) and only those patients who were fully evaluable for each specific efficacy variable (evaluable subjects).

Efficacy

Of the 52 subjects that completed the study, 31 patients had developed an ulcer by day 4. Of these subjects more had received the vehicle patches than OraDisc™: 69% vs. 50% in the intent-to-treat population and 70% vs. 55% in the evaluable population (Table 1). However, the results did not reach statistical significance.

There was no statistical significance between the ulcer size in those patients receiving OraDisc™ and the vehicle patches at day 4. Similarly there was no difference in erythema scores between the two groups at day 4, either in the intent-to-treat or the evaluable population. However, on day 4 there was a statistically significant difference in the mean active thermographic area in the evaluable population and in the difference in thermographic temperatures between the treated area

Table 1 Number (%) of patients who developed an ulcer on day 4

OraDisc™	*Vehicle patches*	*P-value*
Intent-to-treat population		
13/26 (50)	18/26 (69)	0.26
Evaluable population		
12/22 (55)	14/20 (70)	0.36

Table 2 Mean ulcer size, erythema scores, thermographically active areas and differences in thermographic temperatures in subjects treated with amlexanox OraDisc™ mucoadhesive patches and vehicle mucoadhesive patches

	Intent-to-treat population		*Evaluable population*	
Day	*OraDisc™ (N = 26)*	*Vehicle patch (N = 26)*	*OraDisc™ (N = 22)*	*Vehicle patch (N = 20)*
Mean ulcer area (mm^2; SD)				
1	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
4	1.64 (2.94)	1.93 (2.39)	1.53 (2.70)	1.70
Mean erythema score (SD)				
1	2.23 (0.76)	2.58 (0.64)	2.23 (0.75)	2.60 (0.60)
4	0.92 (0.93)	0.92 (1.09)	0.91 (0.92)	0.90 (1.12)
Mean thermographically active area (mm^2; SD)				
1	9.18 (9.8)	11.75 (10.59)	8.14 (8.69)	9.86 (10.20)
4	2.15 (4.43)	5.33 (7.07)	1.12 (2.27)	5.33 (7.83)
Mean temperature difference (°C; SD)				
1	1.10 (0.59)	1.28 (0.58)	1.06 (0.62)	1.29 (0.57)
4	0.06 (0.64)	0.67 (0.76)	0.03 (0.67)	0.70 (0.80)

Table 3 Mean pain scores over time in the intent-to-treat subject population

	OraDisc™		*Vehicle patch*	
Day	*N*	*Mean (SD)*	*N*	*Mean (SD)*
1 AM	26	18.9 (20.0)	26	14.0 (16.6)
1 PM	26	20.5 (18.1)	26	14.5 (16.1)
2 AM	26	19.2 (18.4)	26	13.8 (15.6)
2 PM	26	15.3 (16.1)	26	11.9 (15.0)
3 AM	26	10.4 (10.8)	26	10.6 (12.9)
3 PM	26	6.8 (8.7)	26	8.7 (11.0)
4 AM	23	5.5 (7.3)	26	4.9 (8.1)
4 PM	14	3.0 (5.2)	13	1.7 (4.1)
End point	26	3.5 (5.3)	26	4.6 (8.0)

and a corresponding contralateral area of mucosa in both the intent-to-treat population and the evaluable population (Table 2).

The maximum pain elicited at the treatment site in subjects was similar in the subjects who received OraDisc™ patches (maximum score = 72) and in those who received the vehicle patches (maximum score = 71). Although those who received the active patches experienced a noticeably greater decrease in pain score over the course of the trial, the difference between the groups did not reach statistical significance, either in the intent-to-treat or evaluable population (Table 3).

Safety

A total of 43 adverse events were reported at the application site of the patches in 32 patients. However, more adverse events were reported by more subjects who received the vehicle patches (21 patients, 30 adverse events) than OraDisc™ patches (11 patients, 10 adverse events). All events were self-limiting and rated as mild by the patients with the exception of one report of moderate pain after application of an OraDisc™ patch by one subject (Table 4).

Table 4 Summary of application site and systemic adverse events

	OraDisc™	*Vehicle patch*
Application site adverse reactions		
Paresthesia	5	7
Pain	4	5
Burning	3	2
Reaction NOS+	1	13
Anaesthesia	0	2
Dryness	0	1
Systemic adverse reactions		
Nervous system disorders	7	7
Headache NOS[a]	5	3
Taste disturbance[a]	2	4
Gastrointestinal disorders	5	6
Nausea[a]	4	1
Sore throat[a]	1	2
Vomiting	1	0
Dry mouth[a]	0	1
Dry throat[a]	0	1
Dyspepsia	0	1
General disorders	3	1
Fatigue	2	0
Influenza-like illness	1	0
Lethargy	0	1
Skin and subcutaneous tissue disorders	1	0
Dermatitis NOS[a]	1	0

NOS, not otherwise specified.
Reaction NOS+ for application site adverse events were sensations described by patients as 'cold or cooling' ($n = 8$), 'warm' ($n = 2$), 'soothing', 'white lump', 'texture change' and 'anaesthetic taste' ($n = 1$ each).
[a]Systemic adverse events potentially related to OraDisc™ and vehicle patches.

A total of 31 adverse events, other than at the application sites, were reported by 25 patients during the course of the trial. Systemic adverse events which were deemed to be potentially related to OraDisc™ were headache (five subjects), nausea (four subjects), taste disturbance (two subjects), sore throat (one subject). One subject developed a facial rash on day 3 on both her cheeks that may have represented a potential sensitization reaction. However, the patient declined to re-attend the study centre for further investigation by patch testing. A number of adverse events, which were deemed to be potentially related to the vehicle patches, were also reported. These included headache (three subjects), taste disturbance (four subjects), nausea, sore throat, dry mouth and dry throat (one subject each; Table 4).

No serious adverse events was reported and no subject withdrew from the study due to adverse events.

Discussion

The beneficial effects of 5% amlexanox paste in the treatment of minor aphthae, when frank ulceration is

present, has previously been reported (20–22). Furthermore, studies carried out by ourselves show that treatment with 5% amlexanox paste at the onset of prodromal symptoms significantly reduces the proportion of subjects developing ulcers and significantly reduces symptoms compared with no treatment in those patients in which ulcers do occur (23). However, this is the first study to determine if the new formulation of amlexanox, OraDisc™ mucoadhesive patches, would be effective in preventing the development of an ulcer if applied at the prodromal stage of ulceration.

The results of this study show that 50% of subjects in the OraDisc™ developed an ulcer by day 4 compared with 69% in the vehicle patch group. Although the difference between the two groups was not statistically significant, the results do suggest that OraDisc™ offers some prevention of ulcer development when applied at the prodromal stage. Erythema scores, ulcer size and pain scores showed trends towards healing in the OraDisc™ group but again no statistically significant difference was noted. However, there was a statistically significant difference in mean active thermographic area (evaluable population) and in the difference in thermographic temperature between the treated area and a contralateral control area of mucosa (evaluable population and intent-to-treat population) on day 4 in the OraDisc™. This indicates that OraDisc™ significantly reduces inflammation in the affected area and would further support observations that, compared with the vehicle patches, OraDisc™ promotes healing of ulcers that do develop.

In the present study, only 69% of patients treated with the vehicle patches presented with an ulcer on day 3. Although this is less than expected, high rates of healing and resolution of pain, independent of amlexanox have been reported in previous trials of the efficacy of 5% amlexanox paste. These results were attributed to the self-limiting nature of aphthous ulcers combined with the protective effects of the vehicle paste in covering the wound (22). It is reasonable to suggests that similar factors apply to the present study in relation to the vehicle patch as it would be expected that almost 100% of patients would develop ulcers if they experienced prodromal symptoms and exhibited a thermographically active area. This would help explain the lack of statistically significant differences between the two treatment groups.

In terms of safety, OraDisc™ patches were well tolerated by the subjects. In fact the incidence of adverse events reported at the site of application were less for OraDisc™ than for the vehicle patches. With OraDisc™ 42.3% of patients reported adverse events compared with 80.8% of those receiving the vehicle patches. The difference between the two groups was attributable to the large number of subjects who reported experiencing a 'cooling effect' (eight subjects in the vehicle group). The reason for this finding is unclear, but it does not appear to have any clinical relevance. In all other cases, both for the OraBase™ and the vehicle patches, the adverse events reported were of a self-limiting nature and did not cause any subject to withdraw from the study. Again with the systemic adverse events, a similar number of subjects in the vehicle group had systemic adverse events, which were deemed to be potentially related to the study drug. As with the application site reactions, all reactions were mild and self-limiting. However, it is of note that one subject who was treated with OraDisc™ developed a facial rash which may have represented a sensitization reaction. Nevertheless, this should be considered of minimal concern as in a previous study addressing the safety of amlexanox it was found that dermal rashes were observed in only two of 1509 subjects exposed to study materials and rigorous dermal sensitization procedures failed to induce contact dermatitis (26).

Although the results of this study suggest that OraDisc™ is beneficial in the prevention of minor aphthae, further studies to directly compare its efficacy with that of 5% amlexanox paste in the treatment of frank ulceration, and in the prevention of ulcer development if treatment is commenced at the prodromal stage, is required in order that the true therapeutic effects of OraDisc™ are realized.

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