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A comparative study of the efficacy of Aphtheal™ in the management of recurrent minor aphthous ulceration

Brenda Murray[1], Niall McGuinness[2], Paul Biagioni[1], Paula Hyland[1], Philip-John Lamey[1]

[1]*The Oral Science Research Centre, School of Dentistry, Queen's University Belfast, UK;* [2]*Independent Data Management Limited, Cork, UK*

BACKGROUND: Recurrent minor aphthous ulceration (RAU) is a common condition which is multifactorial in origin.

METHODS: This study, firstly, aimed to treat the prodromal stage of RAU with Aphtheal™ (5% amlexanox paste) to determine if ulcer development could be prevented. A second arm of the study investigated treatment of RAU with Aphtheal™ once ulceration had developed. Ulcer duration, ulcer size and associated pain were measured. Both groups of subjects had previously undergone a no-treatment run-in period to establish these parameters over an untreated episode of ulceration.

RESULTS: By day 3, only 35% of the prodromal group had developed an ulcer compared with 97% of the ulcer group ($P < 0.001$). In the treated ulcer group only 66% had an ulcer present by day 3. Treatment at the onset of prodromal symptoms reduced the maximum ulcer size score by 84% ($P < 0.01$), extent of ulceration by 88% ($P < 0.01$), maximum pain score by 69% ($P < 0.01$) and extent of pain by 85% ($P < 0.01$) compared to no treatment.

CONCLUSION: Treatment with Aphtheal™ at the onset of prodromal RAU symptoms can prevent progression to ulcer development and significantly reduced symptoms if ulcers do develop.

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Introduction

Recurrent aphthous ulceration is the most common disease affecting the oral mucosa. Some 15–20% of the population is reported to be affected by the condition, with the prevalence as high as 66% in certain populations (1–5). The disease is characterized by painful ulcers affecting the non-keratinized mucosa, such as the buccal and labial mucosa and the lateral border of the tongue. The ulcers occur either singly or in multiple locations at intervals ranging from a few months to a few days with some subjects experiencing almost continuous recurrences without ulcer-free days (6, 7). Clinically three distinct forms of the disease are recognized, namely major, minor and herpetiform based on the behaviour, size, number and duration of ulcers (4, 8, 9). Of these, minor aphthous ulcers are by far the most common, affecting up to 87% of recurrent aphthous ulceration subjects (7, 10). For 24–48 h preceding the development of a minor aphthous ulcer subjects may experience a pricking or burning sensation in the mucosa. In this prodromal stage, erythema of the surrounding mucosa may be observed or it may appear normal. Within a day or so an oval or round ulcer with a grey-white centre and erythematous halo develops. Typically the ulcers are less than 1 cm in diameter and less than five occur at any one time. These ulcers are self-limiting and resolve within 7–10 days without scarring (3, 5, 9–11).

The pathogenesis of recurrent aphthous ulceration remains obscure and many factors are implicated in the disease including a genetic pre-disposition, trauma, infective agents, allergic, hormonal, nutritional, immunologic and psychological factors (12). However, the majority of subjects who have recurrent aphthous ulceration tend to be otherwise healthy without signs of systemic disease. Due to the often-uncertain aetiology of recurrent aphthous ulceration and the unpredictable course of the disease, the primary goals of therapy are to control the pain of the ulcer, promote ulcer healing and prevent recurrence. Although topical agents do not prevent ulcer recurrence they are arguably the most commonly used treatment modality. A multitude of topical agents are available for symptomatic relief including antibiotics, local anaesthetics, antihistamines, non-steroidal anti-inflammatory drugs, enzymatic preparations, gammaglobulins and immunosuppressants. However, the problem remains that the efficacy of many

Correspondence: Professor P-J Lamey, The Oral Science Research Centre, School of Dentistry, Queen's University Belfast, The Royal Group of Hospitals and Dental Hospital HSS Trust, Grosvenor Road, Belfast BT12 6BP, UK. Tel: 028 90634240. Fax: 028 90438861. E-mail: p.lamey@qub.ac.uk
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of these agents has not been fully evaluated in adequately designed and controlled clinical trials and contradictory results are reported in the literature (9, 12–18).

Of the topical agents that are available for the treatment of recurrent aphthous ulceration, amlexanox is the most extensively studied (18). Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-(1)benzopyrano-(2,3-b)-pyridine-3-carboxylic acid, a topical anti-inflammatory and anti-allergic drug (19). It is available as a 5% paste in the United States for the treatment of recurrent aphthous stomatitis (Aphthasol®, Access Pharmaceuticals Inc., known as Aphtheal™, UK). There have been a number of studies of the efficacy and safety of 5% amlexanox paste in the management of recurrent aphthous ulceration (20–23). These studies have demonstrated that 5% amlexanox paste accelerates ulcer healing and resolution of pain with subjects experiencing only minor, transient adverse effects. However, it was noted that the magnitude of benefit was significantly variable between subjects and that 5% amlexanox paste might be of further benefit if treatment is commenced during the prodromal stage of ulceration.

To this end, the aim of the present study was twofold. Firstly, the efficacy of application of Aphtheal™ in the prodromal stage of ulceration in preventing progression to ulcer development was determined. Thermographic imaging was used to accurately identify the area of mucosa in which an ulcer would develop. This method has been previously used to identify the site of developing herpes labialis lesions in the prodromal stage (24). Secondly, healing rates and pain scores in subjects treated with Aphtheal™ either at the onset of prodromal symptoms or at the onset of ulceration were evaluated and compared to those receiving no treatment.

Patients and methods

Study design

The study was a single centre, open, parallel comparison study with subjects allocated to one of two treatment groups (treatment at the onset of prodromal symptoms or treatment at ulceration) after a no treatment episode of ulceration. Ethical approval for the study was obtained from the Research Ethics Committee, Queen's University Belfast and all subjects gave their written informed consent in accordance with the Declaration of Helsinki (1996).

After a clinician had screened subjects to confirm that they had recurrent aphthous ulceration, subjects returned at their next ulcer occurrence for randomization into either the treatment at onset of prodromal symptoms group or the treatment at ulceration group. Subjects then entered a no-treatment run-in period so that comparisons could subsequently be made between treatment vs. no treatment. This run-in period commenced at the onset of prodromal symptoms and during the ulcer episode subjects recorded the size of the ulcer, if present, and pain associated with the ulcer in response to light pressure using a visual analogue scale (0–10 categorical scale) twice daily in subject diary cards. At their second ulcer episode, subjects self-administered Aphtheal™ for the duration of the study, four times daily, commencing within 12 h of the onset of the prodromal stage or within 12 h of the onset of ulceration. For subjects that were commencing treatment at the onset of prodromal symptoms, treatment was commenced only if a thermographically active area could be identified and a surface temperature difference of more than 0.05°C could be demonstrated between the symptomatic mucosa and the contralateral asymptomatic area. The system used for thermographic measurements was the Agema 900 Thermovision System. On treatment days 0, 3 and 10 or the day of healing (whichever occurred first), the maximum diameter of the ulcer, if present, were assessed by the investigator using a graduated periodontal probe and both the area of involvement and the surface temperature were determined by infra-red thermography. As with the no-treatment run-in period, subjects completed diaries twice daily, recording the ulcer size and pain score upon application of light pressure. The date and time of all assessments and treatment applications were also recorded in subject diaries (Fig. 1). At the end of the trial, subjects were asked to complete an acceptability questionnaire on the ease of application and likelihood of product use in the future.

Materials and methods

The study drug, Aphtheal™, was supplied by Block Drug Company Inc. United States, in plastic tubes containing 5 g of the paste. The investigator supervised

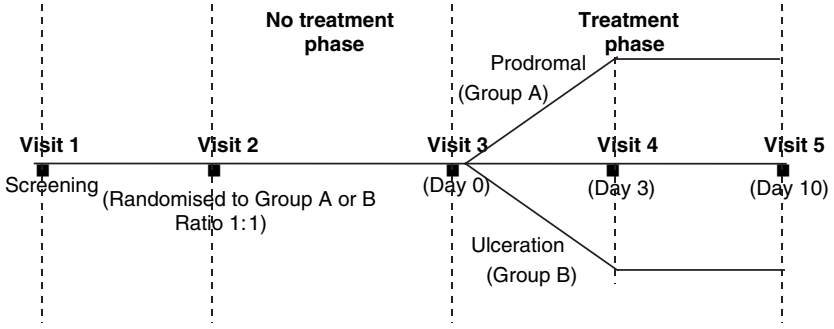

Figure 1 Summary of study design.

the first application of the drug and provided the subject with written instructions on how to apply the drug. Subjects were advised to dry the ulcer by patting it with soft clean gauze, squeeze 0.5 cm (0.25 in.) of the drug onto a wet fingertip and dab the paste onto the ulcer but not rub it into the ulcer, as this would cause irritation. Subjects were advised to apply the drug four times a day, preferably after oral hygiene, after breakfast, lunch and dinner and at bedtime.

Subjects

Subjects were initially recruited from patients referred to the Oral Medicine Clinic, Royal Victoria Hospital, Queen's University Belfast and then subsequently from the wider population via an advertising campaign in the local press. For inclusion in the study males or females, aged over 18 years of age and capable of giving informed written consent were recruited. At the screening visit, all subjects gave a history consistent with that of recurrent aphthous ulceration and associated prodromal symptoms. In addition, to facilitate measurement of the maximum diameter of the ulcer and thermographic imaging, ulcers had to be located in the anterior part of the mouth. Subjects were excluded from the study if they had abnormal haematological or biochemical values, were alcohol dependent, smoked tobacco or used recreational drugs, had a positive pregnancy test or were pregnant or breast-feeding. Subjects were also excluded if they had been diagnosed with immune dysfunction related ulcers, were wearing complete dentures or had an allergy to any of the constituents of Aphtheal^{TM}. Participation in a clinical trial in the previous 3 months or known or suspected poor compliance also warranted exclusion from the study.

Although concomitant medications were recorded at screening and throughout the study period, no disallowed concomitant medications were specified in the exclusion criteria. However, no local treatment other than Aphtheal^{TM} was allowed. No subject was using either topical or systemic steroids on a regular basis at the time of enrolment to the study and subjects were requested not to use steroids for the duration of the study. Subjects starting steroid treatment during the study period were withdrawn from the study.

Treatment compliance

Compliance was monitored by recording the date and time of the drug applications in subject diaries. Each tube of Aphtheal^{TM} was also weighed at the time of dispensing and at the final visit (treatment day 10 or time of healing, whichever occurred first).

Criteria for evaluation

Efficacy

The maximum diameter of the ulcers, if present, were assessed by the investigator, using a graduated periodontal probe on days 0, 3 and 10 or day of healing (whichever occurred first). Area of erythema and surface temperature was measured using infrared thermography at the same time-points during the treatment phase. Subjects assessed the ulcer size and pain in response to light touch twice daily using a visual analogue scale on the diary cards during the no treatment and treatment periods. Time to healing was calculated from subject diaries.

Safety

Vital sign measurements and physical examinations assessing physical appearance and a medical examination of the eyes, ears, nose and throat was performed at the screening visit and final visit. Pregnancy tests were carried out in female patients at risk of pregnancy prior to the commencement of treatment. At the screening visit a blood sample was obtained for haematological (full blood picture and ferritin) and biochemical (urea, sodium, potassium, chloride, bicarbonate, creatinine, glucose, urate, AST, ALT, GT, ALP, total bilirubin, total protein, albumin, calcium, phosphate, cholesterol, globulin, Vitamin B_{12} and red cell folic acid) profiling. A viral screen, for *herpes simplex* virus using PCR technology, was also undertaken. Virus DNA was amplified from extracted oral rinses by nested-PCR (with internal cellular control primers for 1L-1β) using an adaptation of methods previously described (25, 26). Subjects were specifically questioned about adverse events at each visit and any adverse events that were reported were recorded in the Case Report Form (CRF).

Statistical methods

All randomized subjects were analysed in terms of demographic and baseline characteristics. All subjects that were withdrawn or elected to discontinue with the study did so after randomization but before the commencement of treatment and therefore had no efficacy data. A $P < 0.05$ was taken to indicate statistical significance. The primary outcome analysis was performed one-sided, all other tests were performed two-sided.

Baseline characteristics

Fisher's exact probability test was carried out for categorical data and *t*-tests for continuous data.

Efficacy

The primary outcome measure was the proportion of subjects developing ulcers between the onset of prodromal symptoms and treatment day 3. The proportion of subjects in each group was compared using Fisher's exact probability test (one-sided). Secondary end-points of area of erythema and surface temperature were compared using descriptive statistics. Ulcer size and pain score, assessed by subjects, were compared between treatments and on a within subject basis for the no treatment and treatment periods using descriptive statistics. Time to healing was also compared between treatments and on a within subject basis for the no treatment and treatment periods using descriptive statistics.

Safety

Safety measurements of adverse events at each study visit were analysed using descriptive statistics.

Handling of missing data and deviations from study procedure

There were a number of a.m./p.m. indicators missing in the diary cards and the times recorded were considered to be unreliable. Therefore it was assumed that each entry in the diary card was at intervals of 12 h. The subjective pain and size scores in the diary cards were to be recorded on a numerical scale between 0 and 10. On a number of occasions the subjects entered free text rather than a numerical score and assumptions were made to convert these text entries to numerical scores. For example 'slight redness' or 'minimal' was assigned a numerical score of 0.5 and 'healed' or 'clear' was assigned a numerical score of 0.

Results

Demographics and other baseline characteristics

Fifty-seven subjects were randomized to receive treatment at their second ulcer occurrence (24 to treatment at onset of prodromal symptoms, 33 to treatment at ulceration). The majority (60%) of subjects were female and 98% were Caucasian with a mean age of 36.5 years (SD: 10.0 years). Of the 57 subjects that were randomized, 46 entered the treatment phase of the trial. Of those that were randomized but did not enter the treatment phase, seven elected to discontinue with the trial, two were withdrawn by the investigator due to the commencement of steroids and two subjects failed to complete the study as their next aphthous ulcer occurrence had not occurred at the time of stopping the study.

For those subjects that did enter the treatment phase (17 to treatment at the onset of prodromal symptoms, 29 to treatment at ulceration), there was no statistically significant difference between the two groups in terms of age ($P = 0.07675$), sex ($P = 0.5439$) or ethnicity ($P = 0.4389$).

On entry to the trial, no subject had significant medical or surgical histories that may have interfered with the conduct or results of the study. No subject had clinically significant laboratory results (haematology, biochemistry and viral screen) and where appropriate all pregnancy tests were negative. On physical examination, all subjects had a normal general appearance and eyes, ears, nose and throat examination. All vital signs were also normal with the exception that one subject had a blood pressure of 175/115 mmHg. However, it was accepted that this would not interfere with the conduct or results of the study.

Treatment compliance

Each tube of Aphtheal^{TM} was weighed at the time of dispensing on treatment day 0 and again on day 10 or the day of healing (whichever occurred first). The mean amounts of medication used during the study period did not differ significantly between the two treatment groups ($P = 0.30$).

Efficacy

The results of the study showed that only 35% of subjects treated with Aphtheal^{TM} at the onset of prodromal symptoms had developed an ulcer between days 0 and 3, whereas 97% of subjects treated at the onset of ulceration had developed an ulcer between days 0 and 3 ($P < 0.001$). In the latter group only 66% still had an ulcer present at day 3. Both treatment regimens were efficacious in terms of healing ulcers within the 10 days treatment period with only one subject in each group still having an ulcer at the end of the treatment period.

Subjects treated prodromally had a mean maximum ulcer diameter of 0.00 (SD: 0.00) at day 0 and 0.62 mm (SD: 0.99) at day 3 compared with 1.71 (SD: 0.86) at day 0 and 1.74 mm (SD: 1.58) at day 3 for those treated at ulceration. By treatment day 10 (or at the day of healing) mean maximum ulcer diameter was similar whether treated prodromally or at ulceration. The thermographically assessed area of erythema for both treatment groups was similar at the start of the treatment phase. The area of erythema was 84 and 99% less than that observed at day 0 at days 3 and 10 (or day of healing) for those treated at the onset of prodromal symptoms. This compared with a decrease of 1 and 90% at days 3 and 10 (or day of healing) for those subjects treated at the onset of ulceration. The reduction of the area of erythema between days 0 and 3 was statistically significant for those treated at the onset of prodromal symptoms ($P < 0.05$), although this was not the case for those treated at the onset of ulceration. Furthermore, differences in the area of erythema between the two treatment groups between days 0 and 3 were statistically significant ($P < 0.05$). However there was no statistically significant difference in the reduction of the area of erythema between the groups from days 0 to 10. Surface temperature was also similar for both groups at the start of the treatment phase. However surface temperature also decreased more rapidly (between days 0 and 3) for those subjects that were treated at the onset of prodromal symptoms compared to those treated at the onset of ulceration (Tables 1–3).

Table 1 Mean maximum ulcer diameter and thermographically measured area of erythema and change in surface temperature on treatment days 0, 3 and 10 after treatment with Aphtheal^{TM} at either the onset of prodromal symptoms or at the onset of ulceration

Treatment	*At onset of prodromal symptoms*			*At onset of ulceration*		
Assessment (SD)	*Day 0*	*Day 3*	*Day 10*	*Day 0*	*Day 3*	*Day 10*
Size (mm)	0.00 (0.00)	0.62 (0.99)	0.24 (0.97)	1.71 (0.86)	1.74 (1.58)	0.17 (0.93)
Area (mm^2)	12.95 (20.11)	2.13 (3.09)	0.17 (0.72)	11.02 (21.72)	10.89 (24.64)	1.09 (4.73)
Change in surface temperature (°C)	1.08 (0.75)	0.34 (0.61)	0.24 (0.74)	1.08 (0.86)	0.75 (0.90)	0.06 (0.78)

Table 2 Change from days 0 to 3 (95% confidence interval) in efficacy parameters for subjects treated either at the onset of prodromal symptoms or at the onset of ulceration

	Prodromal group	*P-value*	*Ulceration group*	*P-value*
Area of erythema (mm^2)	−10.82 (−21.18, −0.46)	0.0417	−0.13 (−6.15, 5.89)	0.9653
Mean max ulcer size (mm^2)	−2.91 (−4.42, −1.41)	0.0008	−2.05 (−3.17, −0.94)	0.0008
Extent of ulceration (h mm^2)	−359.47 (−509.12, −209.82)	0.0001	−257.90 (−404.73, −111.06)	0.0012
Mean maximum pain scores	−4.53 (−6.12, −2.94)	<0.0001	−2.57 (−3.66, −1.47)	<0.0001
Extent of pain scores	−618.35 (−834.71, −401.99)	<0.0001	−372.00 (−514.34, −229.66)	<0.0001

P-value from paired *t*-test.

Table 3 Statistical summary of efficacy with comparison of treatment groups – estimated treatment difference subjects treated at the onset of prodromal symptoms and subjects treated at the onset of ulceration (95% confidence limits)

	Estimated treatment difference	*P-value*
Area of erythema (mm^2) (change from days 0 to 3)	−9.91 (−19.42, −0.39)	0.0417
Area of erythema (mm^2) (change from days 0 to 10)	−0.93 (−3.30, 1.44)	0.4333
Mean maximum ulcer size (mm^2) (change from days 0 to 3)	−0.86 (−1.51, −0.20)	0.0116
Extent of ulceration ($hr.mm^2$) (change from days 0 to 3)	−117.34 (−209.09, −25.59)	0.0134
Mean maximum pain scores (change from days 0 to 3)	−1.12 (−2.38, 0.15)	0.0822
Extent of pain scores (change from days 0 to 3)	−135.27 (−273.78, 3.23)	0.0553

P-value for comparison of treatment groups from analysis of covariance with treatment as fixed effect and day 0 as covariate.

Subjective measurements of mean maximum ulcer size recorded by subjects were the same for both treatment groups during the no-treatment period of assessment. Between days 0 and 3 there was a reduction of 84% in the mean maximum ulcer size in those subjects treated at the onset of prodromal symptoms and a reduction of 59% in those subjects treated at the onset of ulceration. The reduction in mean maximum ulcer size was statistically significant both within ($P < 0.01$) and between treatment groups ($P < 0.05$). Treatment at the onset of prodromal symptoms compared with at ulceration produced a 60% reduction in mean maximum ulcer size. The extent of ulceration (as measured by the area under the size vs. time curve) was similar during the no-treatment run-in period. The extent of ulceration between days 0 and 3 was 88% less for those subjects treated at the onset of prodromal symptoms and 61% less for those subjects treated at the onset of ulceration. Again the reduction in the extent of ulceration was statistically significant both within ($P < 0.05$) and between treatment groups ($P < 0.05$). Treatment at the onset of prodromal symptoms rather than at ulceration produced a 71% reduction in the extent of ulceration (Tables 2–4).

Subjective measurements of mean maximum pain scores recorded by the subjects were similar for both treatment groups during the no-treatment run-in period. There was a reduction of 69% in the mean maximum pain scores for those subjects treated at the onset of prodromal symptoms and a reduction of 45% for those treated at ulceration between days 0 and 3. The reduction in the mean maximum pain scores was statistically significant within each group ($P < 0.01$), although there was no statistically significant difference between the two groups. Treatment at the onset of prodromal symptoms rather than at ulceration produced a 35% reduction in the maximum pain

Table 4 Shows the mean maximum ulcer size and the mean maximum pain scores subjectively recorded by patients treated with Aphtheal™ at the onset of prodromal symptoms and the onset of ulceration compared with the scores recorded at the no-treatment run-in period

	No treatment	*Treatment at the onset of prodromal symptoms*
No. of patients	17	17
Ulcer size (SD)	3.47 (2.96)	0.56 (0.70)
Pain score (SD)	6.53 (2.35)	2.00 (2.12)
		Treatment at the onset of ulceration
No. of patients	29	29
Ulcer size (SD)	3.47 (2.98)	1.41 (1.24)
Pain score (SD)	5.67 (2.13)	3.10 (1.92)

experienced by subjects. The extent of pain (as measured by the area under the pain score vs. time curve) was similar for both groups during the no-treatment period of assessment. The extent of pain between days 0 and 3 was 85% less for those subjects treated at the onset of prodromal symptoms and 61% less for those subjects treated at the onset of ulceration, compared with the same subjects receiving no treatment. Again the reduction in the extent of pain was statistically significant within each group ($P < 0.01$), although there was no statistically significant difference between the two groups. Treatment at the onset of prodromal symptoms rather than at ulceration resulted in 54% less pain over the time period of the study (Tables 2–4).

From the subject diaries it was calculated that, in subjects in which an ulcer developed, the median healing time was 4.1 days when treated prodromally compared with 8.4 days when treated at the onset of ulceration. Treatment resulted in a healing time 4.1 days faster for those treated at the onset of prodromal symptoms and 0.7 days faster for those treated at ulceration compared

with the same subjects receiving no treatment. Treatment shortly after the onset of prodromal symptoms rather than after ulceration produced, on average, a 51% faster healing of patients' ulcers.

Safety

A total of nine different adverse events were reported during the study, all of which were mild in severity and transient without the need for any action or withdrawal from the study. Three subjects experienced a dry mouth, one had two episodes of burning on the lip and one had numbness at the application site. Burning on the lip was considered to be probably related to the study drug and numbness and dry mouth was considered to be possibly related to the study drug. One subject experienced mild nausea, one subject reported a mild headache, one mild light headedness, one mild stomach cramp, one pain in the abdomen and one mild vaginal pruritis. These events were considered not to be related to the study drug.

Subject acceptability

Overall, 74% of subjects found the product to be either 'easy' or 'very easy' to use. Only one subject (2%) found the product to be 'definitely not easy' to use. Similarly, the majority of subjects (89%) reported that they were 'likely' or 'very likely' to use the product again.

Discussion

The beneficial effects of 5% amlexanox paste, in terms of accelerated ulcer healing and resolution of pain, have previously been reported (20–22). However, this is the first study to determine that by applying Aphtheal^{TM} in the prodromal stage, the development of an ulcer can be prevented, thus enhancing its therapeutic effects. All of the 57 subjects recruited to this study, experienced prodromal symptoms at a specific mucosal site prior to overt ulcer development during the no-treatment run-in period. However, although subjects report that they experience prodromal symptoms (burning or pricking sensation) one of the inherent difficulties in carrying out a study of this nature is the clinical identification of the exact area of mucosa in which an ulcer will develop. However, herpes labialis patients also experience similar prodromal symptoms to those reported by aphthous ulcer patients. In these subjects, the use of thermographic imaging to detect an increase in surface temperature has been shown to be an accurate and reproducible method of identifying the site of the developing lesion in the prodromal stage and measuring the progress of such erythematous lesions (24). In the present study, in addition to the subjects' own reports of experiencing prodromal symptoms, this method has therefore been employed to confirm those areas of mucosa in which subjects experience prodromal symptoms clinically demonstrate significant local inflammation at the prodromal site prior to commencement of therapy. Of those subjects that were randomized to the treatment at the onset of prodromal symptoms group, all subjects had a discrete area of thermographic activity and demonstrated a surface temperature of greater than 0.05°C compared to an asymptomatic contralateral area. Of these subjects, only 35% had developed an ulcer by assessment day 3.

In the previous four studies determining the efficacy of 5% amlexanox paste, it was demonstrated, in vehicle-controlled, randomized, double-blind, multicentre trials comprising of 1335 subjects, that 74% of subjects had complete healing of ulcers after 6 days of treatment vs. 54% of those using the vehicle (22). The results of the present study support these findings in that, whether applied at the onset of prodromal symptoms or at the onset of ulceration, Aphtheal^{TM} was effective in promoting ulcer healing in almost all cases. However, more significantly, only 35% of subjects treated at the onset of prodromal symptoms had developed an ulcer by assessment day 3 compared with 97% of subjects treated at the onset of ulceration ($P < 0.001$). Furthermore in the latter group by assessment day 3 only 66% of subjects still had a clinically confirmed ulcer. Furthermore, the decrease in clinically assessed area of thermographic involvement (erythema), and surface temperature at each post-treatment assessment day indicated that treatment at the onset of prodromal symptoms hastened healing where ulcers had occurred. This accelerated healing was in the order of 4.1 days faster for subjects treated at the onset of prodromal symptoms compared with no treatment. Treatment at the onset of ulceration also accelerated healing but to a lesser extent: healing occurred 0.7 days faster in subjects treated at the onset of ulceration compared with no treatment.

Amlexanox paste (5%) has been shown to result in complete resolution of pain in 83% of subjects compared with 73% of those using the vehicle (22). In the present study, pain was shown to decrease with Aphtheal^{TM} treatment, although again treatment was more effective in reducing pain when commenced at the onset of prodromal symptoms as opposed to at the onset of ulceration. Compared to treatment at the onset of ulceration Aphtheal^{TM} application at the onset of prodromal symptoms reduced the maximum pain score by 35% and the extent of pain by 54%.

The high rates of healing and resolution of pain, independent of 5% amlexanox paste reported in previous trials, were attributed to the self-limiting nature of aphthous ulcers combined with the protective effects of the vehicle paste in covering the wound (22). However, subsequent studies did compare the efficacy of 5% amlexanox paste with no treatment. The results of those clinical trials showed that after 3 days of treatment with 5% amlexanox paste complete healing of ulcers was observed in 21% of subjects compared with 8% of subjects receiving no treatment. Similarly, there was complete resolution of pain reported by 44% of treated subjects compared with 20% receiving no treatment (21). The present study also compared ulcer size and pain scores during treatment with Aphtheal^{TM} with those recorded by subjects during a no-treatment period of assessment. Compared to no treatment, application of Aphtheal^{TM} at the onset of ulceration reduced the maximum ulcer size score by 59% ($P < 0.01$), extent of

ulceration by 61% ($P < 0.01$), maximum pain score by 45% ($P < 0.01$) and extent of pain by 61% ($P < 0.01$) by day 3. Although the positive effects of treatment in the present study would appear greater than those reported by Binnie et al. (21), this is most likely due to the fact that, in the present study, treatment was commenced within 12 h of the onset of ulceration as opposed to when subjects had an 'active' ulcer. More importantly, compared to no treatment, application of Aphtheal™ at the onset of prodromal symptoms reduced the maximum ulcer size score by 84% ($P < 0.01$), extent of ulceration by 88% ($P < 0.01$), maximum pain score by 69% ($P < 0.01$) and the extent of pain by 85% ($P < 0.01$). Furthermore, treatment at the onset of prodromal symptoms resulted in a healing time 4.1 days faster than in subjects receiving no treatment and 0.7 days faster in subjects treated at the onset of ulceration compared with the same subjects receiving no treatment. These results would suggest that Aphtheal™ is more effective in accelerating the healing of ulcers and resolving pain than previously reported.

In terms of safety, only minor transient adverse effects, similar to those previously reported were reported (23) and subjects found Aphtheal™ paste highly acceptable in terms of ease of use and likelihood of using the product again.

In conclusion, the results of this study provide evidence that Aphtheal™ is a well-tolerated effective treatment modality for minor aphthous ulceration. Treatment is more effective in preventing the development of ulcers and providing symptomatic relief of ulcers that do occur if instigated at the onset of prodromal symptoms. Overall, given that current treatments for recurrent aphthous ulceration are unsatisfactory, Aphtheal™ should be regarded as a significant advance in the treatment of recurrent aphthous ulceration, particularly if applied early.

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