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Treatment of common mouth ulcers with topical *Alchemilla vulgaris* in glycerine (Aphtarine®)

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ABSTRACT

Objective: Recurrent aphthous ulceration is the most common oral mucosal disease known, of which there are three types: minor (most prevalent), major and herpetiform, yet there are no well-established effective and reliable treatments. *Alchemilla vulgaris* (Lady's Mantle) has traditionally been used in oral hygiene and it was recently shown that when associated with glycerine, it accelerated wound healing.

Methods: An open-label study was performed in 48 otherwise healthy male and female patients aged between 4 and 44 years to determine the putative healing properties and tolerance of a standard 3 % extract of *Alchemilla vulgaris* in glycerine (Aphtarine®) on common minor oral ulcers. Patients with major or herpetiform ulcers were excluded.

Results: Topical application of Aphtarine® gel to minor mouth ulcers t.i.d relieved discomfort and produced complete healing in the majority of patients (60.5 %) within 2 days and in 75 % within 3 days, compared to 10.4 and 33.3 % respectively without treatment and 15 and 40 % with commonly available treatments. Most patients appreciated the ease of product application, its taste and texture. Aphtarine® was locally well-tolerated and received a majority overall good to excellent rating.

Conclusion: Aphtarine® is a promising new treatment for healing common mouth ulcers which is safe, well-tolerated and highly effective.

Key words: *Alchemilla vulgaris*, glycerine, Aphtarine®, mouth ulcer, recurrent aphthae

INTRODUCTION

Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most common oral mucosal disease known (1, 2, 3, 4) prevalent in up to 25 % of the population with three month recurrence rates as high as 50 % (1, 2, 5). Popularly referred to as mouth ulcers or canker sores, aphthous ulcers are round or oval with a yellow or grey floor surrounded by an erythematous halo of inflamed mucosa (6, 7), can cause considerable pain and may interfere with eating, speaking and swallowing (2, 8).

Aphthous ulcers can be classified into three different types: minor, major and herpetiform (5, 9, 10). Minor mouth ulcers are by far the commonest, representing an estimated 80 to 87 % of all aphthae (2, 11), have a diameter of less than 1 cm, usually occur on the non-keratinized oral mucosa, have good prognosis and do not generally last for more than two weeks, healing spontaneously within 7 to 10 days (1, 7, 8, 11). Major aphthae, also termed Sutton disease, constitute an estimated 10 to 15 % of all aphthae, are larger, being greater than 1 cm in diameter, involve deeper ulceration that heals slowly over weeks or months often with scarring (1, 2, 8, 11). Herpetiform ulcers constitute only 5 to 10 % of all aphthae, are clusters of multiple pinpoint-type ulcers that are 1 to 3 mm in diameter, vesicular in morphology and heal within about a month (1, 2, 8, 11).

The pathophysiology of aphthous ulcers is still poorly understood (5, 7, 8, 12). Aphthae more commonly affect young adults, some cases have a familial and genetic basis, but most patients seem to be otherwise well (7, 8, 11, 13). Attacks may be precipitated by local trauma, stress, food intake, drugs, hormonal changes and vitamin and trace element deficiencies (1, 2, 7, 8, 11). In HIV-seropositive persons, mouth ulcers occur more frequently, may be larger, take longer to heal spontaneously and produce more painful symptoms than in immunocompetent persons (4, 8).

Treatment for oral aphthae can be divided into five categories: antibiotic, anti-inflammatory, immune modulator, symptomatic and alternative. In most

patients, topical agents including over the counter preparations such as antiseptic mouthwashes are recommended. In patients with frequent exacerbations or more severe forms of aphthae that are unresponsive to topical treatments, systemic agents such as corticosteroids, colchicine or antibiotics are indicated (1, 3, 8, 11). However, the treatment of aphthous ulcers remains unsatisfactory, since both topical and systemic therapies are palliative, reducing the severity of the ulceration and none result in permanent remission (3, 7). Moreover, the lack of predictability of the efficacy of a particular treatment reflects the etiology of the condition. Importantly, all of the available conventional topical or systemic treatments for healing aphthous ulcers, not one can be singled out which accelerates the healing process (3, 7, 8, 11, 14). A substantial need therefore exists for an effective and safe agent which can promote complete ulcer healing within a shorter period of time.

The ideal treatment should improve ulcer healing (14) by stimulating mucosal cell growth and by removing bacterial cells which otherwise retard the healing process. The association of *Alchemilla vulgaris* (3 % extract) with glycerine (15) was recently found to accelerate cutaneous lesion healing in rats when applied topically once a day (16). The healing properties of this product were found to be associated with enhanced myofibroblast and epithelial cell growth (16), two key processes involved in granulation tissue formation (17). Since the formation of granulation tissue is a key process in healing aphthous ulcers, the present study was undertaken to determine the potential healing properties and tolerance of a plant extract traditionally used for oral hygiene, *A. vulgaris,* in association with glycerine (Aphtarine®) in otherwise healthy patients presenting minor mouth ulcers.

PATIENTS AND METHODS

Study design

Primary efficacy criteria: Time (in days) required for complete aphthous ulcer healing

Secondary criteria: Tolerance, product taste and ease of application

The study was carried out by I.D. Med Clinical Research, Bioparc de Vichy, France according to the operating GCP standards of the Institute. Aphtarine® tubes were provided to medical and dental clinics in the Clermont-Ferrand area of France. A tube of Aphtarine® and questionnaire were subsequently supplied by the participating clinics to otherwise healthy patients who were recruited when they visited dentists or medical clinics for any purpose and complained of mouth ulcers. The entire study, from patient enrolment to completion, lasted three months.

Inclusion criteria

1. Persons of any sex or age group presenting minor mouth ulcers less than 5 mm in diameter.
2. Persons not suffering from a specific pathology of the oral mucosa other than minor mouth ulcers.
3. Persons willing to apply topical treatment from the beginning of the study until complete ulcer healing.
4. Persons not receiving any other medical treatment susceptible to favour ulcer healing including antibiotics.

Exclusion criteria

1. Patients with major or herpetiform mouth ulcers.
2. Patients receiving any other medical treatment except for oral contraceptives.

Instructions for application

Two to three drops of Aphtarine® t.i.d. directly upon the ulcer. Wipe the tube cannula clean after each application. Continue daily treatment until complete healing.

Data collection

At the beginning of the study, each patient was given a tube of Aphtarine® along with the instructions for application and a questionnaire in which the patient was asked to reply to the following: Do you get mouth ulcers regularly? If so, what is the approximate frequency? Do you apply any treatment? If yes, name the treatment.

Clinical effectiveness of Aphtarine®

Healing performance (to be filled in after using Aphtarine®)

1. How many days are required for complete healing of your mouth ulcer without treatment?
2. With your usual treatment, how many days are required for complete healing? Name your usual treatment.
3. With Aphtarine®, how many days were required for complete healing? (< 48 h, 2 to 3 days, 4 to 7 days, or > 7 days)

Product analysis

1. Texture and 2. Taste (excellent, good, average or unsatisfactory)
3. Ease of application (very easy, easy or difficult)
4. Local irritation (none, slight, moderate or severe)
5. Overall impression of Aphtarine® treatment (excellent, good, poor or bad).

Aphtarine® composition and presentation

Aphtarine® is composed of a standard 3 % *Alchemilla vulgaris* extract in glycerine (glycerol). Both constituents are authorized in the E.U. for oral use (European Pharmacopoeia V). Aphtarine® was manufactured by Laboratoires Biosphere-99, Les Martres de Veyre, France, under GMP requirements using a standard hydroglycerinated extract of *A. vulgaris*. One batch of *A. vulgaris* extract was employed. Aphtarine® contained tannins (0.08 %), of which 3.8 % was ellagic acid; and the flavonoids quercetin (0.02 %) and luteolin (0.0002 %), as determined by HPLC analysis. Aphtarine® product analysis confirmed the absence of microbial contamination and the presence of active ingredients according to the pre-established product specification. Aphtarine® is a viscous, yellow gel with no particular odour. The product was presented in white plastic 10 ml tubes with an inbuilt 4 cm application conical cannula containing approximately 9 ml of Aphtarine®.

Commonly used treatments

These included Pansoral® gel (containing choline salicylate and cetakonium chloride, Pierre Fabre, topical application q.i.d.) and Flogencyl® gel (containing anhydrous beta aescine, Expanpharm, topical application four to six i.d.).

Patients

Patients included males and females aged 4 to 44 years. When children were to receive treatment, the questionnaire was filled in by parent(s) with consideration for the child's appreciation. Patients were informed before the study that they would be treated with Aphtarine®, and their full, signed consent was obtained to enter the study.

RESULTS

Number of patients treated

48 out of an initial number of 59 enrolled patients returned the questionnaire completed.

Healing performance

The effect of topical Aphtarine® on aphthous ulcer healing is shown in Fig. 1. In volunteers treated with Aphtarine®, 29 (60.5 %) indicated complete ulcer healing within 48 h, 7 (14.5 %) between 2 and 3 days, 9 (18.8 %) between 4 and 7 days, and 3 (6.3 %) greater than 7 days (Fig. 1). This compared with 5 (10.4 %) without treatment in patients who indicated ulcer healing within 48 h, 11 (22.9 %) between 2 and 3 days, 26 (54.2 %) between 4 and 7 days and 6 (12.5 %) greater than 7 days (Fig. 1). When commonly available treatments were used, ulcer healing was indicated by 6 (15 %) patients in 48 h or less, 10 (25 %) between 2 and 3 days, 19 (47.5 %) between 4 and 7 days, and 5 (12.5 %) greater than 7 days (Fig. 1).

Thirty six out of 48 (75 %) patients experienced complete ulcer healing within 3 days with Aphtarine® treatment compared to 16 out of 48 (33.3 %) with no or commonly available treatments. This trend is clearly evident in Fig. 1.

Mouth ulcers were not, however, affected by Aphtarine® treatment in two patients. Upon further investigation, it subsequently appeared that both of these patients had herpetiform aphthae which had failed to respond to other local treatments and therefore they should normally have been excluded from the study.

Product appreciation

Patient appreciation of Aphtarine® in terms of texture and taste, ease of application, local tolerance and overall impression are shown in Table 1.

The majority of patients (73.9 %) found Aphtarine® very easy or easy to apply with its long applicator. 19 % found Aphtarine® difficult to apply and 7.1 % declared its application impractical (Table 1). 68.2 % patients found Aphtarine® to be non-irritant, 18.2 % reported slight irritation and 13.6 % moderate irritation (Table 1). The vast majority (> 85 %) of patients found Aphtarine's texture and taste good or excellent (Table 1). In terms of patients' overall impression of Aphtarine®, 84 % estimated the product as a good or excellent topical treatment for mouth ulcers (Table 1).

Patients' comments

The questionnaire was not always fully completed, particularly with respect to previous treatments. However, among the comments made by patients or their practitioner was notably the absence of an effective treatment for mouth ulcers which is safe to use as a household pharmacy product. Product taste was considered to be the second most important asset and ease of application the third.

DISCUSSION

Aphthous ulcers are a common and painful problem. Their pathophysiology is still not fully understood and this is reflected by the lack of reliable efficacy of the currently used topical or systemic antibiotic, anti-inflammatory, immune modulatory or symptomatic treatments (6, 7, 8, 14). A majority of patients with aphthous ulcers are likely to obtain over the counter treatments which are chiefly antiseptic mouthwashes (3, 8, 14). There exists no single well-established treatment for common mouth ulcers (6, 8, 11, 14) and none of the existing treatments accelerates the healing process. The aim of the present investigation was therefore to determine the potential healing properties and tolerance of a standard 3 % *Alchemilla vulgaris* extract in glycerine, called Aphtarine® (15) in 48

otherwise healthy male and female patients aged 4 to 44 years presenting minor oral aphthae, which are the commonest form, accounting for 80 to 87 % of all aphthae (1, 2, 5, 7, 11).

Topical application of Aphtarine® to minor mouth ulcers produced complete healing in 60.5 % patients within 2 days and 75 % within 3 days compared to 10.4 and 33.3 % when untreated and 15 and 40 % with commonly available treatments, respectively. However, no beneficial effects of the product were noted in the two patients with herpetiform ulcers whom had been included by error. More than 85 % patients rated the texture and taste of Aphtarine® as good or excellent, and ease of application with its long applicator as easy or very easy by more than 70 % patients. Aphtarine® was well-tolerated locally and was rated overall as good or excellent by 84 % patients. Aphtarine® also performed favourably compared to over the counter treatments which the patients had also tried.

Collectively, the results suggest promising beneficial effects of Aphtarine® on mouth ulcer healing. Accelerated healing of aphthous ulcers provides relief from pain and discomfort. Thus Aphtarine® allowed complete ulcer healing within two days in more than half the patients in this study compared to four to seven days without treatment.

The mechanisms which may be associated with the beneficial healing properties of Aphtarine® on mouth ulcers have been identified, at least in part (16) and include enhancement of myofibroblast and epithelial cell growth, which are vital to the tissue repair process and removal of bacterial contamination (16). Enhancement of cell growth has been shown to occur with *A. vulgaris*, but not with glycerine (16). Accelerated ulcer healing also requires removal of bacterial contamination from the wound to provide a favourable ground for mucosal cell growth and repair. Although glycerine or *A. vulgaris* are not generally considered to be antiseptics, a physicochemical role of glycerine in removing bacterial contamination from the wound is likely. Hypertonic glycerine solution may create an osmotic gradient on the mucosal surface of the ulcer, which favours plasma exudation from inside the ulcer down its osmotic gradient and into the buccal cavity, thus extruding contaminating bacteria, and consequently favouring wound healing (16). Possible additional antibacterial activities of glycerine (18, 19, 20) could also play a role. Additional antimicrobial effects of *A. vulgaris* cannot be fully excluded. Bacteriostatic activity has been reported (21, 22) for the principal tannin found in *A. vulgaris*, ellagic acid (23). The rapidity of lesion healing in the mucous membrane is dependent upon competition between bacterial multiplication which retards healing and the growth of myofibroblast and epithelial cells which are fundamental for tissue repair to occur (17). Newly formed cells occupy space in the wound, leading to extracellular matrix deposition and neovascularisation (17). *A. vulgaris* was reported to accelerate intercellular matrix regeneration (24) and experimental cutaneous wound healing in rats (16).

A. vulgaris, similarly to other members of the Rosaceae family, contains polyphenols to which the main pharmacological activities of the plant can be attributed (23). *A. vulgaris* contains tannins (pyrogallols) composed of some gallic and mostly ellagic acid, flavonoids, the most abundant being quercetin, along with others, including luteolin and proanthocyanidins (23, 25, 26, 27). Prevention of dermal enzyme degradation, cutaneous lipid peroxidation and enhanced wound healing properties have been described for ellagic acid (28, 29) and polyphenolic compounds containing gallic acid and catechin tannins (30). Anti-inflammatory (31, 32) and antioxidant activity favouring cutaneous wound healing (33, 34) have been described for quercetin, of which 0.02 % was quantified in Aphtarine. Anti-inflammatory activity has also been described for luteolin (35, 36) although only trace amounts of this flavonoid were measured in Aphtarine.

The aphthous ulcer healing properties of Aphtarine® demonstrated in the present study are therefore not unexpected, and are compatible with the well-known astringent properties of *A. vulgaris*. Glycerine is commonly employed for the storage and preservation of biological materials such as skin grafts. The combination of *A. vulgaris* and glycerine would appear to be particularly adapted to topical treatment of minor oral aphthae. The absence of efficacy of Aphtarine® in two patients presenting herpetiform aphthae suggests that the product may not be effective in healing this type of ulcer. The precise reason for the apparent lack of effectiveness of Aphtarine® in herpetiform mouth ulcers is unclear at present, but could be linked to the involvement of different pathophysiological mechanisms which are implicated in the formation of herpetiform and minor aphthae (5, 7, 8, 11). Further studies are nevertheless required to shed light on this issue.

The main limitation of the trial is inherent to its design, which lacks randomization and placebo control. That a significant placebo effect could have occurred in the present study cannot be excluded. The results of non-placebo controlled trials should be interpreted with caution.

Conclusion

Notwithstanding the study's limitations, topical application of Aphtarine® to minor mouth ulcers in otherwise healthy patients produced complete healing in the majority of cases (60.5 %) within two days and 75 % within 3 days compared to 10.4 % and 33.3 %, respectively without treatment and 15 and 40 % with commonly available treatments. Most patients appreciated the ease of product

application, its taste and texture. Aphtarine® was locally well-tolerated and received a majority overall good or excellent rating. No beneficial effects of the product were noted, however, in two patients presenting herpetiform aphthous ulcers. These particularly promising data with Aphtarine® justify a randomised, placebo-controlled trial in order to clearly establish its healing properties in common mouth ulcers.

In conclusion, Aphtarine® is a promising new topical treatment for healing common mouth ulcers which is safe, well-tolerated and highly effective.

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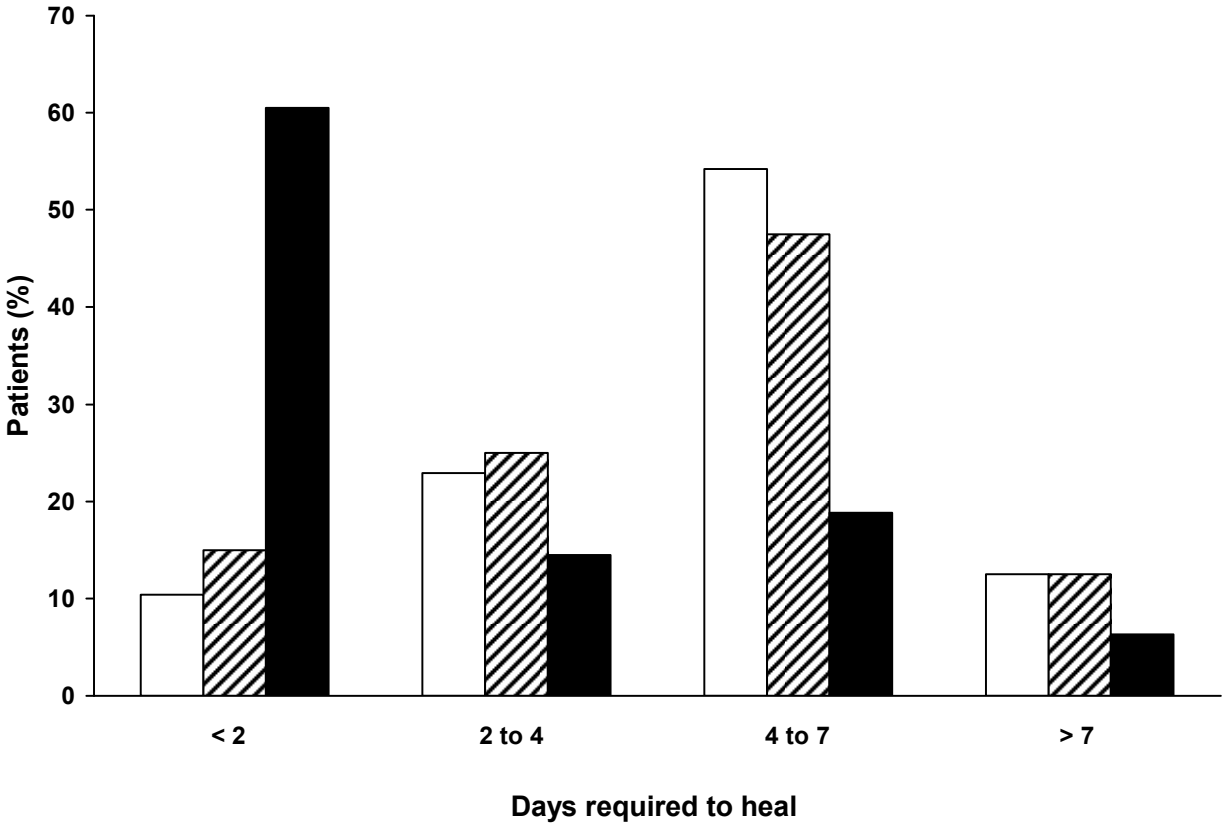
Criterion	Questionnaire replies				
	No. of replies	Very easy	Easy	Difficult	Impractical
Ease of application	42 87.5 %	18 42.9 %	13 31.0 %	8 19.0 %	3 7.1 %
		Non irritant	Slightly irritant	Moderately irritant	Severely irritant
Local tolerance	44 91.7 %	30 68.2 %	8 18.2 %	6 13.6 %	0 0%
		Excellent	Good	Average	Unsatisfactory
Texture	48 100%	32 66.6 %	9 18.8 %	7 14.6 %	0 0%
Taste	48 100%	36 75.0 %	12 25.0 %	0 0%	0 0%
Overall impression	38 79.2 %	14 36.8 %	18 47.4 %	4 10.6 %	2 5.2 %

Table 1.
Patient assessment of Aphtarine® as obtained from the questionnaire. Numbers of patients from a total number of 48 and the corresponding percentage values are indicated for each criterion. See Patients and Methods for further details.

Legend to Figure 1

Comparison of the number of patients, expressed as percent inclusions, with complete healing of mouth ulcers in two days or less, in two to four days, four to seven, or greater than seven days without treatment (unfilled columns), an over the counter treatment of their own choice (hatched columns) or Aphtarine® (filled columns). The total number of patients investigated who returned completed questionnaires was 48 (male and female aged 4 to 44 years).

Fig. 1


70
60
50
40
30
20
10
0
Patients (%)
< 2
2 to 4
4 to 7
> 7
Days required to heal