

The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers

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The aim of the present clinical double-blind crossover study was to investigate the effect of two different toothpaste detergents, sodium lauryl sulfate (SLS) and cocoamidopropyl betaine (CAPB), as compared with a detergent-free paste, on 30 patients with frequent occurrences of recurrent aphthous ulcers. The study consisted of three 6-week periods during which the patients brushed twice daily with the different test toothpastes. The localization and number of new ulcers were assessed. A significantly higher frequency of aphthous ulcers was demonstrated when the patients brushed with an SLS- than with a CAPB-containing or a detergent-free placebo paste. An SLS-free toothpaste may thus be recommended for patients with recurrent aphthous ulcers. □ *Dentifrices; oral mucosa; stomatitis, aphthous; toothbrushing*

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The etiology of recurrent aphthous ulcers (RAU) is unknown, and no therapeutic methods are available for permanent cure of this disease. Etiologic considerations based on local and systemic factors have been reported (1). Inheritance (2), nutritional and hematinic deficiencies (3, 4), hypersensitivity reactions (5), menstrual cycle (6), psychologic stress (7), and trauma of the oral tissues (8) are factors that have been associated with RAU. Attempts to manage RAU, with its apparently multifactorial etiology, serves only to ameliorate the pain from the ulcers. The symptoms can be reduced, but there is still no reliable and safe means of preventing recurrences (9). Topical or systemic steroids seem to provide the best long-term management for patients with RAU (10).

In a preliminary study (11) it was shown that patients with RAU obtained a 60% reduced frequency of new ulcers when brushing with a detergent-free toothpaste compared with a standard 1.2% sodium lauryl sulfate (SLS)-containing toothpaste. The anionic lauryl sulfate is a widely used toothpaste detergent, and it is a strong denaturing agent (12).

Flores de Jacoby et al. (13) reported a reduction of the keratinization of human oral epithelium caused by a 7.9% anionic toothpaste detergent, probably due to rupture of intercellular junctions. However, the authors concluded that there was no cytotoxic effect of anionic detergents at concentrations between 1.0% and 1.5%.

Riethe (14) also indicated that the harmful effect of anionic detergents depends on their concentration and, therefore, concluded that a general precaution against the use of these detergents was not necessary.

Siegel & Gordon (15) observed an increased perme-

ability in rat oral mucosa to both oil-soluble and water-soluble molecules when 0.1% or 1.0% SLS was present. They observed a widening of the stratum corneum due to separation and loss of surface epithelial layers.

In a study by Koch (16) an amelioration in 90% of the participants was observed when 207 RAU patients brushed with an enzyme-containing toothpaste (Zendium). A marked reduction in number of aphthous ulcers and a relieving effect were reported. It was suggested that the enzymes amyloglucosidase and glucose oxidase activate the lactoperoxidase-thiocyanate system in saliva, and, by suppressing streptococci, the toothpaste may give relief to patients with RAU. A control group was not used, and the observations could well have been a placebo effect. Another possibility is that the enzyme toothpaste described above contains a non-ionic detergent, stearylethoxylate, instead of SLS. Donatsky (17) et al. used the same toothpaste (Zendium) and included a true placebo without the enzymes in patients with RAU; they reported no effect on disease severity by these enzymes. Henricsson & Axéll (18) also reported no significant difference between the use of Zendium and a placebo toothpaste without the enzymes.

Cocoamidopropyl betaine (CAPB), a zwitterionic detergent with a C12 alkyl chain, has recently been included in toothpastes recommended for children. Alkyloamidobetaines, such as CAPB, are considered to be less irritating to skin and mucous membranes than anionic detergents, such as SLS (19).

The aim of the present double-blind, crossover study was to investigate the effect of toothpastes containing these two detergents in patients with RAU. A detergent-free toothpaste was used as a placebo.

Table 1. Test toothpaste ingredients

Amorphous silica
Sorbitol syrup
Xanthan gum
Polyethylene glycol
Saccharine
Flavor
Titanium dioxide
Sodium monofluorophosphate
Sodium lauryl sulfate or
cocoamidopropyl betaine or neither detergent

Patients and methods

Thirty patients with RAU (mean age, 38 years; range, 12–67 years), 22 females and 8 males, participated in this double-blind, crossover study. The disease had been present in all participants for periods of 5 to 55 years (mean, 24 years), and all patients had frequent occurrences of ulcers. The test panel was selected from volunteers who responded to a newspaper advertisement requesting patients with RAU. Volunteers with systemic diseases, with use of drugs affecting the oral mucosa, or with other chronic oral diseases were not admitted. Detailed information on the study plan was given, and informed consent was obtained from each participant. They were requested not to take any other treatment for oral ulcers during the entire study period. The protocol was reviewed and approved by the Local Ethics Committee for medical research. Diagnosis was made on the basis of the clinical appearance and the patient history, using the criteria suggested by Gayford & Haskell (20). Only patients with at least one aphthous ulcer during a 6-week period were accepted. During this period, all the patients brushed their teeth with a 1.5% SLS-containing toothpaste, which was comparable to toothpastes on the market. An ulcer registration calibration was performed during the 6-week period by both the patients and the examiner.

Hematologic examinations were performed on each patient to rule out any hematinic deficiency which may influence their aphthous status and included the following estimations: hemoglobin, hematocrit, leukocyte differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), s-iron, total iron-binding capacity (TIBC), vitamin B₁₂, s-folate, and e-folate. More than half of the patients (53%) reported a history of atopic disease, like asthma, rhinitis, or dermatitis. A positive correlation between atopy and RAU has previously been reported (21). Twenty-one participants (70%) had a positive family history of RAU. This corresponds to a study by Pongissawaranun & Laohapand (22) recorded in a population of dental patients.

Three toothpaste formulations, differing only in the nature of the detergent, were used in the study (Table 1). The toothpastes contained either an equimolar

concentration of SLS (1.5%) or CAPB (1.9%) or were detergent-free. After the 6-week calibration period, a detergent-free toothpaste was used for 1 week. The participants were allocated at random to one of six possible usage sequences. The study consisted of three test periods of 6 weeks' duration, during which the patients used the three different test toothpastes. Between the tests a 1-week brushing with a detergent-free paste was included. All toothpastes were tested on each patient, and each participant served as his/her own control. The test panel brushed their teeth with each toothpaste twice daily and refrained from using other dental hygiene products, rinses, or drugs that could alleviate symptoms from the aphthous ulcers throughout the trial period. However, dental floss was permitted. The patients were informed not to change diet, lifestyle, or smoking habits during the trial. Data acquisition throughout the study included combined clinical scoring with detailed patient diaries. Clinical examination was conducted at least every other week by the same clinical examiner. The incidence of illnesses or drugs used, the number and localization of ulcers, and the condition of the oral mucosa were assessed at each examination. Instruction and guidance in the use of diaries were given, and the participants practiced this during the initial calibration period. The patient diary contained 'a map' of the mouth; this facilitated daily recording of localization and number of new ulcers and made it easier to differentiate between old and new ulcers. The diaries were collected and replaced by new ones at weekly or biweekly clinic visits throughout the whole trial. The variable for assessing differences between the toothpastes was the number of new ulcers occurring during a test period.

Statistical analysis

Friedman's non-parametric test was applied to assess evidence of overall differences in the number of new ulcers between the three groups, followed by the non-parametric Wilcoxon matched-pairs signed-ranks test for differences between any pair of experimental groups.

Results

Blood screening showed no abnormal values requiring hematologic adjustments.

Five of the 30 patients in the study were excluded. Of the five patients, one became pregnant during the trial, two initiated systemic prednisone therapy to alleviate painful oral ulcers, one subsequently was diagnosed as having Behçet's syndrome, and the last had too many ulcers to count (>40 on one examination, herpetiform type). None of exclusions were associated with usage of any specific toothpaste.

The mean numbers of aphthous ulcers during the three different experimental test periods are shown in Fig. 1. Brushing with the 1.5% SLS-containing tooth-

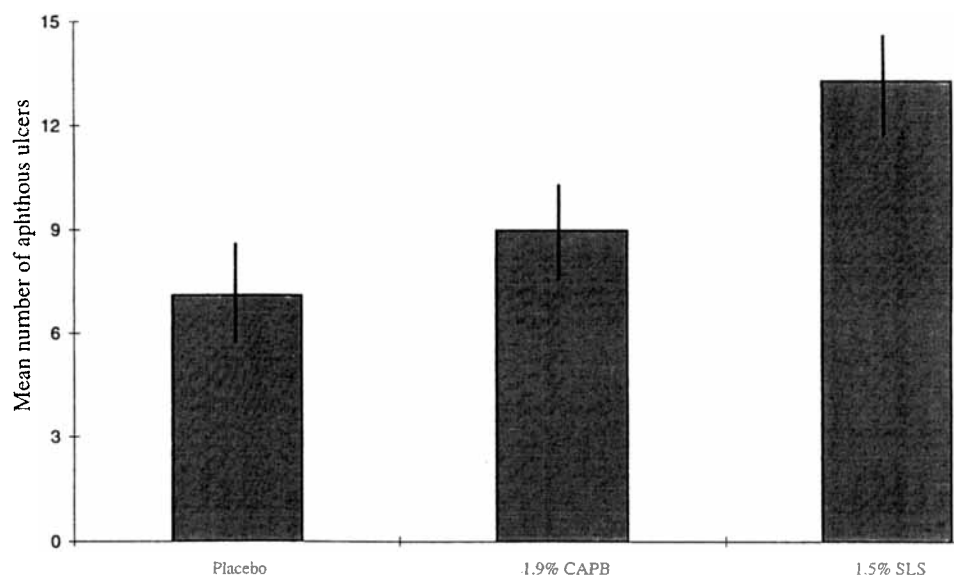


Fig. 1. Mean number of aphthous ulcers with standard error of the means (SEM) during three different 6-week test periods during which the patients brushed their teeth with toothpastes containing either of the two detergents sodium lauryl sulfate (SLS) or cocoamidopropyl betaine (CAPB) compared with a detergent-free placebo toothpaste.

paste gave the highest number of occurrences, with a total of 334 ulcers during this 6-week period. The range of new ulcers varied; 3 patients had only a few (3–5) in all 3 test periods, and 9 had at least 10 in each period. Yet, irrespective of the ulcer prevalence, the ranking order of the products within each patient was generally consistent with the overall result. The ulcers were localized to non-attached oral mucosa. Both detergent-free and 1.9% CAPB-containing toothpaste reduced the frequency of ulcers significantly by 46% and 32%, respectively, compared with the SLS-containing paste ($p < 0.0002$). The detergent-free toothpaste caused significantly fewer ($p < 0.002$) ulcers than the 1.9% CAPB, which in turn caused significantly fewer ($p < 0.0002$) ulcers than the 1.5% SLS toothpaste. Twenty-four (96%) and 18 (72%) patients benefited from using detergent-free toothpaste compared with SLS-containing or CAPB-containing pastes, respectively. Nineteen subjects (76%) benefited from using CAPB-containing toothpaste compared with SLS-containing paste. Three patients were ulcer-free, two during the surfactant-free period and one during the CAPB period.

During the SLS period seven participants (28%) also showed a marked oral epithelial desquamation (Fig. 2).

Discussion

In the present study the effect of an SLS-containing, a CAPB-containing, and a placebo toothpaste on the frequency of RAU was examined in a double-blind, crossover trial involving 30 patients. The recurrence of aphthous ulcers was significantly higher when the

patients brushed their teeth with an SLS-containing than with a CAPB-containing toothpaste or a detergent-free control paste. This was probably due to the difference in toothpaste detergents. These findings confirmed those of a previous preliminary study (11) involving 10 patients, in which a detergent-free toothpaste significantly reduced the mean number of aphthous ulcers compared with an SLS-containing paste.

In a previous double-blind crossover study (23), epithelial desquamation of the oral mucosa was shown in 6 of 10 subjects who were exposed to SLS-containing toothpaste. In that trial a cap splint was used to apply toothpaste to the mucosal tissues. In the present study patients with RAU brushed their teeth with toothpaste in an ordinary manner. Despite this, marked oral epithelial desquamation was observed in the present



Fig. 2. Oral epithelial desquamation and an aphthous ulcer in a patient with recurrent aphthous ulcers (RAU) during the sodium lauryl sulfate test period. Small arrows point at epithelial desquamation. Big arrow shows the aphthous ulcer.

study in seven patients using SLS-containing toothpaste, and this desquamation was clinically similar to the desquamation observed in the previous study (23) (Fig. 2).

Flores de Jacoby et al. (13) and Riethe (14) concluded in their studies that concentrations of anionic detergents between 1.0% and 1.5% were without harmful effects on the oral mucosa. However, the present study demonstrated a clinically adverse effect of a 1.5% SLS-containing toothpaste on RAU. This concentration is within the most widely used concentrations of SLS in commercially available toothpastes (ranging from 0.5% to 2.0%). Siegel & Gordon (15) observed a widening of the stratum corneum due to separation and loss of surface epithelial layers after treatment of rat oral mucosa with 0.1% and 1.0% SLS. This may explain the findings of the present study, because trauma of the oral mucosa is known to be a predisposing factor in the pathogenesis of RAU (8). SLS may also damage the mucin layer, which protects the oral epithelium, by denaturing its glycoproteins. The oral mucosal barrier function may thus be impaired, and the epithelium may be more exposed to irritating agents or allergens. This may, in susceptible individuals, result in an increased incidence of aphthous ulcers. It seems logical to reduce the local irritating effect on the oral mucosa of patients with RAU. The difference in effect of the two detergents on RAU patients may be related to differences in physical properties of the detergent molecules. Surface-active betaines, like CAPB, do not have the strong protein-denaturing effects of anionic detergents, like SLS (24). A difference in critical micellar concentrations (CMC) of SLS (8 mM) and CAPB (2 mM) in aqueous solutions may play a role. The monomer concentration of a detergent is thought to be important with regard to the irritating effect of detergents on skin and on mucous membranes (25). Thus, the zwitterion CAPB is less irritating to the oral mucosa than SLS. This could explain the findings both in the present study and in a previous study in which 28 subjects using a CAPB-containing toothpaste presented only 3 desquamative reactions of the oral mucosa, as opposed to 42 with an SLS-containing paste (26). The detergent-free toothpaste did not cause desquamation either in a previous study (23) or in the present one. It seems justified to recommend an SLS-free toothpaste to patients with RAU.

References

1. Scully C, Porter SR. Recurrent aphthous stomatitis: current concepts of aetiology, pathogenesis and management. *J Oral Pathol Med* 1989;18:21-7.
2. Miller MF, Garfunkel AA, Ram CA, Ship II. The inheritance of recurrent aphthous stomatitis. *Oral Surg* 1980;49:409-12.
3. Wray D, Graykowski EA, Notkins AL. Nutritional deficiencies in recurrent aphthae. *J Oral Pathol* 1978;7:418-23.
4. Rogers RS, Hutton K. Screening for haematinic deficiencies in patients with recurrent aphthous stomatitis. *Aust J Derm* 1986;27:98-103.
5. Wilson CWM. Food sensitivities, taste changes, aphthous ulcers and atopic symptoms in allergic disease. *Ann Allergy* 1980;44:302-7.
6. Ferguson MM, Carter J, Boyle P. An epidemiological study of factors associated with recurrent aphthae in women. *J Oral Med* 1984;39:212-7.
7. Pedersen A. Psychologic stress and recurrent aphthous ulceration. *J Oral Pathol Med* 1989;18:119-22.
8. Wray D, Graykowski EA, Notkins AL. Role of mucosal injury in initiating recurrent aphthous stomatitis. *Br Med J* 1981;283:1569-70.
9. Porter SR, Scully C. Aphthous stomatitis—an overview of aetiopathogenesis and management. *Clin Exp Dermatol* 1991;16:235-43.
10. Vincent ST, Lilly GE. Clinical, historic, and therapeutic features of aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1992;74:79-86.
11. Herlofson BB, Barkvoll P. Sodium lauryl sulfate and recurrent aphthous ulcers. A preliminary study. *Acta Odontol Scand* 1994;52:257-9.
12. Tzutzumi M, Oyama Y, Suda I, Watanabe T. Action of some detergents on succinate dehydrogenase of *E. coli* in vivo. *Bacteriol Abstr* 1982;17:3081-J17.
13. Flores de Jacoby L, Thor G, Lange DE. Vergleichende klinische und zytologische Untersuchungen nach Anwendung von zwei Zahnpasten. *Dtsch Zahnärztl Z* 1975;30:385-8.
14. Riethe P von. Beitrag Zur Wirkung grenzflächenaktiver Stoffe auf Gingiva. *Parodontopathies* 1966;18:347-54.
15. Siegel IA, Gordon HP. Surfactant-induced increases of permeability of rat oral mucosa to non-electrolytes in vivo. *Arch Oral Biol* 1985;30:43-7.
16. Koch G. Effekten af enzymtandpasta på recidiverende, after. Tandlaekartidningen 1981;73:264-72.
17. Donatsky O, Worsaae N, Schiødt M, Johnsen T. Effect of Zendium toothpaste on recurrent aphthous stomatitis. *Scand J Dent Res* 1983;91:376-80.
18. Henriksen V, Axell T. Treatment of recurrent aphthous ulcers with Aureomycin® mouth rinse or Zendium® dentifrice. *Acta Odontol Scand* 1985;43:47-52.
19. Sosada M, Bielowski P. Alkylpolybetaines Synthesis, surface specific properties and biological effect of some alkylpolybetaines. *Tenside Surf Det* 1990;27:194-6.
20. Gayford JJ, Haskell R, editors. Clinical oral medicine. Bristol: John Wright & Sons Ltd, 1979:1-11.
21. Spouge JD, Diamond HF. Hypersensitivity reactions in mucous membranes. *Oral Surg* 1963;16:412-21.
22. Pongissawaranun W, Laohapand P. Epidemiologic study on recurrent aphthous stomatitis in a Thai dental patient population. *Community Dent Oral Epidemiol* 1991;19:52-3.
23. Herlofson BB, Barkvoll P. Desquamative effect of sodium lauryl sulfate on oral mucosa. A preliminary study. *Acta Odontol Scand* 1993;51:39-43.
24. Ernst R. Surface-active betaines as protective agents against denaturation by alkyl sulfate detergents. *J Am Oil Chem Soc* 1980;57:93-8.
25. Miyazawa K, Ogawa M, Mitsui T. The physico-chemical properties and protein denaturation potential of surfactant mixtures. *Int J Cosmet Sci* 1984;6:33-46.
26. Herlofson BB, Barkvoll P. Oral mucosal desquamation caused by two toothpaste detergents in an experimental model. *Eur J Oral Sci* 1996;104:21-6.