The Effect of a Dentifrice in the Prevention of Recurrent Aphthous Stomatitis

Pierluigi Coli[a]/Mats Jontell[b]/Magnus Hakeberg[c]

Purpose: A multicenter, double-blind, randomized, placebo-controlled clinical trial was conducted to determine the efficacy of an experimental dentifrice on the prevention of recurrent aphthous stomatitis (RAS).

Material and Methods: A 3-month pretrial period was used to self-record data pertaining to the frequency, ulcer size, duration, and pain associated with ulcers. Thirty-six participants, who reported at least 3 RAS episodes or 30 days with RAS during the pretrial period, completed the study. Following a stratified randomization for age, sex and disease severity, the participants received the experimental dentifrice (T) or the placebo (C). The test period comprised 3 months of self-evaluation of number of ulcers, size and location. Pain related to RAS was estimated by the use of a Visual Analogue Scale (VAS).

Results: Symptoms were found to decrease in both groups when the pretrial and test periods were compared, although no statistical difference was reached in the C group. A statistically significant difference between the two time periods was obtained for the T group concerning the number of days with ulcers ($p < 0.025$) and VAS ($p < 0.010$). Of more clinical importance was the observation that 50% of the patients in the T group reported a more than 50% reduction in days with ulcers compared to 17% in the C group.

Conclusions: The dentifrice may be used as a treatment strategy for a subgroup of patients with RAS in view of the low adverse effects and the benefit of using a treatment modality that is a part of daily routines.

Key words: aphthae, RAS, dentifrice, prevention, controlled-study

Oral Health Prev Dent 2004; 2: 133–141. Submitted for publication: 22.09.03; accepted for publication: 19.01.04.

Recurrent aphthous stomatitis (RAS) is one of the most common diseases afflicting the oral mucosa. The onset of RAS can appear for no apparent reason, but may be due to mechanical trauma, psychological stress, immune deficiencies and nutritional deficiencies. Most likely, RAS represents a reaction pattern to different etiological insults (Scully and Porter, 1989; Porter et al, 1998).

No effective therapeutic regimen has been found for the entire RAS population. Management of RAS involves treatment strategies with the objectives of controlling active disease and the prevention of recurrences. Topical corticosteroids are still the primary treatment strategy but there is no uniformly-accepted effective treatment (Scully and Porter, 1989; Porter et al, 1998). Corticosteroids are most beneficial when the patient is applying the ointment in conjunction with prodromal symptoms.

The use of a different dentifrice has been advocated as a remedy for RAS. Amyloglucosidase

[a] *Department of Prosthetic Dentistry/Dental Materials Science, Faculty of Odontology, Göteborg University; and the Brånemark Clinic, Public Dental Health, Göteborg, Sweden.*

[b] *Department of Endodontology/Oral diagnosis, Faculty of Odontology, Göteborg University, Göteborg, Sweden.*

[c] *Department of Endodontology/Oral diagnosis, Faculty of Odontology, Göteborg University, Göteborg; and School of Health Sciences, Jönköping University, Jönköping, Sweden.*

Reprint requests: *Prof. Mats Jontell, Department of Endodontology/Oral diagnosis, Faculty of Odontology, Göteborg University, Box 450, SE-405 30 Göteborg, Sweden. Fax: + 46 31 741 3450. E-mail: jontell@odontologi.gu.se*

and glucose oxidase containing toothpaste (Koch, 1981) and mouthrinse (Hoogendoorn and Piessens, 1987; Fridh and Koch, 1999) have been claimed to reduce symptoms. This finding has been disputed by others (Donatsky et al, 1983; Henricsson and Axéll, 1985).

It has been suggested that sodium lauryl sulphate (SLS), the most commonly used detergent in dentifrices, has a denaturing effect and induces an increased incidence of RAS (Herlofson and Barkvoll, 1996; Chahine et al, 1997; Skaare et al, 1997). However, it has been claimed that SLS, at the concentration remaining after use in the mouth, has no adverse effects on the oral mucosa (Fakhry-Smith et al, 1997). Contradictory results have been published where none of the ulcer parameters measured was significantly affected by the use of the SLS-free dentifrice as compared with the SLS-containing dentifrice (Healy et al, 1999).

Patients with frequent episodes of RAS often experience that available treatment modalities aimed at curing or preventing active ulcers are impractical to use. The advantage of an effective dentifrice is that tooth brushing is part of daily activities.

Incidentally, it has been observed that the use of experimental toothpaste both reduced the RAS recurrence in participants using this dentifrice and had hygienic properties. A pilot study indicated effects of the toothpaste on prevention of RAS.

Thus, the objective of the present study was to evaluate the effect of such a dentifrice on the prevention of RAS recurrences. The hypothesis tested was that an experimental dentifrice may reduce the symptoms of RAS.

MATERIALS AND METHODS

Patients

All the participants affected by the *minor* form of RAS referred to the Oral Medicine Clinics in Göteborg, Falun, Karlstad and Vänersborg, Sweden, during the year 1995, were invited to participate to a double-blind, stratified-randomized clinical, parallel 6-month study. The RAS diagnosis was made at the first visit. Participants showing presence of any other oral or skin diseases were excluded as well as participants on drug therapy that could affect RAS. Eighty-two individuals agreed to participate. The patients were required not to take any other RAS treatment medicaments during the study period. The participants were requested to sign a written informed consent statement and complete a health history questionnaire in order to identify their general health background, predisposing factors to RAS, RAS experiences and previous treatment modalities.

Phase I

In phase I, the patients were monitored during the first 3 months without treatment in order to register the occurrence and severity of RAS. At their primary examination, the patients received a modified Patient Daily Record chart (Graykowski and Kingman, 1978) to record the localization, number, size and duration of the ulcers (Fig 1). In addition, they were given a chart containing a 10 cm horizontal visual analogue scale (VAS) to record the degree of discomfort due to the lesions. The left end of the scale indicated 'no discomfort' and the right end 'unendurable discomfort'. The participants were requested to fill in the chart daily during RAS episodes. After each episode, the completed charts were mailed to the Clinic of Oral Medicine in Göteborg. At the end of the 3-month period the participants were recalled, either to be included in the second phase of the study (phase II) or withdrawn from the investigation.

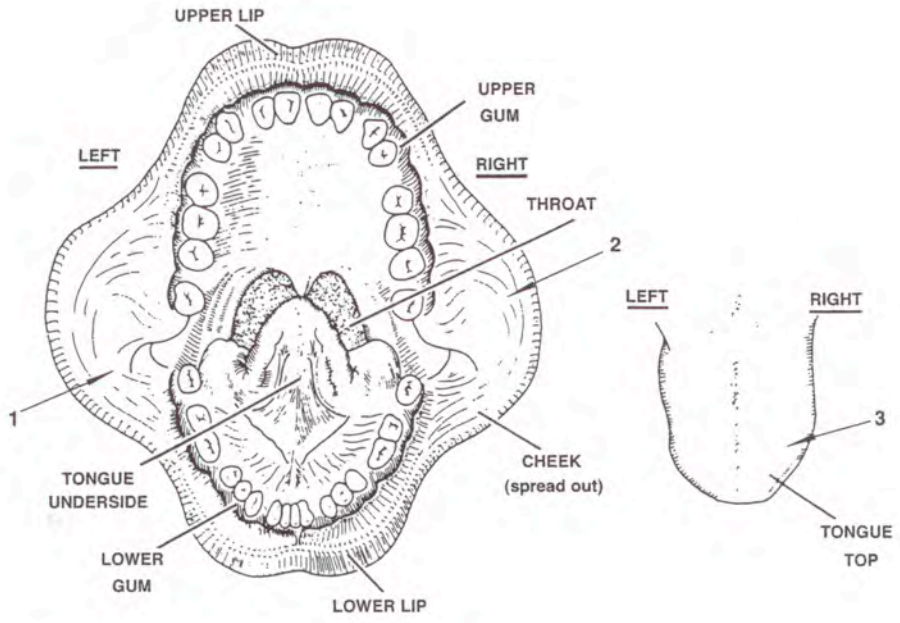
Phase II

Inclusion in the second phase of the investigation required the patients to satisfy one of the following criteria:

- three RAS episodes during phase I, or
- 30 days with ulcers during phase I.

The included patients were stratified according to different parameters: age (younger or older than 18); VAS average (more or less than 35 mm); number of days with aphthae (more or less than 30 days); and number of aphthae (more or less than 10). These parameters were used to assign the participants to one of the two treatment groups according to the minimization method (Pocock, 1983). The group assignments for all patients were decided by the same study coordinator. The clinicians and patients were not aware of assignment results. The participants enrolled for phase II used the same type of charts as during phase I. In addition, the patients were requested to report any pos-

Name:..... Date:.....



Please, estimate the average size of your ulcers based on the circles printed below:

• A ○ B ◯ C ◯ D ◯ or larger E

Please, indicate on the drawing the position of your mouth ulcers today; then number it and grade each ulcer for size (see example):

Ulcer Numbers	Size (A to E)
1	A
2	B
3	A

Ulcer Numbers	Size (A to E)

Please, grade the discomfort produced today by the ulcers:

No discomfort Unendurable discomfort

Fig 1 Patient Daily Record chart. Localization, number, size and duration of the ulcers are self-reported by the participants enrolled in the investigation.

sible subjective side effects of the dentifrices. The examiners continuously reviewed the charts for reports of adverse effects. The patients were asked to fill in the charts for a period of 3 months, after which their enrollment in the investigation ceased. The reasons for eventual participant dropout during Phase II were checked. A schematic drawing of the study design is shown in Fig 2.

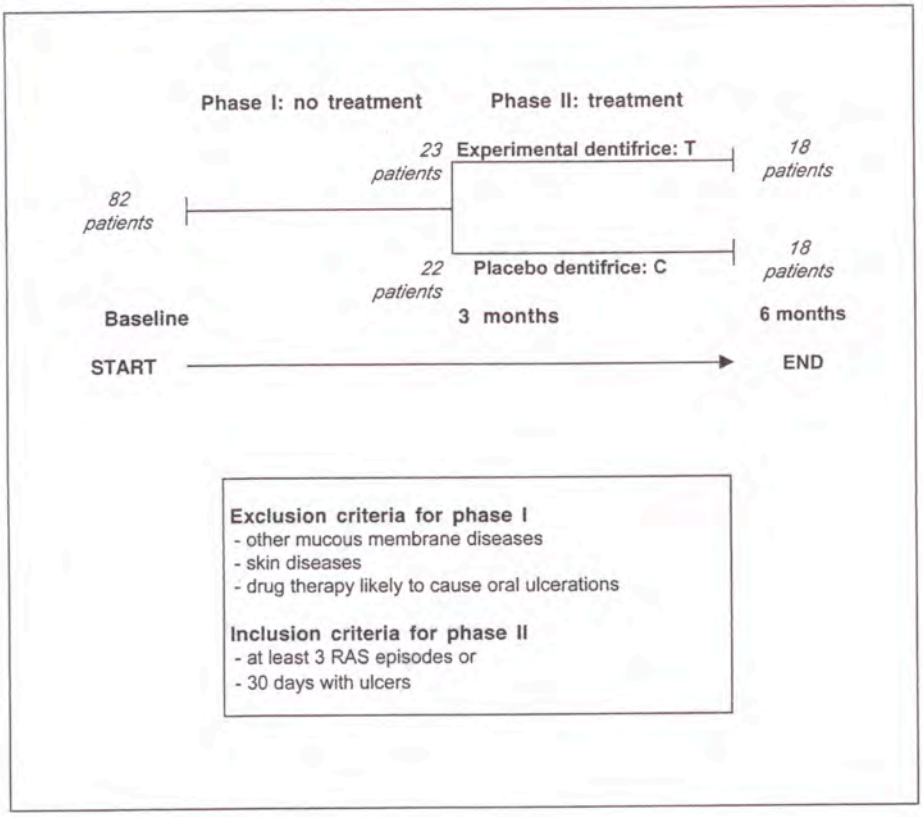


Fig 2 Study design.

Experimental and Placebo Dentifrices

The participants assigned to the test (T) group received the experimental dentifrice, whereas the individuals assigned to the control (C) group received placebo toothpaste. The test product was an experimental dentifrice containing water, glycerol, orange terpenes, polyoxyethylene, sorbitan monostearate, alkyl imidazolinium dicarboxylate, silica, carboxymethylcellulose, E466, liquorice, xylitol, methyl parahydroxybenzoate E218, and sodiumfluoride 0.24% (Sinaftin, Dental Therapeutics AB, Nacka, Sweden). The placebo dentifrice was an inert toothpaste (Pepsodent Super Fluor, Unilever AB, Helsingborg, Sweden) given to the participants in tubes identical to the experimental ones. The individuals were instructed to use the dentifrices as normal toothpaste for the following three months of the trial and not to use water during the procedures until the end of the tooth brushing session. Because of lack of abrasive compounds in the experimental dentifrice, all the individuals were instructed to brush the teeth once weekly with an abrasive toothpaste (Denivit, Barnängen AB, Ekerö, Sweden).

Statistics

The Wilcoxon Signed rank test was used for the data analysis to detect significant differences between phase I and II within the same group. The Mann-Whitney U-test was used for the detection of significant differences between T and C groups. The Chi-Square test was used for the detection of significant differences between test and control groups for improvements of the symptoms above 50%. The level of statistical significance was defined as $p < 0.05$.

The investigation was approved by the Ethical Committee of the University of Göteborg. The study was carried out according to the recommendation of the Helsinki declaration.

RESULTS

Out of the 82 participants enrolled in phase I, only 45 participants met the inclusion criteria for phase II. Twenty-three patients were assigned to the experimental group and 22 to the placebo group.

Eighteen participants from each group completed the study. Five test and four control participants dropped out from the study, two from each group reporting severe pain due to RAS. The remaining five participants did not comply because of loss of interest, familiar problems or other causes independent from the investigation.

The participants were generally healthy, with a RAS history ranging between 2 and 40 years. Previous RAS treatment modalities included use of different toothpastes, local chlortetracycline, antivirals, hydrocortisone, chlorhexidine gluconate rinses and Longovital tablets. These treatments gave unpredictable results according to the participants. None of the patients enrolled in the study was smoking with the exception of one participant in the control group. No differences between control and test groups could be detected with regards to general health, predisposing factors to RAS, RAS experiences or previous treatment modalities. Participants in the C group claimed more often the occurrence of RAS in other family members than the participants in the T group. The data obtained from all the 36 participants who completed the study are shown in Table 1.

No statistically significant difference between T and C groups was present at the beginning of phase II for any of the studied parameters (Table 2). The number of days with ulcers during phase I was 49 (± 22) for C and 46 (± 23) for T (Table 1). During phase II the corresponding figures were 42 (± 27) for C and 32 (± 31) for T. The average number of RAS episodes during phase I was 3.2 (± 1.4) for C and 2.9 (± 1.1) for T. During phase II the corresponding figures were 2.8 (± 1.8) and 2.0 (± 1.5) respectively. The daily discomfort reported (VAS/days) was 2.0 cm (± 1.1) for C and 1.6 cm (± 1.0) for T during phase I; 1.8 cm (± 1.7) for C and 1.1 cm (± 1.2) for T during phase II.

The Wilcoxon statistic test detected a significant difference between phase I and phase II for the T group regarding number of days with ulcers ($P = 0.025$) and VAS/days ($P = 0.010$), with a significant reduction of RAS self-reported features and painful symptoms during phase II (Table 2).

No significant difference was detected between phase I and phase II for the C group for any of the studied parameters, although a market reduction in RAS self-reported features was seen in phase II. No significant difference was detected by Mann-Whitney test between the T and C groups at the end of the study for any of the studied parameters.

For half of the participants using the experimental dentifrice, the number of days with ulcers and the related discomfort (VAS/days) was reduced by more than 50% in phase II (Fig 3, 4). The same result was achieved for only 17% of the placebo group.

When a 50% reduction of the symptoms was used as a cut-off point, a statistically significant difference ($p = 0.034$) at the end of phase II was detected between the T and C groups with regards to the discomfort related to RAS (VAS/days).

The number of participants who showed a 50% reduction in the number of RAS episodes during phase II was similar for the T and C groups (Fig 5). A reduction in the number of ulcers was detected for both groups. This reduction was similar for almost all the ulcer sizes (Table 1).

DISCUSSION

The objectives of RAS treatment are to promote ulcer healing and to prevent ulcer pain and recurrences (Ship et al, 2000). Although there is a wide range of treatments that provide different remedy to RAS (Graykowski and Kingman, 1978; Lehner et al, 1976; Miller et al, 1978; Pimlott and Walker, 1983; Hunter and Addy, 1987; Matthews et al, 1987), topical corticosteroids remain the mainstay of treatment. Corticosteroids reduce symptoms, but ulcers recur after cessation (Porter et al, 1998). Investigation and treatment for underlying systemic diseases are recommended (Ship et al, 2000), as RAS is also associated with diseases such as Behçet's syndrome, Crohn's disease, ulcerative colitis, food allergies and vitamin deficiencies (Scully and Porter, 1989).

The use of toothpaste for the prevention of RAS would have clear advantages in terms of administration and patient compliance since it is a daily routine, without known side effects. The concept of the use of toothpastes for treating RAS is not new, but the results from available studies are contradictory (Herlofson and Barkvoll, 1996; Chahine et al, 1997; Skaare et al, 1997). The use of toothpastes containing the enzymes amyloglucosidase and glucoseoxidase, which activate the antibacterial lactoperoxidase system in saliva, has been suggested to reduce the severity of RAS (Koch, 1981). Others arrived to the opposite conclusion as their results demonstrated that severity and incidence of RAS were not affected in comparison to a placebo group

Table 1 Data from phase I and phase II

			n Days		n episodes		VAS scale				Aphthae size A		B		C		D		E		VAS/days	
G	Age	Gen	I	II	I	II	I Max	I Aver	II Max	II Aver	I	II	I	II	I	II	I	II	I	II	I	II
C	48	F	35	22	3	1	5,5	1,6	3,9	2,4	3	1	7	2	4	2	2	0	0	0	0,62	0,57
C	70	M	27	9	4	2	8,1	5,6	7,6	5,4	12	6	4	1	2	0	1	0	2	0	1,45	0,53
C	57	M	79	62	1	3	5,4	3,2	6,1	3,6	0	1	5	4	5	4	1	2	0	0	1,79	2,41
C	18	F	40	64	3	3	8,0	3,4	10,0	6,4	0	0	1	0	1	4	2	1	0	2	1,49	4,47
C	31	F	37	49	4	8	7,0	4,3	9,1	3,7	1	12	4	5	3	2	0	0	0	0	1,73	2,00
C	40	F	23	24	3	3	5,0	2,6	3,9	2,0	1	0	3	1	1	1	0	0	0	0	0,66	0,53
C	20	M	51	28	7	5	6,6	3,3	6,6	3,3	0	0	2	1	5	7	2	3	6	2	1,87	1,02
C	38	M	27	33	3	3	6,8	3,6	6,9	4,2	0	0	4	1	3	0	0	3	0	0	1,07	1,51
C	25	M	27	0	3	0	5,4	2,5	0,0	0,0	1	0	2	0	4	0	1	0	0	0	0,75	0,00
C	39	M	79	75	3	4	9,9	4,5	5,6	3,1	5	10	6	9	7	1	0	0	0	0	3,90	2,59
C	32	M	65	70	2	4	7,0	2,1	3,0	1,6	4	15	5	5	5	3	1	0	0	0	1,52	1,22
C	30	M	91	86	1	1	9,8	3,7	9,1	3,2	5	5	11	11	11	12	8	4	0	0	3,69	3,04
C	46	F	44	45	3	3	10,0	6,3	7,7	3,8	0	0	5	4	1	1	0	0	0	0	3,04	1,92
C	26	F	40	28	3	3	9,2	5,2	7,4	5,0	0	1	6	3	2	2	5	2	0	0	2,28	1,52
C	44	M	40	19	4	2	6,8	2,7	5,7	1,9	1	0	1	0	3	1	2	1	0	0	1,19	0,40
C	34	F	89	91	2	1	10,0	4,6	10,0	7,2	1	0	4	1	4	3	5	2	2	1	4,50	7,16
C	32	M	43	29	3	2	9,0	4,2	7,4	3,1	2	2	3	5	1	2	3	4	1	0	2,00	0,86
C	11	M	38	17	5	2	9,0	4,3	9,1	5,3	0	0	1	0	4	2	1	1	0	0	1,74	0,98
M	36		49	42	3,2	2,8	7,7	3,8	6,6	3,6	2	2,9	4,1	2,9	3,7	2,6	1,9	1,3	0,6	0,3	2,0	1,8
SD	14		22	27	1,4	1,8	1,8	1,2	2,6	1,8	3,03	4,7	2,5	3,2	2,5	2,9	2,2	1,4	1,5	0,7	1,1	1,7
T	24	M	17	13	3	2	7,9	3,2	6,6	3,7	0	0	1	0	3	2	0	0	0	0	0,61	0,53
T	34	F	42	35	5	3	3,5	2,2	6,0	2,8	0	1	8	4	6	3	0	0	2	0	1,00	1,09
T	56	F	21	0	4	0	5,8	3,2	0,0	0,0	8	0	5	0	5	0	1	0	0	0	0,68	0,00
T	45	M	65	73	3	5	8,4	3,1	7,1	3,0	0	3	7	4	5	5	4	4	1	2	2,07	2,40
T	9	F	17	4	3	3	9,7	5,6	8,3	7,2	1	0	6	5	2	1	1	0	0	0	1,05	0,32
T	36	F	57	85	3	2	8,1	5,2	5,8	3,3	5	2	20	17	17	19	5	5	1	1	3,27	3,07
T	30	M	63	91	3	1	7,7	1,9	9,2	4,3	12	17	2	7	4	5	0	0	1	4	1,32	4,25
T	35	F	28	12	2	1	8,4	4,1	7,8	5,2	0	1	0	0	2	0	1	1	1	0	1,27	0,68
T	40	F	29	0	3	0	2,8	1,3	0,0	0,0	0	0	1	0	3	0	0	0	0	0	0,40	0,00
T	27	M	35	0	1	0	4,9	2,2	0,0	0,0	1	0	4	0	10	0	0	0	0	0	0,83	0,00
T	25	F	34	7	3	2	10,0	4,1	1,5	0,8	1	2	4	0	2	1	0	0	1	0	1,53	0,06
T	51	F	64	40	5	2	8,6	4,0	7,9	3,8	1	1	6	5	5	2	0	1	0	0	2,83	1,69
T	64	F	89	82	1	1	3,4	3,7	2,4	3,6	0	0	0	0	0	0	1	1	0	0	2,38	1,73
T	62	F	62	36	4	2	7,5	4,9	8,3	6,6	2	0	9	2	6	5	3	3	0	0	3,32	2,63
T	38	F	58	28	3	2	10,0	5,1	8,7	3,1	0	0	4	1	3	2	2	1	1	0	3,27	0,94
T	45	F	29	6	3	1	7,3	2,4	2,5	1,4	2	0	1	1	2	0	0	0	0	0	0,75	0,09
T	23	F	86	27	2	4	6,7	2,8	5,6	2,6	0	1	4	2	8	2	1	0	0	0	2,60	0,77
T	25	F	27	32	2	5	2,6	1,7	3,4	1,4	2	0	5	2	0	6	1	0	0	0	0,50	0,48
M	37		46	32	2,9	2	6,9	3,4	5,1	2,9	1,9	1,6	4,8	2,8	4,6	2,9	1,1	0,9	0,4	0,4	1,6	1,2
SD	15		23	31	1,1	1,53	2,5	1,3	3,3	2,1	3,3	4,0	4,6	4,2	4,0	4,5	1,5	1,5	0,6	1,0	1,0	1,2

G: group. C = control, T = test.
Gen: Gender. F = female, M = Male
n Days: number of days with ulcers. I = during phase I; II = during phase II
n episodes: number of episodes of RAU attack
VAS scale, Max: highest value of discomfort reported; Aver: mean value of discomfort reported in case of RAU episode.
VAS/days: daily discomfort during the 90-day phase.
M: mean value
SD: standard deviation

Table 2 Statistical analysis with Wilcoxon and Mann-Whitney tests

	Group C Within group (Wilcoxon)	Between groups (Mann-Whitney)	Group T Within group (Wilcoxon)	
phase I		p = 0.58		phase I
Days	p = 0.07		p = 0.02*	Days
phase II		p = 0.25		phase II
phase I		p = 0.70		phase I
Episodes	p = 0.34		p = 0.07	Episodes
phase II		p = 0.16		phase II
phase I		p = 0.94		phase I
VAS/Days	p = 0.11		p = 0.01*	VAS/Days
phase II		p = 0.14		phase II

* Statistically significant difference with a 95% probability

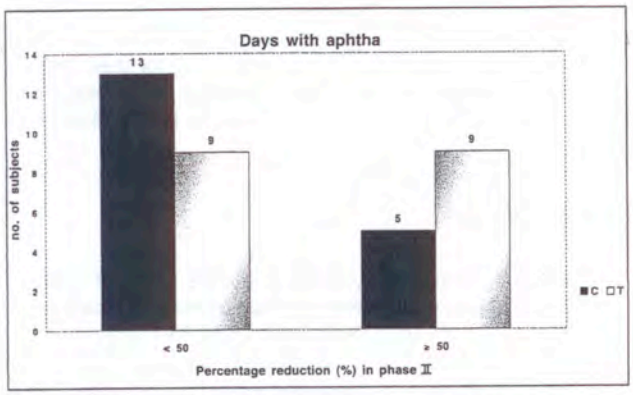


Fig 3 Number of patients showing reduction of the days with aphthae in phase II. Cut-off point: 50% reduction. C: control group. T: test group.

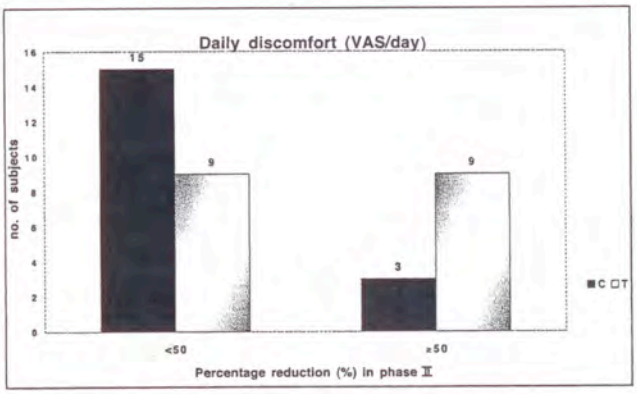


Fig 4 Number of patients showing reduction in daily discomfort (VAS/days) in phase II. Cut-off point: 50% reduction. C: control group. T: test group.

(Donatsky et al, 1983; Henricsson and Axéll, 1985).

Although several other approaches for RAS treatment have been recommended, only a few controlled studies have shown improvements over a placebo treatment. In view of the data from the present study, a strong placebo effect can be expected and therefore future investigations on RAS treatment should always consider the inclusion of a control group.

In the present investigation, the data were obtained by requesting the patients to self-report the ulcer position and size. The reliability of such a technique can be partly questioned. However, in a previous investigation in which the Patient Daily Record chart was developed, the authors reported a very good correlation between the patients' reports and the actual observation made by the investigators, who checked the patients weekly (Graykowski and Kingman, 1978).

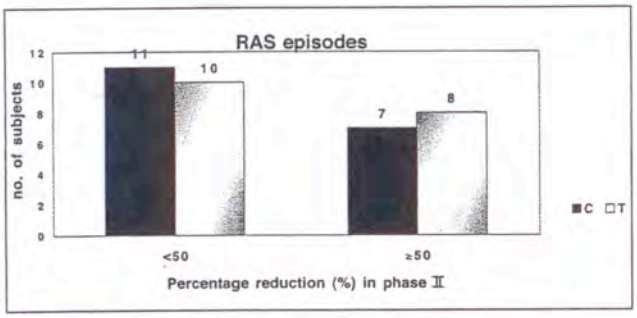


Fig 5 Number of patients showing reduction in the number of RAU episodes in phase II. Cut-off point: 50% reduction. C: control group. T: test group.

In the present study, a comparison between the C and the T group did not reveal any statistical differences. But, comparison between phase I and phase II showed a clear difference, which reached a statistical significance for the T group in two of the studied variables. The differences were not impressive from a clinical point of view. A reduction of 30% vs 15% for the placebo group in the number of days with ulcers may be of limited value for the patient. A reduction of VAS/days, proved to be statistically significant, but the benefit of this improvement from the patient perspective may also be insignificant.

Of more clinical significance is the observed difference between T and C when the days with RAS for parts of the two groups were compared. Half of the T showed a 50% reduction in days with ulcers compared to 17% of the C. It appears that the use of the experimental dentifrice strongly improved the conditions for a proportion of the treated patients. Thus, it seems that there were two types of patients in the study groups who responded rather differently to the dentifrice. Unfortunately, it was not possible to identify the group of patients who responded beneficially to the treatment from data obtained during the primary examination.

It is well known that smokers hardly ever contract RAS and that cessation of smoking may entail ulcers. The reason for this is not known, but is has been speculated that smoke contains substances that alter the oral epithelium in a way that prevents the ulcers from appearing. It is possible that the dentifrice used in the present study has a similar mode of action as smoking. During phase II, some patients noticed that the use of the dentifrice caused a weak burning sensation during the first days of the treatment. It is possible that this symptom reflects an adaptation of the oral epithelium to some of components in the dentifrice resulting in a prevention of ulcers.

In light of the fact that half of the patients in the test group showed a clinically significant improvement, the treatment approach used in the present investigation appears to be a beneficial strategy for prevention of RAS symptoms in some patients and the study hypothesis is accepted.

A dentifrice is advantageous because it is used as part of a daily low-cost routine and without any known collateral effects. Thus, the experimental toothpaste examined in the present investigation may be used as an initial treatment strategy for reduction of symptoms related to RAS.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to the following people: Mrs Marita Nilsson, Klinik för Oral Medicin, Göteborg for the study administration; Sjukhustandläkare Gertrud Malmestrand, Kliniken för sjukhustandvård, Falun; Sjukhustandläkare Ulf Mattsson, Kliniken för käkkirurgi och sjukhustandvård, Karlstad; Klinikchef Michael Thunfors, Kliniken för Parodontologi och oral medicin, Vänersborg; and Docent Leif Helldén, Kliniken för Parodontologi och oral medicin, Vänersborg for their help in recruiting and following the subjects involved in the trial. This study was supported by Dental Therapeutics, Nacka, Sweden.

REFERENCES

1. Chahine L, Sempson N, Wagoner C. The effect of sodium lauryl sulphate on recurrent aphthous ulcers: a clinical study. Compend Contin Educ Dent 1997;18:1238-1240.
2. Donatsky O, Wooraae N, Schiödt M, Johnsen T. Effect of Zendium toothpaste on recurrent aphthous stomatitis. Double-blind clinical trial with cross-over. Scand J Dent Res 1983; 91:376-380.
3. Fakhry-Smith S, Din C, Nathoo SA, Gaffar A. Clearance of sodium lauryl sulphate from the oral cavity. J Clin Periodontol 1997;24:313-317.
4. Fridh G, Koch G. Effect of a mouthrinse containing amyloglucosidase and glucose oxidase on recurrent aphthous ulcers in children and adolescents. Swed Dent J 1999;23:49-57.
5. Graykowski EA, Kingman A. Double-blind trial of tetracycline in recurrent aphthous ulceration. J Oral Pathol 1978;7: 376-382.
6. Healy CM, Paterson M, Joyston-Bechal S, Williams DM, Thornhill MH. The effect of a sodium lauryl sulphate-free dentifrice on patients with recurrent oral ulcerations. Oral Dis 1999;5:39-43.
7. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouthrinse or Zendium dentifrice. Acta Odontol Scand 1985;43:47-52.

8. Herlofson BB, Barkvoll P. The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers. Acta Odontol Scand 1996;54:150-153.
9. Hoogendoorn H, Piessens JP. Treatment of aphthous patients by enhancement of the salivary peroxidase system. J Oral Pathol 1987;16:425-427.
10. Hunter L, Addy M. Chlorhexidine gluconate mouthwash in the management of minor aphthous ulcerations. A double-blind, placebo-controlled cross-over trial. Br Dent J 1987;162: 106-110.
11. Koch G. Effekt av enzymtandkräm på recidiverande aphthe. Tandläkartidningen 1981;73:264-272.
12. Lehner T, Wilton JMA, Ivanyi L. Double-blind crossover trial of levamisole in recurrent aphthous stomatitis. Lancet 1976; 2:926-929.
13. Matthews RW, Scully CM, Levers BGH. Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1987;63:189-191.
14. Miller MF, Silvert ME, Laster LL, Green P, Ship II. Effect of levamisole on the incidence and prevalence of recurrent aphthous stomatitis. A double-blind clinical trial. J Oral Pathol 1978;7:387-392.
15. Pimlott SJ, Walker DM. A controlled clinical trial of the efficacy of topically applied fluocinonide in the treatment of recurrent aphthous ulceration. Br Dent J 1983;154:174-177.
16. Pocock SJ. Clinical trials: a practical approach. Chichester: John Wiley & Sons 1983.
17. Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. Crit Rev Oral Biol Med 1998;3:306-321.
18. Scully C, Porter SR. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. J Oral Pathol Med 1989;18:21-27.
19. Ship JA, Chavez EM, Doerr PA, Henson BS, Sarmadi M. Recurrent aphthous stomatitis. Quintessence Int 2000;31: 95-112.
20. Skaare A, Kjaerheim V, Barkvoll P, Rolla G. Skin reactions and irritation potential of four commercial toothpastes. Acta Odontol Scand 1997;55:133-136.