Treatment of recurrent aphthous ulcers with Aureomycin® mouth rinse or Zendium® dentifrice

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Clinical trials with a cross-over double-blind technique were undertaken to test chlortetracycline (Aureomycin®) and the enzyme-containing dentifrice Zendium® with regard to therapeutic effects on recurrent aphthous ulcers. Aureomycin was found to reduce the number of ulcers and diminish pain when compared with placebo. When groups of patients treated with Zendium and placebo dentifrice, respectively, were compared, no statistically significant difference could be demonstrated. However, when the pH value of Zendium was stepwise changed from 5.9 to 6.8, an increased fraction of patients reported complete relief from pain and ulcer(s) during the trial periods. □ *Aphthous ulcer; chlortetracycline; enzymes; Zendium®*

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Recurrent aphthous ulcers (RAU) are frequent lesions of the oral mucosa, appearing at least once in a 2-year period in about 18% of a general Swedish adult population (1). The lesions are somewhat more frequent among females than among males, are most frequent in younger age groups, and decrease steadily with age (2).

The etiology of RAU is obscure. Autoimmunity to oral mucosa antigens and hypersensitivity to oral streptococci have been reported to be a part of the pathogenesis (3–7).

Remedies such as corticosteroids and antibacterial agents (6, 8–16) have been used to cure or to give relief to patients with RAU. Among these, tetracyclines have shown the best effect (8, 12, 13).

In recent years patients have experienced relief of symptoms by using the enzyme-containing dentifrice Zendium® (17). The enzymes amyloglucosidase and glucose oxidase are thought to produce small amounts of hydrogen peroxide, which stimulates the antibacterial lactoperoxidase-thiocyanate system in saliva (17). By suppressing streptococci, the dentrifrice should then give relief to patients with RAU. This has been supported by results in some reports (17, 18). On the other hand, in a recent study no obvious effect could be demonstrated (19).

The aim of the present investigation was to assess the therapeutic effect of chlortetracycline (Aureomycin®) and the enzyme-containing dentifrice Zendium. In addition, the effect of Zendium at various pH values was also evaluated, since the activity of enzymes is related to the pH value.

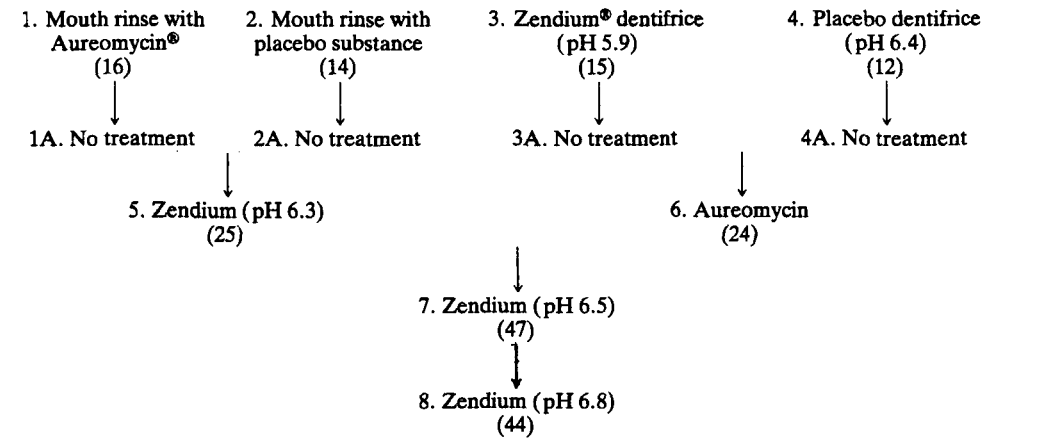
Materials and methods

Patients referred to the Department of Oral Surgery and Oral Medicine, School of Dentistry, Malmö, who had had RAU at least once during the last 3 consecutive months were selected for the study.

Clinical criteria for RAU were demarcated, painful ulcer(s) on the lining, nonkeratinized oral mucosa. They were covered by a thin grey or yellowish fibrinous coating and surrounded by a red inflammatory zone. There was a history of recurrence, and the healing time for each ulcer did not exceed 2 weeks.

Altogether 57 patients, 13 men and 44 women, participated in the study. Mean age was 43.2 years, and age range was 18–76

Table 1. Design of the investigation. Numbers within parentheses comprise number of patients



years. They were randomly divided into four groups (1–4, Table 1). With a double-blind technique the effect on RAU of mouth rinse with Aureomycin was tested in groups 1 and 2 and the effect of Zendium in groups 3 and 4.

Mouth rinse with Aureomycin was carried out with 0.25 g Aureomycin dissolved in 10 ml of water. The placebo substance consisted of herbs dissolved in water, the taste and color of which were very similar to those of Aureomycin. The enzyme-containing dentifrice used was Zendium, containing the enzymes amyloglucosidase and glucose oxidase and 1000 ppm of sodium fluoride. The pH value was 5.9. The placebo dentifrice was a commercial one without enzymes with a pH value of 6.4 and also containing 1000 ppm of sodium fluoride.

The patients were instructed how to use mouth rinses and dentifrices. Thus, mouth rinses were recommended for 1 min four times a day during 4 consecutive days. After that there was a rinse-free period of 1 week, and then, if ulcers were still present, a new period of rinses for 4 days was instituted. The use of dentifrice was recommended twice a day, morning and evening. The patients were instructed to use very little water, and no food intake was permitted within ½ h after they had brushed their teeth. No other toothpaste was allowed during the trial period, which comprised 10 weeks. After this there was a treatment-free period of 10 weeks (indicated by 1A–4A in Table 1).

The study was then continued with a cross-over technique. Patients who had initially used mouth rinses (groups 1 and 2) were instructed to try Zendium (group 5, Table 1) and those who had previously used dentifrice (groups 3 and 4) were recommended to use Aureomycin (group 6, Table 1). The pH value of Zendium was increased to 6.3 at this stage of the study, which continued for 10 weeks. During another two periods of 10 weeks each, all patients were given Zendium with further increased pH values of 6.5 and 6.8, respectively (groups 7 and 8, Table 1).

The patients were given pretyped forms to fill out during each stage of the investigation. They were instructed to record days when pain and/or ulcers were present. The forms were collected after each stage and new ones administered. After each stage, the patients were asked whether they experienced any relief of discomfort. A few patient dropouts were encountered at all stages of the investigation (Table 1), but this was not remarkably prevalent for any particular stage. The reasons for dropping out were in all but two cases various practical problems in participating in the examination (long distance to the clinic for examination, change of residence). For two of the patients, the collected data were incomplete.

Table 2. Days with pain or ulcer(s)

Group	No. of patients examined	Pain, days, %	Ulcer(s), days, %
1	16	10	23
1A	15	34	48
2	14	39	46
2A	13	42	51
3	15	40	57
3A	15	38	57
4	12	27	40
4A	10	22	39
5	25	35	45
6	24	15	27
7	47	31	42
8	44	25	34

Differences between groups were calculated by means of chi-square tests with Yates' correction, and both unpaired and paired *t* tests when found appropriate. *P* values less than 0.05 were regarded as significant.

Results

The lowest frequencies of days with ulcers and with pain were encountered for those groups of patients which had used mouth rinses with Aureomycin (groups 1 and 6, Table 2). A slight reduction as compared with the average values was also seen for the group that had used Zendium dentifrice with pH 6.8 (group 8). Paired *t* tests between all possible test groups (Table 3) also showed a significant reduction of days with pain or ulcer(s) in the groups using Aureomycin when compared with the results from the placebo and Zendium groups. No relief could be demonstrated for the placebo substances. When groups 5 and 8, using Zendium with pH values of 6.3 and 6.8, respectively, were compared, the frequency of days with pain was significantly reduced in group 8 ($P < 0.01$).

During the various test periods of about 10 weeks some groups of patients experienced complete relief from pain and/or ulcer(s) (Table 4). While this occurred only exceptionally for the groups using placebo substances (groups 2 and 4), it was a relatively frequent finding in groups using Aureomycin (groups 1 and 6) and Zendium (groups 3, 5, 7, and 8). The best result in this context was noted for the group using Zendium with the highest pH value (6.8; group 8). In this group 13.6% of the patients reported that they had no ulcer(s) and 20.5% that they had no pain

Table 3. Paired *t* tests between some different test groups with reference to registered number of days with pain or ulcer(s) during each trial period of 10 weeks

		Pain			Ulcer(s)		
Group	No.	Mean values	*t* values	Probability	Mean values	*t* values	Probability
1 vs 1A	15	11.1–30.4	4.60	<0.001	24.5–47.7	4.17	<0.001
2 vs 2A	13	40.1–41.9	0.23	n.s.	48.1–51.0	0.35	n.s.
3 vs 3A	15	40.0–38.4	0.23	n.s.	56.6–57.2	0.07	n.s.
4 vs 4A	10	28.7–21.9	1.47	n.s.	42.6–38.7	0.68	n.s.
5 vs 8	22	34.8–24.0	3.16	<0.01	46.0–35.3	2.06	n.s.
6 vs 7	22	15.8–31.0	2.84	<0.01	29.6–43.3	2.43	<0.05

Table 4. Number and frequency of patients completely without pain or ulcer(s) during each 10-week test period

Group	No. of patients examined	Without pain		Without ulcer(s)	
		No.	%	No.	%
1	16	2	12.5	0	0
2	14	0	0	0	0
3	13	1	7.7	0	0
4	12	0	0	1	8.3
5	25	2	8.0	2	8.0
6	24	2	8.3	1	4.2
7	47	5	10.6	5	10.6
8	44	9	20.5	6	13.6

during the trial period. However, there were no statistically significant differences between any of the groups.

When asked about their general opinion concerning the effect on discomfort at different stages of the investigation, the patients gave the answers summarized in Table 5. Mouth rinses with Aureomycin (groups 1 and 6) was the only regimen that differed significantly from the others, confirming the positive results for this treatment revealed in the paired *t* test (Table 3).

Discussion

In the present investigation the relieving effect of chlortetracycline (Aureomycin) on RAU has been demonstrated, and this is in accordance with the results from the study by Guggenheimer et al. (13). No statistically significant effect could be shown for Zendium dentifrice. That is in agreement with the findings by Donatsky et al. (19). However, it is contradictory to the results of Koch (18). One explanation for the discrepancy could be that Koch did not use any control groups, and thus, mainly a placebo effect may have been recorded. Thus, in the present study 3 out of 22 (14%) obtained substantial relief, and 10 out of 22 (45%) experienced a clear or slight improvement from placebo. Another explanation could be that Koch used a dentifrice with a higher pH value than the one we used. The pH value seems to be of some importance with regard

Table 5. Experience of the patients after treatment in different stages of the investigation. A. Pooled: a) no symptoms left, clearly improved, and b) slightly improved, no change, worse. B. Pooled: a) no symptoms left, clearly improved, slightly improved, and b) no change, worse

Groups tested	No. of patients examined	A		B	
		Chi-square value*	Probability	Chi-square value*	Probability
1 vs 2	14–10	5.02	<0.05	5.53	<0.05
2 vs 6	10–23	6.44	<0.05	6.47	<0.05
3 vs 4	13–12	0.59	n.s.	0.04	n.s.
4 vs 5	12–25	1.09	n.s.	0.04	n.s.
4 vs 7	12–46	0.98	n.s.	0.30	n.s.
4 vs 8	12–43	0.99	n.s.	0.00	n.s.
5 vs 6	25–23	2.13	n.s.	0.70	n.s.
7 vs 8	46–43	0.00	n.s.	0.81	n.s.

* Chi-square tests with Yates' correction.

to the clinical effect of Zendium on RAU. Zendium with a pH of 6.8 gave somewhat better results than Zendium with lower pH values. This was especially so when the results of total absence of ulcers and/or pain was evaluated (Table 4). Thus, there seems to be some effect of Zendium, even though this does not show up at statistical testing between groups. Alternatively, the relief could be assigned to a long-standing effect, since Zendium at pH 6.8 was administered after several months of previous treatment with Zendium with lower pH values. However, the study by Donatsky et al. (19) did not point to such a mechanism.

In the present study no side effects were encountered. This is contradictory to the experience of Guggenheimer et al. (13), who referred to common side effects such as allergic reactions and flush when using Aureomycin. The reason for the disparity in this context could be that Guggenheimer et al. used mouth rinses for somewhat longer periods, 1 week, than were used in the present study, which consisted of rinsing for 4 days with at least a 1-week interval between treatment periods. The risk of, for instance, a candidal infection might then differ.

In conclusion, the present study has shown that mouth rinse with Aureomycin is an efficient local treatment of RAU and that there is no statistically significant difference with regard to relief with RAU between groups using the enzyme-containing dentifrice Zendium and a placebo dentifrice. However, Zendium with a relatively high pH value (6.8) seems to give substantial relief to some patients. In future studies of Zendium and RAU, it may therefore be of interest to evaluate further the effect and importance of various pH values.

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