Effectiveness of a medicament containing silicon dioxide, aloe, and allantoin on aphthous stomatitis

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This research protocol was designed to test the effectiveness of a gel containing silicon dioxide, aloe vera, and allantoin in the healing of recurrent aphthous ulcers. The subjects were patients with histories of developing multiple ulcers on the oral mucosa during a 3-to-4-month period. The parameters used to evaluate healing were number of lesions during a 3-to-4-month period, length of the interval between ulcers, size of ulcers, and pain from ulcers. An approach was used in which data were accumulated from diaries maintained by the subjects throughout the study intervals. Because 3 active substances were present in the gel, a preliminary study (study I) was performed to indicate the effect of each active substance and each combination. In this phase, different combinations of the substances were compared with the use of the 2 factorial experimental design. The results of this study demonstrated that statistical differences in the durations of lesions (P = .017) were present when all 3 substances were included in the gel. In the next study (study II), which was initiated to test the results of study I, additional subjects were divided into 2 groups; one used a control gel with silicon dioxide, and the other a gel with all 3 active substances. Study II found no statistical differences in the parameters when the 2 groups were compared. In study III, a modified crossover design was used with the subjects of study II, and a significant difference was found in lesion-free intervals (P = .0335) and length of time for the study (P = .0001). The differences in lesion intervals may have been caused by the differences in study length. Alteration in the occurrence of aphthous ulcers was demonstrated by the reduction in numbers of lesions in study I and by the increase in length of intervals between lesions in study III. However, a consistent pattern was not present; this indicated a lack of effect of the gel on aphthous ulcers. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:550-6)

Aphthous stomatitis is a common disease of the oral mucosa. There are 3 types, but approximately 80% of the lesions belong to the type designated minor aphthous stomatitis. These lesions are generally less than 1 cm in diameter, occur in groups of 1 to 5, and heal in approximately 7 to 10 days.1 The lesions appear localized on nonkeratinized mucosal surfaces: buccal and labial mucosa, lateral and ventral aspects of the tongue, the floor of the mouth, and soft palate and oropharyngeal mucosa. With respect to prevalence, the lesions occur more often at an earlier age and when the family history is positive.2,3 The cause of the disease remains as yet unclear. Possible viral, bacterial, and immunologic mechanisms have been implicated, as have deficiencies of vitamin B12, folic acid, and serum iron.

Most of the evidence suggests that aphthous stomatitis is a noninfectious inflammatory mucosal disease.1 Therefore, over the years, an empiric approach has been taken for therapeutic management. Among the treatment modalities that have been used are the following: tannic acid in denatured alcohol, camphor, and phenol; 10% carbamide peroxide; and a combination of copper sulfate, iodine, potassium iodide, and alcohol. Many clinical trials have suggested that topical or systemic corticosteroids provide the best long-range treatment results.1

The medicament to be tested in this study was a gel containing the following ingredients: aloe vera extract (0.125%), derived from the aloe barbadensis miller plant; allantoin (0.35%), an active skin protectant substance; and an abrasive material called silicon dioxide (abrasive 113), which is used in many toothpastes. These substances have been used to treat various noninfectious inflammatory ulcers. Silicon dioxide dilutions have been shown to increase wound healing in experimental wounds in the ears of mice.4 Aloe vera is a white-to-tan-colored powder that has been used in cosmetic bases and other products used on the skin. Derivatives of this substance have been used in the treatment of burns, skin ulcerations,5 skin lesions from radiation burns,6 and frostbite,7 as well as as an antibiotic agent. Aloe vera may act directly or indirectly to activate collagen production by way of mannose-6-phosphate binding to receptors of fibroblasts8 or by hydrocortisone acetate suppression of
Wound healing. Aloe vera has been shown to improve healing with enhanced epithelialization and rapid formation of granulation tissue in burn wounds. Aloe has been shown to reduce vascularity by 50% and to stimulate fibroblasts in repair.

Allantoin was discovered by Vanquel and Buniva in 1800 and synthesized by Grimax in 1876. It is a white, nontoxic, nonirritating, nonallergenic powder that has been reported to promote epithelial stimulation and decrease pain. Allantoin is a degradation product of purines in the body and is found in the peripheral blood.

The purpose of this research program was to determine the effectiveness of a gel containing silicon dioxide, aloe vera, and allantoin when used in the treatment of aphthous ulcers. The rationale is that these active substances improve the healing of noninfectious lesions on mucous membranes. The approach was to test the effectiveness of combinations of the active substances with a small sample, then evaluate the effective combinations in second and third studies with larger sample sizes. Because the duration of each study was set at 3 to 4 months to obtain accurate histories of lesions, the technique of obtaining data from subjects' personal diaries, kept during the study, was used. The parameters used to demonstrate effectiveness included ulcer duration, interval between lesions, size, pain, and number of ulcers during the study period. The hypothesis stated that treatment of aphthous ulcers with aloe vera, silicon dioxide, and allantoin, either separately or in combination, would affect the number and duration of lesions, the interval between lesions, and the size and pain of lesions.

MATERIAL AND METHODS

Study 1

Study 1 was a double-blind study that included 40 subjects who responded to advertising in local newspapers. The subjects had an average recurrence of aphthous ulcers of at least twice every 2 months, and an ulcer was present in each subject at the time of baseline examination. The age range was 18 to 60 years, and all subjects were in good health according to the definition of class 1 in the guidelines of the American Society of Anesthesiologists. Female patients could not be pregnant or breast-feeding. At the preliminary examination, biographic data, health history, and history of experiences of oral ulcers were obtained, and an oral examination of the lesions was performed.

The diagnosis of aphthous ulcers was based on (1) a history of recurring ulcers on the oral mucosal surfaces that were painful and healed without scarring and (2) clinical appearance and location of a distinct ulcer on the oral mucosal surface, with a surrounding erythema, ragged borders, and a yellow-white covering on the ulcer. If the lesions were diagnosed as aphthous stomatitis minor and baseline data was within the acceptance criteria, the subject was accepted into the study. 40 subjects were accepted all together. The aims of the study were explained to each subject, and after answering all questions, the subject was asked to sign an appropriate consent form.

Once the subject was accepted into the study, the examiner indicated the location of the lesion on an oral cavity map, noted the date, and assigned a number to the lesion. When the lesion was healed, as determined by the subject, the date was recorded in the log. In addition, the lesion's size was evaluated daily through use of a 5-level scale. The score was based on the diameter of the lesion, which included the ulcerated portion and the red halo, and was defined as follows:

1 = lesion diameter 2 mm or less
2 = lesion diameter greater than 2 mm but no greater than 4 mm
3 = lesion diameter greater than 4 mm but no greater than 6 mm
4 = lesion diameter greater than 6 mm but no greater than 8 mm
5 = lesion diameter greater than 8 mm.

The degree of pain from the lesion was evaluated daily and indicated by means of the following scale:

0 = no discomfort
1 = mild discomfort
2 = moderate discomfort
3 = severe discomfort
4 = intolerable.

This procedure was explained to the subject so that he or she could enter evaluations in a daily log. From these data, the (1) number of lesions for the length of the study, (2) duration of lesions, (3) intervals between lesions, (4) size of lesions, and (5) degree of pain were computed.

After the lesions present at the initial examination were examined and the method of gel application was demonstrated, the subject was assigned to a group by random number and was given the medication for that group. The 8 equal-sized groups were as follows:

Group 1 (5 subjects): control group; carrier gel only (without silicon dioxide, aloe, or allantoin)
Group 2 (5 subjects): carrier gel with silicon dioxide alone
Group 3 (5 subjects): carrier gel with aloe vera alone
Group 4 (5 subjects): carrier gel with allantoin alone
Group 5 (5 subjects): carrier gel with silicon dioxide and aloe vera
Group 6 (5 subjects): carrier gel with silicon dioxide and allantoin
Group 7 (5 subjects): carrier gel with aloe vera and allantoin.
Table I. Means and standard deviations of ulcer duration, interval between ulcers, score of ulcer size over study period, and score of ulcer pain over study period

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean duration (days)</th>
<th>Mean interval (days)</th>
<th>Mean size score</th>
<th>Mean pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: (Control) Carrier gel</td>
<td>4</td>
<td>9.01 ± 1.32</td>
<td>3.53 ± 2.37</td>
<td>2.30 ± 0.40</td>
<td>1.80 ± 0.56</td>
</tr>
<tr>
<td>2: Silicon dioxide</td>
<td>4</td>
<td>10.20 ± 2.52</td>
<td>4.31 ± 8.93</td>
<td>1.81 ± 0.22</td>
<td>2.12 ± 0.14</td>
</tr>
<tr>
<td>3: Aloe vera</td>
<td>3</td>
<td>6.38 ± 0.73</td>
<td>23.70 ± 26.44</td>
<td>1.85 ± 0.33</td>
<td>1.90 ± 0.10</td>
</tr>
<tr>
<td>4: Allantoin</td>
<td>4</td>
<td>7.32 ± 1.31</td>
<td>5.65 ± 6.11</td>
<td>1.95 ± 0.75</td>
<td>1.71 ± 0.52</td>
</tr>
<tr>
<td>5: Silicon dioxide, aloe vera</td>
<td>4</td>
<td>10.68 ± 3.31</td>
<td>6.77 ± 10.45</td>
<td>2.14 ± 0.18</td>
<td>2.21 ± 0.53</td>
</tr>
<tr>
<td>6: Silicon dioxide, allantoin</td>
<td>5</td>
<td>6.41 ± 2.29</td>
<td>12.62 ± 16.06</td>
<td>2.30 ± 0.87</td>
<td>1.74 ± 0.54</td>
</tr>
<tr>
<td>7: Aloe vera, allantoin</td>
<td>5</td>
<td>9.43 ± 3.29</td>
<td>2.10 ± 7.12</td>
<td>1.86 ± 0.81</td>
<td>1.57 ± 0.96</td>
</tr>
<tr>
<td>8: Silicon dioxide, aloe vera, allantoin</td>
<td>5</td>
<td>5.61 ± 1.49*</td>
<td>4.57 ± 7.85</td>
<td>2.18 ± 0.83</td>
<td>1.96 ± 0.43</td>
</tr>
</tbody>
</table>

*Significantly different from control (P < 0.05).

Table II. Results of ANOVA of data for dependent variables of means for duration, interval between lesions, score of lesion size, and score of lesion pain

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Mean</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days)</td>
<td>8.10</td>
<td>3.07</td>
<td>.017</td>
</tr>
<tr>
<td>Interval (days)</td>
<td>7.43</td>
<td>1.21</td>
<td>.333</td>
</tr>
<tr>
<td>Size of lesion</td>
<td>2.06</td>
<td>0.42</td>
<td>.884</td>
</tr>
<tr>
<td>Pain from lesion</td>
<td>1.85</td>
<td>0.61</td>
<td>.746</td>
</tr>
</tbody>
</table>

Group 8 (5 subjects): carrier gel with silicon dioxide, aloe vera, and allantoin.

Each subject applied the gel throughout the lesion surface using cotton swabs and then brushed his or her teeth with the gel, spreading it throughout the oral mucosa. The subject was told not to rinse or eat for one half hour after this procedure. The subject was given a Personal Daily Diary: the Diary contained a map of the oral cavity on which the subject was to note the date and the number and location of the lesion; an entry in the Diary was made every day during the time that lesions were present. The Diary also contained a chart on which the subject was to enter the date of healing, the size score, and the level of pain caused by the lesion. The subject was then released. Subjects were seen weekly by the investigators for the first month and then on a monthly basis for 2 additional months (6 visits altogether). During the weekly appointments in the first month, reinforcement of protocol procedures was performed. At these visits, the Personal Daily Diary was reviewed and the oral mucosa was examined as it had been at the baseline. Compliance with instructions in the use of the Diary and the application of the gel was evaluated by comparison of data obtained from the subject with data gathered by the examiner. The results of these meetings were used to determine whether observations made by the subject were reasonably appropriate with respect to the status of the ulcers. At the end of the study, the Diary was placed in the subject’s records.

Study II

The purpose of research study II was to determine the effectiveness of the gel containing aloe vera and allantoin in the treatment of aphthous ulcers—i.e., in reducing their number, recurrence, duration, size, and pain. This study was carried out according to a parallel design, and it was to be followed by a study using a modified crossover design (study III).

Study II was a double-blind study that included 50 additional subjects who replied to advertising in local newspapers. Twenty-five subjects were included in each of 2 groups. In anticipation of a possible loss of 20% of the subjects, which had characterized study I.

Biographic data, health history, and history of experiences of oral ulcers were obtained, and an oral examination of the lesion was performed. Inclusion and exclusion criteria, diagnosis, evaluation, and data accumulation were the same as in study I. Each of the subjects was assigned to 1 of the 2 groups by random number. The 2 groups were as follows:

Group 1 (25 subjects): experimental gel containing silicon dioxide, aloe vera, and allantoin

Group 2 (25 subjects: control group): gel containing silicon dioxide only.

The subjects were seen weekly by the investigators for the first month and then on a monthly basis, for a total time of 3 months (6 visits); most subjects were seen for 4 months (7 visits). At these visits, the Personal Daily Diary was reviewed and the oral cavity was examined as it had been at the baseline. Compliance on the part of the subject with the protocol was evaluated by comparison of data from examiner and subject.

Study III

The purpose of study III was to determine the effectiveness of the gel containing silicon dioxide, aloe vera, and allantoin in the treatment of aphthous ulcers through use of a modified crossover design. The inclusion and exclusion criteria used in the other
Table III. Averages for lesion parameters in study II: duration of lesion, interval between lesions, score of lesion...and score of lesion pain

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Silicon. aloe vera, allantoin</th>
<th>Group 2 (Control): Silicon dioxide</th>
<th>F value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>20</td>
<td>20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean duration (days)</td>
<td>7.7</td>
<td>7.0</td>
<td>0.63</td>
<td>NS</td>
</tr>
<tr>
<td>Mean interval (days)</td>
<td>5.0</td>
<td>18.3</td>
<td>3.47</td>
<td>NS</td>
</tr>
<tr>
<td>Mean size</td>
<td>2.1</td>
<td>1.9</td>
<td>1.26</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pain</td>
<td>1.9</td>
<td>1.7</td>
<td>1.65</td>
<td>NS</td>
</tr>
<tr>
<td>No. of days of observation</td>
<td>105.7</td>
<td>114.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>12.1</td>
<td>15.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

studies were used in study III; the methods were also the same.

All of the subjects used in study II were asked to return for study III 2 months after completion of study II; however, only 21 of the subjects agreed to participate in study III. Twelve subjects who had belonged to the control group in study II were placed in the experimental group of study III; 9 subjects who had belonged to the experimental group of study II were assigned to the control group of study III. Each subject was seen on a monthly basis for a total time of 3 months (3 visits). The 2 groups were as follows:

- Group 1 (9 subjects: control group): carrier gel only
- Group 2 (12 subjects: experimental gel containing silicon dioxide, aloe, and allantoin.

At each visit the Personal Daily Diary was reviewed and the oral cavity was examined as it had been at the baseline. Number of lesions during the study period, duration of lesions, interval between lesions, size score, and pain score data were obtained.

ANALYSIS

Study I

The primary method of analysis in study I was the 2³ factorial analysis of variance (ANOVA). Multiple comparison tests of means were also used. The number, size, duration, and pain sensation of lesions obtained from each subject's diary were used as response variables. Agreement-of-parameter evaluations between the examiner and subjects were performed through use of the weighted kappa for number of lesions and size of lesions. Analysis was performed after approximately 40 subjects completed the study. Data from the examiner and from each subject's diary were used.

Study II

In study II, the number, size, duration, and pain sensation of lesions that were obtained from the 20 subjects of each group were compared through use of a 2-sample t test. These results were used to determine the effectiveness of the active substances of the gel on aphthous ulcers.

Study III

Data from 21 subjects pertaining to the same parameters used in study II were compared through use of a paired t test or blocked ANOVA (equivalent) in study III.

RESULTS

Study I

Subjects were initiated into study I when one or more mucosal ulcers were present in the oral cavity. Forty subjects agreed to participate in the study and signed consent forms approved by the Institution; however, only 34 subjects completed the entire 3 months of the study. Nine subjects (21%) decided for personal reasons not to participate in the study and did not appear for their clinical appointments; of these, 7 were female and 2 were male. They were assigned to groups 1 (2 subjects), 2 (1 subject), 3 (2 subjects), 4 (1 subject), 5 (2 subjects), and 6 (1 subject). The subjects who participated in study I had a mean age of 35 years, and the age range was 19 to 56 years; there were 24 female and 10 male subjects.

The data for the study were obtained from the Personal Daily Diaries prepared by the subjects; compliance with the protocol on the part of the subjects was therefore extremely important. The investigators met with the subjects every week for the first month to evaluate compliance. In addition, the gel tubes were weighed to evaluate usage. In general, the subjects appeared to adapt to the protocol and recorded their procedures in their Diaries. A weighted kappa was computed as an appropriate measure of agreement between the subjects and the investigator. The data from the second week of the first month, during which 20 subjects had ulcers, was used to compute the agreement. Kappas of 0.78 and 0.76 were obtained for the number of lesions and the lesion size, respectively.
Table IV. Study III data and analysis (modified crossover design): same 9 subjects

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>No. of lesions</th>
<th>Days</th>
<th>Duration</th>
<th>Interval</th>
<th>Size</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study III: control gel</td>
<td>6</td>
<td>10 (6)</td>
<td>91</td>
<td>8.5 (2.9)</td>
<td>1.84 (6.3)</td>
<td>2.3 (.75)</td>
</tr>
<tr>
<td>Study III: experimental gel</td>
<td>9</td>
<td>11 (7)</td>
<td>111</td>
<td>7.5 (2.3)</td>
<td>8.8 (12.3)</td>
<td>2 (.59)</td>
</tr>
<tr>
<td>P value</td>
<td>.6665</td>
<td>.0001*</td>
<td>.2748</td>
<td>.0335*</td>
<td>.1697</td>
<td>.0676</td>
</tr>
</tbody>
</table>

*Significant when P ≤ .05.

This result was considered to be acceptable. The mean amount of gel used varied from 146.7 to 256.4 g for the 3 months of the study; it had been anticipated that each subject would use 120 to 360 g of gel during the study.

The mean duration of lesions ranged from 6 to 11 days (Table I). Lesions lasted an average of 9 days for subjects in the control group; this compared with 11 days for subjects using allantoin alone (group 4), 6 days for subjects using silicon dioxide and allantoin (group 6), 6 days for subjects using aloe vera alone (group 3), and 6 days for subjects using silicon dioxide, allantoin, and aloe vera (group 8). ANOVA (Table II) demonstrated a significant change in ulcer duration (F = 3.07; P = .017). Multiple comparison tests of means showed that subjects using the gel with silicon dioxide, allantoin, and aloe vera (group 8) experienced a significant reduction in lesion duration in comparison with subjects using the control gel (group 1); the P value was .0360. There were no other significant results in other groups in comparison with the control gel group.

The mean interval between lesions was 7 days, with a range among groups of from 2 to 24 days (Table I). The variation was very high, and the ANOVA did not demonstrate significant differences among groups (F = 1.21; P = .333). The mean size of the lesions was a score of 2—ie, the size was greater than 2 mm but no greater than 4 mm. Again, differences among groups were not found in the ANOVA (F = 0.42; P = .884). The mean pain score was 2, indicating moderate discomfort. The ANOVA indicated nonsignificant differences among the groups for the pain score (F = 0.61; P = .746).

Study III

In study III the approach was changed from a parallel to a modified crossover design using subjects from study II. Nine of the original 20 subjects from group 1 (the experimental group) of study II returned for this 3-month study. Instead of the experimental gel that they had received in study II, they received a control gel that did not contain any of the active substances (silicon dioxide, allantoin, aloe vera). Because this group was familiar with the protocol, the weekly sessions during the first month were discontinued. The investigators were those who had conducted studies I and II.

The parameters duration, interval, size, and degree of pain were compared between the experimental group of study II and the control group of study III for the 9 subjects who were involved in both studies. Use of the experimental gel appeared to reduce the number of lesions per day and increase the intervals between lesions. The reduction in number of lesions was not statistically significant and was not demonstrated in the other studies. For the subjects common to studies II and III, the mean lesion intervals for the experimental and control gels were 8.8 and 1.84 days, respectively; the change was significant (P = .0335; Table IV). The mean study durations were 111 days for study II and 91 days for study III; the difference was statistically significant (P = .0001; Table IV).

Twelve subjects from the control group of study II (who had used a gel containing silicon dioxide only) were used in study III as the experimental group; they received the gel containing all 3 active substances (silicon dioxide, aloe vera, and allantoin). The data for this experimental group were compared with the data for the 9 subjects of the study III control group. The study lasted 3 months, and the same protocol was followed. There was no statistical difference between the 2 groups (Table V). The lesion-free intervals were...
Study III data and analysis (modified crossover design): control group (study II) becomes experimental
p (study III) and vice versa

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>No. of lesions</th>
<th>Days</th>
<th>Duration</th>
<th>Interval</th>
<th>Size</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study II experimental/study III control</td>
<td>9</td>
<td>10 (6)</td>
<td>91</td>
<td>8.5 (2.9)</td>
<td>1.84 (6.3)</td>
<td>2.3 (1.75)</td>
<td>2.4 (6)</td>
</tr>
<tr>
<td>Study II control/study III experimental</td>
<td>12</td>
<td>6 (8)</td>
<td>39</td>
<td>8.3 (3.5)</td>
<td>9.5 (21.8)</td>
<td>1.8 (.95)</td>
<td>2.0 (9)</td>
</tr>
<tr>
<td>P value</td>
<td>0</td>
<td>9157</td>
<td>.3251</td>
<td>.2180</td>
<td>.2418</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For evaluation of lesions, same parameters were used as in other studies: mean number of lesions, mean number of days for study, mean duration of lesion (days), mean interval between lesions (days), mean size score, and mean pain score.

reduced in the experimental group; however, the difference was not significant (P = .3251).

**DISCUSSION**

Aphthous stomatitis is a chronic, self-limiting disease of the oral cavity. A gel was formulated with 3 active substances, aloe vera, allantoin, and silicon dioxide; it could be applied to the lesion and then used as a toothpaste for dental cleaning. In this way the gel can be used to brush the patient's teeth and at the same time treat, prevent, and/or delay the presence of the ulcer. This procedure would be an ongoing treatment for the lesion. Our studies were developed to demonstrate the effectiveness of the experimental gel to treat the ulcer.

The purpose of this first study was to determine the effectiveness of silicon dioxide, aloe vera, and allantoin separately and in combination, on the severity and recurrence of aphthous stomatitis minor. The results of the study indicated that a statistically significant effect was generated with the gel when all 3 active substances were included. The method that was used to collect data was the Personal Daily Diary. The Diary appeared to be an acceptable method of evaluation on the basis of personal observation and the reasonably good weighted kappa scores that were computed. Daily examinations of mucosal changes by an examiner during the length of study would have been too costly to conduct, and compliance on the part of the subjects would have been less likely for daily visits. The amount of gel that was used by each subject was evaluated to determine whether the subject adhered to the protocol. The analysis demonstrated small differences among subjects and indicated that they followed the protocol during the study periods. The result of the study was that only a gel containing all 3 active substances was found to be statistically effective with respect to one of the clinical parameters, duration of lesions.

The second study included the medicament combination that had demonstrated an effect; the gel containing silicon dioxide, aloe vera, and allantoin in the experimental group of study I. Power analysis through use of reliability of data demonstrated by the first study was used to determine the number of subjects for study II. It was considered that with a larger sample size and a smaller number of groups, the potential effect of the agents could be evaluated more precisely. The results showed a lack of significant effect of the test substances on the ulcer. However, the presence of silicon dioxide in the control gel of study II may have caused loss of significance of the parameters.

An additional study was used to compare a group that used the experimental gel containing all 3 active substances with a control group that did not contain the active substances. All of the subjects who participated in study II were invited to join in study III; however, only 21 subjects were entered in study III. In a comparison of the data for the 9 subjects who were common to studies II and III in the modified crossover design, there were statistical differences for length of the study (P = .0001) and lesion-free interval (P = .0335; Table IV). Again, these results did not support the effectiveness of the experimental gel on ulcers that was seen in study I. The differences for the lesion-free interval could be related to differences in study length. In fact, in the study III comparison of groups with different subjects (Table V), the lengths of the study and the lesion-free intervals were not significantly different. In addition, for the 9 subjects whom studies II and III had in common, there was one outlier for the parameter of lesion-free interval; when that subject's interval was dropped from the data, the P value turned out to be .08. The lack of consistency of results affects the importance of the effectiveness of the gel for treatment of aphthous stomatitis that was found in the first study.

Graykowski and Kingman, in their study of 35 patients with histories of aphthous ulcer in the oral cavity, used the Personal Daily Diary method and found that the average number of ulcers per week was reduced from 2.40 to 1.33 ulcers per week. In our study, the ulcer experience of patients was reduced from 6.3 to 3.6 ulcers per week (0.8-0.9 ulcers per day). Ulcer duration in days was reduced significantly in the first study by the experimental gel from 9 to 5.6 days (P = .036); this compares with a reduction from 8.2 to 5.46 days (P = .051) demonstrated by Graykowski and Kingman. The intervals between ulcers were not studied in the Graykowski and
Kingman investigation, but an increase was demonstrated statistically in study III ($P = .0335$). Ulcer size and pain were reduced in both our study and that of Graykowski and Kingman, but not significantly.

**CONCLUSION**

The purpose of this study was to evaluate a gel containing allantoin, aloe vera, and silicon dioxide in the treatment and prevention of aphthous ulcers of the oral cavity. For 3 to 4 months, each patient used a daily dairy to document changes in number and duration of ulcers, interval between ulcers, ulcer size, and ulcer pain. The gel did result in reductions of these parameters, and statistical significance was reached for decrease in duration of the lesions in one study and increase in interval between lesions in another study. Our study did not demonstrate any consistent effectiveness for the gel on ulcers in the oral cavity.

**REFERENCES**


**Reprint requests:**

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