STUDY

# The Use of Sucralfate Suspension in the Treatment of Oral and Genital Ulceration of Behçet Disease

## *A Randomized, Placebo-Controlled, Double-blind Study*

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**Objective:** To determine the efficacy of topically applied sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease.

**Design and Setting:** A randomized, placebo-controlled, double-blind study at a university referral center.

**Patients:** Forty patients with Behçet disease were included in the study.

**Intervention:** Patients were given topical sucralfate or placebo 4 times a day for 3 months and examined clinically at biweekly intervals.

**Main Outcomes Measures:** For each lesion, the mean frequency, healing time, and pain were evaluated during the pretreatment, treatment, and follow-up periods. No patients were given any concurrent disease-specific or immunosuppressive topical and systemic drugs during the 9-month study period.

**Results:** Of the 40 patients included in the study, the results in 30 patients (16 patients treated with sucralfate and 14 patients treated with placebo, ranging in age from 16 to 52 years [mean ± SD age, 34.3 ± 8.1 years]) were evaluable for efficacy. Treatment with sucralfate decreased significantly the mean frequency, healing time, and pain of oral ulceration and healing time and pain of genital ulceration compared with the pretreatment period. The effectiveness of sucralfate on the frequency and healing time of oral ulceration continued during the posttreatment period. In the placebo group, no significant difference was found in measured parameters of oral and genital ulceration except the pain of the oral ulceration between the pretreatment and treatment periods.

**Conclusion:** Our results showed that topical sucralfate suspension is an easy, safe, inexpensive, and effective treatment for oral and genital ulceration in patients with Behçet disease.

*Arch Dermatol. 1999;135:529-532*

BEHÇET DISEASE (BD) was first described in 1937 by Behçet[1] as a trisymptom complex characterized by recurrent oral ulceration (OU), genital ulceration (GU), and uveitis. Later studies[2] have shown that BD is a multisystemic inflammatory disease with articular, vascular, intestinal, pulmonary, and neurologic involvement. The cause of BD is still unknown. The most likely hypothesis is that an autoimmune reaction is triggered by infectious (viral or bacterial) or other antigens in genetically predisposed individuals, and the basic pathologic process of BD is vasculitis.[2-4]

The most common mucocutaneous lesions in BD are recurrent and painful ulceration of the oral and genital mucosa. The lesions are punched-out ulcers with rolled or overhanging borders and a necrotic base, surrounded with erythematous rim. No standard therapy has been established yet. The agents, such as topical or intralesional corticosteroids and local anesthetics, are used only for palliative therapy.[2] Clinical trials[2] have shown controversial results of the use of colchicine, thalidomide, and dapsone to treat OU and GU. The use of immunosuppressive medications, such as azathioprine[5] and cyclosporine,[6] which are reserved for the most severe cases, and interferon alfa[7,8] was reported to be effective. However, high cost, toxic effects, the need for parenteral administration, and/or the lack of standard regarding doses or duration have led to a search for alternatives.

Sucralfate, an aluminium salt of sucrose octasulfate, has been successfully used to treat patients with peptic ulcer.[9] Because of the ability of sucralfate to augment healing ulcers of the gastrointestinal tract, it may also be useful for the treatment of OU and GU of BD.

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## METHODS

Forty patients with BD (18 female, 22 male; mean ± SD age, 34.3 ± 8.1 years; range, 16-52 years), diagnosed according to the criteria of International Study Group for Behçet's Disease,[10] were included in the study. Patients were excluded if they had an active eye disease or organ involvement requiring systemic therapy or received recent systemic therapy for at least 12 weeks and topical therapy for at least 4 weeks prior to the study.

The patients were observed for 3 months before the study. The incidence of OU and GU was recorded during this period. The research protocol was approved by the ethics committees, and all patients or their guardians gave their informed consent. The patients in the study were randomly allocated to equal treatment groups. The vehicle of sucralfate that was used as placebo was identical in appearence to the sucralfate suspension. For 3 months, the patient groups received sucralfate or placebo 4 times a day to treat OU and GU. All patients with or without OU were given 5 mL of sucralfate or placebo to use as an oral rinse for 1 to 2 minutes after routine mouth care and before sleep. In patients with GU, either sucralfate or placebo solution was applied to external lesions using a cotton-tipped applicator and to intravaginal lesions using a vaginal douche. The clinical investigator (H.E.) and patients were unaware of the specific drugs that the patients were taking during the course of the study. The patients were examined clinically at biweekly intervals and were followed up for another 3 months after the treatment. The results were obtained by the same investigator and were based on a combination of the data obtained by the physician at clinic visits and the data reported by the patients on the occurrence of OU and GU between the visits. For each lesion, the mean frequency, healing time, and pain were evaluated during the pretreatment, treatment, and follow-up periods. The mean frequency and healing time of lesions were calculated per patient. The level of pain was scored on a scale of 0 to 3 (0, absent; 1, mild; 2, moderate; and 3, severe). The following pain scores were based on a system devised in our department for patients with BD. For OU: 0, no symptoms; 1, mild pain with eating, drinking, and/or speaking; 2, moderate pain and partial difficulty eating, drinking, and/or speaking; and 3, severe pain and marked difficulty eating, drinking, and/or speaking. For GU: 0, no symptoms; 1, mild pain with physical activity; 2, moderate pain and partial difficulty with physical activity; and 3, severe pain and marked difficulty with physical activity. In addition, the overall responses at the end of the treatment period were graded as follows: improvement, decrease in the mean frequency, shortening of healing time, or relief of pain; and no effect or deterioration, ineffectiveness or worsening of clinical signs and symptoms.

Adverse events were also documented during the treatment period. No patients were given any concurrent disease-specific or immunosuppressive topical and systemic drugs during the 9-month study period.

Mean frequency, healing time, and pain of OU and GU in the pretreatment period were compared in the treatment and posttreatment periods in the sucralfate and placebo groups, and the paired Student *t* test was used to test the changes in the groups. Differences in improvement ratings between groups were tested using the $\chi^2$ test.

The present randomized, double-blind, placebo-controlled study investigated whether the use of topical sucralfate suspension alone is effective in the treatment of OU and GU of BD.

## RESULTS

Of the 40 patients in the study, the results in 30 patients were evaluable for efficacy. The demographic data of these patients are shown in **Table 1**. Treatment groups were similar regarding sex, age, and duration of disease.

**Table 1. Demographic Data of the Patients With Behçet Disease**

| Characteristic | No. of Patients* | | |
|---|---|---|---|
| | Sucralfate (n = 16) | Placebo (n = 14) | Total (N = 30) |
| Mean ± SD age, y | 33.0 ± 9.3 | 34.1 ± 5.3 | 33.4 ± 7.61 |
| M/F | 8/8 | 8/6 | 16/14 |
| Mean ± SD duration of disease, y | 9.9 ± 5.6 | 8.8 ± 5.9 | 9.4 ± 5.7 |
| Oral ulceration at the beginning of therapy | 16 | 14 | 30 |
| Genital ulceration at the beginning of therapy | 14 | 13 | 27 |

**Unless indicated otherwise.*

Ten patients (4 sucralfate-treated patients and 6 placebo-treated patients) failed to complete the study. The reasons for their withdrawal were noncompliance (3 patients) and using prohibited concomitant medication (2 patients). The therapy in 2 patients in the sucralfate group and 3 patients in the placebo group was discontinued because of disease progression. In all patients, medication use was well tolerated, and no patients were withdrawn from the study because of adverse events.

Mean frequency, healing time, and pain values of OU and GU for both treatment groups and statistical results are summarized in **Table 2**. The groups were not significantly different in measured disease parameters at the beginning of the study. Treatment with sucralfate decreased significantly the mean frequency, healing time, and pain of OU and the healing time and pain of GU compared with the pretreatment period. In the placebo group, no significant difference was found in measured OU and GU parameters except the pain of OU between the pretreatment and treatment periods.

In the follow-up period, there was a significant difference for only mean frequency and healing time of OU for the patients treated with sucralfate compared with the pretreatment period.

The overall responses of patients with OU and GU associated with BD at the end of the treatment period are summarized in **Table 3**. In patients with OU, the difference in improvement ratings between therapy with su-



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**Table 2. Mean Frequency, Healing Time, and Pain of Ulceration in Patients With Behçet Disease During the Study Period***

| | Sucralfate | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Pretreatment | Treatment | Follow-up | Pretreatment | Treatment | Follow-up |
| **Oral Ulceration** | | | | | | |
| Frequency | 5.44 ± 2.7 | 3.56 ± 1.3† | 3.81 ± 2.1† | 4.50 ± 2.1 | 4.36 ± 2.2 | 3.57 ± 1.9 |
| Healing time, d | 11.50 ± 2.6 | 7.19 ± 1.9‡ | 8.31 ± 2.5† | 10.00 ± 3.8 | 8.28 ± 2.3 | 9.28 ± 2.9 |
| Pain | 2.06 ± 0.6 | 0.69 ± 0.5‡ | 1.47 ± 0.5§ | 1.64 ± 0.7 | 1.07 ± 0.8‖ | 1.28 ± 0.6 |
| **Genital Ulceration** | | | | | | |
| Frequency | 1.50 ± 1.1 | 1.31 ± 0.9 | 1.19 ± 0.9 | 1.21 ± 0.9 | 1.29 ± 0.9 | 1.14 ± 0.9 |
| Healing time, d | 22.1 ± 7.0 | 14.08 ± 3.9† | 20.07 ± 5.4§ | 17.17 ± 5.6 | 18.0 ± 8.6 | 17.4 ± 6.0 |
| Pain | 2.07 ± 0.6 | 1.30 ± 0.6‡ | 1.83 ± 0.6¶ | 2.10 ± 0.7 | 1.54 ± 0.8 | 1.60 ± 0.7 |

*Data are presented as mean ± SD. Of the patients with oral ulceration, 16 received sucralfate and 14, placebo. Of the patients with genital ulceration, 14 received sucralfate and 13, placebo. See the "Methods" section for a description of the criteria used to determine the scores for pain.

†$P<.01$.

‡$P<.001$ compared with the values at baseline.

§$P<.01$ compared with the values at treatment.

‖$P<.05$.

¶$P<.05$ compared with the values at treatment.

**Table 3. Overall Response of Ulceration in Patients With Behçet Disease***

| | Oral Ulceration | | | Genital Ulceration | | |
|---|---|---|---|---|---|---|
| Effect | Sucralfate (n = 16) | Placebo (n = 14) | $\chi^2$ (*P*) | Sucralfate (n = 14) | Placebo (n = 13) | $\chi^2$ (*P*) |
| Frequency | | | | | | |
| Improvement | 14 (87.5) | 5 (35.7) | 8.62 (.003) | 6 (42.8) | 5 (38.5) | 0.05 (.8) |
| No effect or deterioration | 2 (12.5) | 9 (64.3) | . . . | 8 (57.2) | 8 (61.5) | . . . |
| Healing time | | | | | | |
| Improvement | 13 (81.2) | 6 (42.8) | 4.74 (.03) | 12 (85.7) | 7 (53.8) | 3.28 (.07) |
| No effect or deterioration | 3 (18.8) | 8 (57.2) | . . . | 2 (14.3) | 6 (46.2) | . . . |
| Pain | | | | | | |
| Improvement | 16 (100) | 7 (50) | .001† | 12 (85.7) | 8 (61.5) | 2.05 (.15) |
| No effect or deterioration | 0 (0) | 7 (50) | . . . | 2 (14.3) | 5 (38.5) | . . . |

*Data are presented as the number (percentage) of patients unless indicated otherwise. See "Methods" section for definition of improvement and no effect or deterioration. Ellipses indicate not applicable.

†Fisher exact $\chi^2$ test was used to test the differences.

cralfate and placebo was statistically significant. Although, there was clinical improvement in healing time and pain of GU, the difference was not statistically significant (Table 3).

## COMMENT

Sucralfate is widely used in the treatment of ulcers of the gastrointestinal tract. Although the mechanism of action of this drug is still not fully known, we know that it binds to ulcerated tissue and forms a barrier to acid without altering stomach pH or reducing the secretion of gastric acid.[11] Sucralfate induces proliferation of dermal fibroblasts and keratinocytes as well as granulation tissue formation.[12] Sucralfate stimulates mucus production and enhances binding of growth factors, including epidermal growth factor, which may play a role in healing.[13] Sucralfate also activates both the nitric oxide and prostaglandin systems that cooperate in the protective action of this drug.[13,14] The nitric oxide system may contribute to mucosal integrity and preservation of mucosal microcirculation.[14] Because of its antioxidant effects,[15] sucralfate may play a role not only in the healing of damaged mucosa but also in the protection of mucosal surfaces.

Previous studies also reported positive results from the use of sucralfate suspension in patients with stomatitis,[16] chemotherapy-induced oral mucositis,[17,18] and vaginal ulceration.[19] In another study, Rattan et al[20] showed the effectiveness of sucralfate suspension in the treatment of recurrent aphthous stomatitis. They demonstrated a reduction of the healing period, duration of pain, response time to first treatment, and duration of remission in patients using sucralfate compared with placebo and antacid.

Our results showed that sucralfate therapy decreased significantly the frequency, healing time, and pain of OU and the healing time and pain of GU in patients with BD. The effectiveness of the sucralfate on the frequency and healing time of OU continued during the posttreatment period. These results indicated that the continuous use of sucralfate suspension had a protective effect against the development of OU, and it can be given as a prophylactic for OU associated with BD.



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One of the most striking results of the present study was the marked decrease in pain scores in both groups. Although the percentage decrease was higher in the sucralfate group, this finding indicates that coating agents are helpful in the palliation of pain, a finding that was also noted by Barker et al.[21]

Since studies have demonstrated the noteworthy effects of sucralfate in the healing and prevention of oral mucositis, stomatitis, and vaginal ulceration, it is possible that sucralfate will have a similar effect in the oral and genital environment and in stratified squamous mucosa. In our study, the use of sucralfate suspension increased patient compliance and represented a major therapeutic advance and practical use, especially in the treatment of OU.

In conclusion, topical sucralfate suspension is an easy, safe, inexpensive, and effective treatment for OU and GU associated with BD. To our knowledge, the use of sucralfate in patients with BD has not been reported in the literature.

*Accepted for publication January 14, 1999.*

*The study was presented at the Congress of the Seventh European Academy of Dermatology and Venereology, Nice, France, October 10, 1998.*

*We thank Bilim Ilaç Sanayii ve Ticaret AŞ, Antalya, Turkey, for supplying both placebo and sucralfate suspensions for the study.*

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