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Research paper
Wound healing

Efficacy of topical benzydamine hydrochloride gel on oral mucosal ulcers: an *in vivo* animal study

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S. Y. Karavana (Hizarcioğlu), B. Sezer, P. Güneri, A. Veral, H. Boyacioğlu, G. Ertan, J. B. Epstein: Efficacy of topical benzydamine hydrochloride gel on oral mucosal ulcers: an in vivo animal study. Int. J. Oral Maxillofac. Surg. 2011; xxx: xxx–xxx.

Abstract. The aim of this study was to investigate the effect of benzydamine hydrochloride bioadhesive gel on healing of oral mucosal ulceration in an animal model. For *in vivo* determination of the effects of the bioadhesive gel, 36 rabbits were separated into three groups: the first group was treated with the gel formulation without active agent, the second group with the gel formulation containing benzydamine, and the third group received no treatment. Clinical healing was established by measuring the area of the ulcer in each test group on days 3, 6, 9 and 12. Histological healing was determined on the same days. Benzydamine containing gel applications resulted in a decrease in the ulcer area in 12 days ($p = 0.000$). Histological evaluation showed that the benzydamine group had a higher mean histological score than the base and the control groups during the whole test period, and the difference between the benzydamine group and the control group was significant ($p = 0.04$). The bioadhesive gel formulation of benzydamine hydrochloride showed a statistically significant increased rate of mucosal repair in this experimental standard mucosal wound animal study. It is a candidate for the topical treatment of oral mucosal ulcerative lesions.

Keywords: benzydamine hydrochloride; bioadhesive gel; hydroxypropylmethylcellulose; oral mucosa; wound healing..

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Oral ulcers, an end-result of epithelial damage, may occur due to a number of causes including trauma[17,22], immune-mediated conditions such as aphthous stomatitis and lichen planus and lichenoid reactions[13,22], cytotoxic therapy (such as radiation and chemotherapy)[8,9,24], drug-induced hypersensitivity reactions of the mucosa[22] and malignant changes[19].

General treatment modalities for oral ulcers include application of topical corticosteroids, topical tetracycline[11] or tetracycline plus nicotinamide[22], systemic immunomodulators[22,27], topical analgesics[27], antiseptic mouth washes[27], amlexanox and benzydamine hydrochloride[17]. Benzydamine hydrochloride (Bnz HCl) is available in a number of countries and is recommended for the relief of inflammatory conditions of the oral cavity, soft tissues and skin[21]. It is a nonsteroidal drug that possesses analgesic, anaesthetic, anti-inflamatory, antipyretic and antimicrobial properties[9]. Studies have shown anti-TNF alpha effects that may have utility in the management of mucosal ulcerations[4,23]. Other theories about its mechanism of action include membrane stabilization, and anti-inflammatory effects. Even though it has been administered as tablets for systemic use, it is commonly used as a mouth wash or mouth spray in a concentration of 0.15% for the

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relief of inflammatory conditions of the mouth and throat, and in some countries gel preparations are applied to the skin to treat inflammatory conditions[7].

In their thorough review, QUANE et al.[18] reported that the recommended dose of benzydamine as a mouthwash is 15 ml of a 4-mmol/l solution of the hydrochloride salt in water as stated by BALDOCK et al.[2] Following mouthwash administration of benzydamine to rats (1 mg/kg), tissue concentrations in the oral tissues are reported to be as high as 100 μmol/l[20]. The depth of diffusion of the drug into oral tissues is not known but it is probable that surface concentrations are higher than 100 kmol/l. Commercially available benzydamine mouthwash has a pH of 4.5–5.0 but is unbuffered, so should rise quickly to salivary pH (about 7) in the presence of saliva. During a 30 s mouth rinse, only a limited amount is absorbed into the buccal tissue[3,5]. The small amount of absorption into buccal tissue is confirmed by the poor systemic availability (5%). Peak plasma concentrations are obtained at 3 h and reach 0.5 μmol/l[2]. The excretion of unchanged benzydamine has been reported to vary from 5 to 50–60% in the urine[2,6]. Bnz HCl has been studied in a multicenter phase III clinical trial as prophylaxis for radiation-induced mucositis and mucosal pain in cancer patients, and statistically significant benefits of benzydamine rinse were shown compared with placebo[9].

Topical application of appropriate medications for the treatment of ulcerative and inflammatory mucosal conditions is commonly chosen by most dentists and physicians[15]. A recent drug delivery method that can be applied and removed by the patient is a mucoadhesive system, which is especially appropriate for hydrogel-forming polymers, such as cellulose derivatives, natural gums, polyoxyethylenes, polyacrylates and sodium alginate[16]. The application of ointments, creams and gels with bioadhesive properties can enhance the retention time of the formulation at the site of action[25]. Gel formulations are preferred for topical applications due to their ability to release the drug molecules from the systems and are more easily applied to mucosal surfaces than creams and ointments[26]. Hydroxypropylmethylcellulose (HPMC) is suitable for use in buccoadhesive preparations because it can adhere to oral mucosa when hydrated with water and withstand salivation, tongue movements and swallowing for a significant period of time[1]. Even though the advantages of Bnz HCl and buccoadhesive formulations are known, there is no intraoral buccoadhesive Bnz HCl formulation available for oral pathologic conditions.

The aim of this study was to evaluate the effect of a new mucoadhesive gel formulation containing Bnz HCl that was developed by the authors for the clinical and histological healing of oral mucosal ulcers.

Materials and methods

Bnz HCl (Abdi İbrahim Pharmaceutical Company, İstanbul, Turkey) and HPMC K 100-M (Colorcon Ltd., İstanbul, Turkey) were compounded with acetic acid, methyl paraben and pentobarbital (Sigma–Aldrich Chemical Co, St. Louis, MO, USA). The study consisted of three sequential steps: preparation of bioadhesive gels; preliminary investigations for *in vivo* examination; and evaluation of *in vivo* performance of the gels in the animal study.

Preparations of gels

The gels for use in the *in vivo* studies were prepared as described[12]. Briefly, HPMC E 5, E 15 and E 50 were used at the percentages of 5–10–15 and HPMC K 100-M was used at the percentages 1–1.5–2–2.5. HPMC was placed in a 100-ml beaker and wetted with water for 24 h. Bnz HCl and methyl paraben were dissolved in appropriate amounts of water and this solution was added in small portions to the wetted gel base and mixed thoroughly with the aid of vortex (IKA-Labortechnik RW 20 DZM, Germany)[26]. After preparation of bioadhesive gels, rheological characterization, mechanical properties, mucoadhesion studies, drug diffusion studies and stability test of formulation were carried out[12]. These studies guided the most suitable bioadhesive gel formulation for this trial, which was compounded with HPMC K 100-M 25% (80–120 cps), benzydamine 0.15, methyl paraben 0.15, distilled water q.s. 100 (w/w%)[12].

Preliminary investigations for *in vivo* studies

The housing care and experimental protocol of the study were approved by the Animal Ethics Committee. Adequate measures were taken to minimize the pain or discomfort of the animals. Experiments were carried out in accordance with the Guidelines laid down by the National Institute of Health (NIH) in the USA regarding the care and use of animals for experimental procedures and in accordance with local laws and regulations.

Complete wound healing of oral ulcerations occurs in 17 days[10]. In order to establish the observation intervals and to determine the days of histological sample collection, an oral ulcer model was established for this study: oral ulcers were created on the oral mucosa of 17 young adult male New Zealand rabbits, weighing 2.5–3.0 kg. The animals were kept in a room with environmental conditions of $22 \pm 2\ ^{\circ}C$, $50 \pm 10\%$ relative humidity and were fed a standard laboratory diet and water *ad libitum.* Each day, one animal was randomly selected and killed. The wound healing process on each day was evaluated histologically by an expert pathologist (A.V.). Thus, the observation intervals and the days of histological sample collection were set, and the length of the observation period for the oral ulcer model was determined.

Prior to the creation of the ulcers, all animals were anaesthetized with administration of pentobarbital (50 mg/kg). A round filter paper (Whatman, Madison, UK), 5 mm in diameter was soaked in 15 μl of 50% acetic acid and was used to cause aseptic tissue necrosis. In order to create round ulcers, the acid-soaked paper was pressed onto the labial gingival tissue of the rabbits for 60 s[10] (Fig. 1). On each day, one rabbit was killed with an excess dose of pentobarbital. The histological characteristics of the ulcer observed on day 1 were accepted as the baseline histological features. During 17 days, one animal was killed each day, and the histological wound healing process was established daily by the same pathologist. These characteristics were used to create a 'custom-made scale' to evaluate healing progression (Table 1).

Complete wound healing was observed in the specimens obtained on day 12. Therefore, the total observation period for the present study was set as 12 days. The healing process presented histological differences on days 3, 6, 9 and 12, which can be defined as the steps of wound healing for this investigation and determined the schedule of tissue biopsy for the study.

Evaluation of bioadhesive gels

The animals were separated into three groups: the first group (base) comprised animals treated twice a day with the gel formulation (without active agent); the second group (Bnz HCl) was treated with the Bnz HCl gel formulation twice a day; the third group (control) received no treatment and their measurements served as the control.

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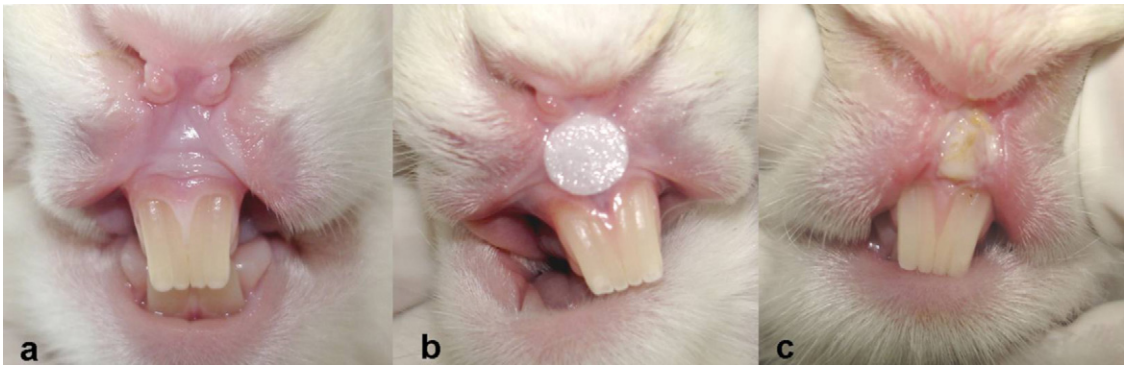

Fig. 1. (a) Healthy rabbit gingival mucosa. (b) Acid-soaked paper application. (c) Ulcer appearance on day 1.

Table 1. The scoring protocol developed to establish the histological level of healing.

Scores	Histological level of healing
1	Presence of epithelial necrosis, but no signs of inflammation
2	The inflammatory reaction has started, with no new capillary proliferation
3	The inflammatory reaction is prominent with few capillary proliferations on the basis of the ulcer, but no epithelization at the surface
4	The inflammatory reaction is decreased, new capillary proliferation has reached the surface and epithelization has started at the surface
5	The epithelization is complete

The clinical healing of each oral ulcer was evaluated by subtracting the most recent reading from the initial ulcer measurement at each observation interval. Thus, clinical healing was defined using the decrease in the ulcer area: the higher the amount of the difference between the initial measurement and the observation day, the better the clinical healing.

In each group, three animals were killed on days 3, 6, 9 and 12 for histological evaluation. 36 rabbits were included (12 rabbits in three groups representing three animals in each test group for each observation period) (Fig. 2).

The treatment started 24 h after ulcer initiation (day 1). The dose of Bnz HCl was 1 mg/kg, with 0.1 g gel formulation applied to the ulcer using a syringe without a needle. The applications were performed twice daily.

Clinical photographs of the ulcers were recorded with a digital camera. In each photograph, a filter paper disc of 5 mm diameter was included to provide calibration of the ulcer area measurement between the images. A free share computer program (Image J, NIH, USA) (http://rsbweb.nih.gov/ij/, accessed on 21 May 2009) was used to measure the area of ulceration as cm^2 (Fig. 3). All measurements were performed by the same researcher (P.G.) in a blinded fashion three times on the same day and a mean ulcer area was calculated.

For histological examination, three animals selected randomly from each group were killed with an excess dose of pentobarbital on each observation day. The ulcers were excised on days 3, 6, 9, and 12 by an experienced oral surgeon and fixed in 10% neutral buffered formalin. In the laboratory, they were embedded in paraffin blocks and 4 μm thick tissue sections prepared. The specimens were stained with haematoxylin–eosin and were examined in a blinded fashion by the same pathologist using a pre-established histological healing score (Fig. 4, Table 1).

Statistical analysis

The differences of the average ulcer area observed in 12 days between the groups were analysed using one-way ANOVA. Pair-wise comparisons were completed using Tukey's test and the paired t test was used to compare observation periods. The Friedman test was used to compare histological scores for each test group. In all statistical analyses, p was set as 0.05 and SPSS 10.0 for Windows program (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

The ulcer areas of the samples on days 3, 6, 9 and 12 are presented in Table 2. Throughout the examination period, which lasted from 3 to 12 days, the mean ulcer area measurement in each group ranged from 0.441 to 0.000 mm^2. The largest ulcer areas were observed on day 3, and a significant decrease was found on day 9, with the smallest ulcer areas on day 12 ($p = 0.00 < 0.05$). The average value of all the mean ulcer area measurements on days 3, 6, 9 and 12 of the Bnz HCl treated animals was significantly less (0.100 cm^2)

Table 2. The mean ulcer area values and histological healing scores for three animals in each test group on days 3, 6, 9 and 12.

Observation days*	Mean ulcer area (the mean of three animals in each group; cm^2)			Histological healing scores		
	Base	Bnz HCl	Control	Base	BnzHCl	Control
Day 3	0.38 ± 0.09	0.19 ± 0.04	0.44 ± 0.17	2.33 ± 0.58	3.00 ± 0.00	2.00 ± 0.00
Day 6	0.13 ± 0.01	0.13 ± 0.02	0.11 ± 0.05	3.33 ± 0.58	3.67 ± 0.58	2.67 ± 0.58
Day 9	0.06 ± 0.01	0.07 ± 0.01	0.05 ± 0.04	4.00 ± 0.00	4.33 ± 0.58	3.67 ± 0.58
Day 12	0.01 ± 0.04	0.01 ± 0.01	0.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	4.67 ± 0.58
Average	0.144	0.100	0.150	3.67	4.00	3.25

p-values: Base-Bnz HCL: 0.009, Base-Control: 0.898, Bnz HCL-Control: 0.002.
* Three animals were killed in each test group for each observation day.

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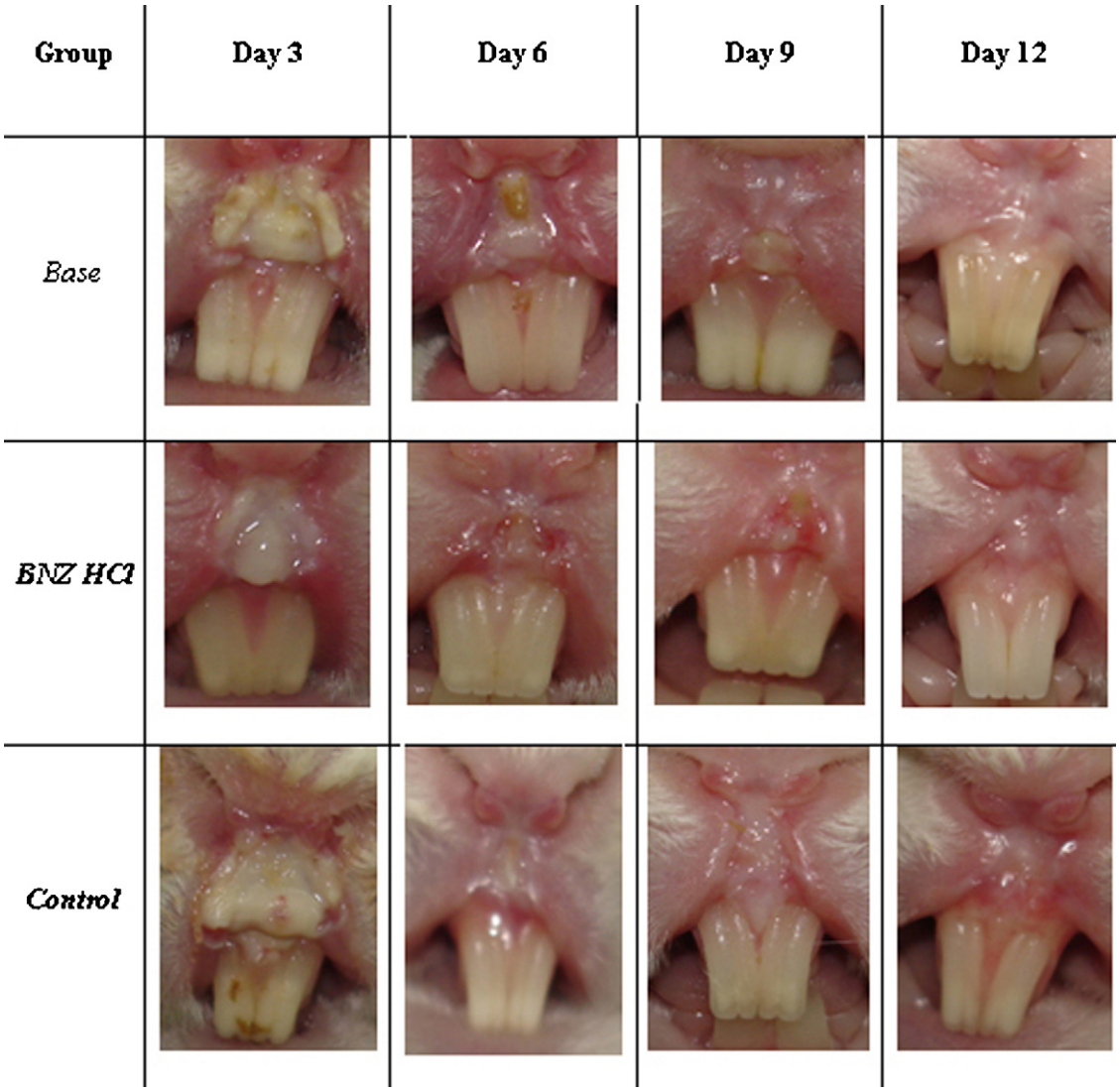

Fig. 2. Samples of ulcers from all test and control groups on control days.

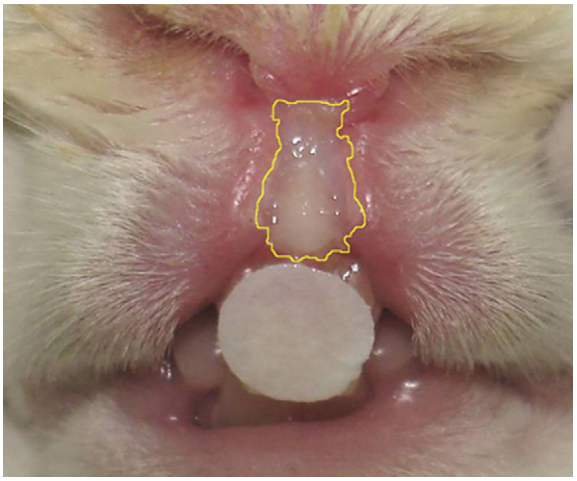

Fig. 3. Assessment of the ulceration area as cm^2 using a free share computer program (Image J, NIH, USA).

and 31% smaller than that of the gel base group (0.144 cm^2) ($p = 0.009$). The average value of the Bnz HCl group was 33% smaller than that of the control animals (0.150 cm^2) ($p = 0.002$) (Table 2).

The histological evaluations of the specimens are presented in Table 2. The base group had a mean healing score of 2.33 on postoperative day 3, that increased to 3.33, 4.00 and 5.00 on the consecutive observation days ($p = 0.03$). The mean healing score for the Bnz HCl group was higher than that for the other groups on day 3, indicating improved healing, which increased to 3.67, 4.33 and 5.00 on days 6, 9 and 12, respectively ($p = 0.04$).

The control group had lower mean healing scores until the end of the observation period, but this group's mean healing scores increased from 2.00 to 2.67 and

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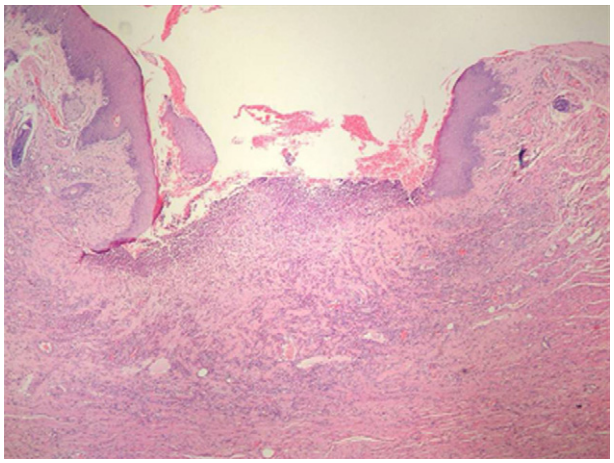

Fig. 4. A sample of the histological presentation of the ulcer area. There is epithelial necrosis at the surface, and subepithelial inflammatory activity. Note the capillary proliferation at the base (control group, day 3) (H-E, ×100).

from 3.67 to 4.67 in time, confirming the progression of healing ($p = 0.03$).

At the end of the test period, all six animals in the Bnz HCl and the base groups had a healing score of 5. Of three animals in the control group, one had a healing score of 4 and the other two received a score of 5.

The study drug ($p = 0.018$) and the time period ($p = 0.007$) affected the histological scores. Over the whole observation period Bnz HCl treated animals had a higher mean histological healing score (4.00) than the base and control groups (3.67 and 3.25, respectively; $p = 0.02$). The overall mean healing score (the average value of all the mean measurements on days 3, 6, 9 and 12) of the Bnz HCl group was higher than the control group ($p = 0.046$) (Table 2).

Discussion

Mucoadhesive applications that increase the retention time of drug at the application site may improve the treatment outcome by providing sustained release of the drug. On the basis of the data obtained from the authors' studies, the F13 formulation including 2.5% HPMC K 100-M was chosen as the formulation for the oral ulcer treatment. The formula provides high cohesion and mucoadhesion and caused sustain release of the drug *in vitro* over a period of approximately 24 h[12].

The ulcer model used in the present study was adapted from Fujisawa et al.[10] The model produces uniform wounds in almost identical positions on the gingival mucosa of the rabbits and allowed the examination of the healing phases by measuring ulcer size[10], and may provide an interesting animal model of tissue wounding for future animal studies of wound healing and wound management. In the present investigation, a 12 day healing period was used because preliminary investigations revealed complete ulcer healing occurred in 12 days. In order to determine clinical healing the ulcer area was measured on each observation day. The same animals were killed and their wound areas were evaluated histologically to determine the healing in each group. Owing to the small number of animals in each group during each observation, the overall outcomes were assessed for the entire study period.

Although decreasing ulcer size and pain are amongst the determinants of healing, the resolution of pain is the most important issue to the subject[13]. In the present study, the most prominent differences between the groups were observed on day 3, probably due to epithelization of the ulcer surface in 3 days. The clinical and histological healing parameters were not concordant even though superficial epithelization was complete on day 3, as ongoing histological healing continued in the subepithelial tissues. Both clinical ulcer size and histological evaluation were assessed to provide detailed assessment of mucosal healing 12 days following tissue injury.

The treatment of the ulcers started at 24 h, and on day 3, the ulcer size for the Bnz HCl group was considerably smaller than for the base only group, which was smaller than for the no treatment group. This suggests that both Bnz HCl and the gel base may promote early stage healing (before day 3), although this was greater for the Bnz HCl group. At the end of the 12-day test period, the mean ulcer area of the Bnz HCl group was 31% smaller than that of the base and 33% smaller than that of the control groups. A similar patient study revealed no differences between Bnz HCl, chlorhexidine and placebo mouthwashes in the treatment of aphthous ulcers[14], even though clinical benefits with benzydamine application have been previously reported[7,9,17,21].

Histological healing was complete in the Bnz HCl and base groups on day 12. Even though the inflammatory changes were decreased, new capillary proliferation had reached the surface and epithelization had started, the control group failed to show complete healing of the mucosa. The base group had better healing scores than the control group, which may be due to the positive effect of covering the ulcer surface with an inert material.

In conclusion, this study demonstrated a rapid decrease in ulcer size with the application of the new bioadhesive Bnz HCl gel formulation. In the experimental standard mucosal wound animal study, Bnz HCl showed a statistically significant increased rate of mucosal repair. Covering the lesion with gel without active ingredient showed moderate improvement, compared with untreated animals, suggesting that the gel base provided a protective layer over the lesion. Thus, this novel bioadhesive gel formulation of Bnz HCl appears to be a candidate for the topical treatment of ulcerative oral mucosal lesions. Considering the various local and/or systemic factors that may influence healing of human oral tissues, the efficacy of bioadhesive gel formulation of Bnz HCl will continue to be investigated.

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Competing interests

None declared.

Ethical approval

Animal Ethics Committee approval was obtained.

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