Aqueous hydrocortisone mouthwash solution: clinical evaluation

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Patients often experience difficulties in applying topical steroids in orabase to the oral mucosa, particularly when large areas need to be covered. An aqueous hydrocortisone mouthwash solution has been developed, one that was anticipated to be more acceptable to patients. The solution contains hydrocortisone (0.3% w/v) in a 4.5% (w/v) 2-hydroxypropyl-β-cyclodextrin solution. Hydroxypropylmethylcellulose (0.5% w/v) was used to increase the viscosity of the solution and to promote the hydrocortisone–cyclodextrin complex. One hundred and two patients with aphthous ulceration, lichen planus, and other mucosal conditions used the mouthwash in an open clinical efficacy study. Most patients reported some or considerable improvement following a 2-week course of treatment with the mouthwash: 26 of 33 (78.8%) patients with aphthous ulceration were 'much better', as were 26 of 54 (48.1%) patients with lichen planus and 5 of 16 (31.3%) patients with other mucosal lesions. No serious side effects were reported. Aqueous mouthwash solutions offer a potential vehicle for topical steroid therapy of oral mucosal lesions. ☐ *Cyclodextrin; hydrocortisone; mouthwash; mucosal disease*

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Steroids are commonly used topically in the oral cavity to treat conditions such as recurrent aphthous ulceration (RAU), erosive lichen planus (ELP), and benign mucous membrane pemphigoid (1, 2). Triamcinolone in orabase (Kenalog in Orabase®) is the preparation most widely available on the market (2). Although specialists in oral medicine and surgery often prescribe potent steroids (1–6), general dentists in many countries are restricted to the use of weaker steroids (2). There are several drawbacks to the use of steroid preparations in orabase: it is difficult to apply the grainy gel to the oral mucosa; it adheres rather poorly; and it is difficult to apply to large areas of the mucosa such as those occurring in ELP or severe RAU. Moreover, steroid release from orabase is poor because of the highly hydrophobic nature of orabase (7). The residence time for orabase in the mouth has been found to be no more than 10 min (8).

We have developed a mouthwash containing cyclodextrin that aims at overcoming some of the drawbacks to these preparations containing orabase (9). The difficulty in formulating a steroid mouthwash is mainly the low solubility of many steroids in water as well as instability at neutral pH and bad taste. It was decided to choose a weak steroid for the study, as the steroid released from the cyclodextrin preparation was considerably greater than that released from steroids in orabase (7, 9). Treatment with potent steroids can induce harmful side effects, especially when used for long periods to treat persistent or recurring lesions such as ELP and RAU. Moreover, dentists in Iceland and several European countries are restricted to varying degrees with respect to permission to use systemic or potent topical steroids (2). The present study was intended to discover whether a weak steroid in an improved vehicle, cyclodextrin, would be sufficient for the treatment of some disorders of the oral mucosa.

Cyclodextrins (CDs) form a new family of pharmaceutical excipients (10, 11). They are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. CDs are capable of forming inclusion complexes with many lipophilic drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such encapsulation of a drug molecule will affect many of its physicochemical properties, such as solubility and stability in aqueous solutions. The 3 most common natural occurring CDs are α-, β-, and γ-CD formed by 6, 7, and 8 glucose units, respectively. A hydroxypropyl derivative of β-CD, 2-hydroxypropyl-β-cyclodextrin (HPβCD), was used in this study. This hydrophilic CD derivative is unable to permeate lipophilic membranes and virtually non-toxic upon intravenous administration (12, 13). This article thus reports the development of a mouthwash containing water-soluble hydrocortisone–cyclodextrin complex and presents the results of a test of clinical efficacy. This was designed only as a test of efficacy and not as a placebo-controlled trial.

Materials and methods

Formulation of the mouthwash

The formulation of the mouthwash has been reported previously (9). A solution was prepared by dissolving hydrocortisone (0.3% w/v) in a 4.5% (w/v) 2-hydroxypropyl-β-cyclodextrin solution by heating. Hydroxypropylmethylcellulose (0.5% w/v) was used to increase the viscosity of the solution, which was preserved with 0.02% (w/v) benzalkonium chloride and 0.1% (w/v) sodium edetate. Hydroxypropylmethylcellulose also promotes the hydrocortisone–cyclodextrin complex (14). The mouthwash solution was flavored with just enough peppermint to

give it an acceptable taste. After dissolving the ingredients in water the final solution was autoclaved at 121°C for 15 min. Tests of preservative efficacy and stability were performed as described previously (9).

Test of clinical efficacy

Hydrocortisone mouthwash was given preliminary approval by the Icelandic Medicines Committee (Lyfjanefnd) for the purpose of a clinical efficacy trial. This was intended to be an open trial with no placebo, as it was deemed unethical to withhold treatment from patients with ELP and from other patients who had been referred to a specialist clinic, usually because of the failure of other treatments. One hundred and two patients were referred for treatment to the oral medicine clinic with mucosal lesions, including RAU, ELP, non-erosive lichen planus (LP), and desquamative gingivitis (DG), for which steroid therapy was thought necessary. All patients gave their informed consent to take part in a clinical trial of the mouthwash and were asked to contact one of the authors (W. P. Holbrook), who was the clinical investigator, should any discomfort or other potential side effects arise. This trial was designed as a study of only the efficacy of the mouthwash, and no attempt was made to compare the efficacy of this preparation with other steroidal or non-steroidal treatments for these oral lesions. At each visit the patients were examined by one clinician (W. P. Holbrook) in the same dental chair. All oral tissues were examined with the light fixed to the dental unit and with a dental mirror. The tissues were also palpated. A detailed history was obtained in each case, and the progress of the lesions following treatment was recorded. Intolerance of hot and spicy foods, fruits, and drinks was specifically recorded.

Treatment regimen

Patients were prescribed the mouthwash following careful clinical examination and taking of their history. Initially, patients were admitted to the study if they presented with RAU, ELP, LP, or DG. Subsequently, the mouthwash was also used to treat oral lesions in seven patients with mucocutaneous disorders, including pemphigoid and erythema multiforme. In addition, it was used for nine patients with oral discomfort, usually on the tongue, for which a diagnosis of exclusion based on the criteria of Rosenberg & Arm (1) for 'burning mouth/tongue' syndrome (BMS) had been made. Care was taken to ensure that the patient was not suffering from a concurrent viral or yeast infection of the mouth, and appropriate specimens were taken prior to steroid therapy on numerous occasions to exclude this possibility. Hematologic investigation was usually carried out in patients with RAU and BMS, and iron and vitamin deficiencies were corrected.

Patients consenting to use of the mouthwash were prescribed 500 mL of 0.3% hydrocortisone mouthwash with instructions to rinse the mouth with 10 mL for 1–2 min 3 times a day, preferably with the last occasion being just before sleep. The mouthwash was to be expectorated after rinsing.

Results

A total of 102 patients (68 females, 34 males; mean age, 55.7 years; age range, 12–82 years) were enrolled in the clinical study. Their oral complaints are listed in Table 1. No serious side effects were reported, although one patient stopped taking the mouthwash because she felt it nauseated her. Hypersensitivity reactions to the mouthwash were neither reported nor observed. One patient developed a mild candidosis during treatment. Most patients found the peppermint flavor of the mouthwash tolerable, although it did not entirely mask the bad taste of hydrocortisone. No patients stopped treatment because of the taste of the mouthwash. After treatment for 2 weeks patients were recalled and asked about the duration and severity of symptoms, and the oral tissues were examined. If the treatment had not been completely successful at the end of the 2-week period, the medication was continued and the patient recalled after a further 2 weeks.

Patients were asked whether they felt their oral condition had 'worsened', had 'not changed', was 'better', or was 'much better'. The oral tissues were examined carefully by the same clinician (W. P. Holbrook), and a clinical estimate of the changes was recorded using the same subjective scale. Specifically, erosions had to have healed to obtain a recording of 'much better'. If erosions were still present but smaller and less painful, a result of 'better' was recorded. To be classified as 'much better', RAU had to have healed and not recurred in the first month. If new ulcers were considerably fewer in number, frequency, and duration but still occurred, a result of 'better' was recorded. The results given in Table 2 show the less favorable of the scores given by the patient and the clinician.

On their first and subsequent recall visits, most patients reported some or even considerable improvement after 2 weeks of mouthwash use. This was particularly stated as a marked reduction in the number or duration of recurrent oral ulcers, or the healing or reduction of the size of erosions. Generally, oral ulcers that were well developed when treatment started improved no more quickly with the mouthwash than the patient had experienced without any therapy whatsoever. Newly formed ulcers or those still forming, however, responded dramatically to the steroid mouthwash, and recurrences were virtually stopped for several months in many patients. Most patients with RAU reported a marked drop in frequency and severity of ulceration, and 26 of 33 patients (78.8%) reported that after treatment they were 'much better'. ELP, LP, DG, and mucocutaneous lesions healed more slowly, as might be expected. Some patients with BMS reported improvements with the steroid preparation, while others did not.

Table 1. Patients treated with hydrocortisone mouthwash according to their age, sex, and oral disease

Oral disease	*n*	Males	Females	Mean age (years)	Age range (years)
Aphthous ulceration					
Minor	23	12	11	31.5	12–67
Major	10	5	5	32.9	23–65
Lichen planus and related conditions					
Erosive LP	22	8	14	56.3	22–82
LP or lichenoid reaction	17	3	14	46.4	29–72
Desquamative gingivitis	4	0	4	32.3	15–57
Erosive LP + desquamative gingivitis	5	1	4	53.4	48–59
LP + desquamative gingivitis	5	3	2	40.8	33–55
Mucocutaneous and other lesions					
SLE, erythema multiforme, pemphigoid	7	1	6	46.4	19–64
Burning mouth syndrome	9	1	8	51.9	28–74

LP = lichen planus; SLE = systemic lupus erythematosus.

Of the 54 patients with ELP, LP, and DG, 26 (48.1%) reported that they were 'much better' after treatment, as were 5 of 16 (31.3%) patients with other mucosal lesions (Table 2).

Discussion

This study has shown that a cyclodextrin mouthwash containing even a weak steroid, hydrocortisone, can be used successfully to treat mucosal lesions, particularly aphthous ulcers. These clinical findings can presumably be explained by the improved pharmacokinetics obtained when the steroid is complexed with cyclodextrin (9).

Treatment of oral mucosal lesions with steroids is widely practiced in oral medicine (1, 2, 4). There are some differences between prescribing practices in the USA and many countries in Europe, as is made clear in the published discussion at the 2nd World Workshop on Oral Medicine (2). Generally, it appears that the steroids used in Europe are less potent those used in the USA. Currently recommended steroids for the treatment of aphthae range in potency from triamcinolone to clobetasol in the recent review by Ship (3), whereas in the list by Scully (4) they range in potency from hydrocortisone to betamethasone. When lesions are widespread on the mucosa, or in areas that are difficult for the patient to treat with orabase preparations containing steroid, a spray or mouthwash preparation seems to be a practical means of applying steroid topically to the mucosa. However, inhalers containing steroids, such as those used in the treatment of asthma, are known to predispose to oral candidosis (15). A steroid preparation in mouthwash form therefore offers some therapeutic advance for treating certain irritating, perhaps painful, oral conditions for which systemic steroid therapy was not considered appropriate because of the increased risk of candidosis, mucosal atrophy, adrenal suppression, or intolerance of systemic steroid therapy (16). The problem of adrenal suppression following topical steroids therapy is perhaps overstated. For example, Plemons et al. were not able to demonstrate adrenal suppression following use of topical fluocinonide (17).

Two main properties of cyclodextrins suggested that the development of a cyclodextrin-based steroid mouthwash would be possible. First, the HPβCD molecules are relatively large with hydrated outer surfaces and, under

Table 2. Results of treatment with hydrocortisone mouthwash*

Oral disease	Patients (*n*)	No change	Better	Much better
Aphthous ulceration				
Minor	23	2	1	20
Major	10	2	2	6
Lichen planus and related conditions				
Erosive LP	22	4	6	12
LP or lichenoid reaction	17	2	8	7
Desquamative gingivitis	4	1	3	0
Erosive LP + desquamative gingivitis	5	0	1	4
LP + desquamative gingivitis	5	0	2	3
Mucocutaneous and other lesions				
SLE, erythema multiforme, pemphigoid	7	3	1	3
Burning mouth syndrome	9	5	2	2

* Each result is the lower score of the patient's reported response and the clinical assessment by the examiner (see text for details).
LP = lichen planus; SLE = systemic lupus erythematosus.

normal conditions, they are unable to penetrate a lipophilic mucous membrane. Second, in aqueous vehicles, cyclodextrins such as HPβCD act as penetration enhancers by solubilizing lipophilic water-insoluble drugs and constantly supplying dissolved drug molecules to the surface of a biologic membrane, such as skin or mucosa, where they partition into the membrane (13). Hydrocortisone molecules bound in the HPβCD cavity are in rapid equilibrium with free hydrocortisone molecules in the mouthwash solution. This results in fast hydrocortisone delivery to the surface of the oral mucosa and, consequently, enhanced hydrocortisone delivery into the mucosa without affecting its barrier properties.

Before any mouthwash can be approved for clinical use, it has to meet certain specific pharmaceutical criteria (18). Minor modifications were made to these criteria, making them somewhat stricter than the minimum standards set out in *British Pharmacopoeia* (9, 18). The mouthwash underwent several modifications prior to the clinical trial in order to fulfill these criteria (9).

The clinical results of this small, open efficacy study were encouraging. No serious side effects were encountered, although the taste of the preparation was not too pleasant. Further flavoring would, however, reduce the amount of hydrocortisone that could be incorporated into the cyclodextrin, as flavor and steroid molecules compete for space in the cyclodextrin cavity. Before beginning treatment with hydrocortisone mouthwash, the mucosa should be examined carefully for evidence of candidosis and swabs taken if necessary. Hydrocortisone therapy is contraindicated until the yeasts have been eliminated. One of the authors (W. P. Holbrook) has some anecdotal clinical evidence of successful treatment of oral lesions, in patients at special risk of developing candidosis, by employing concurrent therapy with amphotericin lozenges 10 mg twice daily. Patients with RAU seemed to derive most benefit from the mouthwash preparation. Many did not need to complete the course of treatment but kept the opened bottle in the refrigerator until the next episode of oral ulceration, at which time treatment was resumed, usually successfully. The results of this open, clinical efficacy study suggest that a double-blind trial of this steroid mouthwash is warranted.

Some patients with ELP used the mouthwash continually for 2 months before reasonable benefit was observed. One patient has used the mouthwash more or less continually for 18 months, after consultation with her medical advisors. The considerably poorer clinical response to the mouthwash seen in patients with ELP, especially if the lichen planus extended to the gingivae as a desquamative gingivitis, suggests that more potent steroids should be used to treat these conditions. A mouthwash containing dexamethasone or fluocinonide may thus prove to be beneficial and warrant further investigation.

In the present study no side effects were seen by the patients or the clinician, and many lesions resolved or improved markedly following treatment. Most of the mucosal lesions that persisted were kept under control with the mouthwash. The mouthwash was well tolerated by the patients. Thus, aqueous mouthwash solutions based on cyclodextrin offer a potential vehicle for topical steroid therapy of oral mucosal lesions.

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