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Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash

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Abstract

Objective: To assess the antiplaque/antigingivitis efficacy of a hexetidine-containing mouthwash.

Methods: This examiner-blind, parallel group, controlled clinical study examined the effectiveness of a hexetidine (0.1%) mouthwash both in inhibiting the development of supragingival plaque and in reducing gingivitis. One hundred and thirty-four adult subjects completed the 2-week experimental gingivitis model study. Following baseline examinations, which included plaque index, modified gingival index and gingival bleeding index, subjects received a full dental prophylaxis. Subjects were randomly assigned to one of three mouthwashes (hexetidine 0.1%, chlorhexidine 0.12% (positive control) or a 5% hydroalcohol negative control) and commenced three times daily supervised rinsing as their sole method of oral hygiene. All indices were rescored after 2 weeks.

Results: Compared to the negative control group, the hexetidine group demonstrated a statistically significant inhibition and reduction of supragingival plaque and gingival inflammation with reductions of 6.3%, 33.5% and 56% for gingivitis, plaque and gingival bleeding, respectively. The results of the chlorhexidine group were used to validate the study.

Conclusion: The study confirms the efficacy of a hexetidine rinse in reducing supragingival plaque and gingival inflammation.

Key words: hexetidine; plaque; gingivitis; mouthwash; prophylaxis

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Hexetidine is a broad-spectrum antiseptic, active in vitro and in vivo against Gram-positive and Gram-negative bacteria as well as yeasts (*Candida albicans*) (Roberts & Addy 1981, Ashley 1984, Wile et al. 1986). Formulated as a mouthwash, it is available in a number of markets worldwide, with indications for the treatment of a variety of conditions of the oropharynx.

Early, mainly open-label, studies on hexetidine mouthwash indicate positive benefits when used in the treatment and prevention of gingivitis (Kimmelman 1958, Graf 1968, Hundkirchen & Lingener 1969) and in another study that was unsupervised and uncontrolled (Bergenholtz & Hanstrom, 1974). A more recent short-term controlled and blinded study (Chadwick et al. 1991) failed to show significant reduction in plaque and gingival bleeding; however, in that study mean baseline scores for plaque and gingival bleeding on probing were low, allowing little room for improvement.

The purpose of this examiner-blind, controlled clinical trial was to evaluate the antiplaque/antigingivitis efficacy of the marketed hexetidine (0.1%) mouthwash using an experimental gingivitis model (Mankodi et al. 1987, Ross et al. 1993). This model was selected as it is suitable for demonstrating the chemotherapeutic efficacy of a mouthwash without the confounding influence of mechanical oral hygiene procedures.

Material and Methods

The test agent, which contained 0.1% hexetidine in a flavoured and coloured hydroalcohol vehicle, was Oraseptic™ solution.* Both a negative and positive control rinse were included in the study, the former being a 5% hydroalcohol solution flavoured and coloured to resemble a mouthwash and the latter a proprietary 0.12% chlorhexidine rinse (Peridex®, Zila Pharmaceuticals, Phoenix, AZ, USA). The test rinse and negative control rinse were carefully matched in appearance, packaged identically and visually indistinguishable, whereas the positive control rinse was dispensed in its original packaging after overwrapping.

Buccal, labial and sublingual mucosae, tongue, hard and soft palate, uvula and oropharynx, and teeth were

*Also known as Hexalen™, Hexoral™, Hextril™, Oraldine™, Oraldene™.

examined at baseline and final visits. Pathoses observed at baseline were recorded. Any change from baseline and any new pathology were noted, severity assessed, and a judgement made as to whether the new finding could be attributed to the test materials. The presence of observed extrinsic tooth stain was recorded by the dental examiner with their impression of severity as slight, moderate or severe.

Gingivitis was scored at baseline and at 2 weeks by the modified gingival index (MGI) (Lobene et al. 1986) on the buccal and lingual marginal gingivae and interdental papillae of all scorable teeth.

Bleeding was assessed at baseline and at 2 weeks according to the gingival bleeding index (BI) (Saxton & van der Ouderaa 1989).

Plaque area (PI) was scored at baseline and at 2 weeks by the Turesky modification of the Quigley–Hein plaque index (Turesky et al. 1970), on the buccal and lingual surfaces of all scorable teeth.

Subjects qualifying for this study had a minimum of 20 natural teeth, a mean PI $\geqslant$ 1.95 and a mean MGI $\geqslant$ 1.95. Grossly carious, fully crowned or restored, orthodontically banded, abutment or third molar teeth were not included in the tooth count. Subjects with moderate to advanced periodontitis, other significant oral soft tissue pathology, or on antibiotic or anti-inflammatory therapy were excluded.

One hundred and thirty-nine healthy male and female volunteers, aged 18-64 years, who met the entry criteria were accepted into the study. Baseline examinations included an oral soft tissue examination and MGI, BI and PI scored in the order listed.

Following baseline examinations, subjects were given a complete dental prophylaxis to remove supragingival plaque (confirmed by disclosing solution), stain and calculus. Subjects were assigned to one of the three rinse groups according to a computer-generated random code. The same day as the prophylaxis, subjects began rinsing with 15 ml of their assigned mouthwash for 30 s, three times daily, and continued this regimen for 2 weeks. Rinsing was supervised twice daily on weekdays. Evening and weekend rinsing was unsupervised; however, subjects were required to keep a diary of these unsupervised rinsings. A minimum of 4 h elapsed between supervised rinsings.

During the study period, subjects followed their usual dietary habits but were discouraged from using chewing gum and mints. They were instructed to refrain from using any other oral hygiene procedures, including the use of dentifrices, other mouthwashes and any oral hygiene devices. They were told to report any use of antibiotics or anti-inflammatory drugs.

At the end of the 2-week experimental period, the examinations performed at baseline were repeated. Subjects were required to refrain from using their assigned rinse for at least 4 h prior to the final examination, eliminating possible olfactory cues that might bias the investigator. Subjects were also required to return their diary cards and test material for compliance checks following each weekend.

In order to ensure (examiner) blinding, neither the examiner nor the recorder had access to a subject's treatment code. Study personnel involved in dispensing test product did not participate in the examination of subjects, further minimizing potential bias.

The same qualified examiner performed all examinations. The study was designed to provide a greater than 90% power of detecting a difference between treatment groups for a mean MGI of 0.20 and a mean PI of 0.31, based on a two-sided test at the 0.05 significance level.

For each of the primary and secondary efficacy variables, between-treatment differences after 2 weeks of treatment were tested by a one-way analysis of covariance model with treatment as a factor and the corresponding baseline value as a covariate.

The treatment groups were compared with respect to age and baseline index scores variables by a one-way ANOVA with treatment as a factor and with respect to other demographic variables by means of a χ^2 test.

Results

Of the 139 subjects entered, 134 completed the study. Two subjects were unable to complete due to illnesses requiring prescription medicines defined in the protocol as reasons for exclusion, one was unable to attend the final examination and the other two withdrew for personal reasons. There were no statistically significant differences among the treatment groups with respect to age, gender, smoking status or any of the baseline measures (Table 1).

Statistically significant reductions from the negative control ($p < 0.001$) in both mean MGI and mean PI in the chlorhexidine-positive control rinse group validated the study.

Plaque index

The hexetidine (0.1%) and chlorhexidine (0.12%) rinses were both significantly more effective than the negative control rinse in inhibiting plaque development (Table 2), producing 33.5% and 33% reductions in mean PI, respectively, when compared with the negative control ($p < 0.001$).

Furthermore, the proportion of sites examined showing improvement in plaque index scores was much greater for the two active treatments when compared with the negative control. For those subjects using hexetidine, improvement was observed in 54% of sites, in subjects rinsing with chlorhexidine improvement was observed in 55% of sites, whereas for those rinsing with the negative control rinse 39% of sites worsened (Table 3).

Modified gingival index and bleeding index

Compared to the negative control group, subjects rinsing with either hexetidine or chlorhexidine achieved statistically significant reductions in the mean MGI ($p < 0.001$) and mean BI ($p \leq 0.05$) (Tables 4 and 5, respectively). The respective reductions in mean MGI for

Table 1. Demographic variables

Group	Average age (years)	Age range (years)	Males		Females		Total
			no.	%	no.	%	
negative control	34.1	18–60	22	46.8	25	53.2	47
hexetidine	38.2	18–61	11	23.9	35	76.1	46
chlorhexidine	37.1	20–64	13	31.7	28	68.3	41

Table 2. Plaque index

Group	Baseline*	2 weeks*	Improvement compared to negative control (%)
negative control	2.82	3.23	
hexetidine	2.75	2.15**	33.5
chlorhexidine	2.77	2.17**	33

*Mean plaque index.

**Statistically significantly different from negative control ($p < 0.001$).

Table 3. Plaque index – % sites changed at 2 weeks

Group	Improved	No change	Worsened
negative control	8	53	39
hexetidine	54	39	7
chlorhexidine	55	37	8

Table 4. Gingivitis index

Group	Baseline*	2 weeks*	Improvement compared to control (%)
negative control	2.19	2.24	
hexetidine	2.18	2.10**	6.3
chlorhexidine	2.18	2.03**	9.2

*Mean modified gingival index.

**Statistically significantly different from negative control ($p < 0.001$).

Table 5. Bleeding index

Group	Baseline*	2 weeks*	Improvement compared to negative control (%)
negative control	0.15	0.16	
hexetidine	0.14	0.07**	56
chlorhexidine	0.15	0.06**	63

*Mean bleeding index.

**Statistically significantly different from negative control ($p < 0.001$).

Table 6. Mean percentage of sites bleeding

Group	Baseline	2 weeks
negative control	12.6	14.5
hexetidine	12.3	6.5
chlorhexidine	12.2	6.0

the hexetidine and chlorhexidine groups were 6.3% and 9.2% compared to the negative control. The mean BI for subjects rinsing with hexetidine or chlorhexidine was reduced by 56% and 63%, respectively, compared to the negative control.

To further characterize the BI results, the mean percentage of sites bleeding (defined as sites with bleeding index scores of 1 or 2) is summarized in Table 6. Also, the proportion of subjects exhibiting at least 33% improvement in their BI, a level consistent with those obtained in a long-term study of the effects of intense preventive programs (Albandar et al. 1984), was far greater with hexetidine (82.6%) and chlorhexidine (85.4%) than for those subjects using the negative control rinse (14.9%) (Table 7).

No reported adverse events were considered to be related to the study rinses. The examiner reported that 4% of those rinsing with hexetidine had slight to moderate staining, while 66% of subjects rinsing with chlorhexidine developed observable extrinsic tooth stain.

Discussion

Dental plaque accumulation and maturation are firmly implicated in the initiation of gingivitis (Loe et al. 1965). A number of studies show high positive correlations between the amount of supragingival plaque and development of gingivitis and between removal of bacterial plaque and the resolution of gingival inflammation (Suomi et al. 1971, Axelsson & Lindhe 1974, 1978). Whereas mechanical means of plaque removal have widespread acceptance, it is interesting to examine the adjunctive benefits of a chemotherapeutic mouthwash using a model, which obviates the confounding influence of mechanical plaque removal.

In the study reported herein, the hexetidine (0.1%) rinse was effective in inhibiting the development of supragingival plaque and reducing gingival inflammation when used 3 × daily for 2 weeks in subjects who temporarily suspended all other oral hygiene measures. Although the study was not designed a priori to compare the hexetidine rinse with chlorhexidine since chlorhexidine was included as a positive control in order to validate the study, it was observed that the two antiseptics produced numerically similar results. It is noteworthy that 2 weeks rinsing with hexetidine resulted in considerably fewer subjects developing extrinsic staining than chlorhexidine.

Earlier studies into the efficacy of hexetidine in reducing gingivitis and inhibiting supragingival plaque were open-label (Kimmelman 1958, Graf 1968, Hundkirchen & Lingener 1969). A more recent study (Chadwick et al. 1991) failed to demonstrate reduction in gingival bleeding and supragingival plaque formation. In this study, baseline

Table 7. Percentage of subjects exhibiting at least 33% improvement (bleeding)

Group	Percentage of subjects with 33% improvement
negative control	14.9
hexetidine	82.6
chlorhexidine	85.4

measurements suggest that the volunteer subjects did not have significant supragingival plaque or gingivitis, making any improvement more difficult to detect. In all the studies, subjects practised normal mechanical oral hygiene.

The model chosen for this study has been designed, and previously shown to determine chemotherapeutic effects in the absence of the confounding caused by mechanical oral hygiene procedures (Ross et al. 1993). Similar experimental gingivitis models of varying durations (Wennstrom 1988, Brecx et al. 1990, Moran et al. 1991, Shah et al. 1993, Mickels et al. 2001, Van Dyke et al. 2002) have also demonstrated the chemotherapeutic efficacy of various chemotherapeutic mouthrinses containing ingredients such as chlorhexidine, hexetidine or essential oils. Furthermore, the inclusion of subjects prone to plaque and gingivitis appears to be more appropriate for determining the efficacy for these clinical endpoints.

Plaque control is the cornerstone in the management of gingival inflammation. Confirmation of hexetidine's efficacy in both reducing supragingival plaque accumulation and gingival inflammation supports its clinical efficacy. The lower propensity to cause extrinsic tooth staining, observed in the study, supports hexetidine's usefulness where staining is a problem in assuring patient compliance.

Zusammenfassung

Antiplaque-und Antigingiuitiseffektinigät einer Hexitidin-Mundspüllösurg

Zielsetzung: Untersuchung der Antiplaque- und Antigingivitiseffektivität einer Hexetidin-Mundspüllösung.

Methoden: Diese kontrollierte klinische Studie mit verblindetem Untersucher im Parallelarm-Design untersuchte die Effektivität einer Hexitidin-Mundspüllösung (0,1%) sowohl für die Hemmung supragingivaler Plaquebildung als auch zur Reduktion der Gingivitis. 134 erwachsene Probanden beendeten die 2 Wochen dauernde Studie mit experimenteller Gingivitis. Nach der Erstuntersuchung, die die Erhebung des Plaque Index, des Modifizierten Gingival Index und des Gingivalen Blutungs Index umfasste, erhielten die Probanden eine professionelle Zahnreinigung. Den Probanden wurden randomisiert 3 Spüllösungen zugewiesen (Hexitidin 0,1%, Chlorhexidin 0,12% [positive Kontrolle] oder ein 5%iger Hydroalkohol [negative Kontrolle]) und begannen damit als alleinige Mundhygienemaßnahme 3 mal täglich unter Aufsicht zu spülen. Nach 2 Wochen wurden die Indizes erneut erhoben.

Ergebnisse: Im Vergleich zur negativen Kontrolle zeigte die Hexitidin-Gruppe eine statistisch signifikante Hemmung und Reduktion der supragingivalen Plaque und gingivalen Entzündung mit Reduktionen von 6,3%, 33,5% bzw. 56% für Gingivitis, Plaque bzw. gingivale Blutung. Die Ergebnisse der Chlorhexidin-Gruppe dienten zur Validierung der Studie.

Schlussfolgerung: Diese Studie bestätigt die Wirksamkeit von Hexitidin zur Reduktion supragingivaler Plaque und gingivaler Entzündung.

Résumé

Efficacité antiplaque et antigingivite d'un bain de bouche à l'héxatidine

Cette étude clinique contrôlée par groupe parallèle avec examinateur aveugle a estimé l'efficacité d'un bain de bouche à 0,1% d'héxatidine tant à inhiber le développement de la plaque sus-gingivale qu'à réduire la gingivite. Cent trente-quatre adultes ont achevé un gingivite expérimentale de deux semaines. A la suite de l'examen de base comprenant l'indice de plaque, l'indice gingival modifié et l'indice de saignement gingival, les sujets ont reçu une prophylaxie dentaire complète. Ils ont ensuite été répartis de manière randomisée pour utiliser un des trois bains de bouche suivants : héxatidine 0,1%, chlorhexidine 0,12% (contrôle positif) ou l'hydroalcool 5% (contrôle négatif), et ont commencé a effectuer un rinçage supervisé trois fois par jour comme unique méthode d'hygiène buccale. Tous les indices ont été relevés après deux semaines. Comparé au groupe négatif le groupe héxatidine montrait une inhibition et une réduction significatives de la plaque sus-gingivale et de l'inflammation gingivale avec des réductions respectives de 6,3, 33,5 et 56% pour la gingivite, la plaque dentaire et le saignement gingival. Les résultats du groupe chlorhexidine ont été utilisés pour valider cette étude. Celle-ci confirme l'efficacité de l'héxatidine à réduire la plaque dentaire sus-gingivale et l'inflammation gingivale.

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