International Journal of Dental Hygiene

Official Journal of the International Federation of Dental Hygienists

REVIEW ARTICLE

F Afennich
DE Slot
N Hossainian
GA Van der Weijden

The effect of hexetidine mouthwash on the prevention of plaque and gingival inflammation: a systematic review

Authors' affiliations:
F Afennich, N Hossainian, School of Dental Hygiene, Hogeschool Utrecht, University of Applied Sciences, Utrecht, The Netherlands
DE Slot, GA Van der Weijden, Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands
F Afennich, GA Van der Weijden, Clinic for Periodontology in Utrecht, The Netherlands

Correspondence to:
D.E. Slot
Department of Periodontology
Academic Centre for Dentistry Amsterdam (ACTA)
University of Amsterdam and VU University Amsterdam
Gustav Mahlerlaan 3004
1081 LA Amsterdam
The Netherlands
Tel.: (31) 20 59 80 179/307
E-mail: d.slot@acta.nl

Dates:
Accepted 4 August 2010

To cite this article:
Int J Dent Hygiene **9**, 2011; 182–190
DOI: 10.1111/j.1601-5037.2010.00478.x
Afennich F, Slot DE, Hossainian N, Van der Weijden GA. The effect of hexetidine mouthwash on the prevention of plaque and gingival inflammation: a systematic review.

Abstract: *Objective:* To review the literature concerning hexetidine-containing mouthwash as a monotherapy or as an adjunct to oral hygiene in the prevention of plaque accumulation and gingival inflammation. *Materials and methods:* PubMed-MEDLINE and the Cochrane-CENTRAL were searched through January 2010 to identify appropriate studies. The primary outcome measurements were plaque accumulation and gingivitis parameters. *Results:* Independent screening of titles and abstracts of 168 papers resulted in six publications that met the eligibility criteria. Mean values and standard deviations were obtained by data extraction. Descriptive comparisons are presented for hexetidine mouthwash and control mouthwashes (chlorhexidine and placebo). *Conclusions:* Considering the potential benefits in the light of the observed side effects, hexetidine appears to be a poor alternative to chlorhexidine.

Key words: bleeding; gingivitis; hexetidine; hexetidine mouthwash; plaque; systematic review

Introduction

Dental plaque consists of a multispecies biofilm of microorganisms that grows as an ecosystem on hard and soft tissues in the oral cavity. Several studies have shown that dental caries and periodontal diseases, the most prevalent diseases affecting the oral cavity, are associated with plaque microorganisms (1–3). Therefore, efficient removal of this organized biofilm and reduction of its formation are necessary and indispensable requirements for effectively preventing caries, gingivitis and inflammatory periodontal diseases.

Axelsson *et al.* (4) have demonstrated that gingivitis can be effectively prevented and treated by well-performed mechanical oral hygiene, including tooth brushing combined with interdental cleaning. However, there is evidence that chemical agents can also be effective against gingivitis. Diverse short-term clinical trials have demonstrated that antimicrobial mouthwashes have the potential to inhibit plaque and prevent the development of gingival inflammation (5). Chlorhexidine digluconate is, to date, the most thoroughly studied and most effective anti-plaque and anti-gingivitis agent. However, several side effects associated with its use have led to a search for alternative agents, such as hexetidine, which has a demonstrated efficiency for inhibiting plaque accumulation and gingivitis (6).

Hexetidine belongs to the group of pyrimidine derivatives. It is a broad-spectrum antiseptic, active *in vitro* and *in vivo* against Gram-positive and Gram-negative bacteria as well as yeast (*Candida albicans*) (7–9). Many clinical studies have verified the sensitivity of bacteria to hexetidine (10, 11). Previously, hexetidine had been used to achieve other results, such as treatment of vaginitis and cervicitis caused by the fungal organism *C. albicans* and the protozoan organism *Trichomonas vaginalis* respectively (12). It has also been proposed as an adjunct to oral hygiene and for use in the treatment of oral infections such as gingivitis, stomatitis, aphthous ulcers, dental ulcers and cases of bad breath (13). Because of its affinity for proteins of the oral mucosa and plaques, hexetidine may reduce as much as 98% of saliva-borne germs directly after rinsing. Oral retention, however, is low, as bacterial counts in the oral cavity return to initial values after 70–90 min (7). There have been a number of reports comparing the activity of chlorhexidine and hexetidine mouthwashes. *In vitro* comparisons suggest that the antimicrobial activities of these two mouthwashes are similar (7, 8), although higher concentrations of hexetidine are necessary to achieve the same killing effect.

There are several narrative reviews (12, 13), but no review has been performed with a systematic approach to date. Therefore, the aim of this review was to provide a systematic overview of the effectiveness of hexetidine-containing mouthwash as a monotherapy or as an adjunct to daily oral hygiene in the prevention of plaque accumulation and gingivitis.

Materials and methods

Focused question

What are the effects of hexetidine mouthwash as a monotherapy or as an adjunct to oral hygiene in the prevention of dental plaque and what are its effects on parameters of gingival inflammation in adults without periodontitis compared with control mouthwashes (placebo and chlorhexidine)?

Search strategy

Two Internet sources were used to search for appropriate papers satisfying the study purpose: the National Library of Medicine, Washington, DC (PubMed-MEDLINE) and the Cochrane Central Register of Controlled Trials. Both databases were searched for studies conducted during or before January 2010. The search was designed to include any published study that evaluated the effect of hexetidine mouthwashes. All reference lists of the selected studies were screened for additional papers that could meet the eligibility criteria of this study. The asterisk (*) was used as a truncation symbol.

Medline and Cochrane search

The following terms were used in the search strategy:

{<Agent> OR <Brand>}

{<*Agent*: Hexetidine [Mesh]OR Hexetidine OR Hexetidinum [textwords]>

OR

< *Brand*: Oraldene OR Hexoral OR Bactidol OR Hextril OR Oraseptic OR Hexalen OR Oraldine [textwords]>}

Eligibility criteria

- Randomized controlled trials (RCTs) or controlled clinical trials (CCTs).
- Studies conducted in humans ≥16 years old with good general health.
- Intervention: hexetidine mouthwash used as a monotherapy or as an adjunct to tooth brushing.
- Comparison: control mouthwash (placebo as negative or chlorhexidine as positive control).
- Parameters mentioned in short-term studies (<4 weeks): plaque.
- Parameters mentioned in long-term studies (≥4 weeks): plaque, bleeding, gingivitis.

Screening and selection

The papers were screened independently by two reviewers (FA & GAW), first by title and abstract. If the search keywords were present in the title, the abstract was selected for reading. Papers without abstracts but with titles suggesting that they were related to the objectives of this review were also selected so that the full text could be screened for eligibility. The full-text papers were read in detail by two reviewers (DES, FA). Those papers that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreement persisted, the judgement of a third reviewer (GAW) was decisive. Two reviewers (FA & DES) hand-searched the reference lists of all included studies for additional articles. Only papers written in English were accepted. Case reports, letters and narrative/historical reviews were not included in the search.

Assessment of heterogeneity

Factors used to evaluate the heterogeneity of the outcomes of the different studies were as follows:

- Study design
- Interventions and regimen
- Side effects, smoking status and industry funding

Quality of assessment

Two reviewers (FA & DES) scored the methodological quality of the included studies. Assessment of methodological study quality was performed by combining the proposed criteria of the RCT checklist of the Dutch Cochrane Center (14), completed with quality criteria as obtained from the CONSORT statement (15) by Moher *et al.* (16–19), Esposito

et al. (20), Needleman *et al.* (21) and the Delphi List (22). This combination resulted in the quality criteria listed in Table 3.

Criteria were designed to address external validity, internal validity and statistical methods. An aspect of the score list was given a '+' for an informative description of the item at issue for a study design meeting the quality standard, a '–' for an informative description but a study design that did not meet the quality standard, and a '?' for a lack of sufficient information.

When random allocation, defined inclusion/exclusion criteria, blinding of both patient and examiner, balanced experimental groups, identical treatment between groups except for intervention, and report of follow-up criteria were present, the study was classified as having a low risk of bias. Studies that were missing one of these five criteria were considered to have a moderate potential bias risk. Studies missing two or more of these criteria were considered to have a high potential risk of bias. In addition, the Centre for Evidence-based Medicine (CEBM) 'Levels of Evidence' (23) resource was used to assess methodological quality.

Data extraction

From the collection of papers that met the inclusion criteria, data were extracted with regard to the effectiveness of self-performed mouth rinsing with hexetidine as a monotherapy or as an adjunct to oral hygiene. When intermediate assessments regarding the use of hexetidine were presented, the baseline and final evaluations were used for this review. Mean values and standard deviations (SDs) were extracted (FA & DES). Some of the studies provided standard errors (SEs) of the mean. Where possible, the authors calculated standard deviation based on the sample size ($SE = SD/\sqrt{N}$).

Data analysis

After a preliminary evaluation of the selected papers, considerable heterogeneity was found in the study designs, characteristics, outcome variables and results. It was therefore impossible to perform valid quantitative analysis of the data and subsequent meta-analysis. Instead, a descriptive manner of data presentation was used.

The American Dental Association (ADA) requirements for a seal of acceptance demand a study period of 6 months to evaluate both efficacy and safety of chemical agents as well as patient compliance (24). Given that mouthrinses are also used and prescribed for short periods, their efficacy over shorter periods remains of interest (25). Consequently, studies with an evaluation period of <4 weeks were also included in this review. The ADA demands an evaluation period of at least 4 weeks for adjunctive devices used to control plaque and gingivitis (26). Therefore, selected studies of 4 weeks or more were considered for extraction of both plaque and gingivitis data. In consideration of the ADA requirements, gingival inflammation data were not evaluated for short-term studies (<4 weeks).

Results

Search and selection results

The PubMed-MEDLINE and Cochrane-CENTRAL searches resulted in 168 unique papers which were screened by title and abstract (Fig. 1). Ten full-text articles were initially selected, and after full-text reading, four papers were excluded (Table 1 shows the reasons for exclusion). Additional hand-searching of reference lists of the selected studies resulted in no additional papers. Ultimately, six papers were processed for data extraction.

Assessment of heterogeneity of the selected studies

Considerable heterogeneity was observed in interventions, regimens, concentrations of hexetidine used and outcome variables. Furthermore, the number, gender and age of participants varied

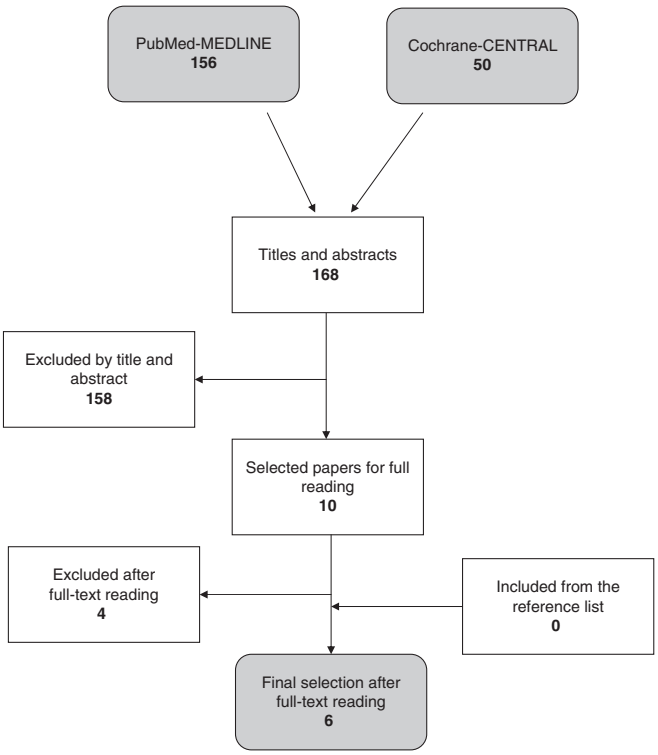

Fig. 1. Search and selection results.

Table 1. **Overview of excluded studies**

Author(s), (year)	Reason for rejection
Virga *et al.* (2002) (27)	Insufficient data presentation
Grytten *et al.* (1987) (28)	
Hefti & Huber (1987) (29)	Hexetidine in combination with zinc
Giertsen *et al.* (1987) (30)	Insufficient control group

among the studies. Information regarding the study characteristics is shown in Table 2.

Study design

Studies #IV and #V used a 3- and 6-week crossover study designs, respectively. At baseline, subjects were assigned either to the active group, the placebo group or the control group. In the second period, treatment subjects and the control group were assigned to the opposite group. As no overall data for this crossover design were presented for the test and control treatments, it was decided that only the data from the first leg of the study would be used. These were listed as being derived from a parallel study design.

Table 2. **Summary and overview of the studies processed for data extraction**

		Author (year) Title	Design and evaluation period	# baseline (end) subjects, gender, age	Comparison	Conclusion
<4 weeks	I	Bergenholtz & Hanström (1974) (31)	CCT Parallel Single-blind 21 days	27 (24) subjects Non perio 12 ♀ 12♂ Mean age: ? Age range: 19–24	Hexetidine 0.1%, Hexetidine 0.14%, CHX 0.2%	0.1% hexetidine is less effective in controllingplaque and gingivitis than 0.2% chlorhexidine. In higher concentrations, hexetidine has side effects and cannot be used routinely as a mouthrinse
	II	Harper *et al.* (1995) (32)	RCT Crossover Double-blind 4 days	21 (21) subjects Non perio ? ♀ ? ♂ Mean age: ? Age range: ?	Hexetidine 0.2%, CHX 0.2%, CHX 0.12%[¶], CHX 0.12%[††], CHX 0.1%, Saline 0.9%	The plaque-inhibiting action of active CHX preparations has again been confirmed
	III	Sharma *et al.* (2003) (33)	RCT Parallel Double-blind 2 weeks	139 (134) subjects Non perio 88 ♀ 46 ♂ Mean age: 36.4[§] Age range: 18–64	Hexetidine 0.1%, CHX 0.12%	Hexetidine rinse is effective in reducing supragingival plaque and gingival inflammation
	IV	Williams *et al.* (1987) (34)	RCT Crossover Double-blind 3 weeks	29 (29) subjects Non perio 19 ♀ 10 ♂ Average age: 28 Age range: 19–58	Hexetidine 0.1%, Placebo	The hexetidine component in Oraldene mouthwash produced a significant reduction in the accumulation of dental plaque on the tooth surfaces within the specific limits of the investigation
≥4 weeks	V	Chadwick *et al.* (1991) (35)	RCT Crossover Double-blind 6 weeks	40 (38) subjects with aphthous ulcerations Perio: ? 27 ♀ 13 ♂ Mean age: 35.5 Age range: 16–66	Hexetidine 0.1%[‡], Placebo[‡]	The hexetidine rinse provided no significant benefit in terms of oral hygiene or gingival health
	VI	Ernst *et al.* (2005) (36)	RCT Parallel Double-blind 4 weeks	101 (90) subjects Non perio ? ♀ ? ♂ Mean age: 30.85[§] Age range: ?	Hexetidine 0.1%[†], CHX 0.1%[†], Placebo[†]	Hexoral is a useful alternative to chlorhexamed mouthrinse. It also causes less discolouration

RCT, randomized controlled trial; CCT, controlled clinical trial; CHX, chlorhexidine mouthwash.
? = Not specified/unclear.
[†]Rinsing after brushing.
[‡]Subjects retaining their normal oral hygiene procedures.
[§]Calculated by the authors of this review.
[¶]Parodex, Médicament, France.
[††]Prexidine, Pred, France.

Interventions and regimen

Four studies (#I, II, III, IV) used hexetidine as a monotherapy; no other oral hygiene procedure was permitted during the experimental period. Other studies (#V, VI) used hexetidine as an adjunct to daily oral hygiene procedures. Baseline prophylaxis was provided in four studies (#I, II, III, IV). Two studies (#IV, V) compared hexetidine with a placebo mouthwash that contained all of the constituents of the test product except hexetidine. The hexetidine mouthwashes used were of various brands such as Oraseptic (#III), Oraldene (#I, IV, V), Hexoral (#VI) and Hextril (#II). Consequently, the mouthwashes used in the studies contained different concentrations of hexetidine. Verbal and/or written instructions were given in all studies. Rinsing was performed unsupervised in all but one study (#III). In that study (#III), all participants rinsed while being supervised during the day and unsupervised on weekend and evenings, but were given a diary to record their rinsing history in order to monitor participant compliance. In two studies (#V, VI), subjects were asked to continue their normal oral hygiene procedures. The rinsing time varied, ranging from 30 s (#III, VI) to 1 min (#I, II, VI). In study #IV, the rinsing time was not mentioned. In four studies (#III, IV, V, VI), the participants rinsed three times daily. In two studies (#II, VI), the subjects rinsed twice daily.

Side effects, smoking and industry funding

Three important side effects were reported in the studies. The most frequently mentioned effect was extrinsic tooth stain. The examiners observed more tooth staining in the chlorhexidine group (66%) than in the group using hexetidine (4%) (#II). Dark stain was more pronounced on the teeth among smokers (#I). A change in taste sensation was reported in study #VI for the hexetidine group. A large number of subjects also complained about sensitivity of the oral mucosa. A high concentration of hexetidine (0.14%) caused more adverse effects than 0.1% hexetidine. Funding was mentioned in four studies; study #IV was funded by the Liverpool School of Dental Hygiene, study #VI by the Department for Operative Dentistry, Johannes Gutenberg University Mainz, Germany, study #V by Parke-Davis Research Laboratories (UK) and study #II by Pred, France.

Quality assessment

Quality assessment values including external, internal and statistical validity are presented in Table 3. Based on a summary of these criteria, the estimated potential risk of bias is low in two of the six studies (#III, VI), moderate for two studies (#II, V) and high for two studies (#I, IV). One study received a score of 1B (#II). Three studies scored 1B because they lacked

Table 3. **Quality assessment of the studies analysed**

	<4 weeks				≥4 weeks	
Study	I	II	III	IV	V	VI
Quality criteria						
Internal validity						
Random allocation	–	+	+	+	+	+
Allocation concealment	?	?	?	?	?	?
Blinded to patient	–	+	+	+	+	+
Blinded to examiner	+	+	+	+	+	+
Blinding during statistical analysis	?	?	+	?	?	?
Balanced experimental groups	+	?	+	?	?	+
Reported loss to follow-up	?	+	+	?	+	+
No. of dropouts (%)	?	–	3.6%§	?	5%§	10.89%§
Treatment identical, except for intervention	+	+	+	+	+	+
External validity						
Representative population group	+	+	+	+	+	+
Eligibility criteria defined	+	+	+	+	+	+
Statistical validity						
Sample size calculation and power	?	?	?	?	?	?
Point estimates	+	+	+	+	+	+
Measures of variability presented for the primary outcome	+	+	–	+	+	+
Include an intention-to-treat analysis	?	+	–	?	?	–
Authors' estimated risk of bias	High	Moderate	Low	High	Moderate	Low
Levels of evidence (23)	2b	1b	1b–	2b	1b–	1b–

? = Not specified/unclear.
+ = Yes.
– = No.
§Calculated by the authors of this review.

confidence intervals (#III, VI, V). Two studies were low quality RCTs with scores of 2B (#I, IV).

Outcome results

Comparison of baseline and end results within groups

None of the selected short-term studies analysed the changes in plaque scores over time. Of the selected studies ≥4 weeks in duration, one study observed no statistical significant change in any of the groups (#V), whereas the other 6-week study (#VI) did find a statistical significant reduction in plaque in all three groups. Analogous to the plaque scores, one of the two studies ≥4 weeks in duration (#VI) also observed statistical significant changes in gingivitis parameters over time for all study groups (see Table 4a–c).

Comparisons between groups

Differences between hexetidine concentrations used and the comparisons are presented in a descriptive manner in Table 5. Two short-term studies (#I, II) showed a statistical significant difference in favour of hexetidine on plaque scores compared with the negative control. One (#VI) of the two studies ≥4 weeks in duration also showed a statistical significant effect between hexetidine and the negative control, while the other study (#V) did not.

Two short-term studies (#I, II) found hexetidine to be less effective than a positive control, while one (#I) observed no difference compared with 0.2% chlorhexidine on plaque control. The study #VI ≥4 weeks in duration observed no difference between 0.1% hexetidine and 0.1% chlorhexidine. With respect to gingivitis and bleeding, neither of the two studies ≥4 weeks

Table 4. **Summary and overview of selected studies**

#	Index	Groups	Baseline	End	Difference	Significant base-end
(a) Outcomes with respect to parameters of interest- short-term effects on plaque						
IV	Silness & Löe (41)	Hexetidine 0.1%	0.48 (0.35[§])	0.72 (0.35[§])	+0.24[§]	?
		Placebo	0.81 (0.45[§])	1.77 (0.49[§])	+0.96[§]	?
I	Silness & Löe (41)	Hexetidine 0.1%	?	0.97 (0.51)	?	?
		Hexetidine 0.14%	?	0.51 (0.26)	?	?
		CHX 0.2%	?	0.20 (0.17)	?	?
III	Turesky modification of Quigley & Hein (42)	Hexetidine 0.1%	2.75	2.15	−0.60[§]	?
		CHX 0.12%	2.77	2.17	−0.60[§]	?
II	Turesky modification of Quigley & Hein (42)	Hexetidine 0.2%	?	1.925 (0.384)	?	?
		CHX 0.2%	?	1.557 (0.327)	?	?
		CHX 0.12%[¶]	?	1.676 (0.307)	?	?
		CHX 0.12%[††]	?	1.673 (0.357)	?	?
		CHX 0.1%	?	2.117 (0.422)	?	?
		Saline 0.9%	?	2.528 (0.444)	?	?
(b) Outcomes with respect to parameters of interest- long-term effects on plaque						
V	Silness & Löe (41)	Hexetidine 0.1%	0.81 (0.32)	0.76 (0.27)	−0.05[§]	No
		Placebo	0.84 (0.27)	0.83 (0.28)	−0.01[§]	No
VI	Modified approximal plaque index (43)	Hexetidine 0.1%	69.0 (21.3)	41.4 (21.0)	−27.6[§]	Yes
		CHX 0.1%	73.4 (18.6)	38.5 (23.2)	−34.9[§]	Yes
		Placebo	67.2 (25.1)	53.6 (20.4)	−13.6[§]	Yes
(c) Outcomes with respect to parameters of interest- long-term effects on gingival parameters						
V	Undefined gingival index	Hexetidine 0.1%	0.64 (0.22)	0.64 (0.27)	+0.00[§]	No
		Placebo	0.62 (0.20)	0.60 (0.23)	−0.02[§]	No
VI	Bleeding on marginal probing index (44)	Hexetidine 0.1%	0.65 (0.34)	0.40 (0.34)	−0.25[§]	Yes
		CHX 0.1%	0.66 (0.31)	0.38 (0.24)	−0.28[§]	Yes
		Placebo	0.66 (0.33)	0.48 (0.34)	−0.18[§]	Yes
VI	Gingival index (45)	Hexetidine 0.1%	1.11 (0.88)	0.47 (0.49)	−0.64[§]	Yes
		CHX 0.1%	1.21 (0.68)	0.45 (0.45)	−0.76[§]	Yes
		Placebo	1.09 (0.71)	0.56 (0.49)	−0.53[§]	Yes

CHX, chlorhexidine mouthwash.
? = Not specified/unclear.
+ = Yes.
− = No.
[§]Calculated by the authors of this review.
[¶]Parodex, Médicament, France.
[††]Prexidine, Pred, France.

Table 5. **Summary of whether there was a reported significant difference in favour of hexetidine mouthwash compared with the control groups**

Author(s) #	Hexetidine (%)	Plaque index	Comparison
(a) Studies with <4-week durations			
IV	0.1	+	Placebo
II	0.2	+	0.9% saline
II	0.2	–	0.2% CHX
II	0.2	–	0.12% CHX[¶]
II	0.2	–	0.12% CHX[††]
II	0.2	?	0.1% CHX
I	0.14	0	0.2% CHX
I	0.1	–	0.2% CHX
III	0.1	?	0.12% CHX

Author(s) #	Hexetidine (%)	Plaque index	Gingival index	Bleeding index	Comparison
(b) Studies with ≥4-week durations					
VI	0.1	+	0	0	Placebo
V	0.1	0	0	□	Placebo
VI	0.1	0	0	0	0.1% CHX

CHX, chlorhexidine mouthwash.
[†]Rinsing after brushing.
[‡]Subjects retaining their normal oral hygiene procedures.
[§]Calculated by the authors of this review.
[¶]Parodex, Médicament, France.
[††]Prexidine, Pred, France.
+ = Significant difference in favour of hexetidine.
0 = No significant difference.
□ = No data available.
– = Control significantly more effective.
? = Not specified/unclear.

in duration found a statistical significant difference between hexetidine and either the placebo or 0.1% chlorhexidine.

Discussion

Plaque control is the cornerstone of the management of gingival inflammation. Whereas mechanical means of plaque removal have gained widespread acceptance, it is interesting to examine the adjunctive benefits of chemotherapeutic mouthwash. In today's Western population, mouthrinses are accepted as adjunctive agents for prophylaxis and the battle against gingivitis, periodontal disease and caries. An increasing level of awareness about oral microbiology and plaque has led to the development of specific strategies utilizing the antimicrobial effects of chemical substances. Hexetidine formulated as a mouthrinse is available in a number of markets worldwide, with indications for the treatment of a variety of conditions of the oropharynx.

This systematic review was conducted to provide insight into the effects of hexetidine mouthwash on the prevention of plaque accumulation and gingival inflammation based on the currently available literature. A systematic review can be defined as a review using a clearly formulated question that attempts to minimize bias using systematic and explicit methods to identify, select, critically appraise and summarize relevant research (37). The results of this review do not allow for a quantitative outcome. Descriptive analysis indicates that a positive effect on plaque can be expected for hexetidine mouthwash compared with a placebo.

Hexetidine and chlorhexidine

It is evident from the literature that chlorhexidine has an antimicrobial effect, inhibits plaque accumulation and prevents gingival inflammation (38). Compared with other antiseptics, chlorhexidine has been shown to be among the most effective (39). However, chlorhexidine may cause serious side effects such as tooth discolouration. Therefore, there is a need for an alternative mouthwash with an effectiveness similar to chlorhexidine mouthwash but without its adverse effects. From the present results, it can be deduced that hexetidine mouthwash tends to be less effective than chlorhexidine in inhibiting plaque. There are no reports of side effects such as discolouration, changes in the sense of taste, hypersensitive reactions of the oral mucosa (36) and an erosive effect of its metabolites on tooth enamel (40). Consequently, hexetidine mouthwash does not appear to be a suitable alternative to chlorhexidine mouthwash.

Hexetidine and side effects

In the studies selected for this review, different concentrations of hexetidine were used, namely 0.1%, 0.14% and 0.2%. Higher concentrations caused more side effects compared with lower concentrations and should not be used routinely in a

mouthrinse. The study by Bergenholtz & Hänstrom (31) that evaluated the plaque-inhibiting effect of hexetidine mouthwash compared with that of chlorhexidine mouthwash showed that 0.14% hexetidine mouthwash was more effective in plaque removal than 0.1% hexetidine mouthwash and was comparable with the chlorhexidine mouthwash used.

Carry-over effect

A highly significant carry-over effect or treatment sequence effect was detected when analysing the data of the crossover study by Williams *et al.* (34) (paired data). This may have been because the 7-day washout period was insufficient to allow adequate bacterial recolonization in the mouth. This, in turn, suggests that the volunteers who received active mouthwash during the first week may have been protected against plaque for a longer period. Volunteers who received placebo during the first week would not have had this protection. Therefore, the authors (34) decided to restrict the analysis to a parallel group study of 1 week only. During this period, the growth of dental plaque was significantly reduced by 59% after the use of hexetidine.

Two studies of ≥4-week durations were selected for this review. One study failed to show any effect for any group; no reduction in gingival bleeding and supragingival plaque formation was observed (35). However, baseline measurements suggested that the volunteer subjects did not have significant supragingival plaque or gingivitis, making improvement more difficult to detect. One reason for this could have been the relatively good oral hygiene of these patients, which may have masked any small plaque inhibitory effects of the active rinse.

The inclusion of subjects prone to plaque and gingivitis appears to be important for determining the efficacy for the clinical endpoints.

Substantivity of hexetidine

The efficiency of mouthrinses in the oral cavity depends on many different physiological factors. Different areas of the oral cavity are exposed differently to a mouthrinse depending for instance on the location of the salivary secretion. Accordingly, it is vital that the mouthrinse agent has an initial bactericidal effect, so that the effectiveness is prolonged through higher adhesion to the tooth surface and oral mucosa. The retention and persistence of the action of the agent in the mouth are often referred to as substantivity. Substantivity can be assessed by measuring the magnitude and, in particular, the duration of decreases in salivary bacterial numbers after a single exposure to the antimicrobial agent or product (7, 38).

The substantivity of hexetidine, as determined by the magnitude and duration of suppression of salivary bacterial counts, is markedly less than that of chlorhexidine, despite having somewhat similar antimicrobial activity *in vitro* (7). Hexetidine showed a statistical insignificant trend compared with saline of persistence somewhere between 1 and 3 h.

Thus, it would appear that increasing the frequency of use to three times a day, as opposed to twice a day, would provide additional benefits to gingival health in this group of individuals.

Conclusion

In conclusion, this review is suggestive of hexetidine mouthwashes to provide better effects regarding plaque reduction than placebo mouthwashes. However, they are statistically less effective than a chlorhexidine mouthwash and also less effective in reducing gingival inflammation than a chlorhexidine. Considering the potential benefits in the light of the observed side effects, hexetidine appears to be a poor alternative to chlorhexidine. Heterogeneity of included and available studies does not allow for any strong interferences.

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest. This study was self-funded by the authors and their institutions.

References

1 Keyes PH, Jordan HV. Periodontal lesions in the Syrian hamster-III Findings related to an infectious and transmissible component. *Arch Oral Biol* 1964; **32:** 377–400.
2 Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. *J Periodontol* 1965; **36:** 177–187.
3 Lindhe J, Hamp SE, Löe H. Experimental periodontitis in the Beagle dog. *J Periodont Res* 1973; **8:** 1–10.
4 Axelsson P, Nyström B, Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. *J Clin Periodontol* 2004; **31:** 749–757.
5 Paraskevas S. Randomized controlled clinical trials on agents used for chemical plaque control. *Int J Dent Hyg* 2005; **3:** 162–178.
6 Eley BM. Antibacterial agents in the control of supragingival plaque – a review. *Br Dent J* 1999; **186:** 286–296.
7 Roberts WR, Addy M. Comparison of the *in vivo* and *in vitro* antibacterial properties of antiseptic mouthrinses containing chlorhexidine, alexidine, cetylpyridinium chloride and hexetidine. *J Clin Periodontol* 1981; **8:** 295–310.
8 Ashley KC. The antimicrobial properties of two commonly used antiseptic mouthwashes–Corsodyl and Oraldene. *J Appl Bacteriol* 1984; **56:** 221–225.
9 Wile DB, Dinsdale JR, Joynson DH. Hexetidine (Oraldene): a case report on its antibacterial and antifungal properties on the oral flora in healthy subjects. *Curr Med Res Opin* 1986; **10:** 82–88.
10 Mörmann JE, Muhlemann HR. Synergistic inhibitory effect of zinc and hexetidine on *in vitro* growth and acid production of *Streptococcus* mutans. *J Dent Res* 1983; **62:** 135–137.
11 Kolokotronis A, Sofianou D, Doumboias I, Papanagiotou P. Comparison *in vivo* and *in vitro* of the antibacterial action of the antiseptics hexetidine and povidone-iodine. *ZWR* 1983; **92:** 44–46.
12 Anonymous. Hexetidine. *J Am Med Assoc* 1957; **165:** 1142–1143.
13 Anonymous. Oraldene – an antiseptic mouthwash. *Drug Ther Bull* 1970; **8:** 87–88.

14 Dutch Cochrane Center. RCT-checklist of the Dutch Cochrane Center. Available at: http://www.cochrane.nl/Files/documents/Checklists/RCT.pdf (accessed 12 October 2008).
15 CONSORT. Consort statement. Available at: http://www.consort statement.org/mod_product/uploads/CONSORT%202001%20check list.doc (accessed 12 May 2009).
16 Moher D, Schulz KF, Altman D. CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; **285:** 1987–1991.
17 Moher D, Schulz KF, Altman DG. CONSORT GROUP (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med* 2001; **134:** 657–662.
18 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357:** 1191–1194.
19 Moher D, Schulz KF, Altman DG; CONSORT. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 2001; **1:** 2.
20 Esposito M, Coulthard P, Worthington HV, Jokstad A. Quality assessment of randomized controlled trials of oral implants. *Int J Oral Maxillofac Implants* 2001; **16:** 783–792.
21 Needleman I, Moles DR, Worthington H. Evidence-based periodontology, systematic reviews and research quality. *Periodontol 2000* 2005; **37:** 12–28.
22 Verhagen AP, de Vet HC, de Bie RA *et al*. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998; **51:** 1235–1241.
23 Centre for Evidence-based Medicine, University of Oxford (England). Levels of Evidence (March 2009). Available at: http://www.cebm.net/index.aspx?o=1025 (accessed 11 August 2010).
24 American Dental Association. Acceptance Program Guidelines. Chemotherapeutic Products for Control of Gingivitis (July 2008). Available at: http://www.ada.org/ada/seal/standards/guide_chemo_ging.pdf (accessed 11 August 2010).
25 Cowell CR, Saxton CA, Sheiham A, Wagg BJ. Testing therapeutic measures for controlling chronic gingivitis in man: a suggested protocol. *J Clin Periodontol* 1975; **2:** 231–240.
26 American Dental Association. Acceptance Program Guidelines. Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis (September 1997). Available at: http://www.ada.org/ada/seal/standards/guide_adjunctive.pdf (accessed 11 August 2010).
27 Virga C, Beltramo D, Landa C, Passalacqua N, Dorronsoro S. A comparative study *in vivo* of the therapeutic effect of triclosan, hexetidine and chitosan. *Acta Odontol Latinoam* 2002; **15:** 3–9.
28 Grytten J, Tollefsen T, Afseth J. The effect of a combination of copper and hexetidine on plaque formation and the amount of copper retained by dental plaque bacteria. *Acta Odontol Scand* 1987; **45:** 429–433.
29 Hefti AF, Huber B. The effect on early plaque formation, gingivitis and salivary bacterial counts of mouthwashes containing hexetidine/zinc, aminefluoride/tin or chlorhexidine. *J Clin Periodontol* 1987; **14:** 515–518.
30 Giertsen E, Svatun B, Saxton A. Plaque inhibition by hexetidine and zinc. *Scand J Dent Res* 1987; **95:** 49–54.
31 Bergenholtz A, Hänström L. The plaque-inhibiting effect of hexetidine (Oraldene)-mouthwash compared to that of chlorhexidine. *Community Dent Oral Epidemiol* 1974; **2:** 70–74.
32 Harper PR, Milsom S, Wade W, Addy M, Moran J, Newcombe RG. An approach to efficacy screening of mouthrinses: studies on a group of French products (II). Inhibition of salivary bacteria and plaque *in vivo*. *J Clin Periodontol* 1995; **22:** 723–727.
33 Sharma NC, Galustians HJ, Qaqish J, Charles CH, Vincent JW, McGuire JA. Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash. *J Clin Periodontol* 2003; **30:** 590–594.
34 Williams MJ, Adams D, Hillam DG, Ashley KC. The effect of hexetidine 0.1% in the control of dental plaque. *Br Dent J* 1987; **163:** 300–302.
35 Chadwick B, Addy M, Walker DM. Hexetidine mouthrinse in the management of minor aphthous ulceration and as an adjunct to oral hygiene. *Br Dent J* 1991; **171:** 83–87.
36 Ernst CP, Canbek K, Dillenburger A, Willershausen B. Clinical study on the effectiveness and side effects of hexetidine and chlorhexidine mouthrinses versus a negative control. *Quintessence Int* 2005; **36:** 641–652.
37 Needleman IG. Guide to systematic reviews. *J Clin Periodontol* 2002; **29:** 6–9.
38 Löe H, Schiott CR. The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. *J Periodont Res* 1970; **5:** 79–83.
39 Gjermo P, Baastad KL, Rölla G. The plaque inhibiting capacity of 11 antibacterial compounds. *J Periodontal Res* 1970; **5:** 102–109.
40 Pontefract H, Hughes J, Kemp K, Yates R, Newcombe RG, Addy M. The erosive effects of some mouthrinses on enamel. A study *in situ*. *J Clin Periodontol* 2001; **28:** 319–324.
41 Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* 1964; **22:** 121–135.
42 Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of Vitamine C. *J Periodontol* 1970; **41:** 41–43.
43 Lange DE, Plagmann HC, Eenboom A, Promesberger A. klinische Bewertungsverfahren zur Objektivierung der Mundhygiene. *Dtsch Zahnärztl Z* 1977; **32:** 44–48.
44 Van der Weijden GA, Timmerman MF, Nijboer A, Reijerse E, Van der Velden U. Comparison of different approaches to assess bleeding on probing as indicators of gingivitis. *J Clin Periodontol* 1994; **21:** 589–594.
45 Löe H. The gingival index, the plaque index and the retention index systems. *J Periodontol* 1967; **38:** 610–616.