Review on Mouth Rinses with Special Consideration to Chlorhexidine in Clinical Practice

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Introduction

A mouth rinse may be defined as a substance that is swished around the oral cavity and then expectorated in order to freshen the mouth and breath. Thus, its purpose is primarily cosmetic. The most popular form is in a liquid, although mouth rinse troches, lozenges, concentrates and sprays are also available. In the case of liquid mouth rinses, the material may be introduced into the oral cavity in either a full strength or in a diluted form (Stallard, 1982). Mouth rinses are also referred to as mouthwashes, gargles and oral antiseptics.

By definition, water and saline solutions could be considered as the simplest mouth rinse. However, the flavored formulations comprise characteristic flavors, such as cinnamon, clove, peppermint, spearmint, wintergreen and anise. Mouth rinses are often prescribed for therapeutic value owing to its antimicrobial action.

Composition of mouth rinses

The basic ingredients in liquid mouth rinse formulations are water, alcohol, flavoring oils and coloring agents. Other components may include humectants, astringents, emulsifiers, sweeteners and antimicrobial agents as therapeutic substances (Darlington 1968, Rosenthal 1972).

Water makes up the highest part of the mouth rinse formulation however ethyl alcohol up to 15-30 % concentration is primarily present to enhance the solubility of the flavoring oils and other components of low solubility in water.

The humectants primarily serve to retain moisture and provide chemical and physical stability, they include glycerine and sorbitol. The astringent when present are usually Zinc and Aluminum salts. Emulsifiers are used to reduce surface tension and assist in the stabilization of the other ingredients; they include polyoxyethylene sorbitan fatty acid esters and esters & block copolymers consisting of polyoxyethylene and polyoxypropylene. Saccharine is widely used sweetening agent. Common anesthetics when used are benzocaine and benzyl alcohol.

Antimicrobials used in mouth rinses

The important ingredient in the mouth rinse formulation is the antimicrobial agent. The most commonly used antimicrobials with marked antiplaque effect are chlorhexidine and macrolide antibiotics. Besides quaternary ammonium compounds such as benzethonium chloride, cetylpyridinium chloride and combination of cetylpyridinium chloride and domiphen bromide are reported to have a moderate effect on dental plaque (Beiswanger et al 1974). The phenolic compounds used are phenol, thymol, betanapthol and hexylresorcinol. Miscellaneous antimicrobial agents include povidone iodine, hexetidine and certain organic mercurial compounds.

Other compounds with antimicrobial properties that have shown a moderate degree of effectiveness in reducing plaque, calculus and gingivitis include thymol & eucalyptol (Gomer et al 1972), hexetidine (Bergenholtz 1974), alexidine (Lobene 1973), various peroxides (Shipman et al 1971, Rundegren et al 1973), Zinc phenolsulfonate & Zinc tribromsalan (Fischman et al 1973), Sodium Hypochlorite (Lobene et al 1972) and amine fluoride (Lobene et al 1974).

Oxygen liberating agents such as Sodium perborate and urea peroxide have also been used to some extent, however they have limited capabilities as antimicrobial agents. The effect of peroxides to deliver oxygen radicals mainly hydrogen peroxide has been demonstrated (Miyasaki et al 1986). The clinical results have been encouraging with the use of peroxides in rinse formulations (Wennstrom & Lindhe 1979, Roseling et al. 1983).

Antibiotic compounds that have also shown effectiveness in clinical trial include vancomycin (Mitchell et al 1967), erythromycin (Lobene et al 1969), kanamycin (Loesche et al 1971), actinobolin (Armstrong & Hunt, 1972) and tetracycline.

A variety of other miscellaneous antimicrobial substances used in mouth rinses include Sodium ricinoleate, urea, polyvinylpyrrolidone, lysozyme, vitamin C as a surface-active organophosphorous compound and Ascoxal (a mixture of ascorbic acid, sodium percarbonate & Copper sulphate) (Parsons 1974).

Mouth rinse containing a proteolytic enzyme obtained from a mutant strain of Bacillus subtilis reported to have shown effect on reducing plaque formation (Schiff & Shaver 1970). Another compound which have shown to reduce calculus when evaluated in a mouth rinse is ethane-1-hydroxy-1,1diphosphonate-hexahydrate (Muhlemann et al. 1970).

Certain fluoride containing mouth rinses also claim to reduce the incidence of dental caries by making the teeth more resistant to caries formation (Torell, Siberg 1962, Weisz 1960). The commonly used Fluoride-containing mouth rinses are aqueous solution of 0.2 % sodium fluoride, 0.05 % sodium fluoride and acidulated phosphate sodium fluoride.

(Table-1) Anti-microbial agents and their clinical status:

Class	*Sub-class*	*Examples*	*Clinical status*
Cationic organic molecules	-Bis-biguanides -Quaternary ammonium salts -Plant alkaloids	-Chlorhexidine -Cetyl pyridinium chloride -Sanguinarine	Good clinical efficacy *in vivo* Poor clinical efficacy *in vivo* Poor clinical efficacy *in vivo*
Metal compounds	_	-Stannous fluoride -Zinc citrate	Moderate clinical efficacy *in vivo* Moderate clinical efficacy *in vivo*
Non-charged phenolics	_	-Triclosan -Essential oils of Listerine	Moderate clinical efficacy *in vivo* Moderate clinical efficacy *in vivo*
Oxidative enzymes	_	-Amyinoglucosidase plus glucose oxidase	Few data to support efficacy *in vivo*
Peroxides	_	-Hydrogen peroxide: peroxydiphosphate	Few data to support efficacy *in vivo*
Antibiotics	_	-Amoxycillin, Tetracyline etc.	Clinically effective, but application limited to refractory cases of periodontitis

(Table-2) Comparative properties of anti-plaque agents:

Agent	*Intrinsic efficacy*	*Broad spectrum*	*Substantivity*	*Lack of adverse effects*	*Compatibility with toothpaste formulations*	*Chemical stability*
Bis-biguanides	++	✓	+	-	-	+
Quaternary ammonium compounds	+	✓	+	-	-	+
Metal ions	+	✓	+	+	+	+
Phenolic compound	+	✓	+	+	+	+
Peroxides	+	?	?	+/-	+/-	+/-
Enzymes	-/+	✓	?	?	?	+/-
Sugar alcohols	-/+	?	+/-	-	-	+
Combination systems	++	✓	+	-	+	+

Functions of mouth rinse

Cosmetic functions: The primary objective in using a mouth rinse is cosmetic whereby the mouth and breath are freshened and masks the halitosis to an extent. In this respect, it could be considered to serve a social function.

Therapeutic functions: A therapeutic mouth rinse is a formulation, which is used to transfer the drug substance to the hard and soft tissues of the oral cavity. This drug substance then imparts a chemical, physiologic or pharmacological action that is manifested clinically as a reduction in the incidence of plaque, dental caries, calculus and gingival diseases. Also, claims in the references to the relief of sore throat and prevention of the common cold would also be considered therapeutic, but primarily from a general aspect, rather than an oral aspect.

Chlorhexidine

More than 350 kinds of microbes have been identified as living in the human mouth (Moore, Holdeman, Cato 1985). They range from gram +ve, gram -ve, aerobes and anaerobes bacteria, virus, yeast, fungus and amoebae. The plaque control methods have been attempted using various mechanical devices, oral irrigation devices and chemical plaque control methods. The ADA Council on Dental Therapeutics adopted a program for acceptance of plaque control agents and accepted chlorhexidine and essential oil mouthwash (Listerine) for the treatment of gum diseases (Carranza, Newman 1996).

Till date chlorhexidine gluconate is the only prescription antimicrobial mouth rinse which is approved by both the FDA (Food & Drug Administration) and the ADA (American Dental Association) for the reduction of gingival inflammation (Carranza, Newman 1996).

Chlorhexidine chemically a diguanidohexane with pronounced antiseptic properties has shown the most positive results and found to be the most commonly used anti-plaque agent.

Properties of Chlorhexidine

Antimicrobial/Antiplaque:

Chlorhexidine is effective against gram +ve, gram –ve, aerobe and anaerobe microorganisms and yeast.

Clinical investigations showed that a mouth rinse containing 0.1 % chlorhexidine is effective against calculus formation (Renggli et al. 1966, Schroeder et al. 1962) and a mouth rinse containing 0.2 % chlorhexidine is effective against plaque and calculus formation and against gingival disease (Davies et al. 1970, Gjermo et al. 1973, Loe *et al.* 1970).

All anti-microbial agents are able to inhibit the growth of microorganisms. However the potent agent such as chlorhexidine, may be bactericidal (Kornman 1986); other less active agents, such as zinc, may act solely as bacteriostatic (Izaquirre - Fernandez *et al.*1989) at clinically relevant levels. Although most of the currently used chemical anti-plaque agents are broad spectrum anti-microbial agents (Cummins1991; van der Ouderaa 1991), not all microbial agents are effective anti-plaque agents *in vivo*. The clinical efficacy of a particular agent is associated with its long-term retention in the oral cavity at sub-MIC (minimal inhibitory concentration) levels (Gjermo *et al.*1970; Rolla *et al.* 1971; Afseth *et al.* 1983; van der Ouderaa and Cummins 1989). Under these conditions, these anti-plaque agent such as chlorhexidine probably affect the normal biological functions of bacterial cells, resulting in the inhibition of cell growth and, in some cases, cell death.

The antimicrobial action of chlorhexidine is exerted against a wide range of bacteria with Gram -ve species being generally less sensitive than Gram +ve types. It has been proposed that the primary action of chlorhexidine is adsorption on to the bacterial cell surface. This adsorption is followed by a disruption of the cytoplasmic membrane, but further events depend on the concentration of chlorhexidine present. Low concentrations allow leakage of cytoplasmic components while higher concentrations coagulate the cytoplasmic components and are thus more rapidly bactericidal (Hugo & Longworth 1966).

(Table-3) Comparative Antimicrobial activity of different mouth rinses

Agent	*Antimicrobial activity*	*Reference*
Chlorhexidine	Good broad spectrum activity with some specificity towards Gram +ve bacteria	Emilson 1977
Zinc	Moderate broad spectrum activity	Scheie 1989
Stannous	Inherent activity	Scheie 1989
Triclosan	Moderate broad spectrum activity	Ritchie et al. 1988
Essential oils	Moderate broad spectrum activity	-

(Table-4) Comparative actions of common mouth rinses:

Agent	*Action*
Chlorhexidine 0.12%	Bactericidal. Kills a wide spectrum of pathogenic microbiota. High substantivity. ADA-approved for reducing gingivitis.
Hydrogen Peroxide 1.7%	Bacteriostatic. Oxidizing effect inhibits anaerobic bacteria
Quaternary Ammonium Compounds	Bacteriostatic. Allows increased bacterial cell wall permeability and Decreased cell metabolism. Low substantivity.
Essential Oils	Bacteriostatic. Alters bacterial cell wall. Low substantivity. ADA-approved for reducing gingivitis.
Sanguinarine	Bacteriostatic. Most favorable results when paste and rinse are used together.
Zinc Chloride 1%	Astringent. Reduces inflammation and bleeding.
Fluorides Sodium 2% neutral Stannous	 Bacteriostatic. Moderate substantivity. Noted for desensitivity & anticaries effect.

It has been suggested that formation and retention of bacterial plaque on teeth might theoretically be interfered by chlorhexidine at various stages;

(1) Microorganisms responsible for plaque formation may be eliminated or reduced in number.
(2) The formation of bacterial and salivary products, which constitute the inter-microbial substance in plaque, may be inhibited.
(3) Established plaques may be dissolved.
(4) Calcification of plaque may be counteracted.
(5) Colonization of bacteria on the tooth surface may be inhibited.

The pathogenicity of plaque may be reduced by interference with the metabolism of the plaque bacteria.

Cationic compound:

Besides quaternary ammonium compounds, sanguinarine and pyrimidine derivatives such as hexetidine, bis-biguanides such as chlorhexidine and alexidine are cationic or positively charged compounds. These compounds are generally efficacious to very efficacious *in vivo* when dosed in mouth rinse formulations, with a broad spectrum of effect (Grossman *et al.* 1986). The structures and aspects in the oral cavity such as mucous membrane, tooth surface and plaque are generally negatively charged, thus chlorhexidine adheres to plaque, reducing the number of microorganisms in saliva and prevents its adsorption to the tooth surface, eliminating the chance to form acquired pellicle of the plaque. It has been shown that chlorhexidine molecule itself adsorb in the tooth surface competing with the microorgunisms

reducing the chance to form the plaque. This property has been attributed to the anti-plaque action of chlorhexidine. Similarly, bacterial cell wall is negatively charged, to which chlorhexidine molecules get attached owing to its positive charge. So the bacterial cell wall gets damaged as the permeability of the cell wall alters and intra-cellular structures leak out and the cytoplasmic proteins gets precipitated resulting to bacterial cell rupture.
It has been shown that there is an additional tooth surface antimicrobial effect with chlorhexidine which has affinity for hydroxyapatite and acidic salivary proteins, adsorbs to tooth surfaces *in vitro* (Rolla, Loe & Schiott 1970).

Substantivity:

Besides the suppression of oral microbial flora by chlorhexidine during its period of application, the pharmacokinetic studies supported the hypothesis that chlorhexidine is retained on oral surfaces and act as reservoirs for slow release of the agent as its concentration in saliva decreases (Gjermo 1989).

A study of the retention of chlorhexidine in the oral cavity reported that antibacterial properties were retained by saliva for 2 hours to several days following a 0.2% rinse (Rolla, Loe & Schiott 1971). Results of antibacterial activity and adsorption tests show that chlorhexidine binds with substances usually found on tooth surfaces i.e. hydroxyapatite, pellicle, bacterial polysaccharide and streptococcus *in vitro.*

The anti-plaque effects of chlorhexidine dosed *in vivo* are a result of the effects of the high concentrations delivered during application (at >MIC, Minimum Inhibitory Concentration levels) coupled with the effects from the retention on oral surfaces and from the presence at sub-MIC levels in saliva between applications. A detailed analysis of the literature suggests that the latter have dominant effects (Gjermo1989, Cummins 1991).

(Table-5) Summary of typical oral substantivity data for anti-plaque agents:

Agents	*Total retention*	*Salivary half-life (min) (period of measurement)*	*Plaque level (m*g/g plaque 1 hour after brushing)*	Reference
Chlorhexidine	32%	120 (0-8 hr)	ND	Goodson 1989
Listerine	ND	ND	ND	Gilbert 1987
Zinc (Zinc citrate / Triclosan)	24%	47 (0-2 hr)	~100	Saxton et al. 1986
Triclosan (Zinc citrate 1987	25%	20	50	Gilbert & Williams
/ Triclosan) Triclosan (+Gantrez)	ND	26	25	Afflitto et al. 1989

Review of the literature

Chlorhexidine is the most studied anti-bacterial mouth rinse (Lang & Brecx 1986). Various data's have been shown on efficacies of the solution in its effect on oral cavity.

Two daily rinses with 10 ml of a 0.2% aqueous solution of chlorhexidine gluconate almost completely inhibits the development of dental plaque, calculus and gingivitis in human model for experimental gingivitis (Loe & Schiott 1970), dissolves newly formed plaque and significantly reduce old plaque (Flotra, 1970). Clinical studies of several months' duration have reported plaque reduction of 45% to 61% and reductions in gingivitis by 27% to 67% (Lang, Hotz, Graf et al. 1982). It has shown that the 0.12% chlorhexidine preparation is the most effective agent currently available in US for reducing plaque and gingivitis (Lang & Brecx 1986). Daily oral irrigation by the patient with 0.06% chlorhexidine has been shown to be the most effective method for the treatment of gingivitis (Brownstein et al. 1990, Flemmig et al. 1990). The daily use of chlorhexidine is highly recommended post-surgically for 1-4 weeks and in patients with certain diseases with oral manifestations, such as acquired immuno-deficiency syndrome (AIDS) and blood dyscrasias. It is also recommended for those unable to perform adequate plaque control due to physical and mental inabilities (Carranza & Newman 1996).

Lang & Ramseier-Grossman showed that 400ml of a 0.02% solution of chlorhexidine (80mg total dose) applied once daily with a supra-gingival oral irrigator results in complete inhibition (Lang, Ramseier-Grossman 1981). Daily application of 200ml of a 0.06% solution of chlorhexidine (120mg total dose) with a supra-gingival oral irrigator is very effective in reducing naturally occurring gingivitis (Flemmig, Newman, Doherty et al. 1990). In this 6-month study, gingivitis was reduced by 42.5% by irrigating once daily with chlorhexidine, 24.1% by rinsing with chlorhexidine gluconate and 23.1% by irrigating with water (Newman, Flemmig, Nachnani et al. 1990).

Daily patient-applied home irrigation with 180ml of 0.04%c.g (72mg total dose) using a marginal irrigation tip significantly reduced gingival inflammation in periodontal maintenance patients (Jolkovsky, Waki, Newman 1990) with a 33.1% reduction in gingivitis scores over a 3-month period.

Daily mouth rinses with 0.2% aqueous solutions with chlorhexidine reduce the number of bacteria in saliva by 95% in the course of a few days. After about 15 days there was a slight increase in the number of bacteria and a new equilibrium was established at a level of 85-90% reduction, which was maintained over a 40 day experimental period (Loe & Schiott 1970).

Acute non-specific gingivitis is frequently very difficult to cure. The aim of the treatment should be to reduce the bacterial flora in the oral cavity. Apart from debridement and meticulous oral hygiene maintenance, chlorhexidine mouth rinses have been proven to assist with plaque control (Collins, Forrest, Walsh, 1986).

Many operators believe that an antiseptic mouthwash such as chlorhexidine should be given to patients 3 minutes before using an ultra-sonic scaler, to reduce the oral bacterial count and hence the bacterial count of the aerosol spray (Collins, Forrest, Walsh, 1986).

Dosage for chlorhexidine irrigation therapy & mouth rinse

The minimal daily dose of chlorhexidine gluconate required to be effective as a mouth rinse in reducing gingivitis may as low as 50mg (50ml of a 0.1% solution) (Cummings & Loe 1973). *In vitro* studies have indicated that chlorhexidine is bactericidal for tested organisms at concentrations of 18 to 33 mg/ml (Schiott & Loe 1972). When irrigating sub-gingivally *in vivo*, the blood and other materials that can interfere with chlorhexidine may be present. Therefore the concentration may have to be as high as 125mg/ml. Investigators have used a 0.02% to 0.06% concentration of chlorhexidine as an irrigant. The total dosage in one irrigation study ranged up to 120 mg/day (Fleming, Newman, Doherty *et al* 1990). In contrast, the total dosage of chlorhexidine as a mouth rinse is 36mg/day (30ml of a 0.12% solution). Therefore, irrigation with chlorhexidine generally requires a larger total dosage than for a mouth rinse.

Post-operative periodontal & oral surgical rinse with 0.12% chlorhexidine gluconate immediately after surgical procedure and twice daily until normal plaque control technique is resumed has been reported to be very effective (Newman, Sanz, Nachnani, Anderson *et al* 1989). A solution of 0.12% mouth rinse has also been used to prevent the development of dilantin induced gingivitis. The same has also been advised for the post-operative care of the implant cases

The initial clinical investigations indicated that a mouth rinse containing 0.1 % chlorhexidene was an effective calculus-preventive material (Stookey et al 1989). This material has been subjected to many clinical investigators, and it has been shown that a mouth rinse containing 0.2 % chlorhexidene is very effective against plaque and calculus formation as well as gingival disease.

The reduction of anaerobes and aerobes after a single 15ml of a 0.12 % chlorhexidine gluconate mouth rinse for 30 seconds are found to be remarkable as shown by a 5-hour study. One minute after rinsing, anaerobes were reduced by 72 % and aerobes were reduced by 74 %. Thirty minutes after rinsing, anaerobes were reduced by 74 % and aerobes were reduced by 72 %. After 1 hour, anaerobes were reduced by 72 % and aerobes reduced by 68 %. After 2 hours, anaerobes were reduced by 86 % and aerobes reduced by 89 %. Three hours after rinsing, both anaerobes and aerobes were reduced by 91 %. And even five hours after the mouth rinse, the reduction for the chlorhexidine group persisted, at that time the salivary anaerobes were reduced to 86 % and aerobes were reduced to 88 % (Buckner, Kayrouz & Briner 1993).

The data in the current study showed an immediate reduction of salivary anaerobes (72 %) and aerobes (74 %), one minute after rinsing with chlorhexidine. This effect continued for 5 hours with an 86 % reduction of anaerobes and 88 % reduction of aerobes. The persistence of chlorhexidine in the oral cavity has been studied. Bonesvoll et al showed that about 30 % of a single-mouthwash dose of chlorhexidine were adsorbed in the mouth, mainly on the soft tissue. The chlorhexidine is then slowly desorbed from the soft tissue into the saliva, providing levels at or above the minimum inhibitory concentration for the growth of many common oral bacteria for up to 24 hours. This substantivity explains the persistence

of chlorhexidine's effectiveness against salivary anaerobes and aerobes observed in the study (Buckner, Kayrouz & Briner 1993).

The effect of sub-lethal concentrations of chlorhexidine on the infectivity of bacteria has been studied *in vivo*. Holloway *et al* showed that treatment with sub-lethal concentrations of chlorhexidine decreased infectivity of Escherichia coli and Klebsiella aerogenes up to 64-folds. In this study, salivary microbes that survived a chlorhexidine rinse were exposed to sub-lethal concentration of chlorhexidine. It follows that the infectiveness of the surviving salivary microbes might also be decreased, thereby decreasing the possibility of dissemination of infectious microbes during dental procedures (Buckner, Kayrouz & Briner 1993).

Complete plaque inhibition has been reported with 0.2 % aqueous solution of chlorhexidine digluconate as mouth rinse (Loe & Schiott 1970). A comparative study on *in vivo* and *in vitro* plaque inhibition ability of eleven different anti-microbial agents against salivary bacteria showed that the chlorhexidine gluconate and acetate were the most effective *in vivo*, while quaternary ammonium compounds proved to be equally or more effective *in vitro* against salivary bacteria but exhibited no effect *in vivo* (Gjermo, Baastad & Rolla 1970).

Irrigation therapy by chlorhexidine solution

In-office sub-gingival irrigation using hand syringe with cannula tip is used as an adjunct to scaling and root planing procedures, which help in suppressing pathogens. As the suppressed organisms return to baseline percentages at varying intervals, the satisfactory clinical results with sub-gingival irrigation have been achieved during active phases of therapy with irrigation at 7-10 days intervals.

Irrigation therapy is helpful in maintaining certain areas that could be susceptible to infection, such as periodontal pockets, furcation areas, bridges and implants. These patients are best suited for home irrigation therapy that employs plastic or rubber-like tips. Chlorhexidine irrigation has resulted in decreased pocket depths and reduction in bleeding sites (Jolkovsky, Waki 1985).

The American Heart Association stated that gingival crevicular irrigation with effective anti-microbial as chlorhexidine digluconate solution may be used as an adjunct to antibiotics prophylaxis, particularly in patients who are at high risk for endocarditis and/or have poor oral hygiene (Sob, Newman, Strahan 1981).

American Heart Association also suggests that irrigation may be beneficial in reducing bacteremia prior to certain dental procedures. In fact, bacteremia was significantly reduced following dental extractions when the sulci surrounding these teeth were irrigated first.

Irrigation therapy is contra-indicated on patients with acute conditions, such as, periodontal abscess or ulcerative lesions. Additionally, healthy patients who exhibit no bleeding, normal pocket depths and clinical attachment levels, and who can control plaque with traditional oral hygiene measures do not require irrigation therapy.

Disadvantages of Chlorhexidine

Since there is little information on the long-term intensive use of chlorhexidine, its use instead of mechanical measures should not be recommended (Collins, Forrest, Walsh, 1986). While the results of short-term evaluation of chlorhexidine are encouraging, much more information is required on the long term effect on oral mucous membrane, on the ecological shifts induced in the oral flora and the effects of swallowed chlorhexidine on the gastrointestinal tract. Desquamative lesions in the vestibular mucosa have been observed with prolonged exposure (Flotra et al. 1971), while in another study no side effect were observed after over 2 years of use (Loe, Fehr, Schiott 1972). Studies in dogs have demonstrated that resistant strains of Proteus, Citrobacter, and Klebsiella may occur after 6 months of application of 0.2% chlorhexidine, twice daily to the teeth.

There are local, reversible side effects to chlorhexidine use, primary brown staining of teeth, tongue, and silicate and resin restorations and transient impairment of taste perception (Loe 1970)

Chlorhexidine is reported to cause brownish-black extrinsic stain on the tooth surface with the continuos use as dentifrices or mouth rinse (Flotra et al 1971).

The established disadvantages are:

- It has an unpleasant taste.
- Transient impairment of taste sensation.
- It may cause extrinsic staining of the teeth and restorations.
- Long-term use may result in calculus formation.
- Allergy to chlorhexidine has been reported, causing desquamation of gingival and oral mucous membrane.

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