

Review Article

Chlorhexidine- A Review

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ABSTRACT:

Plaque control is defined as the removal of microbial plaque and prevention of its accumulation on the tooth surface and adjacent gingival tissues to prevent calculus formation. Plaque control is of two types - Mechanical plaque control and Chemical plaque control. The level of mechanical plaque control achieved at individual level decreases on a time gradient. Hence a chemical plaque has to be addressed on individual level on daily basis for proper maintenance of oral health. 0.2% chlorhexidine (CHX) solution was the first clinically effective mouth rinse that inhibited supragingival plaque formation and thus the development of chronic gingivitis and caries. Due to its broad-spectrum antibacterial effect encompassing gram-positive as well as gram-negative bacteria, yeasts, dermatophytes and some lipophilic viruses, and the prolonged substantivity, chlorhexidine is still recognized as the "gold standard" for chemical plaque control.

Key words: Chlorhexidine, supragingival plaque.

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History of mouth rinse

The first reference to mouth rinsing as a formal practice is credited to Chinese medicine, about 2700 B.C.E. Recommendation was rinsing with the urine of a child. Mouth rinsing as an adjunct to mechanical cleansing became popular with the upper classes in the Roman period. Pliny recommended salty water used in an uneven number of Mouthfuls. Hippocrates advocated a mixture of salt, alum and vinegar. Other included a mixture of honey, oil and beer and a combination of dill, anise seed, myrrh and pure white wine. "Therapeutic rinsing" was especially popular among the Europeans, and persisted until the early 18th century. Mouth rinsing also had a religious connection. The Talmud contains instructions for rinsing the mouth between meals to remove food remnants and prevent admixing of meat and milk products, a violation of the dietary laws. Mechanical tooth cleaning and mouth rinsing were established practices by the 16th century.

The Zene Artzney (Medicines for the Teeth), published in Germany in 1530, contained a section on "How to save the teeth". The recommendations included washing the

mouth with burnt alum mixed with vinegar or myrrh boiled in wine. The final suggestion was "always after eating, wash the mouth with wine or beer, in order to wash away all that might adhere to the teeth and make them decay, produce bad odor, and destroy them".

W.D. Miller, in support of his Chemo parasitic theory of tooth decay, pointed out - There are places around every dentition which will remain untouched by even the most thorough application of an antiseptic, or the antiseptic will reach them in so diluted a condition that it possesses little or no action.¹

Mouth washes has been grouped into 3 categories

Group A Mouth washes with good substantivity and antibacterial spectrum and good anti-plaque effects. Agents with these properties are the bisguanides (the best of which is chlorhexidine), salifluor and delmopinol. These can be used to replace mechanical cleaning methods for short periods when this is not possible. Drawback of the bisguanides is staining which is strongly

linked to their substantivity. It precludes their prolonged use.

Group B Mouth washes with little or no substantivity but with a good antibacterial spectrum. Therefore, they have plaque inhibitory effects. These include Cetyl pyridinium chloride, Essential oil/ phenolic mouthwash, Listerine, Triclosan. They cannot be used to replace tooth brushing but can be used as adjuvants to mechanical cleaning.

Group C Mouthwashes with antibacterial, varying plaque inhibitory effects from moderate to low or no. These include Hexetidine (Oraldene), Povidone iodine, Oxygenating agents, Sanguinarine. These have limited or no adjuvant effects when combined with mechanical cleaning and therefore cannot be recommended for this purpose.²

The present meaning of dental plaque control includes only the supragingival and marginal areas because mouthwashes used under normal conditions do not reach the subgingival area. Only in the presence of inflamed tissues, when the gingiva is not tightly applied to the tooth surface, can a solution have some effect, but only at the entrance of the pocket.³

History of chlorhexidine

In 1947, a complex study to synthesize new antimalarial agents led to the development of the polybiguanides. These compounds showed significant antimicrobial potential. Davies et al (1954) demonstrated that this compound had bacteriostatic activity, especially against Gram-positive bacteria (linked to the central hexamethylene unit and the terminal benzene ring) and bactericidal activity (depending on the concentration). This compound did not modify the action of penicillin, streptomycin, chloramphenicol, oxytetracycline.

Experimental studies in albino mice revealed a low degree of toxicity at 10 days after the subcutaneous, intraperitoneal, intravenous or oral administration of a single dose of Chlorhexidine, as well as after a year of continuous oral administration.⁴

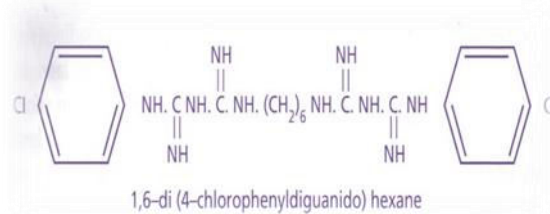
Chlorhexidine was developed in the 1940s by Imperial Chemical Industries, England, and marketed in 1954 as an antiseptic for skin wounds. (As Hibitane). Later, the antiseptic was more widely used in medicine and surgery including obstetrics, gynecology, urology and presurgical skin preparation for both patient and surgeon. Use in dentistry was initially for presurgical disinfection of the mouth and in endodontics. Plaque inhibition by chlorhexidine was first investigated in 1969 (Schroeder 1969). The definitive study was performed by Loe and Schiott (1970).⁵

Study showed that rinsing for 60 seconds twice per day with 10 ml of a 0.2% (20 mg dose) chlorhexidine gluconate solution in the absence of normal tooth cleaning, inhibited plaque regrowth and the development of gingivitis.⁶

Chemical structure

Chlorhexidine is an amphipathic molecule with hydrophilic and hydrophobic groups. Synthesized from proguanil and belongs to the biguanide family, a group of compounds with antimalarial activity.⁴

Chlorhexidine is a bisbiguanide antiseptic; being a symmetrical molecule consisting of two chlorophenyl rings and two biguanide groups connected by a central hexamethylene bridge. The compound is a strong base and dicationic at pH levels above 3.5, with two positive charges on either side of a hexamethylene bridge.⁶



Chlorhexidine is available in three forms- Digluconate, Acetate, Hydrochloride salts (as base molecule is insoluble in water)⁵

Most studies and most oral formulations and products have used the digluconate salt, which is manufactured as a 20% V/V concentrate. Digluconate and acetate salts are water-soluble but hydrochloride is very sparingly soluble in water.

Mechanism of action

The antiseptic binds strongly to bacterial cell membranes. At low concentration this results in increased permeability with leakage of intracellular components. At high concentration, chlorhexidine causes precipitation of bacterial cytoplasm and cell death.⁶ The bacterial cell wall is negatively charged and contains sulphates and phosphates

- Dicationic positively charged chlorhexidine is attracted to the negatively charged bacterial cell wall with specific and strong adsorption to phosphate containing compounds
- Alters the integrity of the bacterial cell membrane and chlorhexidine is attracted to the inner cell membrane
- Chlorhexidine binds to the phospholipids in the inner membrane and there is leakage of low molecular weight compounds like potassium ions
- Cytoplasm of cells get coagulated and precipitated by formation of phosphate complexes (adenosinetriphosphate, nucleic acids)....bactericidal stage which is irreversible.⁷

Substantivity of chlorhexidine

The ability of drugs to adsorb onto and bind to soft and hard tissues is known as substantivity and this property was first described for chlorhexidine in the 1970s. This property of chlorhexidine was associated with its ability to maintain effective concentrations for prolonged periods

of time and this prolongation of its action made it especially suitable for the inhibition of plaque formation.² A more recent study suggested that plaque inhibition is derived only from the chlorhexidine adsorbed to the tooth surface (Jenkins et al. 1988). It is possible that the molecule attaches to pellicle by one cation leaving the other free to interact with bacteria attempting to colonize the tooth surface. This mechanism would, therefore, be similar to that associated with tooth staining. It would also explain why anionic substances such as sodium lauryl sulfate based toothpastes reduce the plaque inhibition of chlorhexidine if used shortly after rinses with the antiseptic (Barkvoll et al. 1989). Indeed, a more recent study has demonstrated that plaque inhibition by chlorhexidine mouth rinses is reduced if toothpaste is used immediately before or immediately after the rinse (Owens et al. 1997).⁶ Wait for 30 minutes after brushing before rinsing with chlorhexidine.⁸ In the mouth chlorhexidine readily adsorbs to pellicle-coated teeth. Once adsorbed, chlorhexidine shows a persistent bacteriostatic action lasting in excess of 12 hours (Schiott et al 1970). Radio-labelled chlorhexidine studies suggest a slow release of the antiseptic (Bonesvoll et al 1974) and this was suggested to produce a prolonged antibacterial milieu in the mouth (Gjerme et al 1974).

Toxicology and safety

The cationic nature of chlorhexidine minimizes absorption through the skin and mucosa, including from the gastrointestinal tract. Primary route of excretion is through faeces. Systemic toxicity from topical application or ingestion is not reported. (poorly absorbed by GIT, oral LD is 1800mg/kg). Even in intravenous infusion in animals, chlorhexidine is well tolerated. (Intravenous LD is 22mg/kg). No tetragenic alterations have been found.² Neurosensory deafness can occur if chlorhexidine is introduced into the middle ear and the antiseptic should not be placed in the outer ear in case the eardrum is perforated. In oral use as a mouth rinse, chlorhexidine has been reported to have a number of local side effects (Flotra et al. 1971).

1. Brown discoloration of the teeth and some restorative materials and the dorsum of the tongue (Dose dependent).³
2. Taste perturbation (Concentration dependent).³
3. Oral mucosal erosion.
4. Unilateral or bilateral parotid swelling. This is an extremely rare occurrence and an explanation is not available.
5. Enhanced supragingival calculus formation. This effect may be due to the precipitation of salivary proteins on to the tooth surface, thereby increasing pellicle thickness and/or precipitation of inorganic salts on to the pellicle layer.

Chlorhexidine also has a bitter taste, which is difficult to mask completely.⁶ For these reasons; the prolonged use of chlorhexidine should be avoided. It is useful for short periods of up to 2 weeks.²

Chlorhexidine staining

The mechanisms proposed for chlorhexidine staining:

1. Degradation of the chlorhexidine molecule to release parachloraniline
2. Catalysis of Maillard reactions
3. Protein denaturation with metal sulfide formation
4. Precipitation of anionic dietary chromogens.

Degradation of chlorhexidine to release parachloraniline appears not to occur on storage or as a result of metabolic processes. Also, alexidine, a related bisbiguanide, does not have parachloraniline groups, yet causes staining identical to that of chlorhexidine. Non-enzymatic browning reactions (Maillard reactions) catalysed by chlorhexidine are a theoretical possibility (Eriksen et al 1985). Maillard reaction is step in the formation of advanced glycation end products. Protein denaturation produced by chlorhexidine with the interaction of exposed sulfide radicals with metal ions is also theoretically possible but there is no direct evidence. Again, the theory does not take into account similar staining by other antiseptics and metal ions. Precipitation of anionic dietary chromogens by cationic antiseptics, including chlorhexidine and polyvalent metal ions as an explanation for the phenomenon of staining by these substances, is supported by a number of well-controlled laboratory and clinical studies.⁶ Cationic group can also attach dietary factors such as gallic acid derivatives (polyphenols) found in some foods and many beverages including tea and coffee and tannins from wines to the molecule and hence to the tooth surface.²

Gold standard

Superior antiplaque effect - in terms of its superior degree of persistence at the tooth surface. Superior persistence of antibacterial effect (both bactericidal and bacteriostatic) at the tooth surface. One charged end of the chlorhexidine molecule binding to the tooth surface and the other remaining available to initiate the interaction with the bacterial membrane as the microorganism approaches the tooth surface – a “*Pin-Cushion*” effect.⁷

Chlorhexidine products

Mouth rinses

Aqueous alcohol solutions of 0.2% chlorhexidine were first made available for mouth rinse products for twice daily use in Europe in the 1970s. A 0.1% mouth rinse product also became available; however questions were raised over the activity. Later, in the US, a 0.12% mouthrinse was manufactured but to maintain the almost optimum 20 mg doses. The studies revealed equal efficacy for 0.2% and 0.12% rinses when used at appropriate similar doses (Segreto et al. 1986). More recently alcohol free chlorhexidine mouth rinses have been available. This possess equivalent effects of inhibiting plaque and gingivitis compared to alcohol containing but with better taste acceptability (Quirynen et al 2001, Van Strydnock et al 2005).⁶

Various mouth rinses –

Peridex oral rinse (0.12%) 3M, Periogard (0.12%) Colgate, Hexide (0.2%) Deys medical, Rexidin (0.2%) Indico remedies ltd., Hexiklin (0.2%) Simpson Brawn pharma, Hexiclo (0.2%) Sunways India Pvt Ltd, Hexidine (0.2%) Icpa Health Products Ltd, Clohex (0.2%) Dr Reddy's Laboratories Ltd, Haa mouth wash (0.2%) Cadila Pharmaceuticals Ltd

Gel

A 1% chlorhexidine gel product is available and can be delivered on a toothbrush or in trays. The distribution of the gel by toothbrush around the mouth appears to be poor (Saxen et al. 1976). In trays the chlorhexidine gel was found to be particularly effective against plaque and gingivitis in handicapped individuals (Francis et al 1987). The acceptability of this tray delivery system to the recipients and the caregivers was found to be poor. More recently, 0.2% and 0.12% chlorhexidine gels have become available.

Sprays

0.1% and 0.2% chlorhexidine in sprays are commercially available in some countries. Studies with the 0.2% spray have revealed that small doses of approximately 1-2 mg delivered to all tooth surfaces produces similar plaque inhibition to a rinse with 0.2% mouth rinses (Kalaga et al 1989) Sprays appear useful for the physically and mentally handicapped.(Francis et al 1987, Kalaga et al 1989)

Toothpaste

Chlorhexidine is difficult to formulate into toothpaste. Chlorhexidine products based on toothpaste and sprays produces similar tooth staining to mouth rinses and gels; taste disturbance, mucosal erosion and parotid swellings tend to be less or have never been reported.

Varnishes

Chlorhexidine varnishes have been used mainly for prophylaxis against root caries rather than an antiplaque depot for chlorhexidine in the mouth.

Slow-release vehicle

A chlorhexidine chip has been produced commercially for placement into periodontal pockets as an adjunct to scaling and root planning.⁶

Chlorhexidine – local drug delivery

- Periochip (2.5mg Chlorhexidine)
- Pericol CG (2.5mg Chlorhexidine)
- Chlosite (1.5% Chlorhexidine)

Small chip composed of biodegradable hydrolyzed gelatin matrix, cross-linked with glutaraldehyde and also containing glycerine and water, into which 2.5 mg of chlorhexidine gluconate has been incorporated per chip. It is a FDA approved small, orange brown, chip measuring 4.0x 0.5x 0.35mm. Studies showed reduction in the numbers of the putative periodontopathic organisms

Porphyromonas gingivalis, *Prevotella intermedia*, *Bacteroides forsythus*, and *Campylobacter rectus* after placement of the chip Study by Soskolne W.A in 1999 showed -There was an initial peak concentration of chlorhexidine in gingival crevicular fluid at 2 hour after the chip was introduced. Slightly lower concentrations being maintained over next 96 hrs. Total degradation occurred between 7-10 days after insertion.⁹

Clinical usage

In the UK, (Corsodyl) contain 0.2% chlorhexidine and recommend a 10 ml volume per rinse. In USA, Peridex, contains 0.12% chlorhexidine and recommends a 15 ml volume per rinse. The factor governing the effectiveness of these mouthwashes is the total dose of chlorhexidine delivered and 10 ml of 0.2% solution delivers 20 mg and 15 ml of 0.12% solution delivers 18 mg. Since both of these amounts are similar, either of the formulations is equally effective.²

Uses:

1. As an adjunct to oral hygiene
2. Post oral surgery including periodontal surgery or root planing, gingivectomy and extraction (reduce the incidence of dry socket)
3. In patients with inter maxillary fixation (reduce bacterial load in saliva)
4. For oral hygiene & gingival health in physically & mentally handicapped, medically compromised individuals predisposed to oral infections (candidacies), including those with blood diseases, those receiving chemotherapy or radiotherapy and bone marrow transplant
5. High caries risk patient
6. Minor recurrent aphthous ulcer.
7. Removable & fixed orthodontic wearers
8. Treatment of denture stomatitis
9. In Implant dentistry - no evidence indicates that the implant success is improved by the use of chlorhexidine rinses or chlorhexidine irrigation.
10. as an immediate prophylactic rinse in the prevention of post extraction bacteremia.
11. Beneficial bacterial changes including reductions in *Streptococcus mutans* have been noted with chlorhexidine rinses used by geriatrics.
12. Rinsing with chlorhexidine or irrigating supragingivally around the gingival margin, reduces the instance of bacteremia.

Bacterial aerosol arising from the use of certain dental instruments, notably polishing devices, ultrasonic scaling devices and even air rotor hand pieces, may be markedly reduced by a single rinse of chlorhexidine prior to use.¹⁰

Chlorhexidine and healing

Langebaek and Bay (1976) studied the effect of chlorhexidine mouth rinse on healing after gingivectomy and found no influence on the amount of plaque under the periodontal dressing (Coe-Pack). However, after the dressing was removed, use of chlorhexidine maintained plaque scores at the same low level as under the dressing,

and healing was promoted. Addy and Dolby reported a clinically unimportant difference postoperatively in gingivectomy wounds covered either with a periodontal dressing or rinsing with chlorhexidine only. Incorporating chlorhexidine powder into the periodontal dressing resulted in significantly less plaque formation under the dressing, less gingival exudate, less bleeding, and increased healing compared with operative sites in which placebo dressing was placed. Paunio and others - reported that experimentally chlorhexidine has a delaying effect on the formation of granulation tissue.¹¹

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