ORIGINAL RESEARCH PAPER

Volume-7 | Issue-1 | January-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CHLORHEXIDINE - THE BENCHMARK CHEMICAL PLAQUE CONTROL AGENT: A MINI REVIEW

Dental Science

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ABSTRACT

Chronic periodontitis can be treated effectively by mechanical debridement and the clinical and microbial benefit of mechanical debridement can be increased by local application of antimicrobial agents. Chlorhexidine is an effective antimicrobial, antiplaque and antigingivits agent and its application can enhance effectiveness of periodontal therapy. It was initially utilized as anti-septic agent but with continued research its effective role as an oral antiplaque agent was discovered. Chlorhexidine is not effective as an antimicrobial but has the property of substantivity and fewer side effects compared to other chemical plaque control agents. The pharmacology of Chlorhexidine and suggestions for its indicated uses, its adverse effects and various forms in which it is available are outlined in this review.

KEYWORDS

Chlorhexidine, CHX, Antiplaque agent, chemical plaque control.

Introduction:

Non surgical periodontal therapy has garnered importance appreciably in the last decade. Chemical plaque control is one of the aspects of non surgical periodontal therapy that as an adjunct to mechanical therapy has many benefits.

Ominous morphology of the periodontal pockets makes it difficult for mechanical instrumentation which leads to inadequate removal of plaque and calculus, incomplete eradication of all periodontal pathogens. Microbes in the oral cavity posses the ability to translocate and invade tissues. All these factors result in short-term effect of scaling and root planning.[1]

Owing to these limitations, chemical plaque control agents are used as an adjunct to mechanical therapy. Systemic or local application, rinsing etc are few of the several methods that are employed in delivering these anti-microbial agents [2]

Chemical plaque control agents are classified into three generations and bisbiguanides belong to the second generation. Bisbiguanides includes octenidine, alexidine and chlorhexidine. Chlorhexidine gluconate (CHX), a cationic bisbiguanide is the most commonly used and commonly acknowledged element of this generation of chemical plaque control agents. CHX has anti bacterial effect on Gram +ve and Gram –ve bacteria as well as facultative aerobes and anaerobes. The anti-microbial and anti-plaque properties of CHX are unrivalled in the present times along with higher substantivity compared to other agents [3].

Chlorhexidine was first discovered by Imperial Chemical Industries in England in 1950 as part of a research program focused on new anti-malarial agents [4]. Initially it was used as anti-septic for cleansing wounds for over 30 years [5]. Its application as an anticalculus or antiplaque agent was suggested by Schroeder in 1969 [6]. CHX has robust affinity towards skin and mucous membranes with low mammalian toxicity and wide-ranging anti-microbial activity [7].

Structure

CHX is made up of two symmetrical chlorophenyl rings and two biguanide groups united by a central hydrophobic hexamethylene chains (1, 6-di (4-chlorophenyl-diguanido). It has both hydrophilic and hydrophobic groups (fig 1). At physiological pH, it is cationic with positive charge dispersed on the nitrogen atoms on both sides of central bridge. The compound is a strong base. CHX is used in salt form because of the relative insolubility of the base molecule [4].

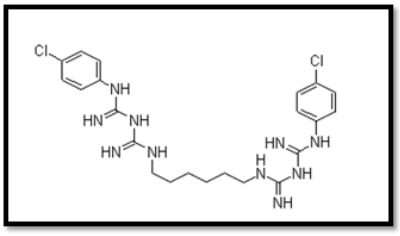

Figure 1: Structure of chlorhexidine molecule

Molecular formula: C22H30Cl2N10

Properties:

Molecular Weight: 505.45, melting point 132-136 ° C, Water-soluble at 0.08 g/100 mL (20°C).

i. Strong base & dicationic at pH>3.5(Albert & Sargeant 1962)
ii. Broad antibacterial activity (Gm +ve, Gm -ve bacteria, yeast, dermatophytes & lipophilic viruses)
iii. Low toxicity
iv. Substantial affinity towards skin and mucous membrane.
v. Varied effects depending on concentrations.

Since it is dicationic in nature, it interacts aggressively with anions which relates to its efficacy, safety and side effects.

Mechanism of action

As stated earlier, CHX molecule is a base and is stable as salt. Chlorhexidine digluconate, most common oral preparation dissociates readily at physiological pH thereby releasing the positively charged unit [8].

Antiplaque mode of action

Addy and Kornman attribute CHX's exceptional anti-plaque activity to its characteristic of having prolonged substantivity [7]. CHX, being a cationic molecule, attracts anionic substrates (hydroxylapatite, pellicle, salivary glycoproteins and mucous membranes). This gives CHX superior anti-plaque efficacy.

Rolla and Melsen illustrated that, chlorhexidine attached to the oral mucosa show plaque-inhibitory action which can be explained with three processes:

1. Preventing pellicle formation: by blocking the acidic groups on the

salivary glycoproteins, thus reducing the protein adsorption to the tooth surface.
2. Reducing adsorption of plaque onto the tooth surface: by binding to the bacterial surface in sub-lethal amounts.
3. Preventing formation of plaque: by displacing calcium from the plaque matrix and precipitating the agglutination factors in saliva.

Microbiological effects

CHX has a broad range of action blanketing gram +ve and gram –ve bacteria, facultative aerobes and anaerobes, fungi and few viruses. Its mechanism of action is membrane-active type, denoting an anti-microbial agent that disintegrates the inner cytoplasmic membrane.

The dicationic CHX molecule gets attracted towards the anionic bacterial outer cell surface with precise affinity towards compounds containing phosphorous. This revamps the integrity of outer cell membrane and CHX is drawn towards the central cytoplasmic membrane. The inner membrane contains phospholipids. CHX binds to these phospholipids, thereby altering the cells osmotic equilibrium which leads to increased porosity of the membrane and seepage of components such as potassium ions, which have low molecular weight [7].

At these sub-lethal doses it acts as a bacteriostatic agent ans its effects are reversible, allowing the bacterial cell to recover by a neutralizer. Electron microscopically cytoplasm appears to be coagulated and precipitated due to the formation of phosphate complexes like adenosine triphosphate and nucleic acids. Such precipitates formed in the cytoplasm leads to irreversible bacteriocidal stage [7]. So CHX is described as bacteriostatic at low doses and as bactericidal at higher doses.

Indications for the use of chlorhexidine

Transient anti-plaque benefits with CHX include:

(1) As a supplement to mechanical cleansing in phase I part of periodontal therapy.
(2) In conditions where at home or in-office mechanical debridement is difficult, including

i. Immediate post-surgery or during post-surgical maintenance period.
ii. Inter-maxillary fixation,
iii. Patients undergoing orthodontic therapy,
iv. Physically and mentally handicapped individuals [9].

(3) In immunocompromised patients, who are predisposed to oral infections like leukaemia.
(4) In denture stomatitis.
(5) As pre-procedural mouth rinse before flap surgery and post oral surgery.
(6) In the treatment of oral malodour.
(7) Chlorhexidine as local drug delivery agent
(8) In the differential diagnosis of erosive lesions to know whether they are of viral or bacterial origin [9].

Adverse effects of chlorhexidine

The most frequent adverse effect associated with the usage of CHX is tooth staining. This mostly occurs in the interproximal and gingival third areas of affected teeth. Approximately 50% of the patients complain about staining within several days. Tongue staining has also been reported. It tends to be more severe in the higher concentrations of chlorhexidine (Heyden 1973). The cationic nature of CHX is responsible for this side effect. It gets attracted towards anionic substances like chromogens in food. Such foods are better avoided while using CHX [8].

Chlorhexidine staining:

The mechanisms proposed for chlorhexidine staining can be debated, but have been suggested as:

a. Relese of parachloraniline due to degradation of chlorhexidine.
b. Maillard reactions and its catalysis
c. Metal sulfide formation due to protein denaturation
d. Presence of anionic chromogens in food and their precipitation.
a. Parachloraniline release due to degradation of chlorhexidine doesn't seem to transpire on storage or due to metabolic processes. Alexine, also a bisbiguanide causes staining similar to CHX but does not have parachloraniline groups. So this theory is not widely accepted. (Addy and Roberts 1981).
b. Non-enzymatic browning reactions (Maillard Reactions) catalysed by CHX is theoretically possible (Nordbo 1979); nevertheless, evidence is unconvincing (Eriksen et al. 1985) [10]. The theory does not consider the fact that other antiseptics and metals such as tin, iron and copper also produce dental staining.
c. Protein denaturation produced by chllorhexidine: It is speculated that chlorhexidine splits disulfide bridges to produce reactive sulfhydryl groups thereby denaturing the proteins. These reactive groups interact with iron or tin ions to release pigmented (Ellingsen et al. 1982) [11] but there is no direct evidence to support this concept. Again, the theory does not take into account similar staining by other antiseptics and metal ions.
d. staining can be caused by interaction of cationic CHX or other metal ions with anionic dietary chromogens. This phenomenon is widely accepted and backed with evidence. (Addy & Moran 1995 [12], Watts & Addy 2001) [13]. polyphenols in dietary substances react with tissue or tooth bound anti-microbial agents or metal ions to produce staining. Beverages such as red wine, coffee and tea are predominantly chromogenic, but other foods and beverages will interact to produce various colored stains. The prolonged use of CHX in preventive dentistry is limited by this staining side effect.

Indeed, the staining side effect can be used to assess patient compliance in the use and activity of formulations.

Other side effects include:

I. Chlorhexidine has a bitter taste.
II. Taste perturbation where the salt taste is particularly affected (Lang 1988).
III. Painful desquamative lesions on the oral mucosa, which may be associated with a burning sensation [14]. This may be an idiosyncratic reaction and may be concentration dependent.
IV. Long-term use leads to increase in the supragingival calculus formation. Precipitation of salivary proteins on the tooth surface leads to thickening of the pellicle and precipitating inorganic salts on it.
V. Unilateral or bilateral parotid swelling [4].
VI. At a concentration of 0.5mg/ml chlorhexidine was shown to have a cytotoxic effect on osteoblast proliferation [15].
VII. In animal studies where CHX was used as anti-plaque agent, a statistically significant amount of DNA damage was detected in oral mucosal cells and in peripheral leukocytes [16].
VIII. Carcinogenicity of CHX is attributed to Parachloroaniline (PCA). It is found as a trace contaminant in CHX products. When subjected to high temperarutres or due to prolonged shelf-life CHX breaks down to form PCA. This can be prevented by storing CHX products at room temperature [8].
IX. Animal studies revealed temporary lingual dyskeratosis and hyperkeratinization as other side effects if the concentration of CHX exceeds 2% [8].
X. CHX must be carefully used with dentrifices containing anionic surfactants. Being a cationic molecule CHX reacts with these anionic components, thus decreasing its activity**.** Care must be taken while selecting the tooth paste before CHX usage [4],[7],[8].

Chlorhexidine commercial products:

Chlorhexidine has been prepared into a number of products like mouth rinses (2nd generation), sprays, gel, tooth paste, varnishes, chewing gums and local drug delivery. PerioChip (2.5 mg Chlorhexidine Gluconate) and Periocol -CG (a sustained release chlorhexidine in fish collagen membrane) are the commercially available forms of locally delivered chlorhexidine.

Conclusion:

To this date, Chlorhexidine is proven to be the most effective antiplaque agent for which commercial products are available. Chlorhexidine doesn't cause systemic toxicity and microbial resistance and supra-infection do not occur. The antiplaque action of chlorhexidine appears dependent on prolonged persistence of antimicrobial action in the mouth (substantivity). A number of vehicles for delivering chlorhexidine are available, but mouth rinses are most commonly recommended.

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