

Chlorhexidine: The Gold Standard in Chemical Plaque Control

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ABSTRACT

Chlorhexidine, to date is the most potent anti plaque agent. It is considered gold standard anti plaque agent, against which efficacy of other anti plaque and anti -gingivitis agents is measured. Its efficacy can be attributed to its bacteriostatic and bactericidal properties and its substantivity within the oral cavity. The antimicrobial properties of Chlorhexidine are attributed to its bi-cationic molecule, and this same property is the basis of its most common side effect, extrinsic tooth staining. Administration of Chlorhexidine requires careful clinical evaluation of clinical situation and an accurate diagnosis hence, should be applied only under professional supervision.

KEY WORDS: Gingivitis, Chlorhexidine, Antimicrobial

Introduction

Chlorhexidine has long been recognized as the primary agent for chemical plaque control. Chlorhexidine to date is the proven most effective antiplaque agent. Its efficacy as a mouth rinse to inhibit dental plaque & gingivitis is well documented. It is considered the gold standard antimicrobial agent against which the efficacy of other antimicrobial & antiplaque agents is assessed.^[1]

In late 1940s, scientists seeking to develop antimalarial agents, formulated a group of compounds called as polybiguanides, which demonstrated a broad antimicrobial spectrum. Chlorhexidine was developed in 1940s by Imperial

Chemical Industries, England.^[2] Later, Davis et al 1954 in a study on polyguanides found that certain bisbiguanides had a very broad antimicrobial spectrum.^[3] By structural variation they arrived at the agent with the greatest bacteriostatic and bactericidal features, 1, 6 bis-4 chloro, phenyldiguanidohexane, a synthetic cationic detergent usually referred as Chlorhexidine. Since 1957 this disinfectant has been widely used to successfully treat infections in gynecology, urology dermatology, medicine, surgery and Dentistry. Use in dentistry was initially for pre-surgical disinfection of mouth & in Endodontics. Plaque inhibition by Chlorhexidine was first investigated in 1969^[4], but the definitive study was performed by Loe & Schiott.^[5] The study showed

that rinsing for 60 sec twice per day with 10 ml of 0.2% (20 mg dose). Chlorhexidine Gluconate solution inhibited plaque re-growth & development of gingivitis, in the absence of normal tooth cleansing.

Chemical Structure

A hundred and twenty Chlorhexidine consists of two symmetric 4-chlorophenyl rings & 2 bisguanide groups connected by a central hexamethylene chain. The compound is a strong base & bi-cationic at Ph levels above 3.5 with two positive charges on either side of a hexamethylene bridge.^[6] Chlorhexidine as a chemical is 1, 6-di (4-chloro phenyldiguanido) hexane.

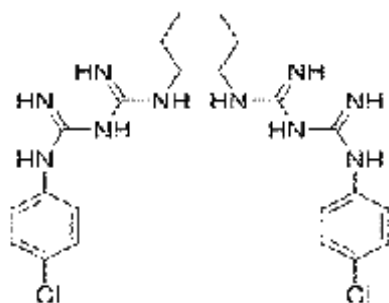


Fig: Chemical Structure of Chlorhexidine Molecule

Chlorhexidine is available in three forms:

1. Digluconate – Most commonly used, and Water soluble
2. Acetate – Water soluble.
3. Hydrochloride salts – sparingly water soluble.

Metabolism and Toxicity

When Chlorhexidine is used as a mouth rinse the mode of action is purely topical. The drug does not penetrate oral epithelium and if some solution is inadvertently swallowed, initial binding of the drug will be to the mucosal surfaces of gastrointestinal tract. Chlorhexidine is poorly absorbed through gastrointestinal tract. Animal experiments have suggested that Chlorhexidine is mainly excreted through feces. The small amount of Chlorhexidine that may be absorbed is metabolized in liver and kidney. There is minimal metabolic cleavage. It is free from systemic toxicity in oral use & microbial resistance & superinfection do not occur. The oral LD 50 value for Chlorhexidine digluconate is 1800mg/kg, whereas the LD 50 for intravenous application is 22mg/kg.^[7]

Mechanism of action

Chlorhexidine has a wide spectrum of activity encompassing gram positive gram –negative bacteria viruses including HBV & HIV, yeast fungi, dermatophytes. Its antimicrobial activity is of the membrane active type used to describe that damages the inner cytoplasmic membrane.

Interestingly Chlorhexidine shows different effects at different concentrations; at low concentrations the agent is bacteriostatic, whereas at higher concentrations the agent is bactericidal. The actual levels at which the activity is bacteriostatic or bactericidal vary between bacterial species.^[8]

The mode of action is that bacterial cell is characteristically negatively charged. The cationic Chlorhexidine molecule is rapidly attracted towards negatively charged bacterial cell surface, with specific and strong adsorption to phosphate containing compounds. This alters the integrity of bacterial cell membrane and Chlorhexidine is attracted towards the inner cell membrane. Chlorhexidine binds to phospholipids in the inner membrane leading to increased permeability of the inner membrane and leakage of low molecular weight compounds such as potassium ions. At this bacteriostatic stage the effects of Chlorhexidine are reversible. Increasing the concentration causes progressively greater damage to the membrane. As the concentration of Chlorhexidine increases, leakage of low molecular weight cytoplasmic components falls, reflecting the coagulation and precipitation of cytoplasm by formation of phosphated complexes such as adenosine triphosphate and nucleic acids. This bactericidal stage is irreversible.^[8]

Chlorhexidine is a potent antibacterial substance but this alone does not explain its antiplaque action. A recent review suggested that plaque inhibition is derived only from the Chlorhexidine adsorbed to the tooth surface.^[9]

Suggested are the following three possible mechanisms for the inhibition of plaque by Chlorhexidine:

1. The effective blocking of acidic groups of salivary glycoproteins will reduce their adsorption to hydroxyapatite and the formation of acquired pellicle.

- The ability of bacteria to bind to tooth surfaces may be reduced by the adsorption of Chlorhexidine to the extra cellular polysaccharides of their capsules or glycocalyxes. This mechanism is of particular interest as further studies have demonstrated that when sucrose is added to bacterial suspensions in vitro the antibacterial effect of Chlorhexidine is actually reduced.^[10] Production of extra cellular polysaccharide increases in the presence of sucrose. A greater proportion of the drug will be absorbed by the cell coatings and less will be available to act upon the cell membrane to effect direct killing of the microorganisms.^[11]
- The Chlorhexidine may compete with calcium ions agglutination factors in plaque.

Laboratory studies have suggested that Chlorhexidine can bond with hydroxyapatite.^[12] However it is now considered that it is the affinity of Chlorhexidine for the acidic proteins in pellicle, plaque, calculus, oral mucosa and on surface of bacteria which is of greater clinical significance than its affinity for hydroxyapatite.^[13]

Chlorhexidine as gold standard

The superior antiplaque effect of Chlorhexidine which makes it gold standard can be attributed to its substantivity. Substantivity is defined as ability of an agent to adhere to soft & hard tissue & then be released over time with retention of potency. Chlorhexidine's superior antibacterial effect (both bacteriostatic and bactericidal) can be explained in terms of its superior persistence at tooth and mucosal surfaces. After rinsing with 10ml of 0.2% aqueous solution of Chlorhexidine for 1 min, approximately 30% of the drug is retained in the mouth.^[14,15] After single rinse with Chlorhexidine, the saliva itself exhibits antibacterial activity for up to 5 hrs^[16] whereas persistence at the oral mucosal surfaces has been shown to suppress salivary bacterial counts for over 12 hrs.^[17] In this regard the dicationic nature of Chlorhexidine must play a part; it can be envisaged as one charged end of Chlorhexidine molecule binding to the tooth surface and the other remaining available to interact with bacterial membrane as microorganism approaches the tooth surface – a pin cushion effect.^[1] This explains the lack of effectiveness of other antimicrobials in terms of

them lacking a large, rigid molecule with two charged interactive ends.

Vehicles for Clinical Application of Chlorhexidine

Chlorhexidine has been formulated into a number of products but mouth rinse is the most commonly documented in literature.^[18] Chlorhexidine mouth rinses are available as aqueous or alcohol based solutions. It is manufactured as 20 percent v/v concentrate which is marketed as 0.2 percent Chlorhexidine. Later in US, 0.12 percent concentration mouth rinse was manufactured but to maintain the almost optimum 20 mg dose derived from 10 ml of 0.2 percent rinse the product was recommended as a 15 ml rinse (18 mg dose).^[2] The antimicrobial effects of 0.12 percent mouth rinses are similar to those of 0.2 percent solutions when used at appropriate similar doses.^[19]

Various other formulations of Chlorhexidine are Gels, usually delivered in tooth brush or trays, Sprays, Varnishes, Chewing gums,^[20] Tooth pastes.

Chlorhexidine has also been incorporated in periodontal dressings which have shown to decrease the bacterial load, during the post surgical phase.^[21] It is also used as local drug delivery agent (Periochip) for site specific, slow & sustained release of drug at diseased site.^[22] Chlorhexidine is also used for Sub-gingival Plaque control as Irrigation in supra and sub gingival area.^[23]

Clinical Indications of Chlorhexidine^{[2], [18], [24]}

There are significant numbers of indications for the use of Chlorhexidine in preventive dentistry. It is more effective as a preventive rather than a therapeutic agent. It's more valuable use is in short to medium term when mechanical tooth cleaning is not possible, difficult or inadequate.

For Short term application:

Chlorhexidine is used as

- An adjunct to mechanical plaque removal by tooth brushing and professional prophylaxis for the maintenance of proper oral hygiene.
- Post oral surgery care including periodontal surgery or root planing.

3. As an immediate prophylactic rinse in the prevention of post – extraction bacteraemia and decrease bacterial content of aerosol spray.
4. Recurrent oral ulceration
5. Treatment of denture stomatitis and dry socket.
6. during therapy for oral infections & acute necrotising ulcerative gingivitis

For intermittent short or medium - term application:

Although literature regarding intermittent short term application is limited but encouraging and also specific regimens have not yet been defined but it is likely that intermittent application of Chlorhexidine can drastically reduce oral bacterial load and prevent oral infections without the side effects associated with prolonged use.

1. For oral hygiene and gingival health benefits in physically and mentally handicapped.
2. Medically compromised individuals predisposed to oral infections.
3. Patients who have high caries risk.
4. Removable and fixed orthodontic appliance wearers.
5. Patients with extensive prosthetic reconstruction on abutment teeth with reduced periodontal support
6. Dental implant patients.

Long term application:

It is perhaps the staining side effect that limits the long term use of Chlorhexidine in preventive dentistry. Although the stain which inevitably develops during prolonged use may pose an esthetic problem. Prophylaxis at 6-month intervals can effectively manage this side effect. One may use lower concentration and achieve only partial plaque reduction. The optimal concentration for long term use has to be determined individually.

Long term use may be beneficial:

1. Patients who have decreased resistance to bacterial infection due to serious medical problems or due to medical therapy which would include patients who have Agranulocytosis, leukaemia, haemophilia,

- thrombocytopenia, kidney disease, allergies, bone marrow transplant, AIDS.
2. Patients who are being treated with cytotoxic drugs, radiation therapy, immunosuppressive drugs.
3. Patients with inter maxillary fixation
4. Patients who are mentally challenged.
5. Patients with physical disability, motor function disturbance, disturbance of muscle coordination
6. Geriatric patients

Adverse Effects [2]

In spite of potent antimicrobial & antiplaque properties of Chlorhexidine, its widespread & prolonged use is limited by local side effects. The main local adverse effect of Chlorhexidine when used as mouth rinse is extrinsic staining of teeth. A dark yellow or brown stain is often seen on natural and artificial teeth after only a few days use. The amount of staining may show greater individual variation and it tends to be more severe with higher concentration of the drug. The precise cause of tooth discoloration is not known but three possible mechanisms may be involved:

1. Carbohydrate and amino acid containing compounds present in pellicle undergoes a series of polymerization reaction to produce pigmented substances called as melanoidins. Such browning reactions are catalysed by Chlorhexidine, which produces a thick pellicle containing more amino groups than ordinary pellicle.
2. Chlorhexidine denatures the proteins in pellicle by splitting sulphide bridges to produce free sulphhydryl groups. The latter then react with iron or tin ions to produce brown and yellow pigmented products.
3. Chlorhexidine reacts with ketones and aldehydes in dietary breakdown or intermediary products to form insoluble, coloured compounds. There is strong evidence to suggest that certain drinks as tea, coffee, red wine, cause more severe discoloration of teeth in presence of Chlorhexidine when compared with its effects when these beverages are not consumed. Such stain as does occur however can be removed by oral prophylaxis.

Other side effect includes transient impairment of taste sensation or taste perturbation where salt taste appears to be preferentially affected.^[25] Parotid swelling is a rare unwanted effect of Chlorhexidine mouth rinse. Over vigorous mouth rinsing may predispose patient to such condition as it may create a negative pressure in the duct and the aspiration of Chlorhexidine.

Occasionally reported are cases of burning sensation and painful desquamative lesion on oral mucosa which appears to be idiosyncratic reaction and concentration dependent.^[26]

There may also be increased supragingival calculus formation due to use of Chlorhexidine mouth rinse as Chlorhexidine causes precipitation of salivary proteins on the tooth surface thereby increasing pellicle thickness and precipitation of inorganic salts on the pellicle layer. Chlorhexidine also has bitter taste which is difficult to mask completely.

Limitations of Chlorhexidine

Antibacterial effect of Chlorhexidine is based on its ability to interact with bacterial cell membrane. However it does not distinguish between bacterial protein and other protein found within mature plaque.^[1]

Also, Chlorhexidine as an antiplaque agent that prevents plaque formation but its mode of action does not allow it to remove plaque already present on tooth surface efficiently, therefore it is used as an adjunct to mechanical plaque control.

Also, Chlorhexidine molecule reacts with anionic surfactants (sodium lauryl sulphate) present in toothpastes formulation, thus reducing the activity of the agent. This has prevented Chlorhexidine incorporation in tooth paste formulations containing anionic detergents.

Chlorhexidine is of limited value in therapy of established oral conditions including gingivitis & is much more valuable in the preventive mode.

Conclusion

Evidence in dental literature support & recognise Chlorhexidine as gold standard against, which other antiplaque and antigingivitis agents are measured. The degree of Chlorhexidine persistence of effect at the tooth surface is the

basis of its clinical efficacy. Administration of Chlorhexidine requires careful clinical evaluation of clinical situation and an accurate diagnosis. Therefore Chlorhexidine and any other potent antimicrobial agent should be applied only under professional supervision.

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