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Chlorhexidine: An Adjunct Anti-microbial in Dental Therapy

G.M. Phadnaik[1]*, Mayuri Ghike[2], Ripunjaykumar Tripathi[3], M.B. Phadnaik[4].
[1]*Department of Chemistry, Institute of Science, Nagpur, India*
[2,3,4]*Department of Periodontology, Govt. Dental College and Hospital, Nagpur, India*

Abstract:
Chlorhexidine is the most extensively used antimicrobial agent in dental therapy .It is a broad-spectrum antiseptic that is mainly bactericidal but also effective against some yeasts and viruses. Its use is becoming widespread as an antiplaque agent and it is an adjuvant to the treatment of mechanical plaque control, particularly in individuals with compromised oral hygiene. It is available indifferent formulations like mouth wash, varnish, gel, spray, chewing gum, candy, toothpaste and even local drug delivery and restorative material and is effectively used by all disciplines of dentistry. The article aims to discuss the synthesis, properties, antimicrobial activity, mechanism of action and the side effects as well.

Key words: *Chlorhexidine,anti-microbial, plaque, mouth rinse.*

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I. Introduction

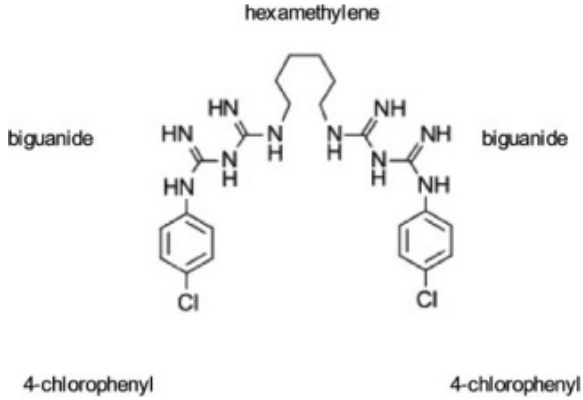
Chlorhexidine is recognized as a basic standard anti-microbial agent among the anti-plaque and anti-gingivitis agents[1,2]. It is the primary agent for chemical plaque control. The most effective and widely used agent against the oral bio-film is Chlorhexidine. Imperical Chemical Industries, England developed the molecule of Chlorhexidine, in 1940. Its activity was first investigated 50yrs ago by Schroeder[3] in 1969but the definitive study was performed by Loe and Schiott (1970)[4,5].

Chlorhexidine which is a cationic bisbiguanide has been used as a broad spectrum antiseptic in medicine since 1950s.1,6 bis-4 chloro, phenyldiguanidohexane, synthetic cation detergent is referred to as chlorhexidine[6]. American Dental Association Council on Dental Therapeutics has approved chlorhexidine to reduce and prevent supragingival plaque and gingivitis[7].

Chlorhexidine mouth rinse is available in 0.1 to 0.2% concentration. Higher concentration do not increase its effect but do increase the adverse effect.[8-9]0.2 % chlorhexidine formulation (20mg dose),rinsing with 10ml for 30secondsand 0.12% chlorhexidine formulation, rinsing with 15ml for 60 seconds is recommended. Mouth rinses with lower concentration (eg. 0.05%), will lower the limit of clinical activity and bioavailabilty might alter, so it is used in combination with other active agents like triclosan, cetylpyridinium chloride[10,11].

II. Chemical Structure And Synthesis

Chlorhexidine is a large symmetrical di-cationic molecule consisting of two 4-chlorophenylrings and two biguanide groups connected by a central hexamethylene chain (Fig 1). As a chemical chlorhexidine is 1,6-di(4-chloro phenyldiguanido)hexane.



(Fig 1) Chemical Structure of Chlorhexidine Molecule

The preparation method comprises the following steps[12]: carrying out a heating reflux reaction on

hexamethylene-dicyanoguanidine and chloroaniline hydrochloride as raw materials and glycol ether or normal butanol as a solvent to directly obtain a target compound in a single step.(Fig 2) The preparation method is simple in process, mild in reaction condition, short in reaction time, rapid and efficient; and as the glycol ether or normal butanol is used as the solvent, the influence of the toxic or side effect of the solvent on a human body is reduced, meanwhile the environmental pollution is reduced; and as the catalyst is not used in the synthesis process, an aftertreatment process is simplified, the synthetic comprehensive cost is effectively reduced, the yield of a final product can reach as high as 84.7%, the purity of the final product can reach as high as 97%, thus the preparation method has a better industrial application prospect.

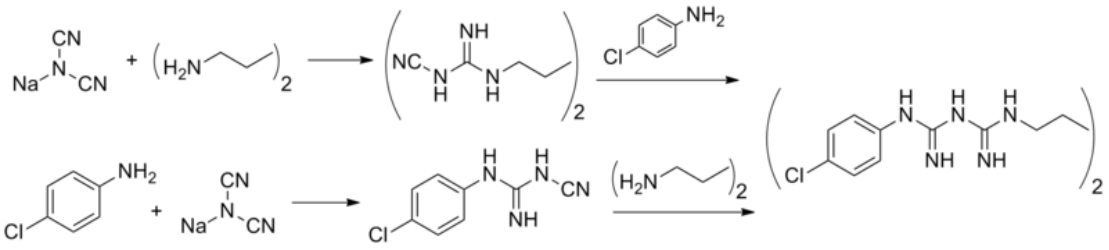


Fig 2 Synthesis of chlorohexidine

III. Different Formulation/Vehicle

Chlorhexidine are obtained in three chemical forms[13-15]:

1. Chlorohexidinedigluconate-water soluble,
2. Chlorohexidine Acetate-water soluble,
3. Chlorohexidine Hydrochoride salts-sparingly water soluble.

Commercially it is available in different formulations[16-19] viz.

a. Aqueous or alcohol-based mouth rinses,
b. Varnishes,
c. Gels (1% chlorhexidine gel)
d. Sprays (0.1% and 0.2% chlorhexidine)
e. Toothpastes
f. Chewing gums

It is sold as following brand names[20,21]

i. Chlorhexidine topical is sold as Betasept, Biopatch, Calgon Vesta, ChloraPrep One-Step, Dyna-Hex, Hibiclens, Hibistat Towelette, Scrub Care Exidine, Spectrum-4 among others.
ii. Chlorhexidine gluconate mouth rinse is sold as Paroex, Peridex, PerioChip, Periogard among others.
iii. Hexoralettene N contains benzocaine, menthol and chlorhexidine hydrochloride. It is used as oral antiseptic candies.

It is also used as a local drug delivery agents like[22-24]

- Periochip: It is a biodegradable gelatin matrix,contains 0.25gram of chlorhexidine gluconate. Available in size 4x5x3.5mm,orange brown colouredstrip.
- Periocol-CG: It is a Type I collagen membrane with 2.5mg chlorhexidine with size 4x5mm and weight 10mg.
- Chlo-site: Gel based system with 1.5% chlorhexidine.

IV. Activity And Mechanism Of Action

Antibacterial activity

Chlorhexidine has wide spectrum activity against Gram-positive and Gram-negative bacteria, viruses, yeast, dermatophytes, fungi, also against hepatitis B virus and human immunodeficiency virus (HIV)[25].

Depending upon the concentration; the agent is bacteriostatic at low concentration which increases the permeability of plasmatic membrane, whereas at higher concentration the agent induces precipitation of cytoplasmic proteins and cell death, thus having a bactericidal effect[26-28].

The mechanism of action is that the cationic molecule of chlorhexidine binds to bacterial cell, which is characteristically negatively charged. Almost a one third to one half of the chlorhexidine retained in the mouth bonds to phosphate groups[29,30].This alters the integrity of bacterial cell wall. Chlorhexidine binds with the phospholipids in the inner cell membrane; results in the increase permeability and leakage of less molecular weight intracellular components including potassium and phosphorus, exerting a bacteriostatic effect, which

causes reversible damage. Increasing the concentration, action continues which leads to the coagulation and fall in the leakage of intracellular components; reflecting the coagulation and precipitation of cytoplasm. This bactericidal stage is irreversible. But under acidic conditions surface ionization of bacteria is suppressed and the bactericidal effect of chlorhexidine is greatly reduced[31].

Antiplaque activity

A review suggested that chlorhexidine achieves plaque inhibition as an immediate bactericidal action during the time of application and adsorption to the tooth surface[32] and interferes with bacterial adhesion.

Three possible mechanisms suggested for plaque inhibition by chlorhexidine are:

1. Chlorhexidine molecules occlude the acidic groups on the salivary glycoproteins, thus reducing the adsorption to the tooth surface and salivary pellicle formation.
2. In sub lethal amount, it influences on the adsorption of plaque to hydroxyapatites by binding to the bacterial surface.
3. It may displace calcium ions and alter the plaque formation by precipitating the agglutination factors in saliva.

Molecules of chlorhexidine adhere to the salivary pellicle by one cation leaving the other free to interact with bacteria attempting to colonize the tooth surface. It would explain that chlorhexidine should not be used before or immediately after using the toothpaste, as interaction with anionic surfactants, like sodium laurylsulfate found within the formulations, will reduce the plaque inhibition of chlorhexidine in an active form. Some studies showed that in the presence of sucrose, organism produces extracellular polysaccharides to which chlorhexidine molecules adsorbs and thereby reduces its anti-bacterial effects[33]. Also lanthanum reduced the clinical effect of chlorhexidine regardless of whether it was applied before or after the chlorhexidine mouth rinse.Ainamo[34] et al. made an observation that bleeding after gentle massage of gingival margin and after rinsing with chlorhexidine for1week occurred more often than after mechanical oral hygiene measures. This bleeding may associate with irritation from debris which seemed to obliterate the gingival sulcus.

Substantivity

In 1970s, Bonsevoll was first to describe the substantivity property of chlorhexidine. Substantivity is defined as an ability of an agent to adhere to soft and hard tissue and then be released over time with retention of potency[35].

After rinsing with 0.2 % chlorhexidine formulation, 10ml for 1 min, approximately 30% of drug is retained in the mouth and allow sustained antimicrobial effect for 12 hours. Saliva exhibits antimicrobial effect for upto 5 hours, after the single rinse with chlorhexidine[36].

Toxicity and Safety

No systemic toxicity from ingestion and topical application reported. Because of the cationic nature of chlorhexidine absorption through the oral epithelium, skin, and from the gastrointestinal tract is minimum. If absorbed it gets metabolized in liver and kidney,and excreted through faeces.

V. Clinical Uses Of Chlorhexidine

It is more effective as a preventive rather than a therapeutic agent.

For short term application

- Used as an adjunct to oral hygiene and professional prophylaxis,
- Immediate presurgical preparations with chlorhexidine rinsing and irrigation.
- Subgingival irrigation.
- 0.2% chlorhexidine solution is an effective antimicrobial agent when used as an endodontic irrigating solution and as an intracanal, inter-appointment dressing where it helped further to reduce bacteria remaining within the root canal.
- It can be used as a prophylactic rinse in the prevention of post extraction bacteremia and during the ultrasonic scaling it help to reduce the bacterial contents of aerosol spray.
- During the post surgical period including periodontal surgery or root planning,
- In oral infections like aphthous ulceration, denture stomatitis, candidial associated infections, acute ulcerative gingivitis, and dry sockets.

F**or intermediate term application**

- Patients with high caries risk,
- For medically compromised individuals predisposed to oral infections,

- For oral hygiene and gingival health benefits in thementally and physically handicapped patients who suffer from recurrent generalized oral infections,
- In the drug induced gingival overgrowth chlorhexidine will help to control accumulation of plaque,
- Removal and fixed orthodontic appliance wearers,
- Chlorhexidine has been shown to reduce markedly the bacterial load, which tends to increase during jaw immobilization, and improve plaque control.

For long term application

At optimal lower concentration chlorhexidine can be used for long-term application, which couldnot achieve complete plaque reduction. Long-term use of chlorhexidine is limited because of its staining side effects, which can be effectively managed by prophylaxis at appropriate time intervals.

- Geriatric patients.
- Patients with motor functional disturbance, physically handicapped patients, disturbance of muscle coordination, used to improve the oral and gingival health.
- Patients with prolonged inter maxillary fixation.
- Patients who are under radiation therapy, immunosuppressive drugs, cytotoxic drugs, bone marrow transplant patients.
- Patients with immunocompromised state, kidney disease, blood dyscrasias like leukemia, hemophilia, thrombocytopenia, Agranulocytosis.

VI. Adverse Effects[37]

Staining of teeth, dorsum of tongue, mucosa, restorations,

Most common adverse effect is staining of teeth. To explain the staining with chlorhexidine different mechanism have been proposed:

a. Catalysis through Millard reaction- It is known as non-enzymatic browning reaction, caused by condensation and polymerization of carbohydrates such as peptones, hexoses and amino compounds like peptides, proteins and form a pigmented substances known as Melanoidins[38]. The discolorations produced were more pronounced on the root surface than on the crown of the tooth surfaces[39].
b. Degradation of chlorhexidine molecules to release parachloraniline –It 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[40].
c. Precipitation of anionic dietary chromogens- Chlorhexidine reacts with aldehydes and ketones from dietary breakdown or intermediate products (some derivatives of food and beverages like red wine, tea, coffee) to form insoluble coloured compounds.Tea, coffee and red wine are not the only drinks to contain chromogenic polyphenols capable of interacting with chlorhexidine or polyvalent metal ions, but the presence of other polyphenols within the diet which are able to interact with chlorhexidine[41].
d. Denaturation of protein by formation free sulphydryl group – Denaturation of protein by splitting of disulfide bridges to form free sulfhydryl groups which reacts with iron and tin to form pigmented products (brown, yellow). In vitro studies demonstrated that iron solution causes staining of enamel surfaces [42].

Recent studies shown that Anti-discoloration system (ADS) help to reduce the staining associated with chlorhexidine. Somestudies have shown that ADS could diminish the efficacy of chlorhexidine.

- Reversible taste alterations[43], mostly affecting salty and bitter taste,
- Mucosal erosion (idiosyncratic reaction and is concentration dependent, rarely seen with 15ml volume of 0.12% rinse products)
- Hypersensitivity reaction,
- Dryness and soreness of mucosa,
- Increase in calculus formation (due to precipitation of salivary proteins on to the tooth surface),
- Extremely rare unilateral or bilateral parotid swelling (vigorous mouth rinsing with chlorhexidine may create negative pressure in the duct and aspiration of chlorhexidine).

VII. Limitations

- Chlorhexidine formulations are stored in dark bottles away from sunlight and should be kept at room temperature, because heating for long period of time can induce the formation of 4-chloroaniline, which is carcinogenic and mutagenic.
- Chlorhexidine prevent plaque formation but does not allow to remove plaque efficiently.
- Chlorhexidine does not distinguish between bacterial protein and other proteins found within mature

plaque.

- Chlorhexidine has less value as therapeutic and more value in preventive mode.
- Chlorhexidine react with anionic surfactants present in toothpaste and reduces the activity of the agent[44].

VIII. Summery

The article reveals the synthesis, mechanism of antimicrobial activity, applications along with limitations of chlorohexidine. Thus Chlorhexidine is considered as a basic standard because of itsantimicrobial, antiplaque activity and substantivity. Though it has many clinical uses and less adverse effects it should be applied only under professional supervision.

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