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Chlorhexidine: First To Be Known, Still A Gold Standard Anti-Plaque Agent.

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ABSTRACT

Chlorhexidine is one chemical plaque control agent which has various clinical applications in dentistry especially in periodontics that have come to stay that it is not inappropriate to call it the gold standard chemical plaque control agent discovered till date. After years of use by the dental profession, chlorhexidine is still considered as the gold standard against which the efficacy of other antiplaque agents is measured. Chlorhexidine's antiplaque effect is a result of the dicationic nature of the chlorhexidine molecule, which affords the agent the property of persistence of antimicrobial effect at the tooth surface, through both bactericidal and bacteriostatic effects. Although other antiplaque agents may show either purely immediate effect, or limited persistence, the degree of chlorhexidine's persistence of effect at the tooth surface is the basis of its clinical efficacy (substantivity). By understanding how the chemical properties of the chlorhexidine molecule can explain the plethora of clinical efficacy and safety data, the use of chlorhexidine can be optimally aimed towards the patient groups who would most benefit from the superior therapeutic effect of the agent. Thus, by understanding the properties and limitations of the chlorhexidine molecule, the dental profession can ensure that the efficacy of the agent is maximized, and the side effects associated with the agent are minimized, allowing chlorhexidine to be the most efficient and the gold standard against which the efficacy of other antiplaque agents will continue to be measured.

Keywords: Chlorhexidine (CHX), Gold Standard, Anti-Plaque Agent.

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INTRODUCTION

Bacterial plaque is one of the main etiologic agents involved in the initiation and progression of periodontal disease. In a report in 2005, for the National Commission on Macroeconomics and Health (NCMH) [1], it was observed that for periodontal diseases, the consensus was alarming. Hence, the need to get the condition under control was of utmost importance. However, the almost ubiquitous prevalence of gingivitis and periodontitis suggested that the control of periodontal biofilms through mechanical means was inefficient. The role of microorganisms in the onset of gingivitis and evolution to periodontitis gained momentum dramatically following the recognition of bacterial plaque as the major cause of gingivitis. Based on the strong association between certain microorganisms and periodontal diseases, antimicrobial agents as an adjunct to mechanical plaque control procedures were introduced. Considering the fact that mechanical plaque control was not properly practiced by most individuals, it was not found to be sufficiently effective in controlling gingivitis, and an adjunct was essential to accentuate the effectiveness of home and in-office measures directed to better oral hygiene. Hence came the first antimicrobial agent which was shown to inhibit plaque formation and the development of chronic gingivitis.

This was Chlorhexidine gluconate used as a 0.2% mouth rinse (Loe and Schiott 1970) [2]. Since its conception, Chlorhexidine (CHX) has proven its effectiveness beyond dispute. Its efficacy as a mouthrinse to inhibit dental plaque and gingivitis is well documented. Chlorhexidine has been recognized as the gold standard by which the efficacy of alternative antiplaque agents is measured. The literature relating to the use of chlorhexidine in plaque control is immense with the proof of the agent's efficacy in such a role is beyond dispute and the different formulations of chlorhexidine (mouth rinse, gel, spray, fibers, varnishes and various other controlled-release formulations) are being used routinely both in general practice and also in Periodontal Departments of teaching institutions. In addition to having gained the acceptance of the dental profession, chlorhexidine has also been recognized by the pharmaceutical industry as the positive control against which the efficacies of alternative agents (antiplaque) are being measured. Thus, chlorhexidine deservedly has a place in the dental armory used to treat and prevent periodontal disease, and has earned its eponym of the gold standard. Moreover, its substantivity and efficacy as an adjunct to periodontal therapy has greatly contributed to the dental scenario. Its uniqueness and ideal properties have made it earn the title of a "GOLD STANDARD"

Rationale for use of chemical plaque control agents: The control of biofilm accumulation on teeth has been the cornerstone of periodontal disease prevention for decades. Despite the essential role of mechanical plaque control agents in the prevention of gingivitis and periodontitis, it is not properly practiced by most individuals. Also, the widespread prevalence of gingivitis suggests the inefficiency of self performed mechanical plaque control procedures in preventing gingival inflammation. This is particularly relevant in light of the evidence suggesting that long standing gingivitis increases the risk of loss of attachment and that prevention of gingival inflammation might reduce the chance of gingivitis getting transformed into periodontitis. [3] It is also proven that the primary and secondary prevention of gingivitis and periodontitis depends on adequate control of supragingival plaque (Axelsson et al 1981, 1991) [4]. This in turn depends on the compliance and dexterity of the individual with maintenance of oral hygiene that is often inadequate .[5] Chemical plaque control almost certainly was introduced to overcome the potential deficiencies of mechanical cleaning.[6] There has been a vigorous search for many years for chemical agents that could supplement patient-dependent mechanical plaque control and thus, reduce or prevent oral disease and for this, five categories of agents have been considered including broad spectrum antibiotics, antiboitics that aimed at specific bacteria, single or combinations of enzymes that could modify plaque structure or activity, non-enzymatic dispersing or modifying agents and agents that could affect bacterial attachment. Their characteristics are best assessed under the range of antibacterial activity against the various plaque bacteria, substantivity to the oral surface, and possible anti-inflammatory effect in addition to their being with acceptable taste. The Council of Dental Therapeutics has recommended the use of these antiplaque agents specifically to replace mechanical tooth brushing when this is not possible especially after periodontal or oral surgical procedures and during the healing period; with acute oral mucosal or gingival infections when pain and inflammation prevent mechanical oral hygiene; after intermaxillary fixation used to treat jaw fractures or following cosmetic surgery; in case of physically or mentally handicapped patients who are unable to practice oral hygiene on their self; as an adjunct to normal mechanical oral hygiene procedures in situations where this may be compromised by discomfort or inadequacies as in case of subgingival scaling and root planing when

the gingiva may be inflamed; when there is hypersensitivity in the cervical areas due to exposed root surfaces; or when the patient's oral hygiene remains inadequate in the post-surgical phases.[7]

A number of antimicrobial agents have been studied in respect to the control of plaque and they can be divided broadly into bisbiguanides, quarternary ammonium compounds, phenolic agents, oxygenating agents, natural products, and miscellaneous agents.[8] The necessity of chemical plaque control measures clearly shows the adjunctive role they possess since mechanical plaque control procedures are particularly limited in their access to the interproximal and other inaccessible areas.[9] A survey conducted in the United Kingdom concluded that an average of one-third of teeth in 72% of all dentate adults examined had visible plaque.[10] Surveys conducted in developing countries reveal that the percentage of individuals who claim to use interproximal cleaning devices on a daily basis range from 11 to 51%.[11] A systematic review of the effectiveness of self-performed mechanical plaque removal procedures in adults with gingivitis concluded that the quality of the mechanical plaque control was not sufficiently effective in reducing gingivitis.[12] An additional limitation of mechanical plaque control procedures was found to be that they concentrated solely on the hard tissue surfaces of the oral cavity. Although the non-shedding surfaces of the teeth provide an excellent surface for the establishment and growth of biofilms, despite representing a relatively small percentage of the total area of the oral cavity (21-23%).[13] Studies have demonstrated that microorganisms involved in the etiology of gingivitis and periodontitis accumulate on several soft tissue surfaces of the oral cavity, which serve as a source of bacteria for the colonization of tooth surfaces.[14]

Table 1: Groups Of Agents Used In The Control Of Dental Plaque And/or Gingivitis: [21]

Group	Examples of agents	Action
Antibiotics	Penicillin, Vancomycin, Kanamycin, Niddamycin, Spiromycin	Antimicrobial
Enzymes	Protease, Lipase, Nuclease, Dextranase Mutanase, Glucose oxidase, Amyloglucosidase	Plaque removal Antimicrobial
Bisbiguanide antiseptics	Chlorhexidine, Alexidine, Octenidine	Antimicrobial
Quaternary ammonium compounds	Cetylpyridinium chloride, Benzalconium chloride	Antimicrobial
Phenols & essential oils	Thymol, Hexylresorcinol, Eucalyptol, Triclosan	Antimicrobial Anti-inflammatory
Natural Products	Sanguinarine	Antimicrobial
Fluorides	Sodium Fluoride ,Sodium Monofluorophosphate, Stannous Fluoride, Amine Fluoride	Antimicrobial
Metal salts	Tin , Zinc, Copper	Antimicrobial
Oxygenating agents	Hydrogen peroxide, Sodium Peroxyborate, Sodium Peroxycarbonate	AntimicrobialPlaque removal
Detergents	Sodium lauryl sulfate	Antimicrobia lPlaque removal
Amine alcohols	Octapinol, Delmopinol	Plaque matrix Inhibition

Chemical antiplaque agents present in mouthrinses or dentifrices could reach these soft tissue surfaces, improving the control of biofilm growth on these surfaces and delaying microbial accumulation on teeth. This mechanism was illustrated in a study that examined the rate of biofilm accumulation on teeth after a 3-week preparatory phase that included oral hygiene instructions and frequent professional cleanings. [15] In the last week of this preparatory phase, the experimental group rinsed and gargled twice a day with 0.2% chlorhexidine gluconate (CHX) solution and brushed their tongue with a 1% CHX gel once a day. This intensive protocol of control of the soft tissue biofilm resulted in a lower mean plaque index (Turesky modified Quigley-Hein index [QHI]) at days 1, 2 and 4 of undisturbed plaque re-accumulation. [16,17] Thus, it was concluded that the adjunctive use of chemical plaque control agents can result in additional reduction in plaque and gingivitis, particularly in hard-to-reach areas such as interproximal spaces. They also reduce the accumulation of biofilms on soft tissue surfaces of the oral cavity, potentially delaying plaque accumulation onto the teeth. Also,

antimicrobial agents such as essential oils are capable of affecting bacteria growing in supragingival biofilms and disrupt pre-existing plaque.

The use of essential oil based mouthrinses and dentifrices containing triclosan/copolymer might affect the subgingival microbiota through the disruption of the contiguous supragingival plaque. Again, the use of a dentifrice containing triclosan/copolymer might prevent the progression of attachment loss in adolescent with a high risk of developing 'early periodontitis'. In addition, they might prevent further loss of attachment in patients with a history of periodontitis, particularly in the absence of a supportive periodontal therapy that includes subgingival debridement. In summation, chemical plaque control agents have an adjunctive role to mechanical plaque control measures in the prevention of gingivitis and periodontitis and maintenance of optimal oral health. The chief modes of action of anti-plaque agents proposed to achieve the same include primarily the inhibition of bacterial growth and metabolism to inhibition of bacterial colonization; disruption of established plaque; modification of plaque biochemistry; and alteration in plaque ecology (Scheie 1994).[18,19] Ideal properties of anti-plaque agents include stability; delivery; substantivity; safety; compatibility; cost effectiveness, in addition to not leading to staining or dysgeusia; and being able to prevent development of resistance in the target bacteria.[20]

Over a period of more than three decades there has been quite an intense interest in the use of chemical agents to control supragingival plaque and thereby gingivitis and periodontitis. It is important to emphasize that formulations based on antimicrobial agents provide a considerably greater preventive than therapeutic action. The first classification of antiplaque agents was given by Kornman in 1986 based on their pharmacological properties and efficacy and substantivity.[18,22] This included first generation antiplaque agents which were capable of reducing plaque scores by about 20-50% but exhibited poor retention, examples included antibiotics, phenols, quaternary ammonium compounds and Sanguinarine; the later in chronology to be discovered to overcome the drawbacks of the first generation products were the second generation antiplaque agents that produced an overall plaque reduction of around 70-90% and were better retained by the oral tissues and exhibited slow release properties (substantivity), examples including bisbiguanides (chlorhexidine), and the various controlled-released agents; and the recent to add, third generation antiplaque agents, which block the binding of microorganisms to the tooth surfaces and to each other, however, as compared to chlorhexidine, they do not exhibit good retentive properties with examples including Octapinol and Delmopinol.

Also, there was another classification proposed for the chemical antiplaque agents: [23]

- Bisbiguanides- Chlorhexidine, Alexidine, Octuedine, Bispyridines;
- Essential oils- Listerine;
- Quarternary ammonium compounds- Cetylpyridium chloride, Benzalkonium chloride;
- Fluorides- Sodium Fluoride, Stannous Fluoride, Organic amine Fluoride;
- Antibiotics- Penicillin, Tetracycline, Vancomycin, Kanamycin, Spiramycin, Actinomyc in, Erythromycin, Niddamycin, Streptomycin, Bacitracin, Gramicidin, CC 10232;
- Oxygenating Agents- Hydrogen Peroxide, Urea Peroxide;
- Antiseptics- Iodine, Povidone iodine, Chloramine-T;
- Enzymes- Amylase, Mutanase, Proteases, Aminoglycosidases, Glucose Oxidase;
- Plant Alkaloids- Sanguinarine; and
- Other Agents- Sodium Hexametaphosphate and Sodium Etedronate.

Also, as a part of chemical plaque control, mouthrinses, cosmetic as well as therapeutic, play a vital role. [20] Cosmetic mouthrinses are products that claim no therapeutic value. Cosmetic mouthrinses are also not included in the acceptance program of the Council on Dental Therapeutics of the American Dental Association. Of concern, is the high alcohol content of these mouthrinses that may be upto about 25% of several marketed antiseptic agents. The alcohol in mouthrinses has no antimicrobial effect, but rather is used as a vehicle with an added disadvantage of not only drying the oral mucosa but also increasing its permeability further compromising the barrier leading to easy penetrance of the invading microorganisms. Although with limited penetrance of less than 1 mm into the sulcus, therapeutic mouthrinses have an advantage of acting as important adjuncts to the mechanical plaque control procedures.

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Chlorhexidine (Peridex, Periogard): Chlorhexidine is a prescription mouthrinse that was first described more than 50 years ago and is the most thoroughly studied antimicrobial substance used orally. Chlorhexidine is the most effective antimicrobial agent for long-term reduction of plaque and gingivitis. For this reason, it is often regarded as the standard against which all other topical chemical plaque control agents are judged. The Council on Dental Therapeutics of the American Dental Association [7] has accepted Chlorhexidine as an antimicrobial and antigingivitis agent. The success of Chlorhexidine is due to the following characteristics:

- Efficacy: Chlorhexidine is bactericidal against gram-positive and gram-negative bacteria and yeasts (such as those responsible for oral candidiasis);
- Substantivity: Chlorhexidine binds with hard and soft tissues in the oral cavity and is slowly released over time in a concentration that is bactericidal;
- Safety: Chlorhexidine seems to have a very low level of toxicity and shows no permanent retention in the body.

With an alcohol content of 11.6%, Chlorhexidine has a significant inhibitory effect on plaque and gingivitis. In periodontal treatment, Chlorhexidine is used for post-operative rinsing and as an adjunct to mechanical plaque control. Use of a Chlorhexidine mouthrinse immediately following periodontal surgery, for 4-6 weeks, has been seen to be effective in facilitating post-surgical healing. Chlorhexidine can be used effectively as a disinfectant for dentures in patients with candida infections. Chlorhexidine is also effective against the bacteria responsible for dental caries. Patients at increased risk for root caries including those with moderate to severe bone loss, geriatric patients, and patients with removable partial dentures, daily or weekly rinsing with a chlorhexidine mouthrinse reduces the counts of mutans Streptococci, Lactobacillus, and Candida.

Structural Formula of Chlorhexidine:

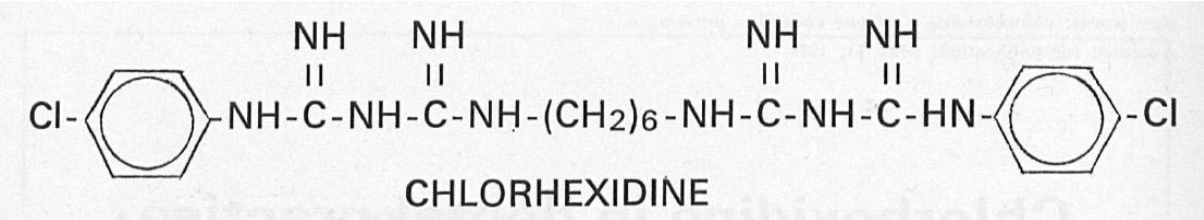

Figure 1: Chlorhexidine- The Molecule

Chlorhexidine is a bisbiguanide formulation with cationic properties. The molecule is symmetric with two 4, chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain. [24] CHX is a strong base and, at physiologic pH, is a large dicationic molecule [1, 6-di (4- chlorophenyl-diguanido) hexane] with two positive charges distributed over the nitrogen atoms on either side of the hexamethylene bridge (Fig.1) (Jones 1997, Albert and Sargeant 1962) [25]. By virtue of its positive charge, CHX has the ability to bind to negatively charged surfaces such as the bacterial cell wall (Koontongkaew and Jitpukdeebodintra 1995). Since most intraoral surfaces are negatively charged, the drug gets well distributed in the oral cavity and is not easily displaced (Loesche 1976) [26]. Once bound, it can exert its bacteriostatic and bactericidal effects. The substantivity of CHX is given by the fact that once adsorbed to intraoral surfaces, it gets only slowly displaced by calcium ions from saliva.

However, the dicationic nature making CHX extremely interactive with anions is not only relevant to its efficacy and safety, but also contributes to the local side effects and difficulties faced with product formulation.[27] In-vivo experiments using 14C-ring-labeled CHX have shown a correlation between clinical action and CHX retention in the oral cavity. These studies suggest a slow release of the antiseptic from surfaces (Bonesvoli et al 1974) [28] and this was suggested to produce a prolonged antibacterial milieu in the oral cavity (Gjermo et al 1974) [29]. CHX is available as digluconate, acetate or hydrochloride salts with digluconate and acetate salts being water soluble while hydrochloride salt being weakly soluble in water. Most studies and oral formulations and products use the digluconate salt, manufactured as a 20% V/V concentrate. [27]

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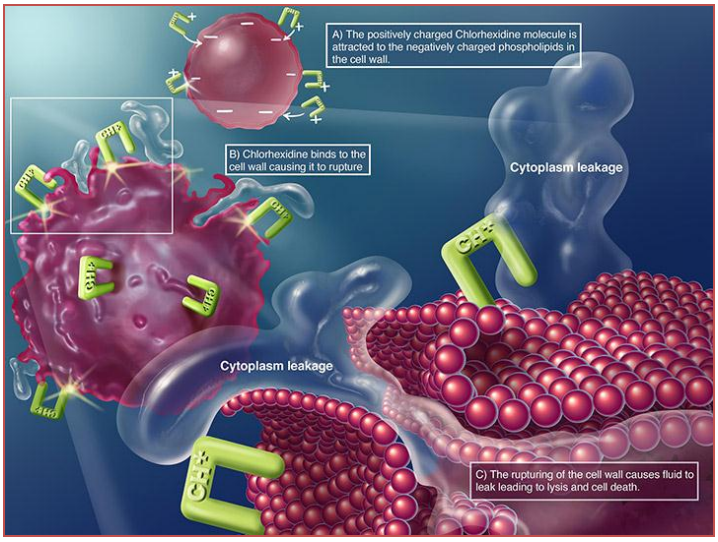
Chlorhexidine: Mode of action: [30] Chlorhexidine is a cationic bisbiguanide with a broad spectrum of antibacterial activity, low mammalian toxicity and a strong affinity for binding to skin and mucous membranes (Denton 1991). Chlorhexidine has a wide spectrum of activity encompassing gram-positive and gram-negative bacteria, yeasts, dermatophytes and some lipophilic viruses. [31] Its antimicrobial activity is of the membrane-active type. [32] (Fig.2) The antibacterial action of the biguanides has been reviewed by Woodcock (1988) and related to the mechanism of action of chlorhexidine proposed by Russell and Chopra (1990) and Denton (1991). Interestingly, and critically, 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 bacteriostatic and bactericidal effects manifest themselves vary between bacterial species (Denton 1991) [33]. The antibacterial action of Chlorhexidine is substantiated on the basis that bacterial cell membrane is characteristically negatively charged. The cationic chlorhexidine molecule is rapidly attracted to the negatively charged bacterial cell surface, with specific and strong adsorption to phosphate-containing compounds.

Figure 2: Mechanism of Action of Chlorhexidine



This alters the integrity of the 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 components, such as potassium ions. At this bacteriostatic (sublethal) stage, the effects of chlorhexidine are reversible; removal of excess chlorhexidine by neutralizers allows the bacterial cell to recover (Denton 1991). This implies that the structural changes to the cytoplasmic membrane caused by low levels of chlorhexidine are minor compared with the gross damage caused by higher concentrations (bactericidal levels) of the agent. Increasing the concentration of chlorhexidine causes progressively greater damage to the membrane (Kuyyakamond and Quesnel 1992, Rolla and Melsen 1975) [34,35].

As the concentration of chlorhexidine increases, leakage of low-molecular weight cytoplasmic components falls, reflecting the coagulation and precipitation of the cytoplasm by the formation of phosphated complexes such as adenosine triphosphate and nucleic acids (Denton 1991). Electron micrographs show the cytoplasm of such cells to be chemically precipitated; this bactericidal stage is irreversible (Denton 1991). It has been difficult to demonstrate specific binding sites in the membrane for chlorhexidine, mainly due to the several different effects the agent causes by disrupting the membrane and also due to the paucity of data in this area.

Working with alexidine and chlorhexidine, Chawner and Gilbert (1989) [36] suggest that there may either be specific binding sites for these molecules in the bacterial membrane or different intra molecular interactions of the two molecules at the membrane, and the differences in the endgroup substitution between the biguanides affecting their ability to produce lipid domains in the cell membrane. Russell and Furr (1986) have suggested that the outer membrane in some mutant Escherichia coli strains may confer some mechanism

by which the bacteria are less susceptible to chlorhexidine, wherein the inner membrane does not seem to be involved. The difference in effects of chlorhexidine on the outer and inner membranes suggests some degree of specificity of the action of chlorhexidine on the membrane(s). Addy and Kornman (1986) [37] ascribed chlorhexidine's superior antiplaque activity to its property of persistence (substantivity). Kornman (1986) differentiated antiseptics into first- and second-generation antiplaque agents, depending on whether or not they exhibit the ability to persist within the oral cavity. At physiological pH, chlorhexidine is a large dicationic molecule, (1, 6-di (4-chlorophenyl-diguanido) hexane, with the positive charge distributed over the nitrogen atoms on either side of the Hexamethylene Bridge.

Thus, chlorhexidine has the ability to adsorb onto negatively charged surfaces, such as bacterial cell membranes, where it exerts its bacteriostatic and bactericidal effects. Chlorhexidine also binds to the different surfaces within the oral cavity (teeth and mucosa) and also to the pellicle and saliva; for example, after a single rinse with chlorhexidine, the saliva itself exhibits antibacterial activity for up to 5 hours (Roberts 1981, Rolla and Loe 1971) [38], whereas persistence at the oral surfaces has been shown to suppress salivary bacterial counts for over 12 hours (Schiott 1973) [37]. Thus, although chlorhexidine is able to bind to different anionically charged elements within the oral cavity, it also, importantly, maintains its antibacterial activity for several hours (Addy 1978, Roberts 1981, Schiott 1973, Schiott 1970) [38]. Given that plaque formation occurs on the tooth surface, paradoxically, the binding of chlorhexidine to the pellicle-covered tooth surface was considered to be small compared with that involved in chlorhexidine-protein interactions at other oral surfaces (Bonesvoll 1974, Davies 1973). Indeed, Waaler and Rolla (1985) [39] considered that neither the teeth nor the tongue were of major importance as receptor sites for chlorhexidine in preventing the accumulation of sucrose-enhanced plaque formation. This led to speculation that it was the interaction of chlorhexidine at sites other than the tooth surfaces that was important for chlorhexidine's antiplaque effect. This involved a "reservoir" of chlorhexidine slowly desorbing from all the oral surfaces, resulting in a bacteriostatic milieu in the mouth (Gjermo 1974). Rolla and Melsen (1975) postulated that chlorhexidine, desorbed from the oral mucosa, might have three mechanisms of plaque inhibition:

- An influence on pellicle formation by blocking the acidic groups on the salivary glycoproteins, thus reducing the protein adsorption on to the tooth surfaces;
- An influence on the adsorption of plaque onto the tooth surfaces by binding to the bacterial surface in sublethal amounts; and
- An influence on the formation of plaque by precipitating the agglutination factors in saliva and displacing calcium from the plaque matrix.

However, Jenkins et al (1988) [40] showed that plaque growth on enamel inserts was inhibited equally well by 0.2% chlorhexidine applied topically or by rinsing. They considered, through electron microscopy of the enamel inserts, that chlorhexidine achieved its antiplaque effect as a result of an immediate bactericidal action at the time of application, followed by a prolonged bacteriostatic action as a result of chlorhexidine adsorbing to the pellicle-coated enamel surface. Thus, bacterial attachment to the enamel surface is not entirely inhibited, but bacterial growth is delayed by the bacteriostatic effects at the surface. This implied that tooth surface-bound chlorhexidine was of greater importance in preventing plaque formation than was first thought. It may be worth attempting to explain the difference in these findings to that of Waaler and Rolla (1985) [39]; this may lie in the findings of Davies (1973), who considered that sucrose enhancement of plaque formation may reduce the effects of chlorhexidine, such that the low "bacteriostatic" levels of chlorhexidine are no longer able to penetrate the cell wall of plaque bacteria grown in the presence of excess sucrose. Based on the work by Jenkins et al (1988) [40], it is worth reappraising the concept of an oral reservoir of chlorhexidine as the basis of the antiplaque activity of this antiseptic. For this oral reservoir to create a "bacteriostatic milieu", there must be adsorption of chlorhexidine to the oral mucosa and saliva at the time of application, followed by a progressive desorption over time, resulting in a reduction in the bacterial challenge to the tooth surface through irreversible adsorption of chlorhexidine to the bacterial cell. The chlorhexidine must move from the mucosa, saliva etc. to the bacterial cell. The methods of analysis of desorbed chlorhexidine (Bonesvoll 1977, 1978, 1974, Gjermo 1975) do not distinguish between "free" chlorhexidine (if such an entity can occur in a mouthrinse with proteinaceous material), reversibly bound chlorhexidine and irreversibly protein-bound chlorhexidine. So, there is no evidence that chlorhexidine slowly desorbs from the oral surfaces at all; it is always likely to be bound to saliva, epithelial cells, pellicle, bacteria etc. In addition, unless one believes there is a preferential removal from the saliva (by chlorhexidine) of the bacteria that are able to begin colonizing the tooth surface, one cannot easily explain why the oral reservoir has an antiplaque

effect. Although chlorhexidine may reduce the salivary bacterial counts- a single rinse with chlorhexidine can reduce the oral flora by over 90% for several hours (Addy 1978, Roberts 1981, Schiott 1970, 1973)- many millions of bacteria present in the saliva and on the oral surfaces are still not affected. As the oral cavity cannot be sterilized, there must be a continual challenge to the tooth surface by bacteria that are able to begin the process of plaque formation. As the salivary bound chlorhexidine patently has not eradicated putative plaque-forming bacteria, it would seem logical therefore to assume that the process of plaque prevention occurs at the tooth surface itself -by tooth-bound chlorhexidine.

Effect on initial plaque formation: [41] Immediately following application of Chlorhexidine in the oral cavity in bactericidal concentrations, a substantial amount of the bacteria gets killed. A reduction of the numbers of bacteria in saliva from 50% to 90% has been reported (Schiott 1973, Schiott et al 1976), however according to Stalfors (1962), this reduction would not be sufficient to prevent plaque formation. Taking the rapid reproduction of bacteria in the oral cavity into consideration, he calculated that 99% of the bacteria had to be killed twice daily to prevent plaque formation. However, due to the substantiveness (retention and sustained release) of Chlorhexidine and related compounds, a bacteriostatic concentration of these drugs may be maintained in the saliva for several hours after the application (Bonesvoll and Gjermo 1977). Bacteria in a bacteriostatic phase do not multiply, and their metabolic activity is strongly inhibited, probably impairing their ability to produce the substances necessary for adherence. In addition, the presence of strong cationic molecules (bisbiguanides, quaternary ammonium compounds) may interfere with the non-specific adhesion mechanisms by competing with, for instance, calcium ions for retention sites (Rolla and Melsen 1975, Bonesvoll 1977) [42,43]. A selective effect upon some of the bacteria involved in early plaque formation may also play a role in this respect (Emilson 1977) [44].

Effect upon established plaque: [41] It has been shown that frequent applications (six times per day) of Chlorhexidine mouthrinses (10ml of 0.2% Chlorhexidine) will cause dispersion and elimination of existing plaque (Loe and Schiott 1970) [2]. Topical application of strong concentrations of this drug and other antimicrobial agents may have similar effects (Stralfors 1962, Davies et al 1970) [45]. Bonesvoll and Olsen (1974) [29] showed that plaque present on the teeth when Chlorhexidine was applied as a conventional mouthrinse (10ml of 0.2% Chlorhexidine) would retain a substantial amount of the agent. Plaque-retained Chlorhexidine is probably bound to phosphate groups on bacterial surfaces and to sulfates in thiol groups of surface-bound bacterial enzymes (Oppermann 1980) [46]. Chlorhexidine and other cationic substances and metal ions were also found to inhibit acid production in established plaque under experimental conditions in humans. The duration of this effect was found to be dependent on the agent's ability to be retained in the oral cavity and in plaque, and also on their rate of release from the binding sites (Oppermann 1979, 1980, Oppermann and Gjermo 1980) [25,46]. In addition to reducing the acidic challenge to the tooth surface per se, the effect may also be that acidophilic and cariogenic organisms such as S mutans will have less favourable conditions for colonization (Rolla, 1988).The expected caries-inhibiting effect of Chlorhexidine has support in clinical experiments (Loe et al 1972, Zickert et al 1982), but the mechanisms behind the effect are still not known. However, it seems that the presence and amount of S mutans may successfully be used for screening purposes to select subjects at high risk and to evaluate the effect of anti-bacterial treatment aimed at establishing a non-cariogenic oral flora (Emilson 1977) [44].

In the nutshell, there are three possible mechanisms suggested for the antiplaque action of chlorhexidine:

- The effective blocking of acidic groups of salivary glycoproteins reduces 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 glycocalyces; 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. [47] Production of extracellular polysaccharides increases in the presence of sucrose. A greater proportion of the drug is then absorbed by the cell coatings and less is available to act upon the cellular membrane of the microorganisms to effect direct killing of them. [48]
- Chlorhexidine may compete with calcium ions agglutination factors in plaque; laboratory studies have suggested that chlorhexidine can bond with hydroxyapatite. [49] However, it is now considered that it is the affinity of Chlorhexidine for the acidic proteins in pellicle, plaque, calculus, oral mucosa and on

the surfaces of bacterial cell membranes which is of greater clinical significance than its affinity for hydroxyapatite. [50]

Clinical uses of chlorhexidine in dentistry: [21] Despite the excellent plaque inhibitory properties of chlorhexidine, widespread and prolonged use of the agent is limited by local side effects. Moreover, because of the cationic nature of the chlorhexidine and therefore its poor penetrability, the antiseptic is of limited value in the therapy of established oral conditions including gingivitis, and is actually more valuable in the preventive mode.

As an adjunct to mechanical cleaning

Chlorhexidine increases the improvement in gingival health through plaque control, particularly following a professional prophylaxis to remove existing supragingival and immediate subgingival plaque;

Immediate preoperative rinsing with chlorhexidine

This can be used immediately prior to operative treatment, particularly when ultrasonic or high-speed instruments are to be used. Such preoperative rinsing markedly reduces the bacterial load and contamination of the operative area and operator and staff (Worral et al 1987). Additionally, in susceptible patients, irrigation of chlorhexidine around the gingival margin has been seen to reduce the incidence of bacteremia (MacFarlane et al 1984);

For oral hygiene in the mentally and physically handicapped

Chlorhexidine has been found to be particularly useful in institutionalized mentally and physically handicapped patients, improving both oral hygiene and gingival health (Storhaug 1977). Spray delivery of 0.2% solutions was found particularly useful and acceptable to patients as well as care workers (Francis et al 1987, Kalaga et al 1989);

Rinsing

In 1970, Loe and Schiott demonstrated that twice daily rinsing with 10 ml of 0.2% CHX solution (20 mg CHX) for 1 minute resulted in complete plaque elimination. This reduction of plaque persisted during the 22 days that were monitored. A later paper by Loe et al reported that reduced plaque levels were maintained for 2 years using daily 0.2% CHX mouthrinses. Using a similar oral rinse, Flotra et al monitored 50 soldiers for 4 months. [51]

They reported a 66% reduction in plaque and 24 % decrease in gingivitis scores with chlorhexidine. The authors noted that the test group which had subgingival scaling demonstrated an 88% reduction in plaque and 43% decrease in gingivitis scores. Lang and Raber [27]reported that daily rinse with 30 ml of 0.1% CHX failed to eliminate plaque and gingivitis, whereas others claimed a 0.1% solution was effective in many cases. Cumming and Loe [27] also suggested a daily rinse should employ 50 ml of 0.1% CHX to provide a larger dose of the drug. In summary, it appears that patients respond differently to a range of concentrations. Therefore, dosages need to be individually determined and low concentrations can be compensated by increasing the volume applied.

Recommended use is twice daily oral rinsing for 30 seconds, morning and evening, after tooth brushing. Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate oral rinse;

Oral Irrigators

Oral Irrigators fail to achieve optimal plaque removal and gingivitis if they are substituted for manual hygiene procedures. However, they can provide a satisfactory vehicle to apply antimicrobial agents interproximally and subgingivally. Lang and Raber [27] compared the inhibitory effect of CHX when applied as a mouthrinse and in oral irrigators and concluded that antimicrobial agents would be more effectively distributed with irrigating devices resulting in a reduced plaque index. The difference was most pronounced

interproximally, an area often missed during toothbrushing. However, their oral rinse consisted of 30 ml of 0.1% solution (30 mg of CHX) whereas 600 ml of 0.05% solution was used for irrigation (300mg CHX). Thus, while the concentration during irrigation was decreased, the dosage of CHX was increased tenfold. This accentuated the need to determine precise concentrations, because suboptimal doses may not provide satisfactory plaque control. Thereafter, Lang and Grossman assessed several different dosages by varying the concentrations and volumes of applied solutions. They found that either 400 ml or 600 ml of 0.02% CHX solution (80 or 120 mg), 600 ml of 0.05% CHX solution (300 mg) or 600 ml of 0.1% CHX solution (600 mg) via an irrigating device were equally effective in reducing plaque levels. It was concluded that 400ml of 0.02% CHX solution, applied once daily, was the lowest concentration and best dosage (80 mg) that could achieve optimal plaque control;

Subgingival Irrigation with CHX

Chlorhexidine application resulted in a decreased plaque index (PI), however not a reduced gingival index (GI) after 2 years. It was hypothesized that this was due to failure of the rinsing solution to penetrate subgingivally. Flotra et al[51] noted that lack of reduction of inflammation was apparent at sites where pockets were greater than 3mm. Possibly, the inflammatory crevicular fluid released in pockets created an osmotic gradient preventing solutions from penetrating. Pitcher et al demonstrated solutions applied as rinses or with direct irrigation at the gingival margin failed to reach the base of deep pockets. Subgingival CHX application using a syringe was assessed by Soh et al who instructed individuals to irrigate with 0.2% solution for 28 days. They found that it was necessary to perform irrigation after a minimum of 2 and a maximum of 4 weeks to obtain a reduction of sulcular bleeding, pocket depth and subgingival plaque. Investigators concluded that CHX irrigation may be a useful adjunct to scaling and root planing. Two studies addressed the efficacy of irrigating deep pockets with 2% CHX as a supplement to oral hygiene and root debridement;

Post-oral surgical procedures including periodontal surgeries or root planing

Chlorhexidine may be used postoperatively since it offers the advantage of reducing the bacterial load in the oral cavity and preventing plaque formation at a time when mechanical cleaning may be difficult because of discomfort. In periodontal surgery, periodontal dressings have largely been replaced by the use of chlorhexidine preparations, in particular mouthrinses, since healing is improved and discomfort reduced (Newman and Addy 1978, 1982);

For patients with intermaxillary fixation

Oral hygiene is particularly difficult when jaws are immobilized by such methods as intermaxillary fixation. Chlorhexidine has been shown to reduce markedly the bacterial load, which tends to increase during jaw immobilization, and improve plaque control (Nash and Addy 1979);

Medically compromised individuals predisposed to oral infections

Chlorhexidine is effective as an anticandidal agent but is most useful when combined with specific anticandidal drugs, such as nystatin or amphotericin B (Simonetti et al 1988). The major indications for chlorhexidine use combined with anticandidal drugs have been for the prevention of oral and systemic infections in the immunocompromised patients, including those with blood dyscrasias, those receiving chemotherapy and/or radiotherapy and notably bone marrow transplant patients (Firretti et al 1987, 1988, Toth et al 1990).

High-risk caries patients:

Chlorhexidine rinses or gels can reduce considerably the streptococcus mutans counts in individuals who are more prone for caries. Additionally, and interestingly, chlorhexidine appears synergistic with fluoride and combining chlorhexidine and fluoride rinses appears beneficial to such “at risk” individuals (Dolles and Gjermo 1980, Lindquist et al 1989).

Recurrent oral ulceration

Several studies have shown that chlorhexidine mouthrinses and chlorhexidine gels reduce the incidence, duration and severity of recurrent minor aphthous ulceration (Addy et al 1974, 1976, Hunter and Addy 1987). The exact mechanism behind this is though not clear but it might be because of a reduction in contamination of ulcers by oral bacteria, thereby hastening healing of such lesions;

Removal and fixed orthodontic appliance wearers

Plaque control in the early stages of orthodontic appliance therapy may be compromised and chlorhexidine can be prescribed for the first 4-8 weeks. Additionally, chlorhexidine has been shown to reduce the number and severity of traumatic ulcers during the first four weeks of fixed orthodontic therapy (Shaw et al 1984);

Implant dentistry

Studies indicate that CHX delivered via irrigation into the peri-implant sulcus is of value in reducing the bacterial load. There is however no evidence to indicate that implant success is improved by the use of CHX rinses or for that matter CHX irrigation.

Side effects of Chlorhexidine

Since 1954, chlorhexidine has been used clinically for several purposes. The effect of chlorhexidine on oral mucosa has been tested (Cawson and Curson 1959) and its calculus-inhibiting capacity has also been studied by Schroeder (1969). However, no harmful effect on the oral mucosa had been reported. However, later in 1971, Flotra and co-workers conducted a study over a 4-month period on the side effects of chlorhexidine. The clinical trial noted that the use of chlorhexidine was associated with problems that merit further consideration. These included oral and other associated side effects.

Oral side effects: [27]

Staining

When used as a mouthrinse, CHX has a number of local oral side effects (Loe and Schiott 1970, Flotra et al 1971) [51], the most common being a brownish discoloration of the teeth (Fig.3), some restorative materials, the mucosae and notably, the dorsum of the tongue (Fig.4), decreasing patient compliance. The amount of staining seems to be dependent on the mode of application, concentration, and presence of the potential discoloring agents within the extraneous factors including diet. The mechanisms of the origin of the CHX-staining are still debated (Eriksen et al 1985, Addy and Moran 1995) and include:

Figure 3: Yellowish discoloration of teeth in an individual rinsing twice a day for 3 weeks with a 0.2% chlorhexidine mouthrinse

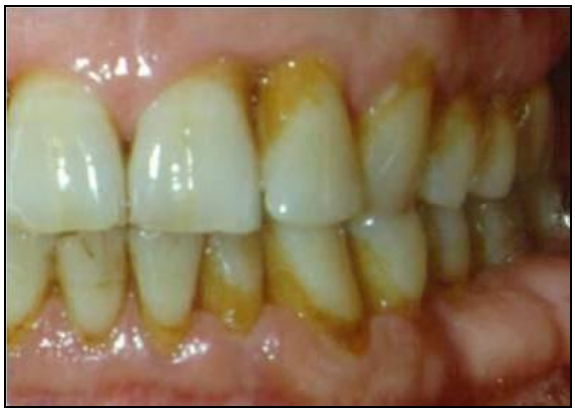
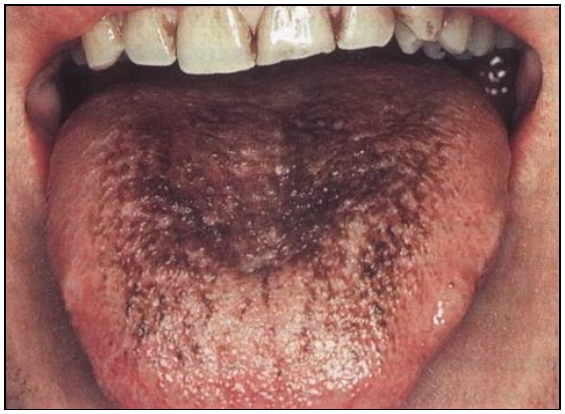


Figure 4: Brownish discoloration of tongue in an individual rinsing twice a day for 2 weeks with a 0.2% chlorhexidine mouthrinse



Degradation of the chlorhexidine molecule to release parachloraniline

Degradation of the chlorhexidine molecule to release parachloraniline appears to occur on storage or as a result of metabolic processes (Addy and Roberts 1981);

Catalysis of Maillard reactions

Non-enzymatic browning reactions (Maillard reactions) catalyzed by chlorhexidine are a theoretical possibility (Nordbo 1979); however, evidence is inconclusive (Eriksen et al 1985). A series of chemical reactions between sugars and amino acids called the non-enzymatic browning reactions or maillard reactions lead to the production of metabolic end-products that are responsible for this prominent side effect.[30] In clinical testing, 56% of oral rinse users exhibited a measurable increase in staining on the facial aspects of anterior teeth, compared to 35% of control users after 6 months;

Protein denaturation with metal sulfide formation

Protein denaturation produced by chlorhexidine with the interaction of exposed sulfide radicals with metal ions from food sources is also theoretically considered to be a possible cause for such staining seen with prolonged chlorhexidine usage (Ellingsen et al 1982, Nordbo et al 1982); and

Precipitation of anionic dietary chromogens.

Precipitation of anionic dietary chromogens by cationic antiseptics, including chlorhexidine and numerous polyvalent metal ions as an explanation for the phenomenon of staining is well supported (Addy and Moran 1995, Watts and Addy 2001). Thus, the locally bound antiseptics or metal ions on mucosa or teeth can react with polyphenols in dietary substances to produce staining.

Bitter taste/taste disturbance (dysgeusia)

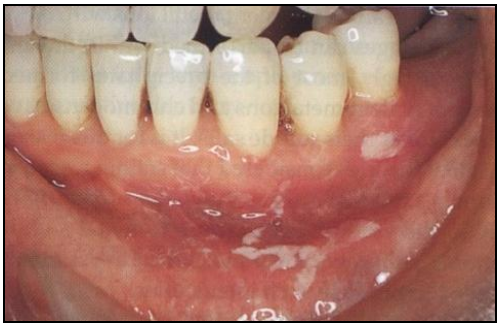
Aqueous solutions of CHX have a very bitter taste leading to transient change in taste perception (dysgeusia). Objective testing of the taste sensation has also confirmed a transient effect on the perception of sweet and salt taste (Gjermo et al 1974)[27] with salt taste preferentially being affected (Lang et al 1988);

Mucosal desquamation

Desquamation and subsequent, ulcerations and erosions of the oral mucosa (Fig.5) in connection with mouth rinses with bisbiguanides have been sporadically reported (Gjermo et al 1970) and have been explained by precipitation of the mucin layer weakening its lubricating effect (Gjermo et al 1974). A few cases of painful desquamations of the oral mucosa have been reported after chlorhexidine mouth rinses (Flotra et al 1971). This side effect though is concentration dependent. To maintain the dose and thereby the effect, a double

volume has to be rinsed. Dilution of the 0.2% formulation to 0.1%, but rinsing with the whole volume to maintain dose, usually alleviates the problem. Erosions are rarely seen with 0.12% rinse products used at 15 ml volume.

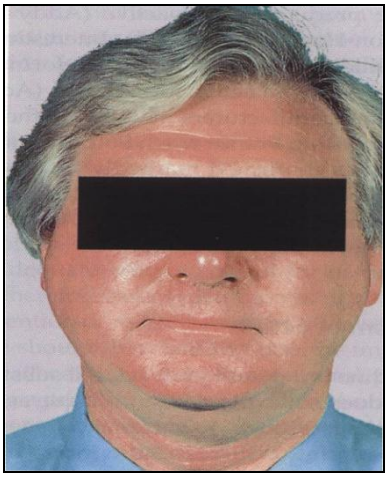
Figure 5: Mucosal erosions in an individual following a few days of rinsing twice a day with a 0.2% chlorhexidine mouthrinse



In addition to these, some local side effects are also seen which include: [51]

D.Unilateral or bilateral parotid swelling (Fig.6): Although not a common adverse effect, this is seen as an extremely rare occurrence with no plaudible explanation. The reports of virus infections (parotitis) in connection with chlorhexidine mouth rinses (Gjermo et al 1970, Flotra et al 1971) [51] might probably be purely co-incidental, but cannot be completely disregarded. Secretory IgA, which is known to possess antiviral activity, accumulates on the mucous membrane (Brandtzaeg 1972). A possible precipitation of acidic proteins in the mucin layer coating mucous membrane of the oral cavity may thus interfere with the anti-viral mechanisms;

Figure6: Bilateral parotid swelling in an individual following a few days of rinsing with a 0.2% chlorhexidine mouthrinse



E.Enhanced supragingival calculus formation: This effect may be due to the precipitation of salivary proteins on to the tooth surfaces, thereby increasing the pellicle thickness and/or precipitation of inorganic salts on to the pellicle layer.[52] Zannata et al in 2010 conducted a study on staining and calculus formation after 0.12% chlorhexidine rinses in plaque-free and plaque covered surfaces in a randomized controlled trial. The presence of plaque was seen to increase as a prominent side effect of chronic usage of 0.12% CHX. These results strengthened the necessity of biofilm disruption prior to the the start of CHX mouthrinses in order to reduce these side effects. Certainly, pellicle formed under the influence of chlorhexidine, showed an early and highly calcified structure (Leach et al 1977).

Limitations of Chlorhexidine

Toxicity of CHX: [27]

Absorption: The cationic nature of CHX minimizes absorption through skin and mucosae including that of the gastrointestinal tract. Studies with radiolabelled CHX showed that when CHX is swallowed, the drug binds to the mucosal surfaces of the alimentary tract. The expired cells are desquamated and together with any on-bound CHX are excreted in the feaces. Thus, practically all CHX swallowed is excreted in the feaces (Winrow 1973). The very small amount of CHX that may be absorbed is minimally metabolized in the liver and excreted in urine (Winrow 1973). No systemic toxicity even from long-term topical application and ingestion has been reported (Gjermo 1989). Intravenous infusion in animals is well tolerated and has even accidentally occurred in humans without serious consequences (Foulkes 1973, Denton 1991). When orally ingested, LD50 for CHX is 2,000 mg/kg body weight. This means that individuals with an average body weight of 70 kg would need to drink 70 liters of a 0.2% CHX solution at once in order to kill 50% of the test population.

Teratogenic effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at CHX gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus (Foulkes 1973). Adequate and well-controlled studies in pregnant women have, however, not been attempted.

Carcinogenesis, mutagenesis, and impairment of fertility: In a drinking water study in rats, carcinogenic effects were not observed at doses up to 38 mg/kg/day. Mutagenic effects were not observed in two mammalian in vivo mutagenesis studies with CHX gluconate. The highest doses of CHX used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1,000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day (Foulkes 1973).

Neurosensory deafness: This can occur if CHX is introduced into the middle ear. The antiseptic should not be placed in the outer ear in case the ear drum is perforated.

Nursing mothers: It is not known whether CHX is excreted in human milk. Because many drugs are excreted in human milk, caution might be indicated when CHX is administered to a nursing woman. In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when CHX gluconate was administered to dams at doses that were over 3 g per day.

Bacterial resistance: Resistance has not been reported even in long-term oral use. There is no evidence of superinfection by fungi, yeasts or viruses. Long-term oral use resulted in a small shift in the flora towards less sensitive organisms but the effect was rapidly reversible after discontinuation of use (Schiott et al 1976). Davies et al (1973) have been able to isolate bacteria with reduced sensitivity to chlorhexidine from human plaque which had formed under the influence of the agent. These bacteria are not thought to represent strains which have developed resistance, but rather demonstrate a selection of strains which are naturally less sensitive to chlorhexidine. Hamp et al (1973) have reported loss of effect of chlorhexidine in dogs after 6 months of use, whereas the capacity of chlorhexidine to prevent plaque formation has been shown to persist in humans even after 2 years of continuous use (Gjermo and Eriksen 1974). This discrepancy may be due to differences in the composition of the canine and human oral flora. Several groups of medical and dental students and some smaller groups of handicapped patients have used chlorhexidine daily for 2 years and no serious side effects have been reported (Eriksen et al 1973, Eriksen and Gjermo 1974, Schiott 1973, Flotra 1973, MacKenzie 1974).

Development of allergic reactions: Allergic reactions to chlorhexidine have been reported with certainty in fewer than 10 cases (Winrow 1973).

Toxic effects: Tracing studies, employing radio-labelled chlorhexidine, have not disclosed any signs of permanent retention (Magnusson and Heyden 1973, Winrow 1973). Both in humans and in a series of animal species, chlorhexidine introduced orally has been shown to be excreted in feaces and urine with 90- 99% recovery (Winrow 1973). Moreover, a series of experiments has confirmed that the chlorhexidine molecule is very stable. This indicates that toxic breakdown products are unlikely to be formed (Winrow 1973).[24,27] In

2007, a study was done on the cytotoxicity of mouthrinses on epithelial cells by micronuclei test . In this study the Micronuclei (MN) incidence increased in Klorhex (0.2% Chlorhexidine Gluconate), Andorex (0.15% Benzydamine HCL and 0.12% Chlorhexidine Gluconate), Tanflex (0.15% Benzydamine HCL) groups after exposure to mouth rinses ($p < 0.05$). But when compared with the control group (physiologic saline), there was no difference between Andorex and control group ($p > 0.05$). In the other study groups, micronuclei incidence was significantly increased after 7 days of treatment ($p < 0.05$). Gingival Index (GI) scores of all groups were decreased significantly (P<.05) while Plaque Index (PI) scores were decreased only in the Klorhex group ($p < 0.05$). The primary findings supported the presence of possible cytotoxic effects of the mouthrinses (especially chlorhexidine containing mouthrinses) on gingival epithelial cells. [53] In 2014, two studies were conducted. One study was conducted on the cytotoxicity and genotoxicity of chlorhexidine on macrophages in-vitro. The cytotoxicity of CHX in RAW264.7 cells presented a dose- and time-dependent manner ($p < 0.05$). The mode of cell death shifted from apoptosis to necrosis when the dosage of CHX increased. The genotoxicity of CHX in RAW264.7 cells had shown DNA damage in a dose-dependent manner ($p < 0.05$). Prolongation of cell cycle and the increase of ROS generation also expressed in a dose-dependent manner. [54] Another study was conducted in 2014 on the assessment of the cytotoxicity of chlorhexidine by employing an in vitro mammalian test system. CHX demonstrated a cytotoxic effect on Chinese hamster ovary cells in a dose-dependent and time-dependent manner ($P < 0.05$). The mode of cell death changed from apoptosis to necrosis as the concentrations of CHX elevated. CHX demonstrated a significant superoxide anion generation in a dose-dependent manner ($P < 0.05$). CHX was demonstrated to exhibit cytotoxicity that could disrupt the stable cellular redox balance, resulting in increasing levels of free radical generation and subsequent cell death. [55] Hence, CHX has been concluded to possess significant potential for cytotoxicity. However, despite the shortcomings (genotoxicity and cytotoxicity) of CHX, it is yet considered the "GOLD STANDARD" as the beneficial effects far supercede the limitations though care should be taken to use it at relatively lower concentrations to achieve the desired therapeutic effects. [56]

Chlorhexidine

The Rationale: Chlorhexidine (CHX) was the first antimicrobial agent shown to inhibit dental plaque formation and the development of chronic gingivitis (Loe and Schiott 1970) [2]. Chlorhexidine is a cationic chlorophenyl bisbiguanide antiseptic. Bisbiguanides are the primary second generation antiplaque agents exhibiting considerable substantivity and broad spectrum antibacterial properties. In dental medicine, CHX was initially used for disinfection of the oral cavity prior to oral surgical procedures and in endodontics. Plaque inhibition by CHX was first investigated in 1969 (Schroeder) but the first controlled clinical study was performed by Loe and Schiott (1970) [2]. This study showed that rinsing for 60 sec, twice a day with 10 ml of a 0.2% (20 mg dose) CHX gluconate solution, in the absence of normal tooth cleaning, inhibited plaque regrowth and the development of gingivitis. Numerous studies conducted in the later years eventually concluded with similar results and projected that CHX is one of the best investigated compounds in dentistry and to date, still remains the gold standard to which the other antiplaque [24] and antigingivitis agents are compared (Gjermo 1989, Addy et al 1994, Moshrefi 2002) [41,57]. CHX is one of the most widely investigated and used antiplaque agents. [58] The advantage of CHX over other cationic agents is that it can bind strongly to many sites in the oral cavity and is released slowly over 7 to 12 hours after rinsing, thus providing considerable substantivity and a sustained antimicrobial effect restricting bacterial proliferation. CHX binds strongly with anionic glycoproteins and phosphoproteins on the oral mucosa and tooth pellicle in addition to its property of binding to the surfaces of bacterial cell membranes affecting the cells ability to adhere. CHX is considered the most potent chemotherapeutic agent currently available. Short-term trials predominantly demonstrate the superior efficacy of CHX on plaque regrowth and numerous other outcome measures. (Netuschil L 1995, Sekino S 2005, Claydon N 2002, Moran J 1992, 2000, Pizzo G 2004) [59]. Plaque reductions of upto 16%-45% and gingivitis reductions from 27%-80% have been demonstrated in six-month trials.[60]

Because of the accumulation of positive clinical research findings, CHX rinses are often used as a benchmark control and similarly as a positive control being accepted as the "gold standard". As CHX has no activity on specific bacterial enzymes or receptors, there is minimal opportunity for bacterial resistance to develop, and no shift in the oral flora has been demonstrated that would allow opportunistic species to flourish. Thus, there are a significant number of indications for the use of chlorhexidine, most of which rely on the antimicrobial properties of the antiseptic and its duration of action. Daily or weekly rinsing with a Chlorhexidine mouthrinse has been seen to reduce the counts of mutans Streptococci, Lactobacillus, and Candida.

Chlorhexidine

The Gold Standard: The superior antiplaque effect of Chlorhexidine which makes it gold standard can be attributed to its substantivity. Substantivity is defined as the ability of an agent to adhere to the soft and hard tissues and then be released over time with retention of potency. [61] 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 10 ml of 0.2% aqueous solution of chlorhexidine for 1 min, approximately 30% of the drug is retained back in the oral cavity. [24,62] After single rinse with chlorhexidine, the saliva itself exhibits antibacterial activity for up to 5 hrs [63] whereas persistence at the oral mucosal surfaces has been shown to suppress salivary bacterial counts for over 12 hours [64]. 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.[30] This explains the lack of effectiveness of other antimicrobials in terms of them lacking a large, rigid molecule with two charged interactive ends.[32] Studies have shown that the daily use of chlorhexidine mouthrinse combined with toothbrushing resulted in reduced interproximal plaque when compared with toothbrushing and daily flossing.[65] Chlorhexidine is also of importance in the maintainance protocol in immediate function implants as a correlation between plaque and bleeding index revealed a good result for 0.2% chlorhexidine gel for daily implant self care at 6 months [66]. The concentration of the drug remains above the minimum inhibitory concentration (MIC) for more than 99% of the subgingival microorganisms from the periodontal pockets. The results of several clinical trials have shown that the use of the chlorhexidine chip in conjunction with scaling and root planing is effective in reducing periodontitis, clinical attachment loss and bleeding on probing over a period of 6 to 9 months. The use of the controlled release chlorhexidine delivery systems during maintenance therapy allows greater improvement in clinical signs of periodontitis. It has even been used as a positive control in many studies. Chlorhexidine is one chemical plaque control agent which has various clinical applications in dentistry especially in periodontics that have come to stay that it is not inappropriate to call it the gold standard chemical plaque control agent discovered till date.

CONCLUSION

After years of use by the dental profession, chlorhexidine is recognized as the gold standard against which the efficacy of other antiplaque agents is measured. Chlorhexidine's antiplaque effect is a result of the dicationic nature of the chlorhexidine molecule, which affords the agent the property of persistence of antimicrobial effect at the tooth surface, through both bactericidal and bacteriostatic effects. Although other antiplaque agents may show either purely immediate effect, or limited persistence, the degree of chlorhexidine's persistence of effect at the tooth surface is the basis of its clinical efficacy (substantivity). The cationic nature of the chlorhexidine molecule however is the basis of the most common side effect associated with the use of the agent- extrinsic tooth staining. Such tooth staining seems to be the result of a local precipitation reaction between toothbound chlorhexidine and chromogens present in extraneous agents. The cationic nature of the chlorhexidine molecule also becomes a reason for its limited effectiveness when it is used in conjunction with certain types of toothpastes that carry free anionic agents; thus care is required when using normal tooth brushing alongside chlorhexidine. By understanding how the chemical properties of the chlorhexidine molecule can explain the plethora of clinical efficacy and safety data, the use of chlorhexidine can be optimally aimed towards the patient groups who would most benefit from the superior therapeutic effect of the agent. Specifically, chlorhexidine would seem to be of most value to patients in whom the ability to perform adequate oral hygiene procedures has been compromised.

In these individuals, the delivery of the correct dose of chlorhexidine to the tooth surface can be optimized through the judicial use of the several different chlorhexidine formulations now available. Thus, by understanding the properties and limitations of the chlorhexidine molecule, the dental profession can ensure that the efficacy of the agent is maximized, and the side effects associated with the agent are minimized, allowing chlorhexidine to be the most efficient and the gold standard against which the efficacy of other antiplaque agents will continue to be measured.

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