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Chlorhexidine, A Medicine for all the Oral Diseases.

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A B S T R A C T

Chlorhexidine is a bisbiguanide antiseptic. It is active against both Gram-positive and Gram-negative strains as well as fungi. It has bacteriostatic and bactericidal actions. Chlorhexidine has excellent antiplaque activity and unique property of substantivity. So it has got wide applications starting from maintaining oral hygiene pre surgically to post operative and also in physically and mentally handicapped patients. Chlorhexidine is now routinely used by clinicians when they treat patients with fixed appliances in orthodontia and maxillofacial surgeries. Chlorhexidine has been extensively used in various medical fields such as gynecology, urology and ophthalmology; also in disinfection of operation fields and treatment of burns. Its products are available in various forms like mouth rinses, gels, sprays, toothpastes and varnishes.

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Introduction

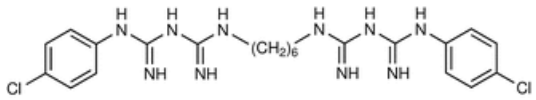
Chlorhexidine was developed in 1940's by Imperial Chemical Industries (ICI, Macclesfeild, England) and marketed in 1954 (Davies et al) as a general disinfectant. 1957, chlorhexidine gluconate was introduced for human use in Great Britain as an antiseptic cream for skin wounds.

In United States, it made its appearance as Hibiclens, a 4% solution used as an antimicrobial skin cleanser. Since then chlorhexidine has been extensively used in various medical fields such as gynecology, urology, and ophthalmology and in disinfection of operation fields and treatment of burns. The first use of chlorhexidine in dental practice was in washing operation sites and disinfecting root canals. Plaque inhibition by chlorhexidine was first investigated in 1969 by Schroeder, but a definitive study was performed by Loe and Schiott in 1970.

Structure

Chlorhexidine is a bisbiguanide antiseptic. It is a symmetrical molecule consisting of four chlorophenyl rings and two biguanide groups connected by a central hexamethylene bridge.

The formula is as follows:



Chlorhexidine is available in three forms- the digluconate, acetate and hydrochloride salts. Most studies and most oral formulations and products have used the digluconate salts, which is manufactured as 20% v/v concentrate.

Mode of Action

Antibacterial activity: The antibacterial action of bisbiguanides has been reviewed by Woodcock (1988).

There is a broad range of susceptibility to chlorhexidine among both Gram-positive and Gram-negative strains. Low Minimum Inhibitory Concentration (MIC) values are noted for Staphylococci, S. mutans, S. salivarius and E. coli, while strains of Proteus, Pseudomonas and Klebsiella are less susceptible. S. sanguis shows intermediate susceptibility with both low and high MIC values. Among the anaerobic isolates, the strains most susceptible to chlorhexidine are Propionibacterium and Selenomonas, while the least susceptible strains are Gram-negative cocci resembling Veillonella.[1]Chlorhexidine shows different effects at different concentrations. At low concentration (i.e. at a concentration of 0.1µg/ml) the agent is bacteriostatic where as at higher concentration (more than 100 µg/ml), the agent is rapidly bactericidal. These concentrations vary between bacterial species. After single rinse with chlorhexidine, saliva itself exhibits antibacterial activity for about five hours and suppresses salivary bacterial counts for over 12 hours. Following several rinses of chlorhexidine, the number of aerobic and anaerobic species can be reduced by 80-90%.

Antiplaque activity [3]

Addy and Kornman ascribe chlorhexidine's superior antiplaque activity to its property of persistence (substantivity). The ability of drug to adsorb and bind to soft and hard tissue is known as substantivity and this property was first described for chlorhexidine in the 1970s. Chlorhexidine is retained on the oral surfaces by reversible electrostatic binding to glycoproteins.

A number of factors have been clearly shown to affect the binding capacity and plaque inhibiting effect of chlorhexidine in vivo. The proportion of chlorhexidine retained is directly dependent both on the concentration and volume of the rinse solution. Approximately half of the quantity retained during a 60 sec rinse will have bonded to receptor molecules in the first 15 sec. The pH in the mouth significantly affects both the binding and release of chlorhexidine. Reducing the pH of the rinsing solution from 6.4 to 3.0 will greatly reduce the drug retention. The mechanism probably involves a reduction in the available, negatively charged receptor sites for chlorhexidine binding when the environment becomes more acidic. Increasing the pH, however, does not appear to affect retention. It was further shown that the detergent sodium lauryl sulphate strongly reduces chlorhexidine retention. Finally, there is evidence that teeth which are acid-etched, primed with sulphate solution and then treated with chlorhexidine show more prolonged antibacterial activity. This activity has been explained by the formation of crystals of calcium sulphate on the acid-treated enamel which may then precipitate the drug as insoluble chlorhexidine sulphate.

Effect on Fungi [5]

Chlorhexidine has been reported to be effective against Candida albicans in vitro, and in vivo. Studies on the effect on denture stomatitis have confirmed its efficacy against fungal infection in man. Furthermore chlorhexidine has been successfully used to control oral Candida albicans infections in leukemic children.

Toxicology, Safety And Side Effects [4,6]

The cationic nature of chlorhexidine minimizes absorption through the skin and mucosa, including from the gastro-intestinal tract and it therefore displays very low toxicity (oral LD50 is 1800mg/kg and the intra venous LD50 is 22mg/kg). Systemic toxicity from topical application or ingestion is therefore not reported, nor is there the evidence of teratogenecity in animal model.

Chlorhexidine gluconate is in the FDA pregnancy category B. There is no evidence of any adverse effects on the foetus arising from the use of chlorhexidine digluconate during pregnancy or lactation. In oral use as a mouth rinse, chlorhexidine has been reported to have a number of local side effects. These side effects are:

1. Brown discoloration of teeth and some restorative materials and the dorsum of tongue.
2. Taste alteration where the salt taste appears to be preferentially affected to leave food and drinks with a rather bland taste.
3. Oral mucosa erosion- This appears to be an idiosyncratic reaction and concentration dependent. Dilution of 0.2% formulation to 0.1%, but rinsing with the whole volume to maintain the dose usually alleviates the problem.
4. Unilateral or bilateral parotid swelling is an extremely rare occurrence.
5. Enhanced supragingival calculus formation: this effect may be due to precipitation of salivary proteins on to the tooth surface, there by increasing pellicle thickness and or precipitation of inorganic salts on pellicle layer.
6. Chlorhexidine also has a bitter taste which is difficult to mask completely.

Chlorhexidine with anti-discoloration system

As the effectiveness of chlorhexidine is strongly correlated to the compliance of the patient, different systems have been introduced in order to reduce the

brown pigmentation and the other side effects caused by CHX. Different products such as peroxiborate, polyvinyl pyrrolidone or sodium metabisulphite and ascorbic acid are added to chlorhexidine. In a single centre, cross over, triple blind randomized clinical trial the efficacy of 0.2% chlorhexidine mouthwash containing anti discoloration system was compared to 0.2% chlorhexidine alone after periodontal flap surgery. The results showed that the test CHX caused consistently less pigmentation than the control CHX. The CHX ADS was found to be more tolerated by patients than the control mouthwash and to cause less food alteration, less alteration to patients perception of salt and to be less irritant to oral tissue.[7]

Applications of chlorhexidine.[6]

The clinical indications for the use of chlorhexidine are associated both with its anti-plaque properties and its capacity to act as a more general, bactericidal antiseptic.

A. AS AN ADJUNCT TO ORAL HYGIENE AND PROFESSIONAL PROPHYLAXIS

Oral hygiene instruction is a key factor in the treatment plan for patients with periodontal disease and as a part of maintenance program following treatment.A study by Loe et al evaluated the effect of mouthrinses and topical application of chlorhexidine on the development of plaque and gingivitis in twenty four male dental students. It was seen that twice daily mouth rinse with 0.2% chlorhexidine effectively prevented plaque formation.[8]Lang etal in 1982, evaluated the effect of supervised chlorhexidine digluconate mouthwash on plaque and gingivitis in 158 school children and concluded that plaque was significantly reduced in all CHX groups when compared with controls and calculus increased significantly in all CHX groups.

In a split-mouth design study, the anti-plaque effect of warm 47ºC and cold 18ºC chlorhexidine gluconate irrigation on mature human plaque was studied. Results showed that cold and warm 0.2% chlorhexidine solution reduced plaque vitality significantly from 99.63% to 77.81% ($p=0.014$) and from 98.98% to 51.77% ($p<0.001$), respectively. Rinsing with warm chlorhexidine solution reduced plaque vitality to a significantly greater degree ($p=0.003$) than did cold chlorhexidine at the same concentration.[10]

B. IMMEDIATELY AFTER FLAP SURGERY OR GINGIVECTOMY

Wounds are usually protected by a standard periodontal dressing and their rate of healing, when assessed by exudates and bleeding tendency, is quicker when chlorhexidine is included in the dressing. Gingivectomy wounds heal adequately when subjected to a twice-daily rinse with a 0.2 percent solution, although patients usually experience greater comfort when a dressing is applied.In a split-mouth double-blind trial the effects of chlorhexidine was compared to placebo gels during the healing phase following mucogingival flap surgery. Gel was applied to the gums using a toothbrush once daily. Comparison of results revealed no significant differences in Plaque Index, Gingival Index, crevicular fluid or depth of pockets. More pain and swelling were recorded on the side treated with placebo gel, and more patients indicated that they preferred the chlorhexidine gel. [11]A double-blind split-mouth clinical trial assessed the effect of incorporating CHX acetate in periodontal dressing on wound healing after gingivectomy dressings. Variables with regard to healing and patient comfort yielded results in favor of the test pack.[6]

C. FOR PATIENTS WITH JAW FIXATION

Chlorhexidine mouth rinse 0.2% has been shown markedly to reduce the bacterial load, which tends to increase during jaw immobilization, and to improve plaque control

D. FOR ORAL HYGIENE AND GINGIVAL HEALTH BENEFITS IN MENTALLY AND PHYSICALLY HANDICAPPED PATIENTS

The long term use of chlorhexidine mouthrinses may be indicated for patients whose mechanical plaque control is severely impaired. Chlorhexidine will help to control plaque accumulation in patients with drug-induced gingival overgrowth, although it has no effect in minimizing the enlargement (Russell& Bay 1978).

E. RECURRENT ORAL ULCERATIONS

It has been shown that chlorhexidine mouth rinses and chlorhexidine gels reduce the incidence, duration and severity of recurrent minor aphthous ulceration. The mechanism of action is unclear but may relate to a reduction in contamination of ulcers by oral bacteria, There have been no controlled studies of chlorhexidine in the management of major aphthous ulceration or other oral erosive or ulcerative conditions, although anecdotally chlorhexidine appears ineffective.

F. HIGH RISK CARIES PATIENTS

Chlorhexidine rinses or gels can reduce considerably the Streptococcus mutans counts in individuals who are caries prone. Additionally, and interestingly, chlorhexidine appears synergistic with sodium fluoride and combining chlorhexidine and fluoride rinses appears beneficial to such at-risk individuals. (Barkvoll et al. 1988).

G. REMOVABLE AND FIXED ORTHODONTIC APPLIANCES

Plaque control in early stages of orthodontic treatment may be compromised and chlorhexidine can be prescribed for the first 4-8 weeks. Additionally chlorhexidine has shown to reduce the number and severity of traumatic ulcers during the first week of fixed orthodontic therapy.

H. DENTURE STOMATITIS:

Chlorhexidine has been recommended in the treatment of Candida associated infections. However in practice even applying chlorhexidine gel to the fitting surface of denture produces in many cases, incomplete resolution of the situation.

I. ORAL MALODOR:

Rinsing with chlorhexidine has been suggested for reducing halitosis. Reduction in volatile sulphur compounds has been noted with the use of chlorhexidine. In a study, the efficacy of a novel 2-phase oil: water mouthrinse (TPM), was compared to a corresponding placebo rinse, and to a commercial 0.2% chlorhexidine mouthrinse to assess the day-long reduction in oral malodor. Both chlorhexidine and TPM were highly effective in reducing microbial flora in comparison to the placebo group. Chlorhexidine appeared to be more effective than TPM in all measurement categories. [12]

J. IMMEDIATE PRE-OPERATIVE RINSING

This technique can be used prior to operative treatment, particularly when ultrasonic scaling or high speed instruments are being used. Pre-operative chlorhexidine mouth rinses also reduce the incidence of dry socket. A non randomized prospective study was conducted in a private practice setting to determine the effect of a 0.12% chlorhexidine gluconate rinse (Peridex) on the incidence of dry socket after removal of impacted mandibular third molars. The group that used Peridex twice daily for 2 weeks after surgery showed a significant reduction (56%) in the incidence of dry socket when compared with either the group that did not rinse or the group that rinsed only once just before surgery. [13]

K. AS SUBGINGIVAL IRRIGANT

Chlorhexidine is used as a subgingival irrigant in the management and treatment of the periodontal disease. In susceptible patients, irrigation of chlorhexidine around gingival margin reduces the incidence of bacteremia.[14] In a study, the relative benefit of CHX irrigation in comparison with CHX rinsing, water irrigation and normal oral hygiene was evaluated. At 6 months GI and BOP were significantly reduced by adjunctive CHX irrigation (42.5% and 35.4%, respectively), CHX rinse (24.1% and 15.0%), and water irrigation (23.1% and 24.0%) compared to tooth brushing alone.[15] In another study, over a 3 month period, Chlorhexidine gluconate (CHX) delivered daily by home-applied marginal irrigation as a 0.04% solution in combination with a single professional irrigation of 0.12% CHX was tested. There was a significant change in clinical parameters in the experimental group compared to control group from baseline to 3 months.

L. OCULAR INFECTIONS: Chlorhexidine has also been investigated as a 0.02% drop for ocular and mucosal infections. Bacterial uptake of chlorhexidine has been shown to be very rapid, with maximum bioavailability reached in less than 20 seconds. Efficacy of chlorhexidine may vary. In a small study of patients infected with Acanthamoeba keratitis, CHX was found to be effective at a concentration of only 0.006%.[17]

M. AS A ROOT CANAL DISINFECTANT: 2% Chlorhexidine solution when used for root canal irrigation along with conventional root canal irrigation methods increases the success rate of the root canal treatment.

N. IN THE TREATMENT OF BACTERIAL VAGINOSIS: Bacterial vaginosis is the most prevalent cause of symptomatic vaginitis in sexually active women. A formulation of a new bio-adhesive vaginal gel containing CHX gluconate 0.25% (Clomirex® - CHXVG) has been recently developed. A study has shown that CHX-VG has induced a clinical cure rate in 95% of women affected by BV with one application every three days.[18]

CHLORHEXIDINE PRODUCTS

MOUTH RINSES

Aqueous alcohol solution of 0.2% chlorhexidine was first made available as mouthrinse products for twice daily use in Europe in the 1970s. A 0.1% mouthrinse product is also available.

In the US, a 0.12% mouth rinse was manufactured but to maintain the almost optimum 20 mg doses derived from 10 ml of 0.2% rinses, the product was recommended as a 15 ml rinse (18 mg dose).The studies have revealed equal efficacy for 0.2% and 0.12% rinses when used at appropriate similar doses. [19] More recently alcohol-free chlorhexidine rinses have become available, some formulated, with the inclusion

of 0.05% CPC. In a double blind parallel group study, the efficacy of chlorhexidine mouthrinses with and without alcohol was evaluated. And it was found that the alcohol free rinse was as effective as one containing alcohol in controlling plaque and reducing gingival inflammation.[20]

In another randomized, double blind, placebo controlled clinical trial the side effect of 0.2% chlorhexidine mouthrinses without alcohol used as an adjunct to non surgical periodontal treatment was evaluated. None of the patients in either group complained of dryness in the mouth. The most commonly reported side effect was the change in color of labial and buccal mucosa, particularly of the gingiva after 3 days of rinsing.[21]

GEL

A 1% chlorhexidine gel product is available and can be delivered on a toothbrush or on trays. The distribution of the gel by toothbrush around the mouth appears to be poor and the preparations must be delivered on all the tooth surfaces to be effective. A study evaluated the effect of subgingival irrigation with a 1% chlorhexidine collagen gel in periodontal pockets as an adjunct to scaling and root planing and it was concluded that 1% chlorhexidine collagen gel is a promising adjunct to SRP in the treatment of adult periodontitis.[22]

SPRAYS

Sprays containing 0.1% and 0.2% chlorhexidine are commercially available in some countries.

In a randomized controlled clinical trial, the two different means of delivering chlorhexidine gluconate for plaque control (spray vs mouthwash) were compared during the 2 weeks following implant surgery. It was concluded that the efficacy of CHX spray in the post-surgical control of dental plaque is similar to that of CHX mouthwash. Tooth staining was however significantly lower in the spray group at non surgical sites.[23] Sprays appear particularly useful for the physically and mentally handicapped groups, being well received by individuals and their carers.

TOOTHPASTE[24]

Chlorhexidine is difficult to formulate into toothpastes as it is difficult to develop toothpastes which can sustain adequate clinical activity whilst retaining good consumer acceptability. Long term studies with toothpaste formulation containing chlorhexidine which have assessment of plaque and gingivitis have been unimpressive as neither plaque levels nor gingival health have being significantly improved by the test toothpaste. It was later reported that there is reduced availability of chlorhexidine when incorporated into dentifrice. Etemadzadeh et al. (1985), found that in a short-term study, the anti-plaque activity of chlorhexidine toothpaste was less than that of a chlorhexidine gel. The chlorhexidine toothpastes significantly increased tooth staining, both when judged for stained areas as well as for staining intensity in both the active groups. The total anaerobic counts were significantly reduced in comparison with the control group. (Yates et al. 1993) Adding zinc to a chlorhexidine containing toothpaste seemed to reduce the staining of tooth surface, without reducing the antiplaque and antigingivitis efficacy of these preparations.

VARNISHES [25]

Varnishes are slow-release systems in which a drug is dissolved in a polymer vehicle. Chlorhexidine varnishes have been used mainly for prophylaxis against root caries rather than as anti plaque depot for chlorhexidine in the mouth.

OPTIMIZING THE USE OF CHLORHEXIDINE [2]

Chlorhexidine's antibacterial effect is based on its ability to interact with, and thus disrupt, the bacterial cell membrane. However, chlorhexidine does not distinguish between bacterial protein and other proteins found within mature plaque. To optimize the effect of chlorhexidine, this extraneous protein must first be removed. The chlorhexidine molecule reacts with anionic surfactants present in the toothpaste formulation, thus reducing the activity of the agent. Thus, chlorhexidine should not be used before, or immediately after, using toothpaste. The tooth surface activity of chlorhexidine can also explain the side effect of chlorhexidine-associated tooth staining. The effect may be minimized by limiting the intake of such foods and beverages during treatment with chlorhexidine, especially just after using the chlorhexidine formulation. There should be reduction in the intake of tea and coffee during the immediate period after the morning rinse.Similarly, use of the mouthwash is the last thing at night is to be recommended, as no beverages will be consumed during sleep.

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