10.5368/aedj.2017.9.4.3.3

ANTI-PLAQUE AND ANTI-GINGIVITIS AGENTS IN THE CONTROL OF SUPRAGINGIVAL PLAQUE.

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ABSTRACT: This review considers the main agents which have been used as anti-plaque and anti-gingivitis agents in mouthwashes and other vehicles to inhibit the growth of supragingival plaque. The agents are classified into first generation, second generation and third generation agents. Bisguanide antiseptics, hexetidine, povidone iodine, triclosan, delmopinol, salifluor, metal ions, sanguinarine, propolis and oxygenating agents are included. The anti-plaque and anti-gingivitis properties of these agents are considered along with their substantivity, safety and possible clinical usefulness. A number of product forms are available to deliver anti-plaque agents (i.e., mouthrinses, dentrifices, aqueous gels, chewing gum and lozenges) and should facilitate optimal bioavailability at the site of action and patient compliance.

KEYWORDS: P**laque, Gingivitis, Anti-plaque agent, Anti-gingivitis agent, Chlorhexidine, Substantivity, Mouthrinse.**

INTRODUCTION

Dental plaque is defined clinically as a structured resilient, yellow grayish substance that adheres tenaciously to the intraoral hard surfaces, including removable and fixed restorations.[1] Dental plaque is the primary etiology for chronic gingivitis, which typically develops within 10 to 21 days in the absence of plaque control. Approximately 50% of the population over the age of 30 has some form of gingivitis[2]. Although mechanical plaque control can be an effective strategy for preventing progression of gingivitis, most individuals do not adequately brush their teeth, and only 11 to 51% of the population admits to using dental floss or some type of inter-dental cleaning device on a daily basis.[2] A relatively high degree of motivation, manual dexterity and compliance in oral hygiene regime are required to achieve the level of oral hygiene necessary to control bacterial plaque formation. So using an anti-plaque or an anti-gingivitis agent to supplement mechanical plaque removal can produce an antimicrobial effect throughout the mouth. An **anti-plaque agent** is defined as the chemical that have an effect on plaque sufficient to benefit gingivitis and/or caries.[3] **Anti-gingivitis agent** is defined as the chemical which reduce the gingival inflammation without necessarily influencing bacterial plaque.[3] The use of anti-plaque agents in controlling plaque formation and preventing gingivitis can be an adjunct to mechanical plaque removal and not a substitute for mechanical plaque control.[4] It is important to emphasize that formulations based on antimicrobial agents provide a considerably greater preventive than therapeutic action. The anti-plaque and anti-gingivitis agents were reported to help in the maintenance of healthy hard and soft tissues and thereby effectively preventing or eliminating these diseases. Based on the reported evidence the long term twice daily use of 0.12% chlorhexidine gluconate (Peridex) and essential oils and methyl salicylate, both anti-plaque and anti-gingivitis mouth rinses approved by the Council on dental Therapeutics of the American Dental Association (ADA), do not have a negative effect on the oral microbial flora.[5] Different anti-plaque agents, their rationale and how they help in prevention of Gingivitis and Periodontal diseases were established by numerous studies.[5,6,7,8,9] There has been an exclusive study regarding the use of Chlorhexidine as an anti-plaque agent, pharmacological actions, applications and side effects by Karpinski TM, et al., in 2015 and it was shown that chlorhexidine is the agent that has shown most positive anti bacterial results till date.[7] The main uses of anti-plaque mouth washes are to replace the mechanical tooth brushing when there is any oral or periodontal surgery and during the healing period, gingival infection, for mentally or physically-handicapped patients who are unable to brush their teeth themselves and as an adjunct to normal mechanical oral hygiene procedures. The use of these chemical agents have shown to reduce the incidence of gingivitis through its property of greater zone of diffusion.[4]

Hence, in the present review an attempt was made to review the importance of anti-plaque and anti-gingivitis agents in the control and prevention of periodontal diseases.

Historical Perspectives

Mouth rinses similarly contained ingredients which would have had some stimulating effect on salivary flow, breath odor masking and antimicrobial actions, albeit not necessarily formulated with all these activities in mind.

Alcohol- based mouth rinses were particularly popular with the Romans and included white wine and Beer. Throughout centuries, most tooth powders, tooth pastes, and mouth rinses appear to have been formulated for cosmetic reasons including tooth cleaning and breathe freshening rather than the control of dental and periodontal diseases. Many formulations contained very abrasive ingredients and/or acidic substances. However, ingredients with antimicrobial properties were used, perhaps not intentionally, and included arsenic and herbal materials. Herbal extracts are perhaps, increasingly being used in toothpastes and mouth rinses, although there are little data to support efficacy for gingivitis. Perhaps the biggest change to toothpastes came with the chemo parasitic theory of tooth decay of W.D. Miller in 1980.[4]

Rationale for use of Anti-plaque agents:[4]

The epidemiologic data and clinical research directly associating plaque with gingivitis perhaps, unfortunately, led to a rather simplistic view that regular tooth cleaning would prevent gingivitis and thereby periodontal disease. Even accepting that a considerable proportion of middle-aged adults will have one or more sites in the dentition with moderate periodontal disease, this will be of chronic type and a minimal threat to the longevity of their dentition. The prevention of chronic periodontal diseases, through improved oral hygiene practices, will therefore be grossly over-prescribed as the early identification of susceptible individuals is important at present.

Approaches to use of Anti-plaque agents:[4,5]

The action of anti-plaque agents could influence plaque quantitatively and qualitatively through a number of processes and based on this they fit into four categories.

1. Anti-adhesive
2. Antimicrobial
3. Plaque removal
4. Anti-pathogenic

Vehicles for the delivery of chemical agents:

The carriage of chemical agents into the mouth for plaque control has involved a small but varied range of vehicles.

1. Toothpaste
2. Mouthrinses
3. Sprays
4. Irrigators
5. Chewing gums
6. Varnishes

Anti-plaque agents:

Over a period of nearly four decades there has been quite intense interest in the use of chemical agents to control plaque and thereby gingivitis. The number and variation of chemical agents evaluated are quite large but most have antiseptic or anti-microbial actions and success has been extremely variable. It is important to emphasize that formulations based on antimicrobial agents provide a considerably greater preventive than therapeutic action. The most effective plaque-inhibitory agents in the anti-septic or antimicrobial group are those showing the persistence of action in the mouth measured in hours. Such persistence of action termed substantivity. Substantivity determines a product's effectiveness. It is the length of time the ingredients remain active after they are applied to the area of treatment, absorption to the available soft tissues and the subsequent slow release into the saliva. The longer the product's active ingredients remain in the oral cavity he greater the products effectiveness. Saliva is continually refreshed, rinsing away the active ingredients of mouth rinse. But plaque remaining after mechanical cleaning absorbs mouth rinse antimicrobials, serving as a reservoir to prolong the product's substantivity. Chemical agents in a mouth rinse should be effective at modifying the microbiota by selectively eliminating pathogens without negatively impacting the normal flora that may result in an overgrowth of pathogenic organisms.

Ideal properties

- Should decrease plaque and gingivitis
- Prevent pathogenic growth
- Should prevent development of resistant bacteria
- be biocompatible
- Should not stain teeth or alter taste
- Should have good retentive properties
- Should be economic

Classification anti-plaque agents:[10]

According to Kormann (1986), anti-plaque agents based on their mechanism of action

First generation anti plaque agents: They are capable of reducing plaque up to 20-50%.They exhibit poor retention within the mouth.

Eg: Triclosan, antibiotics, phenols, quaternary ammonium compounds and Sanguinarine.

Second generation anti plaque agents: They produce over all plaque reduction of up to 70-90%. These are better retained than first generation agents.

Eg: bisbiguanides (chlorhexidine)

Third generation anti plaque agents: They block binding of microorganisms to the tooth or to each other. They have poor retention capacity when compared to the second generation agents.

Eg: Delmopinol

I. First generation agents[11]

1) Triclosan

- It is a Phenol derivative
- It is synthetic and non-ionic
- Used as a topical antimicrobial agent
- Broad spectrum of action including both gram positive and gram negative bacteria
- It also includes mycobacterium spores and Candida species

Mechanism of action: Triclosan acts on cytoplasmic membrane induce leakage of cellular constituents and bacteriolysis.

- Triclosan is included in tooth paste to reduce plaque formation
- Used along with Zinc citrate or co-polymer Gantrez to enhance its retention within the oral cavity
- Triclosan delay plaque formation
- It inhibits formation of prostaglandins and leukotrienes thereby reduce the chance of inflammation.

2). Metallic ions eg: Zn and Cu ions

Antimicrobial actions including plaque inhibition by metal ions have been appreciated for many years, with most research interest centered on copper, tin and zinc.
Mechanism of action • Metal salts reduce the glycolytic activity in bacteria and delay bacterial growth and plaque formation.

3).Quaternary ammonium compounds eg: cetylpyridinium chloride (CPC), Benzanthonium chloride, Benzalleonium chloride

- Cationic antiseptics and surface active agents
- Effective against gram positive organisms and they have greater initial oral retention and equivalent antibacterial activity to chlorhexidine.
- Mechanism of action:
- Positively charged molecule reacts with negatively charged cell membrane phosphates and thereby disrupts the bacterial cell wall structure. They are less effective in inhibiting plaque and gingivitis. The reason for this may be that these compounds are rapidly desorbed from the oral mucosa. Use of 0.1% of cetylpyridinium chloride had the lowest plaque scores.

4)Sanguinarine:

It is a benzo phenanthridine alkaloid derived from the alcoholic extraction of powdered rhizomes of the blood root plant, Sanguinaria Canadensis. The anti-plaque activity is mainly due to the chemically reactive iminium ion which appears to be retained several hours after use, and is poorly absorbed from the gastrointestinal tract.
• It is most effective against gram –ve organisms
• Used in mouth rinses

5).Phenols: Phenols when used at high concentrations relative to other compounds they have been shown to reduce plaque accumulation. Listerine is an essential oil or phenolic mouthwash which has been shown to have moderate plaque inhibitory effects and some anti-gingivitis effects. Its anti-inflammatory action is because of the anti oxidative activity.

6)Antibiotics
Eg: Vancomycin, erythromycin, Nidamycin and Kanamycin

- Despite evidence for efficacy in preventing gingivitis or resolving gingivitis, the antibiotics should not be used either topically or systemically for the anti-plaque effects. The antibiotics have their own side effects due to which their use has been limited in the prevention of gingivitis.

II. Second Generation Agents:

1) Bisbiguanides: Chlorhexidine gluconate (0.2%), Alexi dine and Octenidine

Chlorhexidine gluconate:

- It is a cationic bisbiguanide (1, 6 Di chlorophenyl diguanohexane). It is a synthetic antimicrobial drug which has been widely used in dentistry.
- Effective against gram +ve, gram –ve organisms, fungi, yeasts and viruses
- Exhibit anti-plaque and antibacterial properties

Mechanism of action: Its antibacterial action is due to an increase in cellular membrane permeability followed by coagulation of the cytoplasmic macromolecules. It prevents pellicle formation by blocking acidic groups on salivary glycoproteins thereby reducing glycoprotein adsorption on to the tooth surface. It prevents adsorption of bacterial cell wall on to the tooth surface and it also prevents binding of mature plaque.

Antibacterial action of chlorhexidine: It shows two actions

Bacteriostatic at low concentrations in which bacterial cell wall (-ve charge) reacts with +ve charged chlorhexidine molecule. Integrity of cell membrane is altered CHX binds to inner membrane phospholipids and increase permeability vital elements leak out and this effect is reversible

Bactericidal action: Increased concentration of chlorhexidine and progressive greater damage to

membrane and precipitation of cytoplasm. Free chlorhexidine molecule enters the cell and coagulates proteins vital cell activity ceases followed by cell death.

Substantivity of Chlorhexidine: The ability of drugs to adsorb onto and bind to soft and hard tissues is known as substantivity. It is influenced by the concentration, pH, temperature and the length of time of contact of the solution with the oral structures. This property of chlorhexidine was associated with its ability to maintain effective concentrations for prolonged periods of time and this prolongation of its action made it especially suitable for the inhibition of plaque formation.

Adverse effects of chlorhexidine include:

- Brownish staining of tooth or restorations
- Loss of taste sensation
- Rarely hypersensitivity to chlorhexidine has been reported
- Stenosis of parotid duct has also been reported

III. Third Generation Agents:

1) Delmopinol

- It is a morpholino ethanol derivative.
- Inhibits plaque growth and reduces gingivitis

Mechanism of action: • It interferes with plaque matrix formation and also reduces bacterial adherence.

- It causes weak binding of plaque to tooth, thus aiding in easy removal of plaque by mechanical procedures
- It is therefore indicated as a pre brushing mouth rinse

Adverse effects of delmopino

- Staining of tooth and tongue
- Taste disturbances
- Mucosal soreness and erosion

Enzymes

- Enzymes has been used as active agents in anti plaque preparations
- It is due to the fact that enzymes would be able to breakdown already formed matrix some plaques and calculus
- Mainly enzymes fall into two groups in which those in the first group are not truly antimicrobial agents. They have the potential to disrupt the early plaque matrix, thereby dislodging bacteria from tooth surface. These include dextranase, mutanase, and various proteases. But these agents have poor substantivity and were not without unpleasant local side effects, notably mucosal erosion.
- The second group of enzymes employed glucose oxidase and amyloglucosidase to enhance the host defense mechanism. They catalyze the conversion of endogenous and exogenous thiocyanate to hypothiocyanite via the salivary lactoperoxidase system. Hypothiocyanite produces inhibitory effects upon oral bacteria, particularly streptococci, by interfering with their metabolism.

Other Anti-plaque agents:[4,11]

Fluorides: Amine fluoride and stannous fluoride provide some plaque-inhibitory activity, particularly when combined, however the effects appear to be derived from the non-fluoride portion of the molecules.

Oxygenating Agents: oxygenating agents like hydrogen peroxide has been employed for supragingival plaque control. Similarly, peroxyborate is used in the treatment of acute ulcerative gingivitis.

Detergents: Detergents like sodium lauryl sulfate has antimicrobial activity and probably provides most of the modest-plaque inhibitory action of toothpaste.

Salifluor: It is a salicylanide which has both antibacterial and anti-inflammatory properties. To improve oral retention and to maximize adsorption, Gantrez (PVM/MA) has been incorporated in saliflour tooth paste and mouth rinse formulations. Perhaps, 0.12% of saliflour has shown equal effectiveness with 0.12% chlorhexidine in retarding 4 day plaque growth.

All the anti plaque and anti-gingivitis agents described so far have shown plaque inhibition as shown in numerous studies.[2,5,7,8,9] The effective antimicrobial antiplaque agents show prolonged persistence of action in the mouth. Chlorhexidine is the most effective antiplaque agent to date. The other antiplaque agents like stannous fluoride, triclosan, essential oils have shown antiplaque activity to some extent. Natural product like Sanguinarine has been withdrawn because of the potential to cause precancerous lesions.[4]

Discussion

The formation of plaque on a tooth surface is a dynamic and ordered process, commencing with the attachment of primary plaque forming bacteria. The supra gingival plaque reaches a quantitative and qualitative level of bacterial complexity that is incompatible with gingival health, and gingivitis ensues. Experimental gingivitis studies provided the first empiric evidence that accumulation of microbial biofilm on clean tooth surfaces result in the development of an “inflammatory process around gingival tissue.” Research has also shown that the

local inflammation will persist as long as the microbial biofilm is present adjacent to the gingival tissues, and that the inflammation may resolve subsequent to a meticulous removal of biofilm.[1] Epidemiologic studies revealed a peculiarly high correlation between supra gingival plaque and chronic gingivitis and clinical research led to the proof that plaque is the primary etiologic factor in gingival inflammation.[1,2,5] On the basis that plaque-induced gingivitis always precedes the occurrence and recurrence of periodontitis, the mainstay of prevention of gingivitis is the control of supra gingival plaque. Supra gingival plaque control is thus fundamental to the prevention and management of gingivitis with appropriate advice and instruction from the professionals, which is primarily the responsibility of the individual.[4]

It has been already known that heavy reliance on mechanical methods to prevent gingivitis, which is plaque induced is outdated. The contrary argument must be that the prevention of gingivitis would require the discovery of a "safe and effective agent". Also, such a preventive agent would have to be applied from an early age to a large proportion of populations, many of whom would have low or no susceptibility to periodontal disease. These discussions aside, anti-plaque agents, aimed at the microbial plaque, have been a feature of gingivitis management for almost a century. The consensus appears to be that the use of anti-plaque agents should be as adjuncts and not replacements for the more conventional and accepted effective mechanical methods.[4] Mechanical tooth cleaning is arguably the most common and potentially effective method of oral hygiene practiced. Unfortunately, it is a fact of life that significant proportion of all individuals fail to practice a high enough standard of plaque removal such that gingivitis is highly prevalent and from an early age. This presumably arises either or both from a failure to comply with the recommendation to regularly clean teeth or lack dexterity with tooth cleaning habits. The adjunctive use of chemicals would therefore appear a way of overcoming deficiencies in mechanical tooth cleaning habits as practiced by many individuals.[4]
The number and use of oral hygiene products has grown enormously in recent years and there can be no doubt that the oral hygiene industries through their collaboration and research with the dental profession and their promotion of their products have, in no small way, contributed to the improvement in dental health seen in many countries. Claims for efficacy of oral hygiene products, however are frequently made and it is essential that these are supported by scientific evidence. There are numerous studies[2,5,6,7,8,9,10,11,12] that considered the agents which have been used as anti-plaque agents in mouthwashes and other vehicles to inhibit the growth of supragingival plaque. The agents discussed are bisbiguanide antiseptics, quaternary ammonium compounds, phenolic antiseptics, hexetidine, povidone iodine, triclosan, delmopinol, saliflour, metal ions, Sanguinarine, propolis and oxygenating agents. The plaque inhibitory, anti-plaque and anti-gingivitis properties of these agents are considered along with their substantivity, safety and possible clinical usefulness.

Chlorhexidine gluconate is the most studied bisbiguanide and is the one on which there is more information on toxicology.[4] As an antimicrobial agent, chlorhexidine is effective *in vitro* against both gram-positive and gram negative bacteria including aerobes and anaerobes and yeasts and fungi (Davies G etal., 1954, Emisilon C 1977).[13, 14] It was shown that chlorhexidine can reduce the adherence of Porphyromonas gingivalis to epithelial cells. This effect is probably due to the binding of chlorhexidine to the bacterial outer membrane and therefore it could have similar results on the adherence of other plaque bacteria (Grenier D 1996).[15] A study conducted on chlorhexidine for its "Substantivity" shown that chlorhexidine was associated with its ability to maintain effective concentrations for prolonged period of time and this prolongation of its action made it especially suitable for the inhibition of plaque formation (Bonsevoll P etal., 1974).[16] The most common side effect of chlorhexidine is the formation of extrinsic stain on the teeth and tongue following its use as a mouth wash (Harper PR etal. 1995).[17] Studies on the safety of chlorhexidine through animal experiments with radiolabelled chlorhexidine have shown that the primary route of excretion is through faeces.[18] The factors governing the effectiveness of these mouth washes is the total dose of Chlorhexidine delivered and 10 ml of 0.2% solution delivers 20 mg and 15 ml of 0.12% solution delivers 18 mg.[16]

Quaternary ammonium compounds such as cetylpyridinium chloride (CPC) have moderate plaque inhibitory activity (Loben R etal., 1977).[19] Although they have greater initial oral retention and equivalent antibacterial activity to chlorhexidine, they are less effective in inhibiting plaque and preventing gingivitis and it may be because that these compounds are rapidly desorbed from the oral mucosa (Holbeche J D etal., 1975).[20] A CPC pre-brushing mouth rinse used as an adjunct to mechanical oral hygiene has not been found to have an additional beneficial effect on plaque accumulation (Moran J etal., 1991).[21] One study compared the plaque-inhibitory potential of 0.05% and 0.1% CPC, 0.05% chlorhexidine and control mouth rinses used twice daily during a 4 day period of non-brushing. The 0.1% CPC rinse had the lowest plaque score, being around 26% lower than the control rinse, and and% lower than the 0.05% chlorhexidine rinse (Jenkins S, 1994).[22]

Phenols when used at high concentrations relative to other compounds they have been shown to reduce plaque accumulation (Gomer R M etal., 1972).[23] Listerine is an essential oil or phenolic mouth wash which has been shown to have moderate plaque inhibitory effects and some anti-gingivitis effects. Some studies have shown that it has moderate plaque inhibing effects and some anti-inflammatory effects in reducing gingival inflammation

(Lamster IB etal., 1983)[24] and on the basis of these studies it has been accepted by the American Dental Association to be an aid to home oral hygiene measures.

Hexetidine has some plaque inhibitory activity but this is low in comparison with chlorhexidine (Harper PR etal., 1995)[17] and its substantivity is between 1 and 3 hours, which accounts for the reported low plaque inhibitory effects of Oraldene, the UK product.

Povidone Iodine appears to have no significant plaque inhibitory activity when used as 1% mouth wash (Griffith C etal., 1977)[12] and the absorption of significant levels of iodine through the oral mucosa may make this compound unsatisfactory for prolonged use in the oral cavity. Also, it could cause a problem of iodine sensitivity in sensitized individuals.

Triclosan when used as combination mouth wash produced inhibition of plaque re growth during a 4- day period with abstinence from mechanical oral hygiene (Moran J etal., 1997).[25] The effects of combination of zinc and triclosan mouth washes were investigated in a 3 week clinical trial, where abstinence from brushing was produced by wearing an acrylic tooth shield over the test area of the mouth during brushing (Schaeken MJM etal., 1994).[26] Moreover, triclosan also acts as anti-inflammatory agent in mouth rinses and tooth pastes (Kjaerheim V etal., 1996).[27] In addition, it has been shown to reduce histamine-induced dermal inflammation and reduce the severity and healing period of aphthous ulceration (Skaare AB etal., 1996).[28]

Delmopinol a morpholinoethanol derivative showed inhibition of plaque growth and reduced gingivitis both in vivo and in vitro (Elworthy AJ etal., 1995).[29] One study has shown that Delmopinol has only limited substantivity in comparison with chlorhexidine and in this regard inhibited salivary bacteria for only 30 minutes as compared to several hours for chlorhexidine (Moran J etal., 1992).[30]The suggested mode of action for its plaque inhibiting effects is interference with plaque matrix formation and reduction of bacterial adherence (Simonsson T etal., 1991).[31]

Thus the fact that anti plaque agents that kill or inhibit the growth of bacteria does not necessarily mean they will be effective plaque inhibitors. Also, the mere incorporation of a known antiplaque agent into a formulation is not a guarantee of efficacy because inactivation by other ingredients may occur. Research and development of oral hygiene products needs to be step-by-step processed, making available of a body of knowledge supporting the efficacy of final formulation. Statistical significance should not necessarily be taken as a proof of the benefit of an oral hygiene product to the general public. Clinical outcome, when possible, should be evaluated against side effects and cost-benefit ratio should be determined.

CONCLUSION

Chemical agents for plaque control hold great promise in disease control and prevention and potentially delay plaque accumulation on teeth. Chlorhexedine is the most effective antiplaque agent. Herbal mouth rinses, quaternary ammonium compounds, phenols, antibiotics, delmopinol and several other agents have shown significant anti-plaque activity. The adjunctive use of essential oil mouth rinses and triclosan dentrifices were found to be effective in reducing plaque and gingivitis.

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