MOUTHРИ NES

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Abstract—Mouthrinses have been used for centuries for medicinal and cosmetic purposes, but it is only in recent years that the rationale behind the use of the ingredients has been subject to scientific research and clinical trials. Although Listerine held its position for many years in the vanguard of the anti-plaque agents, the advent of mouthrinses containing chlorhexidine was a major breakthrough in the research for a chemical means to prevent disease. Since that time, and especially in the past ten years, the number of formulations that claim to have anti-plaque, anti-calculus, and anti-caries activity has increased, and much emphasis has been placed on such substances as an adjunct to, or indeed to replace, conventional toothbrushing techniques.

This review covers the literature on mouthrinses over the past five years, concentrating more on the anti-plaque, anti-gingivitis, and anti-calculus formulations. In the first section, the methods of conducting clinical trials of mouthrinses are discussed, and a plea is made for a greater degree of standardization of methodology with agreed acceptable levels of clinical benefit. Trials of established mouthrinses are considered, and the advantages and disadvantages of several newer formulations discussed.

From the review, it appears that chlorhexidine has no equal in its effects on reduction of plaque and gingivitis, but major drawbacks lie in the taste and stain-producing problems. The pre-brushing rinse, Plax, does not have unqualified success in all trials, though the more recent European formulation may have promise. Newer rinses which inhibit bacterial adhesion to tooth surfaces also appear promising, and it is suggested that more work on combinations of active ingredients is necessary.

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Mouthwashes have been in use for centuries as breath fresheners, medicaments, and antiseptics. One of the oldest, which is still in use today, is the combination of essential oil and phenolic compounds, Listerine. This formulation, derived from Lister’s original work with carbolic acid, has been used since the end of the last century. Only in more recent times, however, have mouthrinses been given much credence as preventive agents against dental disease.

The increasing awareness of plaque as a major contributing factor in the initiation of caries and periodontal disease changed the perception of mouthwashes by the dental profession, and caused an upsurge in the search for anti-plaque agents (Mandel, 1988).

The prevention or removal of plaque is logical, since, in the absence of plaque, neither caries nor periodontal disease is found. Mechanical removal of plaque requires manual dexterity and time, but few people can consistently maintain a plaque-free status by this means alone. Additionally, there is little scientific evidence to indicate that mechanical tooth cleaning perse has any influence on caries (Frandsen, 1986). A chemical agent either as an adjunct to or a replacement for mechanical cleansing has long been sought. Hence, the arrival of chlorhexidine was greeted enthusiastically by the profession, and although it has lived up to the early promise, the major disadvantages of staining and unpleasant taste have provided an incentive to continue the search to find equally efficient agents which lack side-effects. So far, none has been found.

Studies in vitro and in vivo on chemical plaque control agents in mouthrinses—in particular, chlorhexidine—are legion, and reviews on the subject in recent years are numerous (for example, see: Hull, 1980; Kornman, 1986; Addy, 1986; Mandel, 1988), and no attempt will be made to re-review this extensive literature. This review will be confined to an update of the information on mouthrinses since 1988.

Before dealing with individual active ingredients in mouthrinses, it is worth clarifying the complex situation of a plethora of models to study a variety of endpoints.

Clinical trials of mouthrinses take several forms, depending on the expected benefit of the active ingredients and, almost, the whim of the individual researchers. This makes comparisons among trials of different materials difficult if not impossible. Trials can be divided into those that effect plaque removal, those that prevent plaque formation, those that inhibit or reduce gingivitis, and those that reduce calculus formation. Additionally, there are studies on the effects on the microflora of the mouth in vitro and in vivo.

PLAQUE REMOVAL

These trials are mainly short-term, with plaque scored before and after a single rinse. They are easily controlled, since the rinsing is supervised, and have been used more recently to
assess the plaque removal effects of several rinses, including a pre-brushing rinse (Binney et al., 1992).

**PLAQUE RE-GROWTH**

In these trials, the subjects are given a thorough prophylaxis at baseline, and plaque is allowed to accumulate over the short term, varying from 16 hours to several days, without any other oral hygiene measures. The aim is to assess the plaque-preventing ability of the agent, on its own.

**GINGIVITIS REDUCTION**

Studies on gingivitis reduction are usually of longer duration than plaque removal or plaque re-growth studies, though in most cases the amount of plaque present is assessed together with the gingivitis. The American Dental Association (ADA) guidelines on the use of trials to measure gingivitis reduction insist on a period of at least 6 months. However, there have been studies of lesser duration, in spite of the guidelines, and known as “experimental gingivitis in man” studies. These may last from days to weeks. The reports are made up of those performed as “natural”, i.e., where other oral hygiene measures are not controlled and patients use their own particular techniques, in addition to using the test rinses, and other trials where the oral hygiene measures are strictly according to a set regime. Most long-term studies of the latter type rely to a large extent on the compliance of the subjects.

The assessment of gingivitis is sometimes made by a gingival index, with or without a “bleeding on probing” score (Hull, 1980).

**CALCULUS**

Trials on the reducing effect of an agent on calculus are of necessity long-term, i.e., for 6 months or longer. Calculus is measured by a calculus index, in particular the Volpe-Manhold Index (Volpe et al., 1967), which has gained almost universal acceptance. Trials have studied mostly effects on an agent on calculus only, but some have included assessments of plaque, gingivitis, and even stain.

**METHODS**

Clinical trials use two main methods. One is the parallel study, where control and test groups of subjects are matched as far as possible for age, sex, and periodontal disease status. Each group uses only the test or the control regime. The other method is the cross-over study, which has the advantage of requiring fewer subjects without loss of power to detect statistically significant differences. Each subject uses either the test or the control rinse, is assessed at the end of the set period, and, after a “wash-out period”, will use the alternative formulation or procedure to that used in the first procedure. Matching of subjects in groups is unnecessary, since every subject uses each procedure and acts as his/her own control. Cross-over studies typically use healthy volunteers and measure the inhibitory effects of agents on the development of plaque and gingivitis, alone or as adjuncts to tooth cleaning. Parallel studies may be used similarly but also are used to study the action of agents in reducing plaque and gingivitis.

Another variant relates to the bias of the clinician or subject. Trials can be “single blind”, where the clinician makes his assessment of the subject without knowing which regime has been used by the subject, or “double blind”, where neither the subject nor the clinician is aware of the “treatment” until the end of the trial.

Finally, studies are designed to test the action of a specific ingredient or ingredients or designed to evaluate a complete formulation or product. Depending on the type of study, controls usually will be quite different.

In this review, the main thrust will be to examine both the studies for each ingredient where it is used as a mouthrinse, and specific mouthrinse formulations available as oral hygiene products to the public.

**LISTERINE**

The mouthrinse with the longest history of use is Listerine, a hydro-alcohol solution of thymol, menthol, eucalyptol, and methyl salicylate. Since Miller (1989) demonstrated that caries was due to micro-organisms, Listerine has been used as a mouthwash to try to prevent dental disease. Probably because of its “disinfectant” smell and taste, it has gained much popular credence, and much of its popular appeal relates to its ability to dispel odors and create a “clean” sensation in the mouth.

Anti-plaque activity has been demonstrated in several studies (reviewed by Ross et al., 1989), and Listerine is of sufficient standing to have received the approval of the American Dental Association (1988a). The mode of action of the active ingredient or ingredients in the mouthrinse is not established, since there are several antimicrobial agents in the hydro-alcohol base.

**SHORT-TERM STUDIES**

Brecx et al. (1990) used a double-blind experimental gingivitis model to compare anti-plaque, anti-gingivitis, and anti-microbial efficacies of Listerine, Meridol, and chlorhexidine. Meridol is a mixture of amine fluoride and stannous fluoride. After professional tooth cleaning, 36 subjects rinsed twice daily for 21 days with one of the three rinses or with a placebo control as their only oral hygiene measure. At the end of 3 weeks, plaque indices were lowest in the chlorhexidine group, with the Listerine and Meridol groups having plaque indices much higher than but not as high as that of the placebo. The reducing effects of Listerine and Meridol on plaque were significant only when the three-week results were compared. Listerine and Meridol were not significantly better than the control at inhibiting gingivitis, whereas chlorhexidine reduced gingivitis by 50% compared with the placebo. These authors used a vitality dye test on plaque bacteria to demonstrate that chlorhexidine had the greatest effect on the proportion of viable organisms, followed by Meridol, with Listerine and the placebo having no significant effect when compared with the baseline.

In a later study, Brecx et al. (1992) reported the effects of similar rinse formulations on plaque and gingivitis when used as adjuncts to normal tooth cleaning.

In this study, two Meridol preparations—one containing Aspartum and one containing Acesulfam—were compared...
with Listerine, chlorhexidine, and a placebo. Plaque indices were lowest with chlorhexidine, with one of the Meridol formulations and Listerine showing a significant reduction in plaque compared with the placebo rinse. The gingivitis scores with the Listerine group were little better than those with placebo, and the authors concluded that there was little advantage in combining Listerine and mechanical oral hygiene measures, which had not been used in the earlier study (a finding contrary to that of Axelsson and Lindhe in 1987).

In another short-term experimental gingivitis study, Moran et al. (1991) compared chlorhexidine and Listerine using a single-blind randomized triple cross-over design. A group of 15 subjects used chlorhexidine, Listerine, or a placebo mouthrinse for 19 days in the absence of normal tooth cleaning. The wash-out periods were of 21 days’ duration. Plaque areas were measured, and these increased from baseline six-fold with saline rinsing and three-fold with Listerine when compared with that in subjects using chlorhexidine. Although the increase in gingivitis indices from baseline was lowest with chlorhexidine and highest with saline, the differences were not significant. Listerine has not been reported previously as producing staining or supragingival calculus compared with placebo, but its ability to reduce plaque compared with placebo, and the authors concluded that there was little advantage in combining Listerine and mechanical oral hygiene measures, which had not been used in the earlier study (a finding contrary to that of Axelsson and Lindhe in 1987).

From these short-term studies, it would seem that Listerine could reduce plaque compared with placebo, but its ability to reduce gingivitis is not marked.

**LONG-TERM STUDIES**

Minah et al. (1989) considered the effect of six months’ usage of Listerine on the plaque flora in 83 subjects using the mouthwash twice daily. No significant increases in numbers of presumptive oral pathogens, spirochetes, black-pigmented Bacteroides, Streptococcus mutans, or Candida albicans were found. The conclusion was that Listerine in the long term did not induce any resistant strains in plaque, nor did it encourage undesirable oral pathogens.

The same group of workers also reported on a study of the development of gingivitis over 6 months (De Paola et al., 1989).

In a double-blind trial, Listerine was used to supplement regular oral hygiene measures. Results showed that both plaque and gingivitis were inhibited by 34% compared with the hydro-alcohol control. The results were highly statistically significant. Overholser et al. (1990), in a six-month study of the development of gingivitis and plaque, compared the effects of supervised rinsing twice daily with Listerine, Peridex (a chlorhexidine solution), and a hydro-alcohol control. The extent of staining and development of calculus over this period were also assessed and compared with the baseline scores, which were measured immediately prior to a thorough prophylaxis at the start of the trial.

The study showed that Listerine inhibited plaque and gingivitis development by 36% compared with results in the group using the hydro-alcohol control. Interestingly, the subjects in the Listerine group did not develop significant levels of stain or supragingival calculus compared with baseline or the control group. In contrast, subjects in the chlorhexidine group did develop significantly more stain and supragingival calculus compared with baseline and control values. This work was submitted to the American Dental Association’s Council on Dental Therapeutics in 1988 prior to being published in full and was accepted as part of the evidence for the seal of approval by the ADA, together with two other reports showing long-term beneficial effects of Listerine on gingivitis and plaque.

In the report by Overholser et al. (1990), it was suggested that Listerine may play a role in the reduction of inflammation by some means other than its effects on salivary bacterial flora, which did not change appreciably over 6 months. Kato et al. (1990) examined the effects of Listerine on the oral microflora and found that the bactericidal effect is not as great as that of chlorhexidine, which adds weight to the possibility that the reduction in gingivitis by Listerine in the long-term studies is not wholly due to the reduction in the amount of plaque.

In a clinical trial, it was shown that Listerine delivered by an oral irrigation device could result in significant reductions in plaque, bacterial cell counts, and gingival bleeding. This study was of relatively short duration (6 weeks) and is interesting in that both plaque removal and plaque re-growth were studied in the same mouths. This was accomplished by each subject having a half-mouth prophylaxis at the start of the trial (Ciancio et al., 1989).

Another interesting aspect of Listerine is in the effect on recurrent aphthous ulceration (Meiller et al., 1991). Listerine was found to reduce the duration of the ulcers on average by two days and also the perception of severity by the patient, compared with either a baseline period of observation or with a control 5% hydro-alcoholic mouthrinse. The numbers and frequency of ulcers were reduced by both Listerine and control mouthrinses.

Disadvantages of Listerine are few. The taste is unpleasant with a burning sensation on the mucosa, although this does not appear to deter its use, and patients appear to adapt to it. It causes little if any staining and no enhancement of pathogenic organisms.

There is some evidence that Listerine could have deleterious effects on dentin (Addy et al., 1991b). Thus, in a study of the effects of mouthrinses on dentin, it has been shown that the smear layer produced by instrumentation of dentin can be removed with soaking for 10 minutes with Listerine. Brushing the dentin after exposure to Listerine enhanced the exposure of dentinal tubules. Although the mouthrinse is not normally in contact with the dentin for this length of time, the repeated use of this agent, particularly as a pre-brushing rinse, is probably questionable at the present time. No doubt the acidity of Listerine (pH 4.4) is related to its effect on dentin. However, these studies were carried out in the absence of saliva, and may not therefore be applicable to the in vivo situation.

**CHLORHEXIDINE**

Chlorhexidine gluconate (CHX) is a cationic bis-biguanide, with a very broad antimicrobial spectrum. The first report of its anti-plaque activity was by Löe and Schiött (1970). It is interesting now to read in this report at the meeting in Dundee in 1969 that “The primary objective of this experiment is not...
to introduce chlorhexidine as a possible antimicrobial agent for the clinical prevention and control of plaque.

By 1974, there were already over 70 articles on the oral use of chlorhexidine, and it has been proven many times over as the most effective agent, not only against plaque but also in long-term studies on gingivitis.

It is now used as a positive control in many clinical trials of new mouthrinse formulations. The reduction in plaque indices is usually found to be on the order of 60%, while the gingival indices are reduced by about one-third (Grossman et al., 1986). The American Dental Association (1988b) has approved its use in Peridex, a 0.12% solution of chlorhexidine.

The main advantage of chlorhexidine over most other compounds lies in its substantivity. It binds to soft and hard tissues in the mouth, enabling it to act over a long period after use of a formulation. Bacterial counts in saliva consistently drop to between 10 and 20% of baseline after single rinses and remain at this level for at least 7 hours (Addy and Wright, 1978) and probably more than 12 hours (Schiott et al., 1970).

The main disadvantage of chlorhexidine is its taste, and a barrier to continued use is its affinity for dietary compounds, some of which cause staining (Addy et al., 1985). In some cases, staining of the teeth is severe, and removal requires a professional prophylaxis (Hoyos et al., 1977). Additionally, tongue brushing may be required to remove the soft-tissue discoloration. To overcome the problem of staining, lowered concentrations of CHX in rinses have been formulated as Peridex (0.12%) and Eludril (0.1%). A comparison in vitro of the 0.1% and 0.2% formulations (Addy et al., 1989b) showed that 0.1% CHX produced no staining of acrylic specimens greater than that of controls, whereas the 0.2% formulation did cause heavy staining. Antimicrobial effects of the two products were similar, but the overall profile for the 0.1% preparation suggested that CHX in the 0.1% rinse was partially or completely inactivated. The authors suggested that the detergent in the 0.1% solutions inactivated the CHX and that the antimicrobial effect of the solution was derived more from the detergent than CHX. They also suggested that the degree of staining in vitro with CHX solutions could be used as an indication of possible antimicrobial activity in the mouth. It has also been reported that 0.1% chlorhexidine was more acceptable than 0.2% solutions to patients using the mouthwashes as post-operative prophylactics (Heps et al., 1988). No statistically significant differences were found in the frequency of loss of taste, burning sensation of the mucosa, and staining. Thirty patients were included in the study; four using the 0.2% solution discontinued the mouthwash because of the side-effects.

It was concluded that 0.1% CHX is preferable to 0.2% CHX as a prophylactic mouthwash after oral surgery (Heps et al., 1988).

Jenkins et al. (1989), in a short-term single-blind cross-over study, compared the effects of two commercially available formulations containing 0.2% (Corsodyl) and 0.1% (Eludril) chlorhexidine on plaque reformation, gingivitis, and staining in a group of 14 volunteers. Gingivitis at 12 and 19 days was considerably less with 0.2% than with 0.1% formulations, but staining was markedly reduced with the lower concentration.

These authors believed that Eludril, which was not simply a lower concentration of chlorhexidine gluconate than in the 0.2% mouthwash, contained substances which inactivated the chlorhexidine, thus reducing its anti-plaque activity.

An attempt to reduce the staining of chlorhexidine by using peroxysterorate after chlorhexidine rinsing showed promise (Addy et al., 1991a). Oxidizing mouthwashes markedly reduced staining after 2½ days' "enforced" staining with tea after chlorhexidine, and the authors suggested that rinsing with peroxyborate may be useful after a course of therapy with chlorhexidine.

Chlorhexidine has been reported as having a toxic effect (Kenrad, 1990), and major changes in the oral mucosa were seen after extreme overdosage of mouthrinising with chlorhexidine gluconate. The changes included a thickening of the mucosa which resembled leukoplaikia and disappeared when the dose was reduced.

Sensitivity to chlorhexidine was reported by Yusof and Khoo (1988). Two cases were reported where the mucosa showed sensitivity to contact with chlorhexidine, but no allergies to chlorhexidine have been reported from the Western countries.

In vitro growth of epithelial cells is inhibited to some extent by 2 hours' exposure to a 250-fold dilution of 0.2% chlorhexidine gluconate. Although in vitro results are not necessarily representative of what happens in the oral cavity, the results suggest that where the oral mucosa has been breached, healing may be delayed if chlorhexidine is used (Shakespeare et al., 1988). This must be balanced against the beneficial effects to healing of bacterial inhibition. Thus, healing of periodontal surgical wounds is enhanced by CHX.

Cline and Layman (1992) evaluated the effects of chlorhexidine on attachment and growth of human fibroblasts and periodontal ligament cells. Treatment of root surfaces with up to 0.12% had no effect on attachment. Morphology and attachment were, however, affected by treatment with 0.2-2% solutions of CHX. Direct exposure of cells to 0.01% chlorhexidine caused a reduction of 90% in H-thymidine uptake. This may be a factor to be considered in using chlorhexidine to irrigate subgingival areas.

In the report by Brex et al. (1992) referred to earlier, chlorhexidine over a three-week period reduced plaque and gingivitis to the same extent, whether mechanical means of oral hygiene were used or not. It was of interest to note that after three weeks' use, the viability of bacteria in plaque was beginning to rise and at 14 and 21 days was not significantly different from baseline.

SANGUINARIA

Sanguinaria is contained in the proprietary mouthwash Viadent in the USA (Perioguard in the UK) and is an alkaloid from the plant Sanguinaria canadensis. It has been incorporated into dentifrices and mouthrinses, but there are conflicting reports on its efficacy.

Wennström and Lindhe (1985) conducted a short-term double-blind cross-over study of plaque re-growth and gingivitis lasting two weeks for each experimental period, using a mouthrinse which was a 0.03% solution of sanguinaria extract.
They controlled the study with a placebo with similar taste and color. Plaque indices were 40% lower and gingivitis scored 25% lower with the sanguinaria rinses compared with the controls. Normal toothbrushing was suspended during the trial period, and with some of the subjects there was a slight discoloration of the teeth and dorsum of the tongue.

There have been other encouraging studies with sanguinaria which are reviewed by Mandel (1988). Clinical trials with this material often have used a dentifrice and a mouthrinse, since the active ingredient can readily be incorporated into a toothpaste (Lobene et al., 1986b).

In a single-blind cross-over experimental gingivitis study, Moran et al. (1988) compared the effects of the sanguinaria-zinc mouthwash Viadent, with 0.2% CHX, in the absence of all other oral hygiene. The positive control, CHX, was significantly more effective than Viadent in inhibiting both plaque and gingivitis. This study did not have a placebo control, but in a later study (Moran et al., 1992a), this group used a four-day plaque re-growth model to compare several rinses, including sanguinaria with and without zinc chloride. In this study, a saline rinse was used as the placebo control. The use of sanguinaria alone produced results which differed little from those of the group using saline. The combination of zinc chloride and sanguinaria produced a “modest” reduction in plaque growth, which could have been due to the zinc chloride (Southard et al., 1987). Quirynen et al. (1990) have shown that zinc chloride on its own was almost as effective as sanguinaria and zinc chloride in a single-blind cross-over study of plaque re-growth. The experimental period lasted 18 days, and during this period rinsing with either Viadent, Viadent without sanguinaria, or CHX was the only oral hygiene procedure. Plaque growth was assessed on 4 teeth in each of 12 subjects, and hence numbers were perhaps not as high as one would wish. However, the differences between the areas of the buccal surfaces of the teeth covered by plaque were highly significant in a comparison of CHX and Viadent. Viadent was only slightly better than the control, and at only one period in the trial (3 days) was there a statistically significant improvement in plaque inhibition with Viadent. The authors concluded that Viadent mouthrinse would have at most only a limited role as a plaque inhibitor.

The possible beneficial effect of sanguinaria used as a mouthrinse over a long term is difficult to assess, since the majority of studies have used the rinse in combination with a sanguinaria dentifrice. For example, Harper et al. (1990a), in a six-month double-blind parallel study, assessed gingivitis and plaque in subjects using Viadent dentifrice together with a mouthrinse with sanguinaria extract and zinc chloride. The negative controls used the same products but without the sanguinaria extract or zinc chloride. Plaque and gingivitis scores in the sanguinaria extract group were 21% and 25% lower than those in the control group at the end of 6 months. “Bleeding on probing” assessments also showed a reduction in the test group compared with controls. Harper et al. (1990b) also reported on the changes in microflora of the buccal mucosa and of the supra- and subgingival plaque in this same clinical trial. No opportunistic overgrowth of pathogens was found, but there were reductions in numbers of the organisms associated with gingivitis, which may have accounted for the reduction in gingivitis. Similar beneficial effects have been found by Hannah et al. (1989) in a six-month trial of gingivitis prevention, in a group of orthodontic patients, using both toothpaste and rinses containing sanguinaria extract and zinc chloride, findings which were confirmed by Kopczyk et al. (1991). It seems likely that if sanguinaria extract is to have any benefit, it needs to be used in combination with zinc chloride, and as both a toothpaste and mouthrinse. Such necessary combinations of products to attain efficacy must have cost-benefit implications.

**TRICLOSAN**

Saxton (1986) reported on the reduction of plaque and gingivitis by 2,4,4’,trichloro-2-hydroxydiphenyl ether (triclosan) and zinc citrate in a dentifrice, in 12 volunteers. The combination of triclosan and zinc citrate significantly improved the efficacy above a simple addition of effects of each alone.

Nabi et al. (1989) showed that the copolymer polyvinylmethyl ether/maleic acid (PVM/MA) enhanced the anti-bacterial activity of solutions of triclosan *in vitro* and enhanced the anti-caries activity of triclosan in rats.

In a cross-over clinical trial, 20 subjects (Abello et al., 1990) used triclosan/copolymer rinses for 7 days without brushing, and the effects were compared with those when subjects used rinses containing alcohol and water placebos and a new pre-brushing rinse, Plax. Results showed that the triclosan/copolymer reduced plaque by approximately one-half, compared with the water placebo or the Plax rinse. Compared with the alcohol placebo, the triclosan/copolymer rinse reduced plaque by 31%.

A similar study (Singh et al., 1990) compared 0.03% triclosan and the copolymer, used as a pre-brushing rinse for six days, with a flavored and colored-water placebo mouthrinse. Twice-daily rinses followed by brushing resulted in a 31% reduction in plaque compared with the placebo. Interestingly, the reduction with water rinse alone in the previous study seemed greater than when followed by brushing, in this trial.

Using virtually the same protocol, 60 subjects rinsed with water, Plax, or triclosan/copolymer (Rustogi et al., 1990). Again, the triclosan/copolymer reduced plaque indices to 40% of the placebo mouthrinse. Plax was not significantly different from the water placebo.

Plaque re-growth over a four-day period was used to compare the efficiencies of triclosan with and without copolymer, stannous fluoride, stannous chloride/flouride mixed, a stannous fluoride gel, and, as negative and positive controls, saline and 0.12% chlorhexidine, respectively (Addy et al., 1990). The saline rinse was significantly worse than all of the other rinses, but chlorhexidine was highly significantly better than the others, which could not be separated on the basis of their ability to reduce plaque formation. It was concluded that triclosan added very little benefit.

This study raises the question of whether other ingredients in the triclosan/copolymer rinse exert plaque-inhibitory effects.

The length of retention time for triclosan and zinc citrate in...
the mouth after use of toothpaste was studied by Cummins (1991). Saliva decay curves indicate a faster rate of clearance from the mouth of triclosan compared with zinc. Triclosan was found in plaque for eight hours and in oral mucosa for at least three hours after brushing. The effects of zinc and triclosan were concluded to be complementary and additive. However, the relevance of retention studies may be questioned, since they indicate only the presence of a compound and not its activity or availability.

It has been shown that 0.2% triclosan reduced salivary bacterial counts significantly up to three hours after rinsing (Jenkins et al., 1991a). In this study, chlorhexidine and sodium lauryl sulfate were included, both of which reduced bacterial counts more than did triclosan. It was suggested that triclosan did not offer any greater possibility of anti-plaque activity than sodium lauryl sulfate alone. This was tested in a follow-up report by this group (Jenkins et al., 1991b) when plaque scores and areas were recorded in a plaque re-growth study comparing chlorhexidine, saline, triclosan, and sodium lauryl sulfate. Sodium lauryl sulfate produced complaints of burning in nearly all users, but the results confirmed that although triclosan (0.2%) significantly reduced plaque, it was not as good as chlorhexidine and only slightly better than the detergent.

Two other studies—by Deasy et al. (1992) and by Lobene et al. (1992)—support the effectiveness of the triclosan/copolymer combination. It seems clear from these studies that triclosan on its own has little place as an antiplaque rinse, but with zinc chloride or copolymer its substantivity is increased and it has greater efficacy. This is supported by two long-term studies where triclosan and the copolymer were incorporated into a dentifrice. In these, a significant improvement in gingival health and plaque reduction, compared with placebo, was found (Garcia-Godoy et al., 1990; Cubells and Dalmau, 1991). The combination of 0.2% triclosan with 0.5% zinc citrate was also found to be beneficial in a six-month double-blind study of gingivitis, calculus reduction, and plaque prevention.

PLAX

The concept of a pre-brushing rinse was put forward by J. Lefoulon of Paris in about 1843. This was given renewed impetus by the aggressive advertising of Plax, a pre-brushing rinse containing a number of ingredients including sodium benzoate and sodium lauryl sulfate, which was claimed to reduce plaque by over 300% compared with brushing alone (Emling and Yankell, 1985). This was confirmed in a later publication, when, with 20 subjects using Plax as a pre-brushing rinse, there was significantly less plaque on buccal and lingual surfaces than with a water rinse as placebo (Emling and Yankell, 1991). One other study, in 1989, compared Plax with Listerine. The ability of the rinse alone to reduce plaque was assessed. The control in this case was water with flavor and color, but no active ingredient. Plax was better than Listerine or placebo, between which there was found to be no statistical difference (Bailey, 1989). A reduction in plaque scores was also found in a three-month study with conditions as "normal" as possible (O'Mahony and O'Mullane, 1991). However, the design of the study calls into question the validity of the findings.

There have been several studies showing that Plax was no better than a placebo or water rinse (Kohut and Mankodi, 1989; Singh, 1990; Freitas et al., 1991; Chung et al., 1992; Binney et al., 1993), and significantly, Lobene et al. (1990), in a six-month study conducted along the guidelines of the American Dental Association, have shown, contrary to their earlier study (Lobene et al., 1986a), that Plax had no statistically significant effect on plaque scores, gingivitis index, and microbiological assays compared with water rinsing, confirming earlier short-term studies.

Plax is now marketed in Europe by a different company with a revised formulation containing triclosan, and a recent report provided encouraging findings for plaque and gingivitis.

SODIUM LAURYL SULFATE (SLS)

This is an anionic detergent with a hydrophobic organic part, which has a high affinity for protein molecules. It is widely used in dentifrices and mouthrinses, but recent work in the dental field has concentrated on its deleterious qualities rather than on its benefits. As mentioned previously, it was used in Plax as a detergent.

In vitro work by Barkvoll et al. (1988) has shown that SLS binds to hydroxyapatite and enamel through the hydration layer. This finding may be a factor in the inhibition of monofluorophosphate protection against caries (Melsen and Rølla, 1983; Barkvoll, 1991) when SLS is incorporated into dentifrices with monofluorophosphate.

In his thesis on interactions of SLS and chlorhexidine, Barkvoll (1991) drew attention to the neutralization of CHX even when these agents were applied separately and with time intervals between their separate applications. The interval between toothbrushing with a dentifrice containing SLS and rinsing with CHX solutions should be "more than 30 minutes, probably nearer 2 hours".

Barkvoll and Rølla (1989) studied the effect of SLS on the oral mucosa in patients with allergic stomatitis. They suggested that the denaturing effect of SLS on the oral mucin layer induced an increased exposure of the mucosa to various food proteins, resulting in hypersensitivity.

Studies have demonstrated that 1% SLS in mouthwashes exhibited plaque-inhibitory properties and substantivity, as measured by effects on salivary bacteria similar to those of a 0.2% triclosan rinse (Jenkins et al., 1991a,b).

HEXETIDINE

Hexetidine is the active ingredient in the product Oraldene. Since the study by Bergenholz and Hansström (1974) showing that Oraldene was less effective than a CHX rinse, there has been a dearth of data on this agent.

A "preliminary" study of Oraldene (0.1% hexetidine) was reported by Williams et al. (1987). This was a plaque re-growth study of seven days' duration, using the mouthrinse three times daily as the only oral hygiene procedure. A highly significant reduction of plaque accumulation was found, with the mean total plaque index of the Oraldene group being 40% lower than that of the placebo group.
There were several reversible side-effects with Oraldene, including soreness, slight ulceration, loss of taste, and numbness.

Recently, Grimm et al. (1989) demonstrated an inhibition of plaque development with a mouthrinse containing zinc, fluoride, and hexetidine.

However, in an evaluation of its effects in the treatment of recurrent aphthous ulcers, Oraldene was found to provide no benefit to oral hygiene or gingival health (Chadwick et al., 1991). This clinical trial was a double-blind cross-over study comparing Oraldene with placebo, with test periods of 6 weeks' duration. The incidental findings on plaque scores and “bleeding on probing” showed no significant differences between the groups at the end of the test periods.

OCTENIDINE

Beiswanger et al. (1990) conducted a three-month clinical trial of 0.1% Octenidine mouthrinse in which 450 adults participated, using their normal oral hygiene practices together with either a placebo or the test rinse twice a day. At 6 weeks and 3 months, soft tissue, gingivitis, and plaque accumulation were assessed, and the degree of staining was measured at the end of the study.

Octenidine reduced plaque by one-third and gingivitis by one-half compared with the placebo, but left a high degree of staining, which was difficult to remove. It would appear that Octenidine offers no advantages over chlorhexidine, and is less effective in its effect on plaque and gingivitis.

DELMOPINOL

An alternative approach to antimicrobial attacks on dental plaque is to prevent the attachment or retention of bacteria on the tooth by affecting its surface characteristics. Relatively little work has been carried out in this aspect of prevention of dental plaque, but recently Collaert et al. (1992a,b) have revived interest with a surface-active agent, delmopinol hydrochloride. This agent is a substituted amino alcohol which has little if any effect on salivary microflora. A significant dose-response effect was found in a group of volunteers when plaque re-growth was assessed over two weeks, with rinsing as the only oral hygiene procedure. When gingival bleeding indices were compared, there was no significant difference between rinsing with chlorhexidine and 0.2% delmopinol solution. Chlorhexidine and delmopinol were compared directly with 0.2% solutions as the only oral hygiene procedure over a period of 2 weeks. At the end of a preliminary two-week placebo period and at the end of rinsing with the active rinses, saliva samples were taken, gingival crevicular fluid flow was measured, gingivitis was scored by gingival index, plaque was measured planimetrically, and the plaque index scored. While there were significant reductions in numbers of anaerobes, aerobes and Streptococcus mutans in saliva of those rinsing with CHX, no changes in these organisms were detected for subjects rinsing with delmopinol. However, there was no difference between delmopinol and chlorhexidine effects in reducing crevicular fluid flow in gingivitis, though mean plaque extension was reduced more by chlorhexidine.

Moran et al. (1992b) studied plaque re-growth with delmopinol in a four-day cross-over study using CHX as a positive control and a placebo rinse. No mechanical oral hygiene was allowed, and although the plaque scores with delmopinol rinsing were higher than those with CHX, the reduction from the scores with placebo rinsing was significant and gave rise to optimism that delmopinol would be of benefit in reducing gingivitis. In a separate investigation in this report, it was shown that delmopinol had very little effect on salivary bacteria after one rinse, and the effect was lost in one hour. Some subjects complained of the taste and a burning sensation on the mucosa when they used this aqueous solution. The conclusion is that delmopinol shows promise as an anti-plaque agent and warrants further investigation.

ZINC SALTS

Heavy metal salts have long been recognized as possessing antibacterial properties. Zinc ions have been found to reduce the acidogenicity of plaque and inhibit its formation (Afseth and Rolha, 1980). While there are several studies of zinc in dentifrices (reviewed by Gunbay et al., 1992), there have been, since 1988, practically no studies of zinc as the main active ingredient of mouthrinses. In the majority of cases, zinc salts have been used in combination with other agents.

Giertsen et al. (1989) examined the dose-related effects of zinc chloride on plaque re-growth and acid production in plaque. The subjects in a four-day cross-over study rinsed twice daily with 0, 5, 10, 20, or 100 mmol/L ZnCl₂ for 4 days in the absence of all other oral hygiene. This study is interesting in that the subjects chewed sucrose-containing chewing gum to enhance plaque formation, and the plaque re-growth results were analyzed as frequency distributions of the plaque index scores 0, 1, 2, and 3. A second panel of six subjects used placebo, 5 mmol/L or 100 mmol/L, in a cross-over study with experimental periods of 3 days. It was found that plaque formation was significantly reduced with 5, 10, and 20 mmol/L ZnCl₂, but 100 mmol/L had little effect. The second panel was made up of six students who were heavy-plaque-formers, and on these the 100 mmol/L concentration significantly decreased plaque accumulation.

Zinc ions are considered to act by inhibition of glycolytic enzymes (Schei et al., 1988), or by displacing magnesium ions and hence inhibiting enzyme systems (Maryanski and Wittenberger, 1975). There is evidence that zinc ions may inhibit both the adsorption of bacteria to the tooth surface and growth of existing plaque (Harrap et al., 1984; Saxton, 1986).

An assessment of the antimicrobial effects of zinc chloride against oral streptococci was carried out by a seven-day mouthrinsing trial. The growth of plaque on Mylar foil was analyzed for colony-forming units of Streptococcus mutans, Streptococcus sanguis, and Streptococcus salivarius. There was a significant decrease in total streptococcal colonies at seven days compared with placebo, and a selectively greater bactericidal effect on Streptococcus sanguis compared with Streptococcus salivarius (Dobl and Nossek, 1990; Nossek and Dobl, 1990).

COMBINATION RINSES

As already noted, triclosan in combination with either zinc...
citrate or a copolymer appears to achieve better results than when the agents are used alone. However, more comparative studies of these agents alone and their various possible combinations are required.

Perdok et al. (1988) used a double-blind cross-over study of plaque re-growth and gingivitis to test the efficacy of an amine fluoride/stannous fluoride rinse. The rinse or a placebo was used as the only oral hygiene procedure for an experimental period of seven days. At the end of the period, the plaque index, plaque area, gingival index, and microbial composition of the plaque were scored. The wash-out period between the cross-overs was eight weeks. Statistical analysis showed that the active-component rinse produced scores of plaque growth and gingivitis lower than those of the placebo group. No differences in microbial composition of the plaque between the two groups were found.

The combination of an amine fluoride and stannous fluoride has been studied for its effect on plaque growth in a trial lasting 5 months (Nemes et al., 1991). The amine fluoride/stannous fluoride combination was formulated as both a toothpaste and a rinse, and compared in the trial with sodium fluoride toothpaste and rinse. The rinse was used after toothbrushing. The results showed that the plaque indices of the group using amine fluoride/stannous fluoride combination were reduced by 64% and those using sodium fluoride by 40% relative to baseline figures. Counts of Streptococcus mutans and lactobacillus decreased in both groups, but no significant differences between the groups were found (Herczegh et al., 1991).

Combinations of materials which might be considered beneficial can sometimes produce an inhibition of action.

Barkvoll et al. (1989) have shown a deleterious effect of SLS when combined with chlorhexidine. The SLS reduced the inhibition of chlorhexidine on the oral flora, and they suggested a two-hour gap between toothbrushing with paste including SLS and chlorhexidine mouthwashing. SLS remained in the mouth for about 2 hours.

In a test of the effects of toothpaste rinses on plaque regrowth, Addy et al. (1989a) found that toothpaste ingredients reduced the efficiency of chlorhexidine, and it is probable that the availability of chlorhexidine from the toothpaste was reduced. It may be that the SLS in the toothpaste material inhibited the chlorhexidine. Monofluorophosphate is another common ingredient of toothpaste, and in a trial with a combination of MFP and chlorhexidine, the action of chlorhexidine was reduced. There did appear to be a precipitation when the solutions of the two compounds were mixed (Barkvoll et al., 1988). Triton X is often added to toothpastes as a detergent, but a combination with chlorhexidine is less effective than chlorhexidine alone.

These are examples of the antagonism between cationic and anionic components when combined in a formulation. All too often, active ingredients are included in formulations which have traditional ingredients, such as detergents, which interact with the active ingredient with consequent reduction in efficacy. It is essential that clinical trials be carried out on any new formulations, even those containing “tried and tested” active agents.

Povidone iodine and hydrogen peroxide have been combined (Perimed) and compared with Listerine and Peridex (Maruniak et al., 1992) in a plaque and gingivitis trial lasting 14 days. Seventy-one subjects used the rinses as their only oral hygiene procedures, and results were based on plaque index and papillary bleeding scores. After 14 days, the average papillary bleeding scores were better for Peridex and Perimed compared with those for Listerine and water. The authors concluded that both Peridex and Perimed were effective in reducing plaque and gingivitis, when used as a twice-daily mouthrinse by subjects refraining from other oral hygiene measures. The combination of Povidone iodine and hydrogen peroxide appears to be better than povidone iodine alone.

ADVERSE EFFECTS

There has been, since 1988, an awareness that mouthrinses may harm as well as aid oral hygiene measures. There have been several reports of adverse effects, some of which have been mentioned in the sections dealing with the individual agents. Other adverse effects are to be found in the following reports.

Alcohol in mouthrinses, especially Listerine, was considered as a pre-disposing factor in cancer of the mouth, but this was subsequently discounted fairly forcibly (Smigel, 1991).

Benzydamine oral rinse has been reported to cause a rash (Winn et al., 1991). Sodium retention in patients with hypertension, using Viadent, Plax, and Cepacol, was reported by Wagner et al. (1989). Approximately 30% of the sodium contained in these mouthwashes was retained by the oral mucosa after rinsing. However, whether this is sufficient to cause harm is not known.

It was stressed by Fleszar (1989) that Listerine and Peridex should be avoided in patients with untreated periodontitis. The reduction in superficial inflammation may allow deeper infection to go untreated.

SLS may cause damage to the oral mucosa (Barkvoll and Rølla, 1989).

SUMMARY

It would appear that chlorhexidine is still the best agent to combat plaque and gingivitis, but its disadvantages remain to be overcome. Listerine, though not as effective, can give good results. The reports on sanguinaria/zinc complexes, when used in a mouthrinse alone, are not encouraging, but triclosan combined with copolymer or zinc seems effective as an anti-plaque and anti-calcus agent.

Plax in its previous formulation had had mainly negative reports, and the addition of triclosan in its new formulation shows promise.

Delmopinol warrants further investigation, and a combination of this agent with an antimicrobial might be an interesting possibility.

There is a great need for more standardization of clinical trials of mouthrinses and dentifrices. Although the ADA has established guidelines for trials of gingivitis-reducing agents, it is necessary that minimum acceptable levels of reduction in the various indices be defined.
If mouthrinses are to be used as adjuncts to normal tooth cleaning with toothbrushes and toothpaste, the ratio of cost to gingival health benefits needs to be addressed. Moreover, it could be argued that proven benefits to periodontitis should be the outcome measure of health benefit.

REFERENCES


