Is there a role for triclosan/copolymer toothpaste in the management of periodontal disease?

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VERIFIABLE CPD PAPER

PRACTICE

IN BRIEF

- Explains the mode of action and safety issues of triclosan and discusses its effectiveness.
- Discusses the clinical topics that need more research before a benefit can be guaranteed.
- Highlights practical advice for GDPs on how the triclosan copolymer may help patients with periodontal problems.

Dental caries and periodontal disease are the most common oral conditions experienced by adults today. The treatment of these diseases by the dental team can only be performed when patients attend dental practices. There is recognition that the preventive measures patients perform at home between dental visits is of vital importance in the control of these diseases. Water fluoridation and fluoridated toothpastes have made enormous progress into the prevention of dental caries worldwide. However, prevention of periodontal disease is yet to enjoy the same success. A number of toothpastes have been developed for the prevention and control of periodontal disease. One such toothpaste – containing triclosan/copolymer - has been thoroughly researched. The literature pertaining to the efficacy, mode of action and safety of triclosan/copolymer toothpaste has been reviewed. A MEDLINE search identified 198 articles dated from 1989 to 2008. The findings of this body of research are discussed and conclusions regarding the efficacy of triclosan/copolymer toothpaste in the home-care management of periodontal disease are presented.

INTRODUCTION

The latter part of the twentieth century witnessed a revolution in the oral health of the majority of people living in western industrialised countries. The prevalence of dental caries dropped at least 50%.[1] An amazing reduction for what had been a ubiquitous health care problem. The principal agent of change was universally agreed to be the addition of fluoride to toothpastes. The daily topical application of fluoride via toothbrushing strengthened enamel and healed the early carious lesion.[2,3]

Dental caries is, however, not the only oral health care problem that the dental team is called upon to deal with. Periodontal disease is common and its treatment and control can be expensive and time-consuming, both for the patient and health care professionals. It is well established that plaque is the main aetiological agent in periodontal disease and plaque control has long been the cornerstone of its management. Dental professionals have placed great emphasis on effective toothbrushing and the use of floss and interdental brushes as additional aids to remove plaque.[4-6] Toothpastes *per se* have been considered to be of little value in the management of periodontal diseases.

The success of fluoride toothpastes has been a driver for researchers and manufacturers to seek agents which could be equally successful at reducing periodontal disease. Over the past decade, a number of toothpastes have been developed which have claimed a therapeutic effect over and above the use of standard fluoride toothpaste in the control of periodontal disease.

In the highly commercial arena of toothpaste marketing it is often confusing for oral healthcare professionals to determine whether these new products are effective and safe. There are competing systems and the evidence for each can be difficult to understand.

This paper will review one system that has been extensively tested, namely the triclosan/copolymer toothpaste. In his meta-analysis, Gunsolley[7] concluded there was insufficient evidence to demonstrate efficacy for other triclosan toothpaste systems containing soluble pyrophosphate or zinc citrate. However, there are products available which use alternative additives, the most readily available being stannous fluoride or essential oils. These particular products will not form part of this review which examines the evidence for triclosan/copolymer in terms of efficacy, mode of action and safety. The literature on all of these topics is considerable and is the main reason for concentrating on the triclosan/copolymer product as comparing competing systems would be an overwhelming task.

METHODS

The literature pertaining to the efficacy, mode of action and safety of triclosan and triclosan/copolymer was examined. A Medline search was performed using the terms 'triclosan and/or copolymer' and 198 articles dated from 1989 – May 2008 were identified and reviewed. The search included papers published in English, French, German and Chinese. No specific

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Table 1 Short term triclosan/copolymer toothpaste studies – plaque and gingivitis results versus placebo toothpaste

Singh *et al.* 1989[109]	Reduction in plaque regrowth		Reduction in plaque severity index	
	2 weeks	11.9%	2 weeks	30.2%
	4 weeks	11.8%	4 weeks	35.4%
	6 weeks	20.0%	6 weeks	65.7%
Palomo *et al.* 1989[110]	**Reduction in plaque regrowth**		**Gingivitis reduction**	
	6 weeks	21.3%	6 weeks	5.5% NS
	14 weeks	38.8%	14 weeks	50.72%
Owens *et al.* 1997[111]	**Reduction in plaque regrowth 18 weeks**		**Gingivitis reduction 18 weeks**	
	NS		NS	
McClanahan and Bartizek 2002[8]	**Reduction in plaque regrowth 3 months**		**Gingivitis reduction 3 months**	
	NS		NS	
Muller *et al.* 2006[112]	**Reduction in plaque regrowth**		**Gingivitis reduction**	
	NS		10 weeks	30%
Feng *et al.* 2007[9]	**Plaque reduction 3 months**		**Gingivitis reduction 3 months**	
	NS		Control 10% NS	Test 52%

All results presented are significant compared to placebo unless indicated by NS

Table 2 Summary of significant plaque and gingivitis results from studies of minimum six month duration, included in systematic review of Davies[12] and the meta-analysis of Gunsolley[7]

Study	Plaque reduction	Gingivitis reduction
Garcia-Godoy *et al.* 1990[87]	58.9%	30.1%
Cubells *et al.* 1991[86]	24.9%	19.7%
Deasy *et al.* 1991[88]	32.3%	25.6%
Mankodi *et al.* 1992[89]	11.9%	19.7%
Denepitiya *et al.* 1992[90]	18.4%	31.5%
Bolden *et al.* 1992[85]	17.0%	29.0%
Lindhe *et al.* 1993[63]	31.2%	26.6%
Triratana *et al.* 1993[14]	32.9%	18.8%
Svatun and Saxton 1993[15]	Not Significant	25.0%*
Palomo *et al.* 1994[68]	11.3%	19.9%
Renvert and Birkhed 1995[13]	38.8%	18.2%
Kanchanakamol *et al.* 1995[19]	12.1%	Not Significant
Hu *et al.* 1997[113]	16.1%	24.3%
McClanahan *et al.* 1997[11]	Not Significant	Not Significant
Charles *et al.* 2001[17]	22.1%	20.7%#
Tiriratana *et al.* 2002[91]	34.9%	25.7%
Mandoki *et al.* 2002[16]	18.7%	22.2%
Allen *et al.* 2002[84]	27.9%	21.4%
Winston *et al.* 2002[18]	Not Significant	Not Significant

All plaque results are statistically significant percentage difference of mean Quigley-Hein Plaque index for triclosan/copolymer toothpaste compared to the placebo toothpaste unless otherwise stated.
Modified Gingival Index
* Gingival Bleeding index

hand searching was undertaken. Abstracts, letters and advertorials were collected but excluded from the review.

RESULTS

The findings from the literature search are presented under three headings – Efficacy, Mode of Action and Safety.

Efficacy

Plaque and gingivitis

The ultimate goal of a toothpaste with anti-plaque and anti-gingivitis properties is to produce clinically significant results during unsupervised home use between a patient's regular dental visits. So while shorter-term studies provide the initial evidence to support the triclosan/copolymer formulation, it is the results of the six month studies which are of most value to the dental team and their patients.

For the sake of completeness, Table 1 presents the results of six short-term studies which highlight that the anti-gingivitis effect seen in the triclosan/copolymer users was most pronounced when the subjects had high levels of bleeding on probing at baseline.[8,9] This is understandable, as one would not expect to see an effect on gingivitis if it was not present in the first place. The active toothpaste only has an effect when the patient is suffering from gingivitis, so whole population studies will dilute the overall efficacy. This was also highlighted in the long-term studies by Archila *et al.*[10] who found that the effect was greatest where there were more than 30% of sites bleeding on probing at baseline. In this context, McClanahan *et al.*[11] commented that additional factors such as the anti-inflammatory effect of triclosan may, in part, account for the fact that the major benefit is seen in patients with a high level of existing gingivitis.

A great deal of the evidence for the efficacy of the triclosan/copolymer toothpaste relates to its effects on plaque and gingivitis. Two systematic reviews undertaken by Davies *et al.*[12] and Gunsolley[7] found 19 studies which investigated the anti-plaque and anti-gingivitis effect of the triclosan/copolymer toothpaste in studies of at least six months duration and all had reduction of plaque and gingivitis as the primary outcomes. Of these studies, 13 were common to both, three were exclusive to Davies *et al.*[13-15] and three were exclusive to Gunsolley.[16-18] Table 2 outlines the studies included in these reviews and the clinical outcomes reached.

While 15 studies support the anti-plaque and anti-gingivitis effects one has shown only an effect on gingivitis but not plaque,[15] one has shown an effect on plaque but not gingivitis (although an effect on gingivitis was seen at three months)[19] and two[11,18] were unable to demonstrate any treatment effect on either plaque or gingivitis at six months although an effect was seen for sites that bled on probing.[18]

When the results of the studies shown in Table 2 are considered, 15 showed that the active toothpaste significantly reduced both plaque and gingivitis. Overall there was around a 23% reduction in both

plaque and gingivitis. In absolute terms the results showed a 15% reduction in number of sites with heavy plaque or a relative reduction of around 49% compared with the placebo toothpaste. Similarly, the absolute reduction in sites that bled on probing was around 12% representing a relative reduction of around 49% compared with the placebo. Gunsolley[7] found no positive evidence for other triclosan-containing toothpastes giving a useful clinical result (ie those containing soluble pyrophosphate or zinc citrate) and concluded that the results of his meta-analysis supported the use a triclosan/copolymer toothpaste for those individuals with gingivitis.

Therefore, a general dental practitioner or hygienist who recommends a triclosan/copolymer toothpaste can be confident that this group of studies reporting six month data, demonstrates that the twice daily use of a triclosan/copolymer toothpaste results in a significant reduction in both mean plaque and gingival index scores and that the reduction is greatest in those sites that harbour the most plaque and have the most gingivitis.

Periodontitis

There have been a number of randomised, controlled, clinical trials that have investigated the efficacy of a triclosan/copolymer toothpaste as an adjunct to mechanical plaque removal in the control of periodontitis. Eight of these studies are summarised in Table 3.

Table 3 Effect of the home use of triclosan/copolymer toothpaste on periodontal patients

	Study	Outcomes
Rosling *et al.* 1997a[20]	Clinical study of highly susceptible periodontal patients	Significant difference in mean probing depth change between the groups (p <0.01) over a three year period.
Furuichi *et al.* 1999[21]	Clinical study of highly susceptible periodontal patients with >2 mm loss of attachment during Rosling 1997a study	Clinically significant reduction in the number of sites with gingivitis following scaling and root planing in the test group but not in the control group. Control and test groups showed a clinically significant reduction in mean PPD and a significant gain in attachment following treatment. The changes were significantly greater in the test group.
Rosling *et al.* 1997b[22]	Microbiological study of highly susceptible periodontal patients (subset of Rosling 1997a)	Significant reductions in total viable counts of subgingival microbiota
Ellwood *et al.* 1998[23]	Clinical study of highly susceptible teenagers with high mean probing depth at baseline	50% reduction in attachment loss compared to placebo
Cullinan *et al.* 2003a[24]	Clinical study of general adult population	Significant reduction of number of sites with probing depths >3.5 mm
Cullinan *et al.* 2003b[25]	Microbiological study of subgingival plaque samples from adults in clinical study	The clinical effect was independent of changes in the periodontopathic bacteria.
Papas *et al.* 2007[26]	Clinical study of xerostomic patients at high risk of periodontitis	Clinically significant reduction in probing depths and inflammation in xerostomic patients.
Kerdvongbundit *et al.* 2003[27]	Clinical study of smokers with chronic periodontitis	Clinically significant improvement in plaque, calculus and gingivitis indices

The first, by Rosling *et al.*[20] took a group of patients who were highly susceptible to periodontal disease in that they had all received treatment for advanced periodontitis and even with regular periodontal maintenance still had recurrent disease. Instead of their usual periodontal maintenance involving three monthly recalls for subgingival debridement of bleeding sites and re-inforcement of oral hygiene, half the patients were asked to use a triclosan/copolymer toothpaste while the remainder used a placebo toothpaste. All patients were monitored every three months and given oral hygiene instruction when necessary, however, they had no further subgingival debridement. Any sites that had progressed by a loss of attachment of 2 mm or more were exited from the study and treated. After three years patients using the triclosan/copolymer toothpaste had very little disease progression, with fewer sites exited for treatment compared with those using the placebo toothpaste and it was found that those in the placebo group had significantly more attachment loss and bone loss than the triclosan/copolymer group. Overall there was a decrease in the mean probing depth at the three-year examination in the triclosan/copolymer group and an increase in the placebo group, resulting in a significant difference in mean probing depth change between the groups (p <0.01). Therefore, susceptible patients using a triclosan/copolymer toothpaste can expect to have less disease progression than those not using it.

The sites that had lost attachment and were exited for treatment (scaling and root planing) were also evaluated at the end of the study.[21] While both groups of treated sites showed a significant reduction in mean probing depth and a significant gain in attachment following treatment, the changes were again significantly greater in the triclosan/copolymer group.

The subgingival microbiota was also studied in a subset of these patients[22] and significant reductions in total viable counts (TVC) were observed at 36 months in the triclosan/copolymer group compared with the control group. However, it is probable the observed antibacterial effect may not be entirely responsible for the improved clinical outcome as triclosan can also exert an anti-inflammatory effect.

Overall, these studies have shown that, while good oral hygiene and a rigorous maintenance programme alone cannot entirely prevent recurrent disease in highly susceptible patients, daily use of a triclosan/copolymer toothpaste can lead to an improved outcome after treatment.

The study by Ellwood[23] adds further support to the notion that use of a triclosan/copolymer toothpaste provides additional benefits over mechanical plaque control alone. For three years, a group

of adolescents who had previously been shown to be at high risk of developing early periodontitis, used either a triclosan/copolymer toothpaste or a placebo toothpaste. Those adolescents using the triclosan/copolymer toothpaste showed a 50% reduction in the mean increment of attachment loss compared with similar individuals using a placebo.

The above studies are complemented by a longer clinical and microbiological study in a general adult Australian population over five years.[24,25] The participants ranged from being healthy to having mild, moderate and advanced periodontitis. It was found that the triclosan/copolymer toothpaste significantly reduced the number of sites with probing depths >3.5 mm at subsequent examinations compared with the placebo. Interestingly, this effect increased as the number of sites >3.5 mm increased. For example, a person with five sites >3.5 mm could expect to have on average 10% fewer sites >3.5 mm a year later and a person with ten sites >3.5 mm, 20% fewer than a similar person not using the triclosan toothpaste. In a similar trend to the gingivitis studies, the effect was more pronounced in those with more disease and after five years could compound to more substantial reductions of 40% and 70% for those starting with five or ten sites >3.5 mm.

A significant reduction in probing depths accompanied by a clinically significant reduction in bleeding on probing (from 88.3% to 9.6% of sites) after using a triclosan/copolymer toothpaste for two years was also observed in a group of xerostomic patients at high risk for periodontitis.[26] The reduction in bleeding on probing lends weight to the contribution of the anti-inflammatory properties of a triclosan/copolymer toothpaste to the clinical benefits.

Improved healing following scaling and root planing has also been observed in smokers with chronic periodontitis after using a triclosan/copolymer toothpaste.[27] There was a significant improvement in plaque, calculus and gingival indices and it was interesting to note that this effect was sustained for up to two years, even in smokers.

Dental professionals should therefore consider recommending the twice daily use of a triclosan/copolymer toothpaste to patients who are susceptible to periodontal disease in the knowledge that it will be a useful adjunct to periodontal preventive and supportive therapies.

Calculus

Although the role of supragingival calculus in the aetiology of caries and periodontal disease is most likely secondary in nature, there can be no dispute that calculus acts as a predisposing factor for plaque accumulation. The addition of ingredients to toothpastes to limit the formation of supragingival calculus has been attempted for some decades.[28,29] Much work has been done utilising combinations that include at least one of the pyrophosphates to limit precipitation and crystal formation which lead to the deposition of supragingival calculus. The addition of a copolymer in combination with triclosan has been investigated as an alternative approach to limiting supragingival calculus formation.

Following early *in vitro* work demonstrating the efficacy and safety of triclosan/copolymer as an anti-calculus agent[30] clinical trials[15,29,31-34] ranging from 2-7 months were undertaken to investigate the *in vivo* anti-calculus potential of a triclosan/copolymer containing toothpaste. All trials utilised the Volpe-Manhold index[35] to quantify the amount of supragingival calculus reformation following scaling of the teeth. The majority of studies have shown that a triclosan/copolymer toothpaste is superior to a placebo in limiting the reformation of supragingival calculus.[31,33,34,36-39]

Two studies have reported contradictory results.[15,32] It is unclear why such different results were achieved but they included subjects who did not necessarily form large amounts of calculus and it is possible that this influenced the outcome.

It should be emphasised that the absolute differences in the amount of supragingival calculus formed in all of the available studies are modest and whether they represent clinically significant results is open to debate. The effect of a triclosan/copolymer toothpaste on subgingival calculus formation has not been studied to the present time. However, it is recognised that the presence of subgingival calculus has an association with subsequent attachment loss and as such studies in this area would add valuable weight to the usefulness of such a toothpaste for home maintenance in susceptible patients. Therefore, at present, the only practical conclusion is that further investigations are required before any claims about the role of triclosan/copolymer toothpaste in calculus reduction both supra- and sub-gingivally of clinical relevance to the dental team can be substantiated.

Caries

A fundamental tenet of producing any new pharmaceutical with multiple actions/ingredients is that any additives do not interfere with the primary mode of action. In the case of toothpaste, the role and effectiveness of the addition of fluoride to produce an anti-caries effect is well documented. While different concentrations and carriers of fluoride have been used across a range of toothpastes, the efficacy of sodium fluoride (NaF) and sodium monofluorophosphate (NaMFP) formulations for caries prevention using fluoride concentrations ranging from 1,000 to 1,500 ppm has been established.[40-43]

Randomised controlled clinical trials have investigated the efficacy of the triclosan/copolymer toothpaste formulations utilising NaF for its anti-caries effect. In particular four long term clinical trials (ranging from 24-36 months with approximately 1,200-3,500 participants each) have been undertaken in accordance with the American Dental Association Council on Dental Therapeutics Guidelines for such trials.[44] Test products were compared using the mean caries increments (number of new DFS lesions) and ensuring the 90% confidence intervals were of a sufficient level to show equivalence/superiority. One trial[45] was able to show 'superiority' to a control toothpaste, one showed 'equivalence'[46] and two reported results that were 'at least as good as' a control toothpaste in terms of mean caries increment.[47,48]

These data support the premise that the addition of triclosan/copolymer to a NaF toothpaste does not interfere with the proven anti-caries effect of NaF toothpastes and that the triclosan/copolymer-containing toothpaste is at least as good as a standard NaF toothpaste in limiting the formation of new carious lesions.

Halitosis

While caries and periodontal diseases are usually the main concerns of the dental team, for many patients their prime concern

may be halitosis. Periodontal disease may be an aetiologic factor for halitosis, however, the symptom may be present without obvious periodontal disease. The scientific assessment of halitosis has only been undertaken in recent times. Much effort has been given to the assessment of volatile sulphur compounds (VSC), which can be quantifiably evaluated. Unfortunately the correlation between these compounds and patient and non-patient perceptions of halitosis is poor.

Three studies[49-51] showed that following use of a triclosan/copolymer toothpaste, the mean organoleptic assessment score equated to 'pleasant breath', as opposed to control subjects who remained above the 'unpleasant breath' cut off. Thus the body of available evidence would suggest that the use of a triclosan/copolymer toothpaste should result in an improvement in halitosis. However, this is an area of clinical research that undoubtedly requires more investigation before definitive answers can be given to patients about managing 'bad breath'.

Mode of action

Anti-microbial effect

Triclosan (2,4,4'-trichloro-2'hydroxydiphenyl ether) is a phenolic agent with broad-spectrum antibacterial activity that disrupts bacterial cytoplasmic membranes by blocking fatty acid biosynthesis. Initially developed in the 1960s, it has been used in a wide range of personal care and health related products for over 40 years, more recently including toothpastes.[12,52,53] Triclosan is effective against both Gram positive and Gram negative bacteria and has low toxicity. When compared to chlorhexidine, it has a lower level of anti-microbial activity, however, it has the advantages of being compatible with other toothpaste ingredients such as ionic surfactants and sodium fluoride and having an acceptable taste.

In order to successfully incorporate triclosan into a toothpaste, it was necessary to develop a formula which optimised its delivery and retention in the mouth while remaining compatible with the other ingredients. Formulating a toothpaste that combined triclosan with a copolymer, polyvinylmethylether/maleic acid (PVM/MA), led to improved substantivity and resulted in long-lasting clinical anti-microbial efficacy.[54-56]

Anti-inflammatory effect

Periodontitis is an inflammatory condition characterised by destruction of the supporting tissues surrounding the teeth and involves an interplay between microbial, host, genetic and environmental factors.[57] The microbial factors are the primary aetiological factors which induce complex inflammatory and immune responses in a susceptible host.[58,59]

While bacteria are necessary for the development of periodontal problems, they are not sufficient to cause disease as plaque-associated periodontal disease is intimately related to the host inflammatory reaction. Therefore any agent which can not only aid in the control of aetiologic agents such as bacteria but also contribute to modulation of the host inflammatory response could have beneficial effects. Inflammation is considered to be a 'two-edged' sword. Initially it aids in the control of infection but if it becomes overextended then tissue damage rather than tissue repair occurs. If chronic inflammation can be controlled (in the presence of reduced bacterial load) then it is possible that the tissues may be 'driven' towards repair rather than destruction.

For many years it has been recognised that triclosan/copolymer toothpaste has the ability to control gingivitis through its antibacterial activity.[12] However, in the early 1990s it was suggested that the anti-inflammatory properties of triclosan provide an additional benefit in the management of the inflammatory periodontal diseases.

A number of *in vitro* studies have addressed the anti-inflammatory properties of triclosan on human gingival fibroblasts. In all of these studies triclosan was studied alone (usually solubilised in ethanol) and not in combination with co-polymer. The results from these studies demonstrated that when exposed to various concentrations of triclosan (0.25 – 1.0 µg/ml) the ability of these cells to produce a number of inflammatory cytokines and mediators of inflammation was diminished. Triclosan in this concentration range was found to inhibit both the cyclo-oxygenase and lipoxygenase pathways.[60] While these results indicate that triclosan has the ability to modulate the production of inflammatory cytokines and thus implies an anti-inflammatory effect it must be noted that all of these studies have been carried out using fibroblasts. It may be that a more appropriate test system would be to study the anti-inflammatory effects of triclosan using crucial inflammatory cells such as macrophages, neutrophils and lymphocytes.

In vivo studies concerning the anti-inflammatory properties of triclosan have been limited. Early studies using a skin model of histamine-induced acute inflammation found that triclosan significantly reduced the degree of inflammation but only if applied after induction of inflammation.[61] When applied before the induction of inflammation triclosan had a slight effect. A further limiting factor of the effect was noted when various solvents were studied.[62] From this study it was noted that the inhibitory effect of triclosan in the skin model was noted for triclosan/zinc citrate and triclosan/ethanol combinations but not for triclosan/propylene glycol or triclosan/copolymer.

The first study to imply that triclosan/copolymer might, in addition to having an antimicrobial effect, exert anti-inflammatory properties in the management of gingivitis was reported by Lindhe *et al.* in 1993.[63] Since this report a number of studies have been published which support the proposal that triclosan/co-polymer has an additional beneficial effect on gingivitis apart from its antibacterial properties.

Kocher *et al.*[64] investigated plaque and gingivitis scores between two groups – one (control) which used a placebo toothpaste as well as the participants undertaking interdental cleaning and another (test) which used a triclosan/copolymer toothpaste but no interdental cleaning by subjects. It was reported that the use of a toothpaste containing triclosan/copolymer reduced plaque and gingival inflammation to comparable levels achieved by regular interdental cleaning.[64]

A study investigating the effect of a triclosan containing dental gel on the gingival conditions of patients undergoing fixed orthodontic treatment did not find any beneficial effects with regards to reduction in the levels of PGE_2 and IL-1β in gingival crevicular fluid.[65] Whether the composition of the gel used in this

study had a negative impact can be questioned since the nature of the solvent used for the delivery of triclosan has been shown to be of importance for its anti-inflammatory properties.[66]

Therefore, from the literature published to date it may be concluded that triclosan demonstrates an ability to modulate (inhibit) inflammatory mediator production by human gingival fibroblasts, however it is important that other inflammatory cells are investigated. Furthermore, while the anti-inflammatory effects in relation to gingivitis are interesting, further studies are needed to confirm this observation.

The role of the copolymer

One of the problems with using topical agents to control periodontal disease is the fact that the mouth can be likened to a river, with saliva washing away products on a continual basis. If agents are to be successful they must adhere to the oral tissues. This adherence is termed substantivity and the bench mark for researchers is chlorhexidine which has the ability to stay in the mouth for long periods of time. However the problems of staining and alterations of taste sensation led researchers to investigate ways of improving the substantivity of other agents.

Previous systematic reviews of the literature reveal that the presence of the polyvinylmethylether maleic acid (PVM/MA) copolymer significantly enhances the beneficial oral health effects of a triclosan-containing toothpaste.[7,12] The PVM-MA copolymer enhances and prolongs the antibacterial and anti-gingivitis effects of triclosan.[13,67-72] The PVM-MA copolymer neither interferes with any ingredients in the toothpaste formulation[73] nor does it contribute to unhealthy shifts in bacterial populations.[74]

Polymers and nano-polymers are successfully exploited in medicine and dentistry to improve and prolong delivery of, and to reduce the therapeutic dose of medicinal agents.[75] The PVM/MA co-polymer is well documented in *in vivo* and *in vitro* studies to impart substantivity to active ingredients. Subjects with 72 hour plaque accumulation who rinsed for one minute with a slurry of a triclosan copolymer toothpaste experienced sustained inhibition of plaque accumulation and plaque bacterial viability. The magnitude of the substantivity was comparable to 0.1% chlorhexidine for 24 hours following rinsing.[69] The PVM-MA copolymer significantly lowers the minimum inhibitory concentration of triclosan necessary to kill aerobic and anaerobic periodontal, endodontic and salivary pathogens.[13,76]

In the oral cavity, the PVM-MA copolymer ingredient in toothpaste acts as a superior oral bioadhesive controlled-release delivery system for triclosan.[13,75,77] It enhances triclosan reservoirs on the buccal mucosa, on hard tooth surfaces and in saliva. It also enhances triclosan reservoirs within plaque biofilm.[54,55,72,78]

The presence of the PVM-MA copolymer appears to be necessary in a triclosan/fluoride toothpaste formulation in order for periodontal health benefits to achieve statistical significance over a prolonged study period. For example, statistically significant reductions in the Gingival Index[79] and the severity of gingivitis were noted only for subjects randomised to the triclosan/PVM-MA copolymer fluoride toothpaste in a six-month double-blind study of unsupervised brushing twice daily (N = 194). Gingival health of subjects randomised to the triclosan/pyrophosphate or to the triclosan/zinc citrate fluoride toothpaste groups was not different from that of subjects in the placebo fluoride toothpaste group in the Polomo study.[68]

The key finding for dental professionals is that the copolymer helps retain the active ingredient – triclosan in the mouth and thereby ensures its beneficial clinical effect.

Safety

A considerable number of papers have been published on the benefits and potential hazards of biocides such as triclosan.[80,81] DeSalva and colleagues[82] reviewed the pharmacological and toxicological information for triclosan and concluded that it was safe for use in toothpaste and mouthrinse products. Triclosan has a wide range of activities, being bacteriostatic at low concentrations and bactericidal at higher concentrations.[83] It is important to note, the effectiveness of triclosan is dependent on the concentration and the type of organisms.

Side effects

Human safety studies for triclosan/copolymer toothpaste, including those evaluating acute toxicity, pre- and post-treatment blood chemistry tests for liver and kidney function and haematological measurements showed no difference between populations using the toothpaste and control populations.[82] To date there have been no reports of adverse effects on the oral hard or soft tissues that could be attributed to the use of a triclosan/copolymer toothpaste.[13-17,19,68,84-91]

Microbial resistance

There have been concerns raised[92] about the wisdom of including triclosan and other biocides in so many commonly used household products, because there may be a link between their use and antibiotic resistance.[93-96] Such claims have been the subject of considerable research and debate about triclosan's mode of action and the possibility of the development of antibiotic resistant strains of bacteria.[97] The key areas of interest in terms of triclosan's mode of action are membrane destabilisation, efflux mechanisms, the inhibition of fatty acid synthesis and the formation of biofilms. The early work on triclosan highlighted its effect on the bacterial membrane structures, particularly its distruptive effects on lipids and proteins.[98]

A more recent line of enquiry has been to investigate the bacterial efflux defence mechanism whereby harmful molecules are removed.[99] It has been reported that the 'upregulation' of the efflux defence mechanism stimulated by sub-lethal levels of triclosan has resulted in some resistance to antibiotics.[100] In laboratory studies this relationship between the use of triclosan and antibiotic resistance has been confirmed.[101,102] However, when studies are undertaken in the home environment no significant differences in the frequency of antibiotic resistant bacteria were found in locations that did or did not use surface antibacterial agents.[103,104] In addition, regular use of a triclosan containing toothpaste did not demonstrate significant decreases in antibiotic susceptibility in dental bacteria.[74,105] Biocide resistance and antibiotic resistance is not a new problem, but current evidence from environmental studies suggests there is no need to curtail triclosan usage.

Studies[106,107] have been conducted on the pathway of fatty acid synthesis. At sub-lethal concentrations triclosan has

been shown to target the enoyl-acl carrier protein (ACP) reductase (Fabl enzyme) in both Gram positive and Gram negative bacteria. The presence of these reductases in bacteria indicates they are potentially susceptible to triclosan through inhibition of fatty acid synthesis.[108]

The inclusion of triclosan with copolymer in toothpastes has stimulated considerable research into the natural biofilm, plaque. Of particular interest is whether there are significant shifts in the oral microbiota following regular brushing over time with a triclosan containing toothpaste. Renvert and Birkhed[13] reported no significant shifts in the oral microbiota despite the fact that supragingival plaque formation and gingival bleeding were reduced.

It is important to note that although triclosan has been used for many years in different household and clinical products in varying settings no increasing bacterial resistance has been recorded in 'real life' environmental studies.[103,104]

DISCUSSION

Overall the results from a number of scientific and clinical studies, together with the two systematic reviews and meta-analyses, strongly support the anti-plaque and anti-gingivitis effect of the twice daily use of a triclosan/copolymer toothpaste. The greatest effect seems to be related to those sites which harbour the most plaque and those sites with the most inflammation as measured by bleeding on probing. The significant reduction in the number of bleeding sites would further suggest that the effect on gingivitis is clinically significant. These results are consistent with the concept that a triclosan/copolymer toothpaste is of greatest benefit to those that have existing disease.

With regard to prevention of chronic periodontal disease, the studies to date suggest that the twice daily, unsupervised use of a triclosan/copolymer toothpaste offers benefits above regular toothpaste in terms of slower progression of disease and improved healing following periodontal therapy. With regard to prevention of periodontal disease, the limited data suggest some benefits but further studies are required for confirmation.

The regular long-term use of a triclosan/copolymer toothpaste may offer benefits in lowered supragingival calculus formation and halitosis control but further investigations are warranted. Future studies may also confirm clinically significant anti-inflammatory properties of triclosan/copolymer toothpaste.

There are other toothpaste products in the market place which also have evidence supporting their use in patients' home care regimens for the control of periodontal disease[11,13,16-18,68] and it is clear that a number of manufacturers and independent research groups are continuing research and development in this important area of clinical prevention.

CONCLUSION

Overall the current evidence suggests that with the twice daily use of a triclosan copolymer toothpaste patients will:

- Gain clinically significant improvements in plaque control and gingivitis
- Benefit from slower progression of periodontal disease.

Given the proven safety profile, demonstrated benefits and relatively low cost of the use of a triclosan/copolymer toothpaste it would seem prudent for dental professionals to recommend the use of such a toothpaste to many of their patients in place of regular fluoride toothpaste.

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