A meta-analysis of six-month studies of antiplaque and antigingivitis agents

John C. Gunsolley, DDS, MS

Multiple antigingivitis and antiplaque over-the-counter products are available commercially for patients. These products are primarily in the form of a dentifrice or a mouthrinse, and the active agents involved include triclosan (dentifrice), stannous fluoride (dentifrice), a combination of essential oils (mouthrinse) and cetylpyridinium chloride (CPC) (mouthrinse). In addition, in the United States, a mouthrinse containing chlorhexidine is available as a prescription drug.

The proper formulation of these active agents into dentifrices and/or mouthrinses is extremely important to maintain the bioavailability of the agents and, in some cases, to improve their substantivity. Thus, different formulations of the same active agents may have different levels of efficacy. This increases the number of choices in the marketplace for products containing these agents and makes it more difficult to evaluate their efficacy.

The clinical evaluation of these products includes short-term trials ranging from four days to two months and long-term clinical trials, most of which are six months in length. The four-day trials are used primarily to evaluate the antiplaque effect of these products.[1-5] The intermediate-length trials (two weeks to two months) can evaluate both the antiplaque and antigingivitis efficacy of these products. As demonstrated by the three-week, no-oral-hygiene model of Löe and colleagues,[6] most people will develop gingivitis in this time frame. The limitation of these intermediate-length trials is that researchers cannot investigate the long-term effi-

ABSTRACT

Background and Methods. The author conducted a systematic review of the literature to evaluate the efficacy of antigingivitis and antiplaque products in six-month trials. He searched electronic databases for six-month randomized clinical studies that evaluated both antiplaque and antigingivitis properties of dentifrices or mouthrinses. In addition, the author solicited unpublished studies from manufacturers.

Results. Seventeen studies support the antiplaque, antigingivitis effects of dentifrices containing 0.30 percent triclosan, 2.0 percent Gantrez copolymer. There was no evidence of efficacy for triclosan products containing either soluble pyrophosphate or zinc citrate. Dentifrices with stannous fluoride had statistically significant, but marginally clinically significant, evidence of an antiplaque effect; however, there was both a statistically and clinically significant antigingivitis effect. The largest body of studies (21 studies) supported the efficacy of mouthrinses with essential oils. A smaller body of studies (seven) supported a strong antiplaque, antigingivitis effect of mouthrinses with 0.12 percent chlorhexidine. Results for mouthrinses with cetylpyridinium chloride varied and depended on the product's formula.

Conclusions. The studies in this systematic review provide strong evidence of the antiplaque, antigingivitis effects of multiple agents. These results support the use of these agents as part of a typical oral hygiene regimen.

Key Words. Antiplaque; antigingivitis; systematic review; plaque control.

JADA 2006;137(12):1649-57.

DISCLOSURE

This study was supported in part by an independent grant from Pfizer, Morris Plains, N.J.

Dr. Gunsolley is a professor of periodontics, Department of Periodontics, Virginia Commonwealth University, Wood Building, Room 302, 521 N. 11th St., Richmond, Va. 23298, e-mail "jgunsolley@vcu.edu". Address reprint requests to Dr. Gunsolley.

cacy of the product, which would reflect more accurately the patient's actual use of the product. For this reason, six-month trials have been used to evaluate efficacy by the U.S. Food and Drug Administration (FDA) in its approval of 0.12 percent chlorhexidine as a prescription drug in the United States, as well as by the American Dental Association in its Seal of Acceptance Program.[7,8]

Although a variety of antiplaque, antigingivitis agents have been evaluated in randomized, six-month trials, no comprehensive systematic reviews of these studies, to my knowledge, have been conducted. The only systematic review of six-month clinical trials of antiplaque, antigingivitis agents has been a review of a triclosan dentifrice containing a copolymer.[9]

Therefore, the goal of this systematic review was to evaluate the efficacy of antiplaque, antigingivitis agents in studies involving six-month randomized clinical trials.

MATERIALS AND METHODS

The focused question for this systematic review was as follows: Are mouthrinses or dentifrices effective (and which ones) as antiplaque and/or antigingivitis agents in six-month randomized clinical trials of adults 18 years and older?

MEDLINE search. Initially, a dental hygienist and I used MEDLINE to search for the studies. We used the abstracts to eliminate any studies that were not relevant. We then obtained the full-length articles of all relevant studies. We used the following sets of key words, for which the resulting number of studies are shown parenthetically:

- plaque, gingivitis and clinical trials (794);
- essential oils, gingivitis and clinical trials (24);
- chlorhexidine, gingivitis and clinical trials (199);
- triclosan, gingivitis and clinical trials (88);
- CPC, gingivitis and clinical trials (18);
- stannous fluoride, gingivitis and clinical trials (49);
- Total [Colgate-Palmolive, New York City], gingivitis and clinical trials (139);
- Listerine [Pfizer, Morris Plains, N.J.], gingivitis and clinical trials (375);
- cetylpyridinium chloride, gingivitis and clinical trials (0).

After duplicate studies were removed, the above search resulted in a total of 838 unique articles. We reviewed the titles to determine if the studies were clinical trials of six months in duration and evaluated plaque and gingivitis.

We conducted a hand search from the initial findings to locate any studies that may have been missed. We also contacted manufacturers to determine if they had conducted any unpublished studies.

The inclusion criteria used to screen published and unpublished reports were as follows:

- study duration of six months or longer;
- use of a normal adult population;
- use of a placebo or vehicle control group;
- use of a minimum of one active agent group (if the study included more than one agent, each active agent was compared against the control group);
- a randomized clinical trial;
- an active agent that was available commercially in the United States;
- use of the Turesky modification of the Quigley-Hein Index[10] to evaluate plaque.

I added this criterion because only three studies did not use this index, but instead used the plaque index (PI).[11] Studies that used the PI to evaluate plaque were included in the evaluation of gingival inflammation.

To be included in the evaluation of gingival inflammation the study had to use the gingival index (GI)[12] or the modified gingival index (MGI).[13] There were too few studies that used the same bleeding index (BI) to use that index as an outcome measure. However, if the study used only a BI, it still was included in the plaque evaluation as long as the investigators used the Turesky modification of the Quigley-Hein Index to evaluate plaque.

- the sample size of the study groups had to be specified.

We found a total of 80 full-length published and unpublished reports that evaluated the antiplaque and antigingivitis effects of mouthrinses and dentifrices in six-month trials. This included 53 published reports and 27 unpublished research reports. Nine of the studies included both a published report and an unpublished research report. Three of the reports from manufacturers had significant problems with regard to protocol violations (in one case, the examiner became ill in the middle of the study) and/or recorded only partial mouth measurements; I excluded these studies from the meta-analysis. An additional 27 reports were eliminated because they evaluated agents that are no longer being manufactured and/or evaluated agents about which there were too few studies to analyze.

We found a total of 50 articles and/or reports that met the inclusion criteria.[14-51] Because some of these studies compared multiple products with placebo groups, there were a total of 70 active groups in these studies. Two reports were unpublished reports that were identified to the plaque subcommittee formed by the FDA to evaluate over-the-counter agents, 13 were unpublished reports that were provided by manufacturers and 36 were published articles (nine of these studies also had unpublished research reports). We abstracted the studies that met these criteria for outcome variables (PI, GI), sample size, blinding, randomization, agent types and formulations, and types of controls.

Data analysis. I performed separate analyses of efficacy for each of the active agents. I first evaluated the data for heterogeneity (a statistical test for consistency among study results). A random-effects model was used to evaluate the overall efficacy of the data[52,53] when heterogeneity was present. I also noted statistically significant heterogeneity when present. Because unpublished research reports were included in the analysis, I compared published and unpublished results. However, I found a sufficient number of published and unpublished reports only for the evaluation of essential oils to enable me to make this comparison. I noted no differences in the results between the published and unpublished studies.

As noted above, some studies had multiple active arms of either similar or dissimilar agents. Data for the arms were entered and analyzed as though they were separate studies. I analyzed the data both with and without these multiple-arm studies, and the findings remained unchanged.

RESULTS

Antiplaque effect of dentifrices. Forty-seven (94 percent) of the 50 studies used the Turesky modification of the Quigley-Hein Index, and I limited my analysis of the antiplaque efficacy to these studies. (The other three studies used the PI.) Owing to the large number of studies that had plaque data, I divided the forest plots presenting the plaque results into studies that evaluated dentifrices (29 active arms) and studies that evaluated mouthrinses (38 active arms) (data available online). (Forest plots are a graphical representation of the effect of an active agent over a control agent for all of the studies included in a systematic review.)

Stannous fluoride. The dentifrices containing stannous fluoride (four published studies[21-24] and one unpublished study [M.E. Mallatt and colleagues, 2005, unpublished data]) exhibited a statistically significant, but small antiplaque effect (mean standardized difference [Std. Diff.] between groups = 0.168). (A mean standardized difference is a mean difference in the active agent's effect minus the control agent's effect adjusted by the variability of each study. This standardization accounts for the difference in variability among multiple studies.)

Triclosan/copolymer. In contrast, the dentifrice composed of 0.30 percent triclosan, 2.0 percent Gantrez copolymer exhibited significant results for 14 of the 18 arms (representing 17 studies) and a substantially larger effect (Std. Diff. = 0.823). Because there was statistically significant heterogeneity, I used the random effects model to evaluate the efficacy of the agent. The overall analysis of the efficacy of the triclosan/copolymer agent using a random-effects model resulted in a highly significant ($P < .0001$) mean group difference that favored the active agent.

Triclosan/soluble pyrophosphate. Although studies of dentifrices containing the triclosan/soluble pyrophosphate agent resulted in marginally statistically significant results, the test for heterogeneity also was significant. The studies were inconsistent, however, because three of the four resulted in nonsignificant results and, thus, did not provide sufficient evidence that this is an effective antiplaque agent.

Triclosan/zinc citrate. The triclosan/zinc citrate agent also resulted in a nonsignificant result.

Of the dentifrices evaluated, then, only those containing the triclosan-copolymer agent showed both a clinically significant and a statistically significant antiplaque effect.

Antiplaque effect of mouthrinses. In this meta-analysis, I evaluated the antiplaque efficacy of three active agents in mouthrinses: 0.12 percent chlorhexidine, CPC and essential oils.

Chlorhexidine. The 0.12 percent chlorhexidine mouthrinse had a consistent antiplaque effect (Std. Diff. = 1.040), and the results of all studies were statistically significant.

CPC. In the efficacy analysis of CPC, four[14-16] (V. Segreto and E. Collins, 1993, unpublished data) of the seven studies exhibited statistical sig-

nificance and three did not (S.G. Ciancio, 1979, unpublished data; R.R. Lobene, 1977, unpublished data; and Menaker and colleagues, 1986, unpublished data). The test for heterogeneity was statistically significant. I should point out that the products evaluated in the studies also varied (Cepacol Antibacterial Mouthwash, Combe, White Plains, N.Y., containing 0.05 percent CPC [Ciancio, 1979, unpublished data; Lobene, unpublished data, 1977]; Scope Mouthwash, Procter & Gamble, Cincinnati, containing 0.045 percent CPC [L. Menaker and colleagues, 1986, unpublished data]; a 0.05 percent CPC–containing mouthrinse[14] [Segreto and Collins, 1993, unpublished data]; and two mouthrinses containing 0.07 percent CPC, one with an alcohol vehicle[15] and one without alcohol[16]). Thus, there was a great deal of heterogeneity in both the CPC agents evaluated and in the results obtained, with some of the agents exhibiting antiplaque effects and some not exhibiting these effects.

Essential oils. The majority of the studies (20 studies, 25 arms) evaluated mouthrinses containing essential oils. Of these studies, only one failed to show statistical significance. Although the test for heterogeneity was positive, the study results clearly support the antiplaque efficacy of the essential oils (Std. Diff. = 0.852, $P < .0001$).

Antigingivitis effects. In the analysis of gingivitis, I found more variety with regard to the index used than I did with regard to the index used to evaluate plaque. Two studies reported using only a BI, and a few used a BI and a GI. However, the number of studies that used a BI was insufficient for analysis. The remaining studies used either the GI[21] or the MGI[11] to evaluate gingivitis. Table 1 presents the results for all agents that were evaluated with the GI (33 studies, 45 active arms), and Table 2 (page 1654) presents the results for agents evaluated with the MGI (17 studies, 22 active arms).

The gingivitis results using the GI (Table 1) were similar to the antiplaque results, except with regard to the antigingivitis evaluation of the stannous fluoride dentifrice. The results were statistically significant and clinically significant with regard to the efficacy of the 0.12 percent chlorhexidine mouthrinse (Std. Diff. = 0.563), mouthrinse containing essential oils (Std. Diff. = 0.306) and dentifrice containing triclosan with 2.0 percent Gantrez copolymer (Std. Diff. = 0.858). The antigingivitis results for the stannous fluoride dentifrice (Std. Diff. = 0.441) also were statistically significant and clinically significant, although the antiplaque effect for this dentifrice was neither statistically significant (owing to heterogeneity) nor clinically significant.

Significant heterogeneity was present in the analysis of antigingivitis effects for 0.12 percent chlorhexidine ($P = .013$), essential oils ($P < .001$), stannous fluoride dentifrice ($P = .010$), CPC ($P = .004$) and triclosan with 2.0 percent Gantrez copolymer ($P < .001$). I found the most consistent results for the 0.12 percent chlorhexidine mouthrinse (five of the six active arms demonstrated statistically significant effects) and for the triclosan with 2.0 percent Gantrez copolymer dentifrice (12 of the 16 arms demonstrated statistically significant effects). Thus, the evidence was consistent and strong in support of the antigingivitis effects of these agents.

The analysis showed moderately consistent results with regard to the antigingivitis effects for mouthrinses containing essential oils and for stannous fluoride dentifrices; the results of one-half of the studies were statistically significant for each agent, but all of the studies demonstrated antigingivitis effects. Similar to the evaluation of the antiplaque effects of mouthrinses containing CPC, I found both statistical heterogeneity and a variety of formulations evaluated; thus, it was difficult to reach conclusions about this agent, although the results of studies of individual CPC products were similar to those for other types of active agents.

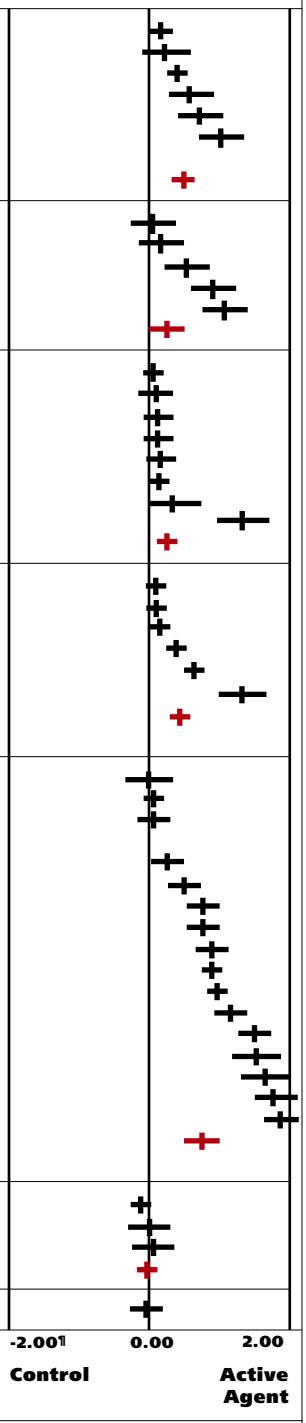
Researchers used the MGI primarily in studies evaluating essential oil–containing mouthrinses (Table 2). Thirteen of the 17 studies[18-20,30,45,48] (S. Mankodi and colleagues, 1993, two arms, unpublished data; S. Mankodi and colleagues, 1989, two arms, unpublished data; N. Sharma and colleagues, two arms, 1997, unpublished data; K. Bauroth and colleagues, 2004, unpublished data) had statistically significant results with regard to the antigingivitis properties of essential oil–containing products compared with the control agents. Again, there was significant heterogeneity ($P < .0001$) for the comparison. However, all of the studies favored the essential oil–containing mouthrinse over the control mouthrinse (Std. Diff. = 0.762). Thus, this evaluation by the MGI provides strong evidence in support of the antigingivitis properties of essential oil–containing mouthrinses.

Few studies evaluated the relative efficacy of

TABLE 1

Analysis of six-month gingivitis data evaluated with the gingival index.

ACTIVE AGENT	STUDY	*P* VALUE	STANDARD DIFFERENCE IN MEANS AND 95% CI*
0.12 Percent Chlorhexidine	Grossman and colleagues,[43] 1989	.037	
	Flemmig and colleagues,[49] 1990	.180	
	Grossman and colleagues,[44] 1986	.000†	
	Segreto and Collins, 1993‡	.001	
	Charles and colleagues,[42] 2004	.000	
	Stookey and colleagues,[15] 2005	.000	
Summary of 0.12 Percent Chlorhexidine	—	.000	
Cetylpyridinium Chloride	Ciancio, 1979‡	.648	
	Lobene, 1977‡	.532	
	Segreto and Collins, 1993‡	.009	
	Stookey and colleagues,[15] 2005	.000	
	Allen and colleagues,[14] 1998	.000	
Summary of Cetylpyridinium Chloride	—	.003	
Essential Oils	Grossman and colleagues,[43] 1989	.514	
	Gordon and colleagues,[46] 1985	.669	
	Hurley and colleagues, 1991‡	.320	
	Segreto and Collins, 1993‡	.295	
	Menaker and colleagues, 1981‡	.386	
	Beiswanger and colleagues,[50] 1997	.046	
	Charles and colleagues,[42] 2004	.036	
	Lamster,[47] 1983	.000	
Summary of Essential Oils	—	.006	
Stannous Fluoride Dentifrice	Beiswanger and colleagues,[51] 1995	.256	
	Beiswanger and colleagues,[51] 1995	.237	
	Perlich and colleagues,[21] 1995	.009	
	Beiswanger and colleagues,[50] 1997	.000	
	Mankodi and colleagues,[23] 1997	.000	
	McClanahan and colleagues,[22] 1997	.000	
Summary of Stannous Fluoride Dentifrice	—	.000	
Triclosan, 2.0 Percent Gantrez Copolymer	Winston and colleagues,[25] 2002	.923	
	McClanahan and colleagues,[22] 1997	.618	
	Kanchanakamol and colleagues,[31] 1995	.755	
	Cubells and colleagues,[37] 1991	.207	
	Palomo and colleagues,[26] 1994	.010	
	Hu and colleagues,[38] 1997	.000	
	Deasy and colleagues,[36] 1991	.000	
	Denepitiya and colleagues,[32] 1992	.000	
	Lindhe and colleagues,[33] 1993	.000	
	Allen and colleagues,[35] 2002	.000	
	Bolden and colleagues,[29] 1992	.000	
	Mankodi and colleagues,[27] 1992	.000	
	Triratana and colleagues,[39] 2002	.000	
	Garcia-Godoy and colleagues,[40] 1990	.000	
	Allen and colleagues,[35] 2002	.000	
	Mankodi and colleagues,[34] 2002	.000	
Summary of Triclosan, 2.0 Percent Gantrez Copolymer	—	.000	
Triclosan Pyrophosphate	Grossman and colleagues,[41] 2002	.448	
	Palomo and colleagues,[26] 1994	1.000§	
	Winston and colleagues,[25] 2002	.866	
Summary of Triclosan Pyrophosphate	—	.647	
Triclosan Zinc Citrate	Palomo and colleagues,[26] 1994	.653	

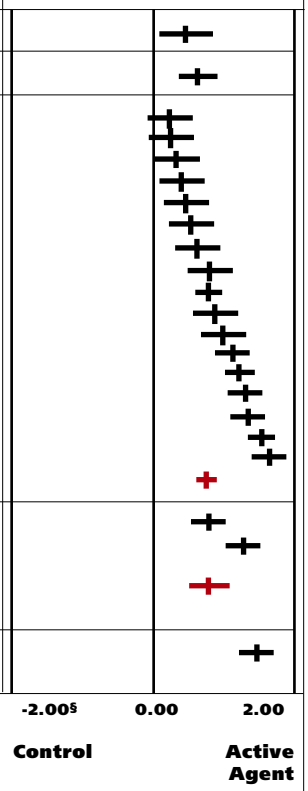


* CI: Confidence interval.
† *P* values shown as .000 are approximate.
‡ Unpublished data (see text for complete information).
§ *P* value shown as 1.000 is approximate.
¶ The numbers represent the standardized mean effect (active agent minus control divided by the standard deviation), which is the relative strength of the active agent.

TABLE 2

Analysis of six-month gingivitis data evaluated with the modified gingival index.

ACTIVE AGENT	STUDY	*P* VALUE	STANDARD DIFFERENCE IN MEANS AND 95% CI*
0.12 Percent Chlorhexidine	Overholser and colleagues,[45] 1990	.007	
Cetylpyridinium Chloride	Mankodi and colleagues,[16] 2005	.000†	
Essential Oils	Overholser and colleagues, 1992‡	.184	
	Mankodi and colleagues, 1991‡	.168	
	Overholser and colleagues, 1992‡	.116	
	Mankodi and colleagues, 1991‡	.093	
	Mankodi and colleagues, 1993‡	.017	
	Mankodi and colleagues, 1993‡	.003	
	Mankodi and colleagues, 1989‡	.004	
	Mankodi and colleagues, 1989‡	.003	
	Bauroth and colleagues,[18] 2003	.000	
	Overholser and colleagues,[45] 1990	.001	
	DePaola and colleagues,[48] 1989	.000	
	Sharma and colleagues, 1997‡	.000	
	Bauroth and colleagues, 2004‡	.000	
	Sharma and colleagues,[19] 2004	.000	
	Sharma and colleagues, 1997‡	.000	
	Sharma and colleagues,[20] 2002	.000	
	Charles and colleagues,[30] 2001	.000	
Summary of Essential Oils	—	.000	
Stannous Fluoride Dentifrice	Mallatt and colleagues, 2005‡	.000	
	Mankodi,[23] 1997	.000	
Summary of Stannous Fluoride Dentifrice	—	.000	
Triclosan, 2.0 Percent Gantrez Copolymer	Charles and colleagues,[30] 2001	.000	



* CI: Confidence interval.
† *P* values shown as .000 are approximate.
‡ Unpublished data (see text for complete information).
§ The numbers represent the standardized mean effect (active agent minus control divided by the standard deviation), which is the relative strength of the active agent.

the different agents described above. Four studies[42,43,45] (Segreto and Collins, 1993, unpublished data) compared mouthrinses containing essential oils with chlorhexidine mouthrinses. The studies compared active agents with control agents, as well as with each other. The results showed statistically significant antiplaque effects for both agents in all four studies. In all cases, 0.12 percent chlorhexidine exhibited greater antiplaque effects than did mouthrinses containing essential oils (the effect for essential oils was about 60 percent of that for the 0.12 percent chlorhexidine mouthrinse).

The results were similar for gingivitis. The four studies showed a statistically significant advantage for the active agents over the control agents. Mouthrinses containing essential oils had about 60 percent of the antigingivitis effect of 0.12 percent chlorhexidine; however, the difference in antigingivitis effects of the agents was close to, but failed to reach, statistical significance ($P = .068$). There were too few head-to-head comparisons of the other active agents (two or fewer) to evaluate.

DISCUSSION

The goal of this meta-analysis was to evaluate the efficacy of antiplaque, antigingivitis agents, as demonstrated in six-month clinical trials. I found a surprisingly large number of studies that supported the efficacy of these products. Dentifrices containing triclosan and the copolymer 2.0 percent Gantrez demonstrated both antiplaque and antigingivitis effects in 18 studies. This is consistent with a previous meta-analysis[9] that had similar findings. Furthermore, it is apparent that the

copolymer 2.0 percent Gantrez is a necessary element for this agent to work, as the formulations containing triclosan alone did not exhibit similar efficacy.

The largest number of studies of mouthrinses evaluated essential oils (22 studies, four with two active arms). These studies show clearly that this agent is effective as both an antiplaque and an antigingivitis agent. Six studies evaluated the 0.12 percent chlorhexidine mouthrinse, and the results of these were remarkably consistent. The results were inconsistent for products containing CPC; however, the concentrations of CPC varied from 4.5 to 7 percent. In addition, the two studies that evaluated the 7 percent concentration involved formulations that were alcohol-based[15] or nonalcohol-based.[16] While the six-month results were promising for the nonalcohol-based agent, more long-term studies are needed to provide the same level of evidence that exists for the other agents.

The goal of antiplaque, antigingivitis agents is to decrease gingival inflammation so that destructive periodontal disease will not develop. The evidence demonstrates clearly that mouthrinses containing 0.12 percent chlorhexidine or essential oils and dentifrices containing triclosan with 2.0 percent Gantrez copolymer or stannous fluoride reduce the level of gingival inflammation. It is not clear, however, what level of reduction is necessary to decrease or prevent periodontal disease. However, gingival inflammation is a necessary, but insufficient, condition for the initiation and progression of periodontal disease. Therefore, reducing gingival inflammation with these agents is highly desirable. More studies are needed to determine if the level of reduction of gingival inflammation produced by these agents is sufficient to prevent, or slow the progress of, periodontal disease.

Dentifrices with stannous fluoride demonstrated a statistically significant antiplaque effect, but most likely not a clinically significant effect, because the effect was much smaller than that of the other agents. These results suggest that the main mechanism of action in stannous fluoride agents is not in the suppression of plaque mass, but in altering the ability of the plaque to affect the levels of gingivitis. Bacca and colleagues[17] suggested that the efficacy of stannous fluoride in reducing gingivitis is due to its alteration of the virulence and effects of the plaque composition, not to the overall quantity of plaque.

Recent studies have evaluated chemotherapeutic agents in relationship to mechanical plaque control. The researchers compared the efficacy of an essential oil–containing mouthrinse with that of flossing.[18-20] Two of the studies[18,20] demonstrated that the chemotherapeutic control of interproximal plaque and gingivitis by an essential oil–containing mouthrinse met or exceeded the interproximal control of flossing. The third study[19] demonstrated that an essential oil–containing mouthrinse adds to the interproximal control of plaque and gingivitis achieved with flossing alone. In concert with the results of this review, there is strong evidence[18-20] of the benefit of using chemotherapeutic agents in addition to mechanical methods of brushing and flossing in adults to control plaque and gingivitis. Adding one chemotherapeutic agent to the typical oral hygiene regimen will reduce the level of gingival inflammation in these patients.[18-20] The most likely benefit is the prevention and/or reduction of periodontal disease, but further studies are needed to demonstrate that use of these agents will result in a lower prevalence and severity of periodontal disease.

One of the goals in reporting a series of studies that evaluate the efficacy of an agent is to determine the factors that influence study outcomes. I evaluated the studies in this meta-analysis to determine which factors might account for the difference between placebo effects and active agent effects. I evaluated the following factors: baseline plaque and gingivitis levels and the level of supervision (that is, whether subjects were supervised on a daily basis in their use of the assigned product) provided for the study agents. I could find no relationship between baseline plaque and/or gingivitis levels and the efficacy of the agents.

The only factor that influenced the outcomes of these studies was the use of different gingival indexes. In evaluating the efficacy of essential oil–containing mouthrinses (the data were insufficient for the other agents to make this comparison), I found that the MGI resulted in a larger difference between the effects of the placebo and those of the active agents than did the GI. The MGI has a wider scale (0-4) than the GI (0-3). It appears that the additional category helps in the identification of antigingivitis effects. These results suggest that supervision in the use of these agents is not necessary in these types of studies, but use of the MGI will improve

researchers' ability to show differences between active and placebo agents.

CONCLUSION

This systematic review provides strong evidence that antiplaque, antigingivitis agents are efficacious. Coupled with reports showing that the relative efficacy of these agents is similar to that of flossing, these results suggest that for optimum gingival health, adults should add an antiplaque, antigingivitis agent to their oral hygiene regimen. ■

Readers interested in additional detailed information regarding this meta-analysis may access it via the Supplemental Data link in the online version of this article on the JADA Web site ("http://jada.ada.org").

The author thanks Procter & Gamble and Pfizer for providing unpublished research reports.

The author thanks Ms. Patricia Sweeney for helping with the MEDLINE searches and reviewing and extracting information from the articles used in this systematic review.

The following research reports are unpublished data. They are designated in the tables with double dagger symbols.

Bauroth K, Goyal, Charles CH. Efficacy of FreshBurst mouthrinse and Listerine antiseptic compared to a hydroalcohol control in inhibiting the development of supragingival dental plaque and gingivitis. Morris Plains, N.J.: Pfizer; 2004. Research report 6361003:1-25.

Ciancio SG. Effect of Cepacol on gingivitis and supragingival plaque. Cincinnati: Merrell Dow Pharmaceuticals. Submitted to U.S. Food and Drug Administration Plaque Subcommittee; 1979:548-57.

Hurley R, Silver J, Charles CH, Hovliaras CA. Effect of Listerine antiseptic compared to a hydroalcohol control in Inhibiting the development of dental plaque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1991. Research report 931-0849, study number 931-825:1-50.

Lobene RR. Effect of Cepacol on gingivitis and supragingival plaque. Merrell Dow Pharmaceuticals. Submitted to U.S. Food and Drug Administration Plaque Subcommittee; 1977:519-27.

Mallatt ME, He T, Walters P, Bartizek R, Decourney M. Anti-gingivitis efficacy of a stabilized 0.454 percent stannous fluoride dentrifrice: a controlled 6-month clinical trial (research report on file). Cincinnati: Procter & Gamble; 2005. Study number 2003146:1-26.

Mankodi S, Besselaar, Vincent JW, Hovliaras CA. Comparative efficacies of LIsterine minus methyl salcylate, Listerine antiseptic and a vehicle control in inhibiting the development of supragingical dental plaque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1993. Research report 931-0902, study number 931-939:1-30.

Mankodi S, Hovliaras CA, Kohut B. Efficacy of Cool Mint Listerine and Listerine antiseptic compared to a hydroalcohol control in inhibiting the development of supragingival dental plque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1991. Research report 931-0866, study number 931-838:1-20.

Mankodi S, Ross NM, Charles CH. Efficacy of Listerine and Listerine Plus Mint in inhibiting the development of dental plaque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1989. Research report 931-0780.

Menaker L, Ross NM. Efficacy of Listerine antiseptic and control for inhibiting the development of dental plaque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1981. Research report 931-135, study number 931-014:1-17.

Menaker L, Ross NM, Olshan AM. Efficacy of Listerine antiseptic compared to Scope and a hydroalcohol control (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1986. Research report 931-0649, study number 931-453:1-15.

Overholser CD, Charles CH, Vincent JW. Efficacy of Listerine minus methyl salicylate and Listerine antiseptic compared to a vehicle control in inhibiting the development of supragingival dental plaque and gingivitis (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1992. Research report 931-0899, study number 931-938:1-26.

Segreto V, Collins E. A clinical investigation to assess the effects on plaque, gingivitis, and staining potential of an experimental mouthrinse (research report on file). Cincinnati: Procter & Gamble; 1993. Study number 002392:1-27.

Sharma N, Charles CH, Vincent JW. Efficacy of a reduced alcohol Listerine mouthrinse in inhibiting the developement of supragingival dental plaque and gingivitis when used as an adjunct to usual oral hygiene for 6 months (research report on file). Morris Plains, N.J.: Warner-Lambert (Pfizer); 1997. Research report 931-1054, study number 931-1176):1-14.

1. Addy M, Willis L, Moran J. Effect of toothpaste rinses compared with chlorhexidine on plaque formation during a 4-day period. J Clin Periodontol 1983;10(1):89-99.
2. Addy M, Moran J. The effect of a cetylpyridinium chloride (CPC) detergent foam compared to a conventional toothpaste on plaque and gingivitis: a single blind crossover study. J Clin Periodontol 1989;16(2):87-91.
3. Addy M, Jenkins S, Newcombe R. Studies on the effect of toothpaste rinses on plaque regrowth, part I: influence of surfactants on chlorhexidine efficacy. J Clin Periodontol 1989;16(6):380-4.
4. Addy M, Jenkins S, Newcombe R. The effect of triclosan, stannous fluoride and chlorhexidine products on (I): plaque regrowth over a 4-day period. J Clin Periodontol 1990;17(10):693-7.
5. Addy M, Renton-Harper P, Newcombe R. Plaque regrowth studies: discriminatory power of plaque index compared to plaque area. J Clin Periodontol 1999;26(2):110-2.
6. Löe H, Theilade E, Jensen SB, Schiott CR. Experimental gingivitis in man, part 3: influence of antibiotics on gingival plaque development. J Periodontal Res 1967;2(4):282-9.
7. Council on Dental Therapeutics. Guidelines for acceptance of chemotherapeutic products for the control of supragingival dental plaque and gingivitis. JADA 1986;112(4):529-32.
8. American Dental Association. Chemotherapeutic products for the control of gingivitis. Chicago: American Dental Association Council on Dental Therapeutics; 1997.
9. Davies RM, Ellwood RP, Davies GM. The effectiveness of a toothpaste containing triclosan and polyvinyl-methyl ether maleic acid copolymer in improving plaque control and gingival health: a systematic review. J Clin Periodontol 2004;31(12):1029-33.
10. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of victamine C. J Periodontol 1970;41(1):41-3.
11. Silness J, Löe H. Periodontal disease in pregnancy, part 3: response to local treatment 197. Acta Odontol Scand 1966;24(6):747-59.
12. Löe H, Silness J. Periodontal disease in pregnancy, I: prevalence and severity. Acta Odontol Scand 1963;21:533-51.
13. Lobene RR, Weatherford T, Ross NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clin Prev Dent 1986;8(1):3-6.
14. Allen DR, Davies R, Bradshaw B, et al. Efficacy of a mouthrinse containing 0.05 percent cetylpyridinium chloride for the control of plaque and gingivitis: a 6-month clinical study in adults. Compend Contin Educ Dent 1998;19(supplement 2):20-6.
15. Stookey GK, Beiswanger B, Mau M, Isaacs RL, Witt JJ, Gibb R. A 6-month clinical study assessing the safety and efficacy of two cetylpyridinium chloride mouthrinses. Am J Dent 2005;18(special number):24A-28A.
16. Mankodi S, Bauroth K, Witt JJ, et al. A 6-month clinical trial to study the effects of a cetylpyridinium chloride mouthrinse on gingivitis and plaque. Am J Dent 2005;18(special number):9A-14A.
17. Bacca LA, Leusch M, Lanzalaco AC, et al. A comparison of intra-oral antimicrobial effects of stabilized stannous fluoride dentifrice, baking soda/peroxide dentifrice, conventional NaF dentifrice and essential oil mouthrinse. J Clin Dent 1997;8(special number 2):54-61.
18. Bauroth K, Charles CH, Mankodi SM, Simmons K, Zhao Q, Kumar LD. The efficacy of an essential oil antiseptic mouthrinse vs. dental floss in controlling interproximal gingivitis: a comparative study

(published correction appears in JADA 2003;134[5]:558). JADA 2003;134(3):359-65.
19. Sharma N, Charles CH, Lynch MC, et al. Adjunctive benefit of an essential oil–containing mouthrinse in reducing plaque and gingivitis in patients who brush and floss regularly: a six-month study. JADA 2004;135(4):496-504.
20. Sharma NC, Charles CH, Qaqish JG, Galustians HJ, Zhao Q, Kumar LD. Comparative effectiveness of an essential oil mouthrinse and dental floss in controlling interproximal gingivitis and plaque. Am J Dent 2002;15(6):351-5.
21. Perlich MA, Bacca LA, Bollmer BW, et al. The clinical effect of a stabilized stannous fluoride dentifrice on plaque formation, gingivitis and gingival bleeding: a six-month study. J Clin Dent 1995;6(special number):54-8.
22. McClanahan SF, Beiswanger BB, Bartizek RD, Lanzalaco AC, Bacca L, White DJ. A comparison of stabilized stannous fluoride dentifrice and triclosan/copolymer dentifrice for efficacy in the reduction of gingivitis and gingival bleeding: six-month clinical results. J Clin Dent 1997;8(special number 2):39-45.
23. Mankodi S, Petrone DM, Battista G, et al. Clinical efficacy of an optimized stannous fluoride dentifrice, part 2: a 6-month plaque/gingivitis clinical study, northeast USA. Compend Contin Educ Dent 1997;18(special number):10-5.
24. Mankodi S, Bartizek RD, Winston JL, Biesbrock AR, McClanahan SF, He T. Anti-gingivitis efficacy of a stabilized 0.454 percent stannous fluoride/sodium hexametaphosphate dentifrice. J Clin Periodontol 2005;32(1):75-80.
25. Winston JL, Bartizek RD, McClanahan SF, Mau MS, Beiswanger BB. A clinical methods study of the effects of triclosan dentifrices on gingivitis over six months. J Clin Dent 2002;13(6):240-8.
26. Palomo F, Wantland L, Sanchez A, Volpe AR, McCool J, DeVizio W. The effect of three commercially available dentifrices containing triclosan on supragingival plaque formation and gingivitis: a six month clinical study. Int Dent J 1994;44(1 supplement 1):75-81.
27. Mankodi S, Walker C, Conforti N, DeVizio W, McCool JJ, Volpe AR. Clinical effect of a triclosan-containing dentifrice on plaque and gingivitis: a six-month study. Clin Prev Dent 1992;14(6):4-10.
28. Renvert S, Birkhed D. Comparison between 3 triclosan dentifrices on plaque, gingivitis and salivary microflora. J Clin Periodontol 1995;22(1):63-70.
29. Bolden TE, Zambon JJ, Sowinski J, et al. The clinical effect of a dentifrice containing triclosan and a copolymer in a sodium fluoride/silica base on plaque formation and gingivitis: a six-month clinical study. J Clin Dent 1992;3(4):125-31.
30. Charles CH, Sharma NC, Galustians HJ, Qaqish J, McGuire JA, Vincent JW. Comparative efficacy of an antiseptic mouthrinse and an antiplaque/antigingivitis dentifrice: a six-month clinical trial. JADA 2001;132(5):670-5.
31. Kanchanakamol U, Umpriwan R, Jotikasthira N, et al. Reduction of plaque formation and gingivitis by a dentifrice containing triclosan and copolymer. J Periodontol 1995;66(2):109-12.
32. Denepitiya JL, Fine D, Singh S, DeVizio W, Volpe AR, Person P. Effect upon plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: a 6-month clinical study. Am J Dent 1992;5(6):307-11.
33. Lindhe J, Rosling B, Socransky SS, Volpe AR. The effect of a triclosan-containing dentifrice on established plaque and gingivitis. J Clin Periodontol 1993;20(5):327-34.
34. Mankodi S, Lopez M, Smith I, et al. Comparison of two dentifrices with respect to efficacy for the control of plaque and gingivitis, and with respect to extrinsic tooth staining: a six-month clinical study on adults. J Clin Dent 2002;13(6):228-33.
35. Allen DR, Battista GW, Petrone DM, et al. The clinical efficacy of Colgate Total Plus Whitening Toothpaste containing a special grade of silica and Colgate Total Fresh Stripe Toothpaste in the control of plaque and gingivitis: a six-month clinical study. J Clin Dent 2002;13(2):59-64.
36. Deasy MJ, Singh SM, Rustogi KN, et al. Effect of a dentifrice containing triclosan and a copolymer on plaque formation and gingivitis. Clin Prev Dent 1991;13(6):12-9.
37. Cubells AB, Dalmau LB, Petrone ME, Chaknis P, Volpe AR. The effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: a six-month clinical study. J Clin Dent 1991;2(3):63-9.
38. Hu D, Zhang J, Wan H, Zhang Y, Volpe AR, Petrone ME. Efficacy of a triclosan/copolymer dentifrice in the control of plaque and gingivitis: a six-month study in China [in Chinese]. Hua Xi Kou Qiang Yi Xue Za Zhi 1997;15(4):333-5.
39. Triratana T, Rustogi KN, Volpe AR, DeVizio W, Petrone M, Giniger M. Clinical effect of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. JADA 2002;133(2):219-25.
40. Garcia-Godoy F, Garcia-Godoy F, DeVizio W, Volpe AR, Ferlauto RJ, Miller JM. Effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: a 7-month clinical study (published correction in Am J Dent 1991;4[2]:102). Am J Dent 1990;3(special number):S15-S26.
41. Grossman E, Hou L, Bollmer BW, et al. Triclosan/pyrophosphate dentifrice: dental plaque and gingivitis effects in a 6-month randomized controlled clinical study. J Clin Dent 2002;13(4):149-57.
42. Charles CH, Mostler KM, Bartels LL, Mankodi SM. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. J Clin Periodontol 2004;31(10):878-84.
43. Grossman E, Meckel AH, Isaacs RL, et al. A clinical comparison of antibacterial mouthrinses: effects of chlorhexidine, phenolics, and sanguinarine on dental plaque and gingivitis. J Periodontol 1989;60(8):435-40.
44. Grossman E, Rijn G, Sturzenberger OP, et al. Six-month study of the effects of a chlorhexidine mouthrinse on gingivitis in adults. J Periodont Res 1986 (supplement):33-43.
45. Overholser CD, Meiller TF, DePaola LG, Minah GE, Niehaus C. Comparative effects of 2 chemotherapeutic mouthrinses on the development of supragingival dental plaque and gingivitis. J Clin Periodontol 1990;17(8):575-9.
46. Gordon JM, Lamster IB, Seiger MC. Efficacy of Listerine antiseptic in inhibiting the development of plaque and gingivitis. J Clin Periodontol 1985;12(8):697-704.
47. Lamster IB. The effect of Listerine antiseptic on reduction of existing plaque and gingivitis. Clin Prev Dent 1983;5:12-6.
48. DePaola LG, Overholser CD, Meiller TF, Minah GE, Niehaus C. Chemotherapeutic inhibition of supragingival dental plaque and gingivitis development. J Clin Periodontol 1989;16(5):311-5.
49. Flemmig TF, Newman MG, Doherty FM, Grossman E, Meckel AH, Bakdash MB. Supragingival irrigation with 0.06 percent chlorhexidine in naturally occurring gingivitis, part I: six month clinical observations. J Periodontol 1990;61(2):112-7.
50. Beiswanger BB, McClanahan SF, Bartizek RD, Lanzalaco AC, Bacca LA, White DJ. The comparative efficacy of stabilized stannous fluoride dentifrice, peroxide/baking soda dentifrice and essential oil mouthrinse for the prevention of gingivitis. J Clin Dent 1997;8(special number 2):46-53.
51. Beiswanger BB, Doyle PM, Jackson RD, et al. The clinical effect of dentifrices containing stabilized stannous fluoride on plaque formation and gingivitis: a six-month study with ad libitum brushing. J Clin Dent 1995;6(special number):46-53.
52. Hedges L. Estimation of effect size under non random sampling: the effects of censoring studies yielding statistically mean differences. J Educ Stat 1984;9:61-85.
53. Hedges L, Vevea J. Estimating effects size under publication bias: small sample properties and robustness of a random effects selection model. J Educ Behav Stat 1996;21:299-333.