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Meta-analyses of studies of 0.2% delmopinol mouth rinse as an adjunct to gingival health and plaque control measures

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Abstract

Background: Delmopinol is a third-generation anti-plaque agent used as a mouthwash to reduce plaque and alleviate gingivitis.

Objective: To create an overview of the anti-plaque efficacy of 0.2% delmopinol as an adjunct to normal oral hygiene measures by meta-analysis of completed clinical trials.

Materials and Methods: Eight double-blind, parallel-group studies were identified. Study durations ranged from 8 to 24 weeks. Five studies ($n = 913$) involved supervised rinsing; three studies ($n = 467$) involved unsupervised rinsing. These sets of trials were analysed separately and in combination. Efficacy outcomes comprised modified plaque index, modified gingival index (MGI) and gingival bleeding on probing (BOP).

Results: Delmopinol 0.2% was superior to placebo for the reduction of plaque scores in both sets of studies. Effects on MGI and BOP were also better with delmopinol 0.2% than with placebo. In most instances, 95% confidence intervals were wholly in favour of delmopinol. Pooled analysis of all eight studies confirmed statistically significant effects of delmopinol 0.2% compared with placebo ($p < 0.00001$). Delmopinol met the efficacy criteria of the American Dental Association in studies of extended duration.

Conclusion: Delmopinol 0.2% mouthwash is effective as an adjunct measure for reducing plaque burden and indices of gingivitis, whether or not it is used under supervision.

Key words: bleeding; delmopinol; gingivitis; meta-analysis; plaque.

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Use of chemical agents, usually as adjuncts to mechanical cleaning, is an established feature of plaque control and, by extension, gingivitis prevention (for a review, see Addy 2003). From a cost–benefit perspective, the ideal vehicle for delivery of chemical plaque-control agents is toothpaste, but ease of formulation and public preferences have favoured the use of mouth rinses, of which chlorhexidine is probably the best known and most widely used and that represents the standard of comparison for newer agents entering the arena (for reviews, see Jones 1997, Addy 2003).

Chlorhexidine preparations have been available for several decades and have shown proven, and as yet unsurpassed, anti-plaque effectiveness (Löe & Schiott 1970; for a review, see Jones 1997). The conspicuous and intractable tooth staining associated with chlorhexidine use, and other local adverse effects such as dysgeusia, remain barriers to the long-term use of these products (Flotra et al. 1971), however, and alternative agents that offer a more acceptable balance of effectiveness and tolerability continue to be sought.

Most effective anti-plaque chemicals, including chlorhexidine, owe their effectiveness to some combination of bacteriostatic and bactericidal activity, together with persistence of activity (substantivity) in the mouth (Schiott 1972, Jenkins et al. 1988). Third-generation agents have begun to emerge, however, which are characterized by an ability to inhibit or disrupt the formation of plaque while having no demonstrable effect on bacteria. The morpholinoethanol derivative delmopinol is an exemplar of this new category of chemical plaque-control agents. Delmopinol has been shown to inhibit plaque and gingivitis (Collaert et al. 1992, Moran et al. 1992, Hase et al. 1995a, b), despite being almost devoid of bactericidal or bacteriostatic actions in vitro or in vivo (Simonsson et al. 1991a, Attström et al. 1992, Rundegren et al. 1992a). Plaque studies involving delmopinol revealed that the nascent bio-film was loosely adherent (Rundegren et al. 1992b) and that there

was a significant reduction in the proportion of dextran-producing Streptococci (Elworthy et al. 1995). Taken together, these findings suggest that delmopinol may interfere with plaque-matrix formation, reducing the adherence of the primary plaque-forming bacteria or of the successional bacteria (Simonsson et al. 1991b). The effectiveness of delmopinol, coupled with its qualitatively and quantitatively greatly reduced potential for tooth staining compared with chlorhexidine (Lang et al. 1998), makes this compound potentially an attractive alternative to chlorhexidine for plaque control.

Initial encouraging experience with delmopinol led the manufacturer to commission a total of eight adjunctive-use studies involving 0.2% delmopinol mouth rinse. Studies were conducted by seven different and independent research groups in five different European countries. Clinical and microbiological data from some of these studies have been reported (Elworthy et al. 1995, Claydon et al. 1996, Hase et al. 1998a, b, Lang et al. 1998).

The completion of these studies produced a substantial databank appropriate for meta-analysis. In an era of evidence-based dentistry, it was anticipated that using such a pooled analysis might provide fuller perspectives on the effectiveness of delmopinol than can be obtained from individual studies. This paper reports the results of meta-analyses of the effects of 0.2% delmopinol mouth rinse in patients with existing gingivitis.

Table 1. Principal investigators, study centres and study durations for the supervised (S) and unsupervised (US) studies of 0.2% delmopinol

Supervision	Study no.	Principle Investigator	Centre	Duration (Months)
S	90014	N. Lang	University of Bern Switzerland	6
S	89016	A. Hugoson	Institute of Postgraduate Education Jonkoping, Sweden	2
S	89017	A. Bergenholtz	University of Umea Sweden	2
S	90018	R. Attstrom	University of Lund Sweden	6
S	90023	P. Adriaens	University of Brussels Belgium	5
US	90019	N. Claffey	University of Dublin Ireland	3
US	91025	M.Addy	Cardiff Dental School Wales	6
US	91027	D. van Steenberge	University of Leuven Belgium	3

Table 2. Study entry criteria

Inclusion conditions
(1) Age $\geqslant$ 18 years
(2) Minimum of 16 natural teeth without crowns, bridgework or defective dental restorations
(3) Gingivitis, defined as bleeding on probing at $\geqslant$25% of six sites around each tooth (all unsupervised studies and three supervised studies) *or* gingival Silness–Löe index score $\geqslant$2 at $\geqslant$25% of sites (two supervised studies)
(4) Written informed consent
(5) Women of child-bearing potential fully informed of the toxicological status of delmopinol and adequately equipped with contraceptives

Exclusion conditions
(1) Removable partial dentures
(2) Caries with cavities
(3) More than four pockets deeper than 5 mm (excluding distal site of second molar and all third molar sites)
(4) Known hypersensitivity to any study treatment
(5) Drug or alcohol addiction
(6) Severe liver or kidney disease, or severely ill patients with multiple drug requirements
(7) Antibiotic treatment within immediately preceding 6 weeks
(8) Psychiatric disorders
(9) Current and ongoing use of anti-inflammatory or anticholinergic drugs
(10) Pregnancy or pregnancy planned (all unsupervised trials and three supervised trials)
(11) Breast feeding (all unsupervised trials and three supervised trials)

Materials and Methods

Eight randomized, double-blind, parallel-group studies were identified from published papers and manufacturer records for inclusion in the meta-analyses. Five of these studies involved supervised rinsing with delmopinol 0.2%; three involved unsupervised rinsing with delmopinol 0.1% or 0.2%. Details of the principal investigators, study centres and study durations are shown in Table 1. Supervised and unsupervised studies were analysed separately and only data for the 0.2% mouthwash are reported here. The meta-analyses of efficacy were based on data obtained at the end of the 2-month studies and the 3-month point of all the other studies.

Summary details of the participation criteria for subjects in all eight studies are shown in Table 2. Salient procedural aspects of all the trials included baseline quantitation of plaque using the Turesky et al. (1970) modification of the Quigley & Hein (1962) plaque index, and of gingivitis using the modified gingival index (MGI) of Lobene et al. (1986) and/or gingival bleeding on probing (BOP). Methodological details of these evaluations appear in Table 3. Sub- and supra-gingival professional cleaning was administered to all patients in every study after these baseline assessments had been completed.

The treatment schedule required patients to rinse with delmopinol for 60 s in the morning, preferably after breakfast, and again in the evening. In the unsupervised studies, patients were advised to rinse after the evening meal; in the supervised studies, evening rinsing took place within a specified time period but without explicit reference to timing relative to the evening meal. In all studies, patients were instructed to continue with habitual oral hygiene measures and to use their usual toothpaste. Any rinsing undertaken in conjunction with toothbrushing was to be performed after mechanical cleaning.

All weekday mouth rinsing was observed in the supervised studies. Weekend rinsing was not supervised.

The protocols of all the studies were approved by local ethics committees,

Table 3. Study assessment criteria

Assessment criterion	Description
Modified gingival index	Assessed on the buccal and gingival sides of the papillary and marginal units of the adjacent gingiva of all teeth except third molars. Mean value of all measurements used as the variable for analysis
Plaque index	Determined on buccal and lingual surfaces of all teeth. Mean value of all measurements used as the variable for analysis
Gingival bleeding	Bleeding on probing to the bottom of the pocket, assessed on the mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual sites on each tooth using a Florida probe with Michigan 0 tip and a pressure of 25 g. Bleeding sites as a percentage of all sites was used as the variable for analysis

Table 4. Unsupervised studies

Study code	Total number of patients recruited	Sex (M/F)	Age (years); mean (SD)	Intention-to-treat at end of study	In-study protocol violations	Per-protocol at end of study
Delmopinol 0.2% cohort						
90019	156	142/14	22 (4)	156	44	112
91025*	150	56/94	35 (11)	142	41	101
91027	150	60/90	26 (7)	146	37	109
Combined	456	258/198	28 (10)	444	122	322
Placebo cohort						
90019	157	143/14	22 (5)	157	23	134
91025*	150	55/94†	33 (10)†	147	30	117
91027	150	69/80†	26 (6)	147	22	125
Combined	457	267/188‡	27 (9)†	451	75	376

*Claydon et al. (1996)
†One missing value.
‡Two missing values.

and the trials themselves were conducted in accordance with the provisions and principles of the World Medical Assembly Declaration of Helsinki (1964 and later amendments). The quality of the studies was high, judged by criteria applied to other published meta-analyses (Davies et al. 2004).

Statistical methods

Summary and demographic data were derived by pooling data across groups using reconstructed sums and sums of squares.

Treatment effects were quantified through pooled weighted point estimates calculated according to the methods of Hedges & Olkin (1985), and using a fixed-effects model. The 95% confidence interval (CI) for differences between treatments in individual studies was estimated on the assumption of equal standard deviations for every treatment group. The 95% CI for the pooled estimate was derived from the *t*-distribution.

Analyses were undertaken for both the intention-to-treat (ITT) and per-protocol (PP) cohorts, with precedence given to the ITT data. Individual patient data were included in the ITT analysis on the basis of the last observation carried forward. The PP analysis excluded data from all patients judged not to be fully in compliance with the stipulations of the study protocols.

Results

Summary details of the studies are presented in Tables 4 and 5, including study code numbers plus the references for the three studies that have been published. A total of 913 patients were randomized to either delmopinol 0.2% or placebo in the unsupervised studies, whereas 467 patients took part in the supervised studies.

Unsupervised studies

The outcomes of the meta-analyses of the three unsupervised studies for the three study endpoints are summarized in Table 6 for the ITT cohort. The findings confirm that delmopinol 0.2% was superior to placebo for all outcomes evaluated in all three studies, with 95% CIs that in most cases excluded 0 and that showed consistency in direction and magnitude between the results of individual studies and the findings of the meta-analyses.

Plaque scores in patients using delmopinol were on aggregate 0.36 points lower than with placebo (95% CI 0.30, 0.41), with good agreement between the mean improvement in individual trials and the meta-analyses. BOP showed more variability, with study 90019 making a substantial contribution to the overall result of a 2.2% improvement with delmopinol, but both the other studies produced 95% CIs that extended beyond 0. All three studies produced acceptably similar mean improvement scores with delmopinol, and were correspondingly in close agreement with the mean estimates from meta-analyses.

The complementary PP analyses produced qualitatively similar results but with smaller (and thus even more statistically robust) CIs than for the ITT cohort. This difference can be attributed to differences in the numbers of patients contributing data, an issue considered later in this report.

Supervised studies

Summary findings of the meta-analyses for the ITT cohorts of the supervised studies are presented in Table 7. Delmopinol 0.2% was superior to placebo for all outcome measures in all studies, with evidence of good consistency between individual studies and the meta-analyses for the endpoint of plaque. More variability was evident in the individual study results for BOP and MGI, but each was directionally consis-

Table 5. Supervised studies

Study code	Total number of patients recruited	Sex (M/F)	Age (years); Mean (SD)	Intention-to-treat at end of study	In-study protocol violations	Per-protocol at end of study
Delmopinol 0.2% cohort						
90014*	55	47/8	39 (8)	53	7	46
89016	40	20/20	28 (7)	40	2	38
89017	40	40/0	20 (1)	38	2	36
90018†	50	50/0	26 (10)	49	14	35
90023	50	20/30	23 (4)	48	7	41
Combined	235	177/58	28 (10)	228	32	196
Placebo cohort						
90014*	53	47/6	43 (11)	53	4	49
89016	40	20/20	30 (6)	40	1	39
89017	39	39/0	20 (1)	39	3	36
90018†	49	49/0	23 (7)	46	12	34
90023	51	25/26	24 (4)	48	6	42
Combined	232	180/52	28 (11)	226	26	200

*Lang et al. (1998).
†Hase et al. (1998a).

Table 6. Effect of delmopinol 0.2% (D 0.2%) versus placebo (P) on indices of clinical effectiveness in three unsupervised controlled trials (ITT analysis)

Study	Number of patients		Adjusted mean		Mean difference	95% CI	
	D 0.2%	P	D 0.2%	P	P–D	lower	upper
Plaque index (modified Quigley & Hein)							
90019	151	155	1.66	2.01	0.35	0.26	0.44
91025	142	147	1.03	1.32	0.29	0.19	0.39
91027	146	147	1.48	1.90	0.42	0.33	0.51
Pooled	439	449	1.40	1.76	0.36	0.30	0.41
Bleeding on probing (% of all sites)							
90019	151	155	49.2	54.6	5.4	1.9	8.8
91025	140	146	23.4	24.6	1.2	−0.7	3.1
91027	146	147	27.3	28.8	1.5	−0.6	3.5
Pooled	437	448	30.7	32.9	2.2	0.9	3.5
Modified gingival index							
90019	151	155	1.90	2.05	0.15	0.07	0.23
91025	142	147	1.37	1.47	0.10	0.01	0.19
91027	146	147	1.84	1.94	0.10	0.01	0.17
Pooled	439	449	1.73	1.84	0.11	0.07	0.16

tent with the evidence of benefit shown in meta-analysis.

PP analyses were consistent with and supportive of the ITT analyses, with the exception of study 89016, which recorded a very small negative result for BOP (mean difference 0.1 in favour of placebo over delmopinol; 95% CI –4.8, +4.7).

Aggregate estimate of treatment effect

Table 8 presents summary ITT and PP analyses for all three endpoints of the studies based on aggregated data from the eight study reports. Salient aspects of these data are, first, that they confirm the superiority of delmopinol 0.2% over placebo for all three outcomes to an extreme degree of statistical significance ($p < 0.00001$) and, second, that they reveal no sustained heterogeneity of outcome according to whether the use of delmopinol 0.2% was supervised or unsupervised.

Studies of extended duration

Inspection of results for BOP from two supervised studies [90,014 (Lang et al. 1998) and 90,018 (Hase et al. 1998a)] of 6 months' duration indicated that the size of the delmopinol treatment effect on gingivitis exceeded the minimum efficacy criteria of the American Dental Association (ADA; Table 9). Complementary data for gingival crevicular fluid flow from study 90023 (5 months' duration) were supportive of this conclusion ($p = 0.023$). Data from these three studies also indicated a substantive although variable effect of delmopinol on plaque burden (Table 8).

Discussion

There has been a move towards evidence-based medicine in dentistry in recent years, and systematic reviews are now a regular feature of many refereed journals. The present meta-analyses of data from more than 1000 patients confirm the effectiveness of delmopinol 0.2% in the management of plaque and gingivitis when used in conjunction with usual oral hygiene practices. The demonstration that delmopinol 0.2% fulfilled ADA effectiveness criteria is important from a regulatory perspective and provides a useful basis for comparative research. The data examined in this exercise provide no insights into the effectiveness of delmopinol used either without toothpaste or without brushing, but early studies using short-term plaque regrowth and experimental gingivitis models without tooth cleaning have demonstrated efficacy for delmopinol mouth rinses alone (Collaert et al. 1992, Moran et al. 1992, Hase et al. 1995b).

The consistency between the findings of individual studies and meta-analysis is a noteworthy aspect of our results. In the case of the unsupervised studies, the results of almost every trial were indicative of the superiority of delmopinol over placebo for all three of the endpoints examined. Consistency between individual results and pooled estimates

Table 7. Effect of delmopinol 0.2% (D 0.2%) *versus* placebo (P) on indices of clinical effectiveness in five supervised controlled trials (ITT analysis)

Study	Number of patients		Adjusted mean		Mean difference	95% CI	
	D 0.2%	P	D 0.2%	P	P–D	lower	upper
Plaque index (modified Quigley & Hein)							
90014	0	0					
89016	40	40	0.73	1.05	0.32	0.12	0.51
89017	38	39	1.44	1.73	0.29	0.09	0.48
90018	49	46	1.27	1.63	0.36	0.15	0.58
90023	48	48	1.06	1.31	0.25	0.05	0.45
Pooled	175	173	1.13	1.43	0.30	0.20	0.40
Bleeding on probing (% of all sites)							
90014	53	53	23.8	33.0	9.3	2.4	16.2
89016	40	40	29.1	29.4	0.3	−4.4	4.9
89017	38	39	23.2	28.7	5.5	−0.1	11.0
90018	49	46	34.1	38.1	4.0	−0.4	8.4
90023	48	48	35.5	36.1	0.6	−4.4	5.7
Pooled	228	226	29.5	33.1	3.5	1.2	5.9
Modified gingival index							
90014	0	0					
89016	40	40	0.67	0.69	0.02	−0.09	0.13
89017	38	39	0.97	1.10	0.13	−0.13	0.40
90018	49	46	2.07	2.22	0.15	−0.03	0.33
90023	47	48	1.43	1.48	0.05	−0.12	0.21
Pooled	174	173	1.34	1.41	0.07	−0.01	0.16

Table 8. Summary of differences between the effects of delmopinol 0.2% (D 0.2%) and placebo (P) on plaque, bleeding on probing and modified gingival index in three unsupervised and five supervised studies

Endpoint	Number of patients		Adjusted mean		Mean difference	95% CI	
	D 0.2%	P	D 0.2%	P	P–D	lower	upper
ITT							
Plaque	614	622	1.32	1.66	0.34*	0.29	0.39
Bleeding on probing	665	674	32.3	35.1	2.8*	1.6	4.0
Modified gingival index	613	622	1.61	1.71	0.10*	0.06	0.14
Per protocol							
Plaque	472	527	1.29	1.66	0.37*	0.32	0.43
Bleeding on probing	517	576	31.8	35.3	3.5*	2.2	4.8
Modified gingival index	471	527	1.57	1.69	0.12*	0.07	0.16

Estimates derived from aggregation of eight separate datasets for each endpoint.
*$p < 0.00001$.

was likewise apparent in the supervised studies, which also demonstrated the value of meta-analysis in consolidating the experience of individual studies and identifying a robust treatment benefit. Results from the longer-term studies of the type advocated by the ADA (Council on Dental Therapeutics 1985) were consistent with the meta-analyses overall and hence supportive of the findings of the studies of shorter duration. Given that many people who use mouth rinses do so for less than 6 months, this indication of benefit from shorter-term use is a fact of some practical importance.

It should be noted that in both sets of studies, the individual trials were similar in size and thus made proportionately similar contributions to the aggregate analysis. The net results are thus the product of uniformity in the results of individual trials, with no dominating, and possibly distorting, influence from any single study. All these considerations suggest that the meta-analyses estimates may be regarded as reliable indicators of the treatment benefit to be derived from delmopinol 0.2%.

The evidence of these studies suggests that the benefits of delmopinol 0.2% are likely to be accessible to many users. For example, there appeared to be a similar scale of benefit from delmopinol 0.2% across the age range 18–73 years, arguing for the broad applicability of these results. Moreover, the data were accrued from patients in five countries, again implying the widespread applicability of the conclusion that delmopinol 0.2% mouth rinse has value as an adjunct to usual care for plaque control and gingivitis management. In addition, the scale of the treatment effect was similar in the supervised and unsupervised studies for all endpoints examined, with no evidence that supervision or lack thereof per se had a consistent influence on the response. We deduce from this finding that the unsupervised use of a mouth rinse containing delmopinol 0.2% is feasible and is likely to be a useful addition to routine oral care procedures. Support for this proposition may be inferred from the observation that the results of PP analyses were almost invariably larger than the corresponding ITT result: the PP results can reasonably be regarded as the benefit likely to be obtained with a compliant population. PP completion rates were 72.5% or more (and usually $>80\%$) in all the studies.

The inclusion of a placebo group in all eight of the studies provides assurance that the results of the meta-analyses are not attributable to the operation of the Hawthorne effect in patients randomized to delmopinol. An improvement was seen in the placebo group of all eight studies for all three endpoints, implying that this influence may have been at work in all the trials. It is equally clear, however, given the larger treatment responses in all the delmopinol groups, that the superiority of delmopinol is not explained in this way. An alternative interpretation of the data could be that the improvement in the placebo groups reflects a persisting benefit from the professional cleaning administered to all patients at baseline, but this is unlikely and in any event provides no explanation for the greater improvements recorded with delmopinol compared with placebo. Use of placebo also conforms to ADA recommendations for the evaluation of chemotherapeutic products (Council on Dental Therapeutics 1985).

A trend in favour of delmopinol was apparent in all studies for the MGI (Lobene et al. 1986) but none produced a statistically conclusive result; pooling the data demonstrated a borderline

Table 9. Summary of differences between the effects of delmopinol 0.2% (D 0.2%) and placebo (P) on bleeding on probing (BOP) and plaque index in supervised studies.

Study	Outcome measure	Time (months)	Number of patients		Adjusted mean		Mean difference	95% CI		Percent reduction	95% CI		*p*-value
			D 0.2%	P	D 0.2%	P	P–D	lower	upper	(P–D)/P	lower	upper	
BOP–three studies													
90018	BOP	6	49	46	32.3	38.8	6.5	1.7	11.3	17	4	29	0.008
90014	BOP	6	53	53	21.8	34.1	12.3	7.1	17.5	36	21	51	<0.001
89016	BOP	2	102	99	32.2	43.2	11.0	6.8	15.1	25	16	35	<0.001
89017													
90023	GFF	5	78	81	13.1	16.8	3.7	0.5	6.9	22	3	41	0.023

Study	Outcome measure	Time (months)	Mean on D 0.2%	Mean on P	*p*-value	Adjusted difference	95% CI	Adjusted difference % *versus* P
Plaque index–five studies								
90018	TQH	6	1.47	1.68	0.055	−0.215	−0.43 to+0.00	13
89016	TQH	2	0.74	1.04	0.002	−0.315	−0.51 to −0.12	30
89017	TQH	2	1.46	1.71	0.005	−0.285	−0.48 to −0.09	17
90023	TQH	5	1.13	1.38	0.0290	−0.22	−0.43 to −0.01	16
90014	Silness–Löe	6	0.50	0.76	0.0005	−0.223	−0.347 to −0.099	29

ITT analysis.
GFF, gingival crevicular fluid flow; TQH, Turesky et al. (1970) modification of the Quigley & Hein (1962) plaque index.

significant advantage of delmopinol 0.2% over placebo. The apparent relative lack of impact of delmopinol on this endpoint may be explained by an effect of delmopinol on gum coloration noted in several of the studies included in this analysis (Bergenholtz et al. 1993, Lang et al. 1995). Heightened redness of the gums is a familiar finding after delmopinol use and may hamper visual assessment of the MGI. The observation by Bergenholtz et al. (1993) that effects on MGI are inversely related to delmopinol concentration would be consistent with this explanation.

These meta-analyses were undertaken to examine effectiveness. Local side-effects data for delmopinol have been reported in earlier publications, including the three published studies included in our meta-analyses (Claydon et al. 1996, Hase et al. 1998a, Lang et al. 1998). All three studies reported increased tongue and tooth staining compared with placebo. Two of these studies also included a chlorhexidine 0.2% rinse group (Hase et al. 1998a, Lang et al. 1998), however, and in both instances rates of tooth and tongue staining with chlorhexidine 0.2% were double those associated with delmopinol 0.2% ($p<0.00001$). Moreover, delmopinol-related staining was more likely to be registered on inspection by investigators than by subjects, and easy removal of staining was consistently reported, whereas chlorhexidine-related staining was mostly reported by patients themselves and was less easily eradicated. The difference in ease of eradication of staining between delmopinol and chlorhexidine may be related to the proposition that delmopinol destabilizes existing plaque as well as prevents new plaque formation. Transient anaesthesia of the tongue was reported with delmopinol in all three studies but, in those studies with a chlorhexidine comparator arm, the incidence of this phenomenon was similar with both agents. Compared with placebo, however, transient anaesthesia of the tongue and/or taste disturbance was much more common with 0.2% delmopinol or 0.2% chlorhexidine. Rates of discontinuation with delmopinol 0.2% in the three published controlled trials featured in these meta-analyses were one-third to one-half those recorded in the chlorhexidine control groups. A review of serious adverse events, undertaken as part of statutory regulatory evaluation, identified four such events in a total of 1633 patients enrolled in delmopinol studies. Three of these events were hospitalizations for surgical procedures and the fourth was an epileptic seizure. All these events were classified as unrelated ($n=3$) or probably unrelated ($n=1$) to delmopinol use.

Finally, the question of the ''clinical significance'' of the findings needs to be considered, although it may be a very difficult if not impossible task. Statistical *versus* clinical significance in periodontal research and practice has recently been reviewed (Addy & Newcombe 2005). As pointed out in this review, statistical significance is a well-understood and agreed mathematical concept based on hypothesis testing. Clinical significance is a much more nebulous concept with no agreed rules and particularly difficult for measures of plaque and gingivitis. These measures are not directly related to periodontitis progression or tooth loss and therefore, unless the effect of an anti-plaque agent is absolute, it is difficult or impossible to agree on a level of plaque or gingivitis reduction compared with placebo that might be clinically significant to the maintenance of a healthy periodontum or dentition.

In this respect, it is interesting to note that rarely, if ever, do authors of longer-term home use randomized-controlled clinical trials of anti-plaque agents comment on the clinical significance of their findings and this includes the published studies from this meta-analysis (Claydon et al. 1996, Hase et al. 1998a, Lang et al. 1998).

In randomized-controlled clinical trials, the problem of assessing clinical significance is made even more difficult because of the Hawthorne effect, which results in improved oral hygiene and gingival health across all participants. The changes from baseline for both

active and placebo groups in all studies must be considered high. The differences between active and placebo, for the more important outcome variable of BOP, ranged considerably across the studies from less than 10% to greater than 30%. Given the very high level of statistical significance of these findings, we feel that it is not unreasonable to conclude that delmopinol has a clinically significant benefit to gingival health.

We conclude that meta-analysis confirms and amplifies evidence, such as that of Lang et al. (1998), for the effectiveness of delmopinol 0.2% mouth rinse as an adjunct measure for the prevention of plaque and gingivitis, and that the balance of benefits and adverse events exhibited by this agent identifies it as a viable alternative to chlorhexidine for many patients.

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Clinical Relevance

The aggregated data presented in this analysis indicate that delmopinol, a recent addition to the repertoire of mouthwashes available for the treatment of gingivitis, has meaningful clinical efficacy when used for this purpose in a 0.2% solution for up to 6 months. This finding usefully amplifies the results of individual clinical trials, some of which were suggestive of efficacy but not statistically conclusive.