J Clin Periodontol 2005; 32: 617–621 doi: 10.1111/j.1600-051X.2005.00721.x

Journal of Clinical Periodontology

The effect of a dexibuprofen mouth rinse on experimental gingivitis in humans

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Rosin M, Kähler ST, Hessler M, Schwahn Ch, Kuhr A, Kocher T. The effect of a dexibuprofen mouth rinse on experimental gingivitis in humans. J Clin Periodontol 2005; 32: 617–621. doi: 10.1111/j.1600-051X.2005.00721.x. © Blackwell Munksgaard, 2005.

Abstract

Objectives: The pharmacodynamic properties of ibuprofen are related nearly exclusively to the *S*(+)enantiomer (dexibuprofen). This study investigated the effect of a 1.5% dexibuprofen mouth rinse in an experimentally induced gingivitis.

Materials and Methods: The trial was a randomized, double-blinded, placebo-controlled, two-period and two-sequence parallel group cross-over study in 24 healthy volunteers aged 21–30 years (16 males, eight females). Customized guards were worn during tooth brushing to prevent any plaque removal from the experimental area (first and second pre-molars and molars in one upper quadrant). After 22 days of plaque accumulation, the mouth rinses (1.5% dexibuprofen and placebo) were administered under supervision three times daily (rinsing for 1 min. with 15 ml) for 8 days. The wash-out time between the two study periods was 14 days. Parameters evaluated at days 0, 7, 14, 22, and 30 were the Löe & Silness gingival index (GI) and the Quigley & Hein plaque index (QHI). Data were tested for treatment, period, and carry-over effects (parametric cross-over analysis).

Results: There was no statistically significant difference ($p = 0.240$) in GI between placebo and dexibuprofen. However, the decrease in QHI was significantly greater ($p = 0.019$) with dexibuprofen as compared with the placebo.

Conclusion: In the present study, a 1.5% dexibuprofen mouth rinse had no effect on gingivitis whereas an anti-plaque effect was demonstrated.

Key words: dexibuprofen; gingivitis; mouth rinse; plaque

Accepted for publication 19 October 2004

There is substantial evidence to suggest that biochemical mediators of host origin, including prostaglandin E_2 (PGE_2), thromboxane B_2 (TxB_2), and leukotriene B_4 (LTB_4), may play a key role in the development and establishment of gingivitis (Goodson et al. 1974, Offenbacher et al. 1986, Heasman et al. 1993b). PGE_2 has also been implicated as an inflammatory mediator in periodontitis contributing to alveolar bone resorption (Williams 1990, Page 1991). Therefore, pharmaceutical control of these host inflammatory mediators may possibly prevent or interfere with the initiation and/or progression of periodontal diseases in spite of the presence of periodontopathic microorganisms. In view of the problems with and limitations of patient performed mechanical plaque control (De LaRosa et al. 1979), this specific use of pharmaceuticals may therefore have an adjunctive preventive and/or treatment effect (Paquette & Williams 2000).

PGE_2 and TxB_2 are products of the cyclo-oxygenase (COX) pathway of arachidonic acid metabolism, which is inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) (Samuelsson 1969, Flower 1974). A wealth of data from pre-clinical and clinical studies indicates that systemic as well as topical administration of NSAIDs diminishes periodontal inflammation and reduces alveolar bone resorption (Howell & Williams 1993, Salvi et al. 1997). Among these drugs with potential therapeutic value, flurbiprofen (Jeffcoat et al. 1986, 1988, Offenbacher et al. 1987, Williams et al. 1987, 1988a, c, 1989, Heasman et al. 1989, 1993a) appears to be the most tested agent, however, other members of the propionic acid class, naproxen (Howell et al. 1991, Jeffcoat et al. 1991) and ibuprofen (Williams et al. 1988b, Kornman et al. 1990) have also been studied.

Ibuprofen is a NSAID with an arylpropionic structure and exists in two enantiomeric forms (Evans 1992). The drug actions of ibuprofen appear to be enantioselective and are nearly exclusively restricted to the dextrorotatory *S*(+)enantiomer, the so-called dexibuprofen (Evans 1996). It is now possible to isolate optically pure dexibuprofen and to make it available for therapeutic applications (Leising et al. 1996, Kaehler et al. 2003). Administration of the pure *S*(+)enantiomer, either systemi-

cally or topically, may reduce undesirable side effects not exposing the individual to the pharmacologically inactive ''enantiomeric ballast''. Using pure *S*(+)enantiomer dexibuprofen, effectively doubles the dose when compared with the administration of racemic ibuprofen. With any pharmacological agent targeting solely periodontal diseases, there should be little doubt that a greater benefit-to-risk ratio can be expected with topical rather than systemic application.

The objective of the present study was to investigate the effect of locally applied dexibuprofen (a 1.5% dexibuprofen mouth rinse) on experimentally induced gingivitis.

Materials and Methods

Study design

The study was performed as a double-blind, randomized, placebo-controlled, cross-over design in a 4-week experimentally induced localized gingivitis model (Fig. 1). The wash-out period between the two plaque accumulation periods was 14 days. Approval for the study was obtained from the Ethics Committee of the Medical School of Greifswald University and volunteers gave written informed consent to participate. Twenty-four healthy subjects (16 males and eight females, between 21 and 30 years of age) were enrolled in the study. All subjects were students at Greifswald University, 22 of whom were dental students. Participants were selected based on the following criteria: at least one maxillary quadrant where the first and second pre-molars and molars were free of restorations on palatal, buccal, and proximal surfaces; a high standard of oral hygiene and good gingival health, i.e. no probing depths >3 mm, no caries, and few restorations elsewhere in the mouth; no intra-oral appliances. In addition, subjects had not taken any medication, which could possibly affect the oral microflora or oral health for at least 3 months prior to the study.

The experimental area selected for this study comprised the first and second pre-molars and molars in one quadrant of the maxilla. Localized plaque accumulation and hence localized experimental gingivitis were induced by means of plaque guards, which prevented plaque removal from the experimental teeth. Prior to the study, polyether impressions (Impregum Penta, ESPE, Seefeld, Germany) were taken of the experimental quadrant and stone casts poured. A wax relief (Thowax, Yeti Dental, Engen, Germany) was modelled on the stone casts, which covered approximately 2 mm of the gingival margins, approximately 3 mm of the adjacent tooth surfaces, and all proximal spaces of the experimental teeth. On duplicates of these models, moulded splints of 1 mm thick resin foil (Erkodur, Erkodent, Pfalzgrafenweiler, Germany) were fabricated. Extensions of these plaque guards over approximately 1 cm of the adjacent palate and vestibule as well as over half of the canine and the third molar (if present) provided support and permitted positive relocation.

In the 2 weeks prior to the start of each study period, all participants were subjected to repeated professional maxillary tooth cleaning and instructed in good tooth-brushing techniques and the use of dental floss (Fig. 1). On day 0 of the induction period, all subjects were instructed to wear the plaque guards every time they cleaned their teeth, so that brushing and flossing were not performed on the first and second pre-molars and molars of the test quadrant (Fig. 1). The induction phase lasted 22 days. The rinse regimen began in the morning of day 23 and lasted 8 days by period. The subjects were allocated to use either the 1.5% dexibuprofen mouth rinse or the placebo according to a randomization list, which was produced using the validated software package ''Rancode professional, Version 3.6 (IDV Gauting, Munich, Germany). The mouth rinses were provided by Gebro Pharma GmbH (Fieberbrunn, Austria) and labelled to identify the subject and study period. Individual, sealed code breakers for the subjects and products were kept by the supervisor of the study (M. R.). The study preparations were administered in the morning, at midday, and in the evening (rinsing for 1 min. with 15 ml solution) under supervision of the investigator. Meals had to be taken before rinsing. Otherwise, intake of food and/or drinking was not allowed for 2 h after rinsing. Any sign or symptoms of adverse reactions of the oral mucosa and all other deteriorations of the health status of the study subjects were documented and analysed. At the end of each of the two trial periods, subjects received professional tooth cleaning to remove plaque, calculus, and staining from the test quadrant.

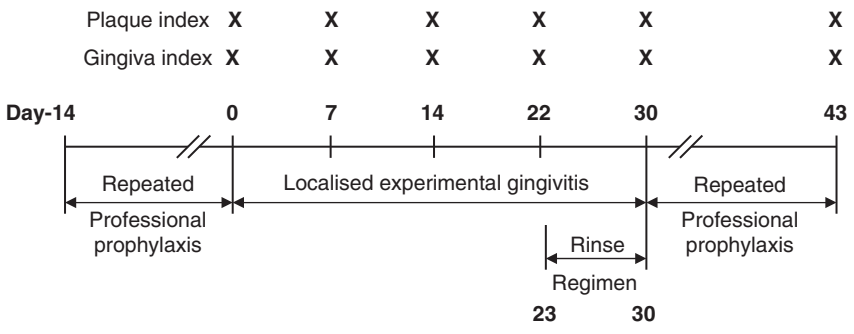

Fig. 1. Outline of the first period of the clinical trial. Day 43 was the end of the wash-out period of the first study period 1 and at the same time day 0 (baseline) of the second study period. The second study period was identical to days 0–30.

Clinical examinations

During each study period, clinical examinations were performed on days 0 (baseline), 7, 14, 22, and 30 (Fig. 1). Plaque was disclosed using a disclosing solution (MIRA-2-TON, Hager & Werken, Duisburg, Germany) and scored using the Turesky et al. (1970) modification of the Quigley & Hein (1962) plaque index system (QHI). The scores were taken at six surfaces of FDI teeth 4, 5, 6, and 7 of the test quadrant: distobuccal, buccal, mesiobuccal, distopalatal, palatal and mesiopalatal tooth surfaces. Gingival inflammation was scored according to the Talbot et al. (1977) modification of the Löe & Silness (1963) gingival index (GI). The GI was assessed at the same six sites of the selected teeth as the QHI using CP-15UNC probes (HU-Friedy Europe, Leimen, Germany). The QHI and GI measurements were performed at each clinical examination.

Calibration of the clinical examiner

Screening and selection of volunteers was carried out by a single investigator (M. H.), who also scored all visits of the trial. Prior to the study, four calibration

sessions were performed to achieve high reproducibility of the QHI and GI scorings. An additional session was performed in the oral hygiene period preceding the second plaque accumulation period. The study investigator (M. H.) was calibrated against a very experienced investigator (T. K.). In the calibrating sessions, two patients were examined by a third clinician (M. R.) while the two investigators (M. H. and T. K.) scored independently. In the last calibration session before the start of the first plaque accumulation period, an inter-examiner reproducibility of $\kappa \geqslant 0.81$ and $\geqslant 0.76$ was achieved for the QHI and GI, respectively. The respective values for the session prior to the second plaque accumulation period were $\kappa \geqslant 0.79$ for the QHI and $\kappa \geqslant 0.77$ for the GI.

Statistical analysis

Inter-examiner reproducibility was determined by calculating κ coefficients. The pairwise comparison of the clinical index values from all examination days with baseline was performed using ANOVA of repeated-measures data. The *t*-test was used for comparisons of the two treatments during the induction period. The GI and QHI data of the treatment phase were tested for difference using a parametric cross-over analysis (ANCOVA) with calculation of period, carry-over, and treatment effects (fixed factor analysis) and adjustment by baseline values. Differences between test and reference were stated below the significance level of 0.05.

Results

Compliance

Twenty-one of the total of 24 subjects completed both periods of the clinical trial and were included in the analysis. One subject contracted tonsillitis shortly after the start of the study and had to withdraw. Two subjects had to be excluded from the study because of repeated failure to attend scheduled examination appointments. The observed pattern of plaque accumulation and gingivitis development in the remaining 21 subjects suggested a high degree of compliance with the study protocol (Fig. 2).

Induction of experimental gingivitis

The changes in the GI and QHI between days 0 and 22 (induction phase) of the experimental gingivitis are shown in Fig. 2. The increase of the GI and the QHI during the induction phase as compared with baseline was statistically significant on all examination days (repeated-measures ANOVA, $p < 0.01$). The GI and QHI values for the respective dexibuprofen and placebo groups did not differ at any examination during the two induction periods (days 0–22).

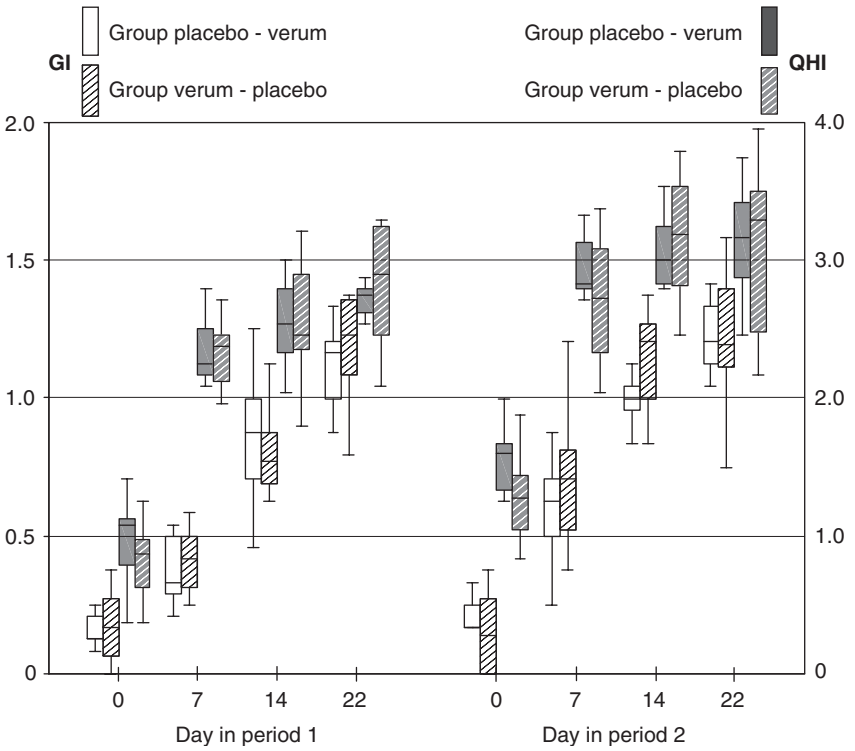

Fig. 2. Clinical parameters (Löe & Silness gingival index (GI) and Quigley & Hein plaque index (QHI)) during the induction phases of experimental gingivitis in the two study periods. Each box is characterized by the median as well as the 25th and 75th percentiles. The minimum and maximum values (without extreme cases) are indicated as whiskers.

Treatment regimen

The examination on the last day of the induction phase (day 22) served as the baseline examination for the treatment regimen, which ended on day 30. The means and standard deviations for the GI and QHI before (day 22) and after the rinse regimen (day 30) are shown in Table 1. Parametric cross-over analysis revealed a significant period effect for the GI ($p = 0.001$). The same test was therefore used to analyse both the pooled data of both study periods and the data of just the first study period. There was, however, no evidence of a significant treatment effect for the GI with $p = 0.240$ (both periods) and $p = 0.765$ (first period). Furthermore, no carry-over effect was observed for the GI. A statistically significant treatment effect for the QHI was observed for the pooled data of both study periods ($p = 0.019$) and for the data of the first study period only ($p = 0.034$). No period or carry-over effects were observed for the QHI.

Adverse reactions

No irritations of the oral mucosa were observed. Two adverse events, one tonsillitis (before the first application of one of the test preparations) and one periimplantitis (affecting a central incisor), were documented and assessed as ''not related'' to either the test area or the test medications.

Discussion

The present study was undertaken to investigate the short-term effects of a 1.5% dexibuprofen mouth rinse on established gingival inflammation in an experimental gingivitis model. Heasman et al. (1989), also utilizing an experimental gingivitis model, were barely able to demonstrate superiority of a *topical* 10 mM flurbiprofen rinse (w/v concentration 0.24%) in a preventive application regimen (Heasman et al. 1989). Flurbiprofen was applied *locally* in 24 volunteers in a split-mouth model

Table 1. Mean (± SD) of GI and QHI during the treatment period (days 22–30) in the dexibuprofen (Dex) and the placebo (Pla) group

	GI				QHI			
	Day 22		Day 30		Day 22		Day 30	
	Dex	Pla	Dex	Pla	Dex	Pla	Dex	Pla
First study period, Dex $n = 12$, Pla $n = 9$	1.188 ± 0.188	1.144 ± 0.208	1.118 ± 0.184	1.074 ± 0.236	2.816 ± 0.413	2.732 ± 0.251	2.798 ± 0.325	3.014 ± 0.239
Second study period, Dex $n = 9$, Pla $n = 12$	1.228 ± 0.135	1.270 ± 0.292	0.671 ± 0.331	0.917 ± 0.311	3.144 ± 0.405	3.104 ± 0.574	3.046 ± 0.154	3.267 ± 0.510
Both study periods, $n = 21$	1.205 ± 0.164	1.216 ± 0.262	0.927 ± 0.337	0.984 ± 0.286	2.956 ± 0.433	2.945 ± 0.492	2.905 ± 0.289	3.159 ± 0.427

Day 22, before commencing rinse regimen; day 30, after 8 days of rinse regimen.

on days 4, 6, 8, 11, 13, and 15 during a 17-day period of abstaining from tooth cleaning. In this study (Heasman et al. 1989), no differences were observed in GI scores between the flurbiprofen and the placebo-treated side. However, in a follow-up study with six subjects from the original study population, when only the placebo was applied to one side, significantly greater median GI values were found in their latter study as compared with their original investigation (Heasman et al. 1989). The authors concluded that systemic absorption of flurbiprofen may have reduced the severity of the developing inflammatory lesions in the original 17-day study period (Heasman et al. 1989). Using pure 1.5% *S*(+)enantiomer dexibuprofen we effectively doubled the dose as opposed to administration of racemic ibuprofen. We therefore hoped to demonstrate a clearer anti-inflammatory effect than Heasman et al. (1989) using 0.24% flurbiprofen. To avoid possible effects of systemically absorbed dexibuprofen, we used a cross-over design rather than a split-mouth design as in the study by Heasman et al. (1989). Therefore, the failure to demonstrate superiority of the dexibuprofen treatment over the placebo in the present study was somewhat unexpected. Our data, however, offer a possible explanation. The increase in inflammation was more rapid and more pronounced in the second induction phase of our study (Fig. 2). Furthermore, the reduction of inflammation in both the treatment and the placebo group were more pronounced in the second rinse phase (Table 1), leading to the observation of a significant period effect. It is therefore possible, that the difference observed by Heasman et al. (1989) between the original and the follow-up study (both reported in Heasman et al. 1989) was caused by a similar period effect and not by a systemic effect of flurbiprofen in the original study. Nevertheless, the period effect strongly suggests that the 2-week wash-out period in our study was not sufficient and/or a cross-over design was not suitable. On the other hand, the observations and conclusions of Heasman et al. (1989) may be valid. The same group (Heasman et al. 1993c) established that flurbiprofen, when applied systemically, was a potent inhibitor of gingival inflammation with both preventive and therapeutic properties. Application of 50 mg b.i.d. flurbiprofen between days 21 and 28 of an experimental gingivitis caused a significant reduction in bleeding scores, while the control group demonstrated a highly significant increase. Interestingly, this treatment effect appeared to be caused by a difference in the lipoxygenase product LTB_4 as there was no difference between treatment and control in the COX products PGE_2 and TxB_2 (Heasman et al. 1993c). The possibility of this indirect NSAID effect having been less pronounced in our present study offers one explanation for the lack of an observed anti-inflammatory effect.

The effect of the splint in terms of accidental removal of plaque from the test teeth is not known. However, the QHI values for the respective dexibuprofen and placebo groups did not differ at any examination during the two induction periods (days 0–21). It may be assumed that any plaque-removing effects of the splints would have been similar in both study groups and that, therefore, the plaque reducing effect of ibuprofen was a valid observation. Furthermore, plaque values in the respective placebo groups increased during the investigational phase, resulting in a statistical difference between treatments. An in vivo plaque reducing effect of ibuprofen would be a novel finding and has not been reported before. However, our findings are supported by a number of in vitro (Hersh et al. 1991, Elvers & Wright 1995, Pina-Vaz et al. 2000) and in vivo (Hockertz et al. 1995, 1996) studies in which an antimicrobial effect of ibuprofen has been demonstrated. Hersh et al. (1991) observed an anti-bacterial effect for both flurbiprofen and ibuprofen against *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Wollinella recta*, and *Eikenella corrodens* at dosages of 125–500 μg. In the study by Elvers & Wright (1995), growth of *Staphylococcus aureus* was suppressed by ibuprofen concentrations of 150 μg/ml at pH 7 with increased anti-bacterial potency of ibuprofen at lower pH values. Ibuprofen has also been shown to exhibit anti-fungal activity against *Candida albicans* and non-albicans strains (Pina-Vaz et al. 2000). At 10 mg/ml, ibuprofen showed a rapid cidal activity while the effect at 5 mg/ml was mainly fungistatic. In view of these studies, an anti-plaque effect of our 1.5% dexibuprofen mouth rinse can be perceived as an anti-microbial effect of ibuprofen, which appears to be established at concentrations much lower than the ones applied in the present study (i.e. 15 mg/ml).

Topical applications of NSAIDs, even if the effects are mostly caused by systemically absorbed drugs, will cause no gastrointestinal side effects. Plasma levels of flurbiprofen in the study by Heasman et al. (1989) were 0.4 μg/ml and were comparable with those reported in adult monkeys (0.22 and 3.2 μg/ml), which significantly inhibited gingival redness and bleeding on probing (Offenbacher et al. 1987). An additional plaque reducing effect would add further benefit to a preventive and/or therapeutic regimen based on topical NSAID applications. This seems to justify further investigation into the effects of topical dexibuprofen using study designs different from the one employed here.

Acknowledgements

The study was supported by Gebro Pharma GmbH (Fieberbrunn, Austria).

References

De LaRosa, M., Guerra, J. Z., Johnston, D. A. & Radicke, A. W. (1979) Plaque growth and removal with daily toothbrushing. *Journal of Periodontology* **50**, 661–664.

Elvers, K. T. & Wright, S. J. (1995) Antibacterial activity of the anti-inflammatory compound ibuprofen. *Letters in Applied Microbiology* **20**, 82–84.

Evans, A. M. (1992) Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs. *European Journal of Clinical Pharmacology* **42**, 237–256.

Evans, A. M. (1996) Pharmacodynamics and pharmacokinetics of the profens: enantioselectivity, clinical implications, and special reference to *S*(+)-ibuprofen. *Journal of Clinical Pharmacology* **36**, 7–15.

Flower, R. J. (1974) Drugs which inhibit prostaglandin synthesis. *Pharmacological Reviews* **26**, 33–67.

Goodson, J. M., Dewhirst, F. E. & Brunetti, A. (1974) Prostaglandin E_2 levels in human periodontal disease. *Prostaglandins* **6**, 81–85.

Heasman, P. A., Benn, D. K., Kelly, P. J., Seymour, R. A. & Aitken, D. (1993a) The use of topical flurbiprofen as an adjunct to non-surgical management of periodontal disease. *Journal of Periodontal Research* **28**, 457–464.

Heasman, P. A., Collins, J. G. & Offenbacher, S. (1993b) Changes in crevicular fluid levels of interleukin 1β, leukotriene B_4, prostaglandin E_2, thromboxane B_2 and tumor necrosis factor alpha in experimental gingivitis in humans. *Journal of Periodontal Research* **28**, 241–247.

Heasman, P. A., Offenbacher, S., Collins, J. G., Edwards, G. & Seymour, R. A. (1993c) Flurbiprofen in the prevention and treatment of experimental gingivitis. *Journal of Clinical Periodontology* **20**, 732–738.

Heasman, P. A., Seymour, R. A. & Boston, P. F. (1989) The effect of a topical non-steroidal anti-inflammatory drug on the development of experimental gingivitis in man. *Journal of Clinical Periodontology* **16**, 353–358.

Hersh, E. V., Hammond, B. F. & Fleury, A. A. P. (1991) Antimicrobial activity of flurbiprofen and ibuprofen in vitro against six common periodontal pathogens. *Journal of Clinical Dentistry* **3**, 1–5.

Hockertz, S. & Heckenberger, R. (1996) Treatment of an acute bacterial infection with a combination of acetylsalicylic acid/ibuprofen and interferon gamma. *Arzneimittelforschung* **46**, 1012–1015.

Hockertz, S., Heckenberger, R., Emmendorffer, A. & Muller, M. (1995) Influence of ibuprofen on the infection with listeria monocytogenes. *Arzneimittelforschung* **45**, 104–107.

Howell, T. H., Jeffcoat, M.K, Goldhaber, P., Reddy, M. S., Kaplan, M. L., Johnson, H. G., Hall, C. M. & Williams, R. C. (1991) Inhibition of alveolar bone loss in beagles with the NSAID naproxen. *Journal of Periodontal Research* **26**, 498–501.

Howell, T. H. & Williams, R. C. (1993) Nonsteroidal anti-inflammatory drugs as inhibitors of periodontal disease progression. *Critical Reviews in Oral Biology and Medicine* **4**, 177–196.

Jeffcoat, M. K., Page, R., Reddy, M., Wannawisute, A., Waite, P., Palcanis, K., Kogan, R., Williams, R. C. & Basch, C. (1991) Use of digital radiography to demonstrate the potential of naproxen as an adjunct in the treatment of progressive periodontitis. *Journal of Periodontal Research* **26**, 415–421.

Jeffcoat, M. K., Williams, R., English, R. & Goldhaber, P. (1986) Flurbiprofen treatment of periodontal disease in beagles. *Journal of Periodontal Research* **21**, 624–633.

Jeffcoat, M. K., Williams, R., English, R. & Goldhaber, P. (1988) Flurbiprofen treatment of human periodontitis: effect on alveolar bone height and metabolism. *Journal of Periodontal Research* **23**, 381–385.

Kaehler, S. T., Phleps, W. & Hesse, E. (2003) Dexibuprofen: pharmacology, therapeutic uses and safety. *Inflammopharmacology* **11**, 371–383.

Kornman, K. S., Blodgett, R. F., Brunsvold, M. & Holt, S. C. (1990) Effects of topical applications of meclofenamic acid and ibuprofen on bone loss, subgingival microbiota and gingival PMN response in the primate *Macaca fascicularis*. *Journal of Periodontal Research* **25**, 300–307.

Leising, G., Resel, R., Stelzer, F., Tasch, S., Lanziner, A. & Hantich, G. (1996) Physical aspects of dexibuprofen and racemic ibuprofen. *Journal of Clinical Pharmacology* **36**, 3–6.

Löe, H. & Silness, J. (1963) Periodontal disease in pregnancy (I). Prevalence and severity. *Acta Odontologica Scandinavica* **21**, 533–551.

Offenbacher, S., Braswell, L. D., Loos, A. S., Johnson, H. G., Hall, C. M., McClure, H., Orkin, J. L., Strobert, E. A., Green, M. D. & Odle, B. M. (1987) Effects of flurbiprofen on the progression of periodontitis in *Maccaca mulatta*. *Journal of Periodontal Research* **22**, 473–481.

Offenbacher, S., Odle, B. M. & Van Dyke, T. E. (1986) The use of crevicular fluid prostaglandin E_2 levels as predictor of periodontal attachment loss. *Journal of Periodontal Research* **21**, 101–112.

Page, R. C. (1991) The role of inflammatory mediators in the pathogenesis of periodontal disease. *Journal of Periodontal Research* **26**, 230–242.

Paquette, D. W. & Williams, R. C. (2000) Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases. *Periodontology 2000* **24**, 239–252.

Pina-Vaz, C., Sansonetty, F., Rodrigues, A. G., Martinez-De-Oliveira, J., Fonseca, A. F. & Mardh, P. A. (2000) Antifungal activity of ibuprofen alone and in combination with fluconazole against Candida species. *Journal of Medical Microbiology* **49**, 831–840.

Quigley, G. A. & Hein, J. W. (1962) Comparative cleansing efficiency of manual and power brushing. *Journal of American Dental Association* **65**, 26–29.

Salvi, G. E., Williams, R. C. & Offenbacher, S. (1997) Nonsteroidal antiinflammatory drugs as adjuncts in the management of periodontal diseases and peri-implantitis. *Current Opinions in Periodontology* **4**, 51–58.

Samuelsson, B. (1969) Biosynthesis of prostaglandins. *Progress in Biochemical Pharmacology* **5**, 109–128.

Talbot, K., Mandel, I. & Chilton, N. W. (1977) Reduction of baseline gingivitis scores with repeated prophylaxis. *Journal of Preventive Dentistry* **4**, 28–29.

Turesky, S., Gilmore, N. D. & Glickman, I. (1970) Reduced plaque formation by the chlormethyl analogue of vitamin C. *Journal of Periodontology* **41**, 41–43.

Williams, R. C. (1990) Medical progress. Periodontal disease. *New England Journal of Medicine* **322**, 373–382.

Williams, R. C., Jeffcoat, M. K., Howell, T. H., Hall, C. M., Johnson, H. G., Wechter, W. J. & Goldhaber, P. (1987) Indomethacin or flurbiprofen treatment of periodontitis in beagles: comparison of effect on bone loss. *Journal of Periodontal Research* **22**, 403–407.

Williams, R. C., Jeffcoat, M. K., Howell, T. H., Reddy, M. S., Johnson, H. G., Hall, C. M. & Goldhaber, P. (1988a) Topical flurbiprofen treatment of periodontitis in beagles. *Journal of Periodontal Research* **23**, 166–169.

Williams, R. C., Jeffcoat, M. K., Howell, T. H., Reddy, M. S., Johnson, H. G., Hall, C. M. & Goldhaber, P. (1988b) Ibuprofen: an inhibitor of alveolar bone resorption in beagles. *Journal of Periodontal Research* **23**, 225–229.

Williams, R. C., Jeffcoat, M. K., Howell, T. H., Rolla, A., Stubbs, D., Teoh, K. W., Reddy, M. S. & Goldhaber, P. (1989) Altering the progression of human alveolar bone loss with the nonsteroidal anti-inflammatory drug flurbiprofen. *Journal of Periodontal Research* **60**, 485–490.

Williams, R. C., Offenbacher, S., Jeffcoat, M. K., Howell, T. H., Johnson, H. G., Hall, C. M., Wechter, W. J. & Goldhaber, P. (1988c) Indomethacin or flurbiprofen treatment of periodontitis in beagles: effect on crevicular fluid arachidonic acid metabolites compared with effect on alveolar bone. *Journal of Periodontal Research* **23**, 134–138.

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