Greenstein, G. Efficacy of subantimicrobial-dose doxycycline in the treatment of periodontal disease: a critical evaluation. Int J Periodontics Restorative Dent 2004:528-43. (50 Refs)

Purpose: To assess the current data regarding subantimicrobial-dose doxycycline (SDD).

Materials and Methods: Since the completion of a phase III clinical trial and subsequent approval by the FDA, the use of the use of doxycycline, 20 mg, b.i.d. as an adjunct to scaling and root planing has been employed by clinicians in the treatment of periodontal disease. To assist the clinician in decisions regarding the usage of SDD, this paper reviews studies with current clinical data.
The length of the studies ranged from 3 months to 9 months, with doxycycline administered for anywhere from 2 months on/2 months off, 12 weeks on/12 weeks off, 3 months, 6months and 9 months. The studies included were for the most part on subjects diagnosed w/ chronic periodontitis, with only a few studies addressed special populations, i.e. elderly, smokers and diabetic subjects.

Findings and Conclusions:
Clinical parameters
Bleeding on probing: A statistically significant decrease of BOP in shallow (0-3 mm) and moderate (4-6 mm) sites has been demonstrated in the phase III clinical trials; however, the reduction of BOP at deep (≥ 7 mm) sites was shown to be similar to that of scaling and root planning. At least 64% of the 4-6 mm sites and at least 75% of the sites ≥ 7 mm presented w/ BOP with and without adjunctive SDD.
Probing Depth: A statistically significant greater reduction in mean probe depth was demonstrated for SDD + root planing compared to root planing only. Probing depth reduction for sites 4-6 mm ranged from 0.95 to 1.64 mm, and for sites ≥ 7 mm ranged from 1.39 to 4.34 mm with SDD + root planning; the range was 0.46 to 0.97 mm for 4-6 mm probe depths and 0.4 to 1.77 mm for root planing only.
Clinical attachment level: Some studies found a statistically significant gain in clinical attachment in moderate and deep sites, while others did not. The author suggests a potential measurement error in one study where the percentage of sites gaining clinical attachment was greater than the percentage of sites with probe depth reduction.
Disease progression: Caton, et al. demonstrated further loss of attachment in sites initially ≥ 7 mm was statistically significantly less in subjects who received a combination SDD + scaling and root planning; however, incidence of disease progression in shallow and moderate sites was similar.
Adjunct to periodontal surgery: Gapski, et al. presented findings from 24 individuals who did not respond to scaling and root planing, and were provided with access flap surgery w/ and w/o SDD for 6 months. Although greater probe depth reduction was achieved, gain in attachment level was not. Further studies are needed.
Study populations

Smokers: In smokers, probing depth reduction in moderate sites was 1.19 mm w/ SDD and 0.93 mm w/o SDD, and deep was 2.25 mm w/ SDD and 1.89 mm w/o. This was statistically significant.
Elderly: Additional studies are needed to be conclusive of a benefit.
Diabetic: One study compared the efficacy of scaling/root planning w/ and w/o SDD in type 2 diabetics and found no improvements in clinical parameters, however a statistically significant reduction in HbA1c was observed. In another study, type 1 or 2 diabetics who had received SDD for 3 months experienced a reduction in probing depths and clinical attachment gain as well as a decrease in HbA1c. Other considerations: The duration of administration of SDD to obtain optimal results is unknown. At probe depths $\geq$ 7 mm, probe depth reduction $\geq$ 1.6 mm has been demonstrated w/ SDD + scaling/ root planning, root planing alone, and scaling/root planning plus tetracycline fibers, minocycline polymer, metronidazole, amoxicillin and repeated scaling/root planning. Studies have demonstrated the proportions of bacteria or the development of resistant strain of bacteria was not affected when SDD was used for 9 consecutive months. In vitro, some strains are susceptible to 0.5 μg/ml of doxycycline, the expected serum level achieved with SDD is 0.6-0.8 μg/ml. The author suggests that although statistical significance was achieved in the phase III clinical trials for subantimicrobial dose doxycycline therapy, the clinical significance should also be considered when deciding to choose this modality of therapy. Factors such as history, severity, medical conditions should be taken into account when considering adjunctive therapy of SDD.

Slots J. Systemic antibiotics in periodontics. J Periodontol 2004; 75: 1553-65.

Purpose: To address the role of systemic antibiotics in the treatment of periodontal disease.

Materials and Methods: Authors and the committee's opinions and literature reviews.

Findings and Conclusions: Relatively few species have been clearly associated with progressive periodontitis. Putative periodontal pathogens vary considerably in sensitivity to several antibiotics making simplistic approaches to antimicrobial chemotherapy problematic. Prime candidates for systemic antibiotic therapy are patients who exhibit continuing loss of periodontal attachment despite diligent conventional mechanical periodontal therapy, recurrent or refractory periodontitis, patients with aggressive types of periodontitis, or with medical conditions predisposing to periodontitis and patients with acute or severe periodontal infections (periodontal abscess, acute necrotizing gingivitis/periodontitis). The efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and the pharmacokinetic characteristics of the drug and by local environmental factors. Systemic antibiotic therapy has certain advantages over topical application of antimicrobial agents. Systemic antibiotics may enable the simple, easy administration of the drug to multiple sites of disease activity. They may also eliminate or reduce pathogens colonizing on oral mucosa and on other extra-dental sites including the tongue and tonsilar areas. The possibility of markedly suppressing or eliminating periodontal pathogens from virtually the entire mouth may reduce the risk for future translocation of organisms and recolonization of the periodontal pocket, thereby potentially reducing the risk for recurrent disease progression. Disadvantages of systemic antibiotic therapy as compared to locally applied antimicrobial agents include inability of systemic drugs to achieve high gingival crevice fluid concentration, an increased risk of adverse drug reactions, increased selection of multiple antibiotic resistant microorganisms, and uncertain patient compliance. Controlled clinical trails will add to current knowledge about the effectiveness of antibiotic therapy in periodontics. Many existing studies are difficult to interpret because of open-study designs, small sample size, short-term evaluation periods, clinically different patient groups, undetermined periodontitis disease activity, unknown baseline microbiota, varying antimicrobial regimens, and insufficient supragingival plaque control. Some studies concerned with patients with disease progression suggest that properly selected systemic antibiotics may provide significant additional clinical benefit to conventional mechanical periodontal therapy, particularly in patients with recurrent or refractory periodontitis. A conservative and selective approach is recommended for periodontal antibiotic therapy. Indiscriminate antibiotic administration is contrary to sound clinical practice and may cause overgrowth of intrinsically resistant pathogens or may unnecessarily increase in vivo resistance to antibiotics that are valuable in potentially fatal medical infections. Antibiotics should target offending

periodontal pathogens, and bactericidal agents are preferred. Since even the most careful clinical examination cannot delineate the likely microbial pathogens in most cases of periodontitis, a microbiological analysis is sometimes necessary to identify the antibiotic therapy that covers resident periodontal pathogens. There is some limited evidence to support microbial culture and sensitivity testing in cases that do not respond to conventional therapy. Relatively few studies have been performed regarding which antibiotics should be selected for aggressive periodontitis patients in whom the subgingival micobiota have been characterized through microbiological testing. In addition, the optimal dose of antibiotics remains unclear since most current antibiotic regimens are empirically developed rather than through systematic research. Systemic antibiotic therapy can provide greatest benefit to periodontitis patients who do not respond well to mechanical periodontal therapy or who are experiencing fever or lymphadenopathy. Single antimicrobial drug therapies may be able to suppress various periodontal pathogens for a prolonged period of time depending on the effectiveness of the host defense and the oral hygiene efforts. Combination drug therapies, which aim at enlarging the antimicrobial spectrum and exploiting synergy between antibiotics, are often indicated with complex mixed periodontal infections. Prescription of any systemic antibiotic therapy requires a careful analysis of patients' medical status and current medications. In severe infections, it may include antimicrobial sensitivity testing.

Sekino S, Ramberg P, Lindhe J. the effect of systemic administration of ibuprofen in the experimental gingivitis model. J Clin Periodontol 2005;32:182-187.

Purpose: The aim of the present clinical trial was to evaluate the effect of systemic administration of ibuprofen on gingivitis and plaque build-up.

Materials and Methods: 11 patients were studies in this controlled single blind clinical trial. Each volunteer had to fulfill the following criteria: (1) be in good general health, (2) exhibit no sign of destructive periodontal disease, (3) have a minimum of 24 teeth and > 6 teeth in each jaw quadrant, (4) not being engaged in ongoing restorative dental treatment, (5) not being exposed to antibiotic treatment in the previous three months, (6) not use anti-inflammatory drugs, (7) not use oral antiseptic products, (8) not use tobacco products. The volunteers were subject to a screening examination to assess the status of their dentition, were given oral hygiene instruction, supragingival scaling and professional mechanical cleaning (PTC). At the end of the preparatory period (day 0), all subjects were given a final PTC and asked to abstain from all mechanical plaque control measures during the course of a 2-week experimental period but to rinse with an assigned mouth rinse or administer ibuprofen according to protocol. Ibuprofen tablets 200 mg, chlorohexidine (CHX) (0.1%)(positive control) and Saline (CTRL)(negative control) were tested. During the test period, the volunteer were administered 1 tablet of ibuprofen twice a day. Immediately following the day 14 examination, the participants received a new PTC and were instructed to perform proper mechanical plaque control measures. After a 2-week " wash out" period, the participants received a final PTC and a second 14-second day experimental period was initiated. The experimental and "wash out" periods were repeated until all volunteers had been involved in all three regimens.
Microbiological examination: plaque samples: samples were obtained from several tooth surfaces on day 0 and day 14. Dark field microscopy": one hundred bacterial cells were counted and classified according to six different morphological groups: coccoid cells, straight rods, filaments, fusiforms, spirochetes and motile rods. Gingival crevicular fluid: (GCF): GCF samples were obtained immediately after plaque sampling on day 0 and 14. The amount of albumin and lactoferrin were assessed using a sandwich ELISA technique. Analysis of variance (ANOVA) and the Student-Newman-Keuls test were applied to evaluate whether there were significant differences between the treatment groups.

Findings and Conclusions: Plaque scores: the amount of plaque formed in the CHX was significantly smaller than that formed in IBUP and CTRL. Bacterial morphotypes: the examination of plaque samples obtained on day 0 disclosed that there were no significant differences between the three groups regarding the distribution of various bacterial morphotypes. In samples obtained on day 14, the proportions of filaments and fusiforms were significantly smaller in CHX (20%) than in IBUP (29%) and CTRL (305). Also there were a significantly smaller proportion of spirochetes and motile rods occurred in CHX. Gingivitis: after 2 weeks of no mechanical tooth cleaning (day 14), the proportions of sites with GI scores ≥ 2 were in all groups significantly higher than on day 0.in the CHX group, the proportion of sites with GI score ≥ 2 had increased from 4% to 12%, while the corresponding increase in the remaining two groups was 17% (IBUP) and 25% (CTRL). Gingival crevicular fluid: the flow of gingival fluid increased in all three

groups between days 0 and 14. Between days 0 and 14, the amount of Lf in the crevicular fluid samples increased in all three treatment groups. The findings from the examination performed prior to and after 2 weeks of no mechanical tooth cleaning demonstrated that the administration of the anti-inflammatory drug reduced gingivitis, but neither the amount of plaque formed nor the distribution of various bacterial morphotypes in the biofilm appeared to be influenced by the daily use of ibuprofen.

Savage MG, Henry MA. Pre-operative non-steroidal anti-inflammatory agents: review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:146-52. (57 Refs)

Purpose: To document the clinical use and benefits of using pre-operative NSAIDs in patients undergoing elective surgery.

Materials and Methods: Literature review

Findings and Conclusions: Acute tissue injury results in primary and secondary hyperalgsia. Primary hyperalgesia that mostly involves peripheral mechanisms can eventually lead to secondary hyperalgesia that involves CNS mechanisms and both are involved in the development of post-operative pain. NSAIDs act at the site of injury and CNS on the inhibition of prostaglandin formation and also have a direct analgesic effect. When tissue trauma occurs, there is formation of arachidonic acid that is metabolized to prostaglandins by COX dependent mechanisms. While there are at least 5 different prostanoids, PGI2 and PGE2 are implicated in inflammatory pain. The PGs are synthesized after tissue injury and significant concentrations form 1 hour after injury. COX-1 is an enzyme that regulates normal cellular mechanisms that protect the gastric mucosa, platelet aggregation etc. hence when NSAIDs which are non-selective COX inhibitors are used, there is analgesia possible accompanied by GI ulcerations, renal dysfunction and such side effects. Coxibs that are COX-2 specific medications have only been partially successful in eliminating the side effects. There is a lack of consistent results concerning preemptive analgesia in humans especially since the drug, route or dosage were changed pre and post-operatively. Among the common NSAIDs used were Ibuprofen, piroxicam, flurbiprofen, fenbufen, aspirin, indomethacin, and diclofenac. In studies evaluating 1000mg aspirin, there was increased bleeding time, blood loss during and after surgery, increased incidence of ecchymosis, hematoma and swelling, yet no difference in pain experienced in either groups. In studies evaluating the use of Ibuprofen 400mg, the results have been varying, although most demonstrate an analgesic effect when used pre-operatively. Interestingly, in one study, diflunisal was associated with the development of dry sockets to a significant extent. As a note of caution regarding the use of NSAIDs, patients on ACE inhibitors, β-blockers, and diuretics need renal PGs for the efficacy of the drugs, since the renal effect of NSAIDs takes approximately 7-8 days, the duration of administration in these patients should be 5-6 days maximum. NSAIDs should be avoided in patients on anti-coagulants especially long term and in elderly patients. NSAIDs should be avoided in patients with impaired renal function and in patients that are on digoxin, lithium, methotrexate that concentrate in the kidneys and have low therapeutic indices. NSAIDs should not be used in patients with known GI hypersensitivity. Thus, in patients with no contraindication to the use of NSAIDs, the peri-operative use of the drug appears to be beneficial.

Rodrigues RMJ, Goncalves C, Souto R. et al. Antibiotic resistance profile of the subgingival microbiota following systemic or local tetracycline therapy. J Clin Periodontol 2004; 31: 420-27. (46 Refs)

Purpose: To evaluate the changes in the tetracycline resistance profile of the subgingival microbiota in subjects treated with local or systemic tetracycline combined with SRP up to 1 year post-therapy.

Materials and Methods: 30 chronic periodontitis patients (mean age 46±11 years) with at least 20 teeth and 4 sites with PPD >6mm at baseline were recruited. Full mouth measurements, including PPD, CAL, BOP, and Plaque existence were carried out at baseline, 3, 6, and 12 months post therapy. The subjects were divided into 3 groups, 1) SRP+Syst Tet; full-mouth SRP+systemically administered tetracycline (Tetraciclina®), 500mg BID 14days, starting on the first day, 2) SRP only, and 3) SRP+Tet fib; SRP followed by placement of tetracycline fibers (Actsite®) at 4 randomly selected non-adjacent sites with PPD >6mm for 10days and rinsing twice daily with 0.12% chlorhexidine solution (Periogard®) for 2 weeks. No subgingival interventions were performed during maintenance except measurements. Subgingival plaque samples were taken from the 4 selected non-adjacent sites with PPD 6-10mm in each subject for microbiological monitoring at baseline, 1 week, 3, 6, and 12 months post therapy. These samples were cultured according to NCCLS to determine the % of resistant isolates, and prepared for DNA probe and the checkerboard DNA-DNA hybridization. Significance of differences among groups was statistically analyzed.

Findings and Conclusions: At baseline, there is no significant difference in clinical parameters and in mean % of resistant isolates among the groups. At 1 week, the tetracycline groups showed a significantly higher % of resistant microorganisms than the control group. The mean % of resistant isolates did not change significantly in the SRP group overtime. SRP+Syst Tet group showed a marked increase in the % of resistant isolates at 1 week, gradually returning to baseline level. Significant changes were observed in the SRP+Tet fib group, between 1 week and all the other time points. This group showed lowest % of resistant isolates at 6 months. Overall, according to the evaluation of species, Streptococcus spp., Veillonella parvula, Peptostreptococcus micros, Prevotella intermedia, Gemella morbillorum and A. actinomycetemcomitans were the most predominant resistant species before and after treatment. Resistant P. gingivalis was present in 28% of subject sites in the control group, while in only 10% and none of the subject in the tetracycline groups. At 3 months after therapy, the SRP+Syst Tet group showed higher % of sites with resistant P. gingivalis than the other groups. Resistant A. actinomycetemcomitans was still detected in all groups after therapy. The greatest reduction in prevalence of A.a was observed in the SRP+Tet fib groups, especially at 6 months post therapy. This study showed local and systemic tetracycline therapy combined with SRP results in an initial transient increase in the % of resistant microorganisms and in a decrease of the prevalence of resistant suspected periodontal pathogens over time.

Preshaw PM, Hefti AF, Novak JM, et al. Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: A multicenter trial. J Periodontol 2004; 75:1068-1076. (25 Refs)

Purpose: The aim of the study was to investigate the role of subantimicrobial dose doxycycline as an adjunct to S&RP in the treatment of patients with moderate to severe chronic periodontitis.

Materials and Methods: A nine-month, double-blind, randomized, placebo-controlled, multicenter, parallel group study was used. The study was conducted at 6 dental schools in the United States. 210 subjects, 30-75 years of age, with CAL and PD between 5 and 9 mm with bleeding on probing in two sites in each of two quadrants, were selected. Full mouth CAL and PD measurements were recorded. Radiographs were taken to confirm the diagnosis of chronic periodontitis, and to rule out any periapical pathology. Demographic information, details of oral hygiene practices and a smoking history were recorded. Scaling and root planing was performed. Subjects were randomly chosen to receive either adjunctive subantimicrobial dose doxycycline (doxycycline hyclate 20 mg bid) or an adjunctive placebo bid for 9 months. Subjects were instructed to take the study medication once in the morning and once in the evening, 1 hour prior to meals, at approximately 12-hour intervals. Study medication and placebo were identical in appearance and dispensed in three-month quantities at baseline, and 3 and 6 months. Subjects received full mouth clinical examinations at 3,6, and 9 months. At month 9, a dental prophylaxis was performed and the study ended. Efficacy parameters included mean changes in CAL and PD from baseline, and the total number of sites with attachment gains and probing depth reductions of >2mm and >3mm from baseline.

Findings and Conclusions: 157 subjects completed the study. There was a significant difference between the number of smokers in the SDD group(38%) vs. the placebo group(25%) based on randomization, but all other variables were similar. Improvements in CAL and PD from baseline were seen in both groups. However, month 9 mean CAL gains and PD reductions were significantly greater with adjunctive SDD than placebo. Compliance with study drug therapy was high (>87% at all time points) and was recorded by counting the number of tablets dispensed and returned.

Effect of subantimicrobial dose doxycycline on clinical attachment gains and probing depth reductions at month

	All Sites (baseline PD	> 4 mm)	Deep Sites (baseline PD	> 6mm)
Change from baseline	SRP + placebo (N=2,964) % (N)	SRP + SDD (N=3,465) % (N)	SRP + Placebo (N=998) % (N)	SRP + SDD (N=1,151) % (N)
CAL > 2 mm	32.0 (949)	42.3 (1464)	44.0 (439)	58.3 (671)
CAL > 3 mm	10.6 (315)	15.4 (532)	20.0 (200)	33.2 (382)
PD reduction >2 mm	31.1 (923)	42.9 (1487)	45.0 (449)	62.3 (717)
PD reduction >3 mm	9.1 (271)	15.4 (535)	20.6 (206)	36.7 (422)

Adjunctive subantimicrobial dose doxycycline enhances scaling and root planing and results in statistically significant attachment gains and probing depth reductions over those achieved by scaling and root planing with placebo.