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CHEMOTHERAPEUTIC AGENTS IN CONTROLLING PERIODONTAL DISEASE

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ABSTRACT

Aim-To review the use of various anti-microbial adjuvants in the treatment of periodontal disease along with mandatory scaling and root planing. **Background**-Periodontal disease is a chronic bacterial infection of the periodontal tissues which can negatively affect the quality of life of the individual.5 to 30% of the adult human population is affected by this disease.Proper diagnosis and appropriate treatment with scaling and root planing along with the judicious use of various anti-microbial agents helps in controlling the periodontal disease.This article is aimed at reviewing the various anti-microbial agents used to combat periodontal disease.

KEY WORDS: *periodontal disease,scaling and root planing,bacterial infection,anti-microbial agents.*

INTRODUCTION

Dental research has provided us with a better understanding of the microbial etiology and the nature of periodontitis. Periodontitis, initiated by bacteria, appears abundantly in the patient's mouth or is confined to localized areas by treatment. These infected localized areas lend themselves well to treatment in which conventional scaling and root planing are carried out along with the use of antimicrobial agents. Antiseptic mouthrinses have been used to aid in controlling plaque buildup. They have been used to complement, not replace mechanical therapy. Two clinically proven ADA-accepted antiseptic mouthrinses are Peridex (Zila, Inc., Phoenix, Arizona; chlorhexidine gluconate) and Listerine Antiseptic Mouthrinse (four essential oils; Pfizer, Inc., Morris Plains, New Jersey), studied in clinical trials of at least 6 months' duration. Both of these rinses have demonstrated an extremely broad spectrum of kill in vitro and in vivo. In a number of randomized, double-blinded, controlled 6-month clinical studies, these two agents demonstrated comparable efficacy for improving reductions in plaque and gingivitis compared with brushing alone[1] Clinical studies have demonstrated additional benefits with the use of these antiseptic mouthrinses, such as control of oral malodor[2] enhancement of the benefits of oral irrigation improvement in the gingival health around dental implants[3] reductions in plaque and gingivitis in orthodontic patients[5] reductions in bacteria in saliva and dental aerosols when used preprocedurally[6] and support of early healing after gingival flap surgery.[7,8]

Chlorhexidine gluconate

Chlorhexidine gluconate is available at 0.12% in the United States and has strong substantivity[5] Chlorhexidine is available only by prescription and is partly to fully covered by some prescription plans. Chorhexidine can stain teeth, the tongue, and aesthetic restorations. It can promote supragingival calculus formation and may alter taste perception[4,] When prescribed, it is recommended that patients rinse twice a day for 30 seconds with 15 mL after brushing and flossing and after the toothpaste has been completely rinsed out of the mouth. Listerine is available over-the-counter and is composed of a fixed combination of essential oils: thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), and menthol (0.042%). Some patients complain of a transient tingling sensation. Listerine's comparable efficacy in reducing interproximal plaque and gingivitis to the ''gold standard'' of flossing was demonstrated in a recent study in which 611 subjects rinsed twice daily or flossed once daily as an adjunct to brushing for 6 months.[9,10] In addition, the incremental benefit (with regard to plaque and gingivitis reduction) of Listerine in patients who were already brushing and flossing was demonstrated in a brush, floss, and rinse study.[11]

The recommendation for use is rinse twice a day for 30 seconds with 20 mL after brushing and flossing.

Toothpaste-Triclosan.

Triclosan is present in a toothpaste (Colgate Total; Colgate Palmolive, Piscataway, New Jersey) currently

available in the United States. Triclosan is a substantive antibacterial agent that adheres to the oral mucosa, hard, and soft tissues for up to 12 hours. Colgate Total is approved by the Food and Drug Administration (FDA) and accepted by the ADA for treatment of gingivitis, plaque, caries, calculus, and oral malodor. Placebo controlled studies in smokers and in subjects with recurrent periodontitis [12], suggest that an oral hygiene regimen including a triclosan/copolymer dentrifice may sustain the short-term effect of nonsurgical therapy in smokers and improve on healing after nonsurgical treatment of recurrent periodontitis as measured by improvements in gingival inflammation. probing depths, and probing attachment levels. Triclosan in vitro has anti-inflammatory effects, inhibiting cytokine-stimulated (interleukin 1b and tumor necrosis factor a) production of prostanoids (prostaglandin E2) from monocytes, reducing the activity of the enzyme cyclooxygenase 2 responsible for the production of prostanoids in culture. and inhibiting bone resorption in a parathyroid hormone–induced release of calcium from bone cultures.[13]

Locally applied antimicrobials
To have a therapeutic effect on the microflora, antimicrobial agents must reach adequate concentrations to kill or inhibit the growth of target organisms. The drug of choice has to reach the site where the organisms exist, stay there long enough to get the job done, and not cause harm. Mouth rinses do not reach the depths of periodontal pockets, whereas irrigation can deliver drugs to the base of the pocket. With regard to the systemic administration of antibiotics to patients with periodontitis, early research suggested that doxycycline administered systemically [14], was highly concentrated in the GCF at levels 5 to 10 times greater than found in serum. Furthermore,tetracyclines show substantivity because they bind to the tooth structure and are slowly released as still-active agents. Even this supposed hyperconcentration of the drug in the GCF resulted in a level of antibiotic to which many organisms were not susceptible. More recent work has challenged earlier findings of hyperconcentration of tetracyclines in the GCF. In the 2 hours after the administration of a single dose of tetracycline (250 mg), minocycline (100 mg), or doxycycline (100 mg), the concentration of these tetracyclines was found to be highest in the plasma, intermediate in the GCF (doxycycline achieving the highest levels), and lowest in the saliva[15].

To address the issue of reaching adequate concentrations at the base of the pocket with adequate duration, controlled local delivery of antimicrobials was developed.

These infected localized areas lend themselves well to treatment with a controlled local delivery system using an antimicrobial,[16] Antimicrobial agents may be applied directly to the pocket, thereby eliminating many of the adverse side effects associated with systemic delivery of antibiotics.

Table 1: Periodontal antimicrobial delivery system

Objective	Mouthrinse or toothpaste	Local irrigation	Systemic delivery	Controlled delivery
Reach the pocket<4mm	poor	good	good	Excellent
Adequate concentration	poor	good	fair	Excellent
Adequate duration	poor	poor	fair	good

Nonresorbable and resorbable intrapocket delivery systems have been used.

Systems have been developed for the release of all three commercially available tetracyclines at high doses and at a regular rate over a 10- to 14-day period. The first such FDA-approved system, Actisite, was developed by Dr. Max Goodson in 1983.[17]

Actisite consisted of a nonresorbable polymer fiber of ethyl vinyl acetate, 25% saturated with tetracycline hydrochloride. Use of this product resulted in substantially higher doses of tetracycline in the pocket (1590 mg/mL in the GCF and 43 mg/mL in the tissue) than could be achieved by systemic dosing (2–8 mg/mL). A local concentration of 30 mg/mL eliminates most pathogenic bacteria associated with periodontal diseases. When using locally applied antimicrobials, the area being treated is saturated with doses of the therapeutic agent that can be sustained for prolonged periods. Despite the high doses of drug that are achieved locally, serum levels of the drug do not exceed 0.1 mg/mL. The use of a singly applied tetracycline fiber as an adjunct to scaling and root planing(SRP) proved to be more effective than scaling alone at reducing bleeding on probing, pocket depth, and achieving attachment gain as early as 60 days after placement, with additional improvements at 6 months. At 6 months after a single application of Actisite, the respective average results for SRP plus tetracycline fiber therapy versus SRP only were1.81 mm versus 1.08 mm for pocket depth, 1.56 mm versus 1.08 mm for attachment gain, and 63% versus 50% for bleeding on probing reductions , Subsequent studies concluded that SRP combined with full-mouth Actisite therapy versus SRP alone resulted in increased bone density (þ2.43 computer-assisted densitometric image analysis [CADIA] versus _2.13 CADIA) and increased alveolar bone height (þ0.24 mm versus _0.29 mm) at 6 months after therapy,[18] Despite its demonstrated efficacy, this product is no longer marketed to the dental community. Actisite was difficult to use, requiring considerable operator skill, and because

it was not resorbed, a second visit had to be scheduled to remove it.

In attempts to improve on ease of placement of local antimicrobials into the pocket and to obviate the need for a second visit to remove the product, bioabsorbable delivery systems were developed.

Atridox. The second FDA-approved locally delivered tetracycline to be developed was Atridox (Atrix Laboratories, Inc., Fort Collins, Colorado), a 10% formulation of doxycycline in a bioabsorbable, ''flowable'' poly-DLlactide and N-methyl-2-pyrrolidone mixture delivery system that allows for controlled release over 7 days. This system is supplied in two prefilled syringes to be mixed at chairside and applied subgingivally to the base of the pocket through a cannula. The flowable polymer gel of Atridox fills and conforms to pocket morphology, then solidifies to a wax like substance after contact with GCF. Significant reductions (60%) in anaerobic pathogens are sustained for up to 6 months after placement of Atridox.

A recent study supports these findings, indicating that locally applied Atridox improves the healing following nonsurgical therapy in smokers [19]. Removal of the offending plaque and calculus deposits by SRP has proved to be effective. Disruption of the biofilm improves on the efficacy of antimicrobial agents. Phase IV studies conducted to support improved outcomes by using Atridox as an adjunct to scaling have demonstrated incremental benefits of use.[20]

Atridox is the only resorbable site-specific locally applied antibiotic proven to promote clinical attachment gains and reduce pocket depths, bleeding on probing, and levels of pathogenic bacteria. Arestin. With regard to minocycline, there is a non–FDA-cleared ointment product of 2% (wt/wt) minocycline hydrochloride known as Dentamycine (Wyeth, United Kingdom) or PerioCline (Sunstar, Japan) and marketed in a number of countries.

A minocycline microsphere system (Arestin; Johnson and Johnson, New Brunswick, New Jersey) has been approved by the FDA. The Arestin microspheres are bioadhesive, bioresorbable, allow for sustained release, and are administered as a powder with a proven safety record. Arestin is indicated as an adjunct to SRP procedures for reduction of pocket depth in patients with adult periodontitis. Arestin may be used as part of a periodontal maintenance program, which includes good oral hygiene and SRP. In subjects with chronic adult periodontitis, the application of minocycline microspheres three times over the course of 9 months (at baseline and at 3 and 6 months) resulted in an average of 0.25 mm improvement above average probing depth reductions seen with SRP alone at month 9.[21]

Metronidazole gel
Another material is Elyzol (Colgate), a metronidazole gel system supplied as 25% metronidazole in a glyceryl mono-oleate and sesame oil base. The concentration of Metronidazole in this system is 250 mg/g of material that is applied as a gel using a syringe method.[22]

Systemic antimicrobials
For the most part, systemic antimicrobial therapy has been reserved for advanced cases of periodontitis: for sites that have not responded as expected to debridement with or without locally applied chemotherapeutic agents and/or host modulatory agents, and for patients diagnosed with aggressive forms of periodontitis that demonstrate progressive periodontal destruction. Systemic antibiotics may be recommended as adjuncts to conventional mechanical therapy, but strong evidence for their use as a monotherapy has not been developed. There appears to be a consensus that systemic antimicrobial therapy should be reserved for situations that cannot be managed with mechanical therapy alone (with or without locally applied antimicrobials or antiseptics), such as severe or acute infections, early-onset periodontal diseases, aggressive types of periodontitis, and recurrent or refractory cases [23]. For these special situations, randomized double-blinded clinical trials and longitudinal assessments of patients indicate that systemic antimicrobials may be useful in slowing disease progression Acute necrotizing ulcerative gingivitis can be cured with metronidazole, and aggressive adolescent periodontitis associated with Actinobacillus actinomycetemcomitans can be controlled or eradicated with metronidazole-amoxicillin combination therapy.

Systemic antibiotic therapy has the advantage of simple, easy administration of a drug or combination of drugs to multiple periodontal sites and extra-dental oral sites that may harbor periodontal pathogens. The disadvantages include uncertain patient compliance, the inability of the drugs to achieve adequate concentration at the site of infection, increased risk of adverse drug reactions, the potential for the selection of multiple antibiotic-resistant organisms, and the overgrowth of opportunistic pathogens. Common antibiotic therapies for the treatment of periodontitis include metronidazole, 500 mg, three times a day for 8 days; clindamycin, 300 mg, three times a day for 8 days; doxycycline or minocycline, 100 to 200 mg, every day for 21 days; ciprofloxacin, 500 mg, twice a day for 8 days; azithromycin, 500 mg, every day for 4 to 7 days; metronidazole and amoxicillin, 250 mg of each drug, three times a day for 8 days; and metronidazole and ciprofloxacin, 500 mg of each drug, twice a day for 8 days.[24] For adult patients with acute periodontal abscesses, an antibiotic regimen as an adjunct to incision and drainage is amoxicillin (1 g loading dose followed by 500 mg, three times a day for 3 days), with patient follow-up re-evaluation. For patients with allergies to b-lactam drugs, antibiotic regimens include azithromycin (1 g loading dose followed by 500

mg, every day for 2 days) or clindamycin (600 mg loading dose followed by 300 mg, four times a day for 3 days).

CONCLUSION

With the availaibility of different antimicrobial agents in easy-to-use forms,periodontal destruction and tooth morbidity has become more manageable than before. Proper diagnosis,treatment planning,patient education and motivation along with frequent recall visits ensure successful management of periodontal diseases.

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