RESEARCH ARTICLE

CHOICE OF ANTI-MICROBIALS IN PERIODONTAL THERAPY

Dr. Vineet Nair *

Abstract

Periodontitis is a polymicrobial infectious disease with marked inflammatory response, leading to the destruction of the underlying periodontal tissues. Periodontal therapy directed to eradicate these pathogens and attain periodontal health can be accomplished by either non-surgical methods alone or in combination with surgical means. Topical and systemic antibiotics are prescribed in both forms of therapy. The aim of this review article is to provide basic details of a few such systemic anti-microbial agents used in periodontal therapy.

Key Words Anti-microbial; Penicillin; Tetracycline; Quinolone

INTRODUCTION

Periodontal disease occurs in a susceptible host when his periodontal tissues become colonized by specific oral pathogens in numbers sufficient to overwhelm the defence system. Clinical success in the treatment of these diseases requires reduction of the bacterial load. This is achieved by education of patients in daily oral hygiene, non-surgical and surgical mechanical debridement and supportive periodontal therapy generally at 3 to 6 months interval. Inspite of these treatment modalities, adjunctive chemotherapeutic agents may be necessary to control the disease process.

An antimicrobial agent is a chemotherapeutic agent that works by reducing the number of bacteria present. Antibiotics are a naturally occurring, semisynthetic or synthetic type of antimicrobial agent that destroys or inhibits the growth of selective microorganisms, generally at low concentrations. Antiseptics are chemical antimicrobial agents that are applied topically or subgingivally to mucous membranes, wounds or intact dermal surfaces to destroy microorganisms and inhibit their reproduction or metabolism. In dentistry, antiseptics are widely used as the active ingredient in anti-plaque mouthrinses and dentifrices. Disinfectants, a subcategory of antiseptics, are antimicrobial agents that are generally applied to inanimate surfaces to destroy microorganisms.[1]

Chemotherapeutic agents can be administered locally, orally or parenterally. Systemic antibiotics may be an essential adjunct in controlling bacterial infection because bacteria can invade periodontal tissues, making mechanical therapy alone sometimes futile.[2,3] Local administration of antimicrobial agents, directly into the periodontal pocket has the potential to provide greater concentrations directly to the infected area and reduce possible systemic side effects.

Systemic administration of antibiotics

Ideally, the causative microorganism(s) should be identified first and then the most effective drug should be selected using antibiotic sensitivity tests. The different anti-microbial agents used in periodontal therapy are penicillins, cephalosporins, tetracyclines, macrolides, nitroimidazole compounds and quinolones. An ideal antibiotic for use in the prevention and treatment of periodontal diseases should be specific for periodontal

ABOUT THE AUTHORS

*Assistant Professor, Department Of Periodontia, Burdwan Dental College And Hospital, Burdwan, West Bengal, India

pathogens, nontoxic, substantive, not in general use for treatment of other diseases and inexpensive.[4] Currently, an ideal antibiotic for the treatment of periodontal diseases does not exist.[5] We shall now discuss some of the commonly prescribed anti-microbials. The common antibiotic regimens used in treating periodontal diseases are presented in Table1.

● Penicillin (Acts by inhibition of cell wall synthesis)

They are natural and semi-synthetic derivatives of broth cultures of Penicillium mold. Penicillin acts by inhibition of cell wall synthesis, is bactericidal in nature and possess substantial anti-bacterial activity against gram-negative species. Amoxicillin exhibits high anti-microbial activity at gingival crevicular fluid (GCF) levels against gram-positive periodontal pathogens except E. corrodens, Selenomonas sputigena and Aggregatibacter actinomycetemcomitans (A.a). It inhibits the growth of gram-positive facultative anaerobes such as Streptococcus and Actinomyces, except Peptostreptococcus which is an obligate gram-positive anaerobe. Penicillin may be associated with hypersensitivity reactions (anaphylaxis). It may develop resistance and may result in diarrhoea.

Administration of beta-lactamase sensitive penicillins is not generally recommended and in some cases might accelerate the periodontal destruction.[6] This can be evaded by the use of a β-lactamase inhibitor such as clavulanic acid. The concentrations achieved in GCF are 14.05 µg/ml (amoxicillin) and 0.40 µg/ml (clavulanic acid).[7] This combination may be useful in the management of patients with localized aggressive periodontitis (LAP).[7,8] Bueno et al (1988) reported that this combination arrested alveolar bone loss in patients with periodontal disease that was refractory to treatment with other antibiotics including tetracycline, metronidazole and clindamycin.[9]

● Cephalosporin (Acts by inhibition of cell wall synthesis)

They are similar in action and structure to penicillins and are effective in the treatment of gram-positive infections. It can effectively inhibit the growth of gram-negative obligate anaerobes like P. gingivalis, P. intermedia, Fusobacterium sputigena and B. forsythus but may fail to inhibit gram-negative facultative anaerobes. [10] No clinical trials in periodontal therapy have been conducted.

● Tetracycline (Acts by reversible inhibition of protein synthesis)

Tetracyclines are bacteriostatic in nature and require access to inside of the bacterial cell. Doxycycline and minocycline are more lipid-soluble than tetracycline and thus pass directly through the lipid bilayer of bacterial cell wall. Within the cell, tetracycline binds specifically to 30S sub-unit of ribosome. There is also evidence that tetracycline may cause alterations in bacterial cytoplasmic membrane, facilitating leakage of nucleotides and other compounds from the cell.[11] Doxycycline has the highest protein binding capacity and the longest half-life while minocycline has the best absorption and tissue penetration capability. Absorption of tetracycline from the gastrointestinal tract is fairly rapid but is reduced if the drug is taken with milk or with substances containing calcium, magnesium, iron or aluminium as it results in chelate formation.

Tetracyclines are effective in treating periodontal diseases because their concentration in the gingival crevice is 2 to 10 times that in serum. This allows a high drug concentration to be delivered into the periodontal pockets.[12] The GCF concentration achieved by tetracycline is 4-8 µg/ml and plasma concentration achieved is 1.9-2.5 µg/ml. Doxycycline GCF levels reach 1.2-8.1 µg/ml while the same for minocycline is 6.0 µg/ml. Plasma concentration achieved by doxycycline and minocycline is 2.1-2.9 µg/ml and 2.6-3.3 µg/ml respectively.[13]

Tetracycline, minocycline and doxycycline are greatly effective in inhibition of gram-negative facultative anaerobes like A.a, Campylobacter rectus, Eikenella corrodens and Capnocytophaga sp. Tetracyclines have proven to be beneficial in the treatment of LAP, generalized aggressive periodontitis (GAP) and chronic periodontitis.[14-17]

Apart from antibacterial activity, tetracycline also exhibits additional pharmacological properties, which include-

i) Collagenase inhibition- Tetracycline has anti-collagenase property but this activity appears to be related to the source of enzyme and tetracycline used. Tetracycline is less active against fibroblast-type collagenase and most active against neutrophil-derived collagenase.[18]

ii) Anti-oxidative property- Tetracycline can scavenge reactive oxygen radicals (e.g., hypochlorous acid and hydroxyl groups) produced by polymorphonuclear neutrophils (PMNs) which have been found to activate latent collagenase. Thus tetracyclines can prevent the oxidative activation of latent collagenase.[19]

iii) Anti-proteolytic property- Tetracycline inhibition of neutrophil collagenase may also prevent other proteolytic events because neutrophil collagenase (MMP-8) as well as neutrophil-derived reactive oxygen species, i.e., hypochlorous acid, hydrogen peroxide and hydroxyl radicals can degrade and inactivate α-1 proteinase inhibitor.[20]

iv) Inhibition of bone resorption - Tetracycline inhibits osteoblast collagenase and may also have a modifying effect on osteoclasts.[21] Tetracyclines inhibit bone resorption induced by parathyroid hormone.[22]

v) Anti-inflammatory action- Tetracycline can suppress PMN activity, in particular, by scavenging action on reactive oxygen metabolites. The drug may block eicosanoid synthesis (especially PGE2) by inhibiting phospholipase A2 activity.[23]

vi) Conditioning agent- Pre-treatment of dentin with tetracycline enhances fibroblast attachment and colonization.[24]

vii) Property of substantivity[25]

viii) Sub-inhibitory concentrations have been shown to reduce adherence and co-aggregation of species including P. gingivalis and P. intermedia.[26]

● Macrolide (Acts by reversible inhibition of protein synthesis)

Erythromycin was the first macrolide used and has a wide range of activity against both gram-positive facultative and anaerobic bacteria. However, most gram-negative microorganisms are resistant to erythromycin due to its inability to penetrate the lipopolysaccharide-cell wall complex. The GCF concentration achieved is 0.4-0.8 µg/ml.[13] Other limitations include its poor tissue absorption.

Newer macrolides include clindamycin and azithromycin. Clindamycin is active against gram-positive cocci, including many penicillin resistant staphylococci and anaerobic species such as bacteroides species. It is effective against most periodontal pathogens with important exception of A.a and Eikenella corrodens.[27] It has good bone penetrating capacity.[28] The GCF concentration achieved is 1-2 µg/ml and plasma concentration achieved is 1-9 µg/ml.[13] Clindamycin has been used for the treatment of refractory periodontitis and rapidly progressing periodontitis (such disease terminologies however no longer exists).[29-31] Clindamycin should be prescribed with caution because of the potential for pseudomembranous colitis as a result of intestinal overgrowth with Clostridium difficile.[32]

Azithromycin shows good bacteriostatic in-vitro activity against a wide variety of organisms. It should be taken one hour before or two hours after food intake. It has a long half-life, provides higher drug concentrations in the tissues than in blood or serum and exhibits excellent ability to penetrate into both normal and pathological periodontal tissues.[33] Also, azithromycin is preferentially taken up by phagocytes and so its level in infected tissues is much higher than in similar non-infected sites.[34] It is active against gram-negative anaerobes and highly effective against all serotypes of A.a and against Porphyromonas gingivalis.[35, 36] Azithromycin has also been used in the treatment of chronic periodontitis.[37,38]

● Quinolone (Acts by inhibition of DNA synthesis)

Ciprofloxacin is effective against a wide range of both gram-positive and gram-negative microorganisms. Clinically, ciprofloxacin is best used for infections caused by facultative and aerobic gram negative rods and cocci. It should be taken one hour before or two hours after food intake. It penetrates readily into the periodontal tissues and GCF and may reach even higher concentrations than in serum. According to Conway TB et al. (2000), mean GCF ciprofloxacin levels observed were 2.5-2.7 µg/ml which were well in excess of ciprofloxacin MIC for A.a (0.010 µg/ml).[39] It should not be prescribed to children and young individuals due to potential joint problems.

Kleinfelder et al. (2000) reported that systemic ofloxacin in conjunction with open flap surgery was able to suppress A.a below detectable levels in 22 study patients for a period of twelve months.[40] It has been used in Papillon Lefevre syndrome patients with A.a and in advanced periodontal disease.[41,42]

● Nitroimidazole compound (Acts by inhibition of DNA synthesis)

Metronidazole has broad in-vitro activity against anaerobic organisms. The gram-negative obligate anaerobes are P. gingivalis, P. Intermedia, Fusobacterium, Selenomonas sputigena and Bacteroides forsythus. The gram-positive obligate anaerobes includes Peptosteptococcus. C. rectus, a facultative anaerobe is susceptible to low concentration of metronidazole. Following systemic administration relatively high peak plasma concentrations are attained within 1-3 hours. The GCF concentration achieved is 13.7 µg/ml and plasma concentration achieved is 14.3 µg/ml.[13] Ornidazole has a higher level of half-life elimination from plasma (14.4 hrs) than metronidazole (8.4 hrs), therefore requires less frequent intake, that is twice-daily. Liew V et al. (1991) stated that metronidazole can readily attain effective anti-bacterial concentrations in gingival tissue and crevicular fluid.[43]

Nitroimidazole compounds have been used for the treatment of ANUG, refractory periodontitis, chronic periodontitis and early onset periodontitis.[44-47] A unique side effect of metronidazole is a disulfiram (antabuse) effect. This effect causes cramps, nausea and vomiting following alcohol consumption.[48] Metronidazole should also be avoided in patients undergoing anti-coagulant or lithium therapy, pregnancy or in those with a history of seizures.[49]

● Combination therapy

It might provide a synergistic reaction as compared to use of any single antibiotic thus helping to lower the dose of individual drugs. Chances of bacterial resistance is decreased by using agents with overlapping anti-microbial spectra. Different

combinations are used for treatment of periodontal diseases. Metronidazole-amoxicillin combination is used in A.a associated LAP, GAP, Papillon Lefevre syndrome periodontitis, chronic periodontitis and also in P. intermedia infected sites.[50-53] Metronidazole-ciprofloxacin combination is used in recurrent chronic periodontitis. Metronidazole-amoxicillin-clavulanic acid combination has been used in refractory periodontitis, though now such a disease terminology does not exist.[54,55]

Disadvantages of combination therapy include increased risk for adverse reactions and antagonistic drug interactions with improperly selected antibiotics. Bactericidal antibiotic (β Lactam drugs or metronidazole) should not be used with bacteriostatic agents (tetracyclines) because the bactericidal agent exerts activity during cell division that is impaired by bacteriostatic drug. Neither erythromycin nor azithromycin should be given concurrently with clindamycin as they have similar modes of action.

CONCLUSION

Since periodontal pathogens display diverse anti-microbial susceptibility, microbiological analysis should be carried out before prescribing antibiotics and as antibiotic resistance constitutes an increasing problem, anti-microbial susceptibility testing of isolated pathogens is important.

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DRUG	REGIMEN	DURATION
SINGLE AGENT		
Amoxicillin	500 mg thrice daily	8 days
Tetracycline	250 mg four times daily	
Doxycycline	100 mg twice daily on first day, then 100 mg once daily	
Minocycline	100 mg twice daily	7 Days
Erythromycin	250 mg thrice daily	
Clindamycin	300 twice daily	8 Days
Azithromycin	250 mg once daily after a loading dose of 500 mg	5 Days
Ciprofloxacin	500 mg twice daily	8 Days
Metronidazole *	250-500 mg thrice daily	8 Days
Tinidazole	300-500 mg twice daily	
Ornidazole	500 mg twice daily	
COMBINATION		
Metronidazole* + Amoxicillin	250 mg of each thrice daily	8 Days
Metronidazole + Ciprofloxacin	500 mg twice daily	8 Days

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