

ADJUNCTIVE USE OF ANTIBIOTICS IN PERIODONTAL THERAPY

Periodontal Tedavide Kullanılan Antibiyotikler

Ece BARÇA, Emine ÇİFCİBAŞI, Serdar ÇİNTAN

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ABSTRACT

Periodontal diseases are infectious diseases with a mixed microbial aetiology and marked inflammatory response leading to destruction of underlying tissue. Periodontal therapy aims to eliminate pathogens associated with the disease and attain periodontal health. Periodontitis is generally treated by non-surgical mechanical debridement and regular periodontal maintenance care. Periodontal surgery may be indicated for some patients to improve access to the root surface; however, mechanical debridement alone may not be helpful in all cases. In such cases, adjunctive systemic antibiotic therapy remains the treatment of choice. It can reach microorganisms at the base of the deep periodontal pockets and furcation areas via serum, and also affects organisms residing within gingival epithelium and connective tissue. This review aims to provide an update on clinical issues regarding when and how to prescribe systemic antibiotics in periodontal therapy. The points discussed are the mode of antibiotic action, susceptible periodontal pathogens, antibiotic dosage, antibiotic use in treatment of periodontal disease, and mechanism of bacterial resistance to each antibiotic.

Keywords: Systemic antibiotics; periodontal disease; treatment; aggressive periodontitis; chronic periodontitis

ÖZ

Periodontal hastalıklar periodontal dokuların doku yıkımına yol açan, karışık mikrobiyal etyolojisi ve belirgin inflamatuvar yanıt ile karakterize enfeksiyöz hastalıklardır. Periodontal tedavinin amacı, hastalık ile ilişkili patojenlerin ortadan kaldırılması ve periodontal sağlığın elde edilmesidir. Periodontitis tedavisi genellikle cerrahi olmayan mekanik debridman ve düzenli periodontal bakım ile yapılır. Periodontal cerrahi bazı hastalarda kök yüzeyine erişimi artırmak için endike olabilir; ancak, yalnız mekanik debridman tüm durumlarda yarar sağlamayabilir. Bu tür durumlarda, ilave antibiyotik tedavisi düşünülebilir. Böylece, serum ile derin periodontal cepler ve furkasyon alanlarının tabanında mikroorganizmalara ulaşım ve aynı zamanda dişeti epitel ve bağ dokusu içinde bulunan organizmalara etki sağlanır. Bu derlemede, periodontal hastalıkta ne zaman ve hangi durumlarda sistemik antibiyotik reçete edilmesi gerektiği üzerine güncel klinik yaklaşımlar değerlendirilmiştir. Etki mekanizmaları, duyarlı periodontal patojenler, dozaj, periodontal hastalıkların tedavisinde kullanımı ve her antibiyotik için bakteri direnç mekanizması tartışılmıştır.

Anahtar kelimeler: Sistemik antibiyotikler; periodontal hastalık; tedavi; agresif periodontitis; kronik periodontitis



Introduction

Periodontitis is an infection caused by bacteria residing in biofilms at or below the gingival margin. Destructive periodontal disease appears to be caused by subgingival infection by specific microbial agent(s). Traditional therapy for this disease has involved elimination or suppression of subgingival microbial complexes by mechanical debridement such as scaling and root planning or surgical procedures. However, the pathogenic microbiota becomes more complex over time, so systemic administration of antibiotics may be required as an adjunct in controlling bacterial infections. Because bacteria can invade periodontal tissues, mechanical therapy alone is sometimes ineffective (1). In this case, the microbial aetiology of inflammatory periodontal diseases provides the rationale for using antimicrobial medication in periodontal therapy.

The complex structure of the periodontal biofilm, consisting of multiple bacterial communities residing in a glycocalyx matrix, has been well described by Marsh (2). It has been demonstrated that once bacteria attach to a tooth surface and reside within a mature biofilm structure, they have reduced susceptibility to antimicrobials compared with planktonic or free-floating bacteria (3). Therefore, mechanical debridement is considered critical to disrupt the biofilm when using systemic antibiotics to treat periodontitis. The rationale for use of adjunctive systemic antimicrobials is to further reduce the bacterial load, enabling resolution of the inflammation in the periodontal pocket. Antibiotics may be prescribed for periodontal patients who do not respond to conventional mechanical therapy, for patients with acute periodontal infections associated with systemic manifestations, for prophylaxis in medically compromised patients, and as an adjunct to surgical and non-surgical periodontal therapy.

Application of antibiotic periodontal therapy focuses on the pathogenic microbiota, the patient, and the choice of drug.

Periodontal Pathogens

The most effective use of antibiotics for the treatment of periodontitis presupposes knowledge of the pathogenic microbiota. More than 700 bacterial taxa have been identified within periodontal pockets (4). However, relatively few species have been clearly associated with progressive periodontitis. Most

putative pathogens are indigenous to the human oral cavity, but possible superinfecting organisms (enteric Gram-negative rods, pseudomonas, staphylococci, and yeasts) may also inhabit periodontal pockets. Periodontitis lesions usually harbour a constellation of putative pathogens rather than a single pathogenic species. Most putative periodontal pathogens are Gram-negative anaerobic rods. However, some pathogens are Gram-positive facultative and anaerobic cocci and rods, and others are Gram-negative facultative rods. Putative periodontal pathogens vary considerably in sensitivity to several antibiotics, making simplistic approaches to antimicrobial chemotherapy problematic (5).

Patients

Prime candidates for systemic antibiotic therapy are patients who exhibit on-going periodontal attachment loss, despite conventional mechanical periodontal therapy. Recurrent or refractory periodontitis is often related to persistent subgingival pathogens and perhaps to impaired host resistance (6). Patients with aggressive types of periodontitis (7), or with medical conditions predisposing them to periodontitis may benefit from antibiotic therapy. Patients with acute or severe periodontal infections (periodontal abscess, acute necrotizing gingivitis/periodontitis) may also need antibiotic therapy (8). Patients with gingivitis or chronic periodontitis usually respond well to mechanical debridement and topical antiseptics and may not derive clinically significant additional benefit from antibiotic therapy (9). However, evidence exists suggesting that antibiotic use in chronic periodontitis may result in improvement in clinical attachment level, although many questions regarding the indications for this therapy remain unanswered (10).

Drugs

The pharmacological characteristics of antibiotics are critical in deciding their use, dosage, and routes and frequency of administration. Important pharmacological determinants include body weight, degree of absorption, rate of metabolism, and duration of effective antimicrobial levels at the site of infection. To maintain effective antimicrobial levels after oral administration, penicillin and clindamycin must be taken three times a day, metronidazole and ciprofloxacin twice a day, and doxycycline and azithromycin once

a day. The efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and the pharmacokinetic characteristics of the drug (11) as well as by local environmental factors including (12); 1) drug binding to tissues, 2) protection of pathogens through binding, consumption, or degradation of the drug by non-target microorganisms, 3) subgingival plaque biofilm protecting the pathogens, 4) total bacterial load relative to the maximum achievable antibiotic concentration, 5) effectiveness of the host defences, and 6) pathogens in periodontal tissues, root surfaces, and extra-dental oral sites not affected by the therapy. The unique therapeutic difficulties imposed by dental biofilms are highlighted elsewhere (13).

Systemic antibiotics may enable simple drug administration to multiple sites of disease activity. Antibiotics may also eliminate or reduce pathogens colonising on oral mucosa and on other extra-dental sites including the tongue and tonsillar areas (14). The possibility of markedly suppressing or eliminating periodontal pathogens from virtually the entire mouth may reduce the risk for future translocation of organisms and recolonisation of the periodontal pocket, thereby potentially reducing the risk for recurrent disease progression. Compared with locally applied antimicrobial agents, the disadvantages of systemic antibiotic therapy include the inability of systemic drugs to achieve high gingival crevicular fluid concentration (19), increased risk of adverse drug reactions (15), increased selection of multiple antibiotic resistant microorganisms (5), and uncertain patient compliance (16). Combination drug therapy may be useful in periodontitis that involves a variety of periodontopathic species with differing antimicrobial susceptibilities or to overcome the drug-protective effects of the biofilm. Therapeutic failure with some antibiotic regimens due to the presence or development of resistant strains may be an emerging problem in periodontal treatment (5). One strategy to combat resistant subgingival bacteria is the use of treatment regimens that incorporate agents with complementary but different mechanisms of action. Combination therapy should include drugs that exhibit synergistic or additive effects in vitro. Metronidazole-amoxicillin and metronidazole-ciprofloxacin act synergistically against *Aggregatibacter actinomycetemcomitans* and other major periodontal pathogens (17). Studies of several types of periodontitis have evaluated systemic antibiotics as an adjunct to periodontal scaling and root planning. This complies with the good medical practice of reducing the bacterial load

as much as possible prior to the administration of antibiotic therapy. Most studies have investigated additional clinical and/or microbiological effects of antibiotics in comparison with a placebo medication or no medication. The outcomes of most studies concerned with patients having 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. Systemic antibiotics are particularly valuable in the treatment of aggressive periodontitis in adolescents, especially cases predominated by *Aggregatibacter actinomycetemcomitans* (previously termed "localized juvenile periodontitis") (18).

The antimicrobial agents used in periodontal therapy are tetracycline, macrolides, nitroimidazole compounds, quinolones, penicillins, and cephalosporins. Important considerations for each antimicrobial agent include dosage, its mode of action, the microorganisms susceptible, its use in treatment of periodontal diseases, and the mechanism of bacterial resistance. Antimicrobial agents are divided according to the following modes of action (5, 19). The first is reversible inhibition of protein synthesis (bacteriostatic), e.g. tetracycline and macrolides (erythromycin, clindamycin, and azithromycin); the second is inhibition of DNA synthesis (bactericidal); e.g. nitroimidazole compounds (metronidazole, tinidazole, and ornidazole) and quinolones; the third mechanism is inhibition of cell wall synthesis (bacteriostatic), e.g., penicillins and cephalosporins; and the fourth is by increasing cell wall permeability, e.g., chlorhexidine and triclosan. The latter two agents are used locally.

Systemic Antimicrobials in Periodontics: Current Concepts

Scientific evidence supporting the use of systemic antimicrobials in periodontitis has been systematically evaluated in different reviews presented at European (20, 21) and North American settings (10).

Herrera *et al.* (21) reviewed 25 clinical trials comparing scaling and root planning (SRP) alone or with placebo with SRP using systemic antimicrobials. The studies considered were randomised control trials (RCT) and case-control trials (CCT) and lasted for at least 6 months. Periodontal conditions included aggressive and chronic periodontitis, and the evaluation of the clinical outcome variables using

meta-analyses (five analyses, each pooling data from two different studies) led to two main conclusions (22). Systemic antimicrobials used adjunctively to SRP can offer additional benefit over SRP alone in terms of clinical attachment level gains (CAL) probing pocket depth reduction (PPD) changes in deep pockets (CAL gains ranging between 0.2 and 0.6 mm; PPD reductions between 0.2 and 0.8 mm). In patients with deep pockets and with progressive or “active” disease or with specific microbiological profiles, this antimicrobial therapy could be of clinical relevance. Haffajee *et al.* (10) included 26 RCTs and three quasi-experimental cohort studies of more than 1 month duration (totalling 36 comparisons). Periodontal conditions included aggressive, chronic, and recurrent periodontitis and periodontal abscess. Evaluation of the clinical outcome variables using meta-analyses (22 RCTs with 27 comparisons) led to the following conclusions (22).

CAL gains should be expected after 6 months if systemic antimicrobials are used in patients with chronic and aggressive periodontitis regardless of initial pocket depths. These results are more significant in patients with aggressive periodontitis and deeper pockets. Metronidazole, tetracycline, and the combination of metronidazole and amoxicillin offered the best results; there is insufficient evidence to support a specific drug regimen (including appropriate dosage and duration). There is insufficient evidence to support the use of systemic antimicrobials as the sole therapy. Herrera *et al.* (20) reported three different reviews, two of them narrative and a third systematic, enlarging the data inclusion from the previous systematic review to 32 publications and 45 comparisons. Based on these reviews, the consensus indicated the following (23). If systemic antimicrobials are indicated as part of periodontal therapy, they should be adjunctive to mechanical debridement, preferably as part of nonsurgical periodontal therapy. Indirect evidence suggests that antibiotic intake should start on the day of debridement completion; antibiotic use should be completed within a short time and at an adequate dose.

Because of the problems related to the indiscriminate use of antimicrobials (especially systemic side effects, microbiological adverse effects, and the increase in bacterial resistances), the use of systemic antimicrobials in periodontitis should be restricted to certain patients and certain periodontal conditions (e.g., aggressive periodontitis, severe and progressing forms of periodontitis). Systemic antimicrobials should be used under optimal

conditions to achieve the best results. Systemic antimicrobials are more effective when the biofilm has been disrupted and is not yet organised; the needed debridement should be carried out in the shortest possible time span (approximately 1 week) to achieve effective drug serum levels on the day of debridement completion. Mechanical biofilm disruption must always be combined with effective supragingival plaque control by the patient.

Recent Scientific Evidence on the use of Systemic Antimicrobials in the Treatment of Periodontitis

In the treatment of patients with chronic periodontitis, recent publications have evaluated alternative systemic antibiotics, such as azithromycin and ornidazole, as well as the combination of amoxicillin and metronidazole compared with metronidazole alone. In the treatment of patients with aggressive periodontitis, the combination of metronidazole and amoxicillin has been extensively evaluated. The results support the combination’s clinical and microbiologic benefits and indicate the most convenient treatment protocol.

Studies of Patients with Chronic Periodontitis

The use of systemic azithromycin adjunctive to SRP was evaluated by Oteo *et al.* (35) in *Porphyromonas gingivalis*-positive moderate chronic periodontitis. This systemic antimicrobial was chosen because of its convenient dosage, and the results showed significant benefits in both clinical and microbiological outcome variables after 6 months. These results, however, were not corroborated in a similar study done without selecting the patients based on a specific microbiological profile; no adjunctive effect was observed after 1 year (24).

Ornidazole, an antimicrobial drug similar to metronidazole, was tested in patients with chronic periodontitis. Ornidazole was combined with SRP and compared with SRP plus placebo. The results in the clinical variables at 6 months were significant in favour of the adjunctive use of the systemic antimicrobial (22). Silva *et al.* (25) compared three SRP treatments in patients with chronic periodontitis: adjunctive use of metronidazole, adjunctive use of a combination of metronidazole and amoxicillin, and a placebo. Clinical and microbiological outcomes after 3 months revealed that the combination of metronidazole and amoxicillin with SRP resulted in significantly better

outcomes when compared with the placebo, whereas the comparisons with the metronidazole-alone group were not statistically significant.

Studies of patients with Aggressive Periodontitis

Several investigations have evaluated the adjunctive use of amoxicillin and metronidazole in patients with aggressive periodontitis. Mestnik *et al.* (26) evaluated patients with generalized aggressive periodontitis and compared the adjunctive use of amoxicillin and metronidazole versus SRP plus a placebo. Both groups used a dentifrice containing triclosan and copolymer and chlorhexidine (CHX) mouth rinse for 60 days. The researchers reported significant short-term (3 months) clinical and microbiological benefits in the test group. Similar findings were described by Yek *et al.* (27), including new information regarding the effectiveness of this treatment against *Tannerella forsythia*.

Other researchers have tested different protocols to find the most effective treatment. Griffiths *et al.* (28) extended the evaluation of a previous study for 2 months. The adjunctive effects of amoxicillin and metronidazole use in generalized aggressive periodontitis were assessed, with the results showing significantly better clinical outcomes in the test group; in a different trial, the two study groups were crossed (10,29) so that the test group was treated with debridement and the control group with a systemic antimicrobial. Griffiths *et al.* (28) concluded that, "Patients that received the antibiotics at the initial therapy showed significant additional benefits compared to those who received the same regime at the retreatment phase." However, the follow-ups were not comparable between study periods (6 months versus 2 months). Heller *et al.* (30) and Varela *et al.* (31) reported, in two different articles, the clinical and microbiological effects, respectively, of a stringent anti-infective protocol (including two periods of debridement combined with CHX irrigation, rinsing, and tongue brushing) with or without amoxicillin plus metronidazole. Although some short-term advantages were observed in both trials, clinical and microbiological observations suggested that both therapies were effective, and there were no significant differences between them. Aimetti *et al.* (30, 31) assessed the adjunctive effect of amoxicillin and metronidazole over a complete full-mouth disinfection protocol, and both clinical and microbiological findings revealed significant

benefits after 6 months.

Discussion

Adjunctive systemic antimicrobials have been evaluated in both aggressive and chronic periodontitis. In patients with aggressive periodontitis, amoxicillin and metronidazole have been extensively studied, and clinical and microbiological benefits reported. In cases of chronic periodontitis, different products, such as azithromycin, are under scrutiny. The clinical efficacy of local antimicrobials, although extensively demonstrated, is still surrounded by a continuing debate regarding the cost-effectiveness of the treatment and how to best assess effectiveness.

Systemic antimicrobial use has been evaluated under two periodontal conditions: chronic and aggressive periodontitis. In chronic periodontitis, two main questions have been raised. One is whether the use of a single antibiotic (metronidazole) may lead to outcomes similar to those obtained using a combination (amoxicillin plus metronidazole). The other question is whether we can use systematic antimicrobials, such as with azithromycin and ornidazole, which have easier dosing protocols and may therefore improve compliance. To answer the first question, the results from a clinical trial clearly showed that similar clinical and microbiological short-term results were obtained when adjunctively using metronidazole alone as compared with the combination of amoxicillin plus metronidazole.

In the treatment of chronic periodontitis, this implies reduced costs for the patient and a diminished risk of adverse events (25). For the second question, the results using adjunctive azithromycin in patients with chronic periodontitis with a specific microbiological profile demonstrated significant clinical and microbiological improvements (33), although this significant benefit was not substantiated in another study (34). The preliminary results with ornidazole have also demonstrated significant benefits in non-smoker patients with periodontitis (35). In aggressive periodontitis, recent clinical research has been focused on studying the adjunctive use of amoxicillin and metronidazole. The main questions raised were (1) whether there is a clear clinical and microbiological benefit, and (2) which is the most appropriate treatment protocol for this patient population. Two studies reported significant clinical and microbiological benefits after 3 (28) and 6 months (27). In terms of treatment protocols, one

study suggested that using the drug combination as a part of the initial treatment offered greater benefits (28). Another study reported significant benefits after 6 months when combining the adjunctive antibiotic treatment with the full-mouth disinfection approach (32). Conversely, when amoxicillin and metronidazole were combined with two periods of debridement (including adjunctive CHX irrigation, rinsing, and tongue brushing), no significant clinical and microbiological benefits were observed after 6 months (30, 31).

One relevant feature of these studies was the exclusion of smokers (four of the analysed studies excluded smokers, whereas one study only excluded those who smoked more than 10 cigarettes per day). This may limit the external validity of these investigations as smoking may clearly influence the patients' response to treatment.

Another relevant issue was the debridement protocol and the time of antibiotic intake (20). Although most studies used protocols with short periods between debridement sessions, some studies (24, 26) performed periodontal debridement during 14 days and started the antibiotic treatment at the first session; this may have influenced the reported outcomes (20). The incorrect use of antibiotics is very common in our country; using these drugs as miracle treatments of periodontal disease is not a realistic approach, as this will increase the inappropriate use of antibiotics. Periodontal treatment is systematic, and antibiotic therapy in this context supports the classical treatment phase (37).

Conclusion

Systemic antimicrobial therapy can be used as an adjunct to mechanical therapy in patients with chronic and especially aggressive periodontitis, patients who do not respond to mechanical treatment, patients with acute or severe periodontal infection, and patients who are systematically compromised. However, systemic anti-microbial agents should be used with caution in patients on long-term medication for cardiovascular disease, asthma, seizures, or diabetes, as there can be drug interactions. Drugs should only be prescribed for indicated patients, as they always have some side effects. All systemic anti-microbial agents, if used in proper doses, can effectively treat periodontal pathogens. Because periodontal pathogens exhibit diverse anti-microbial susceptibility, microbiological analysis is sometimes necessary for proper selection of

antibiotic therapy. As antibiotic resistance constitutes an increasing problem, anti-microbial susceptibility testing of isolated pathogens is important. If microbiological testing is unavailable, combination therapy is preferred. Since periodontitis lesions often harbour a mixture of pathogenic bacteria, use of drug combinations is an area of increasing interest.

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Corresponding Author:**Emine ÇİFCİBAŞI**

Department of Periodontology
Faculty of Dentistry Istanbul University
34093 Capa-Fatih-İstanbul/ TURKEY
Phone: +90212 414 20 20 (30253)
e-mail: ecifcibasi@hotmail.com