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Systemic Metronidazole in the Treatment of Periodontitis

Muthuraj MSA*, Janakiram S and Chithresan K

[1]*Senior Lecturer, Department of Periodontology, Sri Ramakrishna Dental College and Hospital, Tamil Nadu, India*
[2]*Professor, Department of Periodontology, Sri Ramakrishna Dental College and Hospital, Tamil Nadu, India*
[3]*Professor and HOD, Department of Periodontology, Sri Ramakrishna Dental College and Hospital, Tamil Nadu, India*

***Corresponding author:** Maria Subash Aaron Muthuraj, Department of Periodontology, Sri Ramakrishna Dental College and Hospital, Tamil Nadu, India, Tel: +91-9894249551, E-mail: mariasubashaaronm@srdch.ac.in

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Abstract

Periodontitis is a bacterial plaque induced inflammatory disease of periodontium. Some of the bacterial pathogens evade host defence mechanism and diligent periodontal therapy. Antimicrobials when given as an adjuvant play a major role in such situations. Many antimicrobials were used before, but only some showed efficacy against most putative pathogens with significant advantages. Metronidazole is one such antimicrobial which is effective against various anaerobic periodontal pathogens, with minimal side effects and least bacterial resistance. Here in this review we are going to discuss about metronidazole and its application in treatment of periodontitis.

Keywords: Metronidazole; Nitroimidazole; Periodontitis; Scaling and root planning

Introduction

Periodontitis is a bacterial plaque induced inflammatory disease of periodontium characterised by inflammation of gingiva and adjacent attachment apparatus, along with loss of attachment [1]. Some of the bacterial pathogens in dental plaque are tissue invading and evades host defence mechanism. Such pathogens reside and repopulate even after diligent non-surgical and surgical periodontal therapy [2,3]. In such cases antimicrobials as an adjuvant to periodontal therapy will play a role. Many antimicrobials have been employed as an adjuvant to periodontal therapy. Metronidazole (MTZ), a 5-nitroimidazole compound and amoebicide exerts its anti-bacterial activity on gram-negative obligate anaerobes such as Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium, Selenomonas sputigin and Tannerella forsythia. Gram-positive obligate anaerobes such as Peptostreptococcus are also susceptible to MTZ. C rectus, a facultative anaerobe and probable periodontal pathogen, is also susceptible to low concentration of MTZ [4]. The main advantage of MTZ is that it is least affected by drug resistance [5]. Here in this mini review we will discuss about important aspects of MTZ and its application as systemic drug in treatment of periodontitis.

How Metronidazole Acts?

The metabolites of MTZ are cytotoxic, and they directly interact with bacterial DNA, and other macromolecules, resulting in cell death. Upon entry into an anaerobic organism, MTZ is reduced at the 5-nitro position by electron transport proteins that are part of anaerobic metabolic energy-yielding pathways. Alteration of the MTZ molecule creates a continuous concentration gradient favouring diffusion of additional MTZ into the cell. The above process generates free radicals which react with macromolecules such as DNA, resulting in cell death [4].

Pharmacokinetics of Metronidazole and Its Concentration in GCF

MTZ is completely and rapidly absorbed after oral administration. MTZ distributes well throughout body tissues and fluids. Therapeutic levels can be found in various body fluids. The serum half-life is between 5.2 to 8.6 hours (mean- 7.3hours). Its bactericidal effect is not altered by pH changes within the range 5.5 to 8.33. The drug is primarily metabolized in the liver and its metabolites are excreted in the urine and faeces [6]. MTZ penetrates well into gingival fluid achieving levels comparable to serum levels but not demonstrating the concentration effect exhibited by the tetracyclines. For Actinomyces species, a single dose of MTZ does not appear to produce minimal inhibitory drug concentrations in gingival crevicular fluid. A single oral dose of metronidazole would seem to deliver drug levels in serum and gingival crevicular fluid that would not totally inhibit *Eikenella corrodens and Actinobacillus actinomycetemcomitans* [7]. Levels achieved in the gingival fluid following multiple doses (approximately 14 μg/ml with considerable variability) are sufficient to inhibit anaerobic periodontal organisms like B. gingivalis, F. nucleatum Treponema etc in-vivo. In serum it will inhibit the same suspected periodontopathogens for 6 to 7 hours [8].

Resistance and Mechanism of Resistance

Resistance to MTZ is very rare, although strains of trichomonads resistant to the drug have been reported. Two mechanisms were proposed to account for rare instances of acquired resistance: lowered ability to reduce MTZ and decreased drug absorption.

Metronidazole resistance is uncommon and some reports on laboratory findings may be the result of incomplete anaerobiosis. However, when present it is most likely to be the result of a lack of reducing potential through, by implication, a lack of pyruvate–ferredoxin oxidoreductase complex activity, leading to impairment of pro-drug activation [5].

Studies on Effect of Metronidazole on Periodontal Pathogens

W.J. Loesche in 1981 and 1984 reported that MTZ along with scaling and root planing (SRP) significantly reduced B. assacharolyticus, spirochetes and B. gingivalis, but MTZ as a monotherapy hadn't demonstrated long standing effect on reducing periodontal pathogens and creating healthy microflora [9,10]. Gusberti et al. demonstrated statistically significant decrease of gram-negative rods, Fusobacteria and B. gingivalis over 6 months following SRP along with MTZ [11]. Loesche WJ et al. demonstrated clinical improvements accompanied by significantly lower proportions of spirochetes, motile rods, selenomonads and P. intermedia along with increase in the proportions of cocci in the subgingival flora [12]. Saxen et al. had shown that Actinobacillus actinomycetemcomitans was suppressed to below detection level at all test sites only in the MTZ group and was more effective than tetracycline when given as an adjuvant to modified Widman flap in patients with localised juvenile periodontitis [13]. Carvalho LH et al. observed reduction in counts of Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola in subgingival; microflora of subjects received scaling and root planing plus professional cleaning and scaling and root planing plus professional cleaning plus systemic metronidazole 400 mg tid for 10 days [14].

Effect of Metronidazole on Periodontal Parameters

Soder et al. demonstrated a reduction in number of active sites in patients recalcitrant to SRP after giving MTZ 400 mg TDS for 8 days as an adjuvant to SRP [15]. Loesche WJ et al. conducted a clinical study to determine the efficacy of metronidazole (250 mg TDS) for one week, after the completion of scaling and root planing in 33 patients with advanced adult periodontitis. The investigators observed a reduction in the need for periodontal surgery in the metronidazole-treated group of 8.4 teeth per patient versus 2.6 teeth per patient in the control group, a relative reduction of approximately 6 teeth. Significant improvement in clinical parameters was noted in test group [16]. Carvalho et al. observed a significant improvement in clinical parameters after giving MTZ 400 mg TDS for 10 days as an adjuvant to SRP. SRP plus periodical scaling and MTZ showed more significant reduction [17].

Metronidazole as an Agent in Combination Therapy

Combination therapy extends the antimicrobial spectrum and lowers the antimicrobial dose by exploiting possible synergy between two drugs against targeted organisms.

The disadvantages of combination drug therapy are increased drug interactions with improperly selected antibiotics. A bactericidal antibiotic (β-lactam drug or metronidazole) should not be used simultaneously with a bacteriostatic agent (tetracyclines) because the bactericidal agent exerts activity during cell division that is impaired by the bacteriostatic drug [18].

Effective combination therapies include MTZ + amoxicillin (AMX) for A. actinomycetemcomitans and various anaerobic periodontal infections, and MTZ + ciprofloxacin (CPX) for mixed anaerobic and enteric rod/pseudomonas periodontal infections

Primarily, amoxicillin–metronidazole had been introduced as a specific treatment for periodontal infections with a detected presence of the periodontal pathogen Aggregatibacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans). However, this drug regimen is more efficacious than the respective single drugs or placebo, even if

empirically prescribed without diagnostic identification of detectable pathogens in patients exhibiting advanced periodontal disease. Accordingly, amoxicillin+metronidazoleis considered to be an antibiotic regimen of first choice and are used widely.

Application of Amoxicillin plus Metronidazole in the Treatment of Periodontitis

Many studies support the use of AMX + MTZ in treatment of various forms of periodontitis. A study investigated the interactions between MTZ and AMX, MTZ and its hydroxymetabolite, and AMX and the hydroxymetabolite of MTZ using checkerboard titrations in combination with accurately determined Minimal Inhibhitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC). Actinobacillus actinomycetemcomitans was used as the test organism. Synergism was found for all three combinations. The synergistic interactions between these antibiotics may explain the efficacy of the combination of metronidazole and amoxicillin in periodontitis [20]. MTZ plus AMX therapy (Van Winkelhoff cocktail) as an adjuvant to periodontal therapy eliminated A. actinomycetemcomitans in 114 of 118 patients with clinically different forms of periodontitis along with significant improvement in clinical parameters [21]. A controlled, randomized clinical trial involving advanced adult periodontitis reported that 1-week-course of MTZ 250 mg plus AMX 250 mg as a monotherapy, given 3 times every 4 months achieved reduction in active sites and bleeding on probing along with improvement in overall attachment level. Sites exhibiting ≥ 2 mm of attachment loss in 2 successive or alternate evaluations, and periodontal abscess were noticed only in the placebo group [22].

The combination of mechanical therapy and systemic application of AMX + MTZ has been shown to resolve periodontal inflammation effectively in generalized aggressive periodontitis patients, with stability of the improved clinical attachment for up to 5 years [23]. Herrera et al (2002) in a systemic review reported that SRP plus systemic antimicrobial groups demonstrated an improvement in clinical attachment level and probing depth than SRP alone; with a statistically significant additional improvement for amoxicillin/metronidazole in deep pockets [24]. A 6-month double-blind, placebo-controlled, randomized clinical trial assessed the adjunctive clinical effect of systemic antibiotic consisting of 500 mg AMX and 500 mg MTZ three times a day for 7 days to non-surgical treatment in patients with generalized aggressive periodontitis (GAP). All clinical parameters improved at 2 and 6 months in both groups. In test group with deep pockets (≥7 mm), treatment resulted in an added 1.4mm full-mouth probing pocket depth (PPD) reduction and 1mm of life cumulative attachment loss (LCAL) gain at 6 months [25]. SRP combined with MTZ (400 mg three times daily) and AMX (500 mg three times daily) for 14 days reduced orange complex organisms in non-smokers along with increase in proportions of Actinomyces. But smokers with chronic periodontitis benefitted less [26]. Kelly McGowan et al. conducted a systematic review to determine the optimum dose and duration of AMX + MTZ prescribed as an adjunct to non-surgical treatment of periodontitis. Periodontal pocket depth and clinical attachment level were evaluated at 3 months. Secondary outcomes assessed were adverse events and compliance. He concluded that a 7-day regimen of 500/500 mg or 500/400 mg of AMX and MTZ would be most appropriate for treatment of patients with periodontitis [27]. Gómez-Sandoval JR et al. compared the efficacy of clindamycin versus AMX + MTZ, as an adjuvant to SRP in patients with periodontitis and type 2 diabetes mellitus. Both groups showed same efficacy for the reduction of probing depth, plaque index, and bleeding on probing in patients with periodontitis and type 2 diabetes [28].

Application of Ciprofloxacin and Metronidazole in the Treatment of Periodontitis

Rams et al. conducted a clinical study to evaluate the effect of a combined systemic CPX+MTZ therapy (500 mg of each for 8 days) on 17 adults with recurrent periodontitis despite prior mechanical/surgical therapy, plaque control and systemic maintenance care. Clinical and microbiological parameters were evaluated before therapy and 6 to 18 months after therapy. Ciprofloxacin/metronidazole therapy eliminated or significantly suppressed sub gingival putative periodontal pathogens.

Streptococci and occasionally Actinomyces species were the predominant cultivable subgingival microorganisms up to 6–18 months post treatment. Significant improvements in probing depth, clinical attachment loss and bleeding on probing, paralleled elimination or suppression of suspected periodontal pathogens was reported in all patients, with no additional periodontal disease activity detected at any site post treatment [29].

The combination of CPX+MTZ has been suggested as adjunctive therapy for periodontal infections when enteric rods, pseudomonads or *A. actinomycetemcomitans* are present. Metronidazole-ciprofloxacin combination is effective against *A. actinomycetemcomitans*. Obligate anaerobes are more susceptible to metronidazole and facultative anaerobes to ciprofloxacin. This is a powerful combination against mixed infections. Studies of this drug combination in the treatment of refractory periodontitis with enteric rods have documented marked clinical improvement [30].

Summary

Metronidazole is a cheaper antimicrobial effective against protozoa as well as anaerobic bacteria. In treatment of

periodontitis, it is very effective against most of periodontal pathogens with least antimicrobial resistance. On combination with amoxicillin, it can be used as an empirical drug in periodontal therapy, as it has a good track record. When combined with ciprofloxacin it is very effective against cases refractory to periodontal treatment by acting against enteric rods. Thus metronidazole is a wonder drug in treatment of periodontitis when prescribed individually as well as in combination, with Amoxicillin and metronidazole combination (AMX 3x375-500mg /day and MTZ 3x250-500 mg for eight days) being the most effective.

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