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Antimicrobial agents in Periodontics: A review

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ABSTRACT

The association of pathogenic bacteria with a susceptible host is thought to cause periodontal diseases. The primary goal of periodontal disease treatment is to achieve a high level of oral hygiene. Chemical agents can be considered for professional and individual maintenance of oral hygiene. A chemotherapeutic agent is a chemical that is used for therapeutic purposes and is also beneficial to inhibit or kill microorganisms during initial healing phase. Antimicrobials can be locally or systemically delivered. Complementing mechanical therapy with local or systemic antimicrobial therapy can improve treatment effectiveness and thus be beneficial.

Keywords:
periodontal disease, chemotherapeutic agent, antimicrobial therapy.

1. Introduction

The association of pathogenic bacteria with a susceptible host is thought to cause periodontal diseases. The primary goal of periodontal disease treatment is to achieve a high level of oral hygiene. Chemical agents can be considered for professional and individual maintenance of oral hygiene. A chemotherapeutic agent is a chemical that is used for therapeutic purposes. Chemotherapeutic agents can be used as antimicrobials, or as an anti-inflammatory agent to alter the host response. Antimicrobials can be delivered by two methods systemic or local delivery. By balancing the benefits of local and systemic chemotherapy, disadvantages and possible side effects of agents can be resolved. The presence or absence of certain microorganisms, especially Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans after periodontal therapy, appears to be related to the outcome of periodontal therapy, according to data from several clinical trials. Mechanical therapy alone will not be able to fully remove these microorganisms in any subject. Because of their ability to penetrate periodontal tissues or dentinal tubules, pathogens may be resistant to mechanical interference. They can also live in places where instruments are unavailable, such as root concavities or furcations. Furthermore, treated sites may be recolonized by the same pathogenic bacteria or other pathogenic bacteria that have survived elsewhere in the oral ecosystem. Complementing mechanical therapy with local or systemic antimicrobial therapy can improve treatment effectiveness and thus be beneficial.

2 Antimicrobials used in Periodontics

Antimicrobial agents are grouped into the following categories based on their mode of action. -
1. Bacteriostatic – (a) reversible inhibition of synthesis of proteins.
(b) inhibition of synthesis of cell wall.
2. Bactericidal - inhibition of synthesis of DNA
3. Cell wall permeability is increased

The different types of anti-microbial agents used for treatment of periodontal diseases are tetracycline, quinolones, penicillins and cephalosporins.

2.1Tetracycline

Tetracyclines is a broad spectrum antibiotic. All tetracycline compounds consist of four fused cyclic rings, hence named tetracyclines. It is bacteriostatic at low concentrations and bactericidal at high concentrations. Adverse reactions associated with tetracyclines are very less. Similar to any other broad-spectrum antibiotic, it may lead to suppression of the normal flora, followed by overgrowth of resistant organisms or colonization by exogenous pathogens such as Candida.[1]

2.1.1 Systemic administration

The concentration achieved in gingival crevicular fluid (GCF) is 2-10 times more than that of serum even after a single dosage (Gordon et al.). [2] Tetracycline remained in the GCF after 19 hours, but it was no longer detectable after 24 hours. At 3.5 to 7 hours, the GCF reached peak concentrations of 5-12 Rg/ml. As a result, it's very likely that giving 250 mg of tetracycline every day won't reliably minimize pathogenic bacteria. Since most treatment regimens require several dosages, GCF levels of daily tetracycline doses (250 mg every 6 hours) were found to be two to four times higher than blood levels after 48 hours. (Gordon et al., 1981b).[3]
Following the administration of 100 mg every 12 hours for the first day, followed by 100 mg every day for 14 days, gingival fluid levels were 4 to 10 mg/ml (Pascale et al., 1986). [4] When 150-200 mg/day is given for 8 days, GCF concentrations of minocycline are five times higher than serum and can remain bacteriostatic for at least one week after treatment is stopped (Ciancio et al., 1980).[5]
Minocycline at lower doses (100 mg/day) was found in the GCF at concentrations of 4.77 pRg/ml, but with less side effects (Freeman et al., 1992) .[6]

2.1.2 Local drug delivery

Tetracycline fibers (Acticite)
Goodson in 1979used a cellulose acetate tubing system to develop tetracycline fibers. Osmotic pressure is the mechanism used to diffuse the drug into periodontal pockets. The drawback of this system was poor control of drug release. Therefore Goodson worked on ethylene vinyl acetate. This material seemed to be more flexible and release of drug was observed upto nine days. The tetracycline fiber structure comprises of non-resorbable fibers made up of 25 percent of tetracycline hydrochloride loaded with biologically inert plastic copolymer. The fibers are placed in layers to completely fill the periodontal pocket and secured with cyanoacrylate dressing. These fibers are left in periodontal pocket for 10 days, after which they must be removed from the pocket.[7]

Doxycycline gel (Atridox)

The Atridox (doxycycline hyclate) is made oftwo syringe system. First syringe consists of 450mg gel carrier which is bio-absorbable, flowable formulation. Second syringe consists of 50mg of doxycycline hyclate equal to 42.5mg of doxycycline. After combining, this drug delivery

technique involves coupling two syringes, adding a blunt cannula to a single syringe and pressing the gel in the periodontal pocket by slowly pushing the tip of the cannula into the periodontal pocket. The liberation of the medication from the carrier happens within 7 days. It is advised that the region should be filled with a safe covering, such as cyanoacrylate covering, after gel placement. In 28 days almost all of the drug is bio-absorbed or eliminated from the pocket naturally.[7]

Minocycline

1. Arestin

Minocycline in the form of microspheres are developed for the sustained release of the drug in the periodontal pockets. 2% minocycline is incorporated in bioresorbable microsphere. The diameter of these microspheres is 20-60 µm. To carry these microspheres a gel carrier is used. These microspheres resorb in the time span of 21 days. When these microspheres are placed in periodontal pockets, it comes in contact with gingival crevicular fluid and hydrolysis of the microspheres is initiated. This in turn releases minocycline until it gets completely resorbed.[7]

2. Dentomycin

Dentomycin consist of 2% minocycline. In Japan, it is also called as periocline. It is available in ointment formwhich is bio-absorbable. The matrix of glycerine, triacetine and aminoalkyl-methacrylate contains 2% minocycline hydrochloride. The applicator supplied with dentomycin is used to deliver the medication till the base of the pocket.[7]

2.2 Penicillin

In 1928, Sir Alexander Fleming discovered penicillin. The first clinically used antibiotic in 1941 was penicillin. Previously, Penicillium notatum was its original source, but now a days P. chrysogenum is the major source of penicillin. The bactericidal properties of penicillin are the result of inhibition of bacterial cell wall synthesis.[8]

2.2.1 Clinical use in Periodontics

Amoxicillin has high antimicrobial activity against all gram-positive periodontal pathogens except E. corrodens, S. sputigena, and Actinomyces. This drug stops gram-positive facultative anaerobes from growing.These microorganisms include Streptococcous and Actinomycesspecies. Amoxicillin-Clavulanate (Augmentin) is the combination of amoxicillin with clavulanic acid, which is an inhibitor of beta-lactamase. The strains which produce Beta-lactamase are sensitive to this combination. for the treatment of patients with refractory or localized aggressive periodontitis, Augmentin may be successful. Bacterial resistance to penicillins is obtained by two mechanisms, the first is due to mutations in the genes that code for porins and second is structural change which will lead to impairment in uptake of the drug. Earlier studies suggested that, β -lactamases is thought to be arising from penicillin-binding proteins. These are low molecular weight proteins that lose their signal peptide when exposed to naturally occurring lactam antibiotics. As a result, they can be used as lactam detoxifiers or secreting agents. These mutations cause them to become lactam hydrolyzing enzymes.[9] As a result, administering beta-lactamase responsive penicillins is rarely recommended.[10,11] For overcoming such effects β-lactamase inhibitor like clavulanic acid are used. Amoxicillin is given in combination with clavulanic acid and is called Augmentin. It is available in two dosage 375 mg and 625 mg in tablet form. The 375 mg and 625 mg tablets contain 250 mg and 500 mg of amoxicillin,

respectively, as well as 125 mg and the same volume of clavulanic acid. GCF concentrations of 14.05 g/ml (amoxicillin) and 0.40 g/ml (ciprofloxacin) were achieved (clavulanic acid). [12] In the treatment of refractory periodontitis[13]and rapidly developing periodontitis, augmentin may be beneficial. [12]Systemic amoxicillin-clavulanic acid therapy has been utilized in guided tissue regeneration to reduce periodontal infections and improve the gain of clinical attachment. [14]

2.3 Metronidazole

Metronidazole belongs to the group of nitro imidazole. It is a synthetic anti-bacterial and anti-protozoal agent. Metronidazole disrupts the DNA of microbial cells and ultimately inhibits nucleic acid synthesis.[7]

2.3.1 Clinical use in Periodontics

Metronidazole is a drug that is widely used to treat periodontal diseases, including, refractory periodontitis,[15,16]adult periodontitis[17,18] and acute necrotizing ulcerative gingivitis.[19,20]It has been shown that metronidazole used in the treatment of periodontitis patients without mechanical debridement decreases mean probing depths by up to 0.4 to 2.4 mm.[21] It has also been shown that the amount of subgingival bacteria , especially spirochetes and bacteroids, has been reduced. [22,23] In a study done by Lekovic V comparison has been done between metronidazole monotherapy and mechanical periodontal treatment. These studies concluded that drug therapy was inferior to, or at best equal to, mechanical instrumentation, and that metronidazole as a monotherapy should not be used routinely.[21] A combination of mechanical periodontal therapy and metronidazole have been shown to improve the periodontal condition in patients with refractory periodontitis.[24]

2.3.2 Local drug delivery:

Elyzol

Elyzol is a topical medication containing oil based metronidazole gel (25%) in the matrix of sesame oil andglycerol mono-oleate. A syringe with blunt cannula is used to deliver the drug at the base of periodontal pockets. The preparations of elyzol available in the market are 1gm and 0.3gm. The metronidazole content of preparations of 1gm and 0.3mg is 250 mg and 75mg respectively. It takes almost 12-24 hrs for the material to act and resorb. Hence, gel is applied again after seven days.[7] In 1992, Ainamo et al did a comparative study on the effect of metronidazole gel and subgingival scaling on periodontitis patients. The results obtained suggests that bleeding on probing and periodontal pocket depth were decreased to a significant amount in both the groups. [25] Pavio M et al. conducted a meta-analysis in 2004 to assess the efficacy of local delivery of metronidazole alone or in combination with traditional phase I therapy in chronic periodontitis patients. Metronidazole was found to be more beneficial when used in conjunction with traditional mechanical therapy. [26]

Metrogene®

This drug delivery system consists of 5 percent metronidazole in natural bovine collagen. The material is provided in the form of sponge square parts. The sponge is put in the periodontal pocket and quickly forms a resorbable gel as it comes into contact with GCF, which eventually releases the prescription.[7]

2.4 Cephalosporines

Cephalosporins belong to the semisythetic type of antibiotics. Cephalosporins are primarily obtained from a fungus Cephalosporium.[8] Chemical characteristics of cephalosporines are similar to penicillins.

2.4.1 Clinical use in Periodontics

The use of these antibiotics is very common. These drugs can be given to the patients allergic to penicillin. For oral route of administration it is available as cephalexin. Its mechanism of action is inhibition of synthesis of cell wall. Gram-positive bacterial infections can be effectively treated with cephalosporins. Gram-negative obligatory anaerobes are sensitive to this drug, but sometimes can fail to inhibit gram-negative facultative anaerobes.[27]Newer cephalosporins are invented which have extended gram-negative effectiveness.

2.5 Fluoroquinolones

Fluoroquinolones have a bactericidal effect on microorganisms. These are derived from nalidixic acid. Fluoroquinolonesinclude levofloxacinofloxacin, ciprofloxacin, etc. The bactericidal mechanism of Fluoroquinolones is achieved by inhibiting DNA gyrase and topoisomerase IV.[28]

2.5.1 Clinical use in Periodontics

A. actinomycetemcomitans associated periodontitis can be effectively treated with fluoroquinolones [29] Ciprofloxacin is a broad spectrum antibiotic. The dosage for adults is 500 mg twice daily. The drug should be administered either one hour before or two hours after meal. It can penetrate into periodontium and gingival crevicular fluid. Its concentration can be higher in gingival crevicular fluid than in serum. Conway TB in 2000,[30]observed mean gingival crevicular fluid levels of ciprofloxacin. The levels were found to be 2.5-2.7 μg/ml. A pasteurellaeae family of Actinobacillus actinomycetemcomitans is sensitive to fluoroquinolones;[31] hence, it can be an effective treatment modality in periodontitis associated with this bacteria . Kleinfelder et al, in year 2000,[32]conducted a study in 22 patients for a period of 12 months, where systemic ofloxacin was given in conjunction with open flap surgery. He reported that the levels of A. actinomycetemcomitans were found to be lower than detectable levels. It is also found to be effective in patients with A. actinomycetemcomitans infection and advanced periodontal disease with Papillon Lefevre syndrome.[33]

3 Conclusion

The standard periodontal treatment plan can establish with the use of chemotherapeutic agents. To stop the progression of periodontal diseases, mechanical plaque control is used as initial line of treatment. This reduces bacterial load and chemotherapeutic agents are used along with this treatment periodontal destruction and tooth morbidity have become more manageable than ever, thanks to the availability of various chemotherapeutic agents in easy-to-use types. The choice and dosage of antimicrobial agents should carefully selected, based on microorganisms involved and disease severity. In order to administer adjunctive therapy responsibly, the clinician must consider the indications for adjunctive chemotherapy, risk-benefit ratios, as well as the statistical and clinical importance of the treatment modality chosen. Taking these factors into account on a case-by-case basis will result in better outcomes, less side effects, and higher overall patient satisfaction.

4. Future perspective

Periodontal disease management includes accurate diagnosis, recovery preparation, patient education and encouragement, as well as regular follow-up visits. Inappropriate use of chemotherapeutic agents can lead to the development of resistance in microorganisms. Therefore, proper use of these agents is recommended.

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