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Highlights on role of antibiotics in periodontics

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Abstract

Periodontal treatment aims at restoring a micro biota compatible with periodontal health. Scaling and root planing can be classified as 'THE GOLD STANDARD" of periodontal care and has been demonstrated to be successful in order to maintain periodontal health for more than 20 years. Whereas periodontal antibiotic therapy aims to reinforce mechanical periodontal treatment and to support host defense system in overcoming the infection by killing sub gingival pathogens that remains after conventional mechanical periodontal therapy. A number of key elements need to be considered such as the anti-biofilm strategies, drug resistance in biofilm, various routes of antibiotic administration, its efficacy, sequencing of antibiotics while administering antibiotics for periodontitis. Pencillin was the first antibiotic systemically administered; historical background of antibiotics is reviewed here. Earlier choice was based exclusively on empiric evidence but with time tetracycline, metronidazole and beta lactams are among the most widely used agents for treating periodontal condition. This review henceforth attempts to describe the rationale of antibiotics in periodontal therapy. There is also a collection of data from scientific papers clinically relevant to the periodontitis providing description of nature of biofilms in general, oral biofilms in particular as well as approaches to their control, behavior of antibiotics in oral biofilm, potential of systemic and locally applied antibiotic therapy to control the periodontopathic microbiota.

Keywords: Periodontitis, Antibiotic, Biofilm.

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INTRODUCTION

Periodontitis is an inflammatory disease of the periodontium caused by bacterial infection. It signifies the major cause of tooth loss in adults leading to long term disability and increased treatment need [1].

Study described by scientists states that after physical removal of micro-organisms plaque samples were analyzed for microbial species. The data indicated that on average the majority of species did not change significantly [2]. Three species of the red complex B forsythus, p gingivalis and treponemma denticola were significantly decreased but not completely eradicated [2].

Scientific evidence tells that Meta analyses performed by scientists indicated that adjunctive systemically administered antibiotics can provide a clinical benefit in the treatment of periodontal infection [3].

Hence antibiotics like tetracycline, metronidazole, Beta lactams are among the most widely used agents for treatment of periodontol condition in adjunct to regular scaling root planing.

Clinical success in the treatment of these diseases thus requires reduction of the bacterial load or enhancement of host tissue ability to defend or repair itself. Even though mechanical treatment does not predictably eliminate all bacteria from diseased sites completely, a restrictive attitude towards using antibiotics have been recommended basically to limit the development of microbial antibiotic resistance in general [4].

The question that arises regarding periodontal therapy is: Can systemic antimicrobial be efficacious if the biofilm is not disrupted?

Earlier literature has argued that 65% of infections that affect the humans are caused by organisms growing in the biofilm [3]. Biofilm on tooth surfaces causes dental caries and periodontal diseases.

Literature states that biofilm are fascinating structures providing number of advantages to colonizing species from competing microrganisms, environmental factors such as host defense mechanism, and from lethal chemicals or antibiotics [2].

Although the mechanisms of resistance to antibiotics of organisms growing in biofilms are not entirely clear still dental biofilms are difficult therapeutic target [5].

Hence the goal of this review is to make some sense of the myraid of antibiotics that are reported in the literature with a particular emphasis on those that are clinically relevant to the periodontist. Also attempted to provide a description of nature of oral biofilms in particular to antibiotics as well as approaches to their control, attempts to describe and evaluate the potential of systemically and locally applied antibiotic therapy to control peri-odontopathic microbiota and destructive periodontal disease.

Historical Background

The first antibiotic used in periodontal therapy were mainly systemically administered pencillin. Literature states that amoxicillin has been formed for treatment of periodontal disease because of its considerable activity against several periodontal pathogens at levels available in gingival fluid [6].

The nitro-imidazoles were introduced into the periodontal field in 1962 when the lancet published the report of curing vaginitis and acute marginal gingivitis in a female patient. Studies state that metronidazole affects specifically the obligately anaerobic part of oral flora including p gingivalis and other black pigmenting gram negative organisms but not A actinomycetemcomitans, a facultative anaerobes [6].

Tetracycline-Hcl became popular in the 1970s due to its broad spectrum antimicrobial activity and low toxicity. Literature also stated that tetracycline,clindamycin, erythromycin in addition to antimicrobial activity are capable of inhibiting collagenase which may interfere with tissue breakdown in periodontal disease [6].

Tetracycline group of drugs widely used in periodontal disease with clinically and biologically relevant to host tissue modulation [6].

Treatment of Periodontal biofilm: Difficult therapeutic target.

Formation of biofilm on tooth surfaces leads to dental caries and periodontal diseases. The major characteristic of these disease are that they are caused by organisms growing in the biofilm [2].

Anti- Biofilm Strategies includes planktonic cells attach to surface, also the carrier systems to target microbials to biofilm surfaces, there is enhancement of drug penetration into biofilms and also development into glycocalyx – enclosed biofilm. There will also be surface modification to reduce adhesion and biofilm development, also adsorption of antimicrobials onto surface and antimicrobial impregnated matrices [2].

It has been recognized for considerable periods of time that organisms growing in biofilms are more resistant to antibiotics than the same species growing in a planktonic state [7].

Mechanism of resistance appears to be due to slower rate of growth of bacterial species in biofilms, which makes them less susceptible to many but not all antibiotics, also affected by nutritional status, growth rate, temperature, ph and prior exposure to sub effective concentration of antimicrobial agents [8]. Various authors have speculated that the following changes can occur in biofilm -grown bacteria like induction of the general stress response, increasing expression of multiple drug resistance pumps, activating quorum sensing systems and changing profiles of outer membrane proteins [9].

Biofilm a matrix performs a “homeostatic function” such that cells deep in the biofilm experience different condition such as hydrogen ion concentration than cells grown peripherially. Also slower -growing bacteria often over express” non- specific” defense mechanism including shock proteins and multi drug efflux pumps and demonstrate increased exoplymer synthesis [10].

Literarture states that exopolymer matrix of a biofilm is a significant barrier to the diffusion of antibiotics.

Extracellular enzymes such as beta- lactamases formaldehyde lyase, formaldehyde dehydrogenase may become trapped and concentrated in extracellular matrix thus inactivating susceptible typically positively charged hydrophillic antibiotics. But macrolides which are positively charged but hydrophobic are unaffected by this process [11].

Currently alteration of genotype or phenotype of cells growing within a biofilm matrix is receiving increased attention [12].

Borun et al demonstrated that cells of *P. aueruginosa* liberated from biofilms were considerably more resistant to tobramycin than planktonic cells, suggesting that cells become intrinsically more resistant when growing in a biofilm and retained some of this resistance even outside the biofilm [13].

Antibiotics used in treatment of periodontal disease.

Tetracycline, Metronidazole and beta lactams are among the most widely used agents for treating periodontal conditions.

As pointed by van winkelhoff et al a sufficiently high dosage of metronidazole or other antibiotics must be prescribed to ensure efficacy in periodontal treatment [14].

Tenebaum *et al.* showed that effective levels of amoxilcillin and clavulanic acid in the gingival crevicular fluid well above the minimal inhibitory concentrations of some periodontopathic bacteria could be achieved after multiple drug applications. Plasma concentration established an antibacterial concentration within the periodontal environment.

A peak plasma concentration of 2- 2.5 mg/ ml occurs 2-4 hours following oral administration of repeated dose of tetracycline [15].

Tetracycline are bacterisostatic can suppress *A. actinomycetemcomitans* appears to concentrate in periodontal pockets, have been shown to suppress collagenase activity in crevicular fluid [16].

Literature states that factor which influence the antibiotic therapy include substantivity of a drug which is seen in tetracycline and its derivatives minocycline, oxytetracycline, chlortetracycline strongly adsorb to tooth surface retaining their antimicrobial activity [14].

Efficacy of an antibiotic may be decreased by the localization of bacteria within gingival tissues from various forms of human periodontal diseases. Manor et al have demonstrated in cases of advanced periodontitis, bacterial penetration into soft tissues of the apical zone of the pocket [17].

Total bacterial load in periodontal pockets in relation to maximal achievable antibiotic concentration.

Antibiotic regimens in periodontal therapy can be single or combination antibiotic therapy. Tetracycline- hcl, minocycline, doxycycline which inhibit collagenolytic activity [18], metronidazole which specifically target anaerobic micro-organisms, clindamycin which actively act against gram -ve anaerobes, having main association with periodontal flora, azithromycin an macrolide antibiotic has broad

spectrum activity and prolonged drug concentration in tissues and serum [15], amoxicillin a semisynthetic pencillin excellent activity against gram positive and negative bacteria is absorbed well following oral administration and penetrates in GCF [15] are the following drugs recommended for treating periodontists [17].

Effect of systemic antibiotic therapy on clinical variables has been reviewed in literature. In conditions like localized juvenile periodontitis periodontal surgery with systemic tetracycline hcl decreased periodontal a actinomycetemcomitans, as discussed by [19].

Previou studies showed complete eradication of subgingival p.gingivalis after comphrehensisve subgingival scaling and systemic metronidazole or clindamycin therapy [16].

Preventing emergence of bacterial resistance, increased synergy and lowering dose of individual antibiotics, also broadening the antimicrobial range of therapeutic regimen beyond that attained by an single antibiotic are the advantages of combination therapy.

Combination drugs have been proposed for periodontal therapy.

Ng and Bissada reported that systemic doxycycline administered for 6 weeks reduced plaque accumulation [20]. Also Watts *et al*. found that 7 days of systemic metronidazole therapy significantly reduced proportion of gingival bleeding and it is reported by lo-pezard co-workers [21]. Sequencing of antibiotic therapy overcomes potential risk of antagonism between bacteriostatic and bacteriocidal antibiotics [21].

To date, serial drug regimens studied in periodontics include systemic doxycycline administered initially, followed by either augmentin or metronidazole [22].

Ng and Bissada reported that systemic doxycycline administered for 6 weeks reduced plaque accumulation [20]. Also wattas et al found that 7 days of systemic metronidazole therapy significantly reduced proportion of gingival bleeding [23].

Combination therapy of metronidazole- amoxicillin resulted in less gingival bleeding and it is reported by lo-pezard coworkers [21].

Also Winkel *et al*. showed that combination of metronidazole – amoxicillin therapy reduced pocket depth significantly compared with control [24].

Topical use of antibiotics in periodontal pockets.

The concept of local delivery of an antibiotic into the periodontal pocket achieves a greater, more potent concentration of drug than available with systemic delivery is very appealing [25].

The local route of antibiotic can accomplish 100 fold greater therapeutic doses in subgingival sites than possible by systemic therapy also professionally administered topical therapy reduces problem with patient compliance [26].

Disadvantage is difficulty in placing therapeutic concentration of antimicrobial agents into deeper parts of periodontal pockets and furcation lesions [27].

Studies show that tetracycline derivatives doxycycline and minocycline which are more lipophillic than the parent compound resulted in better adsorption following systemic delivery and better penetration into the bacterial cell.

In a recent meta-analysis it states that 2% minocycline gel improved reduction in periodontal probing depth and gain in attachment [28].

Also microsphere containing minocycline hydrochloride (11mg) adheres to periodontal pocket allowing a controlled sustained release [28].

Also a two syringe mixing system for the controlled release of doxycycline resulted in greater reduction of frequency of *P. gingivalis* [28].

Elyzol 25% dental gel is a suspension of metronidazole benzoate 40% in a mixture of glycerol mono-oleate when comes in contact with gingival crevicular fluid after one application showed a minimum inhibitory concentration of 14ug/ml. Even after 24 hours the metronidazole concentration still remain above minimal inhibitory concentration for 50% killing of key periodontal pathogens [28].

Tetracycline has been promoted in several system (powder, gel, irrigation, fibers) [29].

Mac Alpine *et al*. reported that biweekly tetracycline irrigation deep into pockets did not appear to augment the effects of non-surgical periodontal therapy [30]. In contrast Chriterson et al used 10-15nml of aqueous tetracycline-hcl for 5 mins which obtained significant clinical improvement [20].

Tetracycline fibers are non resorbable with 12.7mg of tetracycline hydrochloride powder function in a controlled delivery device above 1590ug/ml crevicular fluid for 10 days.

CONCLUSION

Thus with this we have rendered knowledge that use of antibiotic in the treatment of periodontal disease is essential. Future prospectives is to achieve knowledge and evidence regarding recent advances of drug delivery, its efficacy in periodontium, effect on prognosis of periodontal disease after antibiotic administration in adjunct to mechanical therapy. Thus clinical, interventional and epidemiological studies are required with adequate sample size.

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