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Chemically Modified Tetracycline in Periodontal Therapy

AUTHOR's DETAIL:

1. **Dr. C BABU SALAM M.D.S.,**

   Periodontist and Implantologist,

   Private Practitioner.

2. **Dr. SS YASMIN PARVIN M.D.S.,**

   Senior Lecturer,

   Madha Dental College and Hospital,

   Kundrathur.

3. **DR. SHAKIR HUSSAIN RATHER M.D.S.,**

   Department of Pedodontics and Preventive Dentistry,

   Private Practitioner.

4. **Dr. REMYA RM M.D.S.,**

   Periodontist and Implantologist,

   Senior Lecturer,

   Dayananda Sagar College of Dental Sciences,

   1st Stage, Kumaraswamy Layout,

   Bengaluru, Karnataka 560078.

5. **Dr. ANAND INDUCHOODAN M.D.S.,**

   Specialist Periodontist,

   Aster Medical Center, Doha.

6. **Dr. ANKIT JHA B.D.S,**

   Manipal University,

   Private Practitioner – Indirapuram, Ghaziabad.

7. **Dr. MIDHUN KISHOR S M.D.S.,**

   Periodontist and Implantologist,

   Private Practitioner.

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I. INTRODUCTION:

The members of the tetracycline family are among the most important broad-spectrum antibiotics. The antibiotic spectrum and the chemical properties of tetracycline HCI and its semi-synthetic long-acting analogues, doxycycline and minocycline, are comparable, but not identical. They are generally well-tolerated, have few serious side-effects, and are the most commonly prescribed antibiotics. However, one important limitation to the continued widespread use of tetracyclines is the emergence of resistant oral flora.[1]

II. PHARMACOKINETICS:

The oral administration of tetracycline results in detectable serum levels within 30 minutes, with peak concentrations achieved after 1 to 3 hours. The half-life of tetracycline HCL is about 8 hours. Longer half-lives of 18 hours for doxycycline hyclate and 16 hours for minocycline HCL permit a lower initial dose and less frequent dosing than for tetracycline HCL. Tetracycline HC1 is adequately but incompletely absorbed (75%) from the stomach and upper duodenum in the fasting state, whereas from 95 to 100% of doxycycline and minocycline is absorbed. Multivalent cations chelate tetracyclines and inhibit absorption; consequently, patients should avoid the concurrent consumption of antacids, dairy products, and iron. After absorption, the tetracyclines are widely distributed in the body tissues and fluids. Selective distribution results in the accumulation of tetracycline by adsorption into newly formed bone crystal surfaces, and eventually it becomes incorporated into the crystal lattice. If tetracycline is administered during fetal development or permanent tooth formation, permanent discoloration and inadequate calcification of deciduous and permanent teeth are commonly seen. Tetracycline, doxycycline, and minocycline are detectable at higher levels in gingival crevicular fluid (GCF) than in the serum. Doxycycline is excreted mainly in feces; the other drugs are eliminated primarily in the urine.[1]

III. MECHANISMS OF ACTION:

Tetracyclines are bacteriostatic inhibitors of protein synthesis. They accumulate intracellularly by way of energy dependent transport systems present in bacterial membranes. The rate of tetracycline uptake and the intracellular drug level are dependent on the rate of drug entry through the outer cell membrane and the subsequent rates of uptake or efflux at the inner membrane. Once inside the cell, the drug may be transported out again, bind to cellular constituents, or chemically modified so that efflux does not occur. If tetracycline remains inside the bacterial cell, it binds to the 30S ribosomal subunit, thereby preventing the binding of aminoacyl-transfer RNA to the "A" receptor site on the 30S messenger RNA-ribosome complex. Thus, protein synthesis is suppressed by the inhibition of chain elongation.[1]

IV. SPECTRUM OF ACTIVITY:

All tetracyclines are bacteriostatic at recommended doses, although they can become bactericidal when given in high concentrations. Lower minimal inhibitory concentrations (MIC) are required for Gram-positive than for Gram-negative microorganisms. Generally, the lipophilic second-generation drugs, doxycycline and minocycline, are more active than the hydrophilic parent compound. Strict anaerobic bacteria are susceptible to tetracyclines, although some black-pigmented Bacteroides have been reported to be minocycline-resistant. Gram negative facultative rods are also sensitive to tetracyclines. Some strains of Actinobacillus actinomycetemcomitans (Aa) and Eikenella corrodens are tetracycline-resistant. Susceptible Gram-positive bacteria include Actinomyces israelii, A. naeslundii, A viscosus, Streptococcus mutans, and S. salivarius, although many Gram-positive oral streptococci exhibit tetracycline resistance. Tetracyclines are also effective against a few viruses, such as Mycoplasma, Chlamydia, Rickettsia and Legionellla.[2]

V. THE USE OF TETRACYCLINES IN PERIODONTAL THERAPY:

Antibiotics can directly reach the periodontal pocket through systemic or gingival sulcular administration. Systemic delivery effectively inhibits the growth of the majority of periodontal pathogens in essentially all periodontal pockets, including furcation areas, and may affect bacteria within pocket epithelia and connective

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tissue. Systemic antibiotics may also eliminate bacteria from non-dental sites, which may reduce the risk for bacterial repopulation. Tetracyclines have a distinctive property of concentrating in GCF at levels from two to 10 times greater than that of the serum after a single 250-mg dose. After 19 hours, tetracycline was still present, but by 24 hours it was not detectable in the GCF. Peak concentrations of 5-12 Rg/mL were reached in the GCF at 3.5 to 7 hours. It is therefore quite likely that the administration of 250 mg/day of tetracycline will not reduce pathogenic bacteria consistently. Since most treatment regimens involve multiple dosages, it was found that GCF levels of repeated doses (250 mg every 6 hours) of tetracycline were two to four times the blood levels after 48 hours.

Doxycycline achieved gingival fluid levels of 4 to 10 µg/mL after the administration of 100 mg every 12 hours for the first day, followed by 100 mg/day for 14 days. GCF concentrations of minocycline are 5 times as high as serum when 150-200 mg/day are given for 8 days, and can remain bacteriostatic for at least one week after treatment is discontinued. Lower doses of minocycline (100 mg/day) were also detected in the GCF in concentrations of 4.77 µg/mL but with fewer side-effects. Tetracyclines fit the profile as there is potential for adjunctive therapeutic management of periodontal diseases with the tetracycline group of drugs and other host modulatory agents used to arrest an over exuberant inflammatory response. They have beneficial effects on systemic diseases which are also driven by oxidative stress; in view of their antioxidant, anti-inflammatory and proanabolic effects in addition to their anti-microbial action. These non-antibiotic properties of tetracyclines also include immunomodulatory, angiogenic and anti-apoptotic effects. There are 3 main groups of tetracyclines consisting of the natural product, semi-synthetic compounds and the chemically modified tetracyclines.[2]

VI. APPLICATIONS FOR NON-ANTIMICROBIAL ACTIONS OF TETRACYCLINES IN PERIODONTAL DISEASES AND DIABETES MELLITUS (DM):

Oxidative stress is a unifying mechanism for production of reactive oxygen species and plays a significant role in the manifestation of insulin resistance, atherogenic dyslipidaemia and periodontal disease. The term metabolic syndrome is used to describe a clustering of risk factors of metabolic origin for cardiovascular disease and type 2 diabetes. These include hyperglycaemia, hypertension, dyslipidaemia and a pro-inflammatory state often associated with obesity. It is relevant that patients with metabolic syndrome show significant correlation with the prevalence of severe periodontal disease initiated by pathogenic bacterial plaque. This is associated with high levels of inflammatory cytokines, other markers of inflammation and oxidative stress such as C-reactive proteins and low density lipoproteins, on par with metabolic diseases. Periodontal patients with co-existing features of metabolic syndrome constitute a good model for therapeutic interventions which result in improved metabolic control of their systemic diseases. The non-antimicrobial anti-inflammatory actions of tetracyclines have useful applications in the management of inflammatory diseases as detailed below. Early in the course of diabetes mellitus (DM), mRNAs for IL-1β, TNF-α and other pro-inflammatory mediators are increased in the retina, partly from activated microglia.

Minocycline inhibits diabetes-induced cytokine and cytotoxin production and holds promise in preventing retinal complications of DM. Bacterial LPS also causes marked upregulation and release of IL-1β, TNF-α and NO in retinal microglia; this was inhibited by minocycline which has significant impact in reducing the expression and release of these mediators. Recent investigations have demonstrated that doxycycline was more effective in inhibiting matrix metallo proteinases (MMPs) in human aortic smooth muscle cells than minocycline, by upregulating the MMP inhibitor TIMP-1 (Tissue inhibitor of metallo proteinase-1). These findings have implications on periodontal diseases initiated by lipopolysaccharide mediated inflammatory burden with applications for the MMP inhibitory actions of tetracyclines.

Doxycycline hyclate has been shown to accelerate periodontal wound healing in diabetic mice and humans. Similar studies with Arestin (minocycline microspheres) have shown reduction in HbA1c and improved periodontal disease control over root debridement alone. Adjunctive locally delivered doxycycline in periodontal pockets of smokers has been shown to be more effective than pocket debridement alone in reducing the parameters of inflammatory periodontal disease. A combination of alendronate and low dose doxycycline has demonstrated improved bone remodelling and decreased rate of progression of

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experimental periodontits in rats. Both minocycline and doxycycline cause significant stimulation of osteoblastic cells at levels conventionally detected in plasma and gingival crevicular fluid; long term exposure of these cells to tetracyclines resulted in a proportional increase in mineralised bone matrix; while exposure to higher levels of these drugs resulted in delayed cell proliferation and differentiation.[2]

VII. SPECIFIC ANTI-INFLAMMATORY AND ANTIANGIOGENIC TARGETS OF TETRACYCLINES:

The collagenase MMPs that breakdown collagen are MMP-1, 8 and13 and those that affect basement membrane collagen (collagen IV) are the gelatinases known as MMPs 2 and 9. Tetracycline and its analogues inhibit these enzyme systems. Angiogenesis is facilitated by matrix degrading enzymes such as MMPs. Minocycline and doxycycline have been shown to inhibit angiogenesis by preventing endothelial growth and activity of collagenase. Inhibition of synthesis of MMP-8 and MMP-9 by endothelial cells in response to doxycycline and to a lesser extent by the chemically modified tetracyclines (CMTs) has been demonstrated at the mRNA level. These effects of tetracyclines have therapeutic implications on inflammatory processes associated with vascular tissue development. Elastin degradation and MMP activity are reduced by doxycycline in a model representing aneurismal disease. In a cell culture model of corneal epithelial cells treated with lipopolysaccharide, doxycycline inhibited the degree of formation of IL-1β to an extent that was similar to that of corticosteroids. It also prevents endotoxemia in vivo. Doxycycline can cause dose dependent reduction in the production of the cytokines IL-1β, IL-6, TNF-α and IFN-γ. Matrix metallo proteinases mediate different physiological processes by digesting extracellular matrix components. The pathogenesis of several diseases is characterised by over-expression of MMPs. The activity of MMPs is regulated by tissue inhibitors of MMPs (TIMPs) found in bone and other cells. Their biosynthesis is regulated by local and systemic hormones, uptake and degradation by cells. Considering their actions, abnormal expression of MMPs may lead to pathological conditions affecting bone and cartilage.[3]

VIII. WOUND HEALING ACTIONS OF TETRACYCLINES:

Modulation of basement membrane laminin, MMPs, osteoblast and osteoclast functions by tetracyclines contribute to its effects on wound healing. The effect of low dose tetracycline on modulation of laminin-5 and its association with proliferation of junctional epithelial cells during pocket formation was investigated in 30 patients with chronic periodontal disease. Root surface debridement was performed with or without adjunctive low dose doxycycline for its nonantimicrobial effects and monitored 3 monthly for twelve months. Gingival crevicular fluid (GCF) samples were collected for analysis of laminin and clinical paramenters of periodontal disease were recorded. The test group of patients with periodontal disease was subjected to complete root surface debridement with 20mg bd of low dose tetracycline and compared with the randomly selected control group who received root surface debridement plus placebo only. It is relevant that the low dose doxycycline group showed a significant reduction in GCF levels of Laminin-5 gamma 2 chain fragments compared with the placebo group.

Matrix metallo proteinase mediated fragmentation of laminin-5 can contribute to pocket formation by stimulating epithelial cell migration. Reducing these levels, could be another mechanism whereby low dose doxycycline could contribute to resolution of periodontal pockets in the long term. Chemically modified tetracyclines are effective in inhibiting bone resorption by inhibiting osteoclastic actions and inducing apoptosis of osteoclasts, in addition to reducing bone resorption by inhibiting matrix metallo proteinases. Recent studies demonstrate that the non-antibiotic analogues CMT-3 and CMT-8 of doxycycline and minocycline respectively are potent inhibitors of osteoclastogenesis from peripheral blood monocytes in response to macrophage colony stimulating factor and RANK at a concentration of 250ng/ml. The mechanism is reported to be independent of osteoblast osteoclast interactions. It has been shown that CMT-8 and oestrogen can improve wound healing in ovariectomised rats by changing the quality of wound bed collagen with improved expression of key molecules in wound healing such as laminin-5 gamma 2- chain. Adjunctive low dose doxycycline was shown to improve periodontal healing and reduce local bone resorption. These findings reinforce results of other workers in confirming that tetracyclines and their derivatives have potential therapeutic benefits in the management of metabolic diseases affecting

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bone homeostasis by modulating osteoblast and osteoclast activities. A novel finding regarding the inhibition of IL-1β induced IL-6 expression by CMT- 8 in murine osteoblasts at a post transcriptional level affecting the stability of IL-6 mRNA, provides potential for new incentives for therapeutic management of IL-6 mediated metabolic bone diseases.[3]

IX. ANTI-APOPTOTIC ACTIONS OF TETRACYCLINES:

Several studies demonstrate anti-apoptotic and anti-inflammatory effects of minocycline in the context of neuroprotection and in a lung epithelial cell model. The radical scavenging actions of minocycline are consistent with its multi-substituted phenol ring similar to that of vitamin E, belonging to the class of phenolic antioxidants; they are effective in scavenging free radicals resulting in the formation of phenol derived free radicals which are relatively stable and non-reactive. Minocycline was found to be far more potent than tetracycline in its radical scavenging potency and inhibition of lipid peroxidation by 316- and 200-fold respectively. Minocycline HCl has been shown to be very effective in quenching H2O2 levels; relative rates of various ROS related processes could contribute to a combination of quenching and scavenging of ROS by tetracyclines. These actions of minocycline could explain its potency in reducing the parameters of periodontal disease progression during adjunctive usage and

cardioprotection in reducing the size of myocardial infarcts. ROS are implicated in periodontal tissue damage seen during the progression of inflammatory periodontal diseases. A net damaging outcome is likely to be seen with an imbalance in oxidant /antioxidant activity due to inadequate protection from antioxidants such as glutathione. A study on periodontal patients demonstrated that resolution of periodontal disease parameters resulted in a significant decrease in lipid peroxidation and an increase in salivary glutathione levels. Products of lipid peroxidation contribute to periodontal disease progression. Accumulation of lipid peroxidase products leading to raised levels of oxidative stress and imbalance of endogenous antioxidant defence at inflammatory sites, has been reported in periodontal patients by other workers. ROS activity has been shown to be significantly greater in chronic periodontitis than in non periodontitis subjects. In this context the antioxidant and radical scavenging properties of minocycline are particularly relevant in the adjunctive management of periodontal diseases with or without additional inflammatory burden from co-existing systemic diseases.[4]

X. CONCLUSION:

The optimal design for the evaluation of tetracyclines as adjuncts in the treatment of periodontal diseases should include prospective, randomized, placebo-controlled, double-blind studies. Many existing studies of tetracyclines fall short of these design criteria due to the use of different patient groups, failure to assess disease activity states, the use of various antibiotic regimens, different evaluation periods (often less than one year), and major differences in baseline subgingival microbiota.

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