International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Role of Tetracyclines in Periodontics: A Literature Review

Dr. Rosiline Savio Vadakkan

Private Practice, Mumbai, Maharashtra, India

Abstract: ***Tetracyclines are a unique group of drugs which were discovered in the 1940s, developed as a result of the screening of soil samples for antibiotic organisms. The first of these compounds which was chlortetracycline, was introduced in 1948. Soon, they were found to be highly effective against various pathogens including rickettsiae, Gram-positive, and Gram-negative bacteria, thus becoming a class of broad-spectrum antibiotics.***

Keywords: Tetracyclines, Antibiotics, Minocycline, Doxycycline, Periodontitis

1. Introduction

Antimicrobial agents are used extensively in both medicine and dentistry to eliminate infection, as a prophylaxis to prevent infection in the 'at risk' patient. The microbial etiology of periodontal disease has provided the basis for the use of drugs in the overall management of this disease.It is still an area of controversy if anti microbials should be used in Periodontitis. [1]

The tetracyclines belong from an aging family of broad-spectrum antibiotics. The parent compound, chlortetracycline, was first isolated from *Streptomyces aureofaciens* in 1947 and later led to the discovery of other tetracyclines and many compounds.

Two of the more common semisynthetic tetracyclines used clinically as antibiotics are doxycycline (DOX) and minocycline (MIN), which are essentially well-tolerated and safe compounds. Because of its broad-spectrum antibiotic efficacy, Doxycycline is indicated for the treatment of a variety of infections, namely periodontal infections, anthrax, chlamydial infections, community-acquired pneumonia, Lyme disease, cholera, syphilis and others. Minocycline is also a broad-spectrum antibiotic and is most often used clinically in the treatment of severe acne, but it is also indicated for many of the same infections as DOX.

2. History of the Tetracyclines

Chlortetracycline and oxytetracycline, discovered in the late 1940s, are the first members of the tetracycline group being the products of *Streptomyces aureofaciens* and *S. rimosus*, respectively.

Other tetracyclines were identified later, either as naturally occurring molecules, e.g., tetracycline from *S. aureofaciens*, *S. rimosus*, and *S. viridofaciens* and demethylchlortetracycline from *S. aureofaciens*, or as products of semisynthetic approaches, e.g., methacycline, doxycycline, and minocycline. Inspite of the success of the early tetracyclines, the analogs had improved water solubility either to allow parenteral administration or to enhance oral absorption. These approaches resulted in the development of the sem-isynthetic compounds rolitetracycline and lymecycline. The most recently discovered tetracyclines are the semisynthetic group referred to as glycylcyclines, minocycline, and 9-*t*-(butylglycylamido)-minocycline. These compounds possess a 9-glycylamido substitutent. [2]

3. Chemical Structure

Tetracycline, doxycycline and minocycline are all composed of a four-ring core to which are attached various side groups. The dimethylamino group at the C4 carbon on the upper half of the molecule has been shown to be necessary for antimicrobial activity. 4-De-dimethylamino tetracyclines, also called chemically modified tetracyclines (CMTs), lack antimicrobial activity in vivo presumably due to the inability of the molecule to adapt a zwitter ionic form necessary for activity.

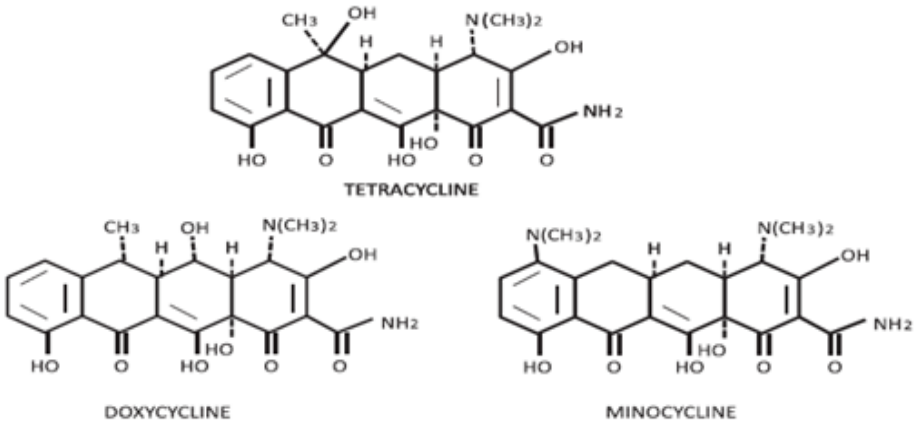

Figure 1: Chemical structure of tetracyclines

However, CMTs do retain the ability to bind other non microbial targets, such as matrix metalloproteinases (MMPs),which facilitates their use in the treatment of other disease processes. The oxygen-rich lower half of the molecule is crucial for binding to both prokaryotic and eukaryotic targets and interference with this region reduces or eliminates the effectiveness of the drug.

This region is important as a site for metal ion chelation. Binding of tetracyclines to proteins, including TetR, may be greatly enhanced when the tetracycline is complexed with divalent metal ions such as Ca2_ or Mg2_ . The binding of tetracyclines to MMPs is thought to be intervened by the chelation of structural and catalytic Zn2_ ions within the enzyme. Also, binding to the bacterial ribosome involves binding to RNA-bound Mg2_ . The strength of tetracycline metal interaction depends on both the tetracycline and the metal ion present.

In general, the affinity of the tetracyclines for different divalent metals is in order of decreasing affinity. The relative affinities of different tetracyclines for a given metal can also differ and are highly dependent on the pH value and the presence of other metal ions. The relative superiority of doxycycline as an MMP inhibitor is due to its increased affinity for Zn2_ compared with tetracycline or minocycline. In general, there is a direct relationship between lipo-philicity and activity against Gram-positive bacteria. The lipo-philicity of tetracycline, doxycycline and minocycline as determined by partitioning between octanol and aqueous buffer, has been determined to be 0.025, 0.600, and 1.1, respectively, and the minimum inhibitory concentration against *Staphylococcus aureus* is 0.21, 0.19, and 0.10 g/ml, respectively. Lipophilicity also affects tissue distribution. Minocycline is able to cross the blood-brain barrier much more readily than Doxycycline or tetracycline and also it attains levels in the brain nearly threefold higher than doxycycline whereas tetracycline is undetectable in the brain.

Antibiotic effect of tetracyclines:

The tetracyclines exert their antibiotic effect primarily by binding to the bacterial ribosome and halting protein synthesis. Bacterial ribosomes have a high-affinity binding site located on the 30S subunit and multiple low-affinity sites on both the 30S and 50S subunits. Upon binding the ribosome, the tetracyclines inhibit binding of the amino acyl-tRNA at the acceptor site (A-site), and thereby protein synthesis ceases.

Resistant microrganisms have resulted in the declined usage of tetracyclines. The primary mechanism of resistance is intervened by increased drug efflux out of the cell by a family of *Tet* proteins located on the cytoplasmic surface of the cell membrane. It also has led to the development of the Tet regulatory system, an important transcriptional regulation tool which is used extensively for eukaryotic targeted gene regulation.

Tetracyclines are effective, slow-acting anti-malarial drugs. Doxycycline treated parasites appear morphologically normal until late in the second cycle of treatment but do not develop into merozoites. Doxycycline impairs the expression of apicoplast genes. Apicoplast are abnormal in the progeny of doxycycline treated parasites. The loss of apicoplast function in the progeny of treated parasites leads to a slow, potent antimalarial effect.

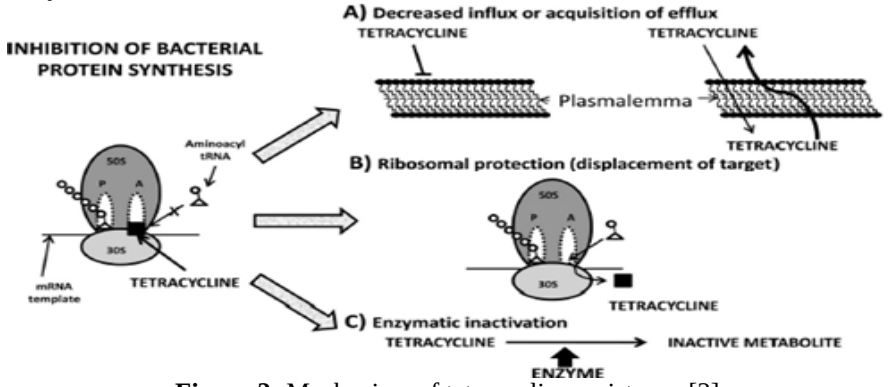

Figure 2: Mechanism of tetracycline resistance [3]

Mechanisms of resistance for characterized *tet* and *otr* genes

Genes
Efflux
tet(A), *tet*(B), *tet*(C), *tet*(D), *tet*(E), *tet*(G), *tet*(H), *tet*(I), *tet*(J), *tet*(Z), *tet*(30)[b] *tet*(31)[b]
tet(K), *tet*(L)
otr(B), *tcr3*[c]
*tet*P(A)
tet(V)
tet(Y)[d]
Ribosomal protection
tet(M), *tet*(O), *tet*(S), *tet*(W)
tet(Q), *tet*(T)
otr(A), *tet*P(B),[e] *tet*[c]
Emzymatic, *tet*(X)
Unknown[f]
tet(U), *otr*(C)

[a] Grouped according to McMurry and Levy (173).
[b] First numbered genes (150).
[c] These genes have not been given new designations (150).
[d] Relatedness to groups 1 to 6 is unclear, since the gene has not been studied extensively.
[e] *tet*P(B) is not found alone, and *tet*P(A) and *tet*P(B) are counted as one gene (164, 273).
[f] *tet*(U) has been sequenced but does not appear to be related to either efflux or ribosomal protection proteins; *otr*(C) has not been sequenced (207, 220).

[2]

TETRACYCLINES (TCs) INHIBIT CONNECTIVE TISSUE BREAKDOWN: PLEIOTROPIC MECHANISMS

(A) Mediated by extracellular mechanisms
- Direct inhibition of active MMPs—dependent on Ca^{++} and Zn^{++} binding properties of TCs
- Inhibition of oxidative activation of Pro-MMPs—independent of cation-binding properties of TCs
- TCs disrupt activation by promoting excessive proteolysis of pro-MMPs into enzymatically-inactive fragments—dependent (?) on cation binding of TCs
- Inhibition of MMPs protects α_1-PI, thus INDIRECTLY ↓ serine proteinase (*e.g.*, PMNL elastase) activity

(B) Mediated by cellular regulation
- TCs ↓ cytokines, iNOS, PLA_2, prostaglandin synthase
- Effects on protein kinase C, calmodulin

(C) Mediated by pro-anabolic effects
- TCs ↑ collagen production
- TCs ↑ osteoblast activity & bone formation

Administration of tetracyclines

Tetracyclines are usually given orally for the periodontal treatment regimen. The usual oral dose is 250 mg four times a day. Tetracyclines are absorbed from the gastrointestinal tract and absorption is reduced when it is taken with dairy products or with substances containing calcium, magnesium (e.g. antacids) or iron. They cause chelation thus impairing absorption.

The half-life of tetracycline is between 6 and 10 hours, while those of minocycline and doxycycline are between 16 and 18 hours. These longer half-lives allow lower initial doses and less frequent administrations than for tetracycline. All tetracyclines are distributed widely in the tissues and are localized in developing dental structures and bone. It is also detectable in crevicular fluid after oral dosing and their respective concentrations can reach levels of 5-10 times those in serum.

[4]

Topical application of tetracyclines

Tetracycline has been delivered locally into the diseased tissues as local drug delivery agents for insertion into periodontal pockets. Of these devices, monolithic ethylene vinyl acetate fibres have been found to be efficacious in achieving prolonged delivery of the drug from the entire length of the fibres. Furthermore, the concentrations of tetracycline in crevicular fluid achieved by controlled local delivery are up to 100 times those obtained from systemic dose (1500 ug ml-l vs 1.5 I-I & ml). These high local concentrations favourably increase the chance of complete suppression of bacterial growth. Placement of such fibres appears to be non-traumatic and compatible with the gingival tissues.

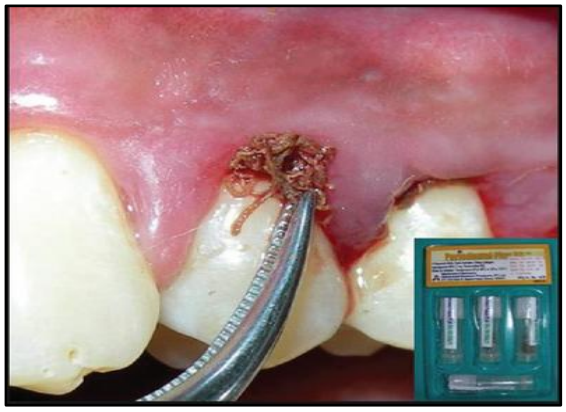

Figure 3: Tetracycline fibres

Figure 4: Tetracycline gel

Further properties of tetracycline for periodontal diseases

Anti-collagenase inhibition

The anti- collagenase activity is the most distant property exhibited by tetracyclines. This action is related to the source of the enzyme and the tetracycline used. Doxycycline is the most potent tetracycline for collagenase inhibition. Collagenases derived from neutrophils are more susceptible to a tetracycline induced inhibition, where as collagenases derived from human fibroblasts are more resistant to the drug. Tetracycline inhibition of collagenase may be caused due to the drug's ability to bind with calcium and zinc ions.

Zn+ is located at the active site of the enzyme, while Ca2+ is an exogenous co-factor. A further mechanism may be linked with the ability of the tetracyclines to scavenge reactive oxygen radicals (e.g. hydroxyl groups or hypochlorous acid) produced by PMNs. These oxygen radicals activate latent collagenases. Inhibition of collagenase may result in further anti proteolytic effects such as inactivation of a-l proteinase inhibitor and neutrophil elastase.

Tetracyclines and bone resorption

Tetracyclines inhibit bone resorption induced by parathyroid hormone, prostaglandins of the E series and bacterial endotoxin. This action is caused because of the antiproteolytic properties of the drug or a modifying effect on osteoclasts.

Anti-inflammatory actions of tetracyclines

Tetracyclines are used widely in dermatological practice due to their general anti proteolytic propertiesand or to some anti-inflammatory action. Potential anti inflammatory properties include the ability of tetracyclines to down regulate PMN activity, to scavenge reactive oxygen radicals and block ecosanoid synthesis by inhibition of phospholipase A activity.

Effect of tetracyclines on the root surface attachement

It has been seen that pre treatment [Root biomodification] of root surfaces with tetracyclines enhances fibroblast attachment and colonizations.It can also bind to and demineralize the dentine. However, it is not confirmed whether these actions of tetracycline on dentine are due to a chemical modification of the properties of the dentinal surface, or to the release of matrix components from the dentine (i.e. type 1 collagen, proteoglycans, osteonectin or growth factors).

Other tetracyclines

Minocycline is a semisynthetic derivative of tetracycline. Short-term studies, in which minocycline 200 mg per day was administered for 7- 8 days to patients with periodontal disease, indicate that the drug produces long-lasting shifts in the subgingival microflora. Minocycline also has the effect of resolving gingival inflammation, although its long-term effects are unknown.

Local application of minocycline

Minocycline is available in a proprietary controlled release system (Dentomycin, Lederle, Gosport, UK). The product contains 2% minocycline gel which is packaged in a syringe for easy application into the periodontal pocket. Local application of minocycline has shown to be a good and a useful adjunct to non-surgical management.

Doxycycline (100 mg per day) has been used as an adjunct to periodontal surgery in the management of aggressive Periodontitis and also chronic periodontitis. A 2 week course of doxycycline with surgery produces a significant reduction in the prevalence of A. actinomycetemcomitans, and this suppression can persist for up to 12 months. A further study has shown that a 3 week course of doxycycline 100 mg/day produced a significant risk reduction in patients with recurrent active periodontal disease. Benefits of this regimen of doxycycline lasted for up to 1 year in most patients.[5]

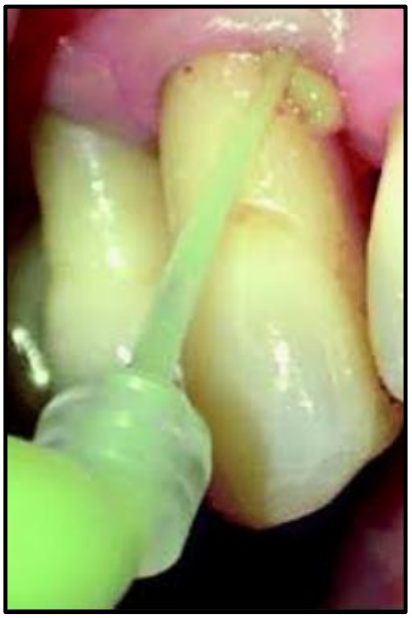

Figure 5: Minocycline gel application

Side effects of tetracyclines

gastrointestinal discomfort, nausea, vomiting, diarrhea
photosensitivity, rash, oncholysis
intra- and extraoral fixed drug eruptions
vertigo (especially with minocycline)
vaginitis
benign intracranial hypertension (pseudotumor cerebri)
permanent tooth discoloration in children up to 8 years of age (all tetracy- clines)
permanent tooth and alveolar bone discoloration in adults (minocyclineonly)
exacerbates systemic lupus erythematosus
avoid during pregnancy and in patients with renal dysfunctions

Possible drug interactions

potentiates anticoagulant effects of Coumadin (warfarin)
potentiates toxicity of lithium
potentiates vasoconstrictive effects of ergot alkaloids
potentiates nephrotoxicity of diuretics (especially in elderly or dehydrated patients)
decreases bacteriocidal effects of penicillins and ciprofloxacin
digestive absorption inhibited by antacids, antianemics, magnesium-containing drugs and milk products

[6]

Principal members of the tetracycline class

Chemical name	Generic name	Trade name	Yr of discovery	Status	Therapeutic administration
7-Chlortetracycline	Chlortetracycline	Aureomycin	1948	Marketed	Oral
5-Hydroxytetracycline	Oxytetracycline	Terramycin	1948	Marketed	Oral and parenteral
Tetracycline	Tetracycline	Achromycin	1953	Marketed	Oral
6-Demethyl-7-chlortetracycline	Demethylchlortetracycline	Declomycin	1957	Marketed	Oral
2-*N*-Pyrrolidinomethyltetracycline	Rolitetracycline	Reverin	1958	Marketed	Oral
2-*N*-Lysinomethyltetracycline	Limecycline	Tetralysal	1961	Marketed	Oral and parenteral
N-Methylol-7-chlortetracycline	Clomocycline	Megaclor	1963	Marketed	Oral
6-Methylene-5-hydroxytetracycline	Methacycline	Rondomycin	1965	Marketed	Oral
6-Deoxy-5-hydroxytetracycline	Doxycycline	Vibramycin	1967	Marketed	Oral and parenteral
7-Dimethylamino-6-demethyl-6-deoxytetracycline	Minocycline	Minocin	1972	Marketed	Oral and parenteral
9-(*t*-butylglycylamido)-minocycline	Tertiary-butylglycylamidominocycline	Tigilcycline	1993	Phase II clinical trials	

Other Clinical Indications of Tetracyclines

Infection for which tetracyclines are:	
First choice	Acceptable alternative to other agents[b]
Respiratory	
Atypical pneumonia due to *Mycoplasma pneumoniae, Chlamydia pneumoniae, C. psittaci*	Community-acquired pneumonia[c] Infective exacerbations of chronic bronchitis[c] Legionellosis (doxycycline)
Bowel	
Cholera Prophylaxis of traveler's diarrhea	
Genital	
Nongonococcal urethritis Cervicitis Lymphogranuloma venereum Pelvic inflammatory disease Granuloma inguinale	Syphilis Epididymitis Prostatitis
Local and systemic	
Rocky mountain spotted fever Endemic and epidemic typhus Q fever Brucellosis (in combination with rifampin or streptomycin) Lyme disease Relapsing fever Periodontal infection (topical therapy with tetracycline or minocycline) Acne vulgaris (topical and systemic treatment) Prophylaxis of mefloquine-resistant *Plasmodium falciparum* malaria	MRSA MRSE (minocycline) when vancomycin or other agents inappropriate Plague Tularerira Bartonellosis Leptospirosis Whipple's disease Cutaneous infections caused by *Mycobacterium marinum* and in multiple-drug regimens for ocular infections caused by *M. cheloni* Gastritis caused by *Helicobacter pylori* (tetracycline in multiple-drug regimens).

[2] It is widely used in Aggressive Periodontitis and Necrotizing Periodontal Diseases.

References

[1] Seymour and Heasman: Antimicrobial agents. J. Dent. 1995; 23(1).
[2] Ian Chopra and Marilyn Roberts. Microbiol. Mol. Biol. Rev. 2001, 65(2):232.
[3] Michael O. Griffin et al. Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature. AJP-Cell Physiol 2010; 299
[4] L.M. Golub, H.-M. Lee, M.E. Ryan, W.V. Giannobile, J. Payne and T. Sorsa. Tetracyclines Inhibit Connective Tissue Breakdown by Multiple Non-Antimicrobial Mechanisms. Adv Dent Res 1998; 12: 12
[5] R. A. Seymour and P. A. Heasman. Pharmacological control of periodontal disease. II. Antimicrobial agents. J Dent 1995; 23(1) : 5-14.
[6] Slots J and Rams TE: Antibiotics in periodontal therapy: advantages and disadvantages. J Clin Periodontol 1990; 17: 479-493.