RESEARCH PAPER

Doxycycline In Periodontal Therapy: Local Drug Delivery Systems, Host Modulation, And Clinical Applications

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Abstract

Doxycycline is a semisynthetic tetracycline antibiotic with well-established antimicrobial, anti-collagenolytic, and host-modulatory properties that support its continued use in periodontal therapy. In addition to its activity against key periodontal pathogens, doxycycline inhibits matrix metalloproteinases, reduces inflammatory mediators, limits connective tissue breakdown, and contributes to improved periodontal healing. These properties have expanded its role beyond conventional systemic antibiotic therapy and positioned it as an important agent in local periodontal drug-delivery strategies.

This review highlights the pharmacologic profile of doxycycline, including its mechanism of action, therapeutic indications, adverse effects, contraindications, and major drug interactions, with particular emphasis on periodontal applications. Special focus is placed on doxycycline-based local delivery systems and controlled-release formulations designed to achieve high subgingival concentrations, prolonged retention within periodontal pockets, sustained therapeutic release, bioadhesion, biodegradability, and reduced systemic exposure. The review also discusses clinically relevant formulations such as subantimicrobial-dose doxycycline, Atridox, and Ligosan, and outlines their roles as adjuncts to scaling and root planing in the management of chronic periodontitis and supportive periodontal care.

Overall, doxycycline remains a versatile therapeutic agent in periodontics because it combines antimicrobial efficacy with host modulation and delivery-system adaptability. Its ability to function in both systemic and locally controlled-release forms makes it especially relevant to modern periodontal treatment strategies aimed at improving clinical outcomes while minimizing unnecessary systemic adverse effects.

Keywords: Doxycycline; Periodontal therapy; Local drug delivery; Controlled-release systems; Host modulation; Subantimicrobial-dose doxycycline; Atridox; Ligosan; Chronic periodontitis; Scaling and root planing

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INTRODUCTION

An American plant physiologist and mycologist, Benjamin Duggar discovered chlortetracycline by examining a product obtained from the fermentation of the bacterium Streptomyces aureofaciens.[1] This lead to the development of the first tetracycline in 1953. Subsequent structural modification of these compounds gave rise to 2 synthetic tetracyclines: doxycycline (in 1967) and minocycline (in 1972).

Molecular Mass: - 444.4g/mol
Molecular Formula: - C22H24N2O8
IUPAC Name: '(4S, 4Ar, 5aR, 6R, 12As)-4-(dimethyl amino)-3,5,10,12,12a, -pentahydroxy-6-methyl-1, -11-dioxo-1,2,3,4,4a, 5a, 6,11,12a -decahydrotetracene-2-carboxamide'

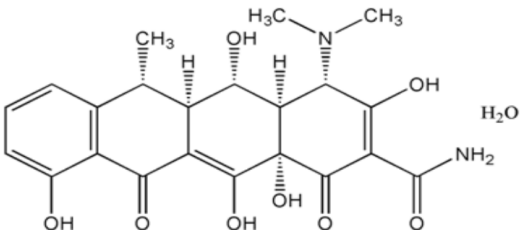

Figure 1: Doxycycline monohydrate structure

DOSE OF DOXYCYCLINE:

Doxycycline is available in various dosage forms like injection, syrup, suspension, capsules, and tablets. For oral administration, doxycycline is available in capsule form (150, 100, 75, and 50 mg)[2,3], oral tablets (20 mg, 50 mg, 75 mg, 100 mg, and 150 mg), and delayed-

release tablets (50 mg, 60 mg, 75 mg, 80 mg, 100 mg, 150 mg, and 200 mg).

Initial dose: Doxycycline is typically initiated with a starting dose of 200 mg/day.[4]

Maintenance dose: A maintenance dose of 100 mg/day is commonly prescribed after the initial dose. However, in severe infections, 100 mg twice daily is prescribed.

Loading dose: In patients with serious infections, optimal dose-dependent killing is achieved by prescribing a higher loading dose of doxycycline (e.g., loading dose of 200 mg twice daily for 72 hours).

Maximum recommended dose: 300 mg/day.

Routes of administration: Doxycycline can be administered orally or intravenously,
depending on the specific requirements of the patient and the nature of the infection.

Oral administration: When taking the oral dose of doxycycline, it is important to consume sufficient fluids. Following administration, the patient should remain upright for 30 minutes to ensure proper absorption.

Paediatric dosing: In children, the use of doxycycline is determined by weighing the benefits against the risks. The dose is typically adjusted based on the child's weight, with a recommended dose of 2.2 mg/kg daily or 2.2 mg/kg twice daily.

Mechanism of Action of Doxycycline:

Doxycycline is an broad spectrum antibiotic. Doxycycline attaches to the '30S ribosomal subunit' decreasing the production of micro- bacterial proteins. Also it adds amino acids to bacteria's polypeptide chains, resulting in the creation of new proteins as well as binding failure between transfer and messenger RNA on the ribosome's subunit.[5] Doxycycline affects the binding rate of the ternary complex to the ribosome.[6] The ternary complex attempts to bind the aa-tRNA to the A site but fails to do so.[7] This leads to a halt in the translation of the growing polypeptide chain, thereby impeding the production of essential proteins and ultimately leading to the death of the bacteria.

Doxycycline's high lipophilicity enables it to cross multiple membranes and reach its target molecules.[8]

Pharmacokinetics of Doxycycline

Absorption

Doxycycline is almost completely absorbed after oral administration, achieving virtually 100% bioavailability. Within 2 hours of dosing, the highest doxycycline concentrations in the bloodstream can be detected, with serum levels ranging from 1.7 to 3g/ml.[9]

The peak plasma concentration following a 200 mg oral dose in adults is approximately 2.6 µg/mL at 2 hours, decreasing to 1.45 µg/mL at 24 hours. In children aged 2 to 18 years, absorption is similarly complete; oral and intravenous dosing have no meaningful difference in systemic exposure.[10]

Protein binding Doxycycline binds to plasma protein at a high rate, approximately 80–90%.[11]

Volume of distribution

Doxycycline has a volume of distribution of 1.33 (0.38–3.18), varying with age.[12] Doxycycline has high protein binding. Furthermore, the drug crosses the placenta and is found in fetal tissues.[13]

Doxycycline can enter practically all human tissues and bodily fluids. Doxycycline is found in high concentrations in the liver, lungs, kidneys, gallbladder, breast milk, genitals, and bone marrow. Doxycycline levels are low in cerebrospinal fluid, aqueous humor, and saliva [14]

Metabolism

Doxycycline undergoes minimal metabolism. Primarily concentrated in the liver and secreted unchanged in bile, doxycycline remains biologically active throughout circulation. It is also broken down in the GI tract. Metabolic clearance plays a minor role in its elimination. On the other hand, it is found that enzyme inducers retard the half-life of doxycycline.[15]

Excretion

Doxycycline is eliminated via both renal and fecal routes.[10] In adults with normal renal function, approximately 40% of the drug is excreted in the urine over 72 hours and in severe renal impairment, urinary excretion decreases to 1% to 5% over 72 hours, leading to a compensatory fecal elimination. Doxycycline concentrations in bile are near fifty grammes per millilitre. The urinary system accounts for 20% of doxycycline elimination. Passive diffusion transports 75% of the doxycycline from the blood to the lumen of the intestine, while the remaining 5% is transported from the bile and eliminated through faeces.[16] The serum half-life remains consistent, despite renal dysfunction, ranging from 18 to 22 hours.[10]

In children, weight-normalized clearance ranges from approximately 0.04 to 0.08 L/kg/h, with no significant differences between age groups or body weights.[10]

Anti-microbial spectrum of activity of doxycycline [17-19]

a) Gram-negative bacteria
    1. Acinetobacter species

2. Bartonella bacilliformis
3. Brucella species
4. Klebsiella granulomatis
5. Campylobacter fetus
6. Enterobacter aerogenes
7. Escherichia coli
8. Francisella tularensis
9. Haemophilus ducreyi
10. Haemophilus influenzae
11. Klebsiella species
12. Neisseria gonorrhea
13. Shigella species
14. Vibrio cholerae
15. Yersinia pestis

b) Gram-positive bacteria
1. Bacillus anthracis
2. Listeria monocytogenes
3. Streptococcus pneumoniae

c) Anaerobes
1. Clostridium species
2. Fusobacterium fusiforme
3. Propionibacterium acnes

d) Parasites
1. Balantidum coli
2. Plasmodium falciparum
3. Entamoeba species

e) Other bacteria
1. Actinomyces species
2. Borrelia recurrentis
3. Chlamydophila psittaci
4. Rickettsiae
5. Chlamydia trachomatis
6. Mycoplasma pneumoniae
7. Treponema pallidum
8. Treponema pertenue
9. Ureaplasma urealyticum

Indications

Doxycycline is indicated in the following conditions or diseases:[20]

- Sexually transmitted infections.
- Respiratory tract infections.
- Specific bacterial infections (e.g., cholera caused by Vibrio cholerae).
- Ophthalmic infections.
- Anthrax (including post-exposure anthrax).
- In patients with contraindications to penicillin (e.g., as an alternate treatment for syphilis caused by Treponema pallidum).
- Rickettsial infections.
- Acute intestinal amebiasis
- severe acne (as adjunctive treatment).
- Prophylaxis of malaria.

Contraindications

1. *Absolute contraindications:*
   Doxycycline should not be used in individuals who have demonstrated hypersensitivity or allergic reactions to any tetracycline antibiotics.[20]
2. *Relative Contraindications:*[21-23]
   - Liver disease due to rare fatal hepatotoxicity
   - Pregnancy or breastfeeding due to teratogenicity and permanent teeth discoloration after in-utero exposure Use with penicillin or isotretinoin
   - History of fungal infections
   - Recent colitis caused by antibiotic use Clostridioides difficile-associated diarrhea (CDAD)
   - History of lupus (autoimmune)
   - Porphyria
   - Myasthenia gravis (rare)

Administration in Specific Patient Populations

1. *Pregnancy*
   As indicated in animal studies tetracycline exerts toxic effects on the developing fetus as it traverse the placenta, and is present in the fetal tissues. The FDA classifies doxycycline as a pregnancy category D medication.[9] Doxycycline is often associated with retardation of skeletal development.

2. *Breastfeeding*
   Short-term maternal use may carry minimal risk due to low drug concentrations in milk and reduced oral absorption in the infant due to calcium binding. However, given the theoretical risks of dental discoloration, effects on bone growth, and alteration of the infant's gastrointestinal flora, prolonged or repeated courses should be avoided during breastfeeding unless absolutely necessary. If extended treatment is needed, clinicians should carefully balance the maternal

therapeutic need against the potential risks to the infant, considering temporary cessation of breastfeeding if appropriate.[24]

3. *Pediatric patients*
   For nearly all indications, doxycycline is contraindicated in patients younger than 8 years. Except for cases where the benefits substantially outweigh the risks associated with tooth development and growth.

4. *Hepatic impairment*
   Doxycycline undergoes minimal hepatic metabolism; no dose adjustment is generally required. However, doxycycline-induced liver injury though rare but is well-documented. Liver injurycan present with a mixed hepatocellular-cholestatic pattern, occasionally associated with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. High-dose IV doxycycline may rarely cause acute fatty liver, particularly in susceptible populations (eg, pregnant women). Although infrequent cases of autoimmune hepatitis and vanishing bile duct syndrome have been reported, recovery is usually rapid after drug discontinuation, with no documented cases of acute liver failure. If hepatotoxicity is suspected, doxycycline should be discontinued.[21]

5. *Renal impairment*
   In patients with renal impairment, no significant difference in the serum half-life of doxycycline (range, 18-22 hours) has been observed compared to individuals with normal renal function. Furthermore, hemodialysis does not affect its elimination. Also, it exerts an antianabolic effect that may lead to increased blood urea nitrogen (BUN) levels.[10]

Adverse Effects

1. **Common Adverse Reactions**
   The most common adverse reactions associated with doxycycline include:[10,25]
   - Mild diarrhea
   - Photosensitivity
   - Nausea
   - Vomiting
   - Skin rash/itching
   - Headaches
   - Tooth discoloration
   - Fixed drug eruption

2. **Rarely observed Adverse Effects [26-30]**
   - Hematochezia
   - Leukopenia
   - Hemolytic anemia
   - Throat irritation or trouble swallowing
   - Esophagitis/esophageal ulcerations if taken without water
   - Chest pain
   - Shortness of breath
   - Irregular or fast heart rate
   - Dysuria
   - Intracranial hypertension
   - Exacerbation of systemic lupus erythematosus

Drug Interactions

1. Tetracyclines, eg, doxycycline, can chelate divalent and trivalent cations found in certain medications, which may reduce the absorption of doxycycline and other drugs when taken

concurrently. They include antacids containing aluminum, calcium, and magnesium-based laxatives, as well as oral iron supplements.[10]

2. Other medications that can decrease doxycycline absorption include antidiarrheal agents containing pectin or bismuth subsalicylate. Therefore, simultaneous administration should be avoided in these drugs.[31]
3. Administration of doxycycline with warfarin has resulted in an enhanced anticoagulant effect due to the competitive interaction for albumin binding and potential inhibition of the cytochrome P- 450 pathway.[32]
4. Barbiturates, carbamazepine, and phenytoin can decrease the half-life of doxycycline.[10]
5. Also the simultaneous use of tetracycline, including doxycycline, may diminish the effectiveness of oral contraceptives.
6. Doxycycline is known to cause phototoxic skin reactions, particularly in areas exposed to sunlight. Other medications linked to photosensitive reactions include nalidixic acid, amiodarone, voriconazole,

hydrochlorothiazide, and thioridazine. Additionally, aminolevulinic acid, commonly used in photodynamic therapy, can increase light sensitivity, increasing the risk of phototoxic reactions.[33]

7. Concurrent use of systemic tetracyclines and isotretinoin increases the risk of pseudotumor cerebri [34]

Doxycycline and periodontics:

Doxycycline is used both as a systemic drug as well as a local delivery drug in periodontal therapy.

a) Doxycycline as a systemic drug:

Nonsurgical periodontal therapy (NSPT) is the cornerstone of periodontal therapy.[35] The efficacy of scaling and root planning (SRP) as a part of the NSPT of periodontitis is well established[36] but SRP alone is not adequate, especially in particularly susceptible individuals, such as those with diabetes mellitus.[37] SRP with adjunct antibiotic therapy is usually performed, which helps in the extermination of pathogenic microbes from infected periodontal pockets.[38] Systemic antibiotics enter the periodontal tissues and the periodontal pocket via serum and can affect organisms outside the reach of cleaning instruments or topical anti-infective chemo-therapeutics. Systemic antibiotic therapy can also potentially suppress periodontal pathogens residing on the tongue or other oral surfaces, thereby delaying subgingival recolonization of pathogens[39]. Systemic antibiotics may even be required for eradication of periodontal infections by A. actinomycetemcomitans and other pathogens.[39]

There are a lot of antibiotics which may be given, locally or systemically. [40] Tetracyclines are a group of antibiotics that have a broad spectrum of activity with the spectrum to inhibit the anaerobic microorganisms.[41] This effect to inhibit them happens in a very short period, usually 5 days.[42] Doxycycline is the most common antibiotic that are active against most perio-pathogens due to low minimum inhibitory concentration (MIC)[43]

The effect of systemic administration of doxycycline on various clinical variables:

1. Supragingival plaque accumulation: systemic antibiotic therapy does not significantly affect supragingival plaque accumulation. It depends mostly on patients oral hygiene efforts. However, Ng & Bissada[44] reported that systemic doxycycline administration for 6 weeks was associated with significantly reduced plaque accumulation at week 12 post treatment compared with placebo.
2. Gingival inflammation: Systemic antibiotics might not have a significant effect on gingival inflammation, with the possible exception of metronidazole, doxycycline and metronidazole–amoxicillin combinations .[44-46]
3. Periodontal pocket depth: Several systemic antibiotic therapies have no significant impact on periodontal pocket depth compared with controls. However, metronidazole and its combination with amoxicillin constitute an important exception. [47-49] However, Aitken et al.[50] reported that systemic doxycycline therapy for 3 weeks followed by systemic metronidazole for 10 days resulted in improved attachment levels and reduced disease recurrence compared with metronidazole treatment alone.
4. Effect on need for surgical therapy: Systemic antibiotics may reduce periodontal surgical needs. Loesche et al. suggested that systemic doxycycline therapy for 14 days might reduce the need for periodontal surgery.[51]
5. Effect on periodontal microorganisms: Doxycycline is documented to have an effect on periodontal microorganisms. Doxycycline for 14 days reduced spirochetes in advanced periodontitis lesions to below detectable levels for at least 3 months.[52]

b) Doxycycline as a local drug delivery agent in periodontics

Nonantibiotic properties of doxycycline

1. Non-Antibiotic Properties (Host Modulation) by its effect on Matrix metalloproteinases: Metalloproteinases (MMPs) participate in multiple biological processes via zinc-dependent multidomain endopeptidases. Doxycycline can inhibit MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13. MMP-8 (or neutrophil collagenase) is also inhibited by doxycycline, especially inendothelial cells and in patients with periodontitis.[53] MMP-9 participates in the degradation of basement membrane components, promoting the migration of immune cells through the basement membrane during inflammatory processes. Doxycycline has been shown to reduce MMP-9 synthesis in vitro.[54]
2. High Subgingival Concentration: Local application achieves higher, more sustained drug concentrations in the periodontal pocket

compared to systemic routes, which helps in treating deep pockets (6–7 mm).[55,56]

3. Bioadhesion**:** Many formulations are designed to adhere to the mucosal membrane, allowing for better retention in the pocket.
4. Safety Profile: Local application avoids the systemic adverse effects often associated with oral antibiotic administration.[55,56]
5. Biodegradability**:** The delivery systems are typically biodegradable, meaning they do not need to be removed after application
6. Controlled/Sustained Release: Biodegradable formulations (like 10% doxycycline in poly (DL-lactide) and N-methyl-2-pyrrolidone) allow the drug to be released over a sustained period, typically maintaining therapeutic levels in the periodontal pocket for at least 7 to 10 days.

Local formulations available

1. **Sub antimicrobial Dose of Doxycycline (SDD)** : it contains 20 mg doxycycline, as opposed to the 50 or 100 mg dose that is available for antibiotic purposes**.**[57] SDD (20 mg twice daily) administered for just 2 weeks inhibited collagenase activity by 60–80% in the gingival tissues of patients with chronic periodontitis.[58] Subsequent studies of relatively short duration (1–3 months) indicated that this dosing regimen could prevent periodontitis progression without the emergence of doxycycline-resistant microorganisms or other typical antibiotic side- effects.[59] Thus, the era of SDD as adjunct for treatment of chronic periodontitis was born .

   US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, have approved it as the only systemic host response modulator and it was introduced under the trade name Periostat (CollaGenex Pharmaceuticals Inc., Newtown, PA). It is a 20-mg dose of doxycycline hyclate that is taken twice daily for periods of 3–9 months as an adjunct to root surface instrumentation in the treatment of periodontitis. The rationale for using SDD as a host response modulator is that it inhibits the activity of MMPs by a variety of synergistic mechanisms independent of any antibiotic properties such as: [60]

   - Direct inhibition of active MMPs by cation chelation (dependent on Ca2+- and Zn2+-binding properties)
   - Inhibits oxidative activation of latent MMPs (independent of cation-binding properties)
   - Downregulates expression of key inflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor-α) and prostaglandin E2
   - Scavenges and inhibits production of reactive oxygen species produced by Neutrophils
   - Inhibits MMPs and reactive oxygen species thereby protecting a1-proteinase inhibitor, and thus indirectly reducing tissue proteinase activity
   - Stimulates fibroblast collagen production
   - Reduces osteoclast activity and bone resorption
   - Inhibits osteoclast MMPs
2. **Atridox**: a two-syringe mixing system, 10% doxycycline hyclate, and a biodegradable liquid polymer gel. Ahamed *et al* in a study while comparing local drug delivery of doxycycline as a supplement to SRP for treating chronic periodontitis found that combining SRP with 10% Atridox gel led to better results as compared to SRP alone.[61] Bogren *et al*., in 2008, analyzed the long-term clinical and microbial effects of mechanical debridement during SPT with controlled-release doxycycline given locally, and it was concluded that locally administered doxycycline was found to have short-term effects on clinical parameters, but annual administrations did not have any additional clinical or microbiological effects on patients in the supportive phase beyond what was seen with scaling and root planing alone.[62] Dannewitz *et al*., in 2009, studied the effect of doxycycline gel during srp as adjunct to scaling and root planing (SRP) in furcation and they, reported that doxycycline used once subgingivally in conjunction with SRP caused temporary reduction in furcation involvement. However, there was no change in frequency of reinstrumentation at furcations for up to a year.[63] Eickholz *et al*., in 2002, found that 15% doxycycline gel with scaling and root planning, compared to SRP alone, offered a clinically relevant and more

favorable PPD decrease and a statistically considerably greater relative attachment level increase.[64] In 2005, Ratka-krüger *et al*. investigated the microbiological effects of the application of biodegradable 14% doxycycline gel and its results in relation to scaling and root planing and found that at three months, there was a noticeable decrease in periodontal pathogens. Furthermore, the findings stabilized up to six months after therapy. No doxycycline resistance was induced.[65] In 2012, Tonetti *et al*. investigated how well slow-release doxycycline gel (SRD) worked when given to people with recurrent or persistent periodontitis alongside non-surgical treatment and discovered that SRD might provide a short-term advantage in reducing inflammation and deep pockets in periodontal patients.[66]

3. **Ligosan** : Ligosan Slow Release is a resorbable doxycycline gel for periodontal application, containing 14% (w/w) of the active ingredient. It comes packaged in a laminate pouch and requires refrigerated storage. It comprises single-application cylinder cartridges, available in quantities of 1, 2, 4, 8, 10, or 16, with each cartridge containing 260 mg of Ligosan Slow Release. To use the product, insert the cartridge into the caulking gun, activate the spray nozzle, and then dispense the gel into the base of the pocket.[67]

CONCLUSION:

Doxycycline remains an important therapeutic agent in periodontal care because its value extends beyond conventional antimicrobial activity to include clinically relevant host-modulatory effects. In addition to suppressing periodontal pathogens, doxycycline can inhibit matrix metalloproteinases and reduce inflammatory tissue breakdown, which supports its role in controlling both infection and disease progression. This dual action has made it useful not only as a systemic adjunct in selected periodontal cases but also as a key component of local periodontal drug-delivery strategies.

Local doxycycline delivery systems offer several practical advantages, including high subgingival drug concentration, sustained release, bioadhesion, biodegradability, and reduced systemic adverse effects, making them particularly attractive as adjuncts to scaling and root planing and supportive periodontal therapy. Formulations such as subantimicrobial-dose doxycycline, Atridox, and Ligosan highlight the adaptability of doxycycline to modern controlled-release approaches and reinforce its relevance in contemporary periodontal treatment. Nevertheless, clinical benefit depends on appropriate case selection, correct adjunctive use, and awareness of adverse effects, contraindications, and drug interactions. Overall, doxycycline continues to represent a versatile pharmacologic option at the intersection of antimicrobial therapy, host modulation, and localized drug delivery, with ongoing relevance for improving periodontal outcomes.

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