

## Review Article

## Overview on Doxycycline- And its Adverse Reactions

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## ABSTRACT

In the treatment of malaria, Doxycycline is used in partial treatment. The (antibiotic) tetracycline is an antibacterial agent in the body. Doxycycline is used for the treatment of a broad range of bacterial infections, like acne, infections of the urinary tract, respiratory infections, eye infections, gonorrhea, chlamydia, syphilis, periodontitis, intestinal infections, etc. It is a large category of agents that is bacteriostatic. The purpose of the formal review was to review all available documents for their negative effects. Our interest was focused on the Doxycycline – Mechanism, its clinical manifestations, adverse effects, and drug interactions. An effort has been made to report all side effects through literature research to develop a safe, effective and therapeutic dosage form. Adverse events and side effects are avoided with appropriate patient care, regular allergy testing before the administration of the drug, avoidance of chronic drug use, and testing of early medical history.

## Introduction

Malaria is a contagious fever that has serious or fatal consequences. Doxycycline can be used for prophylaxis and partial treatment, according to WHO recommendations for the treatment of malaria [1]. Our interest was focused on Doxycycline Machine for its clinical manifestations, adverse effects, drug interactions. Doxycycline is an antibiotic of tetracycline, a type of broad bacteriostatic agent. It is found in tetracycline naturally by bacterial strains, Streptomycin is also known as “Oxytetracycline” that fights foreign antigens in the body [2]. Doxycycline is used to treat a broad range of viral infections, including acne, infections of the urinary tract, intestinal infections, respiratory infections, eye diseases, gonorrhea, chlamydia, syphilis, and periodontitis, among others [3]. Doxycycline was patented in 1957 and was approved by the FDA in 1967 as Doxycycline Hyclate by PFIZER Inc, and in 1992 Pfizer submitted a new drug application to the FDA for malaria prophylaxis and was included in the product packaging; in 1994 this index was added. The adult dosage for malaria prophylaxis is 100 mg per day for 1-2 days before departure, 100 mg per day is localized, and 100 mg per day is localized for 28 days after departure [4,14]. Doxycycline is available in the general market in 2017 is located in India with the brand name DOXY-1- LDR [23]. In Canada,

doxycycline was used as a first-line treatment in 2004 for chlamydia and non-Gonococcal urethritis, and mild gonorrhea.

## Mechanism of Action

Doxycycline inhibits bacterial synthesis proteins by binding to 30S ribosomal subunit and inhibits the synthesis of aminoacyl-tRNA and the bacterial ribosome. In the mitochondria, further inhibition of protein synthesis occurs by binding to 70S ribosomes [7]. Consequently, it is a bacteriostatic drug. Via hydrophilic pores on the outer part of the cell and an active pH-dependent transport mechanism in the inner cytoplasmic membrane, doxycycline enters the cell [13].

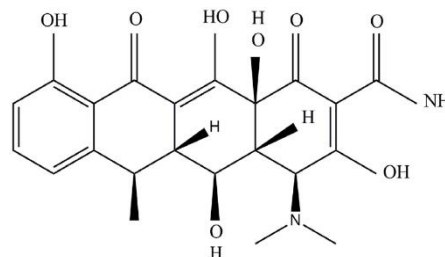


Figure 1: The Structure of Doxycycline

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By preventing ribosomal binding to transfer RNA to the RNA messenger in the ribosomal tunnel means that amino acids cannot be added to the polypeptide chain so new proteins cannot be made. This method gives the system time to prevent killing and removing bacteria and stop the growth of germs. Besides, it has many actions that include inhibition of angiogenesis and apoptosis, improvement of gingival fibroblast attachment, and wound healing [9].

### Pharmacokinetic factors and Pharmacodynamics:

Tetracycline is readily absorbed, such as doxycycline, and is bound to the plasma at various degrees. Doxycycline is completely absorbed by oral administration in the stomach and proximal small bowel. After administration, it forms complexes with the metal ion in food and free form of the drug [5,8].

- Absorption: Doxycycline after oral administration is completely absorbed. It is highly lipid-soluble and has a poor calcium-binding affinity.
- Distribution volume: 0.7 L/kg
- Protein binding: greater than 90 %
- Metabolism: liver, bile-concentrated gastrointestinal tract.
- Elimination route: The active and unchanged drug primarily includes urine and feces. In 92 hours, between 40 percent and 60 percent of the dose administered can be accounted for in the urine, and about 30 percent can be accounted for in the feces.
- Half-life: 16.33 hr. ( $\pm$  4.53 SD) [20]

yeast infection. Another case study that reported doxycycline-induced fixed-drug eruption was completely different from the first. A 35-year-old patient with a complaint of itching and hyperpigmentation of the chest for 2 days was admitted. As a clinical manifestation, numerous clinical tests including the patch test, liver function test, and renal function test have been performed [25]. The history of the patient revealed doxycycline 100 mg twice a day was prescribed to him for skin infection and a similar illness with consumption of the same drug was confirmed. The patient was diagnosed with doxycycline-induced fixed-drug eruption with discontinuation of the drug. Skin infection was then treated with cetirizine 10 mg and topical Betamethasone for 2 weeks [17,23].

### Adverse Effects:

1. Gastrointestinal system- Doxycycline Hyclate salt shows more common side effects than monohydrate salt of doxycycline [19]. The number of formulations of doxycycline that are available in the market includes – immediate release, enteric-coated, modified-release, sustained-release tablets. However, enteric-coated tablet delays the release rate of doxycycline, thus drug bypasses the first-pass metabolism avoiding gastric side effects as compared to immediate-release formulations. The majority of side effects include esophagitis, nausea, and vomiting, gastric irritation
2. Dermatological effects- Phototoxic reactions like sunburn sensation, burning, erythema within 24 hours of sun-exposed areas like the lips,

**Table 1: Comparison between percent drug loading, advantages as well as disadvantages of different osmosis-based systems**

Part affected	Events
Eyes	Optic nerve fenestration
Brain	Co-ordinal loss, visual acuity and visual field loss, intracranial hypertension.
Tongue	Taste perversion
Gastrointestinal	Hiccups, esophagitis, nausea, and vomiting, gastric irritation
Skin	Epidermal necrolysis, Serum sickness, hypersensitivity reactions, Stevens-Johnson syndrome
Lips, nose, forearms, hands, fingers, and nails	Sensation, burning, erythema, itching, redness, and intense pain
Blood	Systemic lupus is erythematosus.
Teeth and buccal cavity	Discoloration of teeth, enamel dysplasia
Bones	Deformity

### Case Report:

Doxycycline is a frequently prescribed antibiotic for a variety of bacterial, viral, and yeast infections. It is a well-tolerated drug, but many times shows some side effects. Thus, it is important to raise awareness by attending conferences, workshops, posters, and brochures [24]. Many reported cases are suggesting doxycycline-induced adverse drug reactions (ADR's). One case study considered 36 patients which were enrolled to check doxycycline therapy, which had 30 men and 6 women subjects ranged from 54-84 years. 33 out of 36 subjects completed the entire course of doxycycline with concomitant anti-hypertensive drug and 92% overall retention was observed. Patients that withdraw treatment of doxycycline drug treatment before 6 months, resulted in tetracycline induced photosensitivity and persistent discoloration of teeth. 25 % of patients showed gastrointestinal effects like nausea, bloating, cramping, and gastrointestinal reflux disease. No patient reported bacterial infection, but one patient developed a mild

nose, dorsal aspects of forearms, hands, fingers, and nails leading to itching, redness, and intense pain in the area were observed. The symptoms were resolved within 10-14 days from the withdrawn day of doxycycline. Serum sickness and hypersensitivity reactions, Stevens-Johnson syndrome as well as toxic epidermal necrolysis may occur. The Jarisch-Herxheimer reaction can occur during the treatment of spirochetal infections. Anaphylaxis has been reported in some cases [10,12].

3. Bones and buccal cavity - Discoloration of teeth is a common side effect of doxycycline in deciduous rather than permanent teeth. The lifelong discoloration is observed in small children with concomitant poor dental hygiene and increased sunlight exposure leading to enamel dysplasia, impairment in bone growth, and bone deformities. Infants administered with doxycycline were shown to have a 40 %

reduction in fibular bone growth that was reversible upon drug cessation.

- Neurological effect- Doxycycline is shown to cause an increase in intracranial hypertension. With the use of acetazolamide, symptoms may gradually increase, with visual acuity or visual field loss occurring in a percentage of patients requiring optic nerve fenestration or CSF shunting.
- Other effects- Or pharyngeal and vaginal candidacies from a fungal overgrowth is common rare effects can include perversion of taste, rhinitis, hiccups, and dyscrasia of the blood. Minocycline can cause drug-include lupus whereas doxycycline may exacerbate systemic lupus erythematosus [15].

## Drug Interactions

Drug interactions are reactions of two or more drugs that alter the expected pharmacological effect of the drug candidate. Sometimes two drugs are prescribed to increase the therapeutic effect called as synergistic effect and vice-versa [25]. Plasma levels of doxycycline are reduced by barbiturates, anticonvulsants like Phenytoin and Carbamazepine, Acetazolamide, and sodium bicarbonate [6]. Ferrous sulfate, antacids, and bismuth impair doxycycline absorption. It is recommended to be given 2 – 3 hours before iron supplement [4,21]. Increased hepatic metabolism is observed due to cytochrome P450 3A4 inducers like rifampicin reduces serum levels of doxycycline. It is reported that doxycycline reduces the efficacy of oral contraceptives which may lead to intermenstrual bleeding [18]. Toxicity is increased by the use of methotrexate (anti-rheumatic) – displacement of the binding site due to Doxycycline, tetracycline, and Methoxyflurane increases fatal renal toxicity [20,22]. Doxycycline for injection may cause *Clostridium difficile* diarrhea which may range from mild to fatal and may require colectomy [11]. People who take Coumadin or warfarin, a popular blood-thinning drug, maybe at an elevated risk of bleeding if they take doxycycline [15,16].

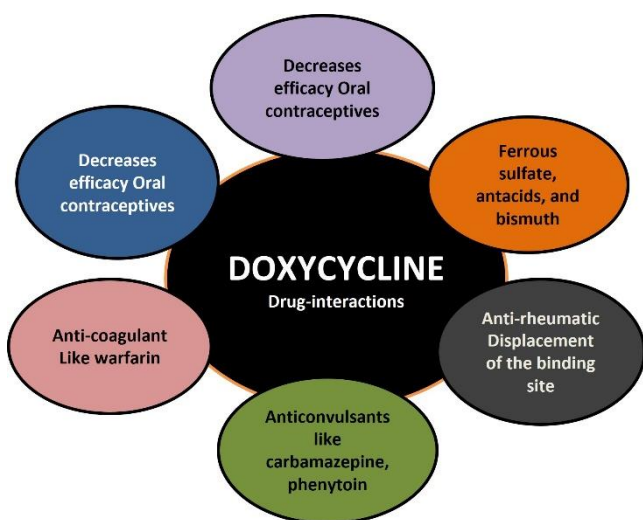


Figure 2: Drug interaction

## Conclusion

Doxycycline is well known, cheap, readily available, and frequently prescribed antibiotic. However, it holds several adverse effects. An effort

has been made to report all the adverse effects through a literature survey to develop a safe, effective and therapeutic dosage form. Adverse events and effects are avoidable by proper care of the patient, frequent allergy checks before prescribing the drug, avoiding chronic use of the medication, and pre-checking of the medical history of the patient.

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## Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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