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Review Article

A Review of Doxycycline-Based Malaria Treatment Regimens: Efficacy, Safety, and Resistance Patterns

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Abstract

The potential of the broad-spectrum tetracycline antibiotic doxycycline to treat and prevent malaria has been investigated, especially when combined with other antimalarial medications. This study examines the pharmacodynamics, clinical effectiveness, possible advantages, difficulties, and new resistance patterns related to the use of doxycycline to treat malaria. Doxycycline's changing function in malaria prevention and the treatment of both severe and uncomplicated malaria is examined. Its significance in treating Plasmodium falciparum, the most prevalent and severe malaria parasite, which is resistant to many drugs, is given particular emphasis. Doxycycline has been used in medicine for almost 40 years and belongs to the tetracycline class of antibiotics. It is a bacteriostatic medication that is well tolerated and works by blocking bacterial ribosomes. Usually, a dosage of 100 mg per day or twice daily is used. It has typically strong tissue penetration and is well absorbed. When renal or hepatic impairment is present, the dose does not need to be changed because the serum half-life is 18–22 hours. It is typically contraindicated in pregnancy or infancy due to worries about discoloration of developing teeth and possible effects on growing bones. The main adverse effects are gastrointestinal and dermatological.

Keywords: Broad-Spectrum; Doxycycline; Plasmodium; Medication; Bacteriostatic.

Introduction

One of the first groups of antibiotics created after the advent of penicillin G and the sulphonamides were tetracycline antibiotics. Pfizer created doxycycline (alpha-6-deoxytetracycline; see Figure 1), a semi-synthetic derivative of oxytetracycline that was initially made accessible in 1967 [1].

Its longer serum half-life and better oral absorption set it apart from other tetracycline family members. A wide variety of Gram-positive, Gram-negative, and "atypical" bacteria, as well as some protozoa like malaria, are susceptible to doxycycline's action. Additionally, it is an effective antibiotic for treating and preventing a number of an important chance biological warfare agents [2].

As a result, it is extensively used around the world, especially for the treatment of specific arthropod-borne rickettsial illnesses, pneumonia of the respiratory tract, malaria prevention, and sexually transmitted infections. Plasmodium, the protozoan parasite that causes malaria, is still a serious public health concern, especially in Southeast Asia and sub-Saharan Africa. Treatment procedures have become more complex due to the advent of drug-resistant forms of malaria [3]. Traditionally used as an antibiotic to treat bacterial infections, doxycycline has drawn interest for its ability to cure malaria, particularly when combined with other treatments. This study evaluates the effectiveness, safety profile, and use of doxycycline in current treatment approaches for malaria [4].

Mechanism of action

By reversibly attaching to the 30S ribosomal subunit and blocking aminoacyl-tRNA from attaching to the bacterial ribosome, doxycycline suppresses the production of proteins by bacteria. By attaching to the 70S ribosomes, it further inhibits the production of proteins in the mitochondria [5]. Thus, it is a bacteriostatic medication.

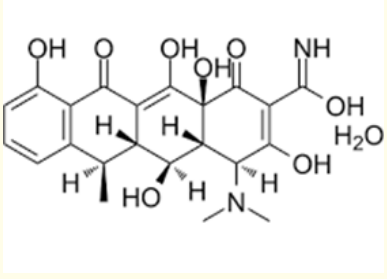

Figure 1: Structure of Doxycycline.

Doxycycline enters the cell through a pH-dependent active transport mechanism in the inner cytoplasmic membrane and hydrophilic pores in the outside cell membrane. Additionally, it prevents Plasmodium falciparum's apoplast ribosomal subunits from functioning properly, which results in compromised fatty late in the malarial cell cycle, acid production and compromised heme biosynthesis [4,6].

It also has a number of other effects, such as promoting gingival fibroblast attachment, wound healing, and preventing angiogenesis and apoptosis.

Certain matrix metalloproteases (MMPs), which are proteolytic enzymes generated by inflammatory cells, are known to be inhibited by it [7]. This has raised the possibility of using it for a number of anti-inflammatory and anti-neoplastic purposes.

When treating periodontitis, sub antimicrobial dosages of doxycycline prevent the gingivae's damaging MMPs and the breakdown of collagen [7,8].

Pharmacokinetics and pharmacodynamics

As an antibiotic belonging to the tetracycline class, doxycycline works by preventing the production of proteins by bacteria. It's interesting to note that the asexual cycle of Plasmodium parasites, like that of many bacteria, depends on protein synthesis [8]. Doxycycline mainly affects the capacity of Plasmodium parasites to proliferate by preventing them from synthesizing proteins in the liver and red blood cells. Because of this substantial reduction in parasite load, doxycycline is a useful adjuvant treatment for malaria. Doxycycline's significance in malaria goes beyond its antibacterial qualities; it can also prevent the parasite from maturing and reproducing, especially when combined with other treatments. Another important aspect of its antimalarial action is its capacity to target the apicoplast, a plastid organelle found in the parasite [10].

After being taken orally, doxycycline is nearly entirely absorbed in the stomach and proximal small intestine. In contrast to tetracycline and minocycline, which only cause a 20% drop in blood levels, food and dairy items had no discernible effect on absorption. Doxycycline reaches the small intestine as a free medication after forming complexes with metal ions in food that are unstable in the stomach's acidic environment. A tiny quantity of doxycycline is not absorbed, nevertheless, since metal complexes that are generated in the duodenum are stable. Multivalent cations will hinder the absorption of doxycycline [11].

Impaired renal function has no effect on the extended serum half-life of 18–22 hours. Within 30 minutes of intravenous injection and 2-3 hours after oral administration, peak serum levels are reached. When 200 mg of doxycycline is taken orally, peak serum concentrations range from 3.0 to 5.0 μg/mL, but when the same dosage is administered intravenously, peak serum concentrations range from 4 to 10 μg/mL [12,13].

Dosage and Administration

An initial dose of 200 mg of doxycycline per day is often administered, followed by a maintenance dose of 100 mg per day (or twice day for severe infections).

It can be given intravenously or orally. In addition to drinking enough water, the patient should stay upright for half an hour after taking the oral dose. The highest dosage that is advised is 300 mg per day. In children, a weight-adjusted dosage of 2.2 mg/kg daily or twice daily is administered when the advantages of doxycycline outweigh the dangers. When treating severe infections, a greater loading dosage of doxycycline—200 mg twice day for 72 hours, for instance—is advised for the best dose-dependent efficacy [14].

For some indications, such as syphilis, scrub typhus, and malaria prophylaxis, there are differences in dosage and duration. For rosacea and acne vulgaris, lower dosages—such as 20 mg twice daily—are administered. There are several topical treatments for periodontitis [9,13].

Efficacy in malaria treatment

Malaria without complications

For the treatment of simple Plasmodium falciparum malaria, doxycycline is frequently used in combination with other antimalarial medications such as quinine or artesunate. When taken in combination regimens, it is very beneficial in lowering parasitemia and minimizing the length of the sickness. Compared to other antimalarial medications like artemisinin-based combination therapies (ACTs), doxycycline requires a lengthier course of treatment (7–10 days), which makes it less frequently utilized as a monotherapy for malaria [12].

Extreme malaria

Doxycycline has mostly been researched as a supplement to intravenous or intramuscular artesunate in situations of severe malaria. Doxycycline is not commonly used as the only therapy for severe malaria because of the requirement for immediate care and injectable drugs, however studies indicate that it may be helpful when combined with other first-line medicines [15].

Malaria resistant to drugs

In situations of Plasmodium falciparum that is resistant to many drugs, doxycycline has demonstrated potential. Doxycycline-based regimens can offer an efficient substitute or supplemental treatment in areas where resistance to first-line medications, such as chloroquine and even certain ACTs, is prevalent. In Southeast Asia, where resistance to therapies based on artemisinin has been documented, this is especially pertinent. Because doxycycline slows the parasite's growth, other medications have more time to do their jobs [16].

Clinical uses

As seen in Table 1,2, doxycycline has a wide range of action against several Gram-positive, Gram-negative, and "atypical" bacteria. It therefore has a wide range of possible applications.

S.no	Organism (Gram-Negative bacteria)	Typical MIC_{90} $_{\mu g}$ per ml	Range
01	*E. Coli*	32	0.5-64
02	*K. Pneumonia*	64	1–64
03	Yersinia pestis	1	0.125–2
04	*Bartonella* spp.	0.12	0.016–0.25
05	*B. pseudomallei*	1.5	0.125–4
06	*H. influenza*	1	0.5–8

Table 1

S. no	Organism (Gram-Positive bacteria)	Typical MIC_{90} $_{\mu g}$ per ml	Range
01	*Staphylococcus aureus*	4	0.03–16
02	*Staphylococcus pyrogens*	8	0.1–16
03	*Staphylococcus pneumoniae*	8	0.04–16
04	*Enterococcus faecalis*	32	0.12–64
05	*Listeria monocytogenes*	0.25	0.125–1
06	*Bacillus anthracis*	0.063	0.031–0.125

Table 2

Safety profile and side effects

Although oxycycline is usually well tolerated, adverse consequences are possible. Gastrointestinal problems (diarrhea, vomiting, and nausea) are the most frequent side effects, and they can be reduced by taking the medication with meals [18]. One well-known adverse effect is photosensitivity, or a heightened sensitivity to sunshine, which can be especially troublesome for people who live in tropical or sunny areas. Dysphagia, or trouble swallowing, or esophageal ulcers can result after long-term doxycycline usage [21].

Due to the drug's propensity to impact bone and tooth development, there are further concerns about its usage in pregnant women and children less than eight years old. In these groups, alternative medications are usually selected [19,22].

Marketed formulation

S. no	Marketed Product	Properties	Drug
01	Artel Care	used to treat malaria infections acquired in drug-resistant regions.	Artemether + Lumefantrine
02	Diginate-120	Intravenous Use	Artesunate
03	Chloquin Care	used to prevent and treat malaria caused by P. vivax	Chloroquine Phosphate
04	Triquin Care	Oral Use	Artemisinin + Piperaquine
05	Shal Artem	treatment of uncomplicated Plasmodium falciparum malaria	Artemether 20mg + Lumefantrine 120mg
06	Artesunate 100	Suppositories	Artesunate
07	Elther	Anti Malaria Injection	Arteether Injection IP

Table 3

Combination therapy and current guidelines

Combination therapy continues to be the mainstay of successful malaria treatment. To increase effectiveness and reduce the development of resistance, doxycycline is frequently used in conjunction with quinine, artesunate, or other antimalarial medications [23]. Though it recognizes its promise in some situations, such as in areas with substantial drug resistance or when ACTs are unavailable, the World Health Organization (WHO) does not presently advise doxycycline as a first-line therapy for uncomplicated malaria [21,24].

Conclusion

Doxycycline is frequently referred to as the "secret weapon of the infectious diseases physician" due to its vast range of therapeutic applications and broad spectrum of action, which includes against certain more obscure and challenging-to-diagnose disorders [25].

Even though many of its applications have been replaced by the long-acting macrolide azithromycin, it still has a significant position in the antibiotic arsenal. In addition to having outstanding clinical effectiveness against a variety of STIs, rickettsial and associated diseases, Lyme disease, brucellosis, anthrax, Q fever, and atypical respiratory pathogens, it is also typically well tolerated and helps prevent malaria [24,26].

When used in combination therapy, doxycycline is a crucial adjuvant medication for the prevention and treatment of malaria. It works well to lower the load of Plasmodium parasites and stop the emergence of resistant strains because it inhibits the production of proteins in these parasites. It plays an important role in regions where Plasmodium falciparum is drug-resistant, even though it is not the first-line therapy for simple malaria. To guarantee its continuous efficacy, future studies should concentrate on enhancing knowledge of its safety profile, particularly with regard to long-term usage, and keeping an eye out for new resistance [27].

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