International Journal of Pharmaceutical research and Applications
Volume 9, Issue 1, Jan.-Feb. 2024, pp:1252-1256 www.ijprajournal.com ISSN: 2456-4494

An Overview on Tetracycline and their Resistance in Humans

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Date of Submission: 04-02-2024 Date of acceptance: 15-02-2024

ABSTRACT
The latest studies indicate that the public health around the world is seriously threatened by antibiotic resistance, hence it is crucial to discuss on how resistance develops. This review main worry is the growing threat of antibiotic resistance associated with the tetracycline use. We begin a thorough examination of the pharmacological properties, mechanism of action and importance of tetracycline in the management of bacterial infections. This review deals with the effective strategies and suggestions to overcome the antibiotic resistance for further interventions. We also discuss the methods for reducing tetracycline resistance, such as combination treatment ,antibiotic stewardship initiatives, and the creation of new antibiotic and formulations

KEYWORDS- Tetracycline , resistance, AMR (antimicrobial resistance), One Health.

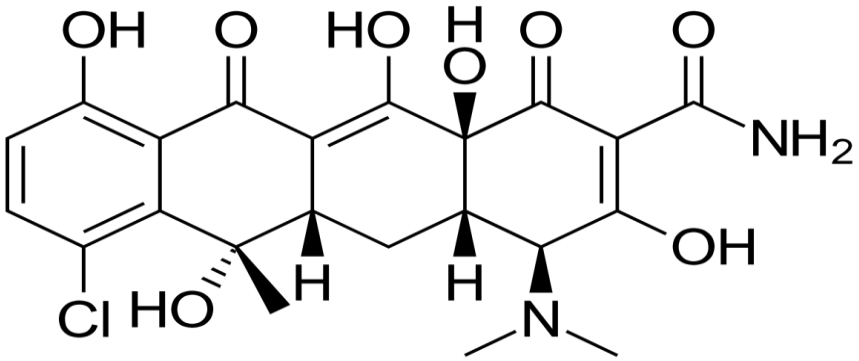
I. INTRODUCTION

Antibiotics allow us to survive from serious bacterial infections. Tetracycline possess many properties considering ideal for antibiotic drugs, including activity against gram-positive and gram-negative pathogens, proven clinical safety, acceptable tolerability and the availability of intravenous(IV) and the oral formulations for most members of the class.

When bacteria become resistant to an antibiotic, it means it can no longer kill that bacteria. If the bacteria develop resistance to all antibiotics, that impact on public health would be devastating. The presence of tetracycline –resistant pathogens limits the use of the agents in the treatment of the disease.

HISTORY AND CLINICAL UTILITY OF TETRACYCLINE-CLASS DRUGS

The first tetracycline is natural product derived from *streptomyces aureofaciens* (chlortetracycline) in late 1940s.



chlortetracycline

Second generation tetracycline class drugs(tetracycline, doxycycline and minocycline) were approved in 1954,1967 and 1971 respectively. Tetracycline in clinical use for the treatment of uncomplicated respiratory, urogenital, gastrointestinal and others serious infection.

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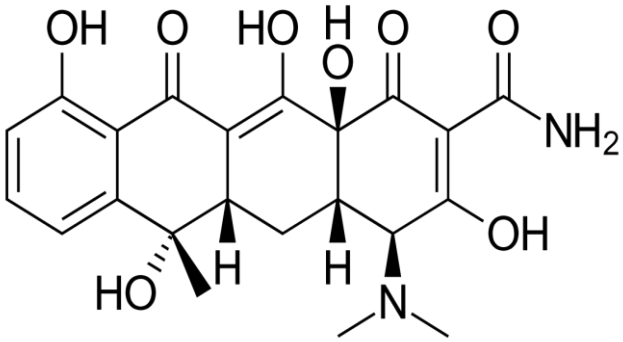
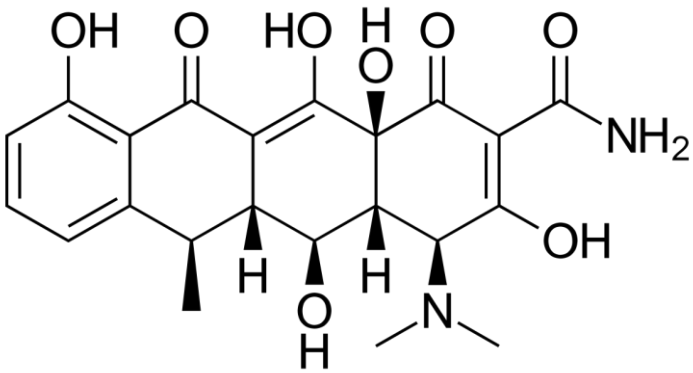
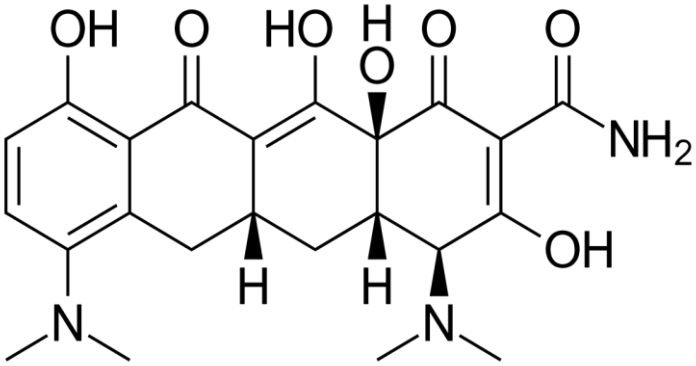
TETRACYCLINE



DOXYCYCLINE

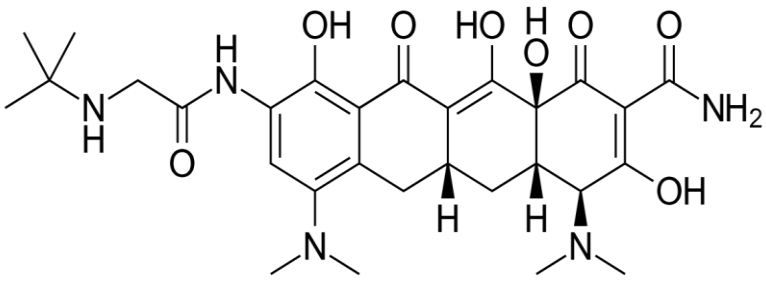


MINOCYCLINE



Tigecycline, a semi-synthetic parenteral glycylcycline , was discovered in 1993 and introduced into clinical use in 2005.

TIGECYCLINE



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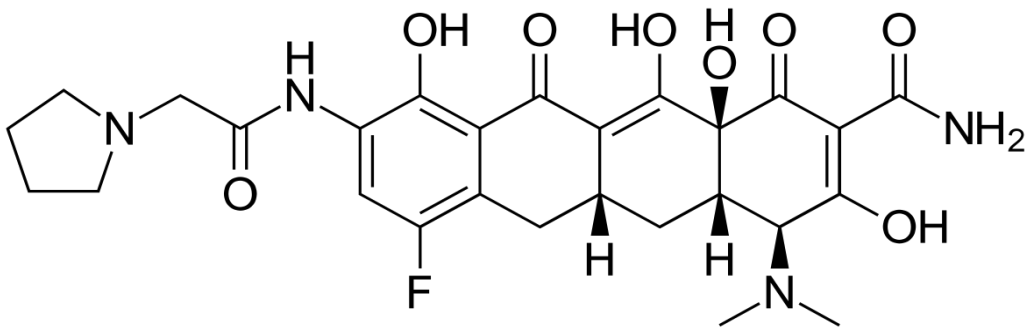
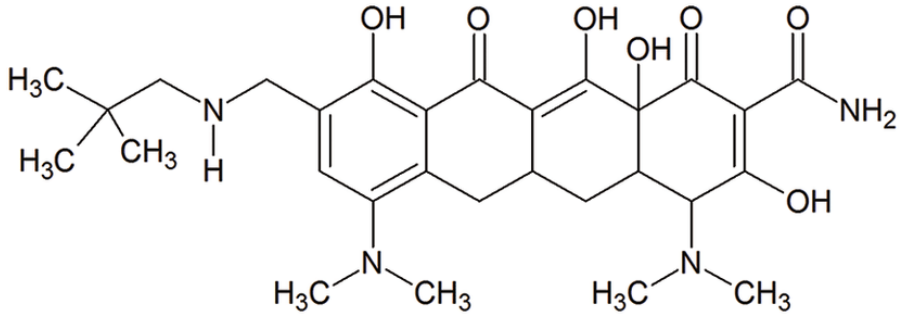
ERVACYCLINE



OMADACYCLINE



In recent years, two new tetracycline have entered in clinical development: omadacycline and eravacycline.

USES :

- Tetracycline are the drug of choice in infections with,
  - Mycoplasma pneumonia.
  - Chlamydiae .
  - Rickettsiae .
- Used in combination regimens to treat gastric and duodenal ulcers caused by *H. pylori.*
- They are used in combination with aminoglycosides to treat plague, tularemia and brucellosis.
- Other uses include in the treatment of acne, exacerbations of bronchitis, community acquired pneumonia, lyme diseases, relapsing fever, leptospirosis and some typical mycobacterial infections (mycobacterium marinum)

RESULTS AND DISCUSSION ON TETRACYCLINE RESISTANCE

In research surveillance studies, the prevalence of tetracycline resistance in selected European countries was found to be 66.9% and 44.9% for extended spectrum beta-lactamase (ESBL) producing *E.coli* and *klebsiella* species respectively and global tetracycline resistance – resistance percentages were 8.7% and 24.3% for methacillin-resistant *staphylococcus aureus* (MRSA)and *streptococcus pneumonia* respectively.

MECHANISM OF ACTION : TETRACYCLINE AND THEIR RESISTANCE

Tetracycline passively diffuses through porin channels in the bacterial membrane and reversibly binds to the 30s ribosomal subunit, preventing binding to tRNA to the mRNA-ribosomal complex, and thus interfering with protein synthesis.

Bacteria could use three strategies to become resistant to tetracycline

1. Protection of the ribosome : tetracycline resistant can result from production of a protein that interacts with the ribosome such that protein synthesis is unaffected by the presence of the antibiotic. Six classes of *Tet* determinants that confer tetracycline resistance on the level of protein synthesis have been identified. Most of the work on the mechanism of ribosomal protection has been done on *TetM* . The ribosomal protection proteins encoded by the other classes have an amino acid sequence similarity atleast 40% to *TetM* . Therefore, the mechanism of action may be similar for all ribosomal protection proteins.*TetM* ribosomal protection protein resembles elongation factors (EF) in three properties:

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- It has amino acid sequence similarity to EF-G (which translocates the peptidyl transfer RNA during protein synthesis)
- It has a ribosome-dependent guanosine triphosphate activity.
- It seems to confer resistance by reversible binding to the ribosome

2. Altering the ribosome to prevent effective binding of tetracycline: a second way to limit access of tetracycline to ribosome is to reduce intracellular concentrations of tetracycline by pumping the antibiotic out of the cell at a rate equal to or greater than its uptake. This resistance mechanism, tetracycline efflux, is the best studied and most familiar mechanism of tetracycline resistance.

3. Producing tetracycline- inactivating enzymes: tetracycline modifying enzyme mechanism was first described as an activity encoded by a *Bacteroides* plasmid expressed in *E.coli.* this activity was subsequently characterized as a flavin- dependent mono-oxygenase, encoded by an expanding family of *tet(*X) orthologs, capable of covalently inactivating all tetracycline's with the addition of a hydroxyl group to the tetracycline ring.

Resistance to tetracycline is governed by *tet* genes, which are involved in either active efflux of the drug, ribosomal protection or enzymatic drug modifications. Among the various *tet* genes, the *tet*(A), *tet(*B), *tet(*D),*tet(*E) and *tet*(G) are reported in gram- negative bacteria. Whereas, the *tet(*K),*tet(*L),*tet(*M),*tet*(S) and *tet(*S) are significantly found in the gram- positive bacteria.

CLINICAL IMPLICATIONS : Tetracycline resistant has significant clinical implications, affecting patient outcomes and health care practices. The spread of antibiotic resistance genes among the bacteria is a growing concern as it limits the effectiveness of the tetracycline and other antibiotics. This resistance can be transferred between bacterial species, leading to the emerging of multi drug resistance strain. Furthermore, the misuse and overuse of the tetracycline in both human and veterinary medicine contribute to the selection and spread of resistance bacteria. This resistance can lead to treatment failure, prolonged hospital stays and increases healthcare costs.To combact this issue, it is crucial to promote antibiotic stewardship programs, rise awareness among health care professionals and the general public health and invest in research and development of new treatment options. By understanding the clinical implications, healthcare professionals can make informed decisions to optimize patient care and combact antibiotic resistance

STRATEGIES TO COMBACT RESISTANCE

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
2. Advance development and use of rapid and innovative diagnostic tests.
3. Accelerate basic and applied research and development.
4. Improve international collaborations and capacities.
5. Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials(including antibiotics) , improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by the multidrug resistant organisms.

FUTURE INTERVENTIONS

To address AMR (antimicrobial resistance)globally, countries adopted the GLOBAL ACTION PLAN(GAP) on AMR during the 2015 world health assembly and committed to the development and implementation of multi-sectoral national action plans with One health approach tackle AMR. The GAP was subsequently endorsed by the governing bodies of the Food and agriculture organization of the United Nations (FAO) and the world organization for Animal Health (WOAH, formerly known as OIE) and the United Nations Environment Program.

In India One Health concepts plays a major role in antimicrobial resistance research activities. The main research agenda of this concept in 2023 are

1. Improve our understanding of transmission of

AMR; drivers and impact :

AMR transmission and impact, AMR magnitude & trends link to human and animal health ,high-risk populations, social determinants of AMR innovative approaches to measure AMR , surveillance for action.

2. Strengthen the evidence base for interventions:

Development of interventions, frame work for prioritizing between interventions, impact/ cost of interventions, implementation in LMIC, social, cultural and behavioral insights tailored interventions, immunizations, surveillance for action.

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3. Advocate for the prioritization of AMR mitigation and inform policy-making:
Improve understanding of the social and economic impact of AMR over the One Health spectrum, value of investing in AMR mitigation, socio economic burden of AMR,policy f enablers economic evaluations, sustainability enablers, surveillance informing policy.

MANAGEMENT OF TETRACYCLINE RESISTANCE

✔ Tigecycline is the first member of a new class of antibacterial agents, the glycyclines. It is a derivative of minocycline. This group has been specially developed to overcome the two main mechanisms of tetracycline resistance (ribosomal protection and efflux)

✔ Avoid taking tetracycline's unnecessarily , unless it is prescribed.

✔ Prevent the infection in the first place.

II. CONCLUSION

Most drugs of tetracycline are available for use in humans and animals. Tetracycline resistance can be reduced when tetracycline are used only as a treatment, rarely for prophylaxis. Tetracycline resistant is a concerning issue in the field of medicine. It refers to the ability of bacteria to resists the effects of tetracycline antibiotics, making them less effective in treating infections. This resistance can be acquired through various mechanisms, such as genetic mutations or the transfer of resistance genes between bacteria. It's very important for physicians and researchers to keep an eye on tetracycline resistance and come up with new strategies to combat it. That way, we can make sure that these antibiotics continue to be effective in fighting infections. To combact AMR , it is important to support "One Health" approach. Success will require strict and efficient control of the types and amounts of antimicrobial use in medical practice and monitoring and controlling the proliferation of resistant bacteria that spread to the environment.

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