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**COMPOSED BY:**

**MUHAMMAD AFNAN**

**THANKS TO SAAD QAMAR FOR PROVIDING ME WITH HIS CLASS NOTES.**

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Tetracycline pharmacology:

Introduction:
Tetracyclines are broad spectrum antibiotics which possess bacteriostatic action.

They are protein synthesis inhibitors. Tetracyclines are not commonly prescribed because of the increased chance of resistance that is associated with it.

The official names of tetracyclines end with the suffix “cycline”.

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Source and discovery:
Tetracyclines are obtained from natural sources. Various of its variants are isolated from different strains of soil dwelling bacteria.

For example;
The prototype drug is isolated from a soil living bacteria ”Streptomyces’s”.
Similarly chlorotetracycline is isolated from “Streptomyces aurofacians”. Chlorotetracycline was discovered by dugger who was employed in lederle company in late 1940.
Oxytetracycline was isolated from Streptomyces for the first time by “ac finley”.

Chemistry:
Tetracyclines are derivatives of polycyclic napthacene carboxamide.
The basic ring is a napthacene nucleus which is common in all of its members with a difference in methyl groups.

Classification:
Tetracyclines are classified taking different basis of classification under considerations. These are their source, pharmacokinetic or duration-based classification.

Source based classification:
On basis of source tetracyclines are classified into natural and semisynthetic.

Tetracyclines of natural source:
Following of its members are isolated from natural source with no chemical modification involved;
- Tetracycline
- Chlortetracycline.
- Oxytetracycline.
- Demeclocycline.

Tetracyclines of semisynthetic source:
Semisynthetic are those for which the starting material is of natural source followed by chemical modifications. These are;
- Doxycycline
- Lymecycline
- Meclocycline
- Methacycline
- Minocycline
- Rolitetracycline.
Duration/ pharmacokinetic based classification:
In this classification tetracyclines are classified into short acting, intermediate and long acting i.e.
their duration of action. this is also called pharmacokinetic based classification because these are
directly associated with their pharmacokinetic properties like absorption etc.

Short acting tetracyclines:
The duration of action of these drugs lasts from 6-12 hours. they are from 30-60% absorbed from
the gut. These drugs as oral, topical or in iv.

Their dosage frequency is QID.

Short acting includes the following examples.

- Oxytetracyclines
- Chlortetracycline
- Tetracycline (prototype drug).

Intermediate acting:
Intermediate acting tetracyclines lasts from 12-16 hours in their duration of action. and the peak
get absorption from get is 60-80%. Their dosage frequency is two times daily B.D. and are often
administered orally.

Following are the members of this class.

- Demeclocycline
- Methocycline etc.

Long acting tetracyclines:
The long acting tetracyclines as evident from their name have a long duration of action ranging
from 16-24 hours.

The peak GIT absorption is more than 95%. These are administered often as oral or in IV.

Doxycycline and minocycline are the examples of long acting.

Mode of action pharmacodynamics of tetracyclines:
Tetracyclines are protein synthesis inhibitors. This indicated that they alter the protein synthesis
which involves the alteration of some steps which are involved in the protein synthesis in
bacteria.

Following are some intermittent steps involved;

- tetracyclines enters the bacterial cell.
- They bind to 30S (smaller) ribosomal subunit.
- This prevents access of aminoacyl tRNA to mRNA-ribosome complex.
- This prevents the addition of amino acid to the growing peptide chain.
- The final effect is that the protein synthesis in inhibited.
The binding of tetracyclines to smaller subunit is irreversible that’s why these drugs are bacteriostatic however in large doses they behave bactericidally.

**Spectrum of tetracycline antibiotics:**
Tetracyclines are effective against a wide range of microbial infections caused by different species of gram positive and negative bacteria.

Following pathogens are included in its spectrum;
- Mycoplasma pneumoniae
- Chlamydia trachomatis
- Treponema pallidum
- Borellia spp.
- Yersinia pestis spp.
- Brucella melitensis
- Francasilla tularensis
- Protozoal spp
- Plasmodium spp
- Bascillus anthrax
- Vibrio cholera
- Amoeba.

Tetracyclines are less efficacious against gram positive than penicillin’s and cephalosporins and are less efficacious against gram negative than aminoglycocides and chloramphenicol.

They are also effective against some protozoans.

Tetracyclines also have considerable clinical effectiveness against rickettsia, chlamydia, spirochetes and mycoplasma.

**Clinical uses of tetracyclines:**
Tetracycline is drug of choice for;

A) Chlamydial infections: the chlamydial infections against which tetracycline is drug of choice includes; trachoma (infectious blindness), lymphogranuloma venurum (std infections). Pelvic inflammatory diseases like endometritis, salpingitis, urethritis.

B) Mycoplasma infections: tetracycline is the drug of choice for mycoplasmal infections like mycoplasma pneumoniae.

C) Rickettsial infections: tetracycline is also found effective in rocky mountain spotted fever, typhus fever, rickettsial pox, Q-fever, scrub fever.
D) Spirochetes infections: borellia, lyme disease is caused by bite of a tick infected with borrelia. This is an infection of spiral bacteria origin and can be clinically managed with spirochetes.

**Bacterial Resistance against tetracyclines:**
The bacterial resistance against tetracyclines may develop via different mechanisms. They may include;

**Efflux pump development:**
They bacteria develops permeases proteins that flush outs the drug from the cell via active transport.

**Target site alteration:**
Bacteria can modify the receptor site for tetracycline.

**Enzymatic degradation:**
The bacteria develops such enzymes that bring lyses of the bacterial cell wall.

**Side effects:**
Git distress even opportunistic infections can develop like pseudomembranous enterocolitis can be caused which is characterized by bloody diarrhea.

Nephrotoxicities can result especially by improper used i.e by the use of expired drug. The ailment is called fanconi syndrome characterized by severe kidney damage.

It can adversely effect growing teeth and bones because of the deposition of calcium or phosphate complexes deposition. This discoloration is permanent.

Moreover it also stops the growth of bones and cartilage and teeth so should not be used in children.

Hypersensitivity especially photosensitivity is also a common side effect with Sulphur containing drugs. So exposure to sun should be avoided.

Drug induced diabetes insipidus can be caused by tetracyclines especially more prominent with dimocycline. This is because of its antagonism with ADH. The syndrome is called SIADH syndrome if inappropriate adh seretion.

Demeclocycline is safe in terms of ADH antagonism and cannot induce diabetes insipidus which can serve as an alternate option.

With minocycline oto and vestibular toxicities can result.

Tetracyclines can also necrosis.

**Drug-drug interactions:**
Tetracyclines should not be used with diary products, multivitamins or antacids.
Because this can result into decreased bioavailability due to complexes formation.

Contraindications:
Tetracyclines are contraindicated in pregnancy, in children (except demecyclines) and in patients with renal insufficiency.