Other β-lactam Antibiotics

Tetracyclines (Broad spectrum antibiotics)

* These drugs come under the category of protein synthesis inhibitors.
* First discovered Tetracycline → Chlortetracycline.
  - ↓ Streptomyces aureofaciens
  - ↓ no longer used but was active against all gram +ve, gram -ve, Rickettsia, Chlamydia etc.

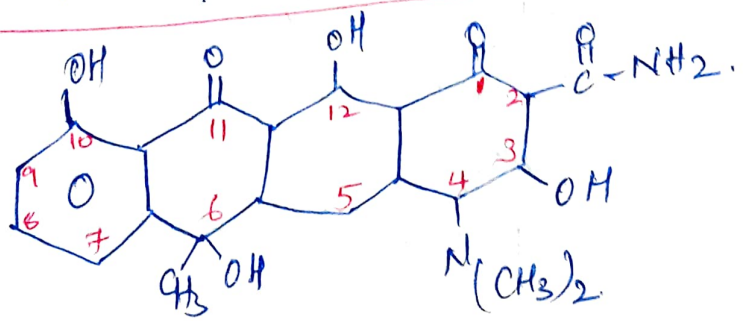
Oxytetracycline → Streptomyces rimosus

Natural Tetracyclines → chlor, oxy

* Tetracycline is a semisynthetic derivative of Chlortetra
* Demeclocycline → obtained from Mutant strain of S. aureofaciens

Methacycline
Doxycycline
Minocycline. } → Semisynthetic derivative.

Chlortetracycline, Oxytetracycline, Demeclocycline, Methacycline, Doxycycline, Minocycline.



changes in position → 5, 6, 7 → give diff. types of tetracyclines

	7
	-Cl
1*) Chlortetracycline	
2*) oxytetracycline. -OH	
3) Demeclocyclin	-OH -Cl
4) methacyclin -OH	$=CH_2$
5) Doxycycline -OH	$-CH_3$
6) Minocycline	-H $-H-N(CH_3)_2$

more lipophilic.

Antibacterial spectrum

Against all anerobic, aerobic gram +ve & -ve bacteria

gram +ve is more effected than gram -ve.

*) active against organisms which are resistant to cell-wall active agents.

Eg: Rickettsia
Coxiella burnetii
Mycoplasma pneumoniae
Chlamydia species
Legionella species.
Ureaplasma
Atypical mycobacteria
Plasmodium species.

Active against many spirochetes like.
→ Borrelia recurrentis
→ Borrelia burgdorferi (Lyme disease)
→ Treponema pallidum.
→ T. pertenue.

No action against Fungi.

MIC < 4μg/ml.

S. aureus ≤ 0.5 μg/ml.

H. influenza, S. pneumoni } ≤ 2μg/ml.

Streptococcus & Enterococcus ≤ 0.25 μg/ml

N. gonorrhoea → ≤ 0.25 μg/ml

Anerobic bacteria → 8 μg/ml.

Bacteriostatic Against V. cholerae
Brucella
H. pylori
C. jejuni
~~Yers~~ Yersenia pestis
N. gonorrhoea ; N meningitidis
~~Bact~~

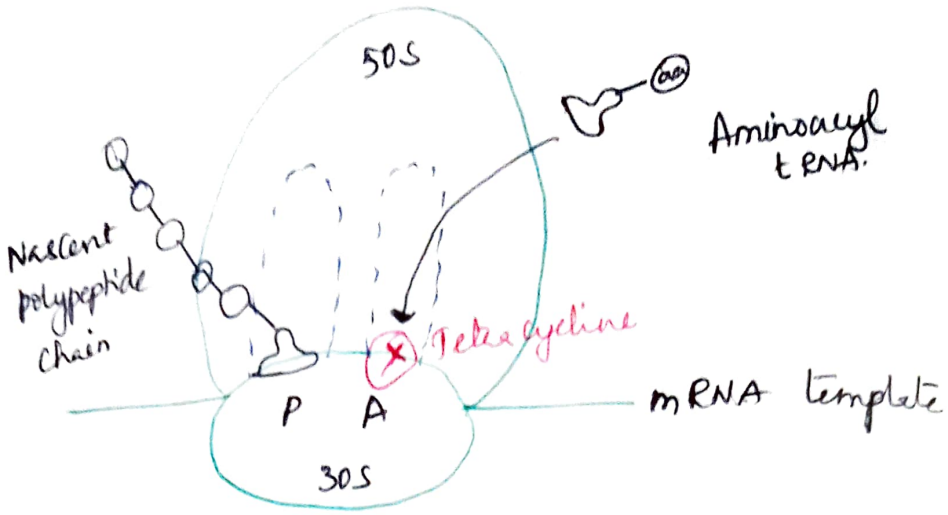
~~for~~ Others Bacillus anthracis
Listeria monocytogenes
Bacteriodes fragillus.

Tetracycline, Doxycycline, Minocycline → Highly active against Staphylococci including MRSA.

1. Can also act against bacteria resistant to tetracyclines.

Also against org. causing Rocky mountain spotted fever.
Murine typhus
Scrub typhus
Epidemic typhus
Q-fever & Rickettsial pox.

MOA



→ Inhibit the protein synthesis by binding to the 30S ribosomal unit and preventing access of amino-acyl t RNA to ~~A~~ecceptor site on the mRNA ribosome complex.

→ These drugs enter gram -ve bacteria by passive diffusion through Hydrophillic channels formed by porin proteins of the outer cell membrane

→ Entry into cytoplasmic membrane is an energy dependent process through Active transport across the membrane.
↓
which pumps all drugs.

→ In gram +ve bacteria, they require metabolic energy but the process is not well understood.

→ .

Development of Resistance :→

1→ ↓ Accumulation of tetracycline by
↓ antibiotic influx or
↑ in energy-dependent efflux pathway
Eg:- S.aureus prod. tetK →

2→ Production of a ribosomal protection protein that displaces tetracycline from its target which occurs by mutation.
Eg:- S.aureus producing tetM
↓
Cross resistance to doxycycline & minocycline

3→ Enzymatic inactivation of tetracyclines

ADME :→

A → incomplete oral absorption — stomach & upper small intestine
Tetracycline and Demeclocycline → 60-80% absorbed.
doxycycline and Minocycline → 95% & 100% respectively.

→ The percentage of unabsorbed drug rises as the dose increases.

→ absorption greater in fasting stage.

→ impaired by ingestion of divalent & trivalent ions. [Ca^{2+}, Mg^{2+}, Al^{3+}, $Fe^{2+/3+}$, Zn^{2+}] due to chelation of ions to form complex structures with poor solubility.

→ Doxycycline & Minocycline less affected with ions but co-admn. of antacids or mineral supplements should be avoided.

→ Variable absorption of orally given drugs leads to wide range of plasma conc. in diff. individuals.

→ peak plasma levels → 2-4 hrs.

P.T.O.

→ 1/2 lifes of drugs vary from 6-12 hrs. frequently are administered 2 to 4 times dail

→ Doxycycline and minocycline 16-18 hrs 1/2 life
↓
plasma conc^n are same if given orally or paren

D → widely distributed throughout the body and in tissues, secretions including urine & prost

→ Accumulates in reticuloendothelial cells of liver, spleen, Bone marrow, Bone, dentine, enamel of unerupted teeth.

→ Tigecycline distributes rapidly and extensively in tissues. ~ 7 to 10 L/kg.
with peak plasma levels ~ 1 µg/ml.

→ penetrate CSF, Synovial fluid & mucosa of maxi sinus. plasma levels same in these.

→ cross placental barrier & enter into fetal circulation and Amniotic fluid.
60% in Amniotic fluid & 20% in umbilical cord plasma.

→ High conc^n found in Breast milk.

E → primary route of elimination is kidney, liver bile.

→ After biliary excretion, they are partially reabsorbed via enterohepatic recirculation.

→ Elimination via intestinal tract when drugs given parenterally.

→ Doxycycline excreted via both bile & urine.

→ Tigecycline mostly excreted in unchanged form along with small amount of glucuronidated metabolites.

→ Minocycline is extensively metabolized in liver before excretion.

→ ↓ Hepatic function or obstruction of common bile duct ↓ biliary excretion ∴ ↑ ½ life and higher plasma conc^{n}
∴ Dose adjustments required in such patients.

→ Bcoz of their enterohepatic circulation, these drugs may remain in the body for a long time after cessation of therapy.

DI :→

→ Hepatic enzyme inducers like phenytoin, Rifampin seen only with Doxycycline.

T. Uses :→

RTI
Skin and soft tissue infections.
Intra abdominal infections.
GI infections.
UTI
STD
Rickettsial infections, Anthrax etc.

Adverse effects :→

→ GI distress, N, V, abdominal discomfort, & diarrhoea may occur.

→ Since most teliacyclines are incompletly absorbed, they affect the microflora of intestines

→ Photosensitivity → mild to severe reaction.

→ Onycholysis and pigmentation of nails may develop with / or without photosensitivity

painless separation of Nail from Nail bed

→ Hepatotoxicity → developed in patients with renal failure but can also occur in large quantities admn. orally.

Rarely reported for Doxycycline, Minocycline, Tigecycline admn.

Pregnant women → Susceptable to teliacycline induced Hepatic damage

→ Renal toxicity → aggravate Azotemia in patients with renal diseases

→ Fanconi syndrome → Characterised by N, V, polyuria, polydipsia, proteinuria, acidosis, glycosuria, aminoaciduria

seen in patients ingesting outdated & degraded teliacycline.

- due to toxic effect of degraded products on proximal renal tubules.

→ Children receiving long term or short term the may develop Brown discoloration of teeth. since large doses are deposited in Enamel.

develop when given 2 months to 5 years & due to formation of tetracycline - calcium orthophosphate complex.

→ Deposited in skeleton during Gestation & may result in depressed Bone growth in pre infants. (Reversible feature)

→ Thrombophlebitis

→ Long term therapy may produce Leucocytosis Atypical lymphocytes, toxic granulation of granulocytes, Thrombocytopenic purpura.

→ ↑ intracranial pressure in infants with usual therapeutic dose.

→ Minocycline — dizziness, Ataxia, N, V. with vestibular toxicity.

→ Hypersensitivity reactions., Asthma