MACROLIDES

Macrolide antibiotics contain many membered lactone rings attached to one or more deoxy sugars.

Erythromycin → 14-membered lactone Ring.

Clarithromycin → Methylation of -OH group at 6th position of Erythromycin

Azithromycin → 15 membered. Methyl substituted Nitrogen atom into lactone ring.

TELITHROMYCIN → 3-keto group replaced by α-L-Cladinose.

∴ called as Ketolides.

↓

less susceptible for Resistance and Efflux mediated Mechanisms

∴ Active against macrolide resistant strains.

⇒ Structural changes in Macrolides improve Acid stability, tissue penetration and Broaden the spectrum of activity.

Erythromycin :→

* Discovered in 1952 by Mcguire & Coworkers as metabolic products of *Streptomyces erethreus*.

Antibacterial Spectrum :→

* In Normal Doses, Bacteriostatic and in high doses Bactericidal

Staphylococci susceptible at ≤ 0.5 μg/ml

Streptococci susceptible at ≤ 0.25 μg/ml

Clostridium perfringens at 0.2 – 3 µg/ml

Corynebacterium diphtheriae, Listeria monocytogenes } at 0.25 – 4 µg/ml

Inactive against most gram –ve Bacilli

Good activity against Pasturella multocida
Borrelia species
Bordetella pertusis
C. jejuni
M. pneumoniae phila.
Legionella pneumophila.
C. trachomatis

Sensitive in vitro against Atypical mycobacteria
M. scrofulaceum
M. kansasii } vary in sensitivity
M. avium

No effects on Yeasts, Fungi or Viruses.

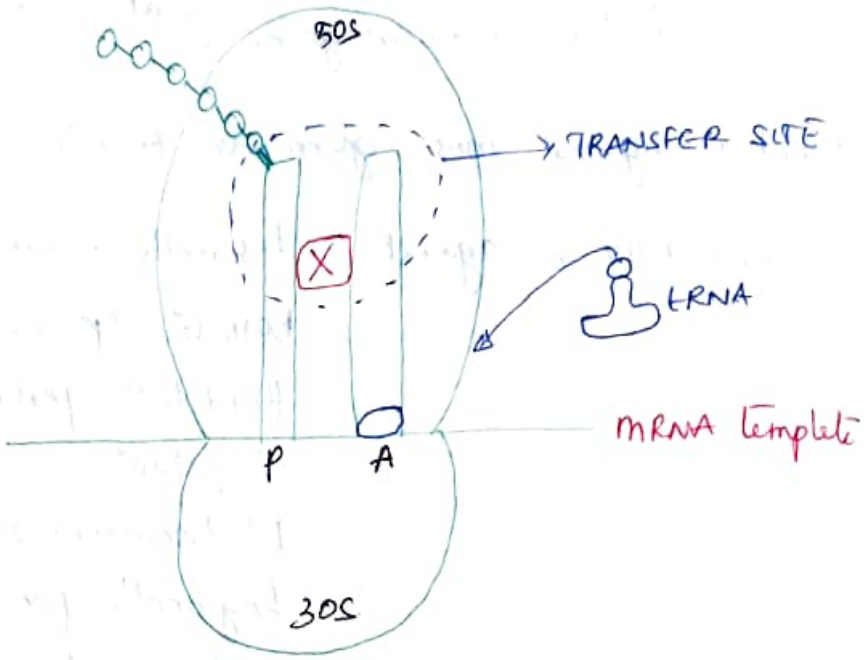
Clarithromycin → slightly more potent than Erythromycin

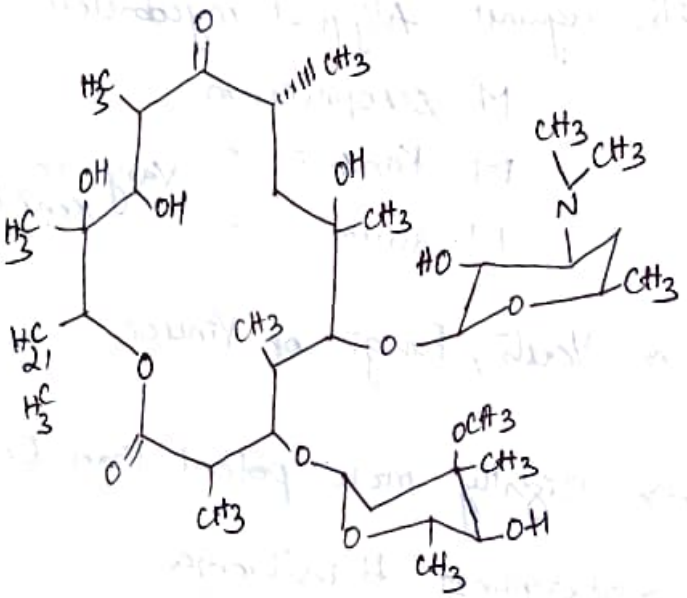
Azithromycin → active against H. influenza
less active than Erythromycin against gram +ve organisms and slightly more active than both drugs against H. influenza and Campylobacter species.

⇒ Good activity against M. Catarrhalis, chlamydia, Pneumophila, B. Burgdorferi, Mycoplasma pneumoniae, H. pylori.

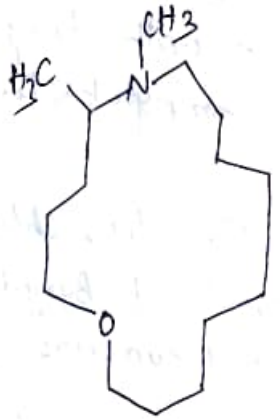
Telithromycin → Activity similar to above, but can be given in those who are macrolide resistant S. pneumoniae & S. aureus.

Mechanism of Action :→





Erythromycin



Azithromycin

* Macrolides are bacteriostatic agents that inhibit protein synthesis by reversibly binding to 50S ribosomal subunits.

* The site of binding is very near to the site that binds to chloramphenicol.

* They inhibit translocation step wherein a newly synthesized peptidyl tRNA molecule moves from Acceptor site to peptidyl donor site.

* Gram +ve bacteria accumulate 100 times more erythromycin than gram -ve bacteria

* Cells are more permeable to the unionised form of drugs ∴ ↑ antimicrobial activity at Alkaline pH

Development of Resistance :→

1→ Drug efflux by an active pump mechanism → encoded by genes ~~mef A~~ msrA, mefA or mefE
↓
Staphylococci
or group A in Streptococci

2→ Ribosomal protection by inducible or constitutive prod^n of Methylase enzymes mediated by ermA, ermB and ermC genes → which modify ribosomal target and reduce the drug binding.

3→ Hydrolysis of Macrolides by enzymes Esterase produced by Enterobacteriaceae.

4→ Chromosomal mutations that alter 50S ribosomal protein [Eg: B. subtilus, Campylobacter & Mycobacteria etc].

P.kinetics :→

Absorption :→

Erythromycin → incompletly but adequately absorbed in the upper part of small intestine, since it is inactivated by gastric acid
→ given as Enteric coated tablets)
→ Food delays the absorption of Erythromycin

250 mg ⟶ 0.3 – 0.5 µg/ml after 4hrs of admn.
500 mg ⟶ 0.3 – 1.9 µg/ml " " "

Esters of Erythromycin → improves acid stability & No alterations in presence of food.
Eg: Erythromycin Stearate
E. Succinate
E. Estolate
~~E. Lobiolate~~ E. lactobionate
~~E. Etbi~~

250 mg of E. estolate → 1.5 µg/ml with in 2hrs of admn.
500 mg of " → 4 µg/ml " "

E. lactobionate → IV admn. ≈ 10 µg/ml within 1hr.

Clarithromycin :→ Absorbed rapidly from GIT after oral admn. but reduced bioavailability to 50% due to 1st pass metabolism.

→ peak conc. seen only 2 hrs after admn. of the drug
→ Can be given with/without food but in the form of Extended release formulations.

→ 1 g per day + food → improved bioavailability.

→ steady peak plasma levels : 2-3 µg/ml within 2 hrs with 500mg every 12 hrs. or after 2-4 hrs with 500mg, Extended release is given once daily.

Azithromycin :→ orally rapidly absorbed
→ Coadmn. of $Al(OH)_3$ and $Mg(OH)$ Antacids ↓ the peak levels but overall bioavailability is maintained.
→ Not to be given with food.
→ can be given in IV formulation also.

Telithromycin :→
→ NO parenteral form available.
marketed as 400mg oral tablets.
→ Well absorbed with ~ 60% bioavailability
→ peak plasma levels achieved within 30 min of admn. dose to 4 hrs.

Distribution :→

Erythromycin → Readily distributed in all fluids except Brain and CSF.
penetrates prostatic fluid ~ 40% of that in plasma
middle ear exudate ~ 50% " "

Protein Binding 70-80% for Erythromycin & 96% For E. estolate
Crosses placenta and 5-20% levels in fetal plasma.
Breast milk 50% of that in plasma.

Clarithromycin :→ Undergoes First pass metabolism to active metabolite →
14-OH clarithromycin
↓
distributed widely and achieve high intracellular Conc^n throughout the body.

→ Tissue conc^n generally exceed Serum conc^n
→ 40-70% protein binding and ↓ Conc^n dependent.

Azithromycin :→ Has unique properties with extensive tissue distribution and high drug conc^n. with in cells like phagocytes than serum levels.

→ tissue Fibroblasts act as natural reservoir of the drug in vivo.
→ 50% protein binding at low conc^n of plasma.
and even less % of binding at high plasma conc^n

Telithromycin :→ Well penetration into tissues, exceeding the plasma Conc^n

→ Conc^n in macrophages, WBC are maintained 24 hrs after admn.

Metabolism :→

Erythromycin
↓
met. in liver
via demethylation
by CYP3A4

Azithromycin
↓
Inactive metabolites
in liver.

Clarithromycin

↓

In liver metabolised to 14-OH derivative. which is active.

↓

oxidised by N-demethylation & Hydroxylation

Follow Non-linear Pkinetics. metabolism is saturable. inhibits CYP3A4

Telithromycin

↓

Met. in liver.

↓ 50% met. by CYP3A4

↓ 50% by CYP independent metabolism

Elimination :→

Erythromycin

↓

conc^n in liver & excreted in Bile

2-5% orally admn. is excreated unchanged

→ Removed completly by peritoneal dialysis or Hemodialysis

Azithromycin

↓

Excreted majorly via Bile & 12% in unchanged form in Urine

e t½ → 40-68hrs

Clarithromycin

↓

Renal and Non Renal routes

20-40% excreted unchanged in Urine

10-15% as active metabolite

Elimination t½ → 3-7 hrs. for clarithro

14-OH-derivative → 5-9hrs

Telithromycin

↓

Renal excretion

e t½ 9.8 hrs

~~E Uses~~ :→

Adverse effects :→

→ Hepatotoxicity → observed with Erythromycin primarily by E. estolate & Rarely by E. Succinate or Stearate

Illness starts after 10-20 days of treatment → N, V, Abdominal cramps
↓
Jaundice.
↓
Fever, leucocytosis, Eosinophilia, ↑ serum enzyme levels in plasma.

Resolve within few days after cessation of therapy & rarely prolonged.

For clarithromycin, Azithromycin → Hepatotoxicity is seen but at a lower rate than Erythromycin.

→ GI Toxicity → Epigastric distress which may be severe & seen even after admn. of IV, N, V, cramps

→ Cardiac toxicity → may cause arrythmias including QT prolongation with Ventricular tachycardia.

→ Allergic reactions were observed rare.
Fever, Eosinophilia, Skin eruptions → which disappear after cessation of therapy.

→ large doses (4 g/day) → may cause Auditory impairment which is Transient

→ Visual disturbances — Blurred vision, difficulty in focusing, Diplopia in < 1% of patients with Telithromycin

Drug interactions :→

→ Inhibit CYP3A4 ∴ potentiates effects of Carbamazepine, corticosteroids, Cyclosporine, Digoxin, Theophylline, Triazolam, Valproate, Warfarin etc.

→ Azithromycin is free of DI because of 15 membered ring.

T. Uses :→

→ Depending upon the nature and severity of infection

→ Oral dose of Erythromycin

Adult dose → 1-2g per day in equal divided doses every 6 hrs. before food.

Erythromycin base is available as immediate release and delayed release formulations.

Oral dose for children → 30-50 mg/kg per day in 4 divided portions. It may be doubled in severe infections.

→ IM route not recommended due to pain upon injection

→ IV therapy reserved for therapy of severe infections like legionellosis.

0.5-1g every 6hrs for 4 wks. with no side effects except Thrombophlebitis at site of administration.

→ Combination of Erythromycin + Sulfisoxazole

↓

Synergistic activity used primarily in otitis media in Children.

→ Clarithromycin usually given bid at a dose of 250 mg for children > 12 yrs and in adults with mild to moderate infections.

< 12 yrs → 7.5 mg/kg

→ Clarithromycin 500mg packed along with Lansoprazole 30mg & Amoxicillin 1g → as a combination regimen for H. pylori infections for 10-14 days.

→ Azithromycin → should be given 1hr before and 2hrs after Meal → daily.

↓

For outpatient therapy of community-acquired pneumonia, Pharyngitis, Skin or skin structure infections

↓

a loading dose of 500 mg on 1st day followed by 250 mg per day from next day till 5 days.

⇒ Azithro → Extended-release microspheres oral

2g of dose → Community acquired pneumonia as an alternative treatment or Acute exacerbations of Chronic Bronchitis

For M. Avium → Azithromycin → requires higher doses (600mg or 1200mg) especially in AIDS patients

Azithro → useful in treatment of STD's, especially during pregnancy where tetracyclines are contraindicated.

1g/week of Azithro → Alternative regimen for treatment of granuloma inguinale or lymphogranuloma venereum..

Dosage

Erythromycin

Adult → 250mg q6h in equally spaced doses.
↓ or 500mg bid every 12 hrs.
may be given upto 4g per day.

children dose → 30-50 mg/kg/day in equal divided doses.
Should not exceed 4g/day.

→ Conjunctivitis in newborn → Chlamydia trachomatis
↓
Oral suspension
50 mg/kg/day in 4 divided doses for 2 weeks.

→ Pneumonia infancy (C. trachomatis) → Oral suspension → 50 mg/kg/day in 4 divided doses for at least 3 wks.

→ Urogenital infections during pregnancy due to C. trachomatis → Suggested treatment.

500 mg orally → qid for atleast 7 days.

for women who can't tolerate this dose.

250 mg orally → qid for 14 days.

→ In Non gonococcal Urethritis where tetracycline is contraindicated → 500 mg → qid → 7 days

→ primary syphilis → 30 - 40 g in divided doses for 10 - 15 days.

→ Acute pelvic inflammatory disease caused by N. gonorrhoea → 500 mg E. lactobionate IV. every 6 hrs for 3 days followed by 500 mg orally / 12 hrs for 7 days.

→ Intestinal Amoebiasis →

Adults { 500 mg | 12 hrs or 250 mg | 6 hrs for 10 - 14 days.

Children { 30 - 50 mg/kg/day in divided doses for 10 - 14 days.

→ Pertusis → 40-50 mg/kg/dy in divided doses for 5-14 dys.

→ Legionnaires disease → 4g daily in divided doses.

Clarithromycin :→

→ Acute Bacterial exacerbation of chronic Bronchitis → 250-500 mg/12hrs 7-14 days.

→ Acute maxillary sinusitis → 500 mg for 12hrs. for 14 days.

→ Community Acquired pneumonia → 250 mg/12 hrs for 10 days

→ Pharyngitis/Tonsilitis → 250 mg/12hrs → 7-14dys.

→ Uncomplicated Skin & Skin structure infections → 250mg/12hrs. ↓ 7-14 dys.

→ H. pylori eradication to reduce the risk of recurrence with Amoxycillin + omeprazole → 500mg/12 hrs. + 1g Amoxycillin for 12 hrs + Lansoprozole 30mg. for 10-14 dys.

→ H. pylori eradication to reduce the recurrence with omez → 500 mg | 8hrs + 40 mg omez for 14 dys.

→ Pediatric dosing → 15 mg/kg/dy divided dose every 12 hrs for 10 dys.

Azithromycin →

→ Non-gonoccocal Urethritis, cervicitis ↓ due to C. trachomatis ↓ 1g single dose (suspension)

→ Mycobacterial infections → prophylactic treatment M. avium Complex ↓ 1200 mg taken once weekly or 600 mg Alone or in Combination with Rifabutin; Ethambutol in HIV.

Children → Azithromycin Oral suspension

for otitis media pneumonia → 10mg/kg on first day 5mg/kg on 2-5 days max → 250 mg/day

Tonsilitis or Pharyngitis → 12 mg/kg per day max → 500 mg for 5 days.

Telithromycin

↓

Effective in treatment of community acquired pneumonia, Acute exacerbation of Chronic Bronchitis, acute Bacterial Sinusitis.

→ Has a potential advantage over other macrolides in region where macrolide resistant strains are common.

→ Due to high risk of Hepatotoxicity → should be use only where other therapies wean off.