MACROLIDES

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Macrolides - Properties

—**Macrocyclic Lactone ring attached with deoxysugar**

—**Effective against Gm +ve bacterias**

—**Inhibits Bacterial Protein Synthesis– by inhibiting 50 S – ribosomal subunit**

—**Has bacteriostatic effect**

—**Used as an alternative to Penicillin**

(I) ***Prototype drug*** **:-** Erythromycin –1950

(II) ***New Generation Macrolides*** **: –**

- **Roxithromycin**
- Clarithromycin &
- **Azithromycin**

Macrolides – Mechanism of action

Macrolides administered

↓

Binds to 'P' (Peptidyl) site of 50 S-ribosomal subunit

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Interferes with translocation step

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Prevents the translocation (shifting) of t-RNA (the growing peptide chain) from Acceptor site (A) back to Peptidyl site (P)

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Site A not available for attachment of the next amino acid brought by tRNA

↓

Peptide chain get prematurely terminated

↓

Inhibits Bacterial Protein Synthesis

↓

Bacteriostatic action

ANTI-BACTERIAL SPECTRUM OF MACROLIDES

1) Gm +ve Cocci :	Streptococci pneumoniae
	Streptococci pyogenes
	Staphylococci
2) Gm –ve Cocci :	Neisseriae Gonococci
	Moraxella catarrhalis
3) Gm +ve Bacilli :	Corynebacterium diptheriae
	Bacillus anthraxis
4) Gm –ve Bacilli :	Legionella pneumophilia
	Bordetella pertussis
	Haemophilus influenza
	H.ducreyi
5) Acid-Fast Bacilli :	Mycobacterium leprae
	Mycobacterium ComplexAvium (MAC)
6) Spirochaetes :	Trepenoma pallidum

ANTI-BACTERIAL SPECTRUM OF MACROLIDES

7) Miscellaneous : Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae
Chlamdyia psittacis

Roxithromycin : Moraxella catarrhalis, Legionella

Clarithromycin : Moraxella catarrhalis, Legionella pneumophilia, H. influenzae, Chlamydia trachomatis... MAC, My. Leprae, H.Pylori

Azithromycin : MAC, Toxoplasmagondii, Chlamydia, Mycoplasma, H.Ducreyi, H.influenza

ERYTHROMYCIN - Properties

- A **prototype** of macrolide – 1950s
- Is derived from **Streptomyces erythreus**
- Is **bacteriostatic**
- **Inhibits** bacterial **protein synthesis**
- **Has narrow antibacterial spectrum : Gm +ve bact.**
  - **Str. Pyogenes, Str. Pneumoniae, C. diphtheriae**
  - **Widely distributed in body**
  - **Achieves higher concentration in Tonsilar tissue, Middle ear fluid, Lungs, Alveolar macrophages, Prostatic fluid, Skin & soft tissues (Abscesses, cells)**

Erythromycin –Limitations

- Is **acid labile**
- Is available in **enteric coated** form for oral administration
- Is available in **three** different **esters form :-**
- ***Estolate, Stearate and Succinate***
- **Food interferes** with the **absorption** of Erythromycin
- **Incomplete absorption**à **Poor bioavailability**
- Estolate form à produces **Cholestatic Jaundice**
- Lactobionate for I.V injection
- **Short Plasma Half-Life (1.5 hr)**
- Administered four times in a day orally
- **Poor concentration in CSF and brain**
- **Excreted through bile** & also crosses placental barrier
- High risk of **fatal drug-drug interactions**

Erythromycin – Adverse Effects

—1) **Hepatitis with cholestatic jaundice** after 10 days of treatment with erythromycin estolate salt

—2) **Epigastric distress, diarrhoea, nausea & vomiting.**

—3) **Diarrhoea due to stimulation of** Motilin receptors in GI à induces gastric contraction à **enhances gastric emptying à** This property is used in diabetic gastroparesis

—4) **Reversible hearing impairment (Ototoxicity)**

—5) **Cardiac arryhthmias (Torse de Pontes) a life – threatening drug –drug interactions occur ….. when**

Erythromycin + **Cisapride**/ Ketoconazole/ Loratadine or **Astemizole à** due inhibition of cytochrome P450 enzyme (CYP 3A4) à Prolongation of QTc interval à Precipitation of serious Ventricular Tachycardiaà **Death** (due to ↑ plasma levels of co-administered drugs)

Erythromycin - uses

1) **Mycoplasma pneumonia:** Erythromycin – 500mg i.v. or **orally q 6hrly (DOC)**
2) **Legionnaire's pneumoniae : Erythromycin 500mg** i.v. for 10-14 days **(DOC)**
3) **Whooping cough : (DOC)** for the treatment and exposure prophylaxis of close contacts **(eradicates B. Pertussis) à 1-2 week course**
4) **Diptheria :** effective in acute stage though antitoxin is life saving. Also eradicates pharyngeal carrier state. **(DOC)**
5) **Chanchroid :** 2g/d for 7 days à Equivalent to Azithromycin / Ceftriaxone **(DOC)**

Erythromycin – Uses (Contd...)

7)As an alternative to Penicillin :

(a) Syphilis & Gonorrhoea

(b) Strep. Pyogenes (O.M.,sinusitis, tonsilitis, pharyngitis)

(c) Strep. Pneumoniae

(d) Staph. Infections (Except MRSA)

(e) H. influenza (Otitis media (O.M.), sinusitis)

(f) Anthrax (g) Leptospirosis—250 mg qid for 7 days

– (h) Tetanus :adjuvant to antitoxinsà Eradicates carrier state

–8) Prophylaxis :

– (a) As an alternative to Penicillin invalvular heart diseasepts

– undergoing dental surgery à to prevent SABE.

– (b) In acute - oropharyngeal infections in dentistry

– 9) Topical : Ointment (2-4%) for skin infections , boils.

– Lotion for acnevulgaris

–10) Other uses : in gastroparesis in postoperative patients

– and in diabetic gastroparesis.

ROXITHROMYCIN -Properties

- **Second** generation **semisynthetic macrolide**
- **Longer acting – acid stable**
- **Overcomes** some of the **limitations of erythromycin**
- Is **bacteriostatic , inhibits protein synthesis by binding at 50S ribosomal subunit of the bacteria**
- Has **narrow antibacterial spectrum** covering Gm +ve aerobes
- **Is longer plasma t1/2 – 12 hrs à Twice daily dosing**
- **More potent à B. Catarrhalis, Legionella**
- **Better enteral absorption** on empty stomach
- Better tissue penetrability than erythromycin

Roxithromycin - Properties

- **Does not inhibit metabolism of other drugs,** hence **no fatal drug- interactions causing cardiac arryhthmias**
- To be taken **30 mins before food to avoid food-drug interaction & poor absorption**
- Can be **used as an alternative *to* *erythromycin***
- Available as :-
- **Tablets :** 150 mg ; 300mg & 50 mg kidtab
- **Suspension : 50 mg / 5ml** for children
- **Paediatric Drops :** for infants

CLARTHROMYCIN

- Second generation semisynthetic macrolide
- Structurally similar to Erythromycin, hence prone to produce drug - interactions

- ***Advantages :-***
- Acid stable à No esters required
- Rapid and better absorption
- Good oral Bioavailability, Largely distributed
- Metabolized to active metabolite à 14 – Hydroxy clarithromycin
- Metabolized by Saturation Kinetics :-
- T1/2 life prolonged from 3-6 hrs at lower dose to 6-9 hrs at higher dose
- Excreted unchanged in Bile à no dosage modification in RF or renal disease

CLARTHROMYCIN

- **Advantages (Contd…)**

- **Broader antibacterial spectrum** – covers :-
- Gm +ve bacteria plus **H. Influenzae,**
- Legionella,
- **Atypical mycobacteria à** Mycobacterium Avium Complex (MAC)
- **H. Pylori** and **some anaerobes**
- **M. Leprae and Toxoplasma Gondii.**

Clarithromycin - Uses

- 1) **For URTIs** (**sinusitis**, pharyngitis, **tonsillitis**, otitis media) & **LRTIs** (**Pneumonia** & **AECB**)

- **2) H.Pylori eradication in Peptic ulcers :** As one of the ingredient of **One / Two Week Triple Regimen** of **H. Pylori Eradication kit :-**

- i) **Lansoprazole 30 mg BD** + Clarithromycin 500mg BD + **Amoxicillin 1 Gm BD for 2 weeks.** (USFDA)

- ii) **Omeprazole 20 mg BD** + **Clarithromycin 500mg BD** + **Metronidazole (400mg)/Tinidazole (500mg) BD** for **1 week.**

Clarithromycin - Uses

- 2) **For prevention and treatment of Atypical Mycobacterium Avium Complex (MAC)** infection contracted as a secondary infection in HIV- AIDS patients.
- **A)Intensive Phase :-**
- **Clarithromycin 500mg BD+ Ethambutol 1 Gm OD + Rifabutin 300mg OD** for 2 months
- **B) Continuous Phase :-**
- **Clarithromycin 500mg BD + Ethambutol 1 Gm OD / Rifabutin 300 mg OD + Levofloxacin 500mg OD** for 4 months

- **Available as :** 250 & 500 mg tablets.

AZITHROMYCIN -Pecularities

- Newer second generation semisynthetic macrolide
- More potent than Erythromycin, Roxithromycin and Clarithromycin
- Acid stable, rapid absorption, food interferes with its absorption, hence, administer 1 hr before or 2 hr after meals
- Larger tissue distribution and intracellular penetrability (Macrophages, Fibroblasts)
- Volume of distribution = 30 L /kg
- Expanded antibacterial spectrum, Better tolerability & drug interactions profile , improved pharmacokinetics profile
- Excreted unchanged in Bile
- Is Bacteriostatic and inhibits bacterial protein synthesis

Azithromycin - Pecularities Contd....)

- Effective against Gm +ve bacteria, MAC, Mycoplasma, Toxoplasma Gondii, H. Influenzae, Legionella
- Longer plasma half- life of 50 hrs (slowly release from intracellular site)
- Has Post-antibiotic effect (PAE)
- Hence, administered 500mg once a day for 3 consecutive days or as a single loading dose of 500mg on day one, followed by 250 mg once daily for next 4 days
- Does not suppress microsomal enzymes in the liver and thereby does not interferes with hepatic metabolism of other drugs. No drug interactions

Azithromycin - Uses

- 1) **URTIs** (Pharyngitis, tonsillitis, sinusitis, oitis)
- 2) **LRTIs** (AECB, Pneumonia)
- 3)**Skin & soft tissue infections** (SSTIs)
- 4) **Genitourinary tract infections**
- 5) **Acne vulgaris**
- 6) **Mycobacterial Avium Complex** (MAC) infection in AIDS patients
- 7) **Donovanosis :-** caused by **Calymmobacterium Granulamotis à 500mg OD for 7 days or 1 Gm weekly for 4 weeks** (as effective as Doxy)

Azithromycin - Uses

- 8) **Legionnaire's pneumonia :** 500mg OD oral / I.V for 2 weeks
- **9)Chlamydia Trachomatis :** 1 G single dose for non specific urethritis & genital infections in both sex
- **10) Lymphogranuloma venerum : 1gm / week for 3 weeks**
- **11) Trachoma infection of Eye : preferred to Tetracycline**
- **12) Chanchroid & Urethritis :** 1 Gm single dose

- **ADVERSE EFFECTS :-**
- **GI discomfort, headache, dizziness.**

- **Available as : 250, 500 & 1G tablets .**