Clindamycin, Vancomycin, Linezolid, Teicoplanin, Spectinomycin & Spiramycin

Dr. Kamlesh P. Patel

Associate Professor

Department of Pharmacology

Smt. NHL Municipal Medical College

Ellisbridge, Ahmedabad

Clindamycin(Lincosamides)

- **PROPERTIES-:**
- **Clindamycin** belongs to **'Lincosamide'** group
- Has a potent **narrow antibacterial spectrum**
- **Antibacterial spectrum covers :- Gm+ve cocci, Penicillinase producing Staphylococci** except **MRSA, C. Diphtheriae, Actinomyces , Nocardia, Toxoplasma gondii and anaerobes** like B.fragilis
- Is **bacteriostatic**
- **Inhibits bacterial protein synthesis** by inhibiting **50s ribosomal subunits**

Clindamycin: Properties (Contd…)

- Well absorbed orally
- **Presence of food does not reduce** its **absorption**
- Tightly bound to **plasma protein** (90%)
- High Tissue penetration :- Bones, soft tissues, Phagocytes (except CSF)
- **Plasma Half life** -2.5 - 3 hrs
- **Metabolized** in **liver** and excreted in **urine & bile**
- Available as : inj, tabs/ caps, syrup, ointment
- Dose : 500mg TDS-QDS orally

  600mg i.m .or i.v. infusion

Clindamycin: Uses

1) Serious **anaerobic** infections due to B. fragilis
2) Serious **Staphylococcal** & **Streptococcal** infections like :- **liver abscess, lung abscess, staphylococcal bone and joint infections, septicaemia** & **PID** with **Aminoglycosides**
3) **Prophylaxis of endocarditis** in **Penicillin allergic patients**
4) **Topical ointment for acne (pimples) treatment**
5) **Pneumocystis Carinii Pneumonia** in **AIDS patients:-**

—**(i) Clindamycin (300 - 450mg QID orally) + Primaquine (30mg/ day orally)** for **21 days** as an **alternative to Co-trimoxazole**

6) **Toxoplasmic Encephalitis** in **AIDS patients :-**

—**(i) Clindamycin (600mg orally) + Pyrimethamine (75mg/ day orally)** for **6 weeks as an alternative to pts who cannot tolerate sulphonamide**

Clindamycin– Adverse Effects

1) **Clindamycin** associated **Pseudomembranous enterocolitis** and **diarrhoea : d**ue to Toxinsproduced **by Difficle Clostridium.**

—**Treatment :-** 1) **Withdraw - Clindamycin**

2) **Administer: Vancomycin 125-500mg TDS** orally

or

Metronidazole 400mg TDS * 10 days orally

2) **High I.V. dose** of **Clindamycin à Neuromuscular blockade**

3) **Leukopenia, exfoliative dermatitis, hepatotoxicity and hypersensitivity reactions**

4) **Nausea, vomiting** and **gastric discomfort**

VANCOMYCIN Properties

- Is a *Glycopeptide* antibiotic
- Used as an alternative to Penicillin resistant MRSA (Methicillin Resistant Staphylococcus Areus)
- Highly effective against - Strep. Viridans, Enterococcus, Cl. Difficle, Gm +ve cocci, Niesseria etc..
- Is Bactericidal
  - Acts by inhibiting bacterial cell wall synthesis, acts by binding to the terminal dipeptide 'D-ala D-ala' sequence of peptidoglycan units
- Poorly absorbed orally, widely distributed i.v.ly in serous cavities, inflamed meningitis & excreted in urine
- Plasma Half-Life = 6 hrs

VANCOMYCIN - USES

1) **Psedomembranous enterocolitis caused by Clindamycin : Oral vancomycin 125 – 500 mg TDS * 10 days**
2) **Serious MRSA infections : 500 mg I.V. Infusion 6 hrly or 1 gm 12 hrly over 1 hr .**
3) **Enterococcal Endocarditis along with Gentamicin in Penicillin allergic patients**
4) **Bacterial Meningitis : For Empirical treatment :- I.V. Vancomycin + I.V.Cefotaxime / Ceftriaxone**
5) **Cancer chemotherapy patients undergoing Dialysis**
6) **Penicillin – resistant Pneumococcal infections**
7) **Surgical Prophylaxis in MRSA prevelant areas & in Penicillin allergic Pts**

VANCOMYCIN- Adverse Effects

1) **Vancomycin Resistant Staphylococcus Areus (VRSA)** and **Vancomycin Resistant Enterococcus (VRE)**

2) **Ototoxicity – permanent deafness**

3) **Nephrotoxicity**

4) **Hypotension on i.v. administration, skin allergy**

5) **'Red Man Syndrome'** on **rapid I.V. administration of Vancomycin – causes chills, fever, urticaria & intense flushing**

Teicoplanin

- Newer **Glycopeptide** antibiotic after Vancomycin
- **Mixture of six similar compounds**
- **Narrow antibacterial spectrum** à **Gm +ve bacteria**
- **Inhibits bacterial cell wall synthesis**
- Notable pecularities are :-
- **More active against enterococci** than vancomycin
- **Effective against MRSA, VRE. Injected i.m, i.v**
- Has **longer pl t1/ 2 – 3 to 4 days**
- **Excreted unchanged** in **urine - decrease dose in RF**
- ***Uses:-*** **Enterococcal endocarditis** along **with Gentamicin**
- **MRSA** & **Penicillin - resistant streptococcal innfections**
- **Osteomyelitis**
- **Alternative to Vancomycin** for **Surgical prophylaxis**
- **Dose : 400 mg first day** then **200 mg daily i.v or i.m**
- **Side effects :- reversible hearing loss, Granulocytopenia**

LINEZOLID - Properties

- **Complete synthetic** - new antibiotic belonging to **'Oxazolidinones'** group
- **Minimum** chances of developing **bacterial resistance**
- **Narrow antimicrobial spectrum** – limited to **Gm +ve pathogens**
- **Reserved for Multi-drug resistant Gm +ve infections**
- Is **'Bacteriostatic'** for most pathogens **Except for Streptococci** it is **'Bactericidal'**
- Available as **'Oral' (Tab-600 mg-BD)** and **Parenteral (200 mg/ 100 ml i.v. infusion) form**

LINEZOLID - Properties (Contd…)

- Is **completely absorbed orally à Significant Oral bioavailability -- Hence, dose adjustment not required while switching the drug from oral to i.v or vice versa**
- **Food does not interfere** with the **absorption of linezolid**
- **Plasma Half-life is 4-6 hrs**
- Demonstrates **Post- antibiotic effect**
- **Metabolized** in liver & **excreted** in urine
- **Highly active against Gm +ve cocci** and **anaerobes & bacillary infections**
- Is **active against 'MRSA', 'VRE' &Penicillin – resistant Strep. Viridans, Pyogens & pneumoniae; My. tuberculosis**

LINEZOLID - Mechanism of Action

- **Linezolid is 'Bacteriostatic' but 'Bacteriocidal'** against **Streptococci .**
- Has **unique mechanism** which **prevents cross resisitance**

- **Linezolid à binds to 23S fraction of 50S ribosomal subunits near the interface with 30S subunità interferes with the formation of tertiary N-formylmethionine –tRNA (tRNA tMet)à Inhibits Bacterial Protein Synthesis à by acting at early stage**

- **Hence, it prevents the formation of 'initiation complex'** required **for bacterial protein translation** & **thereby, inhibits protein synthesis before it starts.**

Linezolid - Uses

1) **Complicated & Uncomplicated skin & soft tissue infections (SSTIs)**
2) **Hospital - acquired (Nosocomial) & Community – acquired pneumonia**
3) **Bacteraemias & drug – resistant Gm+ve infections**
4) Kept as a **'Reserve Drug'** for **all Hospital - acquired serious infections, febrile neutropenia, wound infections, Vancomycin Resistant Enterococci (VRE)** and **Methicillin Resistant Staphylococcus Aereus (MRSA) Endocarditis infections**
5) **Effective against Cornybacterum diphtheriae, B. Anthrax, B.Fragilis** produced **infections**
6) **Approved for use in Paediatric infections and in Diabetic Foot infection**

Linezolid – Adverse Effects

1) **Gastric pain & discomfort,** diarrhoea, **Pseudomembranous enterocolitis** (rarely)
2) **Reversible Thrombocytopenia (if used for more than 15 days) and Neutropenia (**if patient is predisposed to Bone Marrow Suppression) **à monitor Platelet count weekly**
3) **Headache, Taste alteration & oral candidiasis**
4) **Inhibits MAO enzyme** à causing **'Cheese Reaction'** containing **Tyramine**
5) Produces **'Serotonin syndrome' (confusion, seizures, hypertension, tachycardia, muscle rigidity)** when co-prescribed **with Selective Serotonin Reuptake Inhibitors (SSRIs) like Fluoxetine, Sertraline etc…**

Spectinomycin

- Has amino-cyclitol – chemically differs from others
- Narrow antibacterial spectrum – limited Gm –ve bacteria
- Bacteriostatic - N. Gonorrhoea
- Binds to 30s ribosomal subunit – inhibits protein synthesis – but differs from aminoglycosides
- ***Uses :-***
- Single approved indication – Resistant Gonorrhoea or treatment refractory to conventional beta-lactams or macrolides
- Dose :- 2 g i.m. single inj
- Severe infection: 4 Gm (2gm at 2 sites i.m.)
- Well tolerated , less side effects

Spiramycin

- **Macrolide antibiotic**
- **Resembles erythromycin** in **anti-bacterial spectrum**
- **Effective in limiting Transplacental Transmission of Toxoplasma Gondii infection in pregnant women**
- ***USES :***

1) Toxoplasmosis and **Recurrent abortion in pregnant women**

- **Dose :**
- **3 MU 2-3 times a day , repeated after 2 weeks gap till delivery. 3 week course**

Pharmacotherapy of Typhoid (Enteric) Fever

- Typhoid fever is also known as 'Énteric Fever'
- Causative organism : Salmonella Typhii
- Sign & Symptoms : High Grade fever, chills, anorexia, nausea, bodyache, red spots on trunk & abdomen, intestinal perforation & intragastric bleeding on prolonged disease
- Diagnosis : Widal Test after 5 days of fever, Typhi – Do T- Test
- Typhoid fever Positive if Salmonella Typhii Titres are high
- Treatment includes :-
- Bed rest, Liquid diet
- Antipyretic, analgesic, H-2 Blockers/ Proton –pump inhibitors
- Fluoroquinolones, 3rd Generation cephalosporins, Chloramphenicol, Ampicillin/ amoxicillin, Cotrimoxazole

Pharmacotherapy of Typhoid (Enteric) Fever

(I) Fluoroquinolones :-

Drug of First Choice (DOC)

Examples :-

Ciprofloxacin, Ofloxacin, Gatifloxacin, Moxifloxacin, Levofloxacin

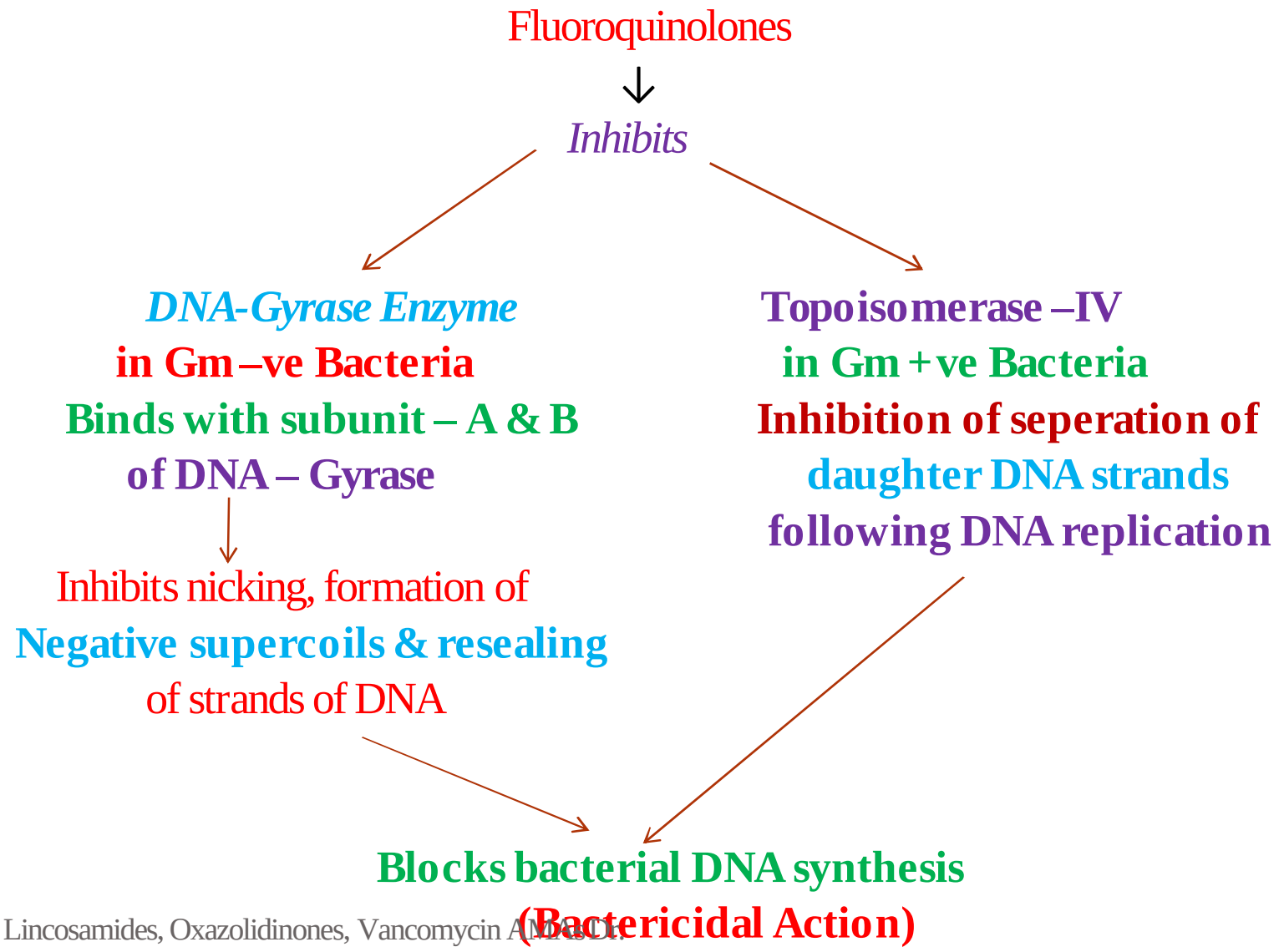
Available as tablets, IV infusion

Are **Bactericidal**

Acts by inhibiting bacterial DNA synthesis

Higher tissue penetration in lungs, intestines, urinary tract, prostate in males, bones

Fluoroquinolones - MOA



Fluoroquinolones

Advantages in Typhoid fever:-

1) **Drug of First Choice**
2) **Given by both oral & parenteral route**
3) **Early abatement of symptoms**
4) **Produces early defervescence of fever (within 72 hrs)**
5) **Produces 98-100% bacteriological & clinical cure rates**
6) **Eradicates carrier state** (Ciprofloxacin 750 mg BD * 8 weeks)
7) **Less chances of recurrent & relapses**
8) **Switch-on Therapy from parenteral to oral therapy ,once pt. can tolerate oral food & medicines**
9) Oral Dose : **Ciprofloxacin 500 – 750 mg BD * 10-14 days**

Fluoroquinolones

Diasdvantages of Fluoroquinolones in typhoid fever :-

1) **Contraidicated in children below 12 yrs à due to risk of tendinitis & arthrosis (Damage to the joint cartilages)**

2) **Cannot be given during pregnancy**

3) **Increases toxicity of aminophylline when concurantly administered**

Cephalosporins in Typhoid Fever

- **Third Generation Cephalosporins effective :-**
- **I) Parenteral :- Ceftriaxone, Cefoperazone, Cefotaxime**
- **II) Oral :- Cefixime, Cefpodoxime Proxetil, Cefdinir**

1) Ceftriaxone in Typhoid Fever:

- **3rd generation parenteral cephalosporin**
- **Longer plasma t1/ 2 life - 8 hrs**
- **Once or twice daily dosing**
- **Good penetration** into **tissues, CSF**
- **Effective DOC** in **Typhoid fever, multi-resistant typhoid fever in adults and children**
- Acts by inhibiting **Bacterial Cell wall synthesis**
- **Is Bactericidal**

Cephalosporins in Typhoid fever

- ***Advantages of Ceftriaxone in Typhoid fever :-***
- **DOC in children** where **Fluoroquinolones** are **contraindicated**
- **Rapid onset of action**
- **Early abetment of symptoms**
- **Early defervescence of fever**
- **Nearly 100% Bacteriological & Clinical cure rate**
- **Eradicates carrier state à Less chances of relapse and recurrences**
- **Well tolerated, less side effects**
- ***Dosage of Ceftriaxone in Typhoid Fever :–***
- ***1) Adults :-*** **4 G i.v. daily for 2 days , followed by 2 G / Day till 2 days after fever subsides**
- ***2) Children :-*** **75mg/ Kg / day**

Cephalosporins in Typhoid fever

- ***2) Cefoperazone :***
- ***Dose :*** **1-3 g i.m / i.v 8 – 12 hrly**
- **Risk of Disulfiram – like reaction with alcohol, thrombocytopenia**
- ***3) Cefotaxime :***
- **As an alternative to Ceftriaxone in Typhoid fever**
- **Pl t1/ 2 is 1 hr ,** but **metabolized to active metabolite - hence 12 hrly dosing**
- **Bactericidal** and **inhibits bacterial cell wall synthesis**
- **Dose :- 1-2 gm i.v 12 hrly in adults; 50-100 mg/ kg/ day in children**

Ampicillin / Amoxicillin/ Chloramphenicol/ Cotrimoxazole

- In the past used to treat typhoid fever
- Currently, S.Typhii has developed resistant to all the above drugs à Not used routinely
- *Drawbacks of all above drugs in Typhoid fever are :-*
- Slow onset of action, takes longer time to cure pt
- Slower abetment of symptoms
- Longer time for defervescence of fever
- Not effective in carrier state
- Less bacterial & clinical cure rates
- Higher relapse rate
- Development of resistance
- Poorly tolerated , increase risk of side effects
- Different dosage pattern