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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Miscellaneous :** Chloramphenicol*, Clindamycin.



Miscellaneous Antibiotics

- Miscellaneous antibiotics are a group of antibacterial agents that do not fit into major antibiotic classes based on structure or mechanism of action.
- They possess different mechanisms, spectrums, and therapeutic uses.

Classification

Common miscellaneous antibiotics include:

- Chloramphenicol
- Vancomycin
- Metronidazole
- Rifampicin
- Fosfomycin
- Nitrofurantoin
- Linezolid

Mechanism of Action

A. Chloramphenicol

- Binds to 50S ribosomal subunit
 - Inhibits peptidyl transferase enzyme
 - Prevents protein synthesis
- ➡ Bacteriostatic

B. Vancomycin

- Inhibits bacterial cell wall synthesis
 - Binds to D-Ala-D-Ala terminus
- ➡ Bactericidal

C. Metronidazole

- Reduced in anaerobic bacteria
 - Forms toxic free radicals
 - Damages DNA
- ➡ Bactericidal

D. Rifampicin

- Inhibits DNA-dependent RNA polymerase

- Blocks RNA synthesis
➔Bactericidal

E. Nitrofurantoin

- Reduced by bacterial enzymes
- Produces reactive intermediates
- Damages DNA and proteins

Spectrum of Activity

Drug	Effective Against
Chloramphenicol	Gram +, Gram –, anaerobes
Vancomycin	Gram + (MRSA)
Metronidazole	Anaerobes, protozoa
Rifampicin	Mycobacterium tuberculosis
Nitrofurantoin	Urinary pathogens
Linezolid	Gram + resistant strains

Therapeutic Uses

Chloramphenicol

- Typhoid fever
- Meningitis (alternative drug)

Vancomycin

- MRSA infections
- Severe *C. difficile* infection

Metronidazole

- Amoebiasis
- Giardiasis
- Anaerobic infections
- *H. pylori* infections

Rifampicin

- Tuberculosis
- Leprosy
- Meningococcal prophylaxis

Nitrofurantoin

- Urinary tract infections (UTI)

Adverse Effects

Chloramphenicol

- Bone marrow suppression
- Aplastic anemia
- Gray baby syndrome

Vancomycin

- Nephrotoxicity
- Ototoxicity
- Red man syndrome

Metronidazole

- Metallic taste
- Peripheral neuropathy
- Disulfiram-like reaction with alcohol

Rifampicin

- Hepatotoxicity
- Orange discoloration of body fluids

Nitrofurantoin

- Pulmonary fibrosis (long term)
- GI disturbances

Resistance

Resistance occurs due to:

- Enzyme inactivation
- Altered target sites
- Decreased permeability
- Efflux mechanisms

Chloramphenicol

- Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae* and now produced synthetically.
- It is primarily bacteriostatic, but may be bactericidal against certain organisms at high concentrations.
- Chloramphenicol inhibits bacterial protein synthesis and shows activity against Gram-positive, Gram-negative, and anaerobic bacteria.

Classification

Based on Source

Synthetic antibiotic (originally natural)

Based on Spectrum

Broad-spectrum antibiotic

Based on Mechanism

Protein synthesis inhibitor

Structure

→ Chloramphenicol is a nitrobenzene derivative.

Important structural features:

- p-Nitro phenyl ring
- Dichloroacetamide side chain
- Propane-1,3-diol moiety
- Two chiral centers at C-1 and C-2

Molecular formula: $C_{11}H_{12}Cl_2N_2O_5$

Structural Characteristics

- Small, non-bulky molecule
- Highly lipophilic
- Easily penetrates bacterial cell membrane
- Crosses blood-brain barrier

Nomenclature

Chloro → presence of chlorine atoms

Amphenicol → amide + phenyl structure

Available forms:

- Chloramphenicol
- Chloramphenicol palmitate (oral prodrug)

- Chloramphenicol sodium succinate (injectable)

Stereochemistry

- ▲ Chloramphenicol contains two asymmetric carbon atoms.
- ▲ Only the D-(-)-threo isomer is antibacterially active.
- ▲ L-isomer and erythro forms are inactive or toxic.
- ▲ Correct stereochemistry is essential for ribosomal binding.

Mechanism of Action

- Chloramphenicol enters bacterial cell by passive diffusion.
- Binds to 50S ribosomal subunit.
- Inhibits peptidyl transferase enzyme.
- Prevents peptide bond formation.
- Protein synthesis stops.
- Hence, chloramphenicol is bacteriostatic.

Spectrum of Activity

Gram-positive bacteria

Gram-negative bacteria

Anaerobes

- *Salmonella typhi*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Rickettsia*

Uses

- ▲ Typhoid fever
- ▲ Bacterial meningitis
- ▲ Severe anaerobic infections
- ▲ Eye infections (topical)
- ▲ Alternative drug when no safer antibiotic is available

Adverse Effects

Aplastic anemia (rare but fatal)

- Dose-related bone marrow suppression

Gray baby syndrome

- Gastrointestinal disturbances

Chemical Degradation

1. Acid Degradation

- Relatively stable in acidic conditions

2. Alkaline Degradation

- Hydrolysis of amide linkage

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat causes degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid moisture

Structure–Activity Relationship (SAR)

p-Nitro Group

- Essential for antibacterial activity
- Removal → loss of activity

Dichloroacetamide Side Chain

- Required for activity
- Contributes to toxicity

Propane-1,3-diol Moiety

- Necessary for proper binding

Stereochemistry

- Only D-threo form is active

Clindamycin

- Clindamycin is a semi-synthetic lincosamide antibiotic derived from lincomycin.
- It is primarily bacteriostatic, but may be bactericidal at high concentrations.
- Clindamycin is especially effective against anaerobic bacteria and Gram-positive cocci.
- It inhibits bacterial protein synthesis and is commonly used in penicillin-allergic patients.

Classification

Based on Chemical Class

Lincosamide antibiotics

- Lincomycin
- Clindamycin

Based on Origin

Semi-synthetic antibiotic

Structure

→ Clindamycin is a chlorinated derivative of lincomycin.

Important structural features:

- Amino acid (proline-like) moiety
- Octose sugar unit
- Chlorine atom substitution (increases potency)
- Thioether linkage

Molecular formula: $C_{18}H_{33}ClN_2O_5S$

Structural Advantages

- Increased lipophilicity
- Better oral absorption

Nomenclature

Clin-da → chemical modification of lincomycin

Mycin → antibiotic of microbial origin

Available as:

- Clindamycin hydrochloride
- Clindamycin phosphate (injectable/topical)

Stereochemistry

- Clindamycin contains multiple chiral centers.
- Correct stereochemical configuration is required for:
 - Ribosomal binding
 - Antibacterial activity
- Change in configuration reduces potency significantly.

Mechanism of Action

- Clindamycin penetrates bacterial cell.
- Binds reversibly to the 50S ribosomal subunit.
- Inhibits peptide chain initiation and translocation.
- Blocks protein synthesis.
- Bacterial growth is inhibited.
- Hence, clindamycin is bacteriostatic.

Spectrum of Activity

Gram-positive cocci

- *Streptococcus*
- *Staphylococcus* (including some MRSA)

Anaerobic bacteria

- *Bacteroides fragilis*
- *Clostridium*

Protozoa

- *Toxoplasma gondii* (with pyrimethamine)

Uses

- Anaerobic infections
- Skin and soft tissue infections
- Bone and joint infections (osteomyelitis)
- Dental infections
- Acne vulgaris (topical)
- Alternative in penicillin allergy
- Toxoplasmosis (with pyrimethamine)

Adverse Effects

- ◇ Pseudomembranous colitis (*Clostridioides difficile*)
- ◇ Diarrhea
- ◇ Abdominal pain
- ◇ Skin rashes
- ◇ Hepatotoxicity (rare)

Chemical Degradation

1. Acid Degradation

- Relatively stable

2. Alkaline Degradation

- Hydrolysis of ester linkage

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid moisture

Structure–Activity Relationship (SAR)

Chlorine Substitution

- Increases antibacterial potency
- Improves lipid solubility

Amino Acid Moiety

- Essential for ribosomal binding

Sugar Moiety

- Important for activity and solubility