

UNIT - II

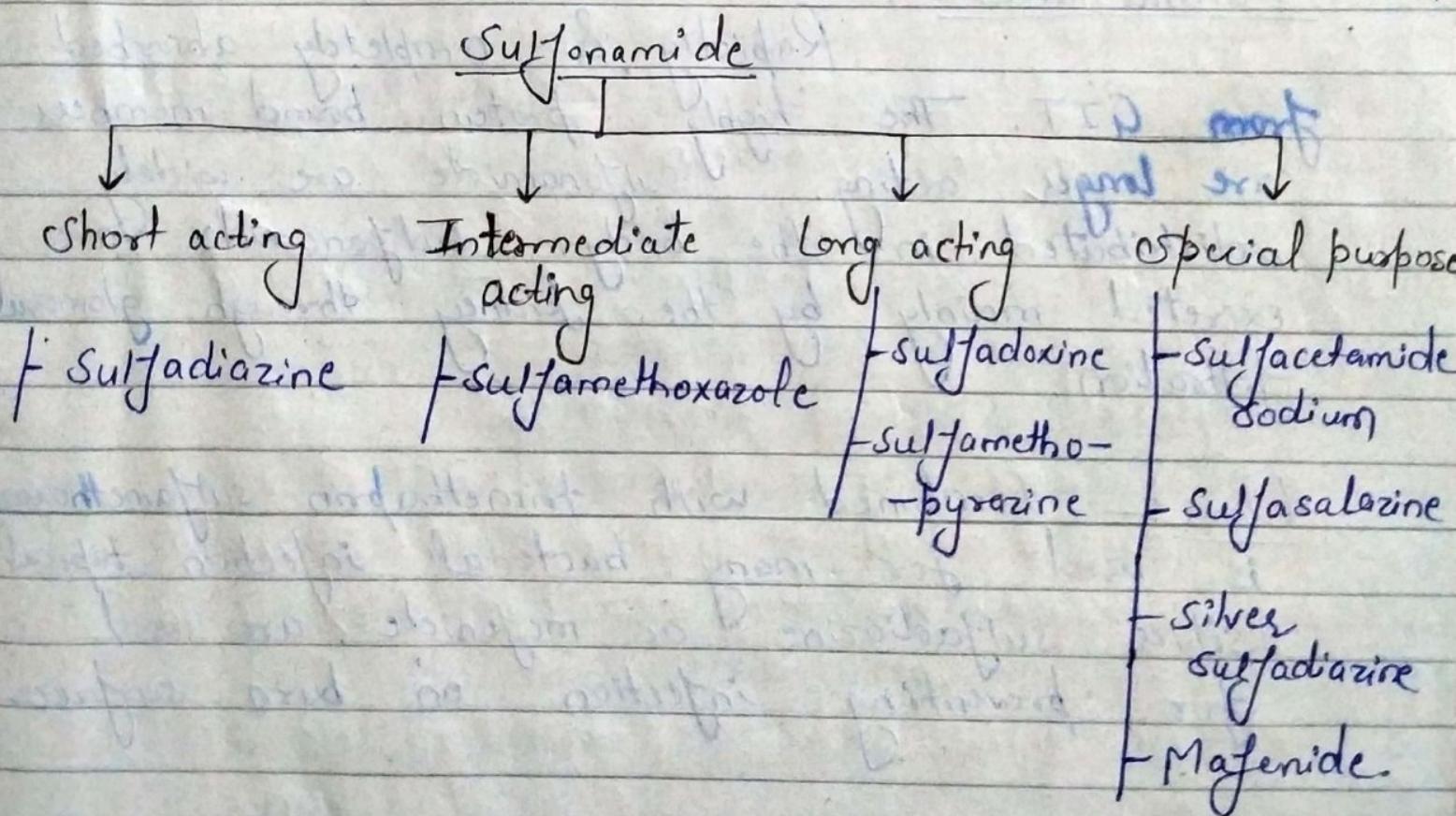
- * Chemotherapy *

- * Sulfonamide & cotrimoxazole. *

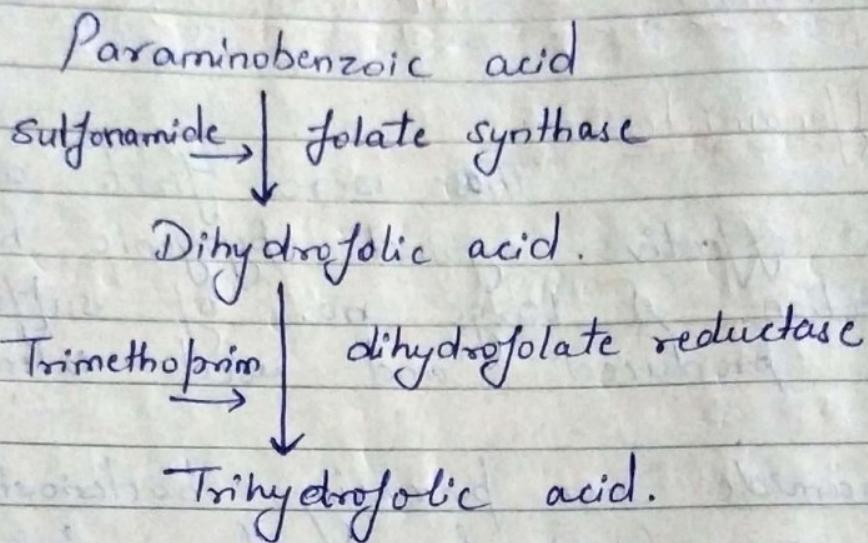
• Sulfonamide :-

These were first antimicrobial agents effective against pyogenic bacterial infection. A large no. of sulfonamide were produced and used extensively.

Sulfonamide are primarily bacteriostatic against many gram (+ve) & gram (-ve) bacteria.



Mechanism of Action :-



Pharmacokinetic :-

Rapidly & completely absorbed from GIT. The highly protein bound members are longer acting. Sulfonamide are widely distributed in the body. Sulfonamide are excreted mainly by the kidney through glomerular filtration.

Uses :- Combined with trimethoprim sulfamethoxazole is used for many bacterial infection topical silver sulfadiazine or mefenide are used for preventing infection on burn surface

- Cotrimoxazole :-

The fixed dose combination of trimethoprim and sulfamethoxazole is called cotrimoxazole. Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same $t_{1/2}$ (10 hrs).

Trimethoprim adequately crosses BBB & placenta, while sulfamethoxazole has a poorer entry.

Trimethoprim is more rapidly absorbed than sulfamethoxazole. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound.

Adverse effect :-

- Nausea
- Vomiting
- Headache
- Rashes
- folic acid deficiency (reguloblastic anaemia)

Uses :-

- UTI
- Respiratory Tract infection
- Bacterial diarrhoea & dysentery.
- Typhoid.

* Antibiotics :-

β -lactam antibiotics :-

- Pencillin was the first antibiotic to be used clinically in 1941. It was originally obtained from the fungus Pencillium notatum. The pencillin nucleus consists of fused thiazolidine and β -lactam rings to which side chain are attached through an amide linkage.

Classification :-

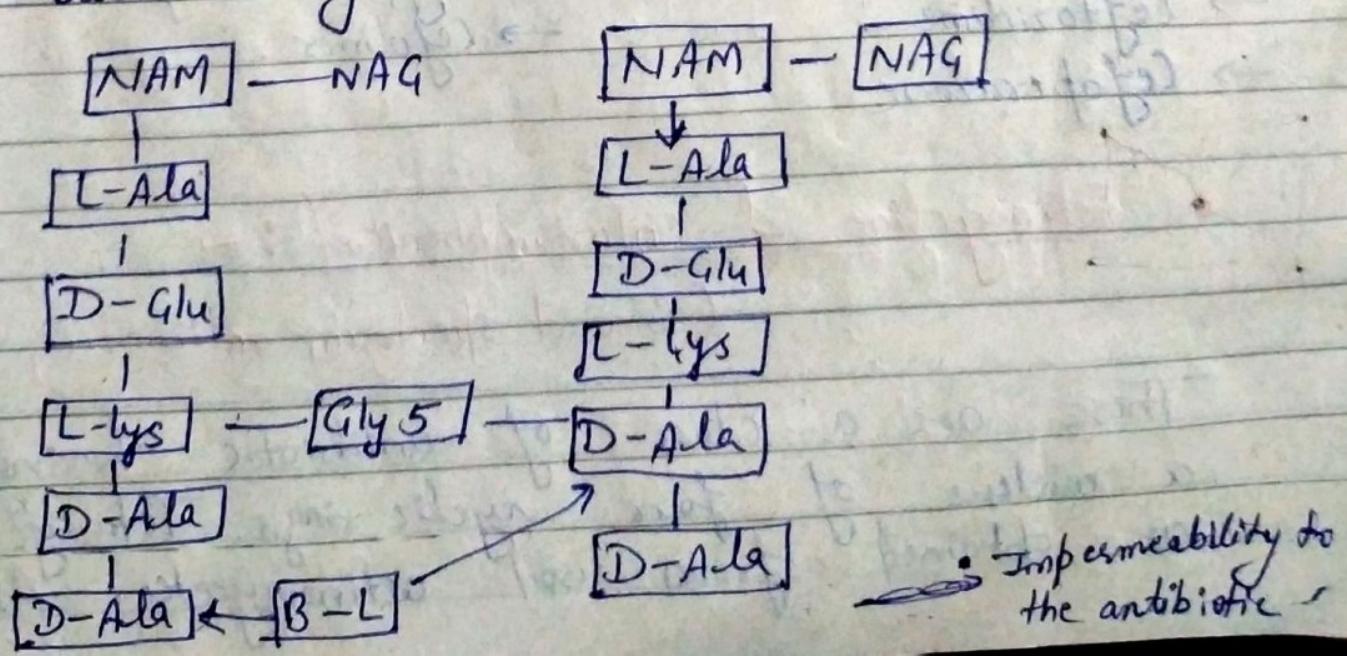
- 1.) Acid-resistant alternative to pencillin G :-
Phenoxymethyl Pencillin (Pencillin V)
- 2.) Pencillinase-resistant pencillins :- Methicillin, cloxacillin
- 3.) Extended spectrum pencillins :-
 - a) Aminopenicillins :- Ampicillin, Bacampicillin, Amoxicillin.
 - b) Carboxy penicillin :- Carbenicillin, Ticarcillin.
 - c) Ureido penicillin :- piperacillin, Mezlocillin

β -Lactamase inhibitors :- clavulanic acid
Salbactam.
Tazobactam.

Mechanism of Action :-

All β -lactam antibiotics interfere with the synthesis of bacterial cell wall. The bacteria synthesize UDP-N-acetylglucosamine. The peptidoglycan residues are linked together forming long strand and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by β -transpeptidase.

The β -lactam antibiotics inhibit the transpeptidase so that cross-linking does not take place. These enzymes and related protein constitute the penicillin binding protein. When susceptible bacteria divide in the presence of β -lactam antibiotic cell wall deficient forms are produced. Because the interior of the bacterium is hydro-organic the cell wall deficient forms swell & burst — bacterial lysis.



Classification :-

1) first generation cephalosporin :-

<u>Parenteral</u>	<u>Oral</u>
→ Cefazolin	→ Cephalexin
	→ Cefadroxil

2) Second generation :-

<u>Parenteral</u>	<u>Oral</u>
→ Cefuroxime	→ Cefaclor
→ Cefoxitin	→ Cefuroxime axetil
	→ Ceffazol.

3.) Third generation cephalosporin :-

<u>Parenteral</u>	<u>Oral</u>
→ Cefotaxime	→ Cefixime
→ Ceftriaxone	→ Cefpodoxime proxetil
→ Ceftazidime	→ Cefdinir.
→ Cefoperazone	

• Tetracycline & chloramphenicol :-

(Broad spectrum antibiotic)

These are a class of antibiotic having a nucleus of four cyclic rings. Tetracyclines are obtained from soil actinomycetes. All

tetracyclines are mildly bitter solids slightly water soluble. All have practically the same antimicrobial activity. Clinically relevant are:-

- Tetracycline
- Oxytetracycline
- Doxycycline
- Minocycline.

Mechanism of Action :-

Tetracyclines are primarily bacteriostatic inhibit protein synthesis by binding to 30s ribosome → attachment of aminoacyl t-RNA to the acceptor (A) site of mRNA - ribosome complex is blocked → Peptide chain fail to grow.

- The messenger RNA attaches to 30 ribosome
 - start protein synthesis & polysome formation
 - Nascent peptide chain attached to the peptidyl (P) site of 50s next amino acid (a) is transported to the acceptor (A) site of the ribosome.
- a) Amino glycoside bind to several sites at 30s & 50s subunits as well as their interface. If initiation interface with polysome formation cause misreading of mRNA code.
- b) Tetracyclines bind to 30s ribosome and inhibit aminoacyl tRNA attachment to the A_i site.
- c) Chloramphenicol binds to 50s subunit - interface with peptide bond formation & transfer of peptide chain from 'P' site.
- d) Erythromycin & clindamycin also bind to 50s ribosome & hinder translocation of the elongated peptide chain back from A site to P site & the ribosome does not move along the mRNA to expose the next chain.

Pharmacokinetic:- older tetracycline are incompletely absorbed from GIT absorption is better if taken in empty stomach. Doxycycline &

minocycline are completely absorbed. Tetracycline widely distributed in body.

Adverse effect :— Liver damage, kidney damage, sunburn like as other severe skin reaction.

Uses :— cholera, typhoid, plague.

• Chloramphenicol :-

M.O.A :— Inhibit bacterial protein synthesis by interfering with transfer of the elongating peptide chain to the newly attached amino-acyl - tRNA at ribosome → → acceptor (A) site → prevents peptide bond formation.

Chloramphenicol — obtained from Streptomyces venezuelae in 1947.

Pharmacokinetic :-

Rapidly & completely absorbed after oral ingestion. 50-60% bound to plasma protein widely distributed. Cross placenta & secreted in bile & milk → excreted unchanged in urine. $t_{1/2} = 3-5$ hrs.

• Quinolones :— Synthetic antimicrobials having a quinolone structure that are active primarily against gram (-ve) bacteria through newer fluorinated compound also inhibit gram +ve ones.

The first member nalidixic acid introduced in mid- 1960s usefulness limited to urinary & GIT tract injection because of low potency, limited spectrum of high frequency of bacterial resistance.

Nalidixic acid :— Active against gram - ve bacteria , E-coli , Proteus , klebsiella .

It acts by inhibiting bacterial DNA gyrase & is bactericidal Resistance to nalidixic acid develops rather rapidly .

Absorbed orally , highly plasma protein bound partly metabolized in liver . It is excreted in urine with a plasma $t_{1/2} \approx 8$ hrs .

Adverse effect :— Infrequent , consist mostly of G.I. upset & rashes . Most important toxicity is neurological — headache , drowsiness , visual disturbance , phototoxicity is rare .

Uses :— used as urinary antiseptic , also employed in diarrhoea .

Fluoroquinolines

These are quinolone antimicrobials having one or more fluorine substitutions.
first generation Fluoroquinolone introduced in 1980s

Classification



first generation

- Norfloxacin
- Ofloxacin
- Ciprofloxacin
- Pefloxacin



second generation.

- Lomefloxacin
- Levofloxacin
- Sparfloxacin
- Gatifloxacin
- Moxifloxacin

Mechanism of Action :— It inhibit the enzyme bacterial DNA gyrase which nicks double stranded DNA introduces (+ve) supercoils & then reseals the nicked ends. The DNA gyrase consist of two A & B subunits. The A subunit carries out nicking of DNA, B subunit introduces (-ve) supercoils and then A subunits reseals the strands. Fluoroquinolones binds to A subunit → high affinity → interfere with its strand cutting & resealing function.

Ciprofloxacin :— Most potent first generation Eq active against a broad range of bacteria the most susceptible ones are the aerobic gram -ve bacilli especially the enterobacteriaceae and Neisseria.

Pharmacokinetic :— Rapidly absorbed orally, but food delays absorption & first pass metabolism occurs. Excreted primarily in urine both by glomerular filtration & tubular secretion.

Adverse effect :— Good safety record :— GIT upset, vomiting, bad taste, dizziness, headache, insomnia, rash, swelling of lips.

- Macrolides :—

These are antibiotics having a macrocyclic lactone ring with attached sugars. Erythromycin is the 1st member discovered in 1950s.

Roxithromycin, clarithromycin, telithromycin and azithromycin are the later additions.

Erythromycin :— Isolated from Streptomyces erythraeum in 1952 water solubility is limited.

Mechanism of Action :— It is bacteriostatic at low but bactericidal of high concentration. Cidal action depend on the organism concerned with

and is rate of multiplication.

It acts by inhibiting bacterial protein synthesis. It combines with translocation. After peptide bond formation between the newly attached amino acid & the nascent peptide chain at the receptor (A) site the elongated peptide is translocated back to the peptidyl (P) site making.

A site available for next aminocyl tRNA attachment → Prevented by cozymyxin and the ribosome fails to move along the mRNA to expose the next codon.

Pharmacokinetic :- Acid labile - To protect it from gastric acid. it is given as enteric coated tablets → absorption is incomplete → food delays absorption crosses serous membranes & placenta widely distributed in body Not BBB. 70-80% Plasma protein bound partly metabolized & excreted primarily in bile in the active form. Renal excretion is minor. $T_{1/2} = 1.5 \text{ hrs.}$

Adverse effect :- Nausea
Anorexia
Rashes.