

UNIT - 2

Chemotherapy

Introduction: —

The word chemotherapy can be defined as the treatment of any disease by synthetically & microbiologically derived drugs by killing or inhibiting the growth of micro-organisms & fast growing cell in the body.

→ It is used for treating cancer.

General principles of chemotherapy

① Selectivity - All the antimicrobial agents effective clinically show selective toxicity for the bacterium rather than host.

② Therapeutic Index - (TI)

Define the ratio of toxic dose to the effective therapeutic dose.

Higher TI then better better antibiotic effect.

③ Categories of Antibiotics —

Categorised as per their action of producing cidal or static effect.

④ Antibiotic ~~susceptibility~~ Testing -

(i) minimum bactericidal concentration (MBC)

(ii) minimum inhibitory conc. (MIC) -

⑤ Combination Therapy -

⑥ i) Emergency cases diagnosis is still in progress

ii) " " of resistant strain

⑦ Antibiotic synergism —

↓
(2 substance combine then the Action.)
then the ↑es Action

Classification of chemotherapeutic Agent According to mechanism of Action

- i) Agents that inhibit cell wall synthesis - osmosis, ex - pen. cephalo. cycloserine bacitracin
- ii) Agents that cause misreading of m-RNA code & Affect permeability - Aminoacyl casides - streptomycin gentamycin
- (iii) Agents that cause leakage from cell membrane - polypeptides - polymyxins, colistin Bacitracin, polyenes, amphotericinB, mystatin, Hmmycin
- (iv) Agents that inhibit DNA Gyrase - Fluoroquinolones - ciprofloxacin
- (v) Agents that interfere with DNA function - Rifampicin & metronidazole
- (vi) Agent that interfere with DNA Synthesis Acyclovir, zidovudine
- (vii) Agents that interfere with intermediary metabolism - Sulphonamide, sulphones, PAs, Trimethoprim, pyrimethamine Ethambutol
- (viii) Antimetabolites - They inhibit the biochemical pathway - Sulphonamide, sulfone, PAs, Isoniazid, anticancer, ethambutol,

(ix) Agents that damage cytoplasmic membrane -
polymyxin, colistin amphotericin-B

(x) Agents that inhibit protein synthesis -
Tetracycline, streptomycin gentamycin
Kanamycin

selection of Antimicrobial Agent

① Drug Related factors -

- i) Nature of the drugs
- ii) Risk of drug toxicity
- iii) Selectivity of the drug
- iv) Pharmacokinetic properties of drug.
- v) Compliance

② patient Related factors -

- i) Age of patient
- ii) pregnancy & normal person
- iii) Immuno competency status of patients
- iv) Hypersensitivity

③ pathogen related factors

possibility of drug resistance

(B) Sulfonamide & Co-trimoxazole

Introduction of Sulfonamide

Sulfonamides were the first antimicrobial agents effective against pyogenic bacterial infection.

Sulphonamides are synthetic antimicrobial agent derived from sulfanilic acid & are also called Sulfa drugs.
→ In bacteria these drugs are competitive inhibitors of PABA.

→ molecular structure of Sulphonamide is similar to PABA.

Classification -

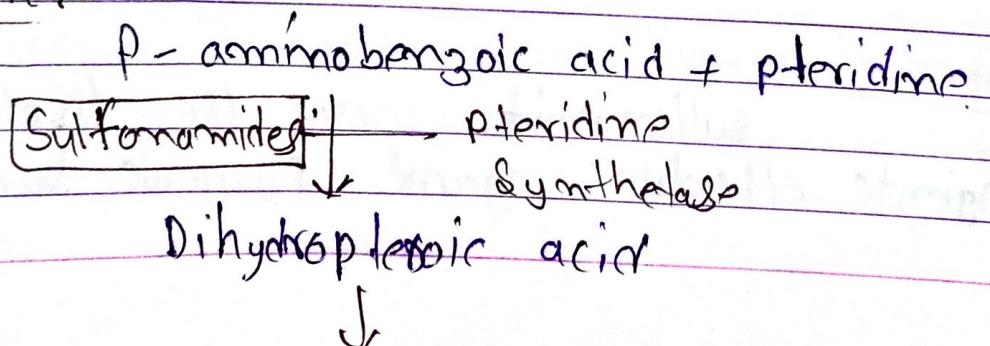
- (1) Short Acting (4-8 hours) - Sulfadiazine
- (2) Intermediate Acting (8-12 hours) -
 - Sulfamethoxazole, sulfamethole
- (3) Long Acting (7 day) -
 - Sulfadoxine, sulfamethypyrazine
- (4) Special purpose Sulphonamides -
 - Sulfacetamide, sulfasalazine
 - malamide silver sulfadiazine etc.

Antibacterial Spectrum -

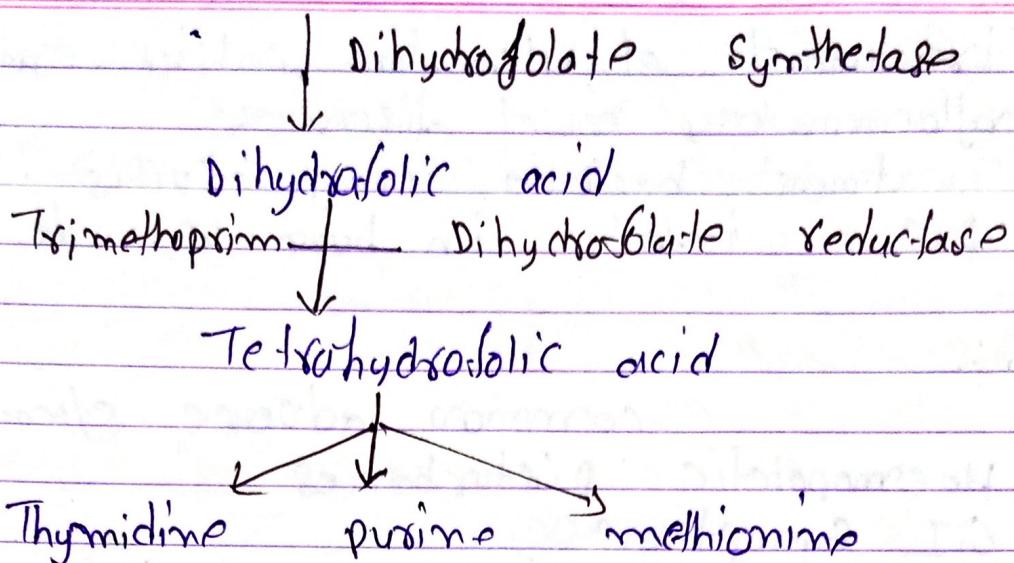
→ Sulphonamides are primarily bacteriostatic against many G(+) & G(-) bacteria.

→ The sensitive bacteria include *Streptococcus pyogenes*, *Haemophilus influenzae*, *H. ducreyi*, *Calymmatobacterium granulomatis*.

Mechanism -



Sulphonamides act by blocking the synthesis of folic acid which is a vitamin that helps make DNA & RBC (blood cell). The stop the bacteria from being able to reproduce so it's considered a bacteriostatic.



Resistance

It act as bacteriostatic antimicrobial agent & inhibit *Mycobacteria* G(+) & G(-) bacteria, *trachomatis*, *chlamydia* & some protozoa.

Pharmacokinetics —

Absorption - Absorb in the GIT.

Distribution - Sulphonamides bind with protein.

Sulfadiazine in free form attains the same conc. in CSF in plasma & freely cross placenta.

metabolism - metabolism in liver.

Acetylation at N4 by non microsomal enzymes.

Excretion - Kidney

uses! —

- ① It is used urinary tract antibiotic
- ② It is used in the treatment of UTI.
- ③ Treatment of malaria
- ④ It is used as 1 line drug for treating cat toxoplasmosis.

- ⑤ Treatment of ulceration colitis, enteritis other inflammatory bowel disorders
- ⑥ Treatment bacteria conjunctivitis.
- ⑦ prevent infection in burn wounds.

Adverse effect -

(1) common adverse effects

- ① Haemopoietic disturbances
- ② GI symptoms
- ③ Renal Toxicity
- ④ Haemopoietic Toxicity
- ⑤ Nervous System Toxicity

Drug interactions ! →

Interfering drugs

- ① Phenybutazone, Salicylate, probenecid
- ② methamphetamine
- ③ sulfonylureas
- ④ Anticoagulants
- ⑤ PABA, local anaesthetics

Effect of interacting drugs

- gt displaced from plasma binding with enhancement activity
- sulfonamides crs. ppt in urine
- protein binding with possible hypoglycaemia
- TD activity enhanced.
- direct inhibition of sulfonamide activity

Cotrimoxazole

Introduction -

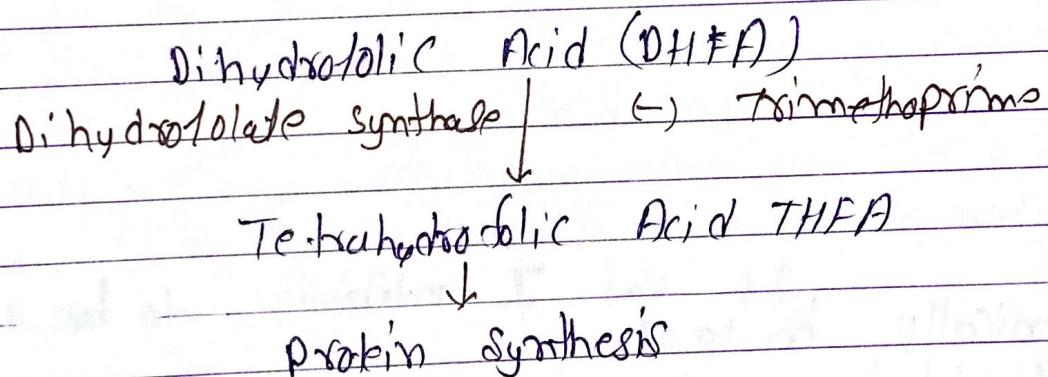
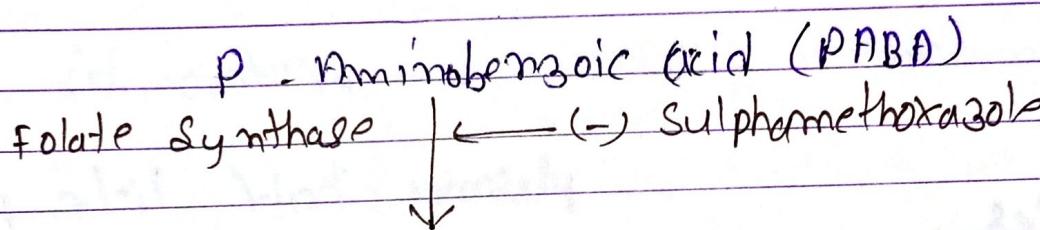
→ Cotrimoxazole is a combination of Trimethoprim with Sulphamethoxazole.

- It shows the better antimicrobial activity than individual drug used alone in equivalent quantities.

Antibacterial Spectrum -

Cotrimoxazole is effective in the treatment of UTIs, respiratory tract infection

Mechanism of Action -



Pharmacokinetics

Absorption - well absorb the body.

Distribution -

metabolism - Liver

Excretion - Urine

- use -
- ① HIV infection
 - ② Typhoidal fever
 - ③ Respiratory tract infection
 - ④ UTI
 - ⑤ STD
 - ⑥ inflammatory infection
 - ⑦ infection by pneumocystic carinii

Adverse effect -

- ① Dermatologic
- ② Gastrointestinal
- ③ Haematologic
- ④ HIV patient

Drug interaction -

- ① Trimethoprim + Warfarin - prothrombin time ↑
 - ② phenytoin + co-trimoxazole - plasma half life of phenytoin ↑
- its T_{1/2}.

(C)

Antibiotics -

- Penicillins -

Introduction -

→ β + and I antibiotic to be used clinically in 1941.

→ It obtained from the fungus penicillium notatum.

MoA - medicinal

Classification -

→ All ~~vise versa~~ part of the classification fall via

Resistance -

Many bacteria are inherently insensitive

to Pn G because the target enzymes and PBPs are located deeper under lipoprotein barrier where Pn G cannot penetrate or have low affinity for Pn G.

→ The primary mechanism of acquired resistance is production of penicillinase

→ Some resistant bacteria become penicillin-tolerant & not penicillin destroying.

→ It is narrow spectrum β -lactamase which opens the β -lactam ring & inactivates Pn G & some closely related congeners.

Pharmacokinetics: →

→ Pn G is acid labile as it gets destroyed by gastric acid. As such less than $\frac{1}{3}$ of an oral dose is absorbed in the active form.

→ Distribution - extracellularly. About 60% in plasma

→ It is little metabolised because of rapid excretion.

The pharmacokinetics of Pn G is dominated by very rapid renal excretion.

use → M. Chemistry

Adverse effect -

- ① Local irritation
- ② Direct toxicity

③ Nephropathy -

- (i) Cation intoxication
- (ii) Haemolytic Anaemia

Drug interaction -

① Anti-coagulants (warfarin & Heparin) - ↑s bleeding

② Aspirin, Furosemide, Indomethacin, sulphonamides
Thiazide Diuretics - prolonging the half life.

③ Contraceptives (Hormonal) - Reduce efficacy.

④ Live vaccines - ↓s effectiveness of live vaccine

⑤ methotrexate - ↑s serum conc.

⑥ probenecid - ↑s Serum conc.

⑦ Tetracyclines - impair bactericidal.

Cephalosporins

Introduction - MC
class I - MC

Antibacterial spectrum -

- progression from the

first to third generation cephalosporins exhibits
 $\text{G}(-)$ spectrum loss of efficacy.

⇒ II & IV G(+) spectrum

MOT - m.c.

Resistance - same penicilino

Pharmacokinetic:-

(1) Absorption -

poorly absorb orally.

The administered via i.v. & i.m. route

(2) Distribution - It distribute very well into body fluid & placental barrier & CSF

(3) Elimination - Tubular secretion &/or glomerular filtration is excreted through bile in the faeces.

Adverse effects -

- ① Allergic reaction
- ② Disulfiram-like effect
- ③ Bleeding

Drug interactions -

① probenecid + cephalosporins - Yes & prolong plasma level.

② Loop Diuretics + cephalosporins - Yes nephrotoxicity

③ Alcohol + cephalosporine -> Alcoholic beverages may produce acute

chloramphenicol

Introduction - m.c.

Antibacterial spectrum -

→ It is a broad-spectrum antibiotic & is active against numerous bacterial strains & other microorganisms such as rickettsiae.

→ The drug is either bactericidal or bacteriostatic depending on the organism

MOA - m.c.

Resistance -

- ① Resistance occurs due to the presence of R factor that codes for acetyl coenzyme A transferase enzyme which inactivates chloramphenicol
- ② Another mechanism involves inability of the antibiotic in penetrating inside the organism
- ③ This change in permeability might be associated with multidrug resistance.

Pharmacokinetics

① Absorption - oral route

② Distribution - Enters normal CSF.

③ Metabolism - Liver to a glucuronide.

④ Excretion - excreted by glomerular filtration
It is also secreted in breast milk.

use - M.C.

Adverse effects -

- ① Bone marrow Depression
- ② Grey Baby Syndrome
- ③ Gastro intestinal
- ④ Neurological

Drug interactions -

- ① chloramphenicol + Alendanil or chlorpropamide or phenobarbital or phenyltoin or Tolbutamide or warfarin — Inhibit the hepatic microsomal enzymes
- ② chloramphenicol + Rifampin / Phenobarbital — ↑↑ the metabolism resulting —
- ③ chloramphenicol + Anticoagulant Therapy — prolonged prothrombin time.
- ④ chloramphenicol + Iron preparations / Vit B₁₂ / folic acid — less absorption of iron Vitamin B₁₂

Macrolides

Introduction - M.C.

MCA - M.C.

use - M.C.

Adverse effect -

cholestatic hepatitis with fever, jaundice
& impaired liver function fever eosinophilia &
rashes.

Individual Drugs -

- ① Erythromycin
- ② clarithromycin
- ③ azithromycin
- ④ Ketolides
- ⑤ clindamycin

① Erythromycin -

Introduction -

Resistance -

- 1) Reduced permeability of the cell membrane or active efflux.
- 2) production of by a macrolide inducible or constitutive methylase
- 3) production of esterases that hydrolyse macrolides.

Pharmacokinetics -

- 1) Food interferes with absorption
- 2) Stearates & esters are fairly acid resistant & somewhat better absorption
oral dosage of 2gm/day

Use -

- ① Diphtheria
- ② Respiratory, neonatal
- ③ pneumonia
- ④ Legionella
- ⑤ dental procedure.

Adverse effects -

cholestatic hepatitis with fever,
Jaundice and impaired liver function.
Fever, eosinophilia & rashes.

- ① Gastrointestinal effect
- ② Liver toxicity.

Drug interaction -

Erythromycin metabolized can inhibit cytochrome P-450 enzyme & increase serum conc.

- ① Theophylline ② oral anticoagulant ③ Cyclosporine
- ④ methylprednisolone ⑤ Digoxin

Clarithromycin

It has improved acid stability & oral absorption compared with erythromycin.

Antibacterial Spectrum -

1) clarithromycin shows activity against M. uprae & Toxoplasma gondii

2) more active against mycobacterium avium complex.

MRA - Same as erythromycin.

Pharmacokinetics -

① Absorption & Distribution -

It is well penetrated

in most tissues with conc equal to or exceeding serum concentrations.

2) metabolism - Liver, 14 hydroxyclarithromycin.

3) Excretion - Eliminated in the urine.

-! Quinolones !-

Classification & Antibacterial spectrum -

Generation	Example	spectrum
1 st	Malidixic acid cinoxacin	G-ve but not pseudomonal species
2 nd	Norfloxacin ciprofloxacin	G-ve some G+ve (S. aureus)
3 rd	Enoxacin ofloxacin levoflaxacin	G+ve & some atypical
3 rd	Levofloxacin	
	Spaflloxacin moxifloxacin gemifloxacin	Same as 2 nd with extended coverage
4 th	Trovafloxacin	Same as 3 rd generation with broad anaerobic coverage

pharmacokinetics - oral absorption

use - M. C.

A

adverse effect - common

Fluoroquinolones

⇒ Fluoroquinolones are the derivatives of quinolone, antimicrobial in which one or more fluorine group is substituted at 6th position.

⇒ Antimicrobial activity towards G+ve cocci & anaerobes.

Classification & Antimicrobial spectrum -

⇒ Same as Quinolones

MRA - Same

p' rokiness - same -

use - same.

Adverse effect - common.

Tetracyclines

introduction - m.c.

classification - m.c.

Antimicrobial spectrum -

① Tetracycline are drug of choice for diseases caused by following microbes
i) Gram(-) infections - Tularaemia, plague & cholera

ii) mycoplasma pneumoniae - pneumonia

iii) Rickettsia - Typhus fever, Q fever

② It also shows activity against pneumococci, staphylococci & group A streptococci

③ combine therapy anti ulcer drugs

MoA - M.C.

Resistance -

Resistance is transmitted by plasmids. Enzymatic inactivation & inhibition of tetracyclines binding to ribosomes are other mechanism of resistance development.

Pharmacokinetics -

Absorption, oral

Distribution - distributes body tissues also cross the placental barrier.

Elimination - glomerular filtration.

They are also secreted in mother milk.

use - M.C.

- 1) Lyme disease
- 2) Rocky mountain spotted fever
- 3) Various types of oculog infectious like
 - i) Acute conjunctivitis & blepharitis
 - ii) Gonococcal
 - iii) Trachoma
- 4) Treatment of many sexually diseases
- 5) Hyponatraemia
- 6) Treating trypomastigotes
- 7) Glaucoma

Adverse effects -

- ① GIT
- ② Bone & teeth
- ③ Hepatotoxicity
- ④ Renal toxicity
- ⑤ vestibular disturbances

Drug interaction -

- ① Tetracycline - oral contraceptive - reduce absorption
- ② Reduces when administered with calcium supplement, iron products, laxative containing Mg. & Vi. antacids. taking 2 hours after

Aminoglycosides -

Introduction - m.c.

Classification - m.c.

MRA - m.c.

Pharmacokinetics -

Absorption - I.m. or I.V. route

Distribution - Being non lipid soluble & poorly cross the BBB. enter tissue cell.

& cross placental barrier cause foetal toxicity
pregnant women

metabolism - liver

Excretion - Excreted in urine by glomerular filtration

use - m.c.

Adverse effect

- ① ototoxicity ② nephrotoxicity
- ③ neuromuscular paralysis ④ allergic reaction.