UNIT-2

General Principles of Chemotherapy

Chemotherapy → It is a drug treatment that uses powerful chemicals to kill fast-growing cells in the body.

Generally, chemotherapy is used for treating cancer.

Anti-biotics → These are substances produced by microorganisms which selectively suppress or kill the other microorganisms at very low concentrations.

Anti-microbialagents → are the synthetic or naturally obtained drugs that attenuate microorganisms.

General Principles

1) Selectivity → All the anti-microbial agents show selective toxicity for the bacterium rather than the host. Same goes for antibiotics also. However, antibiotics may cause certain severe side effects.

2) Therapeutic Index → It is defined as the ratio of toxic dose to the effective therapeutic dose. Higher the therapeutic index, better the antibiotic effect.

3) Categories → Antibiotics are bactericides if they kill the bacterium and bacteriostatic if they reversibly inhibit the growth of bacteria.

4) Anti-biotic susceptibility Testing

The basic measures of the in vitro anti-biotic activity are as follows:

(i) Minimum Bactericidal Concentration (MBC) → It is the minimum concentration of antibiotics that kills 99.9% of the total.

(ii) Minimum inhibitory Concentration (MIC) → It is the minimum concentration that inhibits the visible growth of bacteria.

5) Combination Therapy → Two or more antibiotics together combined.

6) Antibiotic synergism → It occurs when the effects of a combination of antibiotics is greater than the sum of the effects of the individual antibiotics.

Classification of chemotherapeutic agents

1) Based on chemical structure

Antibiotics →

a) β-lactam Antibiotics :- Penicillins, cephalosporins, monobactems
b) Aminoglycosides :- Streptomycin, Gentamycin, Neomycin, etc.
c) Macrolides :- Erythromycin, clarithromycin, Azithromycin
d) Tetracyclines :- oxytetracycline, Doxytetracycline, Minocycline
e) Nitrobenzene derivatives :- chloremphenicol
f) Polypeptide antibiotics :- Colistin

Non-Antibiotics →

a) Sulphonamides :- Sulphadiazine
b) Diaminopyrimidines :- Pyrimethamine
c) Imidazole derivatives :- Miconazole, clotrimazole, Ketoconazole
d) Nicotinic acid derivatives : Isoniazid, Pyrazinamide, Ethionamide

2) Based on Mechanism of Action

(i) Agents that inhibit cell wall synthesis
e.g. penicillins, bacitracin, vancomycin
(ii) cause leakage from cell membranes
e.g. Amphotericin B, Nystatin
(iii) Interefere with DNA function
e.g. Rifampin and Metronidazole
(iv) Interfere with DNA synthesis
e.g. Acyclovir, Zidovudine
(v) Inhibit protein synthesis
e.g. streptomycin, gentamycin, kanamycin.

3) Based on Range of Action

(i) Broad spectrum :- Tetracycline, chloramphenicol
(ii) Narrow spectrum :- Penicillin, Vancomycin

4) Based on Type of action

Bacteriostatics	Bactericidals
Sulphonamides	Penicillins
Tetracyclines	Aminoglycosides
Chloramphenicol	Polypeptides
Erythromycin	Rifampicin
Clindamycin	Isoniazide
	Cephalosporins.

Problems arising due to Anti-microbial Agents (AMA's)

i) Local toxicity - toxicity at the site of administer
ii) Hypersensitivity - allergic reactions
iii) Drug resistance - unresponsiveness towards AMA's.
(iv) Supra infection - infection over the previous infection.

Sulfonamides

Sulfonamides were the first anti-microbial agents effective against (pyogenic) bacterial infections.
→ pus forming

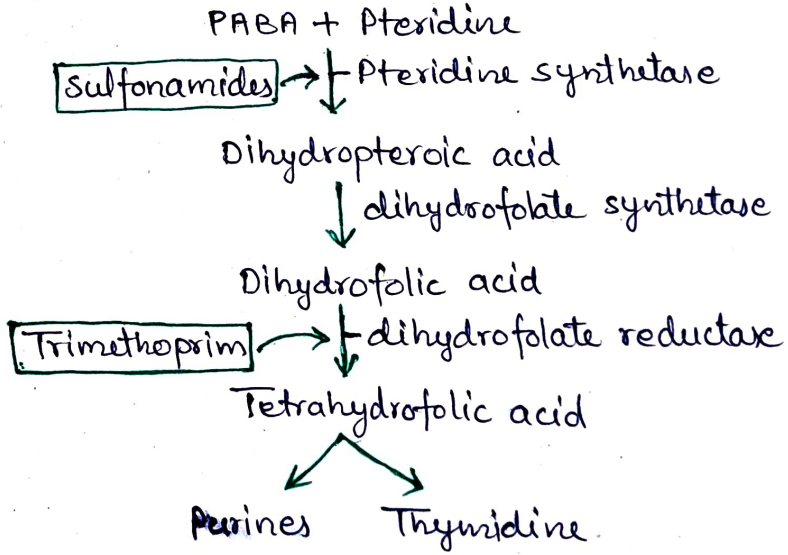
Sulfonamides are synthetic agents derived from sulfonic acid and are also called sulfa drugs.
Sulfonamides are chemically and structurally related to para-aminobenzoic acid (PABA).

Classification

a) Short-acting → 4-8 hrs. e.g. Sulfadiazine
b) Intermediate acting → 8-12 hrs.
e.g. sulfamethoxazole, sulfamoxole
3) Long-acting → 7 days
e.g. Sulfadoxine, Sulfamethopyrazine
4) Special Purpose Sulfonamides
e.g. Sulfacetamide, Mafenide, Sulfasalazine

MoA

Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria.
Bacteria need PABA to synthesize folic acid which is required by bacteria to produce purines and then nucleic acids.
Sulphonamides inhibit the folic acid synthesis which further stops the synthesis of RNA/DNA and ultimately growth of bacteria.



Most of the bacteria have become resistant against sulfonamides. Resistance may be due to following reasons:

(i) Adopt an alternative pathway in folate metabolism
(ii) Produce increased amount of PABA
(iii) The folate synthetase enzyme has low affinity for sulfonamides.
(iv) Cell permeability for sulfonamides is lost.

Pharmakokinetics of sulfonamides

(i) Absorption → absorbed from GIT.
(ii) Distribution → widely distributed and also can easily pass placenta.
(iii) Metabolism → The main pathway of sulfonamides metabolism in Liver is acetylation at N_4 by non-microsomal enzymes.
(iv) Excretion → excreted through glomerular filtration by kidneys.

Adverse effects

(i) Fever, rash, nausea, vomitting, diarrhoea
(ii) Stevens-Johnson's syndrome
(iii) Renal toxicity
(iv) Haemopoeitic toxicity

Drugs

- sulfadiazine
- sulfamethoxazole
- sulfadoxine and sulfamethopyrazine
- sulfacetamide sodium

Cotrimoxazole

Cotrimoxazole is a combination of trimethoprim with sulfomethoxazole. Its better microbial activity than individual drugs.

The ratio for the drug combination of sulfamethoxazole and trimethoprim is 5:1.

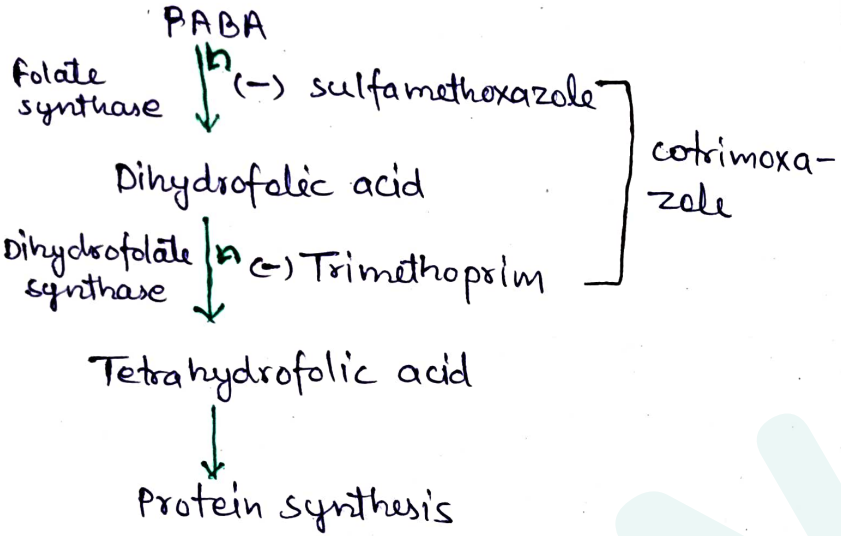
Cotrimoxazole is effective in the treatment of;

- UTIs and RT infections
- Pneumocystis jeroveci pneumonia
- salmonella infections.

MoA

Cotrimoxazole inhibits the synthesis of tetrahydrofolate.

1) Sulfamethoxazole inhibits incorporation of PABA into folic acid.
2) Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.



Pharmakokinetics

(i) absorption occurs throughout the body
(ii) distribution throughout the body
(iii) metabolised in liver
(iv) excreted out through urine

Therapeutic uses

(i) GI infections like shigellosis
(ii) Typhoid fever
(iii) Prostatitis
(iv) STDs (gonorrhoea)
(v) Meningitis, osteomyelitis
vi) Plague
vii) Brucellosis

Adverse effects may be:

(i) Dermatologic (skin reactions)
(ii) Gastrointestinal (nausea, vomitting)
(iii) Haematologic (leukopenia)
(iv) HIV patients (dru-induced fever, diarrhoea)

Some Drug Combinations

1) Trimethoprim + Warfarin: Prothrombin time ↑
2) Phenytoin + cotrimoxazole: Plasma half-life of phenytoin ↑
3) Methotrexate + cotrimoxazole: level of methotrexate ↑

Antibiotics

Refer to Unit-I & Unit-II of Medicinal Chemistry.

Antibiotics are descussed in Detail.