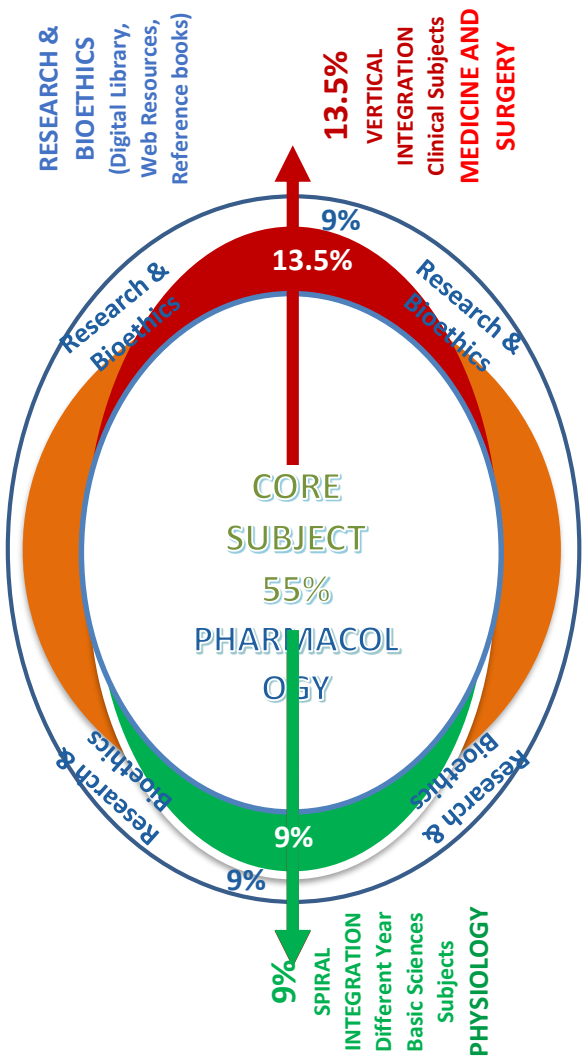
Sulfonamides

Sources:
Bertram G. katzung Basic & Clinical Pharmacology 14th Edition
Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition.

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

Learning objectives

- At the end of the session, the students should be able to:
  - Understand classification of sulphonamides and their anti bacterial spectrum.
  - Discuss mechanism of action and resistance of sulphonamides
  - Enumerate clinical uses and adverse effects of this drug group

Core Subject

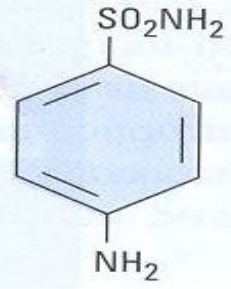
Antimetabolites – Folate Antagonists

- Sulfonamides
- Trimethoprim
- Pyrimethamine
- Co-trimoxazole

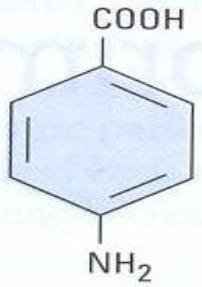
Chemistry - Sulfonamides

- Sulfonamides are derivatives of para-aminobenzenesulfonamide (sulfanilamide) Structural analog of PABA (p-aminobenzoic acid)

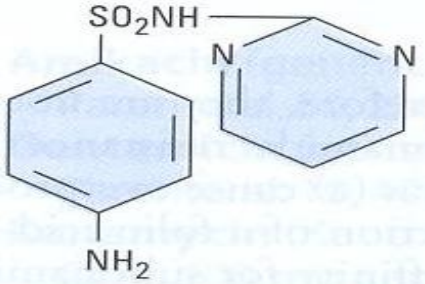
- Different Sulfonamides are produced by substitution at :
  - Amido gp (-SO_2 – NH – R)
  - Amino gp. (-NH2) of sulfanilamide nucleus.
- Differ in chemical, physical, pharmacological and anti bacterial properties.
- More soluble at alkaline than acidic pH



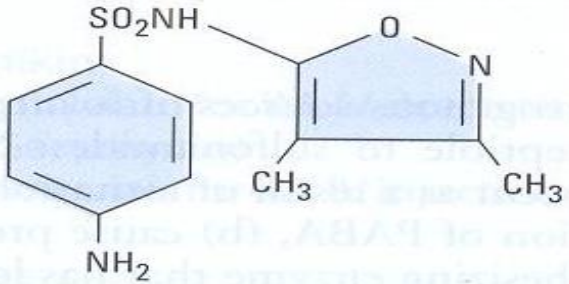
Sulfanilamide



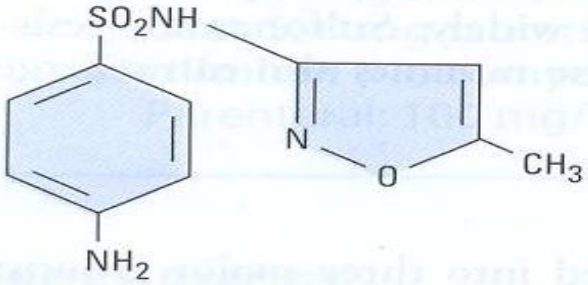
***p*-Aminobenzoic acid (PABA)**



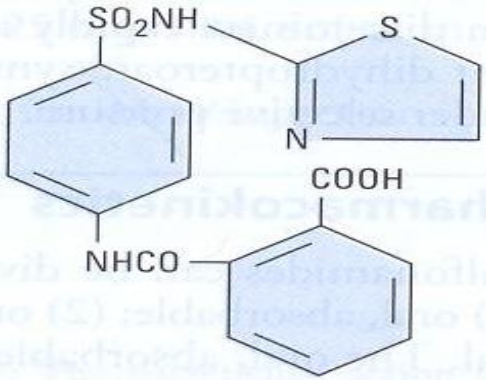
Sulfadiazine



Sulfisoxazole



Sulfamethoxazole



Sulfathalidine
(phthalylsulfathiazole)

Classification - Sulfonamides

A. Oral absorbable agents

B. Oral non-absorbable agents

C. Topical Applications

D. Sulfonamide Combinations

A. Oral absorbable agents

(agents that are absorbed and excreted rapidly)

a. Short Acting (Half life 6-9hrs)

- Sulfacytine
- Sulfisoxazole
- Sulfamethizole

b. Intermediate Acting (Half life 10- 17 hrs)

- Sulfadiazine
- Sulfamethoxazole
- Sulfapyridine

c. Long Acting (Half life 7-9 days)

- Sulfadoxine

Classification – Sulfonamides..

B. Oral non-absorbable agents

(agents that are absorbed very poorly when administered orally and hence are active in the bowel lumen)

- Sulfasalazine (salicylazosulfapyridine)

C. For Topical Application

- Sulphacetamide
- Silver sulfadiazine
- Mefenide

D. Sulfonamide Combination

- **Cotrimoxazole** (Sulfamethoxazole & trimethoprim)
- **Fansidar** (Sulfadoxine & Pyrimethamine)

Pharmacokinetics- Sulfonamides

Divided into three major groups.

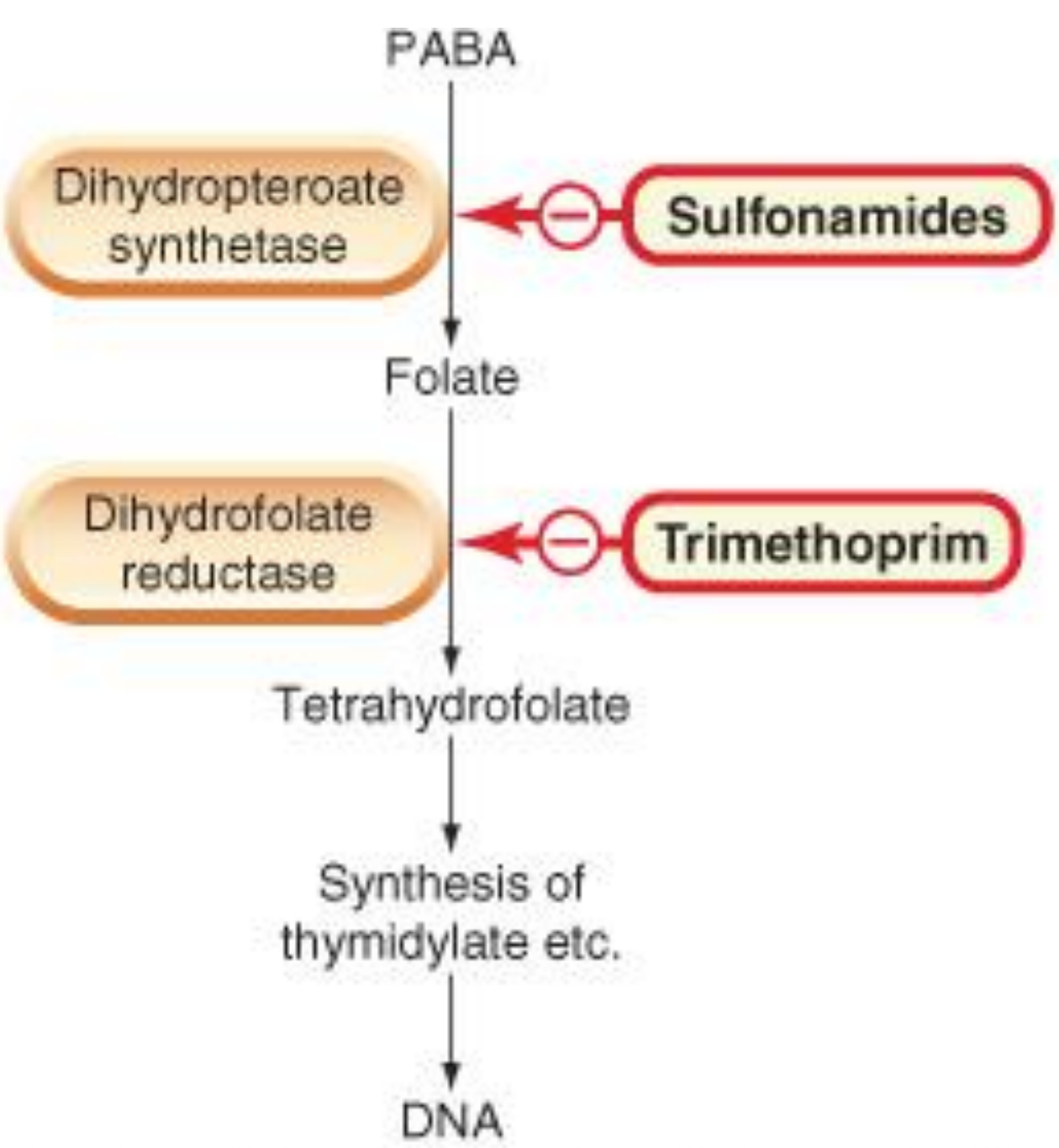
- Oral absorbable
- Oral non absorbable
- Topical

Oral absorbable

Mostly well absorbed after oral administration
On the basis of their half lives divided into **Short , Medium & Long** acting

Distribution: Wide; tissues & fluids including CSF, Placenta & Fetus.
PPB 20 – 90 % to serum albumin
PPL (Peak plasma levels) 2 – 6 hrs
Metabolism –in Liver by Acetylation & Glucuronide conjugation
Excretion – Urine

MOA - Sulfonamides


PABA
Dihydropteroate synthetase
Sulfonamides
Folate
Dihydrofolate reductase
Trimethoprim
Tetrahydrofolate
Synthesis of thymidylate etc.
DNA

Horizontal Integration-Pathology

Antibacterial Spectrum - Sulfonamides

- G +ve , G-ve bacteria
- Some enterobacteria, E.Coli, Shigella, Salmonella, Klebsiella
- Nocardia
- Chlamydia trachomatis
- Some protozoa.

Core Subject

Resistance - Sulfonamides

Resistance to Sulfonamides can result from :

- Overproduction of PABA
- Production of folic acid synthesizing enzyme that has low affinity for sulphonamides
- Impaired permeability to sulphonamides

Vertical Integration-Medicine

Therapeutic Uses Sulfonamides

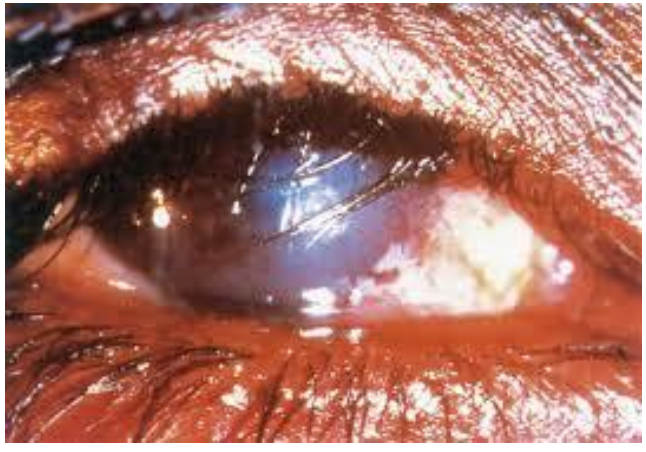
Rarely used as single agents

I. As Topical Agents in
   - Adjunctive therapy for Trachoma (Na -Sulfacetamide)
   - Bacterial Conjunctivitis--- (Na - Sulfacetamide)
   - Prevention of infection of burn wounds (Silver sulfadiazine, Mafenide)

II. UTI: Short & intermediate acting drugs.

III. Ulcerative Colitis, enteritis, other inflammatory bowel diseases (Sulphasalazine)

Trachoma



Therapeutic Uses Sulfonamides…

IV. Rheumatoid arthritis (Sulphasalazine)

V. Dermatitis herpetiformis (Sulfapyridine)

VI. Used in combination in

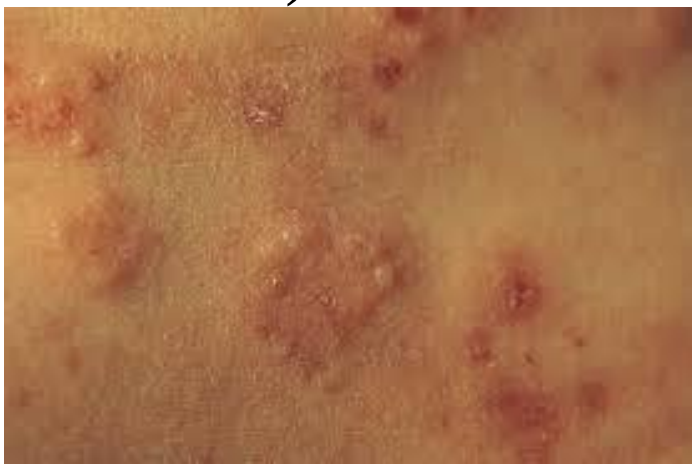
- Resistant Malaria

(Sulfadoxine + Pyrimethamine = Fansidar)

- Acute toxoplasmosis & Leishmaniasis

(oral Sulfadiazine + Pyrimethamine + Folinic acid)

Dermatitis herpetiformis



ADVERSE EFFECTS - Sulfonamides

A. Hypersensitivity Reactions

1. Fever, Skin rashes, exfoliative dermatitis, photosensitivity

2. **Hematopoietic Disturbances** : Hemolytic or Aplastic anemia, Granulocytopenia, Thrombocytopenia, Leukemoid reactions

ADVERSE EFFECTS - Sulfonamides

B. Urinary Tract Disturbances

1. Precipitation in acidic urine- Crystalluria, Hematuria / obstruction .

2. Nephrosis of various types & Allergic Nephritis.

ADVERSE EFFECTS - Sulfonamides

C. Kernicterus in premature babies

D. Haemolysis in Glucose 6-Phosphate Dehydrogenase deficient patients.

Core Subject

Drug interactions

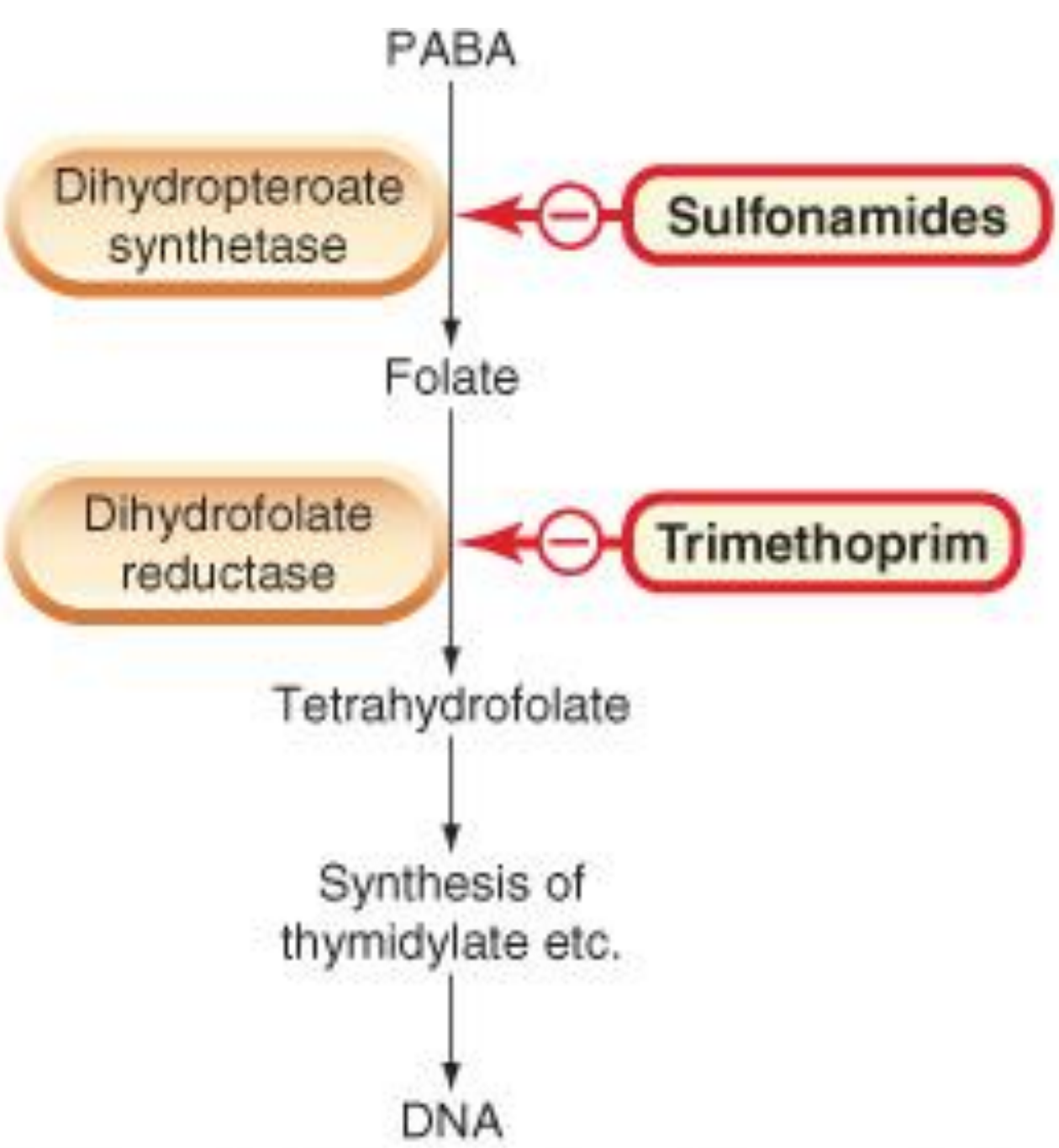
- Competition with warfarin & methotrexate for PPB ---- increase level

Contraindications

- Known hypersensitivity.
- Newborns & infants less than 2 months
- Pregnant woman at term – Kernicterus

MOA –
Trimethoprim & Pyrimethamine

- They selectively inhibit **Dihydrofolate reductase enzyme** (DHFR) which converts Dihydrofolic acid to tetrahydrofolic acid.
- Synthesis of purines & subsequently DNA can not occur.
- Bacterial growth is inhibited
- **Trimethoprim** is 50000 times < efficient in inhibiting mammalian DHFR.
- **Pyrimethamine:** Equally inhibits protozoal & mammalian DHFR


PABA
Dihydropteroate synthetase
Sulfonamides
Folate
Dihydrofolate reductase
Trimethoprim
Tetrahydrofolate
Synthesis of thymidylate etc.
DNA

TRIMETHOPRIM

Chemistry: Trimethoxybenzyl Pyrimidine

Chemically related to pyrimethamine; folate antagonist.

Pharmacokinetics: **Given orally, fully absorbed from GIT.**

Wide Distribution in body fluids and tissues, including CSF

Concentrates in prostatic & vaginal fluid; (more acidic than plasma)

PPB: 65 – 70 % Excretion : 50-60- in urine within 24 hrs.

Clinical Use: Acute UTI: 100 mg –twice daily.

CO-TRIMOXAZOLE

CO-TRIMOXAZOLE

Combination of Trimethoprim with Sulfamethoxazole

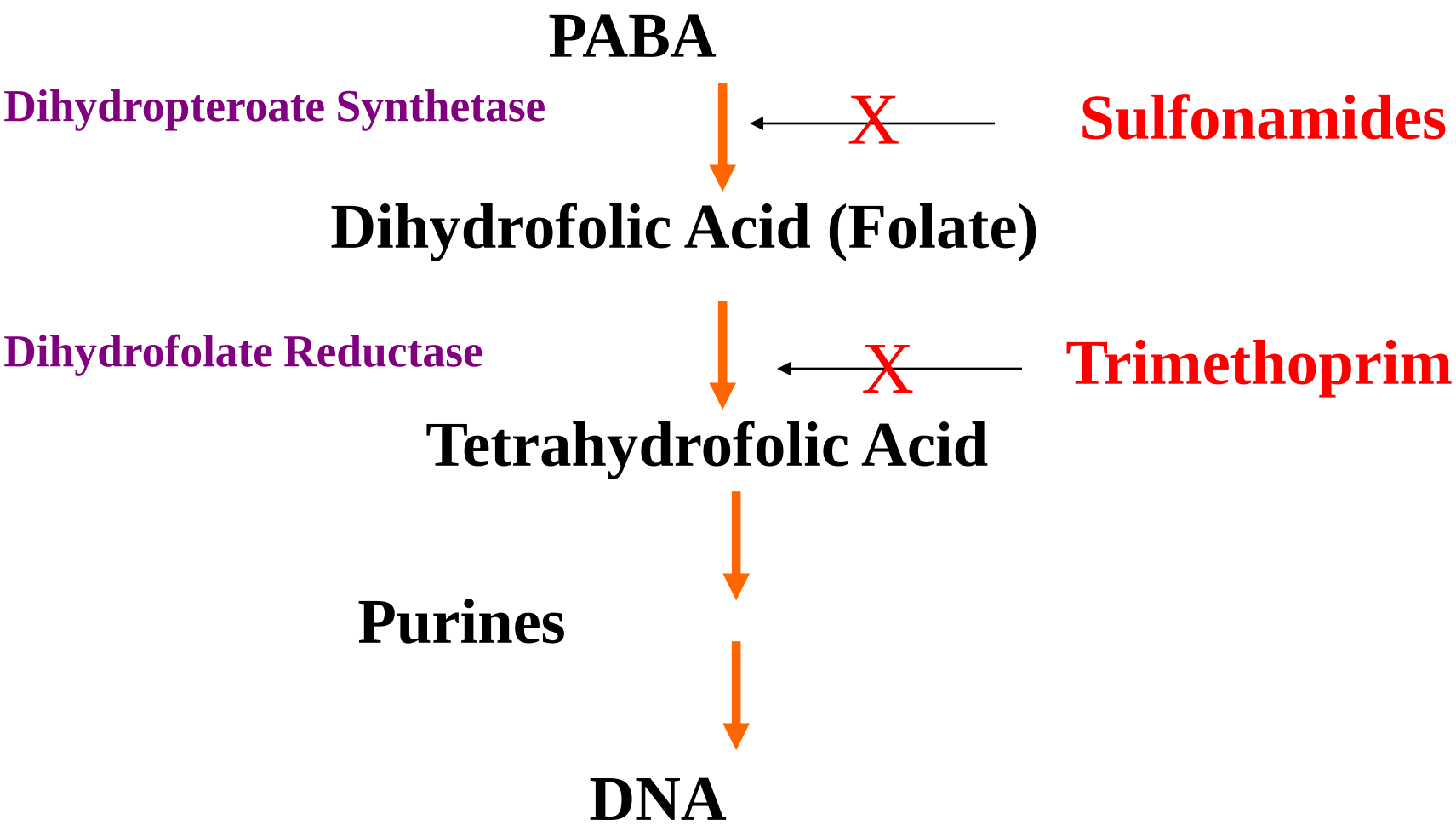
- Trimethoprim – 80 mg
- Sulfamethoxazole – 400 mg

Ratio 1:5

PHARMACOKINETICS - CoT

- Can be given orally or I/V
- **Trimethoprim**: well absorbed from GIT & distributed widely in body fluids& tissues (more lipid soluble than sulfamethoxazole, has large Vd)
- When given in 1:5 ratio
- **Excretion** : 30-60 %--- Trimethoprim / metabolites &
  50-60 %---Sulfamethoxazole / metabolites
  are excreted in urine within 24 hrs

MOA


PABA
Dihydropteroate Synthetase
X
Sulfonamides
Dihydrofolic Acid (Folate)
Dihydrofolate Reductase
X
Trimethoprim
Tetrahydrofolic Acid
Purines
DNA

Resistance

Resistance to Trimethoprim can result from :

- Reduced cell permeability
- Overproduction / alteration of Dihydrofolate reductase – Less binding.

Alteration commonly plasmid- encoded, may be due to mutation.

Horizontal integration- Pathology

Antibacterial Spectrum

- Broader
- Resistant UTI & Resp infections
- Pneumocystis jiroveci (carini) infections
- Listeria monocytogenese - Ampicillin resistant
- Salmonella, Shigella — resistant cases.

Vertical integration- Medicine

Clinical uses - CoT

1. Pneumocystis Jiroveci Pneumonia in AIDs patient
   (For treatment & prevention)

2. Respiratory, ear & sinus infections by
   Hemophilis influenzae, Pneumococcus, Moraxella Catarrhalis, Staphylococcus (methicillin sensitive /resistant) Klebsiella Pneumoniae

3. Nocardosis. ---DOC

4. Shigellosis, Typhoid Fever, cholera-- Back up drug

Clinical uses - CoT

5. G-ve bacterial sepsis by resistant micro-organisms specially Enterobacter & Serretia.

6. For treatment & prophylaxis of recurrent UTI

7. Prostatitis by susceptible micro-organisms.

Advantages of Co-trimoxazole

- **Synergistic effect – Potentiation.**
- **Bactericidal (Individual drug - bacteriostatic)**
- **Wider antibacterial spectrum than individual drugs**
- **More efficacy than individual drugs**
- **Less dose of each drug**
- **Less incidence of toxicity**

Adverse Effects - CoT

1. Hematological

- Trimethoprim (Anti-folate) Megaloblastic Anemia, Leukopenia, Granulocytopenia

Prevented by simultaneous administrations of folinic acid

6 – 8 mg/d which does not enter bacteria.

2. Due to Sulphamethoxazole--- A/E of sulphonamides

Nausea, Vomiting, Rashes, Fever, Vasculitis.

Occasionally: renal damage & CNS disturbances

Haemolysis in Glucose 6-Phosphate Dehydrogenase deficient patients

Adverse Effects - CoT

3. AIDS patients with pneumocystis pneumonia show high incidence of fever, rashes, leukopenia, diarrhea, elevation of hepatic aminotransferases, hyperkalemia, hyponatremia.

4. D/Is

With Warfarin– prolonged prothrombin time.

Metabolism of Phenytoin inhibited.

Methotrexate displaced from PPB sites--- Increased levels

Research

- Sohani ZN, Butler-Laporte G, Aw A, Belga S, Benedetti A, Carignan A, Cheng MP, Coburn B, Costiniuk CT, Ezer N, Gregson D. Low-dose trimethoprim-sulfamethoxazole for the treatment of pneumocystis jirovecii pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial. BMJ open. 2022 Jul 1;12(7):e053039.

- Mori S, Ueki Y, Miyamura T, Ishii K, Hidaka T, Yoshitama T, Nakamura K, Suenaga Y. Outcomes and risk factors for mortality in Pneumocystis pneumonia patients with rheumatoid arthritis: A multicentre retrospective cohort study. Modern Rheumatology. 2023 Jul 1;33(4):723-31.

Artificial Intelligence

- Aher P, Surana K, Ahire E, Patil D, Sonawane D, Mahajan S. Development and Validation of RP-HPLC Method for Quantitative Determination of 4-Amino Benzene Sulphonamide in Sulphonamide Hydrochloride. Trends in Sciences. 2023 Mar 15;20(6):5209.

- Khan S, Iqbal S, Shah M, Rehman W, Hussain R, Rasheed L, Alrbyawi H, Dera AA, Alahmdi MI, Pashameah RA, Alzahrani E. Synthesis, in vitro anti-microbial analysis and molecular docking study of aliphatic hydrazide-based benzene sulphonamide derivatives as potent inhibitors of α-glucosidase and urease. Molecules. 2022 Oct 21;27(20):7129.

Bioethics

- Use of sulphonamides in specific conditions

EOLA

- Sulphonamides are competitive inhibitors of which of the following bacterial enzyme

a. Dihydrofolate reductase
b. Dihydropteroate synthetase
c. RNA Polymerase
d. Topoisomerase
e. Transpeptidase

- A baby developed the signs and symptoms of kernicterus after being given an antibiotic. Which is the most likely drug

a. Ampicillin
b. Chlormphenicol
c. Cotrimoxazole
d. Gentamycin
e. Tetracyclin

- Which of the following is the most common causative agent of UTI and is sensitive to trimethoprim-sulfamethoxazole

a. Bacteriods fragilis
b. Chlamydia trachomatis
c. E. coli
d. Enterococcus
e. Pseudomonas aeruginosa


Thank You!