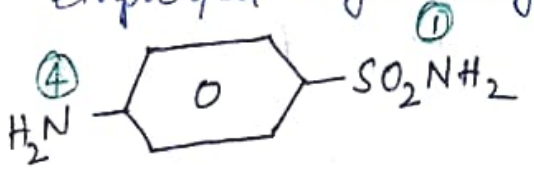
Sulphonamides

→ The first effective chemotherapeutic agents to be employed systemically.



Basic structure

→ Nature :→ White powder, insoluble in H_2O & Acidic in nature.

When treated with bases, it forms a salt which is insoluble in Nature. Whereas Sodium salt are very soluble.

For Eg :- Sodium Sulfacetamide → Soluble in H_2O
pH → Basic (very high) → damages the tissues
∴ used topically.

History :→ PRONTOSIL → Sulfonamide group.

→ 1933, Foerster reported that prontosil given to 10-month old infant with staphylococcal septicemia and achieving a dramatic cure.

→ Also used in puerperal sepsis, meningiococcal infections etc

→ Development of Carbonic anhydrase inhibitor type diuretics & Sulfonylurea hypoglycemic agents were followed by development of Sulfonamide antibiotics.

→ For discovery of Prontosil value, Domangk was awarded Nobel prize.

Chemistry :→ Derivative of Para-Aminobenene Sulfonamide [Sulfenilamide]

The important feature is the Sulfur linked directly to benzene ring.

→ Para-NH_2 group is essential and can be replaced only by moieties that can be converted invivo to a free amino group.

→ Substitutions made in N_1 ($-NH_2$) group have variable effects on Antibacterial activity of molecule.

→ N_1 substitution by Heterocyclic aromatic nuclei yeilds highly potent compounds.

Classification :→

Based on Rate of absorption and excretion.

I. Rapidly absorbed and Rapidly excreted

	$t_{1/2}$
Sulfisoxazole	5-6 hrs
Sulfamethoxazole	11 hrs
Sulfadiazine	10 hrs.

II. Poorly absorbed & remain active in bowel lumen
Sulfasalazine

III. Topically used : Sulfacetamide
Silver Sulfadiazine
Mefenide

IV. Long acting : Sulfadoxine 100-230 hrs.

Based on Uses :→

I. Used in Treatment of Systemic infections.

Short acting → Sulfadiazine, Sulfamethizole
~~Sulfacetamide~~
Sulfafurazone, Sulfadimidine

Intermediate acting :→ Sulfamethoxazole

Long acting :→ Sulfamethoxy pyridazine
Sulformethoxine, Sulfadoxine,
Sulfadimethoxine

II. Used in the treatment of ulcerative colitis
Sulfasalazine.

III. Used topically : Silver Sulfadiazine, Sulfacetamide,
Mefenide.

Antibacterial spectrum :→

Active against both gram +ve & gram -ve bacteria.

Bacteriostatic in Nature.

Susceptible strains :→ Streptococcus pyogens
" pneumoniae
Haemophilus influenzae
" ducreyi
Nocardia
Actinomyces
Calymmato-bacterium granulomatis
Chlamydia trachomatis

Staphylococci
Gonococci
Pneumococci
Meningiococci

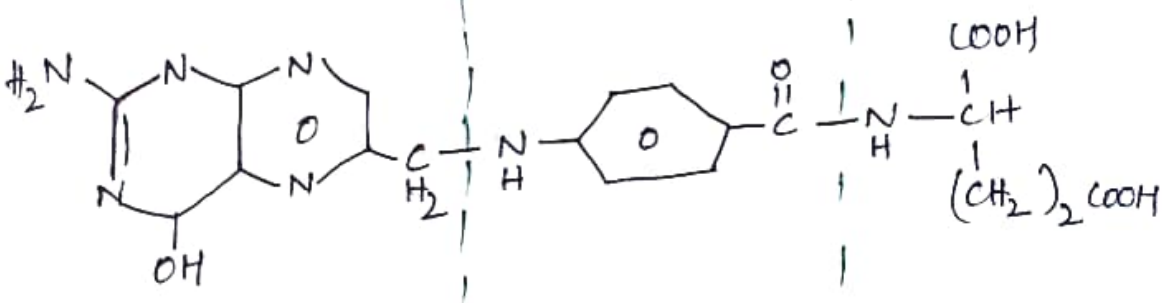
MIC for chlamydia ~~4-64~~ 0.1 µg/ml

E.coli 4-64 µg/ml

Peak plasma conc^{n}. in vivo ⇒ ~100-200 µg/ml.

Resistant strains :→ Neisseria meningitidis
Shigella & E.coli from UTI.

Mechanism of Action :→ competitive inhibitors of dihydropteroate synthase



Pteridine | PABA | Glutamic acid.

Folic Acid

Folic acid synthesis :→

PABA + pteridine

↓ dihydropteroate synthase (X) Sulfonamide

Dihydropteroic acid

↓ Glutamate

Dihydro folic acid

↓ NADPH → NADP + dihydro folic acid reductase (X) Trimethoprim

Tetra hydro folic acid

→ Dihydropteroate synthase is a bacterial enzyme responsible for the incorporation of PABA into dihydropteroic acid, the immediate precursor of folic acid.

→ Sulfonamides are structural analogs of PABA & prevent normal bacterial use of PABA for the synthesis of folic acid.

→ Synthesis of folate is a metabolic pathway found only in bacteria but not in humans. Humans can't synthesize folic acid but are absorbed from the diet via transport mechanism across the cell.

→ Cells utilize folate in the form of Tetrahydrofolate as a cofactor in thymidylate synthesis.

→ Bacteria which use preformed folic acid can't be killed / stopage of growth by sulfonamides.

→ Synergistic effects : combination with trimethoprim

Development of Resistance :→

→ Resistance once developed, is usually is persistent and irreversible.

→ Acquired resistance doesn't involve cross resistance

Resistance is the consequence of altered enzymatic constitution of Bacterial cell. The alteration may be characterized by.

→ lower affinity of dihydropteroate synthase for sulfonamides

2) Decreased bacterial permeability or Active efflux of the drug.

3) An alternative metabolic pathway for synthesis of essential metabolite

4) ↑ production of an essential metabolite or drug antagonist.

5) Plasmid-mediated resistance: is due to plasmid encoded drug-resistant dihydropteroate synthase.

Pharmacokinetics :→

Absorption :→

→ Except sulfasalazine, All other drugs are absorbed rapidly from GIT. (Small intestine).
70-100% absorbed and can be found in urine within 30 minutes.

→ Small intestine is the major site of absorption. However, some drugs are absorbed from stomach.

→ Absorption from other sites like vagina, respiratory tract or abraded skin is variable & unreliable, but sufficient amount may enter the body to cause toxic reactions.

Peak plasma levels within 2-6 hrs.

Distribution :→

→ Distributed throughout all tissues of the body.

→ Distributed in pleural, peritoneal, synovial, ocular, etc.

→ Adequate doses of Sulfadiazine & sulfisoxazole attain Conc? in CSF upto 50-80% of that of plasma levels.

→ Varying degree of plasma proteins especially to albumin. Atleast 50% bound to plasma proteins. Drugs with high pKa exhibit low degree of protein binding & vice versa.

→ Crosses placental barrier & reach fetal circulation. The Conc? attained in the fetal tissues cause both antibacterial and toxic effects.

Metabolism :→

→ Metabolism in liver to metabolic derivative N_4-acetylated sulfonamide. It is not active but toxic potential is retained.

→ Acetylation occurs differently with different drugs.

→ Rapid acetylators : 62-90% metabolised
Slow acetylators : 40-53% " "

→ Acetylated form → is devoid of antibacterial activity
→ Possess toxic potentialities of parent drug
→ poorly soluble in Urine → causing crystalluria & renal complications.

→ $t_{1/2}$ depends on renal function.

Protein Binding :→

→ Bound sulfonamide has much less Bacteriostatic activity and cannot normally pass into tissue fluids or BBB.

→ Since the bound form is not available for renal excretion, protein binding helps to prolong their action.

→ The highly protein bound sulfonamides are not so effective in the treatment of acute infections bcoz of low plasma levels of free sulfonamide.

Excretion :→

→ Eliminated from body in unchanged & metabolised form. through kidneys.

→ also eliminated through Bile, milk & other secretions

→ May ppt. in urine → crystalluria.

Adverse effects :→

→ Drug fever, Urticaria

→ Crystalluria → Can be Treated with ↑ Water intake to make daily Urine volume 1200 ml/day in adults. (or)

Alkalinize Urine → Acidic drugs in alkaline pH will be more ionised. No reabsorption and excretion done quickly.

→ Acute Hemolytic anemia → seen in people with glucose-6-phosphate dehydrogenase deficiency.
↓
(protect RBC)

→ Agranulocytosis → ~0.1% of patients

→ Aplastic anemia, Thrombocytopenia → due to depression of Bone marrow.

→ Hypersensitivity Reactions → Variable. (long acting drugs)
↑ type
Erythema multiforme of Stevens-Johnson
Drug fever, Eosinophilia, Serum sickness
↓
may develop within 2 weeks of therapy.
fever, joint pain, Urticaria, Bronchospasm, Leucopenia

→ Anorexia, Nausea, Vomiting in 1-2% of patients

→ In Newborn, admn. of Sulfonamides may lead to displacement of Bilirubin from plasma albumen. The free Bilirubin deposited in Basal ganglia & Subthalamic nuclei of Brain → encephalopathy called Kernicterus.

→ CNS toxicity → Confusion, depression, Ataxia, fatigue, Acute psychotic episodes, peripheral neuritis etc.

→ Not to be given in pregnancy → cross placental barrier & secreted in milk.

Drug Interactions :→

1→ oral anticoagulents (Warfarin) → Albumin displacement
↓
Same carrier protein
↓
excessive bleeding

2→ sulfonylureas → potentiate effects of hypoglycemic activity

3→ Hydantoin → Synergistic activity due to inhibition of metabolism . ∴ actions ↑

T. Uses :→

→ In UTI
→ NOCardiosis
→ Toxoplasmosis
→ prophylactically used in rheumatic fever; Streptococcal infections in people sensitive to penicillin.