Sulphonamides

- **synthetic antimicrobial agents**
  - simply called **sulfa drugs**
- Primarily **Bacteriostatic** drugs
  - Cellular & humoral immunity of host is essential for eradication of the infection.

Spectrum

- **Gram positive & Gram negative**
  - Emergence of resistance
  - Usefulness has declined

Susceptible microorganisms:

- **Streptococcus pyogenes**
- **Streptococcus pneumoniae**

- **Nocardia, Actinomycetes, Calymmato bacterium granulomatis & Chlamydia trachomatis**

- H. influenzae
- H. Ducreyi

Organisms now Resistant

- N. Meningitidis - Serogroups A, B, & C
- Shigella
- E.Coli

Mechanism of action

- Competitive inhibitors of dihydropteroate synthase

  bacterial enzyme responsible for the incorporation of PABA into dihydropteroic acid

  immediate precursor of folic acid.

Pteridine + PABA/ sulpho..

↓ Dihydropteroate synthase

Dihydropteroic acid

↓

Dihydrofolic acid

↓ Dihydrofolate reductase

Tetrahydrofolic acid

- Folic acid is used for the synthesis of purines and thymine
  - Required for formation of DNA
  - Therefore folic acid is required for replication of cellular genes.
- Important function of folic acid is to promote growth so in its absence organism grows very little.

Sulfonamides are

- Also anti-metabolites
  - i.e. They block the essential enzymes of folate metabolism.

Mechanism of action

- Structural analogues of **PABA (para-amino benzoic acid)**
- Sulfonamide gets incorporated to form an **altered folate** which is metabolically injurious.

- Sensitive micro-organisms are those that must synthesize their own folic acid. Bacteria that can use preformed folate are not affected.
- Bacteriostasis induced by sulfonamides is counteracted by PABA competitively.
- Mammalian cells are not affected, they require preformed folic acid and cannot synthesize it

Absorption, Fate & Excretion

- Absorbed rapidly from GIT
  - Small intestine(major site) & stomach
- Distributed throughout the body
  - Readily enter pleural, peritoneal, synovial, ocular fluids
  - Conc. 50-80% that in blood

- Readily cross placenta (antibacterial + toxic effects)
- Metabolised in **liver**,
- Excreted in **urine**
  - Small amounts in **faeces**, **bile**, **milk** and other **secretions**.

Classification

- Agents that are absorbed & excreted rapidly
  - Sulfisoxazole
  - Sulfamethoxazole
  - Sulfadiazine
- Agents that are absorbed very poorly when administered orally, hence active in bowel lumen
  - Sulphasalazine

- Long acting sulphonamides absorbed rapidly excreted slowly
  - Sulfadoxine
- Agents used topically
  - Sulfacetamide
  - Mafenide
  - Silver sulfadiazine

Pharmacological properties of Individual Sulphonamides

Sulfisoxazole

- Rapidly absorbed & excreted sulfonamide with excellent antibacterial activity
- Half life 5-6 hrs
- High solubility, no crystalluria
- Replaced less soluble agent.
- Bactericidal activity in urine.

Sulfisoxazole acetyl

- Tasteless – oral use in children
- Fixed dose combination with erythromycin ethylsuccinate for children with otitis media

Sulfamethoxazole

- Close congener of sulfisoxazole
- Half-life :8-12 Hrs
- Fixed dose combination with **trimethoprim**
- High fraction is acetylated, which is relatively insoluble **crystalluria** can occur.
- Precautions to avoid crystalluria

Poorly absorbed sulfonamides

Sulfasalazine

- poorly absorbed from GIT
- **Active in bowel lumen**
- **Ulcerative collitis, regional enteritis**
- Intestinal bacteria - sulfapyridine (toxic)

+ 5 aminosalicylate (effective agent in IBD)

Sulfonamides for topical use

Sulfacetamide

- Extensively-management of Opthalmic infections (Trachoma/Inclusion conjunctivitis)
  - Penetrates ocular fluids & tissues in high concentrations.
  - Advantage: very high aqueous conc. not irritating to eyes & are effective against susceptible microorganisms.

- Sulfacetamide sodium 10-30%

Silver Sulfadiazine

- Inhibits growth of nearly all pathogenic **bacteria** & **fungi**
- Used topically to reduce incidence of infections of wounds from burns
  - Slowly releases silver ions - antimicrobial action
  - DOC for prevention of infection of burns.

Mafenide

- Prevention of colonization of **burns** by a variety of gram negative & gram positive bacteria
  - Limited usefulness: inhibits carbonic annhydrase metabolic acidosis

LONG ACTING SULFONAMIDES

Sulfadoxine

- Long acting
- Half-life :7-9 days
- Combination

Sulfadoxine 500mg + Pyrimethamine 25 mg

Prophylaxis & **treatment** of malaria caused by chloroquine resistant strains of plasmodium falciparum.

- Clinical curative
- Three tablets single dose
- Both long half-life

Advantage of combination

- **Good compliance** due to single dose therapy

Resistance to sulfonamides

- Resistant mutants
  - Produce increased amounts of **PABA**
  - Their **Folate synthetase** enzyme has low affinity for sulfonamides
  - Adopt **alternate** pathway of folate metabolism.


Untoward reactions
to sulphonamides

Crystalluria

- **Older, less soluble** sulphonamides
- Insoluble in acidic urine
- Precipitate, forming crystalline deposits that can cause urinary obstruction.

- Fluid intake sufficient to ensure a daily urine volume of at least 1200ml
- Alkalinization of the urine if pH low
- **Sulfisoxazole** more soluble, incidence of this problem is low

kernicterus

- Administration to **newborn infants esp. premature**
  - Sulfonamides displace bilirubin from plasma albumin.
  - Free bilirubin is deposited in basal ganglia & sub-thalamic nuclei of the brain causing an encephalopathy called **kernicterus**.

- **Hypersenstivity reactions**
- **Acute hemolytic anaemia** in G-6PD deficient patient
- **Agranulocytosis -** sulfadiazine
- **Aplastic anaemia**
- **Anorexia, nausea, vomiting**

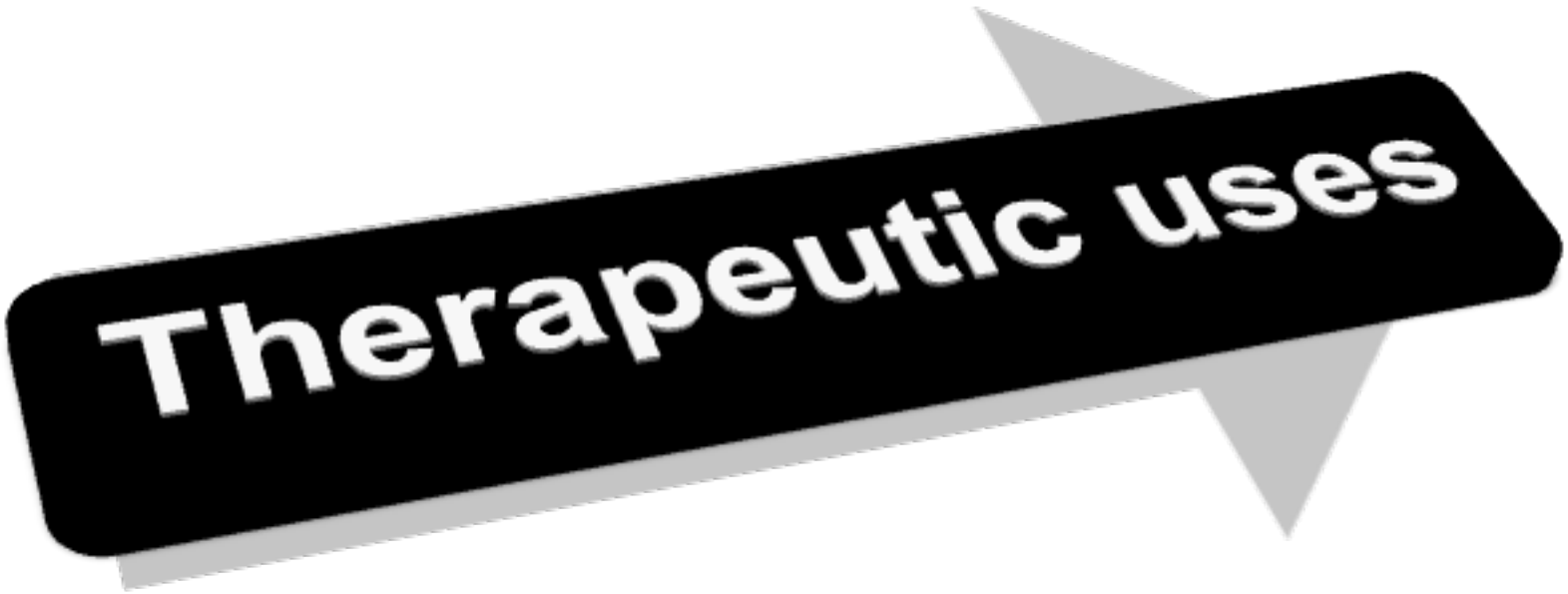

Drug interactions

- **Potentiate** the effect
  - Oral anticoagulants
  - Sulphonylurea hypoglycaemic agents
  - Hydantoin anticonvulsants

  Inhibition of metabolism of these drugs + displacement from albumin.

  Dosage adjustment

- Cautious use in patients with **impaired renal functions**.


Therapeutic uses

- **Urinary tract infections**
  - No longer therapy of first choice
  - **Quinolones**
  - **Co-trimoxazole**
  - **Fosfomycin**
  - **Ampicillin**
  - **Urinary antiseptics**

- **Nocardiosis**
  - **Sulfisoxazole/Sulphadiazine;**
  - Complete recovery with adequate treatment
  - 6-8 g daily/80-160 µg/ml
  - Schedule continued for several months after all manifestations have been controlled.

Toxoplasmosis

- **Pyrimethamine-sulphadiazine combination is Tt of choice**
- Pyremethamine loading dose- 75 mg
  25 mg orally per day
- Sulphadiazine 1 g orally every 6 hrs.
- **Folinic acid 10 mg orally every day.**
  For 3-6 weeks.
- **2 litres of fluid intake daily.**

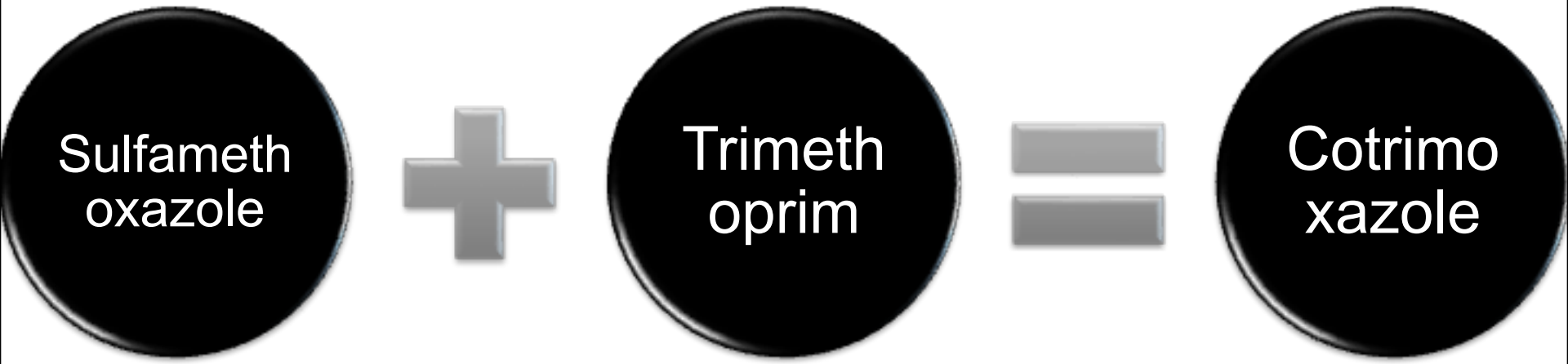
- **Prophylaxis & treatment of malaria**
- **Prophylaxis of streptococcal infections** in patients hypersensitive to Penicillin.
  - Sulphonamides are as efficacious
  - Should be used without hesitation in patients hypersenstive to penicillins

Topical uses

- Used extensively in the management of **Opthalmic infections**
- Used topically to reduce incidence of infections of wounds from **burns,** DOC.
- **Ulcerative collitis, regional enteritis**

COTRIMOXAZOLE

COTRIMOXAZOLE



Sulfamethoxazole

- competitive inhibitors of **dihydropteroate synthase**

Trimethoprim

- **Trimethoprim inhibitis dihydrofolate reductase**
- prevents reduction of dihydrofolate to tetrahydrofolate

Pteridine + PABA

↓ Dihydropteroate synthase

Dihydropteroic acid

↓

Dihydrofolic acid

↓ Dihydrofolate reductase

Tetrahydrofolic acid

- Acts on **Sequential steps**
- **Synergism**
- **Two drugs interfere with two successive steps in the same metabolic pathway& produce supraadditive effect. (Sequential blockade)**
- Individually both are bacteriostatic but the combination has cidal effect
- Chances of development of bacterial resistance are also greatly reduced

- **Pk properties of both the drugs match closely**

Synergism

- Optimal ratio of the **concentrations** of the two agents for Synergism **20:1**
  - **Sulfamethoxazole** : **Trimethoprim**
    Combination is formulated to achieve a sulfamethoxazole conc. in vivo 20 times greater than that of trimethoprim

- Trimethoprim is a highly selective inhibitor of DHFRase of lower organisms
- Approx. 1,00,000 times more drug is required to inhibit human DHFRase than than bacterial enzyme
  - Do not interfere with folic acid metabolism in human beings
- Mammalian cells preformed folate from the diet

Spectrum

- Broad spectrum
  - Both Gram negative & Gram positive

Combination:

- **Chlamydia, diptheriae, N. meningitidis**
- **S. aureus, S. pyogenes, proteus,**
- **Pneumocystis carinii,**
- **Salmonella typhi, shigella, Klebseilla**,
- Resistance can develop when trimethoprim is used alone

- Resistance to co-trimoxazole is reportedly formed in almost 30 % of urinary isolates of **E. coli**.

Resistance

- **Mutational**

- **Plasmid** mediated acquisition of **altered DHFRase** having low affinity for trimethoprim.

Adverse effects

- No evidenve of folate deficiency in **normal** person at the **recommended** doses
- Folate deficiency can occur in patients **deficient in folate in diet**:
  - Megaloblastosis,
  - leukopenia,
  - thrombocytopenia,

- Hypersensitivity reactions involving skin
  - AIDS patients frequently have hypersenstivity reactions with co-trimoxazole
- Nausea vomiting
- Glossitis
- Stomatitis
- CNS: headache ,depression, etc

Therapeutic Uses

Urinary tract infections

- Uncomplicated lower urinary tract infections
  - Highly effective for enterobacteriacae

Chronic & Recurrent UTI Women in reproductive age group

- Post coitally.
  - S; 200 mg +T; 40 mg/day.
  - Or 2-4 times once/twice per week.
- Presence of trimethoprim in vaginal secretions.

Bacterial prostatitis

- Presence of therapeutic concentrations of trimethoprim in prostatitic secretions

Respiratory tract infections

- Acute & chronic bronchitis

- Acute otitis media in children
- Acute maxillary sinusitis. & H. influenzae (if susceptible)

GI tract infections

- **Alternative to fluoroquinolone for treatement of Shigellosis.**
- Second line drug for **typhoid** fever.

Infection by Pneumocystis carinii/ jiroveci in neutropenic & AIDS patients

- Causes severe pneumonia in these patients
- High dose therapy T-15-20 mg/kg/day,S-75-100 mg/kg/day is effective for infection by pneumocystis jiroveci infection in patients with AIDS.

- THANK YOU