CHEMOTHERAPEUTIC AGENTS-I

SULFONAMIDES

R. MAITI,

SENIOR LECTURER IN PHARMACY

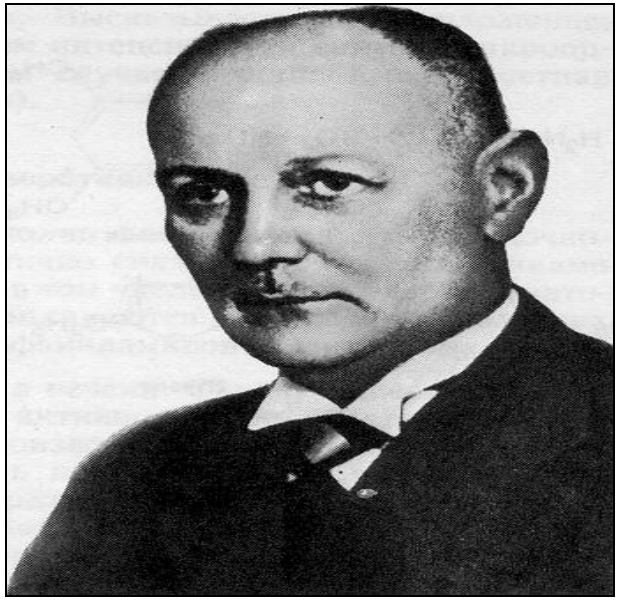
SULFONAMIDES

G. Domagk

(1895–1964),

bacteriologist and pathologist

discovered the first sulfonamide in 1935. Nobel prize for Physiology and Medicine in 1939.



Domagk tested the new comp. Azo-dye (Prontosil) & observed that mice with Streptococcal & other infections could be protected by prontosil (active metabolite was sulfonamide) & was very useful

SULFONAMIDES

- First effective chemotherapeutic agents to be employed systemically for the prevention & cure of bacterial infections in humans.
- The discovery of Penicillin & subsequent of other antibiotics has diminished the usefulness of the sulfonamides.
- Presently sulfonamides occupy small place in therapeutic armamentarium of the physicians.
- In 1970s however the combination of Trimethoprim & Sulfmethoxazole has increased the use of sulfonamides for the treatment & prophylaxis of specific microbial

SULFONAMIDES

Chemistry :

- Sulfonamide is a generic name for derivatives of Para – amino benzoic sulfonamide (Sulfanilamide).
- Insoluble in water but sodium salts are soluble. The para-NH2 group is essential for activity.

Effect on Microbes:

- Wide range of AM activity against both G+ve & G- ve bacteria.
- But now resist. strains have become common & usefulness of these agents has diminished .
- The Sulfonamides exert only bacteriostatic action .
- Cellular & humoral defense mechanism of the host are essential for final eradication of the infection.

SULFONAMIDES

Anti bact. Spectrum :

- **Resistance is increasingly a problem**

  Still sensitive strains are-

  Most of the Strept. pyogenes , Haemophilus ducrei & influenzae , Vibrio cholerae & Calymmatobacterium - granulomatis.

  Few strains of Staph. aureus , pneumococci, Meningococci & gonococci , E.coli & shigella are sensitive (most of the strains are resistant).

- **Anaerobes are not sensitive**
- **Chlamydiae (causing trachoma , lymphogranul.venereum ,inclusion conjunctivitis), Actinomyces,**

  Nocardia & Toxoplasma are sensitive

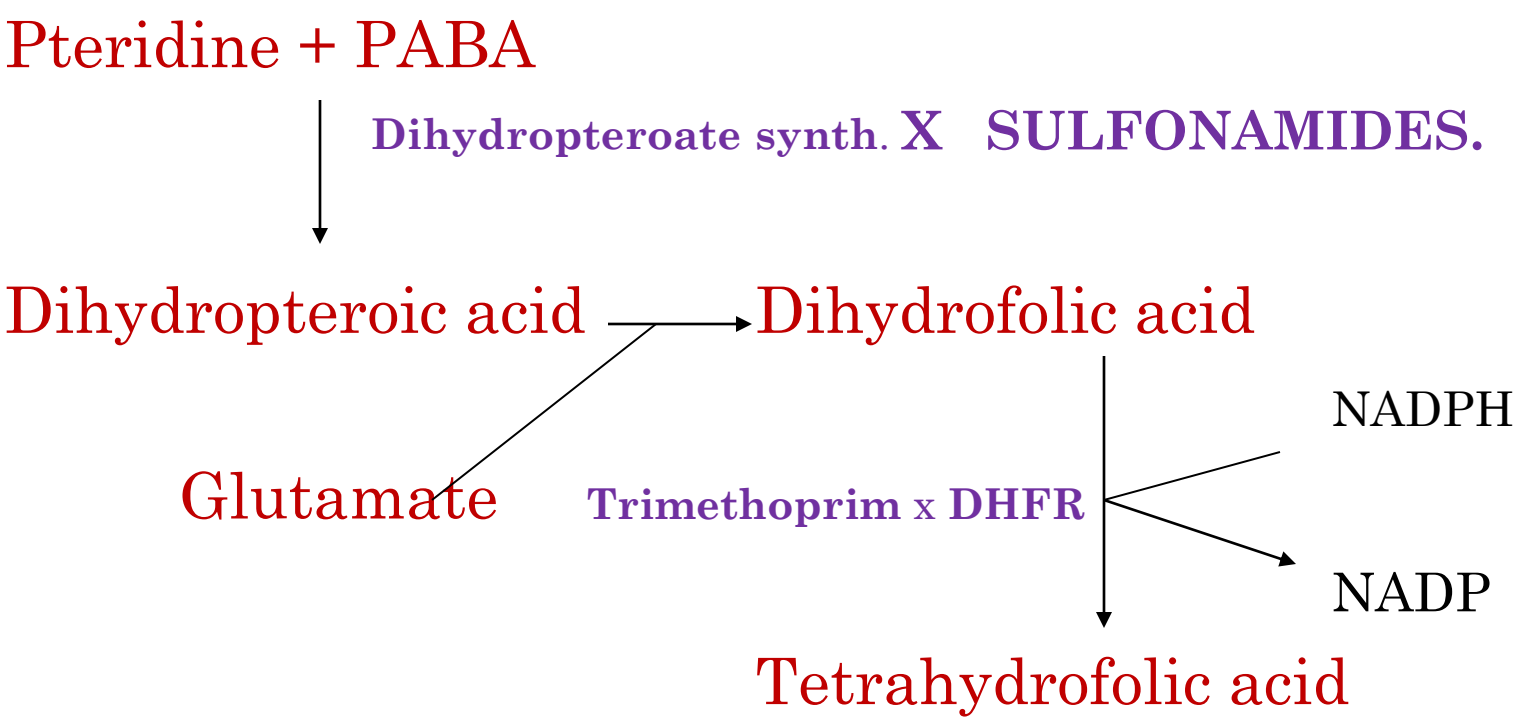
SULFONAMIDES

Mech. of action :

- Sulfonamides are structural analogue & competitive antagonists of - **Para- aminobenzoic acid(PABA)**.
- Prevent normal bacteria, utilization of PABA for the synthesis of folic acid (Pterylglutamic acid).
  - Specifically Sulfonamides are **competitive inhibitor of dihydropteroate synthase** (bacterial enzyme responsible for incorporation of PABA into dihydropteroic acid (immediate precursor of folic acid)
- Sensitive organisms are those that must synthesize their own folic acid & bacteria that utilize preformed folate are not affected .
- PABA competitively counteract Sulfonamide's bacteriostatic action .

SULFONAMIDES

(Sulfonamides do not affect mammalian cells because they require preformed folic acid and can not synthesize it).



SULFONAMIDES

Synergists :

Most active agent that exerts a synergistic effect with Sulfonamides is **Trimethoprim** It is a potent & selective competitive inhibitor of microbial **dihydrofolate reductase** (enzyme that reduces dihydrofolate To tetrahydrofolate).

Simultaneous administration of Sulfonamide & Trimethoprim Thus introduces **Sequential Block** in the pathway & kill the bacteria.

SULFONAMIDES

Acquired bact. resistance to Sulfonamides :

- Originate by random mutation & selection or by transfer of resistant Plasmids (this type of resistance is persistent & irreversible), posses enzymes that are less readily inhibited by sulfonamides.

May be due to-

i) Lower affinity for Sulfonamides by dihydropteroate synthase .

ii) ↓ bacterial permeability or active efflux of the drug.

iii) Alternate metabolic pathway for synthesis of essential metabolite.

iv)↑ production of essential metabolite or drug antagonists.

(↑ production of PABA is not a constant finding in sulfonamide resistant Bacteria & resistant mutants may different in other way.)

SULFONAMIDES

Pharmacokinetics:

- They are absorbed rapidly from GIT except locally acting sulfonamides .
- Peak plasma levels are achieved in 2-6 hrs depending on the drug (100-200 μg / ml).
- Small intestine is the major site of abs. but Some of the drug absorbed through stomach .
- Absorption from other site e.g.–vagina, respiratory tract or abraded skin is variable & cause toxic reaction in susceptible person .
- All sulfonamides are bound to plasma protein especially albumin & distributed throughout all tissues of the body .

SULFONAMIDES

- They readily enter pleural , peritoneal synovial,ocular & similar body fluids .
- After systemic absorption of adequate doses ,
  Sulfadiazine & Sulfisoxazole attain concentration in CSF which may be effective in meningeal infection .
- They reach the fetal circulation in placenta in pregnant mothers & can cause toxic as well as antibacterial effect .
- They undergo metabolic alteration in vivo
  esp. in liver . Major metabolite is N4 - acetylated sulfonamide .
- Excreted from the body partly unchanched & partly as metabolic products .The largest fraction excreted in urine.
- In acidic urine the older Sulfonamides are insoluble & form crystalline deposits that can cause urinary obstruction.
- Small fractions are eliminated in the feces bile , milk etc.

SULFONAMIDES

Pharmacological properties: -

They are classified into four gps on the basis of the rapidity with which they are absorbed & excreted .

CLASS	SULFONAMIDE	SERUM T-½ in Hrs
1. Absorbed & Excreted rapidly	**Sulfisoxazole**	5-6
	Sulfamethoxazole	11
	Sulfadiazine	10
2. Poorly absorbed- Active in bowel lumen	**Sulfasalazine**	---
3. Topically used	**Sulfacetamide**	---
	Silver sulfadiazine	---
4. Long acting	**Sulfadoxine**	100 - 230

SULFONAMIDES

1. **Agents that are absorbed & excreted rapidly:**

   e.g. **Sulfisoxazole & Sulfadiazine**

Sulfisoxazole:

- having excellent AM activity
- high solubility eliminates much of the renal toxicity.
- It is highly protein bound .approx. 95% of a single dose is excreted by the kidney in 24 hrs., conc. in urine thus exceeds than in blood & may be bactericidal .
- 1/3rd of the blood conc. reaches CSF

SULFONAMIDES

Sulfamethoxazole : congenial of sulfisoxazole. Enteric absorption & renal excretion is slower. Given orally & employed for both systemic & urinary tract infections. Precaution must be taken to avoid crystalluria (i.e. take plenty of water).

Also marketed in fixed dose combination with Trimethoprim.

Sulfadiazine :

Given orally , absorbed rapidly from GI tract & peak conc. reaches in 3-6 hrs after single dose. Fluid intake is must so that 1200 ml. urine output is maintained (to avoid crystalluria)

SULFONAMIDES

2.Poorly absorbed Sulfonamides :

Sulfasalazine - poorly absorbed from the GI tract therefore used in the therapy of Ulcerative colitis & Regional Ileitis in mild to moderate cases Sulfasalazine is preferred, but if relapses occurs, Corticosteroids are better.

It is broken down by intestinal bacteria into-

Sulfapyridine, an active Sulfonamide + 5-aminosalicylic acid which reaches high levels in feces.

- **5-aminosalicylic acid** is the effective agent in inflammatory bowel disease . Whereas Sulfapyridine is responsible for toxicity e.g. –

  Heinz body anemia , acute hemolysis in patients of G6PO4 dehydrogenase enzyme deficiency--

SULFONAMIDES

(G6PD enzyme is required for regeneration of NADPH &

Which is required for reduction of oxidized glutathione.

Reduced glutathione protects –SH dependent enzyme

& other proteins against oxidation.

- Thus in presence of pro-oxidants (e.g.- Aspirin , Nitrofurantoin, Primaquine, Chloroquine , Quinine , **Sulfonamide**, Vit. K etc.) in a patient with deficiency of G6PD , there is no protection to RBCs & so hemolysis occurs .)
- agranulocytosis & may cause rev. infertility in males .

SULFONAMIDES

3.Sulfonamides For Topical use :

Sulfacetamide – Sodium Salt of drug is extensively employed in ophthalmic infections .

Advantages –High aqueous conc. not irritating to eyes .

-The drug penetrates in high conc. into ocular fluids & tissues .

-Sensitivity reactions are rare.

Silver Sulfadiazine: The comp. is used topically to reduce microbial colonization & the incidence of wounds from burns(one of the agents of choice for the prevention of burn infections) .

other is **Mafenide.**

SULFONAMIDES

4. **Long acting Sulfonamides :**

e.g. – **Sulfadoxine** – having long half life ≈ 7-9 days .

- It is used in comb. with **Pyrimethamine** (500 mg Sulfadoxine + 25 mg Pyrimeth.) as Fansidar in prophylaxis & Treatment of Malaria caused by resist strains of Plasmodium falciparum.

SULFONAMIDES

Sulfamethoxazole combinations has revived the use of sulfonamides.

1. **Urinary Tract Infections :**

Sulfonamides are no longer a therapeutic choice in UTI. Preferred agents are –Trimethopreme + Sulfamethoxazole , Quinolones , Trimethopreme alone , Fosfomycin , Ampicillin & Cephalosporins. Sulfisoxazole may be used effectively.

2. **Nocardiosis** – good response with Sulfonamides.

e.g.- Sulfisoxazole & Sulfadiazine

Dose – 6 - 8 Gm. / day continued for several months. Second antibiotic along with sulfonamide is recommended in advanced cases e.g.- Ampicillin & Erythromycin.

SULFONAMIDES

3. **Toxoplasmosis :**

   Sulfadiazine(1Gm.) + Pyrimethamine (75 mg loading & 25 mg later on) is given 6 hrly x 3-6 weeks with folic acid 10 mg orally.

4. **Treatment & Prophy. of resist. Malaria :**

   Sulfadoxine + Pyrimethamine(Fansidar)

5. **Use of Sulf.s for Prophylaxis :**

   They are as efficacious as Penicillins in preventing Streptococcal infections & recurrence of Rheumatic fever .

6. **Ophthalmic inf.s :** topical –e.g.- Sulfacetamide.

7. **Infection of Burns :** e.g.- topical Silver sulfadiazine.

SULFONAMIDES

Adverse reactions :

1. Disturbance of urinary tract – risk of crystalluria - high with older less soluble Sulfonamides but very less with more soluble agents e.g.- Sulfisoxazole.

-Fluid intake should be sufficient – daily ensure urine out put of 1200ml.

- Alkalization of urine is desirable .

2. Disorders of Hematopoietic system :

- **Acute hemolytic anemia-** sometimes sensitization phenomenon & in others haemolysis due to G**6**PO**4** dehydrogenase deficiency - **Agranulocytosis** – most patient recovered spontaneously with supportive care.
- **Aplastic anemia** –complete suppression of bone marrow activity with anemia.

SULFONAMIDES

3. **Hypersensitivity reactions :** **Skin & mucous membrane manifestations-** urticarial rash, pemphigoid, perpurial & petechial rashes , erythema nodosum multiform of Stevenson Jonhson's type, Exfoliative dermatitis & photosensitivity most often occurs after 1st wk. of therapy of granulocytopenia & thrombocytopenia. It can occur with fever , malaise & pruritis.

- Focal or diffuse necrosis of liver, fever, headache, hepatomegaly, jaundice – leading to yellow atrophy of liver & death.

Misce. :

Anorexia , nausea & vomiting -1-2% in new born – free bilirubin can deposit in the basal ganglia & ant thalamic nuclei of the brain causing encephalopathy called Kern-icterus . (Sulf.s are not given to pregnant women near term because these drugs pass through placenta & secretes in milk).

SULFONAMIDES

Drug interaction :

with oral anticoagulant , sulfonylurea hypo-glycemic agents & hydantoin --

In each case sulfonamides can potentiate the effect of the other drugs by inhibition of metabolism & possibly displacement from serum-albumin binding site.

SULFONAMIDES

TRIMETHOPRIM & SULFAMETHOXAZOLE:

- Constitutes important advancement in the development of clinically effective Anti Microbial agents.
- If the drugs act on sequential steps in the pathway of an obligatory enzymatic reaction in bacteria , the result of their combination will be synergistic . This combination is known popularly as **Cotrimoxazole.**
- Trimethoprim also comes in single entity preparation.

Chemistry :

Trimethoprim is Di-amino pyrimidine.

SULFONAMIDES

Spectrum :

- It is equivalent to Sulfamethoxazole , although Trimethopreme is 20 -100 times more potent. Most G+ve & G-ve micro-org. Are sensitive (resist. occurs when used alone).
- Pseudomonas aeruginosa ,Bact.fragilis & Enterococci are resist.

Efficacy of combination :

- Additional micro-org. covered by this combination – Klebsiella , S. typhi , Serratia , Yersinia enterocolitica , Enterobacter, Brucella abortus, Proteus mirabils , Pseudo-

monas , Klebsiella , Brucella abortus, Pneumocystis jiroveci .

- Many sulfonamide resistant strains of -

S. pyogenes , Staph. aureus, Shigella, E.coli , H. influenzae, meningococci & gonococci becomes sensitive .

SULFONAMIDES

Max. degree of synergism occurs when micro-org. are sensitive to both component .

Mech. of action :

Sequential block in Folic acid synthesis occurs. Trimethopreme is selective inhibitor of DHFR enzyme of lower organisms, about 100,000 times more drug is required to↓ human reductase than bacterial enzyme.

(**Optimal synergy exhibited at a conc. ratio of sulfamethoxazole 20:Trimethoprim 1. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1**).

Bact. Resist. :

It is a rapidly increasing problem but lower than the resistance to either drug alone (due to acquisition of a plasmid that codes for an altered DHFR enzyme). However, resistant to the combination has been slow to develop compared to either drug alone.

SULFONAMIDES

Absorption ,Distribution &Excretion:

- Constant ratio of 20: 1 in their conc. in blood & tissues is not perfectly matched by the two drugs .The ratio in blood is often greater than 20:1 & that in tissues is frequently less.
- After single oral dose of the comb. prep. Trimethopreme is absorbed more rapidly than Sulfamethoxazole.
- Half life of trimethopreme & sulfmethoxazole is 11 & 10 hrs respectively.

(800 mg. of Sulfamethoxazole + 160 mg. of Trimethopreme is the combination dose).

- The drug readily enters in CSF & sputum. High conc. is also found in bile .
- About 60% of administered Trimethopreme & 25-50% of Sulfamethoxazole are excreteted in urine.

SULFONAMIDES

Uses :

1. UTI (uncomplicated) – more efficacious in chronic & recurrent infection of the UT. small doses / day or usual dose once or twice a week appears to be effective in reducing the no. of recurrent UTI in adult female .

(Enterobacter surrounding the urethral orifice may be eliminated or markedly low in number. Thus diminishing the chance of ascending reinfection .) Also effective in bacterial prostatitis.

2.Respiratory tract infection :

- Effective in acute exacerbation of chronic bronchitis (1 tab BD is sufficient to ↓ sputum , fever & purulence) .
- Effective in acute otitis media in children & acute maxillary sinusitis in adults caused by H. influenzae & S. pneumoniae.

SULFONAMIDES

3. GIT :

- Alternative to Fluoroquinolones for Shigellosis .
- Second line drug for **Typhoid fever**

(1st line drug is Ceftriaxone or fluroquinolones)

Also effective in carriers of S. typhi.

4. Inf. by Pneumocystis jiroveci :

high dose is effective for this severe infections in patients of AIDS ≡ Pentamidine.

5. Prophylaxis in Neutropenic patients.

6. Miscellaneous :

Nocardia , Brucellosis & Methiciline resistant Strains of S. aureus (MRSA) .

SULFONAMIDES

Adverse Effects : More or less same as Sulfonamides

- Folate deficiency in normal person may produce megaloblastosis, leukopenia or thrombocytopenia.
- 75% of ADRs involves skin exfoliative dermatitis, Stevenson Johnson's syndrome & toxic epidermal necrolysis (Lyell's syndrome).
- GIT-Nausea, vomiting ,diarrhea is rare, glossitis, stomatitis & allergic cholesystisitis, hepatitis.
- CNS –headache ,depression & hallucination.
- Hematological – Aplastic ,hemolytic & microcytic anemia, coagulation disorder, granulocytopenia, agranulocytosis & perpura.
- Patients with AIDS have increased chances of hypersensitivity reaction.

SULFONAMIDES

ICLAPRIM (a Trimethoprim analogue with improved activity)

- Recently introduced
- Given I.V.
- More effective & better tolerated than Trimethoprim
- ≡ Linezolid
- Effective in Pts. Suffering from skin & soft tissue infection caused by MRSA .
- Highly effective against Vancomycin resist. Staph. Aureus (VRSA)
- In Streptococcal Pneumonia .(Phase III trials are going on for oral use)