SULFONAMIDES

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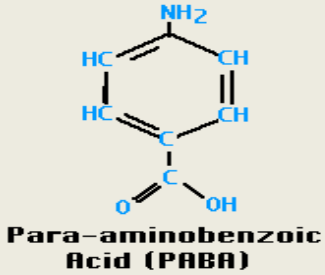
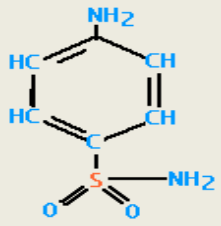
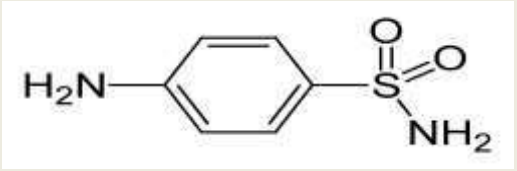


Para-aminobenzoic Acid (PABA)



Sulfanilamide

Sulfonamides



- The first antimicrobials effective against Pyogenic Bacterial infections.
- Derivatives of Sulfanilamide containing a “sufonamido “ring (SO_2NH_2).
- Structurally and chemically related to p-aminobenzoic acid (PABA).
- Structurally similar to many drugs – thiazides, acetazolamide, dapsone and sulfonylureas etc.
- Physically – available as white powder, mildly acidic and form water soluble salts with bases.
- However, indications and practical uses are very few these days.

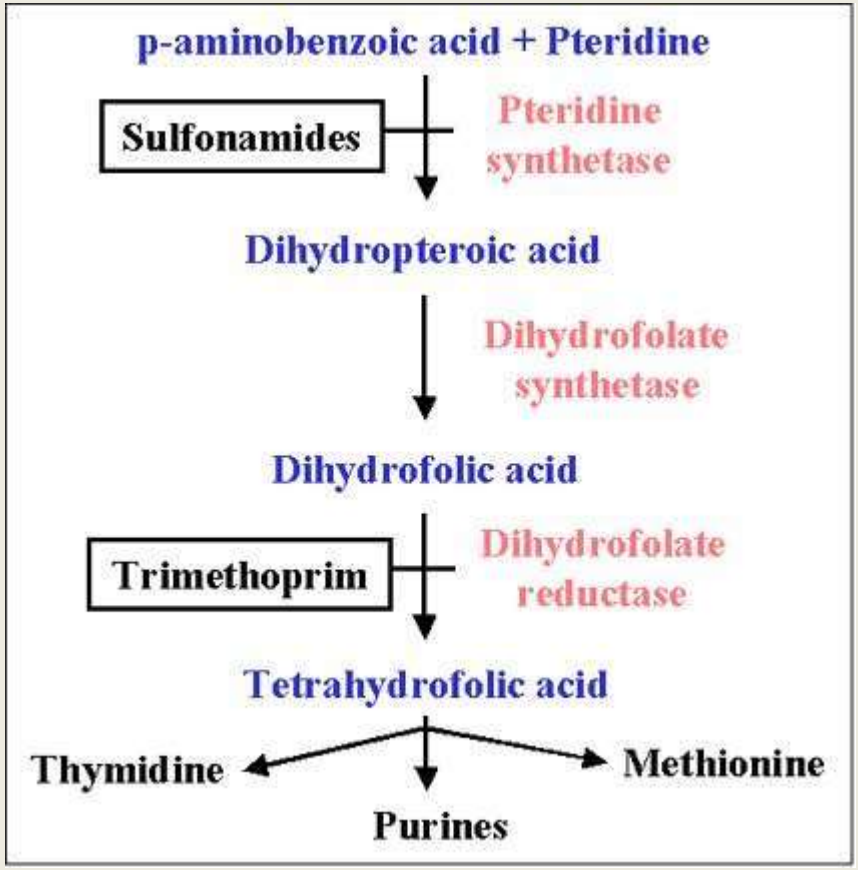
Sulfonamides - Classification

- **Short acting:** Sulfadiazine, Sulfadimidine, Sulfacetamide
- **Intermediate acting:** Sulfamethoxazole
- **Long acting:** Sulfadoxine, Sulfamethoxypyrazine, Sulfadimethoxine etc.
- **Topically used:** Mafenide, Silver sulfadiazine and Sulfacetamide
- **Ulcerative colitis:** Sulfasalazine

Sulfonamides – Antibacterial Property

- Bacteriostatic against gm +ve and gm –ve bacteria
- Bactericidal in urine
- Susceptible organisms: Str. pyogens, H. influenzae, H. ducreyi, Callymatobacterium grannulomatosis, V. cholerae, Chlamydia, Actinomyces etc.
  - Few strains of Staph aureus, gonococci, meningococci, pneumococci, E. coli and Shigella
- Chlamydiae: trachoma, lymphogrnuloma venereum., inclusion conjunctivitis. Also Actinomyces and Nocardia
- Protozoa:
  - Plasmodium (Sulfadoxine + Pyrimethamine)
  - Toxoplasmosis (Sulfadiazine + Pyrimethamine)
  - PCP (Sulfamethoxazole + Trimethoprim = SXT)

Sulfonamides – MOA



Sulfonamides - Resistance

- Many strains – S. aureaus, pneumococci, gonococci, meningococci, Strep. Pyogens, E. coli and Shigella
- Mechanism:
  1. Production of increased amounts of PABA (Staph, Neisseria)
  2. Folate synthase enzyme has low affinity to sulfonamides
  3. Adopt alternative pathway of folate synthesis – structural changes in folate synthase (E coli) – encoded chromosomally and plasmid mediated
- Resistant to one sulfonamide – resistant to all
- No cross resistance

Sulfonamides – Kinetics

- Rapidly and completely absorbed from GIT
- Extend of plasma protein binding differs (10 – 95%)
  - Longer acting ones are highly plasma protein bound
  - Widely distributed – enters in serous cavity easily
- Metabolized by non microsomal acetyl transferase in liver – slow and fast acetylators
- Acetylated product – inactive excreted in urine (but, more toxic than parent) – crystalluria
- Acetylated form accumulates in blood – toxic in renal faiure
- Reabsorbed in tubule

Sulfonamides - ADRs

- Nausea, vomiting and epigastric pain
- Crystalluria – alkanization of urine
- Hypersensitivity (2 – 5%) – rashes, urticaria, drug fever. Exfoliative dermatitis, SJ syndrome (long acting ones)
- Hepatitis
- Haemolysis – G-6-PD deficiency
- Kernicterus – displacement of bilirubin

Individual Sulfonamides

- Sulfadiazine: General purpose use – absorbed orally and rapidly
  excreted. More crystalluria. Preferred in meningitis.
- Sulfamethoxazole: slower absorption and lower excretion. 10 Hrs. half life. Combination with Trimethop
- Sulfadoxine:Ultra-long acting >1 week. High protein bound – long excretion. Not suitable for Pyogenic infections – low plasma conc.. Used in Malaria, *Pneumocystis jiroveci* and toxoplasmosis
- Sulfacetamide: Ophthalmic use – infections by bacteria, chlamydia, ophthalmia neonatorum etc
- Mafendie: Atypical sulfonamide. Local application – inhibits variety of bacteria – active in presence of pus – pseudomonas and clostridia
- Silver sulfadiazine: Bacteria, fungi, Pseudomonas. In burn cases

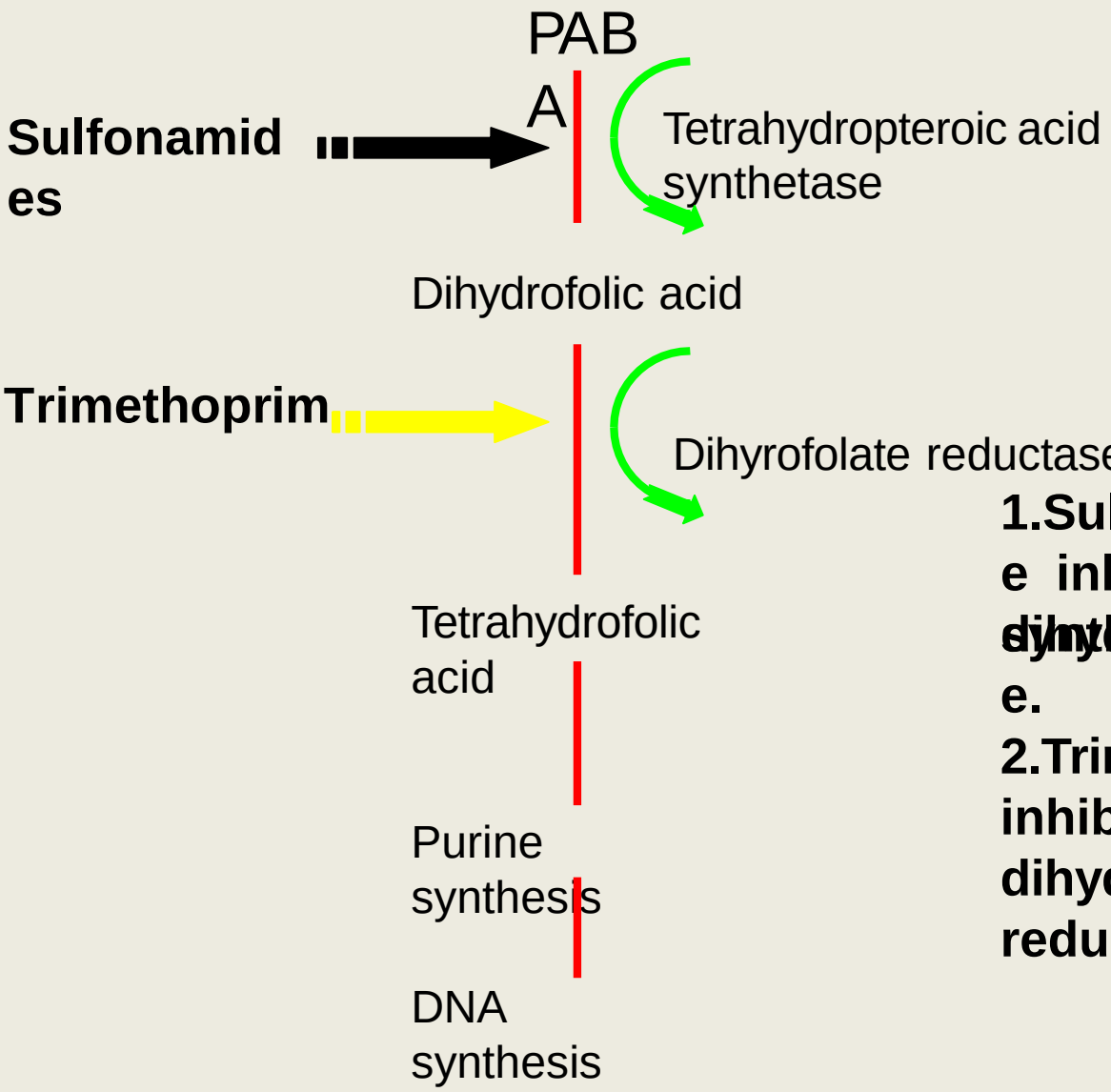
Sulfonamides - Uses

- Rarely used now a days systemically
- **UTI:** caused by E. coli and P. mirabilis: Sulfisoxazole – 1 gm 4 times daily
- **Malaria:** sulfadoxine and pyrimethamine combination
- **Toxoplasmosis:** sulfadiazine + pyrimethamine
- In Combination with Trimethoprim: Cotrimoxazole
- **Ulcerative colitis**: Sulfasalazine – 1-4 gm initially and 500 mg 6 Hrly.
- **Locally:**
  - Sodium sulfacetamide: 10-30% ophthalmic solution in bacterial
    conjunctivitis, trachoma etc.
  - Mafenide acetate (1% cream) and Silver sulfadiazine 1% cream): Burn dressing and chronic ulcers

Trimethoprim

- **Trimethoprim** (trimethyl benzyl pyrimidine) is a diaminopyrimidine, chemically related to Pyrimethamine
- **Do not confuse: Clotrimazole (antiungal) - Cotrimoxazole** is TMP – SMZ, but Sulfadoxine + Pyrimethamine is **antimalarial**
- **MOA:** Sequential block of folate metabolism
- Trimethoprim is 50,000 or more times more active against bacterial DHFRase enzyme than mammalian
- So, no harm to human folate metabolism

MOA OF TRIMETHOPRIM-SULFAMETHOXAZOLE



1.Sulfamethoxazol e inhibits dihydrofolate synthase.
2.Trimethoprim inhibits dihydrofolate reductase.

Cotrimoxazole – general points

- Individually, both are bacteriostatic, but combination is – bactericidal
- Both drugs have almost similar half lives (10 Hrs)
- Maximum synergism if the organism is sensitive to both the agents
- Optimal synergism is obtained at 20 (S) : 1 (T) concentration (MIC of both is reduced by 3 - 6 times)
  - This ratio is obtained at 5:1 dose ratio (e.g. 800 mg:160 mg)
  - Because TMP has large Vd and enters many tissues – plasma conc. is low
- But, TMP crosses BBB and placenta and SMZ not
- TMP is more rapidly absorbed than SMZ
- TMP is 45% plasma protein bound but SMZ is 65% bound
- TMP is partly metabolized in liver

Cotrimoxazole – antibacterial spectrum

- Similar to sulfonamides
- Additional benefits: Salmonella typhi, Serratia, Klebsiella Enterobacter, Yersinia and Pneumocystis jiroveci
  - Sulfonamides resistance strains of S. aureus, E. coli, gonococci, meningococci and H influenzae
- RESISTANCE: Slow to develop
  - By mutational changes or plasmid mediated acquisition of a DHFRase enzyme having lower affinity for the inhibitior.

Cotrimoxazole - ADRs

- All adverse effects of sulfonamides – nausea, vomiting,stomatitis,rash etc
- Folate deficiency (megaloblastic anaemia) – patients with marginal folate levels
- Blood dyscrasias
- **Pregnancy:** teratogenic risk, Neonatal haemolysis and methaemoglobinaemia
- Patients with renal disease may develop uremia
- Fever, rash and bone marrow hyperplasia
- Elderly – risk of bone marrow toxicity from cotrimoxazole
- Diuretics given with cotrimoxazole have produced a higher incidence of thrombocytopenia
- Bone marrow hypoplasia among AIDS patients with Pneumocystis jiroveci infection

Cotrimoxazole - Uses

- Uncomplicated infection of the lower urinary tract infection
  - Cystitis (5 tablet dose)
  - chronic and recurrent urinary tract infections (including enterobacteriaceae) – 3-10 days
- Respiratory tract infection – lower and upper, chronic bronchitis, facio-maxillary infections, otitis media due to gm+ve cocci and H influenzae etc
- Typhoid
- Bacterial diarrhoeas & dysentery: due to campylobacter, E coli, Shigella etc.
- Pneumocystis jiroveci: Severe pneumonia - Prophylactic use in AIDS patients with neutropenia. Dose – DS tablet 4-6 times 2-3 weeks
- Chancroid – H. ducreyi
- Alternative to penicillin in agrannulocytosis patients, scepticaemia etc.

Thank you