Sulfonamides & Cotrimoxazole

Pharmacology-III (BP602)

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SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections. Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective.

By 1937, it became clear that prontosil was broken down in the body to release sulfanilamide which was the active antibacterial agent.

A large number of sulfonamides were produced and used extensively in the subsequent years, but because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, their current utility is limited, except in combination with trimethoprim (as cotrimoxazole) or pyrimethamine (for malaria).

SULFANILAMIDE

N^1 (Sulfonamido N) substitution, which governs solubility, potency and pharmacokinetic property.

A free amino group in the para position (N4) is required for antibacterial activity.

Sulfonamides that are still of clinical interest are:

1. **Short acting (4–8 hr):** Sulfadiazine
2. **Intermediate acting (8–12 hr):** Sulfamethoxazole
3. **Long acting (~7 days):** Sulfadoxine**,** Sulfamethopyrazine
4. **Special purpose sulfonamides:** Mafenide, Silver sulfadiazine, Sulfasalazine

Antibacterial Spectrum

Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria.

However, bactericidal concentrations may be attained in urine. Sensitivity patterns among microorganisms have changed from time-to-time and place-to-place. Those still sensitive are: many *Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio cholerae. Only a few Staph. aureus, gonococci,* meningococci, pneumococci, *Escherichia coli, and Shigella respond, but majority are resistant.* Anaerobic bacteria are not susceptible.

Mechanism of action: Many bacteria synthesize their own folic acid (FA) of which para aminobenzoic acid (PABA) is a constituent, and is taken up from the medium. Sulfonamides, being structural analogues of PABA, inhibit bacterial folate synthase → FA is not formed and a number of Essential metabolic reactions suffer.

Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid Which conjugates with glutamic acid to produce dihydrofolic acid.

Resistance to sulfonamides: **Most bacteria are** developing resistance to sulfonamides like gonococci, pneumococci, *Staph. aureus,* meningococci, *E. coli,*
The resistant mutants either:

(a) produce increased amounts of PABA, or

(b) their folate synthase enzyme has low affinity for sulfonamides, or

(c) adopt an alternative pathway in folate metabolism.

PHARMACOKINETICS

✓ Rapidly and completely absorbed from g.i.t.

✓ Extent of plasma protein binding differs considerably (10–95%) among different members. The highly protein bound members are longer acting.

✓ Sulfonamides are widely distributed in the body enter in CSF and cross placenta freely.

✓ The primary pathway of metabolism of sulfonamides is acetylation at N4 by non microsomal acetyl transferase, primarily in liver.

✓ Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption also occur.

✓ The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

ADVERSE EFFECTS

- Nausea, vomiting and epigastric pain.
- Crystalluria (can be minimized by taking plenty of fluids and by alkalinizing agents).
- Hypersensitivity reactions (rashes, urticaria and drug fever) occur in 2–5% patients.
- Photosensitization
- Hepatitis, unrelated to dose, occurs in 0.1% patients.

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- Sulfonamides cause haemolysis in a dosedependent manner in individuals with G-6PD deficiency.
- Kernicterus may be precipitated in the newborn, especially premature, by displacement of bilirubin from plasma protein binding sites and more permeable blood-brain barrier.

Interactions

Sulfonamides inhibit the metabolism (possibly displace from protein binding also) of phenytoin, tolbutamide and warfarin - enhance their action.

They displace methotrexate from binding and decrease its renal excretion-toxicity can occur.

USES

- ✓ In chronic urinary tract infection
- ✓ In streptococcal pharyngitis and gum infection
- ✓ Combined with trimethoprim (as cotrimoxazole) sulfamethoxazole is used for many bacterial infections, *P. jiroveci*.
- ✓ Along with pyrimethamine, certain sulfonamides are used for malaria and toxoplasmosis.
- ✓ Ocular sulfacetamide sod. (10–30%) is a cheap alternative in trachoma/inclusion conjunctivitis,
- ✓ Topical silver sulfadiazine or mafenide are used for preventing infection on burn surfaces.

Cotrimoxazole

- The fixed dose combination of trimethoprim and sulfamethoxazole is called *cotrimoxazole.*
- Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits *bacterial dihydrofolate reductase* (DHFRase).
- Trimethoprim is >50,000 times more active against bacterial DHFRase than against
- the mammalian enzyme. Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim.
- Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms.
- Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t½ (~ 10 hr).

Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1

Spectrum of action

Antibacterial spectra of trimethoprim and sulfonamides overlap considerably. Additional organisms covered by the combination are—*Salmonella typhi, Serratia, Klebsiella, Enterobacter, Yersinia enterocolitica, Pneumocystis jiroveci and* many sulfonamide resistant strains of *Staph. aureus, Strep. pyogenes, Shigella,* enteropathogenic *E. coli, H.influenzae,* gonococci and meningococci.

Adverse effects:

- Nausea, vomiting, stomatitis, headache and rashes are the usual manifestations.
- Folate deficiency (megaloblastic anaemia) is infrequent, occurs only in patients with marginal folate levels.
- Blood dyscrasias, teratogenic risk, Neonatal haemolysis.
- Patients with renal disease may develop uremia.
- A high incidence (upto 50%) of fever, rash and bone marrow hypoplasia due to cotrimoxazole.
- The elderly are also at greater risk of bone marrow toxicity from cotrimoxazole.

USES

- ✓ Urinary tract infections
- ✓ Respiratory tract infections
- ✓ Typhoid
- ✓ Bacterial diarrhoeas and dysentery
- ✓ Pneumocystis jiroveci
- ✓ Chancroid
- ✓ Effective alternative to penicillin
- ✓ For protecting agranulocytosis patients and treating
- ✓ Respiratory and other infections


THANKS