SULFONAMIDES AND COTRIMOXAZOLE

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. 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) (for malaria).

All sulfonamides may be considered to derivatives of sulfanilamide (p-aminobenzene sulfonamide).

1. Short acting (4-8 hr): Sulfadiazine

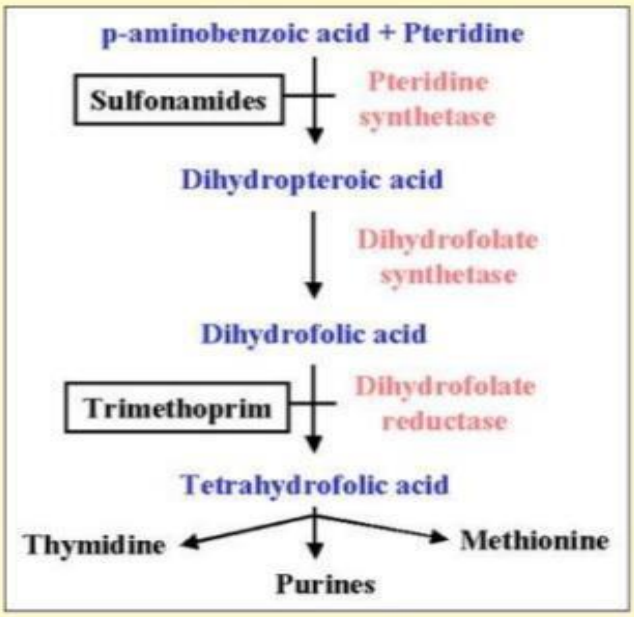
2. Intermediate acting (8-12 hr): Sulfamethoxazole

3. Long acting (-7 days): Sulfadoxine, Sulfamethopyrazine

4. Special purpose sulfonamides: Sulfacetamide sod., Mafenide, Silver sulfadiazine, Sulphsalazine

Mechanism of Sulfonamide

- Sulfonamide molecular structure is similar to p-Amino benzoic acid (PABA) which is needed in bacteria organisms as a substrate of the enzyme dihydro pteroate synthetase for the synthesis of Tetra Hydro Folic acid (THF).
- Folic acid - synthesized from PABA, pteridine and glutamate.
- All sulfonamides are analogs of PABA.
- All sulfa drugs are bacteriostatic.



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).

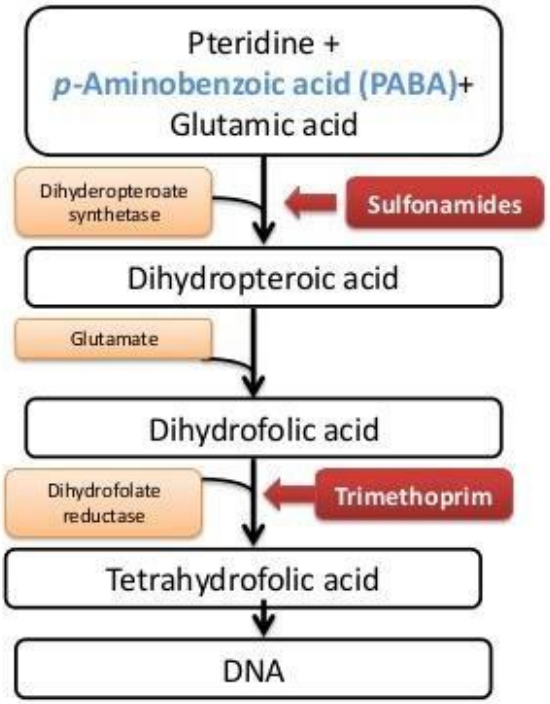
Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim. Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms.

Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t hal f(- 10 hr). Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1, the MIC of each component may be reduced by 3-6 times. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1, because trimethoprim enters many tissues, has a larger. Cotrimoxazole volume of distribution than sulfamethoxazole and attains lower plasma concentration. However, the concentration ratio in many tissues is less than 20 : 1 . Trimethoprim adequately crosses blood-brain barrier and placenta, while sulfamethoxazole has a poorer entry. Moreover, trimethoprim is more rapidly absorbed than sulfamethoxazole--concentration ratios may vary with time. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound. Trimethoprim is partlymetabolized in liver and excreted in urine.

Cotrimoxazole

- Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same $t_{1/2}$ (~10 h).

- Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole: trimethoprim (20:1), the MIC of each component may be reduced by 3-6 times.



Uses

1. Urinary tract infections
2. Respiratory tract infections
3. Typhoid
4. Bacterial diarrhoeas and dysentery
5. Pneumocystis
6. Chancroid