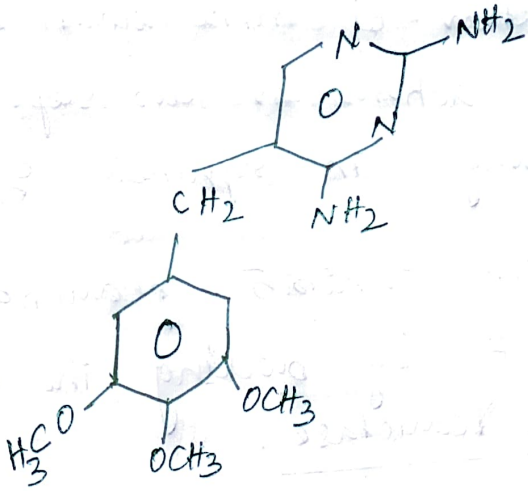
Cotrimoxazole :→ [Trimethoprim – Sulfamethoxazole]



Chemistry :→ diaminopyridine

Sulfamethoxazole + Trimethoprim.

5 : 1

400 : 80 mg. in 500mg dug.

Antibacterial spectrum :→

→ Has similar spectrum to that of sulfamethoxazole

Trimethoprim 20–100 times more potent than "

→ Most gram +ve & –ve m.o. are sensitive but resistance can develop when the drug is used alone

Resistant strains → Pseudomonas aeruginosa
Bacteroides fragillus
Enterococci

Susceptible strains for cotrimoxazole. →

Yersinia pseudotuberculosis
Y. enterocolitica.
Nocardia asteroids

Chlamydia
N. meningitidis
S. aureus
MRSA, Proteus mirabilis
P. morgani
Salmonella typhae
shigella, klebsiella,
Brucella, pasteurella,

Mechanism of Action :→

→ The combination of Trimethoprim & Sulfamethoxazole results from its actions on two steps of the enzymatic pathway in synthesis of THF.

→ Trimethoprim inhibits reduction of DHF to THF by blocking the enzyme dihydrofolate reductase.

THF → essential for one carbon transfer reaction from deoxyuridilate to thymidylate.

→ Approximately, 100,000 times more drug is required to inhibit Human DHF reductase than Bacterial enzyme.

→ optimal ratio of conc^n of both agents is required for synergistic activity and equals to ratio of MIC of drugs individually

→ Most effective ratio for greatest no. of M.O. is 20 : 1
(S) (T)

Bacterial Resistance :→

→ Often is due to acquisition of plasmid that codes for an altered DHF reductase.

P.kinetics :→

Absorption :→ The optimum Ratio 20:1 but often it is > 20:1 in blood and in tissues much lesser.

→ Trimethoprim absorbed more rapidly than Sulfamethoxazole.

→ Concurrent admn. of Sulfamethoxazole, slows down the absorption.

→ Peak plasma conc^n Trimethoprim is 2hrs
Sulfamethoxazole in 4hrs.

$t^{1}/_{2}$ life → Trimethoprim is ~ 11 hrs.
Sulfamethoxazole is ~ 10 hrs.

Eg: 800 mg Sulfamethoxazole + 160mg Trimethoprim
↓ Orally
peak conc^n are 40 and 2 μg/ml
↓ Intravenously
peak conc^n 46 & 3.4 μg/ml. in 1hr.

Distribution :→

→ Trimethoprim is distributed and conc^n rapidly in tissues.

→ ~ 40% plasma protein binding in the presence of Sulfamethoxazole.

Vd is 9 times than that of Sulfamethoxazole

→ enters in CSF and sputum.
High conc^n are also found in bile.

→ 65% of Sulfamethoxazole is bound to plasma proteins.

metabolism :→ In liver, by Acetylation.

Excretion :→

→ With in 24 hrs. — 60% of trimethoprim & 25–50% of Sulfamethoxazole ↓ are excreted in Urine.

2/3rd of Sulfonamides are unconjugated & trimethoprim metabolites are excreted.

→ Rates of excretion and conc? of both compounds in urine are ↓ in Uremia patients.

Adverse effects :→

→ Folate deficiency

→ Megaloblastosis, Leucopenia, thrombocytopenia

→ Exfoliative dermatitis, Stevens-Johnson syndrome, Lyelli syndrome (epidermal Necrosis) rarely seen.

→ Gastritis, Stomatitis are Common.

→ Mild Hepatitis

→ CSF effects Headache, depression, hallucination, etc.

→ patients with AIDS → Hypersensitivity reactions etc.