Folate antagoists

\*in the absence of folate, cells cannot grow or divide / \*bacteria rely on their ability to synthesize folate de novo

\*sulphonamides inhibit de novo synthesis of folate(inhibit the synthetase). / \**trimethoprim-prevents converting dihydrofolic acid to tetrahydrofolic(inhibit the reductase)*

*\*interfere with DNA synthesis/ \**

Slufonamides (starts with sulfa)

\*sulphonamides are synthetic analogs of p-aminobenzoic acid(PABA) which is used to synthesie dihydrofolic acid

\*competitive inhibtors for the dihdrofolate synthetase / \*bacteriostatic/*sulfadiazine+pyrimethamine >treatment for toxoplasmosis*

\*against Enterobacteriaceae in the urinary tract and Nocardia infections/*Sulfadoxine+pyrimethamine >antimalarial drug*

\*Resistance (Bacteria that can obtain folate from their environment are naturally resistant to these drugs / Acquired resistance /

Resistant to one is resistant to all / resistance is irreversible due to (1-altered dihydropteroate synthetase/2-decreased permeability

3-enhanced production of PABA)

\*oral exept *sulfasalazine* /\**sulfasalazine reserved for treatment of chronic inflammatory bowel disease(ulcerative colitis)*

*\*intestinal flora split sulfasalazine exerting the anti-inflammatory effect./* *Absorption of sulfapyridine > toxicity in patients who are slow acetylators / Intravenous sulphonamides > patients who are unable to take oral preparations /*

\*not usually applied topically Because of the risk of sensitization exept in burns (*silver sulfadiazine* or *mafenide acetate)*

*\*Silver sulfadiazine is preferred because mafenide produces pain /\*bound to serum albumin/smaller pKa >greater binding*

*\*body fluids + CSF + placebtal barrier /\*metabolised in the liverby acetylation /\*acetylated product loses antimicrobialactivity but is still toxic /\*eliminated by glomerular filtration(kidney) and may be eliminated in breast milk/*

Adverse (Crystalluria –solved by hydration and alkalinization of urine , Hypersensitivity , Hematopoietic disturbances-Hemolytic anemia in patients with (G6PD) deficiency , Kernicterus-in newborns because it displaces bilirubin and bilirubin enter CNS,

Drug potentiation-potentiation of the anticoagulant effect of *warfarin and ethotrexate levels may also rise)*

*\*Contraindications (avoided in newborns and infants less than 2 months and pregnant women because of kernicterus and patients receiving methenamine- Because it can crystallize)*

Trimethoprim

\* inhibitor of bacterial dihydrofolate reductase / antibacterial spectrum similar to that of the sulphonamides

\* *cotrimoxazole = Trimethoprim+ sulfamethoxazole/\* trimethoprim is 20- to 50-fold more potent than the sulphonamides*

*\** *may be used alone in the treatment of UTIs and in the treatment of bacterial prostatitis(although fluoroquinolones preffered)*

*\** *Resistance( in gram (-) -* *presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim ,efflux pump)*

*\** *oral /\** *higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids /\*fluids+ CSF*

*\** *60% to 80% is renally excreted unchanged the else O-demethylation /\**

*\*adverse (effects of folic acid deficiency -* *megaloblastic anemia, leukopenia, and granulocytopenia) reversible by* administration of *folinic acid*

COTRIMOXAZOLE (*cotrimoxazole = Trimethoprim+ sulfamethoxazole)*

*\** *greater antimicrobial activity / broader spectrum*

*\** *inhibition of two sequential steps in the synthesis of tetrahydrofolic acid(synthetase and reductase)*

*\** *treating UTIs and respiratory tract infections, as well as Pneumocystis jirovecii pneumonia (PCP), toxoplasmosis, and ampicillin- or chloramphenicol-resistant salmonella infections(H.influenzae and legionella pneumophila)*

*\** *activity against MRSA-* *community-acquired skin and soft tissue infections/\**

*\*treats infections caused by susceptible Nocardia species and Stenotrophomonas maltophilia*

*\*treats listeriosis caused by (listeria monocytogenes)*

*\*ampicillin and cortimaxazole treat spectemia and meningitis caused by (listeria monocytogenes)*

*\*treat shigellosis and non typhois salmonella*

*\*management of carriers of S.typhi*

*\** *Resistance(E. coli and MRSA-resistent to both drugs that form this one)*

*\** *orally or IV in patients with severe pneumonia caused by PCP*

*\** *treatment of prostatitis because of trimethoprim ability to concentrate in prostatic fluid.*

*\** *readily crosses the blood–brain barrier.*

*\** *excreted in the urine(all folate anaagonists)*

\* Glossitis and stomatitis , Nausea and vomiting , Hyperkalemia , Megaloblastic anemia, leukopenia, and thrombocytopenia,

Hemolytic anemia in patients with G6PD deficiency ,

\* hematologic effects may be reversed by the concurrent administration of *folinic acid*

\* Prolonged prothrombin times (increased)in patients taking it with warfarin.

\* *phenytoin* *half-life* *may be increased (inhibit metabolism)/\* Methotrexate levels may rise(displacement from albumin)*