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SULFONAMIDES AND COTRIMOXAZOLE

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ANTIMETABOLITES/ ANTIFOLATE ANTIBIOTICS

- These drugs are able to interfere with the role of an endogenous compound e.g folic acid, in the cellular metabolism.

Examples:

- *Dapsone*
- *Para-amino salicylic acid*
- *Sulfonamides*
- *Pyrimethamine*
- *Proguanil*
- *Methotrexate*
- *Trimethoprim*

SULPHONAMIDES

- These are first antimicrobial agents used in treatment of bacterial infections.
- Derivative of sulphanilide and are synthetic congener of PABA.
- Due to emergence of resistance and availability of better drugs, sulfonamides are less frequently used nowadays.
- These drugs are ***bacteriostatic* agents** and act by ***inhibiting dihydropteroate synthase (DHPS)/ folate acid synthase competitively, involved in folic acid synthesis*.**

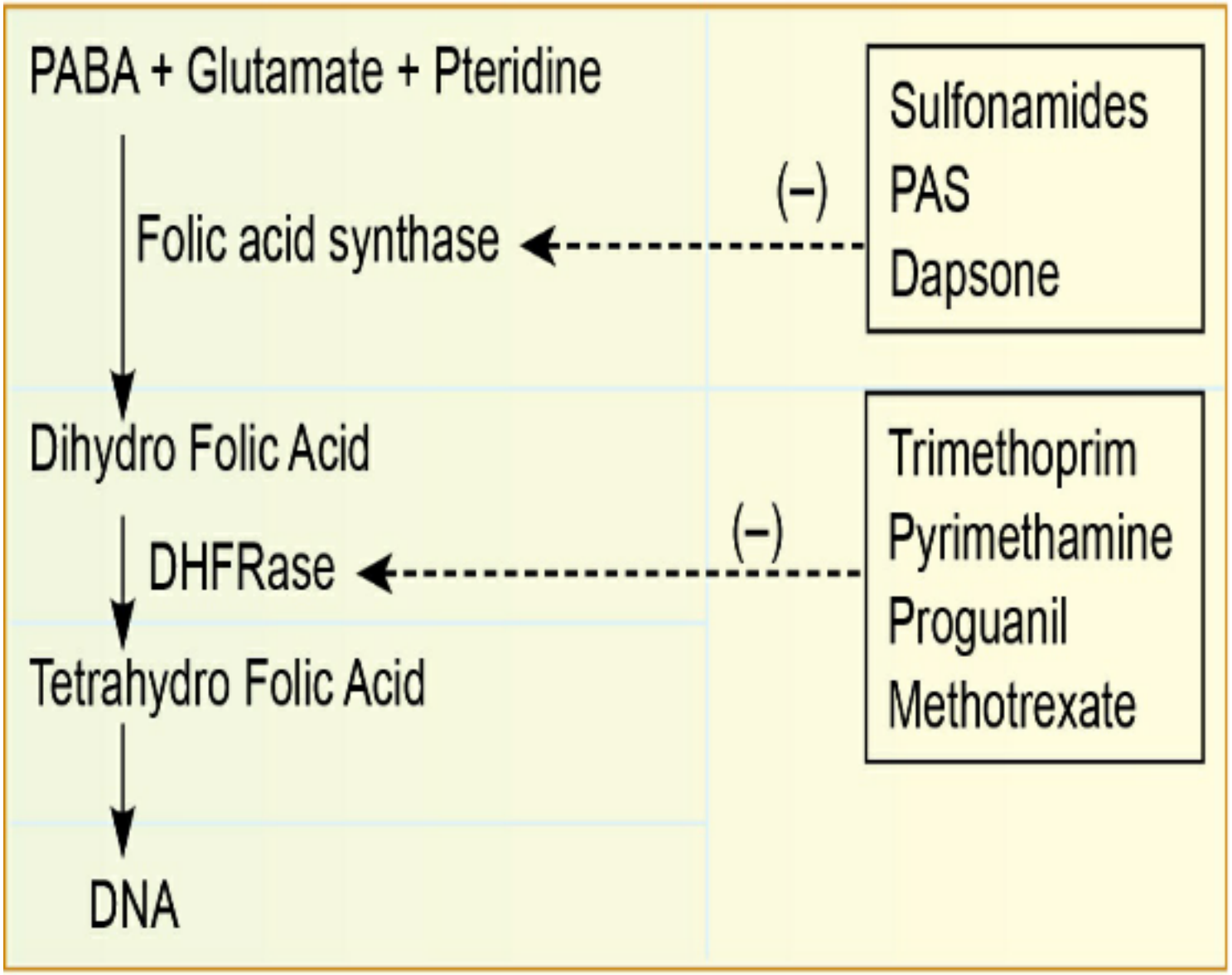
MECHANISM OF ACTION

- Bacteria can synthesize folic acid via PABA-very essential for purines and nucleic acid synthesis.
- **Drugs inhibiting folic acid synthesis:** Folic acid synthase (dihydropteroate synthase) results in the formation of folic acid by incorporation of PABA.
- *Sulfonamides, dapsone and paraaminosalicylic acid (PAS)* are structural analogues of paraaminobenzoic acid (PABA).
- There drugs act as **competitive inhibitors** of folic acid synthase.

- **Dihydrofolate reductase (DHFRase) inhibitors:** DHFRase is the enzyme responsible for conversion of dihydrofolic acid to tetrahydrofolic acid.

- Latter is the active form required for the transfer of one carbon units.

- Drugs inhibiting this enzyme are *pyrimethamine, methotrexate, proguanil and trimethoprim.*


PABA + Glutamate + Pteridine
Folic acid synthase
(–)
Sulfonamides
PAS
Dapsone
Dihydro Folic Acid
DHFRase
(–)
Trimethoprim
Pyrimethamine
Proguanil
Methotrexate
Tetrahydro Folic Acid
DNA

- The selective toxicity to bacteria is due to the reason that mammalian cells do not synthesize folic acid and utilize preformed folic acid in the diet.

- Sulfonamides are **not effective in the presence of pus** because it contains large amount of PABA.

PHARMACOKINETICS

- Rapidly absorbed from GIT
- Widely distributed in body tissues
- Can enter pleural, peritoneal, synovial, ocular and other body tissues
- Cross BBB and Placenta.
- Binds to plasma protein albumin.
- The solubility of sulfonamides decrease in the acidic urine, which may result in precipitation of the drug causing **crystalluria.**
- Risk is **minimum with** soluble drugs like **sulfisoxazole**.

- **Sulfadoxine** is **longest acting** whereas **sulfacytine** is **shortest** acting sulfonamide.
- These drugs undergo hepatic metabolism by **ACETYLATION**
- Drugs undergoing acetylation are **SHIP:** Sulfonamides including ***dapsone, Hydralazine, Isoniazid and Procainamide***) and can cause SLE.
- Excreted via kidney, so dose to be reduced in renal failure

CLASSIFICATION

- **Systemic acting oral agents**
- *Short acting: (4-8 hrs)* Sulfisoxazole, Sulfacytine, sulfadiazine
- *Intermediate acting: (8-12 hrs)* Sulfamethoxazole, sulfamoxazole
- *Long acting: (7 days)*Sulfadoxine, sulfamethopyrazine

- **For use in GIT as orally nonabsorbable agents:** Sulfasalazine, olsalazine, balsalazine

- **For topical use:** Sulfacetamide, silver sulfadiazine, mafenide

ANTIBACTERIAL SPECTRUM

- Active against gram negative bacteria- Ecoli, salmonella, proteus, Vibrio cholera.
- Some gram negative bacteria- Staph, Gonococci, Meningococci, Pneumococci
- Others- Toxoplasma gondii, P. falciparum, Chlamydia

MECHANISM OF RESISTANCE

- Mutation in the enzyme folate synthase
- Efflux of drug
- Low permeability of drug
- Increase production of PABA via alternate pathway

CLINICAL USES

- **UTI:** Sulfisoxazole has the most rapid oral absorption and most water soluble sulphonamide, hence it causes less crystalluria.
- It is used for acute cystitis.

- **Otitis media-** Sulfisoxazole can also be used in otitis media

- **Ulcerative colitis and Enteritis:** Sulfasalazine and olsalazine are used for the treatment of ulcerative colitis.

- Its active component for anti inflammatory activity is 5-ASA.

- **Nocardiosis-**Sulfadiazine can be used for nocardiosis

- **Trachoma and Chancroid-** Sulphonamides can be used as an alternative to azithromycin and tetracycline

TOXOPLASMOSIS

- **Sulfadiazine and Pyrimethamine** combination can be used for the treatment of toxoplasmosis.
- Combination used for 6 months.
- Pt should receive 2L of fluid daily to prevent crystalluria.
- Since antifolates are contraindicated in pregnancy, **Spiramycin** is DOC for toxoplasmosis in pregnancy.

PNEUMOCYSTIS JIROVECI INFECTION PROPHYLAXIS

- Combination of **Sulfadiazine and pyrimethamine** is also used for prophylaxis of Pneumocystis jiroveci pneumonia in AIDS patients.

Other drugs:

- Dapsone
- Pentamidine
- Atovaquone

CQ RESISTANT MALARIA

- **Sulfadoxine** (longest acting sulfonamide) **plus pyrimethamine and Artesunate (ACT)** is used for treatment of CQ resistant malaria and mefloquine resistant malaria.

WHO RECOMMENDED ARTESUNATE COMBINATION THERAPY (ACT)

- Artemether-Lumefantrine
- Artesunate-Amodiaquine
- Artesunate-Mefloquine
- **Artesunate-Sulfadoxine-Pyrimethamine**
- Dihydroartemisinin-Piperaquine

TOPICAL AGENTS

- Mafenide, sulfacetamide, Silver sulfadiazine are used as topical sulphonamides.
- Silver sulfadiazine> Mafenide are used in burn patients to prevent infection.
- Silver sulfadiazine has antifungal effect as well, hence used in fungal keratomycosis.
- Sulfacetamide is used for ocular infections as eyedrops.

ADVERSE EFFECTS

- **Skin rash and SJS** due to hypersensitivity is the **most common adverse effect.**

- **BM Suppression:** These can also cause **granulocytopenia, thrombocytopenia and aplastic anemia** (more common in HIV infected patients).

- **Hemolysis:** Sulfonamides can cause **acute hemolysis in patients with G-6 PD deficiency.**

- **Crystalluria:**These can precipitate in the urine at acidic pH and may result in **crystalluria and hematuria.** (mostly with older sulphonamides).

- It can be prevented by taking large amount of water and alkalization of urine by sodium bicarbonate.

- **GIT:** Nausea, vomiting diarrhea.

- **Kernicterus**: These can displace bilirubin from plasma protein binding sites and may result in **kernicterus** in the new born (if given in third trimester of pregnancy) as it crosses BBB and deposited in basal ganglia.

- Mafenide is toxic of all three topical agents. It can cause allergy, pain on application and metabolic acidosis (by inhibiting carbonic anhydrase)

ADVERSE EFFECTS (Mnemonics)

- **B-** Bone marrow suppression
- **I-** Insoluble in urine (Crystalluria)
- **K-** Kernicterus in neonates
- **A-** AIP, Agranulocytosis
- **S-** SJS, Rash
- **H-** Hemolysis

STEVENS JOHNSON SYNDROME

TRIMETHOPRIM

- It is a **bacteriostatic antimetabolite** that inhibits dihydrofolate reductase.
- It is highly selective for bacterial DHFR and doesn't effect human folate metabolism.
- It attains **high concentrations in the prostate and vaginal fluids.**
- For most of the indications, it is combined with sulfonamides; however it can be used **alone in prostatitis and UTI.**
- **Chances of resistance develops if used alone, hence used in FDC.**

- It can cause **megaloblastic anemia** (can be ameliorated by folinic acid), leucopenia and pancytopenia.
- It can also result in **hyperkalemia** (due to amiloride like action i.e., inhibition of epithelial Na+ channels in CD).

Note:

- Other DHFRase inhibitors are pyrimethamine, methotrexate, proguanil and pentamidine.
- All DHFRase inhibitors can cause **megaloblastic anemia**.

COTRIMOXAZOLE

- Cotrimoxazole is a fixed dose combination of **sulfamethoxazole and trimethoprim** in a ratio of **5:1.** because of high volume of distribution of trimethoprim than sulphonamide.

- Both drugs have similar half life and the combination is **bactericidal** to most pathogens.

- The bactericidal activity is due to **sequential blockade** at two steps in the DNA synthesis (sulfamethoxazole inhibits folate synthase and trimethoprim inhibits DHFRase).

- This is a **synergistic combination**.
- Due to different bioavailability (more for sulfamethoxazole), plasma concentration of the two drugs attained is **20:1.**
- **Chances of resistance develops if trimethoprim or sulphonamide used alone, hence used in FDC.**

COTRIMOXAZOLE DOSAGE

Sulfamethoxazole (mg)	Trimethoprim 1/5th dose (mg)	Preparations
100	20	Pediatric tablet
200	40	Oral suspension
400	80	Oral(single strength) , i.v.
800	160	Oral tablet double strength (DS), i.m.

USES

- **UTI:** caused by Ecoli, proteus and Enterobacter
Acute Uncomplicated and chronic recurrent UTI.
- **Prostatitis**
- **URTIs and LRTIs-**middle ear and sinus infections caused by hemophilus and moraxella.
- **Bacterial gastroenteritis and dysentery** – caused by , E.coli, salmonella, shigella, travelers diarrhea due to V. chlorea
- **Typhoid fever**

- **Pneumonia by** Pneumocystis jiroveci infection
- **Chancroid**
- **MRSA**
- **Whipples disease**
- **Meliodosis**
- **Nocardiosis (DOC)and brucellosis**

- It is the **drug of choice for pneumocystis jiroveci, nocardiosis, burkholderia cepacia, isosporiasis, cyclosporiasis, sarcocystosis and cystitis.**

ADVERSE EFFECTS

- Adverse effects are similar to sulfonamides and trimethoprim.
- Permanent impairment in renal function can occur in prexsiting renal disease.
- **Contraindicated in pregnancy** as it causes neonatal hemolysis and **methemoglobinemia.**

Note: Nowadays, Resistance is common due to **plasmid mediated mutation.**

DRUG INTERACTION

- Sulphonamides increases toxicity of phenytoin, tolbutamide and warfarin, aspirin due to displacement from plasma protein binding sites.

- Sulphonamides causes methotrexate toxicity via inhibiting its renal toxicity

THANKS