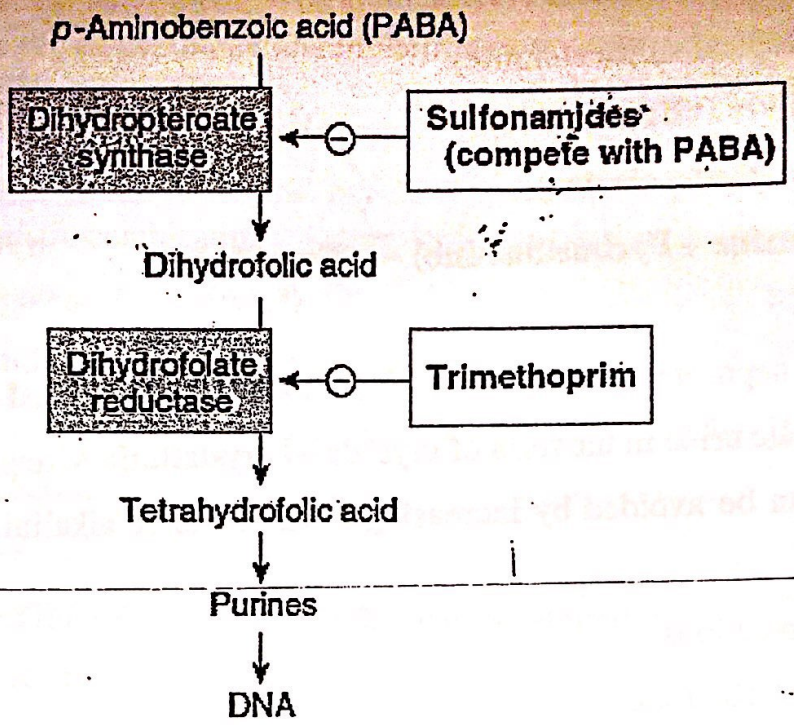
(3) Folate antagonists



Sulphonamides

Members:

- Sulfadiazine.
- Sufamethoxazole.
- Sulfadoxine.
- Sulphacetamide (eye drops).

Mechanism of action: *Bacteriostatic*.

- Sulphonamide is structural analog of PABA.
- They compete with it for the enzyme DHPS (dihydropteroate synthetase) → inhibition of folate synthesis → inhibition of DNA & RNA synthesis.

N.B. Human cells utilize already formed folic acid while bacterial cells synthesize its own folic acid from PABA.

Pharmacokinetics:

- Sulphonamides are well-absorbed orally except sulfasalazine.
- They are distrebuted all-over the body (including CSF).
- Metabolized by acetylation and execreted by kidney.

Therapeutic uses:

1- Antibacterial: Sulfamethoxazole + Trimethoprim (***Cotrimoxazole***).

2- Eye infections (topical **sulfacetamide**).

3- Burns (topical silver **sulfacetamide**).

4- Ulcerative colitis (**Sulfasalazine**).

5- Malaria (**Sulfadoxine + Pyrimethamine**) → (***Fansidar***).

Adverse effects:

1- Crystalluria & nephrotoxicity: sulfonamides metabolites formed in liver precipitate in acidic urine in the form of crystals → crystalluria & nephritis.

N.B. Crystalluria can be avoided by increasing fluid intake & alkalinization of urine.

2- Hypersensitivity reactions.

3- Hematological disturbances:

- Granulocytopenia & thrombocytopenia.
- Hemolytic anemia in patients with G6PD deficiency.

4- Kernicterus (jaundice with CNS affection): Sulphonamides in newborn displace bilirubin from P.P. binding → free bilirubin crosses immature BBB and reach CNS.

5- Sulphonamides increase the level of oral hypoglycemics & anticoagulants in blood (by displacement from P.P. binding).

Trimethoprim

Mechanism of action:

- Inhibition of DHFR (dihydrofolate reductase) enzyme, which converts folic acid to tetrahydrofolic acid (folinic acid) which is essential for DNA synthesis.

Adverse effects:

1- Megaloblastic anemia (folate deficiency).

2- Granulocytopenia & leucopenia.

Co-trimoxazole

- It is a combination of **sulfamethoxazole** (400 mg) + **trimethoprim** (80 mg).
- They cause ***sequential block*** and inhibition of the two steps of folate synthesis → synergistic effect.

Advantages:

1- Synergistic combination.

2- More potent (***bactericidal***).

3- Less and delayed bacterial resistance.

4- Wider spectrum including Proteus, Salmonella, Shigella, H. influenza & Gonococcus.

Therapeutic uses:

1- Urinary tract infections, prostatitis & gonococcal urethritis.

2- Salmonella & Shigella infections.

3- Respiratory tract infections due to H. influenza & S. pneumonia.

Adverse effects:

- As sulphonamides & trimethoprim.

Inhibitors of Nucleic Acid Synthesis

1- Quinolones. 2- Rifampicin. 3- Folate antagonists.

(1) Quinolones

Mechanism of action: *Bactericidal.*

- Inhibit topisomerase II (DNA gyrase) enzyme, which is responsible for inhibition of supercoiling of DNA double strands during DNA replication.
- Inhibit topoisomerase IV, which is responsible for separation of the newly formed DNA strands.
- Like aminoglycosides, they have *post-antibiotic effect* (continued inhibition of bacterial growth even after falling of drug concentrations below MIC).

Classification:

1- Non-flourinated quinolones - 1st generation "Nalidixic acid":

- Not used in systemic infections.
- > 90% is bound to plasma proteins with insufficient plasma concentration.
- Was used in urinary tract infections (UTIs) with Gm-negative bacilli.
- Rapid resistance limits its use.

2- Flourinated quinolones (2nd – 4th generations):

- Fluoroquinolones (2nd generation) are effective mainly against aerobic Gm-negative organisms, weak against Gm-positives & ineffective against anaerobes.
- Newer generations have increased activity against Gm-positive cocci & anaerobes.

- 2nd generation (norfloxacin, ciprofloxacin, ofloxacin & pefloxacin):
  - Excellent against Gm-negative organisms: Pseudomonas, E. coli, H. influenza, Proteus, Salmonella & β-lactamase-producing gonococci (ciprofloxacin is superior to all especially against Pseudomonas).
  - Moderate against Gm-positive organisms: Staph. (but not MRSA), weak against Strept. & pneumococci.
  - Effective against agents of atypical pneumonia.

N.B. Norfloxacin is used only in UTIs as it does not achieve systemic therapeutic levels.

- **3rd generation** (levofloxacin):
  - ❖ Called "Respiratory quinolones".
  - ❖ Less active against Gm-negative organisms than 2nd generation.
  - ❖ Greater activity against Gm-positive organisms (including Pneumococci and MRSA).
- **4th generation** (moxifloxacin):
  - ❖ The broadest spectrum generation.
  - ❖ Very effective against anaerobes.

Pharmacokinetics:

- Oral bioavailability of norfloxacin is 35 to 70% compared to 80 to 99% of the other fluoroquinolones.
- They are well-distrebuted into all tissues and body fluids.
- Levels are high in bone, urine (except moxifloxacin), and lungs, but low in CSF (except ofloxacin).
- Most of fluoroquinolones are execreted renally but moxifloxacin cleared by the liver.

Uses of quinolones:

1- Typhoid & infective diarrhea (ciprofloxacin).
2- Anaerobic infections (clinafloxacin).
3- UTIs (Gm-negative bacilli) & prostatitis.
4- Gonorrhea (ofloxacin single dose).
5- Atypical pneumonia (chlamydia, mycoplasma, legionella) and resistant respiratory tract infections to β-lactams (levofloxacin & moxifloxacin).
6- Bone & soft tissue infections.
7- Resistant TB.

Adverse effects:

1- G.I.T.: nausea, vomiting & diarrhea (common).
2- C.N.S.: headache, dizziness, insomnia & convulsions in susceptible patients.

3- Phototoxicity.

4- Connective tissue problems:

a. Arthropathy "articular joint erosion" (avoided in pregnancy, lactation and in children < 18 ys).

b. Tendinitis or tendon rupture:

- ✓ The Achilles tendon is frequently affected.
- ✓ This can occur during treatment, or up to several months after completion of therapy.
- ✓ The risk is increased in patients over 60 years of age and those receiving corticosteroid therapy.

5- ***Drug interactions:***

- ❖ Enzyme inhibition → increased level of warfarin & theophylline.
- ❖ Mg^{+2} & Al^{+3} (cations in antacids) decrease absorption of quinolones.
- ❖ Prolonged Q-T interval → arrhythmia, especially if given with erythromycin, class Ia & class III antiarrhythmics & TCAs.

Contraindications:

1- Quinolones are contraindicated in pregnancy & lactation.

2- Not routinely recommended in patients less than 18 years (arthropathy).