Quinolones, Sulfonamides, Trimethoprim

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Inhibitors of Bacterial Nucleic Acid Synthesis Quinolones

- Bactericidal
- Concentration-dependent bacterial killing.
- Effective against gram negative organisms: Pseudomonas species, enterobacteriacea, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia and gonorrhea

Generations of Quinolones

First Generation

Nalidixc Acid (NegGram)

- G-ve Bacteria like Escherichia coli
- No systemic effect
- Urinary Tract Infection (UTI)

Second Generation

Fluoroquinolones

Ciprofloxacin

Lomefloxacin

Norfloxacin

Ofloxacin

Pefloxacin

- Systemic effect
- G-ve > G +ve Bacteria

Third Generation

Levofloxacin

Moxifloxacin

- (Enhanced activity against G+ve) … Lower Respiratory Tract Infection

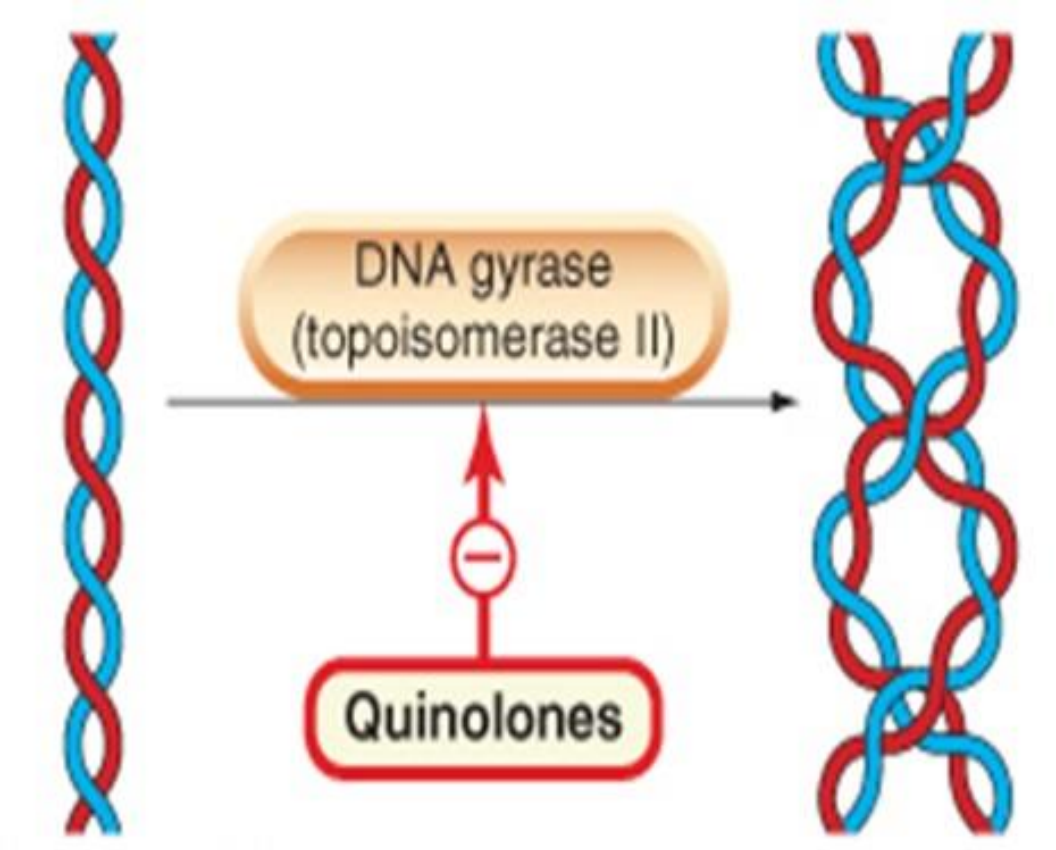
Fourth Generation (Anaerobes)

- Clinafloxacin
- Gemifloxacin
- Trovafloxacin **(Removed from clinical used)**

Mechanism of Action Quinolones

Impairment of bacterial nucleic acid synthesis by inhibiting the replication of bacterial DNA

- In Gram Negative bacteria
  These drug inhibit the enzyme DNA gyrase (topoisomerase II)
- In Gram Positive bacteria
  These drug Inhibit the enzyme topoisomerase IV during bacterial growth and reproduction.
- Can cause cell death by inducing cleavage of the DNA.


DNA gyrase
(topoisomerase II)
Quinolones

Clinical Uses of Quinolones

1. Urinary tract infection
2. Acute cystitis in females
3. Chronic bacterial prostatitis
4. Lower respiratory tract infection
5. Acute sinusitis
6. Skin infection
7. Bone and joint infection
8. Infectious diarrhea
9. Uncomplicated gonorrhea

Adverse Reactions of Quinolones

1. Nausea, vomiting and diarrhea (most common).
2. Phototoxicity
3. prolong QT interval
4. Liver toxicity: Trovafloxacin (life-threatening).
5. Risk of permanent damage to the joints (Arthropathy)

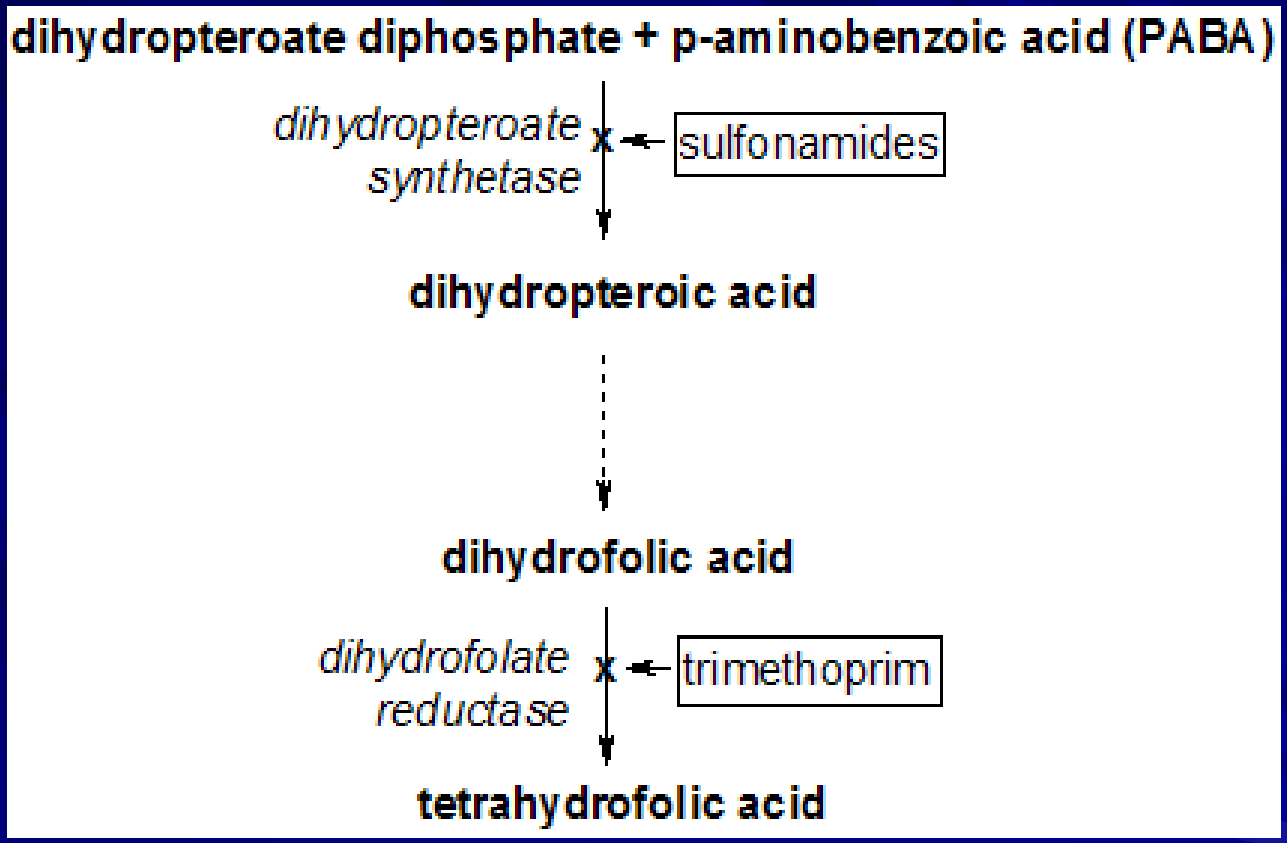
Note: Avoided in pregnancy, in nursing mothers, and in children under 18 years of age. In adults, fluoroquinolones can infrequently cause ruptured tendons.

Inhibitors of bacterial metabolism
Sulfonamides

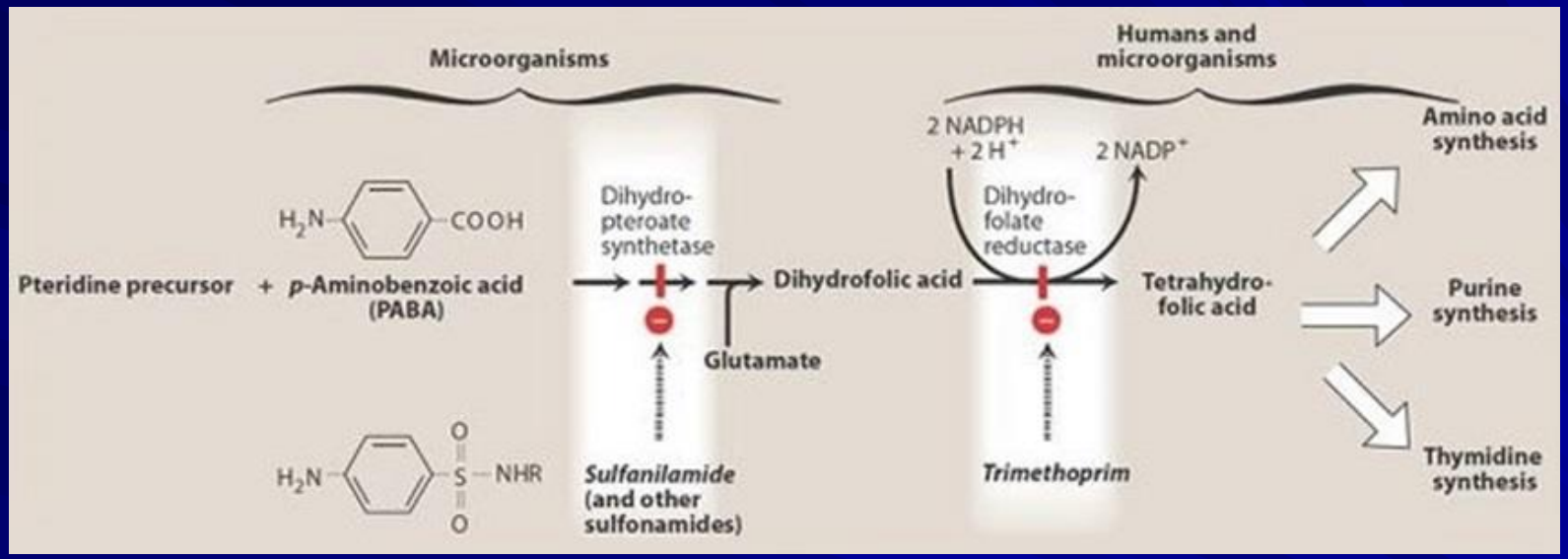
- Sulfa drugs are still employed in developing countries because of their low cost and their efficacy in certain bacterial infections, such as trachoma and UTIs.
- Active against selected enterobacteria in the urinary tract .
- Sulfadiazine + pyrimethamine (dihydrofolate reductase inhibitor) used for treatment of toxoplasmosis and chloroquine-resistant malaria.

Mechanism of Action of Sulfonamides

- Sulfonamides are synthetic analogs of PABA
- compete with PABA for the bacterial enzyme, dihydropteroate synthetase
- inhibit the synthesis of bacterial dihydrofolate (dihydrofolic acid)
- Finally lead to inhibition purine & pyrimidin synthesis(inhibition the synthesis of the building-blocks of nucleic acid)


dihydropteroate diphosphate + p-aminobenzoic acid (PABA)
dihydropteroate synthetase
sulfonamides
dihydropteroic acid
dihydrofolic acid
dihydrofolate reductase
trimethoprim
tetrahydrofolic acid

Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim.



Pharmacokinetic of Sulfonamides

- Orally & IV (for patients who are unable to take oral preparations)
- Well absorbed via the small intestine, except Sulfasalazine, not absorbed when administered orally or as a suppository, used for chronic inflammatory bowel disease (Crohn disease or ulcerative colitis).
- Local intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate which have the anti-inflammatory effect.
- Creams of silver sulfadiazine have been effective in reducing burn-associated sepsis.

Note: sulfas are not usually applied topically (Because of the risk of sensitization)

Side Effects of Sulfonamides

1. Nephrotoxicity (Crystalluria), adequate hydration and alkalinization of urine prevent the problem sulfisoxazole and sulfamethoxazole are less liable to this side effects
2. Rashes, angioedema and Stevens-Johnson syndrome & other Hypersensitivity reactions
3. Hemolytic anemia (in patients with G6PD deficiency), Granulocytopenia & thrombocytopenia.

4. Kernicterus because sulfa drugs displace bilirubin from binding sites on serum albumin in newborns. The bilirubin enter into the CNS (because the baby's BBB is not completely developed)

Note: Sulfa drugs should be avoided in newborns and infants less than two months of age, as well as for pregnant women at term

5. Rise the level of many drugs (tolbutamide &warfarin methotrexate) through displacement from binding sites on serum protein.

Trimethoprim

- 20-50-fold more potent than the sulfonamide
- May be used alone in the treatment of acute Utls and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred) and also used in vaginitis.

Mechanism of Action of Trimethoprim

- Inhibit formation of of tetrahydrofolate (tetrahydrofolic acid) by inhibition of dihydrofolate reductase, finally lead to inhibition of purine & pyrimidin synthesis (inhibit the synthesis of the building-blocks of nucleic acid

Co-Trimoxazol

- Co-Trimoxazole has a broader spectrum of antibacterial action than the sulfa drugs.
- The synergistic antimicrobial activity occurs by the combination of trimethoprim & sulfamethoxazole
- This synergism cause inhibition of two sequential steps in the synthesis of tetrahydrofolic acid

Co-trimoxazole is effective in treating UTIs and respiratory tract infections& and ampicillin-or chloramphenicol-resistant systemic salmonella infections.

Adverse Effects of Co-trimoxazole

1. Skin reactions (common)
2. Nausea, vomiting, glossitis & stomatitis.
3. Hemolytic anemia (in patients with G6PD deficiency) Megaloblastic anemia, leukopenia& thrombocytopenia .