College of Dentist medicine
3rd year stage, pharmacology lecture.

Quinolones, Folic Acid Antagonists

I. Fluoroquinolones

- Introduction of the first fluorinated quinolone, **norfloxacin**, was rapidly followed by development of other members of this group, such as **ciprofloxacin**, which has had wide clinical application.
- Newer fluorinated quinolones offer 1- greater potency, 2- a broader spectrum of antimicrobial activity,3- greater in vitro efficacy against resistant organisms, and in some cases,4- a better safety other antibiotics.

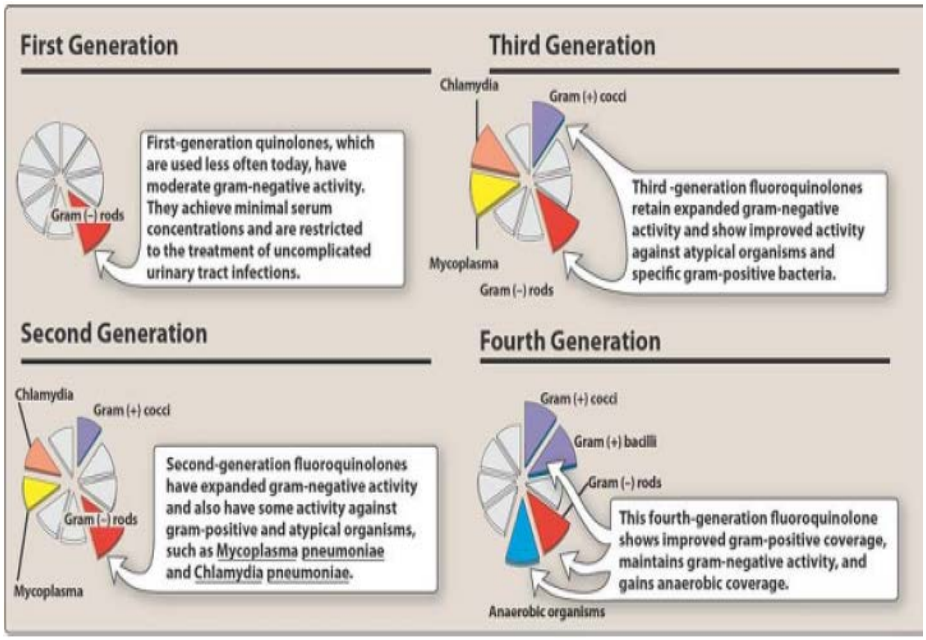
Mechanism of action

- The fluoroquinolones enter the bacterium by passive diffusion through protein channels (porins) in the outer membrane.
- Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction.

Antimicrobial spectrum

- All the fluoroquinolones are bactericidal.
- In general, they are effective against gram-negative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia.
- They are effective in the treatment of gonorrhea .
- The newer agents (for example, **levofloxacin and moxifloxacin**) also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae.
- **Moxifloxacin** has activity against many anaerobes. If used prophylactically before transurethral surgery, fluoroquinolones lower the incidence of postsurgical urinary tract infections (UTIs).

- **Nalidixic acid is the first generaton.**
- **Ciprofloxacin and norfloxacin** are assigned to the second generation because of their activity against aerobic gram-negative .
- **In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and legionella).**
- Levofloxacin is classified as third generation because of its increased activity against gram-positive bacteria.
- Lastly, the fourth generation includes only moxifloxacin because of its activity against anaerobic as well as gram-positive organisms.



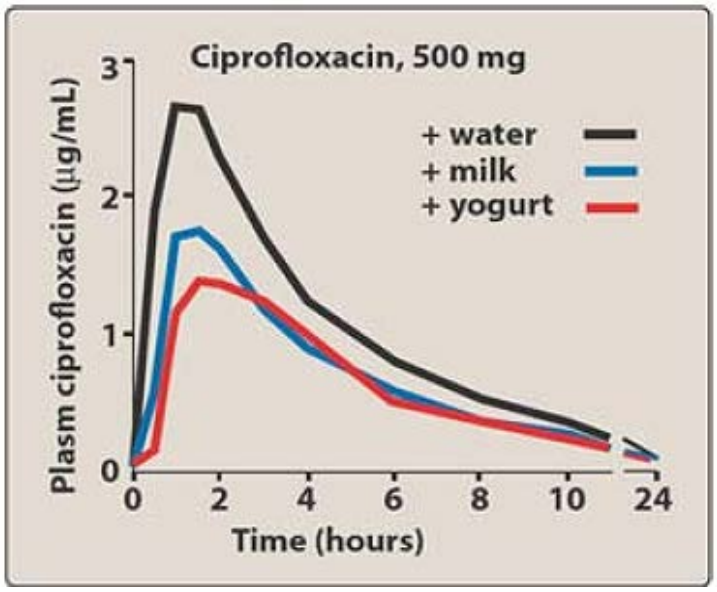
Examples of clinically useful fluoroquinolones

- **Ciprofloxacin:** Ciprofloxacin is particularly useful in treating infections caused by many Enterobacteriaceae and other gram-negative bacilli. For example, traveler's diarrhea caused by E. coli can be effectively treated.
- Ciprofloxacin is also the drug of choice for prophylaxis and treatment of anthrax.
- It is the most potent of the fluoroquinolones for Pseudomonas aeruginosa infections and, therefore, is used in the treatment of pseudomonal infections associated with cystic fibrosis.
- The drug is also used as an alternative to more toxic drugs, such as the aminoglycosides. **It may act synergistically with β-lactams .**

- **Norfloxacin**: Norfloxacin is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in treating complicated and uncomplicated **UTIs and prostatitis.**
- **Levofloxacin**: Levofloxacin can be used in the **treatment of prostatitis due to E. coli and of sexually transmitted diseases**. It may be used as alternative therapy in patients with gonorrhea.
- Additionally, due to its broad spectrum of activity, levofloxacin is utilized in a wide range of infections, including skin infections, acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, as well as nosocomial pneumonia.
- Levofloxacin has excellent activity against respiratory infections due to S. pneumoniae.

- **Moxifloxacin:**Moxifloxacin not only has enhanced activity against gram-positive organisms (for example, S. pneumoniae) but also has excellent activity against many anaerobes. It has very poor activity against P. aeruginosa.

Pharmacokinetics
Ingestion of the fluoroquinolones with sucralfate, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents.



Fate:1- All the fluoroquinolones distribute well into all tissues and body fluids. 2- Levels are high in bone, urine, kidney, and prostatic tissue and concentrations in the lung exceed those in serum.

Adverse reactions

Gastrointestinal: The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea, which occur in three to six percent of patients.

Phototoxicity: Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens. However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity.

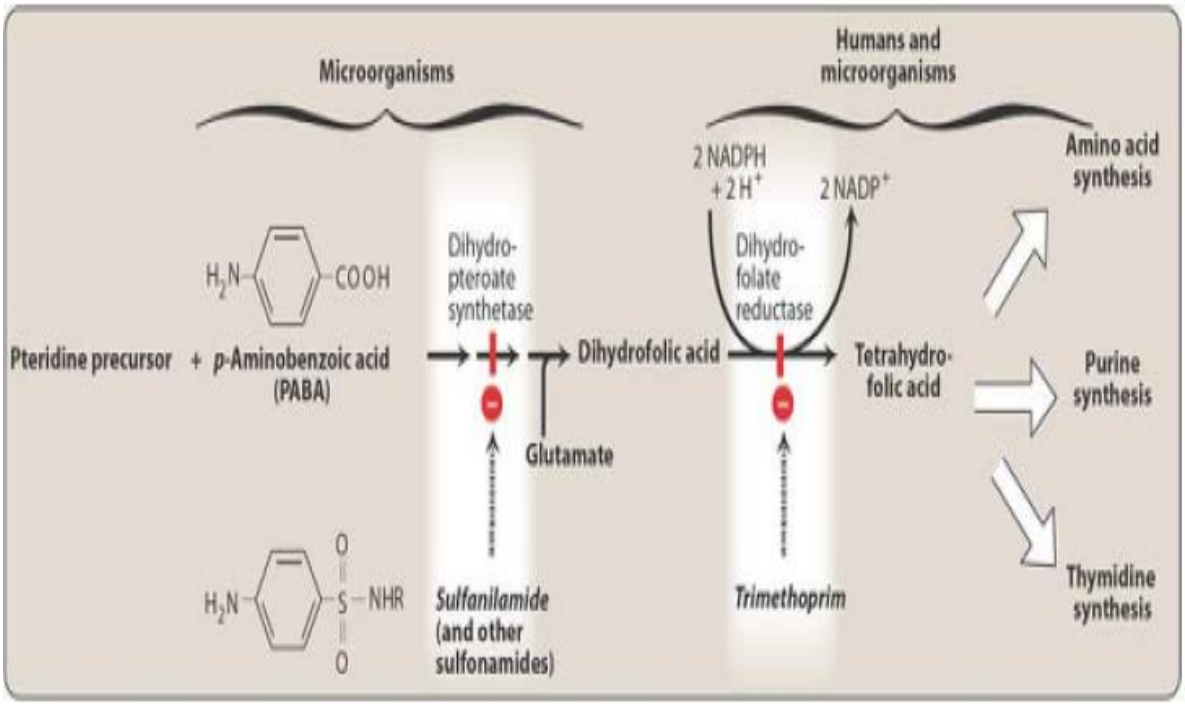
Connective tissue problems: Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age, because articular cartilage erosion (arthropathy) occurs in immature experimental animals.

Folate Antagonists

Sulfonamides
The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and their efficacy in certain bacterial infections, such as trachoma and those of the urinary tract.

Mechanism of action

In many microorganisms, dihydrofolic acid is synthesized from p-aminobenzoic acid (PABA), pteridine, and glutamate . All the sulfonamides currently in clinical use are synthetic analogs of PABA. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms.



Antibacterial spectrum

- Sulfa drugs are active against selected enterobacteria in the urinary tract and nocardia.

Resistance

Resistance is generally irreversible and may be due to **1)** decreased cellular permeability to sulfa drugs, 2**)** enhanced production of the natural substrate, PABA.

Pharmacokinetics

- **Administration**: After oral administration, most sulfa drugs are well absorbed via the small intestine .
- An exception is **sulfasalazine**.
- It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel disease (for example ulcerative colitis).
- In burn units, creams of **silver sulfadiazine** have been effective in reducing burn-associated sepsis, because they prevent colonization of bacteria.

- **Distribution**: They can also pass the placental barrier and enter fetal tissues.
- **Excretion**: The sulfonamides may also be eliminated in breast milk.

Adverse effects

Crystalluria: Nephrotoxicity develops as a result of crystalluria. Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug and promoting its ionization.

Hypersensitivity: Hypersensitivity reactions, such as rashes, angioedema.

Kernicterus: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the baby's blood-brain barrier is not fully developed.

Drug potentiation: Transient potentiation of the anticoagulant effect of warfarin results from their displacement from binding sites on serum albumin.

Contraindications: Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term.

Trimethoprim

Trimethoprim , a potent inhibitor of bacterial dihydrofolatereductase, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis.

exhibits an antibacterial spectrum similar to that of the sulfonamides. **(Trimethoprim is most often compounded with sulfamethoxazole, producing the combination called cotrimoxazole).**

Antibacterial spectrum

Trimethoprim may be used alone in the treatment of acute UTIs and in the treatment of bacterial prostatitis and vaginitis.