Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

FLUOROQUINOLONES

Nalidixic acid is the predecessor to all fluoroquinolones. Today typically offer greater efficacy, a broader spectrum of antimicrobial activity, and a better safety profile than their predecessors.

Mechanism of action

Fluoroquinolones enter bacteria through porin channels and exhibit antimicrobial effects on:

1. DNA gyrase (bacterial topoisomerase II) {gram-negative, (Pseudomonas aeruginosa)}(cipro)
2. bacterial topoisomerase IV. {gram-positive (Streptococcus pneumoniae)} (moxi)

Antimicrobial spectrum

Concentration dependent bactericidal

Effective against:

- ✓ Gram-negative organisms (Escherichia coli, P. aeruginosa, Haemophilus influenzae),
- ✓ Atypical organisms (Legionellaceae, Chlamydiaceae),
- ✓ Gram-positiv eorganisms (streptococci),
- ✓ Mycobacteria (Mycobacterium tuberculosis).

not used for:

- ❖ Staphylococcus aureus or
- ❖ enterococcal infections.

- ❖ syphilis and
- ❖ Neisseria gonorrhoeae (limited utility)

Levofloxacin and moxifloxacin are sometimes referred to as "respiratory fluoroquinolones," because they have excellent activity against S. pneumonia. Moxifloxacin also has activity against many anaerobes. Fluoroquinolones are commonly considered alternatives for patients with a documented severe β-lactam allergy.

Fluoroquinolones may be classified into "generations":

1. First generation (nalidixic acid) : with a narrow spectrum of susceptible organisms.

2. Second generation (Ciprofloxacin and norfloxacin): aerobic gram-negative and atypical bacteria.

significant intracellular penetration (chlamydia, mycoplasma, and mycobacteria).

3. Third generation (Levofloxacin): increased activity against gram-positive bacteria.

4. Fourth generation (moxifloxacin): anaerobic and gram-positive organisms.

Norfloxacin

- Poor oral bioavailability
- Short half-life.
- Effective in treating nonsystemic infections, such as urinary tract infections (UTIs), prostatitis, and infectious diarrhea (unlabeled use).

Ciprofloxacin

- Effective in the treatment of many systemic infections caused by gram-negative bacilli

- It has the best activity against P. aeruginosa (cystic fibrosis).
- Traveler's diarrhea caused by E. coli
- typhoid fever caused by Salmonella typhi.
- Second-line agent in the treatment of tuberculosis.
- With 80% bioavailability, the intravenous and oral formulations are frequently interchanged.
- typically dosed twice daily,
- an extended-release formulation is available for once-daily dosing.

Levofloxacin

- Levofloxacin is the L-isomer of ofloxacin and has largely replaced it clinically.
- Due to its broad spectrum it utilized in:

- a wide range of infections (prostatitis, skin infections, CAP, and nosocomial pneumonia).

- Has excellent activity against S. pneumoniae respiratory infections.
- 100% bioavailability
- Given once daily.

Moxifloxacin

- enhanced activity against gram-positive organisms (for example, S. pneumoniae).
- excellent activity against many anaerobes (resistance to Bacteroides fragilis has been reported).
- poor activity against P. aeruginosa.
- Does not concentrate in urine (not indicated for UTIs).

Resistance

1. Altered target: Chromosomal mutations in bacterial genes have been associated with a decreased affinity for fluoroquinolones at their site of action. Both topoisomerase IV and DNA gyrase may undergo mutations.

2. Decreased accumulation: Reduced intracellular concentration is linked to 1) porin channels and 2) efflux pumps.

Cross-resistance exists among the quinolones.

Pharmacokinetics

Absorption

- Only 35% to 70% of orally administered norfloxacin is absorbed, compared with 80% to 99% of the other fluoroquinolones
- Intravenous and ophthalmic preparations of ciprofloxacin, levofloxacin, and moxifloxacin are available.
- Ingestion of fluoroquinolones with sucralfate, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents.

Distribution

- Binding to plasma proteins ranges from 10% to 40%.
- distribute well into all tissues and body fluids.(high in bone, urine (except moxifloxacin), kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lungs exceed those in serum).
- Penetration into cerebrospinal fluid is relatively low except for ofloxacin.
- accumulate in macrophages and polymorphonuclear leukocytes, thus having activity against intracellular organisms.

Elimination

- Most fluoroquinolones are excreted renally.
- Moxifloxacin is excreted primarily by the liver.

Adverse reactions

- nausea, vomiting, and diarrhea.
- Headache and dizziness or light-headedness (caution with CNS disorder: epilepsy)
- Peripheral neuropathy
- glucose dysregulation (hypoglycemia and hypoglycemia)
- Phototoxicity
- Articular cartilage erosion (arthropathy) (avoided in pregnancy and lactation and in children under 18 years of age.)
- tendinitis or tendon rupture
- Prolong the QT (Moxifloxacin)
- Enzyme inhibitores

THE FOLATE ANTAGONISTS

SULFONAMIDES

Antibacterial spectrum

- Sulfa drugs are active against select Enterobacteriaceae in the urinary tract and Nocardia infections.
- sulfadiazine in combination with the dihydrofolate reductase inhibitor pyrimethamine is the preferred treatment for toxoplasmosis.
- Sulfadoxine in combination with pyrimethamine is used as an antimalarial drug.

Resistance

1) an altered dihydropteroate synthetase,
2) decreased cellular permeability to sulfa drugs,
3) enhanced production of the natural substrate, PABA.

Pharmacokinetics

Absorption

- well absorbed orally (exception is sulfasalazine)
- I.V reserved.
- Silver sulfadiazine is preferred in burn because mafenide produces pain on application and its absorption may contribute to acid–base disturbances.

Distribution

- bound to serum albumin (depends on the ionization constant pKa)
- distribute throughout the bodily fluids and penetrate well into cerebrospinal fluid—even in the absence of inflammation.
- They can also pass the placental barrier and enter fetal tissues.

Metabolism

The sulfa drugs are acetylated and conjugated primarily in the liver. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria "stone formation" and, therefore, potential damage to the kidney.

Excretion

Sulfa drugs are eliminated by glomerular filtration and secretion and require dose adjustments for renal dysfunction. Sulfonamides may be eliminated in breast milk.

Adverse effects

1. Crystalluria (Nephrotoxicity)
2. Hypersensitivity (rashes, angioedema or Stevens-Johnson syndrome)
3. Hematopoietic disturbances ((G6PD) deficiency)
4. Kernicterus
5. Drug potentiation (warfarin, methotrexate)

Contraindications

- Sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in pregnant women at term.
- Sulfonamides should not be given to patients receiving methenamine, since they can crystallize in the presence of formaldehyde produced by this agent

TRIMETHOPRIM

Trimethoprim, a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides. Trimethoprim is most often compounded with sulfamethoxazole, producing the combination called cotrimoxazole.

Antibacterial spectrum

- The antibacterial is similar to that of sulfamethoxazole.
- Trimethoprim is 20- to 50-fold more potent than the sulfonamides.
- Trimethoprim may be used alone in the treatment of UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred).

Resistance

1. Altered dihydrofolate reductase that has a lower affinity for trimethoprim.
2. Efflux pumps
3. Decreased permeability.

Pharmacokinetics

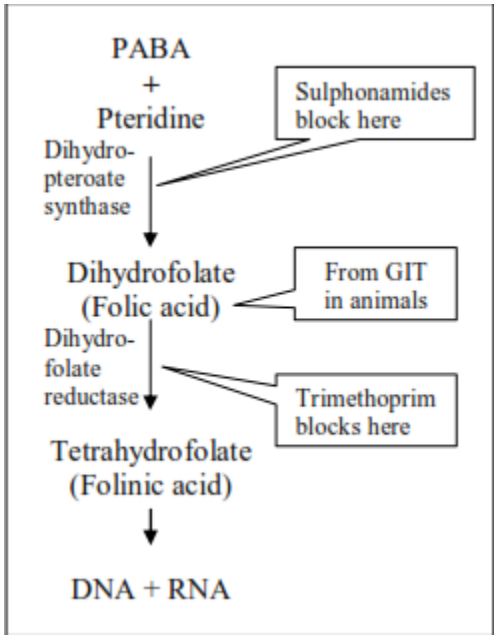
- rapidly absorbed following oral administration.
- higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids.
- widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid.
- undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

Adverse effects

- Trimethoprim can produce the effects of folic acid deficiency (megaloblastic anemia, leukopenia, and granulocytopenia), especially in pregnant patients and those having very poor diets.
- reversed by the simultaneous administration of folinic acid, which does not enter bacteria.

COTRIMOXAZOLE

- The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole,
- shows greater antimicrobial activity than equivalent quantities of either drug used alone.
- selected because of the synergistic activity and the similarity in the half-lives of the two drugs.



Antibacterial spectrum

- ✓ broader spectrum of antibacterial action than the sulfa drugs alone.
- ✓ UTIs and respiratory tract infections,
- ✓ Pneumocystis jirovecii pneumonia (PCP),
- ✓ toxoplasmosis, and
- ✓ ampicillin- or chloramphenicol-resistant salmonella infections.
- ✓ MRSA (CA MRSA, skin and soft tissue infections).
- ✓ Nocardia species and Stenotrophomonas maltophilia (the drug of choice).

Resistance

- Resistance to combination is less frequently than to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs.
- resistance of E. coli and MRSA documented.

Pharmacokinetics

- administered orally and IV (severe pneumonia).
- Both agents distribute throughout the body.
- Trimethoprim concentrates in the relatively acidic milieu of prostatic fluids.
- Cotrimoxazole readily crosses the blood–brain barrier.
- Both parent drugs and their metabolites are excreted in the urine.

Adverse effects

- Reactions involving the skin are very common and may be severe in the elderly
- Nausea and vomiting
- Glossitis and stomatitis
- Hyperkalemia (especially with higher doses).
- Megaloblastic anemia, leukopenia, and thrombocytopenia (The hematologic effects may be reversed by the concurrent administration of folinic acid)
- Hemolytic anemia in patients with G6PD deficiency due to the sulfamethoxazole component.
- Immunocompromised patients with PCP frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.
- increased INR
- half-life of phenytoin may be increased
- Methotrexate levels may rise due to displacement from albumin-binding sites by sulfamethoxazole.

URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

- In addition to cotrimoxazole and the quinolones previously mentioned, UTIs may be treated with any one of a group of agents called urinary tract antiseptics, including methenamine, nitrofurantoin, and the quinolone nalidixic acid.
- These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

Methenamine

Mechanism of action

- Decomposes at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria.
- Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug.
- The urinary pH should be maintained below 6.

Antibacterial spectrum

- Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.
- Not recommended Catheter associated bacteriuria or catheter-associated UTI.
- Should not be used to treat upper UTIs (for example, pyelonephritis).
- Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of methenamine.

Pharmacokinetics

- Methenamine is administered orally.

- Contraindicated in patients with hepatic insufficiency, as ammonia can accumulate.
- Methenamine is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur, and the drug is eliminated in the urine.

Adverse effects

- Gastrointestinal distress (major, at higher doses),
- albuminuria,
- hematuria,
- rashes.
- Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate.
- Sulfonamides, such as cotrimoxazole, react with formaldehyde and must not be used concomitantly with methenamine. The combination increases the risk of crystalluria and mutual antagonism.

Nitrofurantoin

Mechanism of action

Nitrofurantoin sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA.

Antibacterial spectrum

It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Grampositive cocci (for example, S. saprophyticus) are typically susceptible.

Adverse effects

- Hemolytic anemia may occur with nitrofurantoin use in patients with G6PD deficiency.

- gastrointestinal disturbances,
- acute pneumonitis,
- neurologic problems.
- Interstitial pulmonary fibrosis (chronic use).
- should not be used in patients with significant renal impairment or women who are 38 weeks or more pregnant.