Pharmacology Sheet

Doctor 2022 - أثر - Medicine - MU

Pharmacology of Quinolones& Sulphonamides

DONE BY:

Farah almflh

CORRECTED BY:

Farah almflh

DOCTOR:

Dr. Nashwa Aborayah

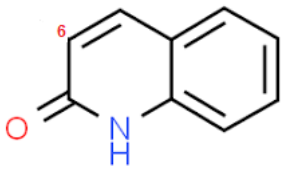
Pharmacology of Quinolones (the most important drugs) & Sulphonamides

- ✓ **Synthetic antimicrobials** (NOT antibiotics; since antibiotics are used to describe natural ones only. However, now it is common to call them all antibiotics).
- ✓ **Bactericidal** (works on DNA synthesis).
- ✓ **Primarily gram- negative bacteria.**

Nalidixic Acid:

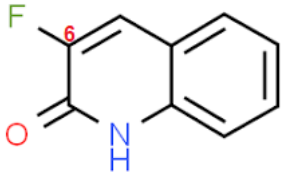
- First member: prototype (1962).
- Advantages of nalidixic acid:
  1. Covers G-ve bacteria.
  2. Rapidly excreted in urine in concentrations enough for treatment of UTIs.
- Disadvantages of nalidixic acid:
  1. Concentration of free drug in plasma& most tissues is non- therapeutic for systemic infections.
  2. Narrow spectrum (not all gram -ve bacteria are covered, only SOME of them), So:
  3. Limited therapeutic use.
  4. Rapid development of bacterial resistance.
- The chemical structure of the lead compound used to produce nalidixic acid has a functional group structure called quinoline (heterobicyclic -has two rings different from each other- aromatic structure).
- Carbon number (#) 6 was attached to a fluorine (F) atom to modify this drug, yielded what is known as fluorinated quinolones or fluroquinolones. That being said, nalidixic acid is not a fluroquinolone, it is a quinolone. **Important.**

FROM EXTERNAL SOURCE



Quinoline

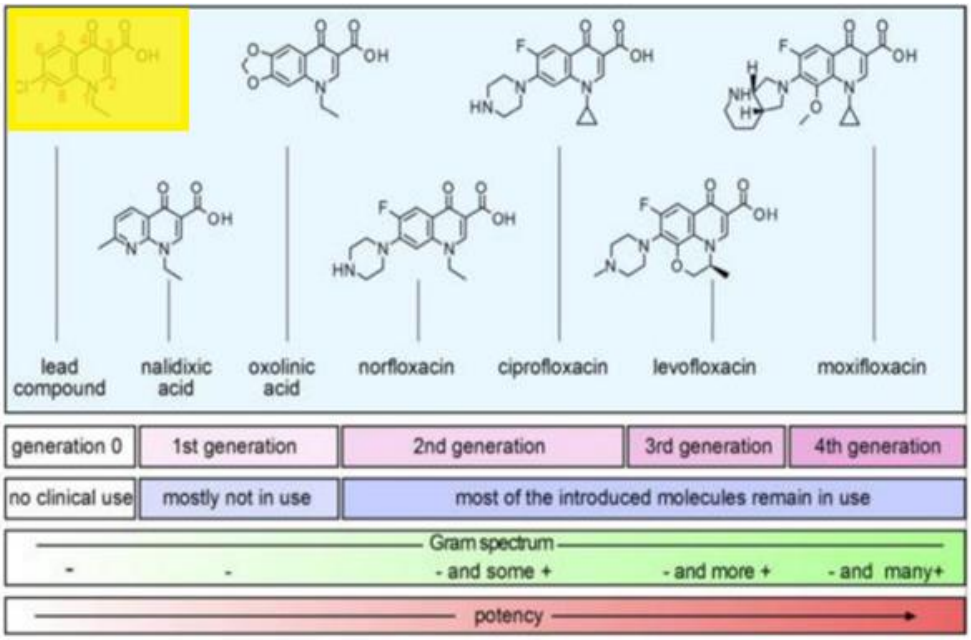
FROM EXTERNAL SOURCE



Fluroquinolone Ring

Fluoroquinolones:

- Quinolones are molecules structurally derived from the heterobicyclic aromatic compound quinoline.
- Fluorination of quinolone structure at position 6 resulted in derivatives called fluoroquinolones.



Advantages of Quinolones:

- **High potency (according to concentrations: higher effects in lower doses).**
- **Expanded spectrum/ broad antimicrobial activity.**
- **Slow development of resistance.**
- **Better tissue penetration.**
- **Prolonged duration of action.**
- **Used for wide variety of infectious diseases.**
- **For all of these advantages, we can roughly say that fluroquinolones are one of the mostly used group of drugs.**

Generation	1st	2nd	3rd	4th
Examples	Nalidixic acid	Norfloxacin, ciprofloxacin.	Levofloxacin.	Moxifloxacin, Gemifloxacin
Spectrum	1. Only some G -ve	1. More G -ve	1. Both G -ve and G +ve 2. Atypical bacteria	1. Both G -ve and G +ve. 2. Atypical bacteria 3. Anaerobic bacteria
Duration of action (the time of its activity inside our bodies)	0	3 hours, 8 hours	12 hours	24 hours
Potency	+	++	+++	++++

Pharmacokinetics (PKs):

- **Key: molecular weight (MWs) less than 500, chemical structure has no -OH groups.**

Absorption:

- **Rapid and complete oral absorption, avoid with food containing Al, Ca, Iron**

Distribution:

- **High tissue penetration: concentration in lung, sputum, muscle, bone, cartilage (minerals), prostate, and phagocytes & neutrophils (IC) exceeds that in plasma.**
- **Can pass BBB: attain concentrations to treat CNS infections.**
- **Pass placental barrier: teratogenic.**
- **Excreted in breast milk.**

Metabolism:

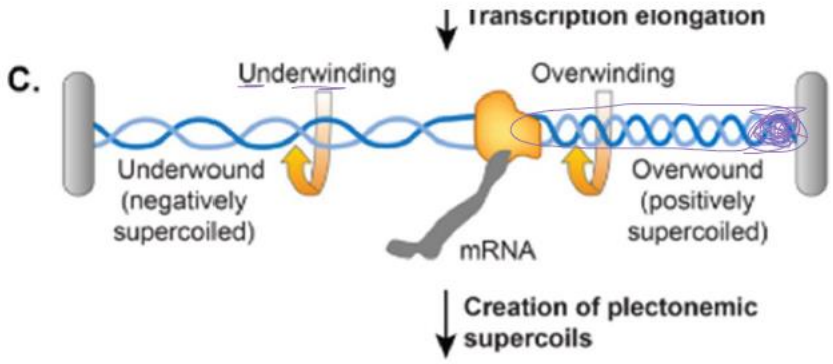
- **Liver**

Excretion:

- **In urine unchanged: Urinary are 10- 50 folds higher than in plasma: UTIs**
- **Moxifloxacin: excreted by non- renal routes: not used in UTIs.**

Mechanism of Action:

- **Quinolones target bacterial DNA gyrase& topoisomerase IV**
  - **Gram negative bacteria – DNA gyrase (a specific type of topoisomerase II that is found in prokaryotes; specifically, gram -ve bacteria. Targeting topoisomerase enzymes will result in more supercoiling -> complex DNA).**
  - **Gram positive bacteria – Topoisomerase IV.**
- **In mammalian cells (human cells) Topoisomerase II:**
  1. **Low affinity for fluoroquinolones.**
  2. **Inhibited by quinolones only at much higher concentrations.**
- **Low toxicity to host cells.**
- **Double helical DNA.**
- **Two strands must separate to permit DNA replication/ transcription.**
- **"over winding"/ excessive positive supercoiling of DNA leads to faulty protein synthesis and bacterial death.**



Mechanism of Resistance:

- **Chromosomal mutation:**
  - **Bacteria produce DNA gyrase/ topoisomerase IV with reduced affinity for quinolones.**
- **Increased efflux of these drugs across bacterial membranes.**
- **Resistance is slow to develop.**

Therapeutic Uses:

1. *Urinary tract infections:*

- **Most commonly used antimicrobials for UTI.**
- **Very effective against Gram negative bacilli like:**
  - **E. coli**
  - **Proteus**
  - **Enterobacter**
  - **Pseudomonas**
- **Ciprofloxacin 500 mg BD**

2. *Salmonella typhi infection (typhoid fever):*

- **Ciprofloxacin 500 mg BD x 10 days.**
- **Prevents carrier state also.**

3. *Respiratory Infections:*

- **How? 1. It can cross to lungs and sputum, 2. Can be distributed to macrophages and neutrophils where it can pass to infection side and 3. Can affect gram +ve bacteria.**
- **Pneumonia.**
- **Acute sinusitis.**
- **Chronic bronchitis.**
- **Respiratory quinolones: levofloxacin, moxifloxacin, Gemifloxacin. They are distributed IC in macrophages and polymorphs. Cover G+ve and atypical bacteria.**

4. *Bone and Joint Infections:*

- **Osteomyelitis and joint infections.**

5. *Meningitis.*

6. *Atypical Infections:*

- **However, 1st line is macrolides then clindamycin then quinolones.**

Adverse Effects:

1. Musculoskeletal:

- Tendonitis & tendon rupture: ciprofloxacin: tendinopathy of Tendo Achilles. It starts with tendonitis and then suddenly without any cause will develop into tendinopathy and tendon rupture.
- Arthropathy (joint disease) in immature animals (possibly due to minerals affinity), then the studies were generalized to human babies:
  - Use in children less than 6- 12 years, pregnancy and during breast feeding contraindicated.

2. CNS:

- Excitation due to blocking of GABA receptors: seizures have occurred predominantly in patients receiving theophylline (bronchodilator) or NSAIDs and epilepsy patients.

3. QT Interval Prolongation:

- Time it takes the hearts' ventricles to depolarize and then repolarize.
- Trovafloxacin withdrawn in 2016.
- Cautious use in patients who are taking drugs that are known to prolong the QT interval:
  - Tricyclic antidepressants.
  - Phenothiazine.
  - Class I anti- arrythmics.

4. Drug Interactions:

- NSAIDS & theophylline:
  - May enhance CNS toxicity of FQ's
  - Seizures reported.
- Antacids, Sucralfate, Iron salts:
  - Reduce absorption of FQ's
- Quinolones are cytochrome p450 inhibitors (a great care should be paid when combined with any other drug generally).

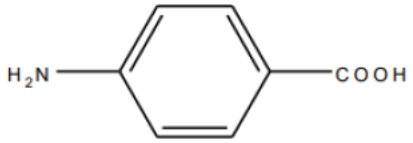
Inhibitors of Synthesis of Essential Metabolites

✓ **Antimicrobials in this class;**

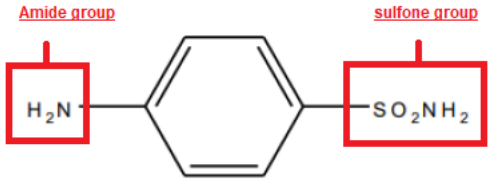
- **Sulfonamides**
- **Trimethoprim**

✓ **Bacteriostatic (like any antimicrobial that works on metabolism).**

✓ **Sulfonamides have sulfone group and amide group in its ring structure, this structure is so close to P- amino- benzoic acid (PABA); which is used by bacteria to synthesize folic acid. Note that since PABA is only found on bacteria, the effects of these drugs on host cells will only be related to pharmacokinetics.**



P-amino-benzoic acid (PABA)



Sulfanilamide

Pharmacokinetics (PKs):

Example:

- **Sulphadiazine**

Absorption:

- **Good oral absorption, not affected by food.**

Distribution:

- **BBB: pass: used with penicillin for treatment of bacterial meningitis in 1930s- 1940s.**
- **Used now for treatment if CNS toxoplasmosis (1st line) and plasmodium falciparum (causes the malignant malaria).**
- **Good tissue penetration: prostate.**
- **Placenta: pass and excreted in breast milk.**

Metabolism:

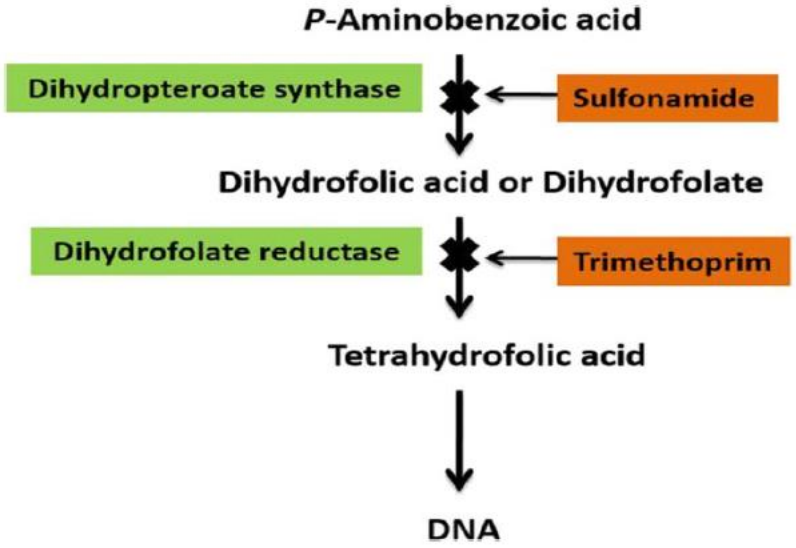
- **Liver**

Excretion:

- **Renal: acylated but active metabolite (UTIs, alkalization of urine).**
- **Whenever this drug is prescribed, we should advise the patient to take effervescent tablets to alkalinize urine and to drink water in massive amounts as this drug has a great tendency to crystalize in acidic urine.**

Pharmacodynamics (PDs):

- Competitive inhibitor of dihydrofolate synthase bacterial enzyme responsible for the incorporation of PABA into dihydrofolic acid (immediate precursor of folic acid). This is attributed to the great similarities between sulfonamides and PABA structures.
- Folic acid required for synthesis of purine and nucleic acid.
- Sulfonamides mimic P- aminobenzoic acid (PABA).
- Trimethoprim antimicrobial drug works on inhibiting dihydrofolate reductase enzyme in the same pathway, inhibiting the bacteria from synthesizing tetrahydro folic acid (the active of folic acid). Sulfonamide
- Co- trimoxazole is a new drug that works on inhibiting the previous 2 mechanisms (like a 2 in 1 drug). Since it worked on inhibiting 2 processes in a row (on a sequence), it causes sequential block.



CO- TRIMOXAZOLE: very important

- Sulfamethoxazole (400 mg) with trimethoprim (80 mg) in 5:1.
- Tablets contain 400 mg of sulfamethoxazole plus 80 mg of trimethoprim.
- Trimethoprim inhibits the enzyme dihydrofolic acid reductase (sequential block)
- Bacteriostatic activity.
- Spectrum:
  - Some G+ve: streptococcal tonsillitis, pharyngitis.
  - Some G-ve: E. coli: UTIs (85% of UTIs are caused by E. coli)
  - Atypical bacteria: chlamydia: eye, genital.
  - Toxoplasma:
  - Plasmodium falciparum: Causes malignant malaria in brain. Drug of choice
  - Pneumocystis carninii: causes a type of pneumonia that is mostly common in immunocompromised patients (typically with AIDS). A very possible exam question. Drug of choice

Indications of co- trimoxazole:

1. **UTIs: excreted in high concentration in urine (alkalization of urine is important because it acidifies urine and forms crystals).**
2. **Streptococcal pharyngitis, tonsillitis.**
3. **AIDS: PCP: Pneumocystis carinii (drug of choice).**
4. **Toxoplasmosis of CNS.**

Other Sulphonamides Combinations:

1. *Silver Sulfadiazine (Cream)*

- **Silver moiety itself has an antimicrobial activity.**
- **Sulfadiazine has antimicrobial and bacteriostatic activities= sulfonamide.**
- **It inhibits the growth of nearly all pathogenic bacteria (pseudomonas) & fungi.**
- **Used topically to reduce the incidence of infections of wounds from burns.**
- **Slowly releases silver ions -antimicrobial action.**

2. *Sulphadoxine & pyrimethamine:*

- **Sulphadoxine is a sulfonamide, inhibits 1st step in folic acid synthesis.**
- **Pyrimethamine is not a sulfonamide, it is an anti-protozoan and 2nd step inhibitors in folic acid synthesis.**
- **Can be used in malignant malaria (plasmodium falciparum): sequential block.**

3. *Sulphasalazine:* important

Inhibition of ifection

- **Sulphapyridine (anti-microbial) & 5- aminosalicylic acid (immunosuppressant): ulcerative colitis (autoimmune disease of the colon).**

Adverse Effects:

1. *Allergy:*

- **Skin rash: common.**
- **Stevens- Johnson syndrome (SNS): TEN (toxic epidermal necrolysis): rare (it is a sever allergic reaction in the skin that causes hemorrhage).**

2. *Crystalluria:*

- **Sulfonamides are insoluble in acidic urine (when excreted in urine and its pH is low – acidic- sulfonamides will:**
- **Precipitate, forming crystalline deposits that can cause urinary obstruction.**
- **Fluid intake sufficient to ensure a daily urine volume of at least 1200 mL.**
- **Alkalization of the urine.**

3. *Kernicterus:*

- **Administration to newborn infants esp. premature:**
  - **Sulfonamides displace bilirubin (jaundice) from plasma albumin.**

The binding site of bilirubin is the same binding site of sulfa so when the sulfa come to the body, it will bind in the site of bilirubin (the affinity of the sulfa more than bilirubin)

- **Free bilirubin is deposited in basal ganglia & sub- thalamic nuclei of the brain causing an encephalopathy & permanent brain damage called kernicterus.**

4. *Anemia:*

- **Hemolytic anemia: G6PD deficiency (fauvism)**
- **Megaloblastic anemia (anemia caused by deficiency in folic acid) treated by folic acid tablets 5 mg once daily.**

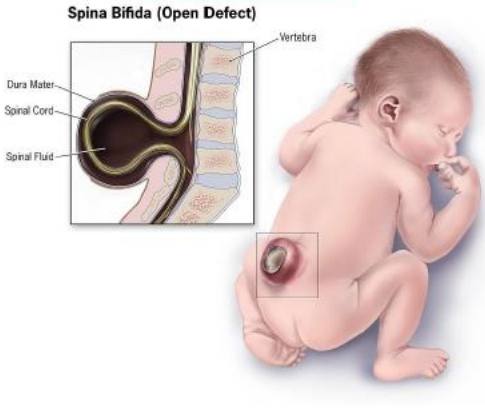
5. *During pregnancy:*

- **1st trimester: neural tube defect (spina bifida): teratogenic.**
- **3rd trimester: kernicterus.**

Contraindications:

- **Pregnancy, children less than 2 y, allergy to sulpha, fauvism, renal stones.**

Spina Bifida:



SJS: