Pharmacology of Quinolones & sulphonamides

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- ✓Synthetic antimicrobials
- ✓Bactericidal
- ✓Primarily gram-negative bacteria

Nalidixic acid

- **First member: prototype**
- **Advantages:**
- **1- Cover G-ve bacteria**
- **2- Rapidly excreted in urine in concentrations enough for treatment of UTIs**

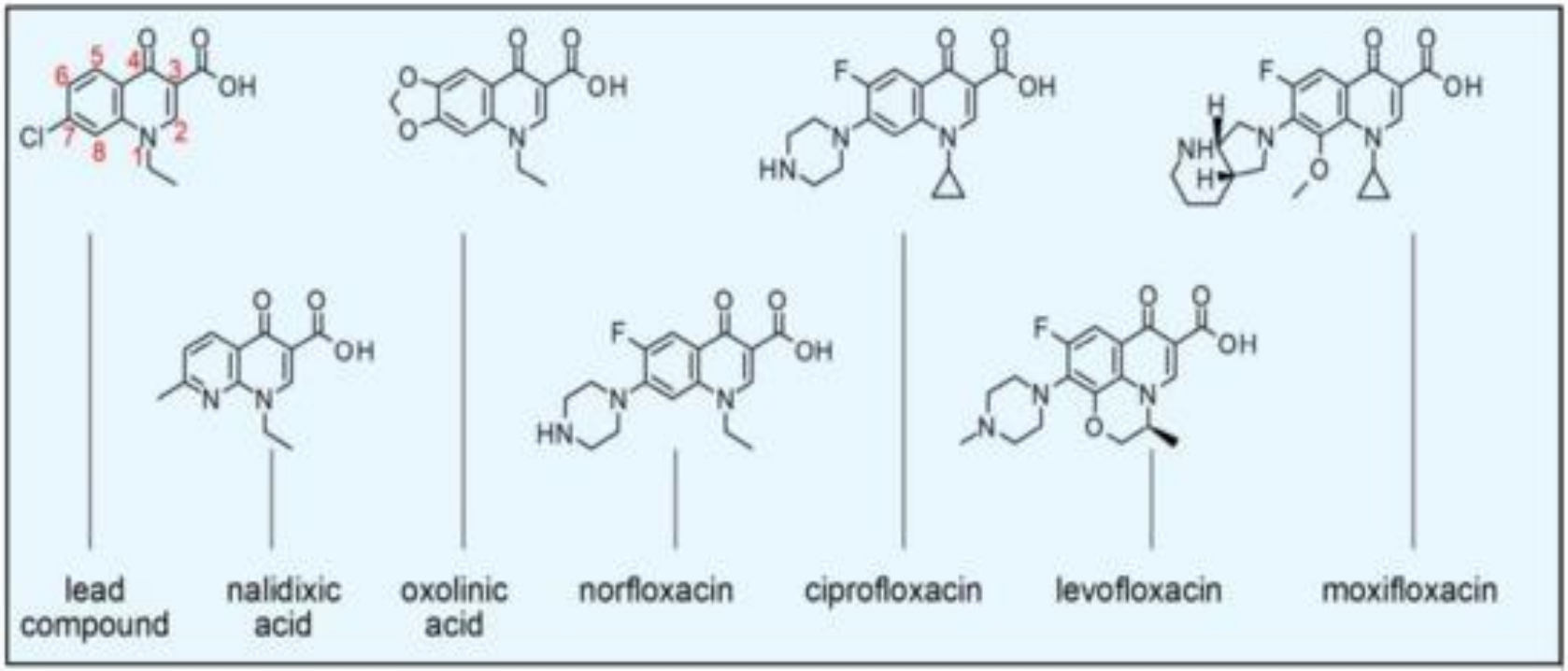
❖Disadvantages of nalidixic acid

- ❖Concentration of free drug in plasma & most tissues is **non-therapeutic** for **systemic infections**
- ❖Narrow spectrum
- ❖ Rapid development of bacterial resistance.
- ❖So:
- ❖Limited therapeutic use

Fluoroquinolones

- Quinolones are molecules **structurally derived from the heterobicyclic aromatic compound quinoline.**

- **Fluorination** of quinolone structure at position 6 resulted in derivatives called **fluoroquinolones**



generation 0	1st generation	2nd generation	3rd generation	4th generation
no clinical use	mostly not in use	most of the introduced molecules remain in use		

Gram spectrum

\- | - | - and some + | - and more + | - and many+

potency

Advantages of quinolones

- High potency
- Expanded spectrum/Broad antimicrobial activity
- Slow development of resistance
- Better tissue penetration
- Prolonged duration of action
- Used for wide variety of infectious diseases

Generation	1st	2nd	3rd	4th
	Nalidixic acid	Norfloxacin, ciprofloxacin	Levofloxacin	Moxifloxacin, Gemifloxacin
Spectrum	Only some G-ve	More G-ve	• Both G-ve and G+ve • Atypical bacteria	• Both G-ve and G+ve • Atypical bacteria • Anaerobic bacteria
Duration of action	0	3hs, 8hs	12hs	24hs
Potency	+	++	+++	++++

Pks

- Key: MW 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 placentral barrier: teratogenic
- Excreted in breast milk
- **Metabolism**: liver
- **Excretion**: in urine unchanged : Urinary are 10-50-fold 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**

- Gram positive bacteria - **Topoisomerase IV**

- **In mammalian cells(human cells) Topoisomerase II**

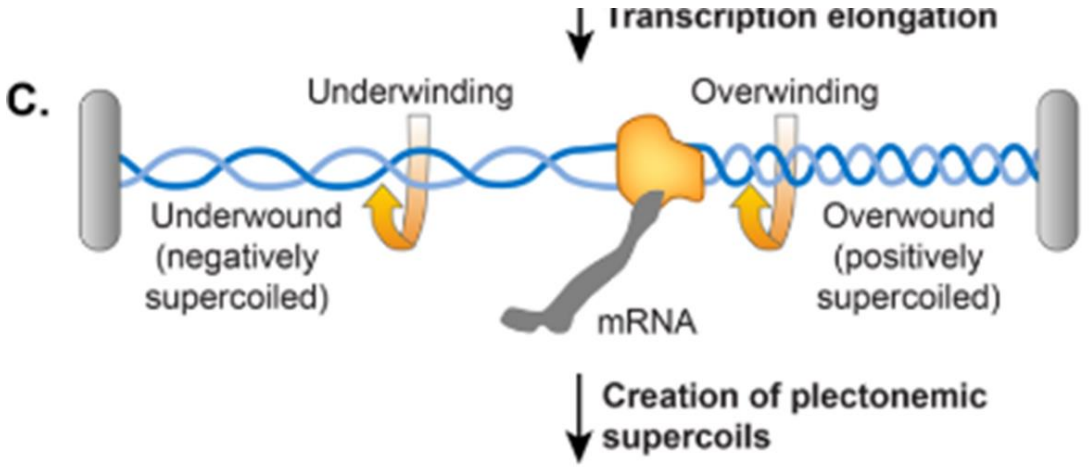
1- Low affinity for flouroquinolones

2- Inhibited by quinolones only at much higher concentrations.

Low toxicity to host cells

Mechanism of action

- 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.

-  **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

  Psuedomonas

  Ciprofloxacin 500 mg bd

2- Salmonella typhi infection (typhoid fever)

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

3- Respiratory infections:

- Pneumonia
- Acute sinusitis
- Chr. Bronchitis
- Respiratory quinolones: levofloxacin, moxifloxacin , Gemifloxacin

They are distributed IC in macropgages and polymorphs

Cover G+ve and atypical bacteria

4-Bone and joint infections: Osteomyelitis & joint infections

- **5- Meningitis**
- **6- - Atypical infections**

Adverse effects

1- Musculoskeletal:

- **Tendonitis** & tendon rupture: ciprofloxacin: tendinopathy of Tendo Achillis
- **Arthropathy (Joint disease)** in immature animals,
  - –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 or a NSAIDs and epilepsy patients

- 3- QT interval prolongation: 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-arrhythmics

➢ 4- drug interactions:

➢ NSAIDs & theophylline may enhance CNS toxicity of FQ's

  – Seizures reported

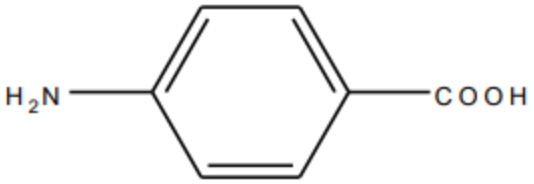
➢ Antacids, Sucralfate, Iron salts

reduce absorption of FQ,s

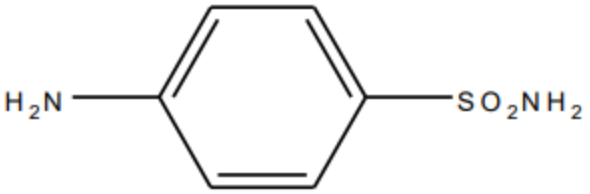
➢ Quinolones are cytochrome p450 inhibitors

Inhibitors of synthesis of essential metabolites

- Antimicrobials in this class;
- • Sulfonamides • Trimethoprim
- Bacteriostatic



P-amino-benzoic acid (PABA)



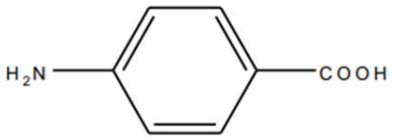
Sulfanilamide

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 of CNS toxoplasmosis and plasmodium falciparum
- Good tissue penetration: prostate
- Placenta: pass and excreted in breast milk
- **Metabolism**: liver
- **Excretion**: renal: acylated but active metabolite (UTIs, alkalinization of urine)

PDs

- Competitive inhibitors of dihydrofolate synthase bacterial enzyme responsible for the incorporation of PABA into dihydrofolic acid (immediate precursor of folic acid).
- Folic acid required for synthesis of purines and nucleic acid
- Sulfonamides mimic P-aminobenzoic acid (PABA)



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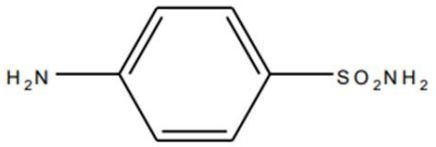
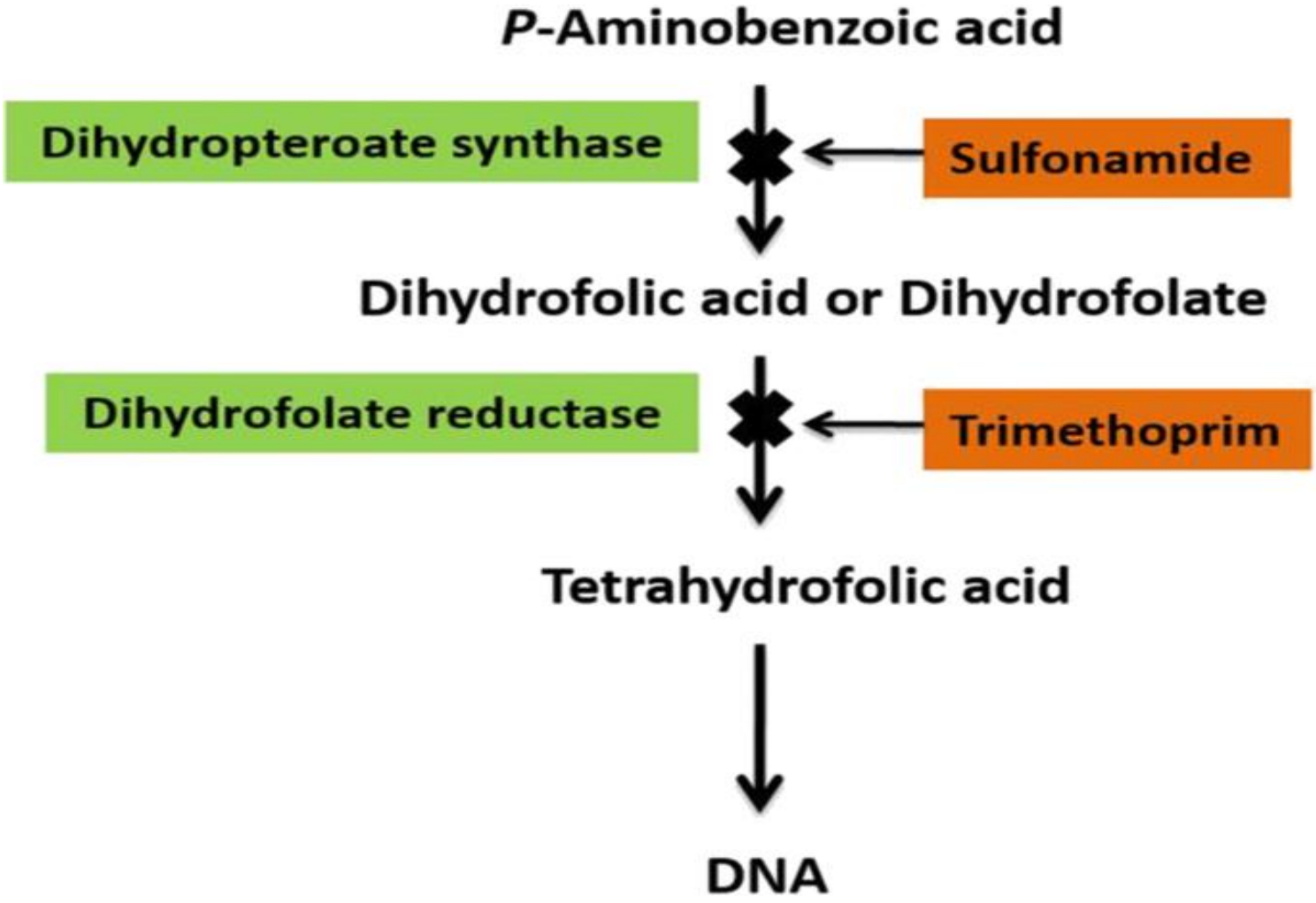


Sulfanilamide


P-Aminobenzoic acid
Dihydropteroate synthase
Sulfonamide
Dihydrofolic acid or Dihydrofolate
Dihydrofolate reductase
Trimethoprim
Tetrahydrofolic acid
DNA

CO-TRİMOXAZOLE

- Sulfamethoxazole with **trimethoprim** in 5: 1
- Tablets contain 400 mg of sulfamethoxazole plus 80 mg of trimethoprim.
- Trimetoprim inhibits the enzyme dihydrofolic acid reductase (sequential block)
- Bacteriostatic activity.
- **Spectrum:**
- Some G+ve: streptococcal tonsillitis, pharyngitis
- Some G-ve: E.coli: UTIs
- Atypical bacteria: chlamydia: eye, genital
- Toxoplasma
- Plasmodium falciparum
- **Pneumocystis carinii**

Indications of co-trimoxazole

- 1- UTIs: excreted in high concentration in urine (alkalinization of urine)
- 2- Streptococcal pharyngitis, tonsillitis
- 3- AIDS: PCP: **Pneumocystis carinii (drug of choice)**
- **4- toxoplasmosis of CNS**

Other sulphonamides combinations

Silver Sulfadiazine (cream)

•Inhibits growth of nearly all pathogenic **bacteria (psudomonus)** & **fungi**

•Used topically to reduce incidence of infections of wounds from burns

–Slowly releases silver ions -antimicrobial action

–Sulphadoxine & pyrimethamine: malignant malaria (plasmodium falciparum): sequential block

–Sulphasalazine: sulphapyridine & **5-aminosalicylic acid: ulcerative colitis**

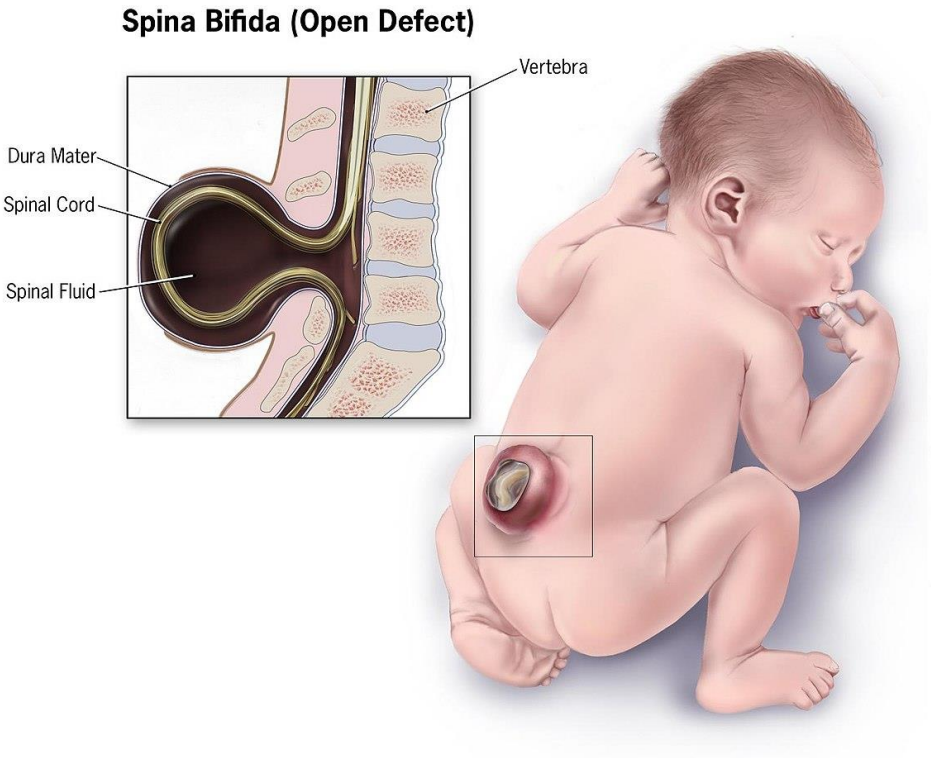
Adverse effects

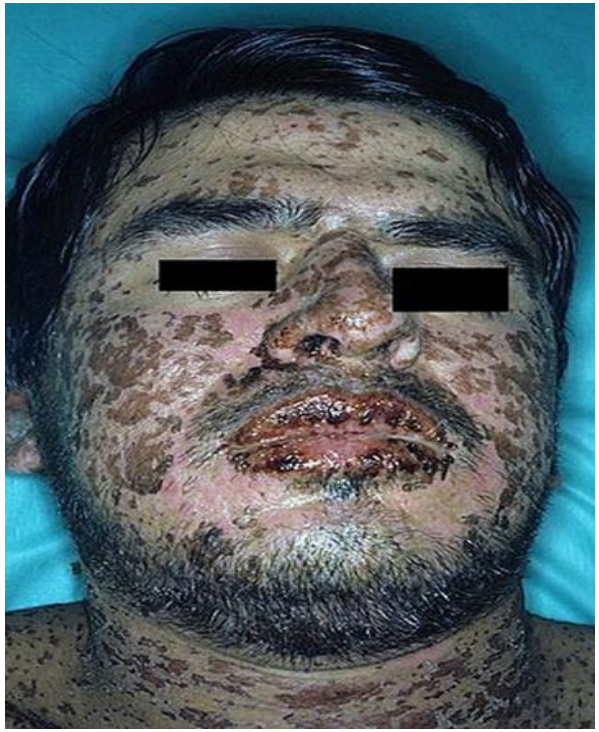
- 1- **Allergy**: skin rash: common
- Stevens-Johnson syndrome (SJS) (TEN: toxic epidermal necrolysis): rare
- 2- **Crystalluria**
- Insoluble in acidic urine
- Precipitate, forming crystalline deposits that can cause urinary obstruction
- Fluid intake sufficient to ensure a daily urine volume of at least 1200ml
- Alkalinization of the urine

3- kernicterus

- Administration to **newborn infants esp. premature**
  - Sulfonamides displace bilirubin (jaundice) from plasma albumin.
  - 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
- Megaloblastic anemia: treated by folic acid tab. 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 (Open Defect)
Vertebra
Dura Mater
Spinal Cord
Spinal Fluid



THANK YOU