Quinolones and sulpha drugs - lec14

-Synthetic antimicrobials

-Bactericidal –inhibit nucleic acid synthesis

-Primarily gram-negative bacteria

- Nalidixic acid and pipemidic acid :

-First member: prototype (1st gen.)

Advantages: 1- Cover G-ve bacteria . 2- Rapidly excreted in urine in concentrations enough for treatment of UTIs

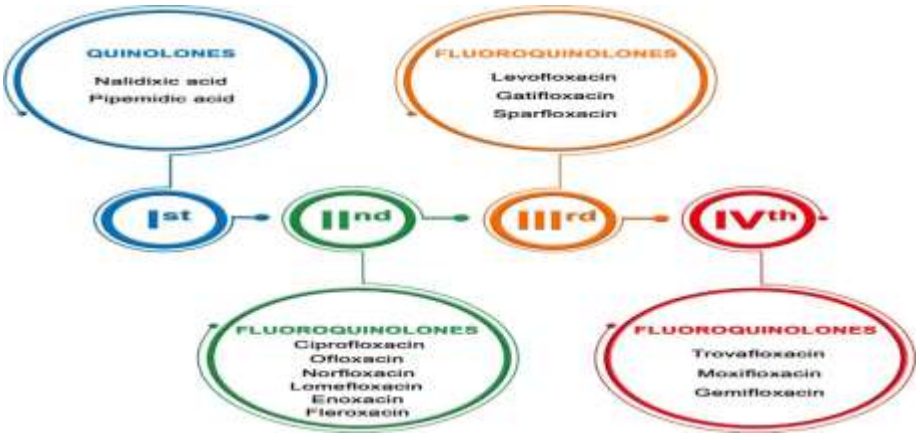
Disadvantages: 1- Concentration of free drug in plasma & most tissues is non-therapeutic . 2- for systemic infections .3- Narrow spectrum (limited range:not all gram negative). 4- Rapid development of bacterial resistance.

So: Limited therapeutic use

((So how will we get rid of these disadvatages????)) FLURINATION OF QUINOLONE STRUCTURE ON POSITION 6 :

FLUOROQUINOLONES

حفظ 3 من كل جيل



	Gram negative aerobes		
Anerobes +	++	+++	++++
Gram +ve +	++	+++	++++
Atypical +	++	+++	++++
Long (bd)	Longer + (qd)	Longer ++ (qd)	Longer ++ (qd)

UTI, Gonorrhea, Typhoid fever, Respiratory, CAP, Mycoplasma, Chlamydia, Tuberculosis, Post-op/Hospital infections, Gynecological infections

When the spectrum of an antibiotic increases, it means it can target a broader range of infections. This includes respiratory tract infections caused by organisms like Staphylococcus and Streptococcus, community- acquired infections such as pneumonia, atypical infections like Mycoplasma and Chlamydia, tuberculosis (TB), hospital- acquired pneumonia, and certain gynecological infections

Advantages of floroquinolones:

-High potency

-Broad antimicrobial spectrum

-Slow development of resistance

- Better tissue penetration

- Prolonged duration of action

(Used for wide variety of infectious diseases)

PK of fluoroquinolones:

-MW<500

-Absorption: Rapid and complete oral absorption, avoid with food (or drugs) 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: reaching concentrations to treat CNS infections

.Pass placentral barrier: teratogenic- contraindications for pregnancy.

-Excreted in breast milk (contraindicated for breast feed)

-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

-So, it can't inhibit topoisomerase II in human cells

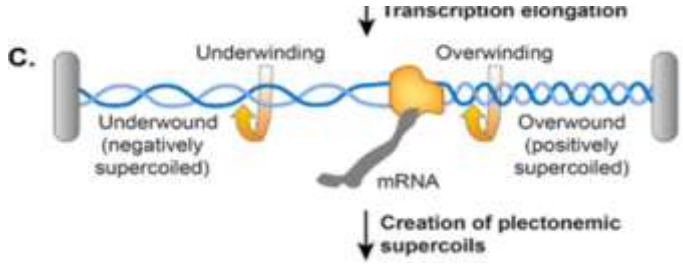
1- Low affinity for flouroquinolones

2- Inhibited by quinolones only at much higher concentrations.

((Low toxicity to host cells))

MOA: Two strands of double helical DNA 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:

1- Chromosomal mutation: bacteria produce DNA Gyrase/ Topoisomerase IV with reduced affinity for quinolones.

2- Drug efflux: across bacterial membranes

Resistance is slow to develop

Therapeutic indications:

1- Urinary tract infections: (**important**)

Most commonly used antimicrobials for UTI Very effective against Gram negative bacilli

E.coli ,Proteus ,Enterobacter, Psuedomonas (every patient enjoy paste-mnemonic)

Ciprofloxacin 500 mg bd (twice daily)

2- Salmonella typhi infection (typhoid fever):

Ciprofloxacin 500 mg bd x 10 days

Prevents carrier state also

3-Respiratory infections: (**important**)

Pneumonia

Acute sinusitis

Chr. Bronchitis

Respiratory quinolones: levofloxacin, moxifloxacin, Gemifloxacin. why?

They are distributed IC in macropgages and polymorphs

Cover G+ve and atypical bacteria

4- Bone and joint infections: Osteomyelitis & joint infections

5- Meningitis (cross BBB)

6- Atypical infections

Adverse effects :

1-Musculoskeletal: important

Tendonitis& tendon rupture: ciprofloxacin: tendinopathy of Tendo Achillis

Arthropathy (Joint disease) in immature animals

Contraindication: children less than 6-12 years, pregnancy and during breast feeding contraindicated

2- CNS: excitation due to blocking of GABA receptors : seizures have occurred predominantlyin patients receiving theophylline or a NSAIDs and epilepsy patients (contraindications)

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 and class I anti-arrhythmics

4- Drug interactions:

-NSAIDs & theophylline may enhance CNS toxicity of floroquinolones-Seizures reported

-Antacids (Al), Sucralfate (Ca), Iron salts reduce absorption of quinolones

-Quinolones are cytochrome p450 inhibitors (so we must decrease the dose of drugs metabolized by CYP450)

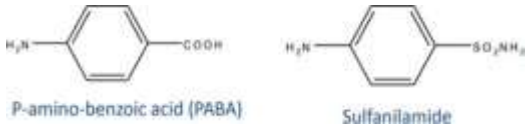
Inhibitors of synthesis of essential metabolites

-Antimicrobials in this class:

-Sulfonamides

-Trimethoprim

-Bacteriostatic

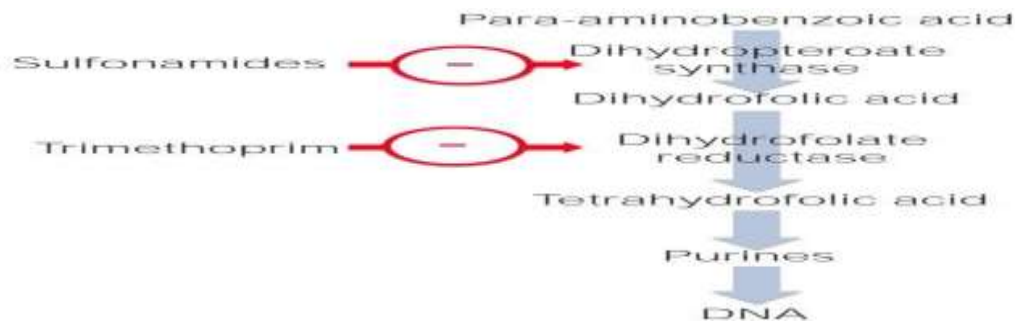


PKs: Example: sulphadiazine (systemic effect)

- **Absorption**: good oral absorption, **not affected by food**
- **Distribution**:
- **BBB**: pass: used with penicillin for treatment of bacterial meningitis in 1930s-1940s
- Good tissue penetration: prostate (prostatic infections)
- Placenta: pass and excreted in breast milk
- **Metabolism**: liver
- **Excretion**: renal: acylated but active metabolite (UTIs, alkalinization of urine) (We must alkalinize the urine when giving sulfadiazine to prevent stone formation, as this
- drug precipitates in acidic urine.)
- **Uses**: treatment of CNS toxoplasmosis and plasmodium falciparum

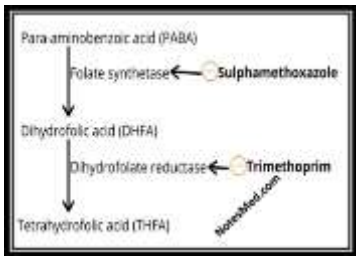
PDs:

- 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 are structural analogue of P-aminobenzoic acid (PABA).



co-trimoxazole(important)

- Sulfamethoxazole(400mg) with trimethoprim(80mg) in 5: 1
- MOA: Trimethoprim 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(yeast infection cause pneumonia ,especially in AIDS pateints ''Opportunistic infection'') –**DRUG OF CHOICE**

Indications of co-trimoxazole:

- 1- UTIs: excreted in high concentration in urine (alkalinization of urine)
- 2- Streptococcal infections: pharyngitis, tonsillitis
- 3- AIDS: PCP: Pneumocystis carinii : oral or IV for 3 weeks
- 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

-The antiseptic action of silver sulfadiazine comes from the silver, while the function of sulfadiazine is to help release silver ions.

- **Sulphadoxine & pyrimethamine**: malignant malaria (plasmodium falciparum): sequential block
- **Sulphasalazine**:sulphapyridine & **5-aminosalicylic acid: ulcerative colitis: will not cure the disease but reduce number of attacks** ((5-aminosalicylic acid acts as an anti-inflammatory agent. Sulphasalazinehas some immunosuppressive properties.))

Systemic effect	Local effect
sulphadiazine	Silver Sulfadiazine (cream)
Sulphasalazine	Sulphasalazine
Sulphadoxine	
co-trimoxazole	

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 (That's why we advise the patient to drink plenty of water and take an alkaline effervescent tablet; like sodium bicarbonate.)

3-kernicterus:
Administration to newborn infants esp. premature
-Sulfonamides (higher affinity to bilirubin) 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 (Sulfa drugs are among the oxidizing agents that can trigger hemolytic anemia in individuals with G6PD deficiency)

-Megaloblastic anemia: treated by folic acid tab. 5 mg once daily (The folic acid tablets that the patient will take won't be used or utilized by the bacteria)

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