Pharmacology of Quinolones

Dr.Nashwa Abo-Rayah

Assistant prof. (clinical &experimental pharmacology)

Mu'tah University- Faculty of Medicine

Objectives

- 1- Nalidixic acid: spectrum, uses, disadvantages
- 2- Urinary antiseptics
- 3- Floroquinolones: source, advantages, classification
- 4- Mechanism of action
- 5- Mechanism of resistance
- 6- Spectrum
- 7- PK, dosage
- 8- Adverse effects and drug interactions
- 9- Therapeutic uses
- 10- Post antibiotic effect

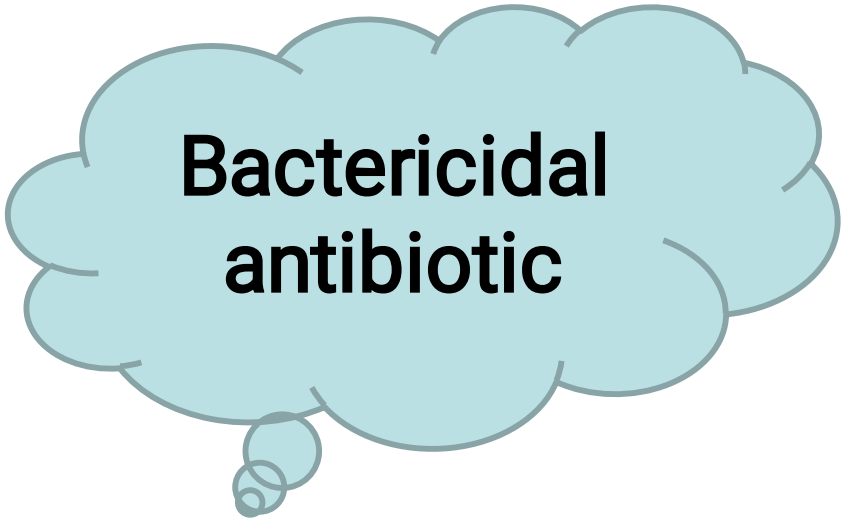
- ✓Synthetic antimicrobials
- ✓Bactericidal
- ✓Primarily gram-negative bacteria

Nalidixic acid

- First member

Spectrum

- **Gram negative bacteria** especially **coliforms**
- E.coli
- Proteus
- Kleibseilla
- Enterobacter
- Shigella
- Psuedomonas: RESISTANT



- Concentration of free drug in plasma & most tissues is **non-therapeutic** for **systemic infections**

- Therapeutic concentrations attained in **urine** & **gut** lumen are lethal to common **urinary** pathogens & **diarrhoea** causing coliforms.

Therapeutic uses

- **Urinary antiseptic**

- **Diarrhoea** caused by coliforms
- Norfloxacin/ciprofloxacin preferred

Nalidixic acid was the drug of choice for Urinary tract infections for many y**ears**

❖ Disadvantages of nalidixic acid

- ❖ Low potency
- ❖ Narrow spectrum
- ❖ Rapid developmemt of bacterial resistance.
- ❖ Limited therapeutic use
- ❖ No longer used.

URINARY ANTISEPTICS

1.Some antimicrobials, in orally tolerated doses, **attain anti-bacterial concentration only in urine,** with **little** or **no systemic anti-bacterial** effect.

2.Like many other drugs, they are concentrated in the kidney tubules, and are useful mainly in lower urinary tract infection.

3.They have been called **urinary antiseptics** because this may be considered as a form of local therapy.

4.Nitrofurantoin and methenamine are two such agents: Infrequently used now. Nalidixic acid can also be considered to be a urinary antiseptic

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
- Expanded spectrum/Broad antimicrobial activity
- Slow development of resistance
- Better tissue penetration &
- Good tolerability
- Used for wide variety of infectious diseases

Classification

First generation

Norfloxacin
Ciprofloxacin
Ofloxacin
Pefloxacin

Second generation

Levofloxacin
Lomefloxacin
Moxifloxacin
Sparfloxacin
Gemifloxacin

Mechanism of action

Quinolones target bacterial DNA **gyrase** & **Topoisomerase IV**

- Gram negative bacteria - **DNA Gyrase**
- Gram positive bacteria - **Topoisomerase IV**

- **In mammalian 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 inhibition of bacterial growth.

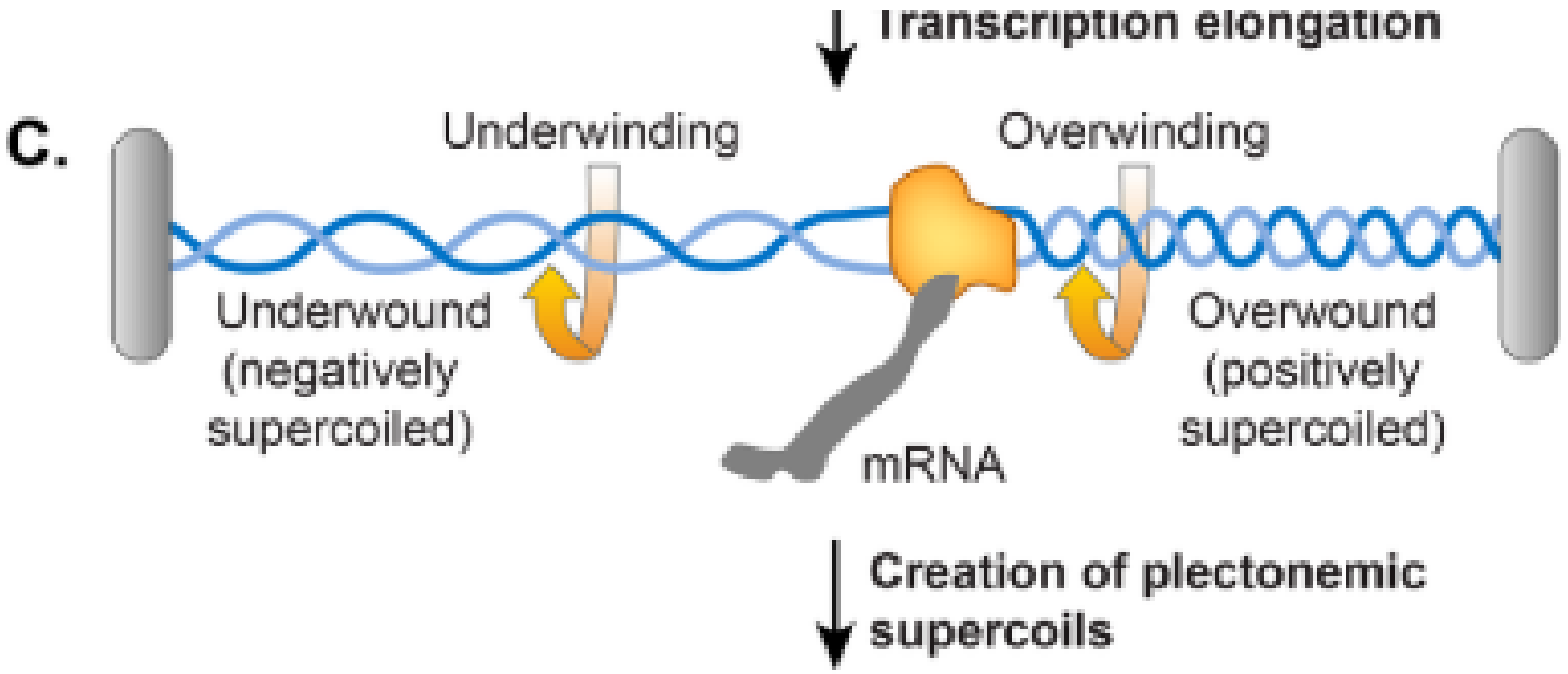
DNA Gyrase has (A & B subunit)

- A subunit - strand cutting function of DNA gyrase.

- B subunit - introduces negative supercoils

  DNA Gyrase - introduces negative supercoils into DNA allowing TRANSCRIPTION & REPLICATION.

- A subunit reseals the strand


C.
Transcription elongation
Underwinding
Overwinding
Underwound
(negatively
supercoiled)
Overwound
(positively
supercoiled)
mRNA
Creation of plectonemic
supercoils

Quinolones

- bind to **A - subunit** with high affinity & interfere with **strand cutting & resealing function**

- Prevent **replication of bacterial DNA** during bacterial growth & reproduction.

- In addition bacterial DNA gyrase inhibition also leads to extensive filamentation and
- vacuole formation

&

degradation of chromosomal DNA
Leading to: bactericidal activity to FQ's

Mechanism of resistance

- **Chromosomal mutation**

  bacteria produce DNA Gyrase/ Topoisomerase IV with **reduced affinity** for FQs

-  **Efflux** of these drugs across bacterial membranes

- Resistance is **slow** to develop

Spectrum

Potent **bactericidal** against Gram negative bacteria:

- E.coli
- Salmonella
- Shigella
- Enterobacter
- Campylobacter & Neisseria

Ciprofloxacin is more active against

- Pseudomonas aeruginosa

- Flouroquinolones also have good activity against
  - **Staph. aureus** but **not** against **methicillin resistant strains**
  - **Moxifloxacin**

  Excellent Activity against **streptococci**
- **Intracellular bacteria** are also inhibited
  - **Chlamydia**
  - **Mycoplasma**
  - **Mycobacterium** including **Mycobacterium tuberculosis**

Several - **anaerobic** bacteria

- Gemifloxacin
- Moxifloxacin

Pk

- Rapid **oral** absorption
- High tissue penetraion
- Concentration in lung, sputum, muscle, bone, prostrate, and phagocytes exceeds that in plasma
- CSF & aqueous levels are low
- Excreted in urine
- Urinary & biliary concentrations are 10-50 fold higher than in plasma

Pk

- Excreted in urine
  - Dose adjustment in renal failure

- Exception Pefloxacin & moxifloxacin
  - Metabolized by liver
  - Should not be used in hepatic failure

Dosage

- Every 12 Hrs for Ofloxacin, Norfloxacin & Pefloxacin
- 250-750 mg every 12 Hrs for Ciprofloxacin
- 500 mg OD (**omne in die** or "once daily" : Levofloxacin
- OD : Lomefloxacin,Sparfloxacin, Gemifloxacin

Adverse effects

- Generally safe
  - Nausea, vomiting, abdominal discomfort, bad taste
- CNS:
  - headache, dizziness, rarely hallucinations, delirium.
  - & seizures have occurred predominantly in patients receiving theophylline or a NSAIDs

Adverse effects

- Hypersenstivity; rashes including photosenstivity

- **Tendonitis** & tendon rupture

- **Arthropathy (Joint disease)** in immature animals,
  - Use in children contraindicated

Adverse effects

- QT interval prolongation
  - Sparfloxacin
  - Moxifloxacin

- Cautious use in patients who are taking drugs that are known to prolong the QT interval
  tricyclic antidepressants
  phenothiazines
  and class I anti-arrhythmics

Drug interactions

- NSAIDs & theophylline may enhance CNS toxicity of FQ's
  - Seizures reported

- Antacids, Sucralfate, Iron salts

  reduce absorption of FQ,s

THERAPEUTIC USES

Urinary tract infections

- Most commonly used antimicrobials for UTI
- Very effective against Gram negative bacilli like
  E.coli
  Proteus
  Enterobacter
  Psuedomonas
- Norflox 400 mg bd
  Ciprofloxacin 500 mg bd
  Ofloxacin 400 mg bd

Prostatitis

- **Norfloxacin**
- **Ciprofloxacin**
- **Ofloxacin**

All are effective.

FQ’s administered for 4-6 wks.

Quinolones with activity against **G +ve bacteria** & **anaerobes** such as

- Gemiloxacin
- Moxifloxacin

can be used in infections of the oral cavity

Sexually transmitted diseases

Active against

- N. gonorrhoea
- Chlamydia trachomatis

- FQ's lack activity against T. pallidum

GASTROINTESTINAL AND ABDOMINAL INFECTIONS

- Traveller's Diarrhoea
- Shigellosis
- Diarrhoea in cholera
- Peritonitis

Salmonella typhi infection

- **Ciprofloxacin** 500 mg bd x 10 days
- Prevents carrier state also
  - 750 mg bd x 4-8 wks
- IN MDR enteric fever (Multidrug-resistant typhoid fever (MDRTF) - Ceftriaxone,Cefotaxime,Cefixime(oral) and oral Azithromycin can be used.

Ofloxacin

Levofloxacin

Pefloxacin

Equally efficacious

Ceftriaxone

- Most reliable
- Fastest acting bactericidal drug for enteric fever
- i.v 4g daily 2 days
- 2g daily till 2 days after fever subsides
- **Preferred drug**

Bone, joint, soft tissue & wound infections

- Skin & soft tissue infections
- Osteomyelitis & joint infections

- **Respiratory infections**
  - Pneumonia
  - Acute sinusitis
  - Chr. Bronchitis
  - **Multi drug resistant TB.**
  - Myco. Avium complex in AIDS pts.
  - & Leprosy

Myco. Avium complex in AIDS pts.

- Mycobacterium Avium complex
- Infection is common in HIV patients CD4 count < 100 cells/µl
- Clarithro mycin/ Azithromycin most active drugs against MAC

Postantibiotic effect

- The antibacterial effect continues for approximately two to three hours after bacteria are exposed to these drugs, despite subinhibitory concentrations.

THANK YOU