By Dr Ayesha jamil

QUINOLONES

- The quinolones are a family of synthetic broad spectrum anti bacterial drugs.
- The first generation fluoroquinolones (FQs) introduced in 1980s had one flouro group attached to it.
- In1990s even more flouro groups were attached, further extending the antimicrobial activity —even covering the gram positive cocci and anaerobes & also conferring them greater metabolic stability (longert1/2). These were referred to as 2nd generation flouroquinolones.

MECHANISM OF ACTION

- The quinolones enter the bacterial cell wall via water filled channels called the porins.
- Once inside they inhibit the bacterial DNA enzymes called DNAgyrase (Topoisomerase II) & Topoisomerase IV during the bacterial growth and DNA replication. (these enzymes are responsible for nicking , pass through & resealing)
- Binding of quinolones with DNA inhibit the resealing step causing cell death and inducing the cleavage of DNA.
- Second it inhibits the Topoisomerase IV preventing the negative supercoiling as well as inhibiting the transfer of replicated DNA
- In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas

in gram-positive organisms (for example, the staphylococci), the opposite is true.

- **First generation:**
- *Nalidixic acid*
- **Second generation**:
- *Ciprofloxacin*
- *Norfloxacin*
- *Ofloxacin*
- **Third generation**
- *Levofolxacin*
- **Fourth generation**

  Moxifloxacin

- This classification in 4 generations is dependent upon their antimicrobial targets.
- ***Nalidixic acid (*1st gen) :** non flourinated, only effective against narrow spectrum of suseptible organisms confined to urinary tract (UTI,s).
- ***Ciprofloxacin & norfloxacin (*2nd gen)** : effective against gram negative bacteria as well as some gm +ivecocci and some atypical bacteria.
- ***Levoflxacin (*3rd gen):** has increased activity against gram positive bacteria.
- ***Moxifloxacin* (4th gen)** : effective against gram positive , gram negative and some anaerobic organism.

- Flouroquinolones are bactericidal in nature. They are effective against gram negative organisms like
- Enterobacteriaceae, pseudomonas, H-influenzae, moraxella catarrhalis, legionellaceae,chlymidia,mycoplasma also some mycobacteria.
- Some newer agents (***moxifloxacin, levofloxacin***) have activity against some Gram positive bacteria such as streptococcus pnemoniae.

CIPROFLOXACINS ANTIBACTERIAL SPECTRUM

- Ciprofloxacin is highly effective against gram negative organisms
- *E-coli*
- *Enterobacter*
- *Proteus*
- *Klebsiella,*
- *Salmonella*
- *Shigella*
- *H-influenzae*
- *N-gonorrhoea*
- *N-meningigitides*
- *anthrax*

CIPROFLOXACIN ANTIBACTERIAL SPECTRUM

- Cipro is modetrately effective against
- *S-aureus*
- *Pseudomonas*
- *Chlymidia*
- *mycoplasma & Mycobacterium.*

The serum level of ciprofloxacin that are achieved are effective against many systemic infections with the exception of *MRSA Sttaphlococcus aureus*, the *enterococci* and the *pneumococci.*

Travelers dairhea caused by *E-coli*.

Cystic fibrosis (due to *Pseudomonas Aeruginosa*).

Compliated & uncomplicated UTI's Gonnorhea

Chancroid : 500mgs BD for 3 days.

Used as an alternative to more toxic aminoglycosides . Act synergistically with β-lactams

Also used in resistant Tuberculosis.

Is also the drug of choice of enteric fever. It is also used for the prevention of carrier stage of the disease due to high billiary and intestinal mucosal concentrations.

Once the carrier stage has been developed than750mgs BD for 4-8weeks will completely eradicate the carrier stage in 92% of the cases.

Bone . Soft tissue , gynaecological & wound infections .Conjunctivitis: is very effective topically.

- *Norfloxacin:*
- It is effective against both gram positive and gram negative (including *P.auregenosa)* bacteria causing
- Complicated and uncomplicated UTI’s
- Prostatitis
- Travelers diarrhea.
- It is **not** recommended for respiratory tract infections as well as other systemic infections particularly those caused by gram positive cocci.

- **Ofloxacin** :
- This FQ is an alternative between cipro & norfloxacin in activity against gram –negative bacteria but is comparable or even more potent than cipro against gram-positive and certain anaerobes.
- **Effective against**
- Cervicitis
- Urethritis
- Atypical pnemonia
- Can be used in place of cipro against *Mycobacterium Tuberculosis.*
- Highly effective against *Mycobacterium Laprae.*
- Also used as an alternative in multidrug therapy regimens.

LEVOFLOXACIN

It is an isomer of ofloxacin . *(main target of action is topoisomerase IV)*

Used to treat sexually transmitted diseases except syphyllis. Also used to treat gonorrhea.

Also effective against **prostatitis** due to *E-coli*.

Due to broad spectrum activity it is also used to treat **acute sinusitus**, acute exacerebration of **chronic bronchitis** , **community- aquired pneumonia** as well as **nosocomial pneumonia**.

Levofloxacin has excellent activity against respiratory infection due to ***Streptococcus pneumonia***.

MOXIFLOXACIN

- *(main target of action is topoisomerase IV)*
- Has high activity against *str.pneumonae,*
- effective against gram-positive bacteria including β-lactam /marolide resistant ones and some anaerobes.
- **Therapeutic uses**
- **Pneumonias**
- **Bronchitis**
- **Sinusitus**
- **Otitis media**
- It is **NOT** effective in UTI’s.

MECHANISM OF RESISTANCE

Altered target:

Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones. Topoisomerase IV also undergoes mutations. Resistance is frequently associated with mutations in both gyrase and topoisomerase IV.

Decreased accumulation:

Reduced intracellular concentration of the drugs in the bacterial cell is linked to two mechanisms.

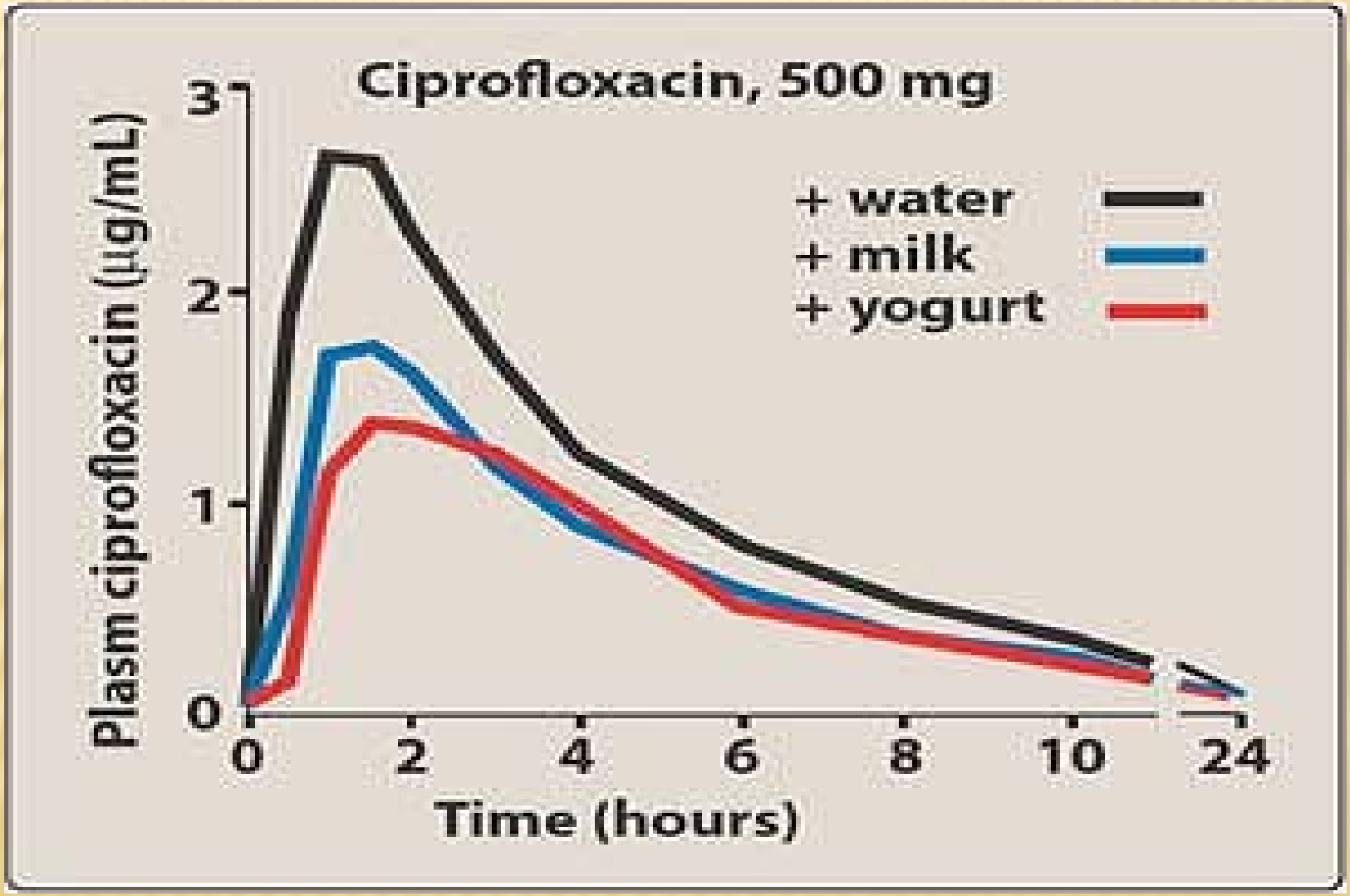
i. One involves a **decreased number of porin proteins** in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases.

ii. The other mechanism is associated with **an energy-dependent efflux** system in the cell membrane.

ENZYME DEGRADATION

PHARMACOKINETICS

- **Absorption**:
- Only 35 to 70 percent of orally administered *norfloxacin is absorbed, compared with 85 to 95* percent of the other fluoroquinolones .
- Intravenous preparations of ***ciprofloxacin, levofloxacin*** **and** ***ofloxacin*** *are available.*
- *Ingestion of the fluoroquinolones with sucralfate, antacids containing aluminum or* magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs.
- Calcium and other divalent cations have also been shown to interfere with the absorption of these agents . The fluoroquinolones with the longest half-lives (*levofloxacin and moxifloxacin)* permit once-daily dosing.


Ciprofloxacin, 500 mg
Plasm ciprofloxacin (µg/mL)
3
2
1
0
+ water
+ milk
+ yogurt
0
2
4
6
8
10
24
Time (hours)

- Binding to plasma proteins ranges from 10 to 40 percent. *All the fluoroquinolones distribute well into* all tissues and body fluids.

Levels are high in bone, urine, kidney, and prostatic tissue (but not prostatic fluid),and concentrations in the lung exceed those in serum. Penetration into cerebrospinal fluid is low except for *ofloxacin.*

The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellularorganisms such as Legionella pneumophila. They are excreted by the renal route.

ADVERSE REACTIONS

- **Gastrointestinal:** The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea,which occur in three to six percent of patients.
- **Central nervous system problems**: The most prominent central nervous system (CNS) effects of fluoroquinolone treatment are **headache and dizziness or light-headedness.** Thus, patients with CNS disorders,such as epilepsy, should be treated cautiously with these drugs. [Note: *Ciprofloxacin interferes in the* metabolism of *theophylline and may evoke seizures.]*
- **Phototoxicity:** Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens.
- However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity.

ADVERSE REACTIONS

- Musculoskeletol: they damage the growing cartilage causing arthopathy
- Tendinitis: Achilles tendinitis ---- rupture of tendons. Common in elderly and specially those on steroids.
- Prolongation of QTc interval even sometimes leading to torsade pointes.(seen with Moxifloxacin)

CONTRAINDICATIONS:

- *Moxifloxacin may prolong the QTc interval and, thus, should not be used in patients who are* predisposed to arrhythmias or are taking antiarrhythmic medications.

- **Drug interactions**: The effect of antacids and cations on the absorption of these agents was considered above.
- *Ciprofloxacin and ofloxacin can increase the serum levels of theophylline by inhibiting its metabolism* . This is not the case with the third- and fourth-generation fluoroquinolones, which may raise the serum levels of *warfarin, caffeine, and cyclosporine.*


THANK
YOU