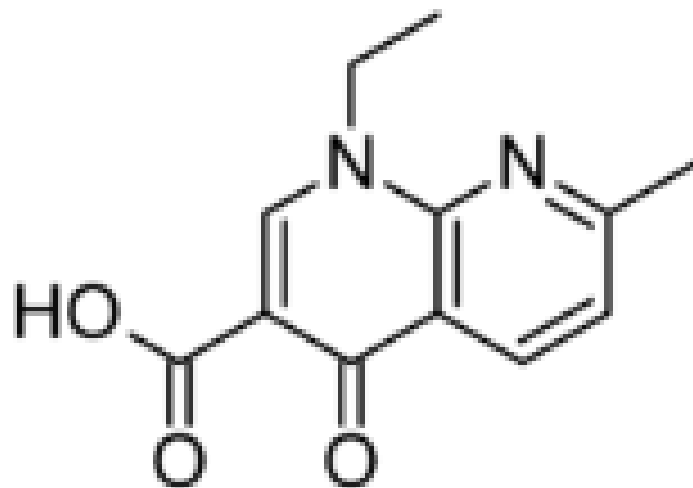


# **FLUOROQUINOLONE**

**DNA GYRASE INHIBITORS**

# Introduction

- Fluoroquinolone exhibit concentration dependent bactericidal activity. The important quinolones are synthetic fluorinated analogs of nalidixic acid.



# Members

- **1<sup>st</sup> Generation:** Nalidixic acid
- **2<sup>nd</sup> Generation:** Ciprofloxacin, Norfloxacin,  
Ofloxacin
- **3<sup>rd</sup> Generation:** Levofloxacin
- **4<sup>th</sup> Generation:** Moxifloxacin

Underline products are mostly prescribed.

# Mechanism of Action

- The fluoroquinolones enter the bacterium by passive diffusion through water filled protein channels in outer membrane. Once inside cell they inhibit the replication of bacterial DNA by interfering with action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction.
- Topoisomerases are enzymes that change configuration or topology of DNA by pass through, resealing mechanism.

1. DNA Gyrase is a topoisomerase II that catalyzes the negative supercoiling of the circular DNA found in bacteria.
2. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication

# AntiBacterial Activity

## 1<sup>st</sup> Generation (Nalidixic Acid)

- For gram-ive only UTI

## 2<sup>nd</sup> Generation (Norfloxacin, Ofloxacin, Ciprofloxacin)

- Is for gram –ive, gram +ive, atypical like mycoplasma and chlamydia

## 3<sup>rd</sup> Generation (Levofloxacin)

- Is for gram –ive and +ive.
- S.Pneumoniae, anaerobes

## 4<sup>th</sup> Generation (Moxifloxacin)

- Gram +ive
- And many aerobes

# Clinically Useful Fluoroquinolones

## Ciprofloxacin:

- Serum level of ciprofloxacin that are achieved are effective against many systemic infections
- With the exception of serious infections caused by methicillin resistant staphylococcus aureus (MRSA), the enterococci and pneumococci.
- Traveler's Diarrhea caused by E.coli can be effectly treated.
- In 3<sup>rd</sup> world countries it is also use to treat typhoid fever.

# **Norfloxacin**

- It is effective against both gram –ive and gram +ive organisms in treating complicated and uncomplicated urinary tract infections, prostatitis and traveler's diarrhea.
- It is not effective against systemic infections



# Levofloxacin

- Levofloxacin is an isomer of ofloxacin and has largely replaced it clinically.
- It can be used in treatment of prostatitis due to E.coli and of sexually transmitted diseases, with exception of syphilis.
- Due to its broad spectrum, levofloxacin is utilized in a wide range of infections including skin infection, acute sinusitis, bronchitis, community acquired pneumonia.

# Moxifloxacin

- Moxifloxacin not only has enhanced activity against gram+ive organism (e.g *S.pneumoniae*)
- But also has activity against many aerobes.
- Moxifloxacin does not concentrate in urine so it is not indicated for treatment of urinary tract infections.

# Resistance

- Possible mechanism responsible are:
  1. Altered Target: Mutation in bacterial DNA gyrase have been associated with decrease affinity for fluoroquinolone topoisomerase IV also undergoes mutation. Resistance is usually associated with mutation in both DNA gyrase and topoisomerase IV.
  2. Decrease Accumulation: Reduced intracellular concentration of drug in bacterial cell due to decrease number of channels (porins) of proteins in outer membrane or other mechanism is associated with energy dependent efflux system in cell membrane.

# **Pharmacokinetic**

- Orally well absorbed, metabolism in liver
- Form chelates calcium, Mg, Fe, Zn
- High tissue penetration bone and lungs
- Excreted primarily in urine

# ADRs

1. **Gastrointestinal** : Nausea, Vomiting, Diarrhea
2. **CNS problems**: Headach, dizziness or light headness
3. **Phototoxicity**: Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sun screens
4. **Connective tissue Problems**: should be avoided in pregnancy, nursing mothers, and in children under 18 of age.

# Toxicity

- Because human gyrases and topoisomerases are quite dissimilar to the corresponding bacterial enzymes, quinolones are in general well tolerated.