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YU-Medicine

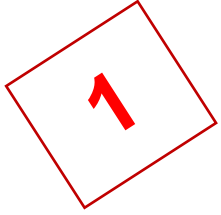
Sheet #19

Lec. Date :

Lec. Title : Inhibitors of Nucleic acid Synthesis **1**

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- In antibiotics, we used pathways that not overlapped between bacteria and humans

- يعني انا دائماً بدي اشتغل على Mechanism مش موجوده عندي في الانسان, مثل :  
cell wall , protein synthesis .

لذلك ما فيه Overlapped toxicity فيه selective toxicity

# 1. Fluoro-quinolones

## Inhibitors of Nucleic acid Synthesis

- **MOA:** Inhibit bacterial DNA synthesis by inhibiting:
  - DNA gyrase (topoisomerase II) in G- bacteria
  - DNA gyrase (topoisomerase IV) in G+ bacteria
- Bactericidal - concentration-dependent killing.
- Effective against G-ve organisms
  - Enterobacteriaceae
  - Pseudomonas species,
  - H. influenzae, Moraxella catarrhalis, Legionellaceae,
  - Atypical bacteria: chlamydia, Mycoplasma and mycobacteria Tuberculosis
  - Effective in the treatment of gonorrhoea but not syphilis.



- MIC ( Minimum inhibitor concentration):
  - Minimum concentration of the drug that inhibit bacteria.
  - The concentration of the drug in the plasma that kills 50% of bacteria.
- concentration- dependent killing : it means that the higher the concentration of the drug than MIC , the higher the bacterial inhibited.
- Frequency of a drug isn't important , the dose is the important.
  - فيه انواع بكتيريا صعب تلاقيلهم حل مثل : -

A typical bacteria.....but Fluoro-quinolones are very effective to it.

Generation	Drug Names	Spectrum	Main Uses:
1 <sup>st</sup> Non-fluorinated (narrow spectrum)	Nalidixic acid	Gram(-) but not Pseudomonas species	Urinary tract infection
2 <sup>nd</sup>	Ciprofloxacin Norfloxacin	Gram(-) (including Pseudomonas species), some Gram(+) (S. aureus) and some atypicals	Urinary tract infection
3 <sup>rd</sup>	levofloxacin Gemifloxacin	Same as 2 <sup>nd</sup> generation with extended Gram(+) and atypical coverage	Community acquired pneumonia (CAP).  Urinary tract infection
4 <sup>th</sup>	Moxifloxacin	Same as 3 <sup>rd</sup> generation with broad anaerobic coverage	Community acquired pneumonia (CAP). Anaerobic Infection

- We have 4 generation of flouro-quinolones , used mainly for the treatment of : urinary tract infection and community acquired pneumonia.
- To treat urinary tract infection the drug must be **in high concentration** and **in active form**.

ال- Drug لازم يمشي من ال Kidney لل urinary bladder لل Urethra بنفس التركيز

Without that the drug isn't systemic.

- The first generation of flouro-quinolones is nalidixic acid :
  - It found in high concentration in the urine so, we use it for urinary tract infection.

- بالفترة الاخيرہ صار عليه Resistant فبنستخدم بداله ( Ciprofloxacin ) .Second generation

# Fluoroquinolones

- **Ciprofloxacin**

- Used for systemic infection, useful in treating infections caused by many Enterobacteriaceae and other G- bacilli.
- **An alternative to more toxic drugs** (e.g. **Aminoglycosides**).
  - First line for Urinary tract infection (UTI)
  - Drug of choice for prophylaxis and treatment of **anthrax**.
  - The most potent of the fluoroquinolones for **P. aeruginosa** infections
  - Second line for treating resistant **tuberculosis**
  - **traveler's diarrhea** caused by E. coli

- Twice daily doses

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- لما نحكي G- bacteria & pseudomonas بنبدا من عند ال penicillin group الي فيه

antipseudomonal بعدها ببحث عن بدائل .... بروح عال third generation cephalosporins

بعدها عال Flouro-quinolones

- كل الادوية الي اخذناها عن ال tuberculosis تعتبر Second line for treating it

- traveler's diarrhea: لما نساfer على منطقه ثانيه ونوكل او نشرب مي بصير فيه Diarrhea

بسبب اختلاف ال Normal flora



# Fluoroquinolones

- **Norfloxacin**
  - Not effective in systemic infections?
  - poor oral bioavailability and a short half-life
- Uses: nonsystemic infections, such as urinary tract infections (UTIs), prostatitis, and infectious diarrhea
- **Levofloxacin**
  - Primarily used in the treatment of prostatitis due to *E. coli*
  - Very good activity against respiratory infections due to *S. Pneumoniae*.
  - *Levofloxacin* has 100% bioavailability and is dosed once daily

- Norfloxacin:
  - Highly concentrated in the urine but it's poorly absorbed and has poor oral bioavailability so, it has low concentration in the plasma ... because of that it hasn't systemic effect...only local effect ... that's mean if it found in urine it will treat urinary tract infections ,in prostatitis to treat prostatitis infections and so on.
  - we can't use it as alternative drug for tuberculosis.
- Levofloxacin:
  - First line for prostatitis .... Second line for respiratory infections.
  - Expensive & not commonly used.
  - Good for the treatment of urinary tract infection but it is better for CAP.
  - Most of CAP(70-80)% ----- G+.

# Fluoroquinolones

- **Moxifloxacin**

- *It has* enhanced activity against **gram-positive** organisms (S. pneumoniae) and also has excellent activity against many **anaerobes** Bacteroides fragilis .
- It has very **poor** activity against P. aeruginosa.
- *Moxifloxacin does not* concentrate in urine and is not indicated for the treatment of UTIs.

# Fluoroquinolones -pk

## 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 and levofloxacin** are available
- Antacids (with Al or Mg), or dietary supplements (with Zn or Fe, divalents) – decrease absorption

## Distribution

- Levels are high in bone, urine, kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lung exceed those in serum.

## Excretion:

- excreted by the renal route.
- once-daily dosing in renal failure

# Fluoroquinolones S/E

- **GIT:** nausea, vomiting, diarrhea
- **CNS:**
  - headache and dizziness or light-headedness.
  - **Patients with epilepsy – Contraindicated ???**
- **Phototoxicity:**
  - Discontinue therapy at the first sign of phototoxicity.
- **Hepatotoxicity:**
- **Connective tissue problems**
- **C/I** in pregnancy, in nursing mothers, and in children under 18 years??
  - Can cause articular cartilage erosion
  - In adults - they can infrequently cause ruptured tendons.
- Sparfloxacin and moxifloxacin **prolong the QT interval** so **C/I in patient with arrhythmia**
- Epilepsy

Tendon  
rupture



# Fluoroquinolones

- Drug interactions:

- ↓ absorption:  $\text{Al}^{3+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Ca}^{2+}$  antacids

- CYP450 inhibition: potential drug interactions

- ciprofloxacin: increases serum level of theophylline (induce seizure),

- 3<sup>rd</sup> & 4<sup>th</sup>- generation fluoro. may increase serum level of warfarin, caffeine and cyclosporine

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- Ciprofloxacin:

= Drug –drug interaction كبيره لذلك:

- ما بنعطى مع ال (AL,Mg,Zn....) dietary products

- ممنوع ينعطى لل Teenagers لانه فيه مرحلة النمو بعمل tendon rupture

- ما بنعطى للحامل لانه ممكن ياتر على ال development

- Sparfloxacin & moxifloxacin:

- الهم تاثير عالقلب

QT interval: delay between 2 pulses.

- fluoro quinolones :

- ما بنعطيا للاشخاص الي عندهم Epilepsy ليش؟

لانه الصرع بصير لما توصل ال Electrical charge حد معين فهاي الادويه بتقلل هاظ الحد

Decrease threshold .