Athar Batch

Pharmacology

Lecture: 32

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النادي الطبي

Quinolones and Folic Acid Antagonists

Pharmacology and Toxicology
General Pharmacology
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Textbook: Chapter 31 pp 400-412

Fluoroquinolones

بداية بهالمحاضرة بتتضمن مجموعتين ..

1-floroQuinolones

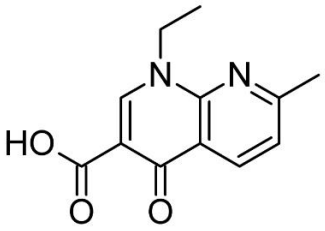
2-folic acid antagonist

These drugs target DNA related process but both of them have distinct mechanism of actions ..

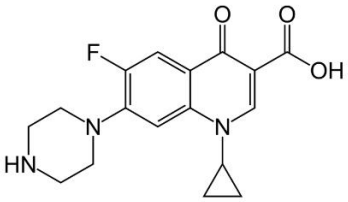
In this lecture they are discussed together because the have the same clinical uses and they both target DNA synthesis.

مج

Quinolones



Nalidixic acid



Ciprofloxacin

FLUOROQUINOLONES

Ciprofloxacin CIPRO
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX
Nalidixic acid
Norfloxacin NOROXIN
Ofloxacin

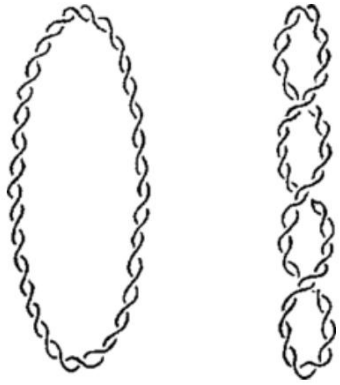
1-quinolones are big class of drugs and not only used as antibiotics.

2-the prototype of this drugs family is Nalidixic acid → this drug was the basic quinolone to be used.

هلا الرسمة تبع الناليدكسيك اسيد عبارة عن حلقتين متصلين ببعض .. بعدين صار في تعديلات عهاد الدوا واضافو ذرة فلور جديدة عن طريقة عملية اضافة الهالوجين.. المهم ف صار اسم المجموعة فلوروكوينولونز .

رح نلاحظ بالسلايدات الجاية انو هاي المجموعة متخصصة بالعدوى الي بتصيب الجهاز التنفسي والجهاز البولي .

DNA Supercoiling



Some information to revise about DNA in bacterial cell.

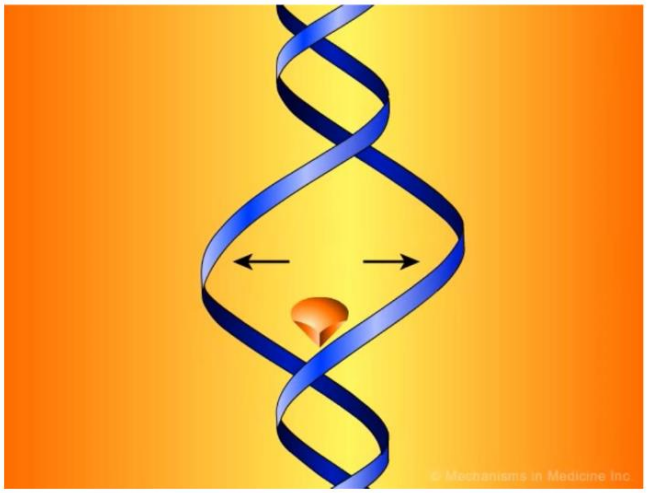
1- Bacterial DNA is circular in contrast to humans DNA which is leaner.
2- The bacterial DNA is subjected to supercoiling during replication and this is a problem.
3- We know that DNA helicase is the enzyme responsible for separation of the 2 DNA strands

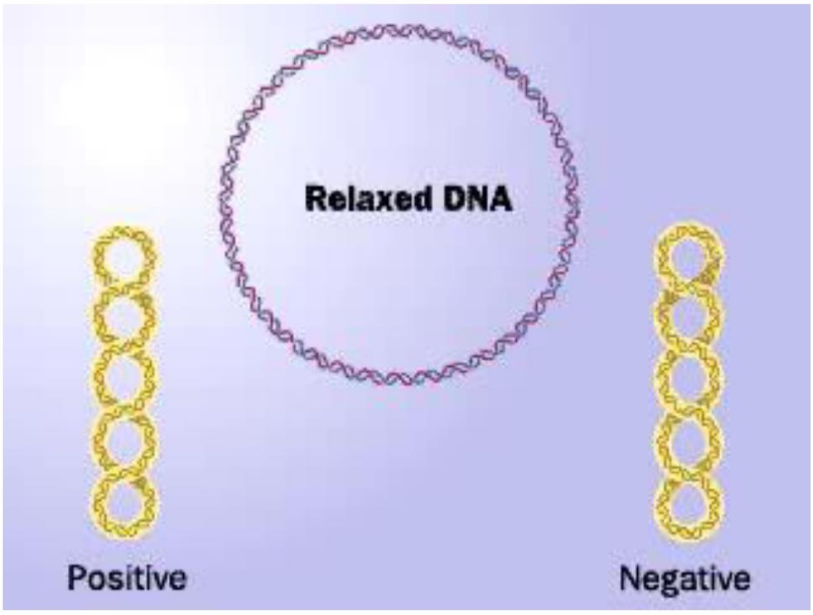
خلال شغل هاد الانزيم ممكن قدامو تتكون عقدة وتأثر على شغلو وبالتالي لازم يكون في عنا حل لمشكلة العقد الي بتتكون .. هلا هاي العقد تنقسم لنوعين

- Negative coils → عكس عقارب الساعة
- Positive coils → مع عقارب الساعة وهاي هي الي غالبا بتتكون

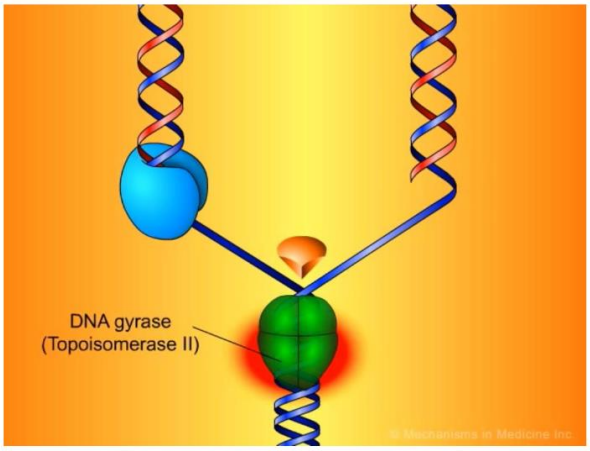
There is an enzyme called DNA gyrase or topoisomerase II that is responsible of relief of the supercoils --> so when the positive supercoils form this enzyme will produce negative supercoils against the positive supercoil that formed → leading to relief the supercoil.

DNA Helicase



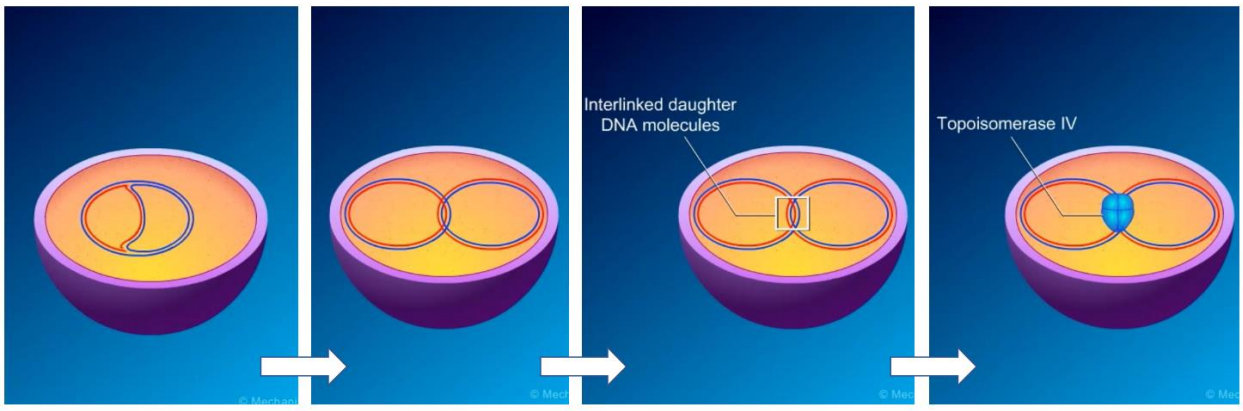


DNA Gyrase



شرح هاي الصور بالكلام الي مكتوب فوق ..

Topoisomerase IV



After replication the result is → interlinked daughter DNA molecules so in this case we need enzyme that separate them.

The enzyme responsible for this step is topoisomerase IV

هاد الانزيم رح يقصهم وينفصلهم عن بعض وبعدين يرجع يلزق الجزء الي قصو بس طبعا بكونو خلص انفصلو عن بعض

So, we can say that DNA GYRASE and DNA topoisomerase IV have cut and ligation functions.

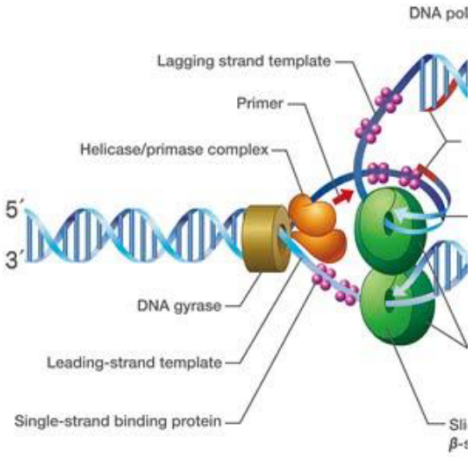
Quinolones

Mechanism of action

- Inhibit ligation step of bacterial DNA gyrase and bacterial topoisomerase IV

-Inhibition of gyrase: increases the number of permenant chromosomal breaks

-Inhibition of topo IV: interferes with the separation of newly replicated DNA



If the function of gyrase inhibited the number of breaks along DNA molecule will increase which will lead to the death of the cell (apoptosis)→ so these drugs are bactericidal.

Quinolones

Mechanism of action

In gram-negative: inhibition of gyrase>topo IV

In gram-positive: inhibition of topo IV>gyrase

What does that mean?

12/29/2020

Wolters Kluwer

الحكي بهالسلايد مش مهم كثير بس الدكتور حكا شغلة وحدة هون

The important thing to know that fluroquinolones inhibit both the DNA gyrase and DNA topoisomerase IV but the selectivity of these drugs to these enzymes may differ between species (g(+) and g(-))

وهاد ببرر الكلام المكتوب فوق بالسلايدات.

Quinolones→ commonly used in UTIs.

Antibacterial spectrum:

• Bactericidal→bacterial cell killing

• Time-dependent killing → there effect depend on their concentration in plasma so they are given in a frequent dose and their concentration must be maintained near or above the MIC

• Effective against gram-negative (including E. coli and Pseudomonas),

atypical, gram-positive (strep), mycobacteria….

هدول الادوية ببدايات اكتشافهم كان شغلهم بشكل اساسي على جرام(-) بكتيريا بس بعدين ومع تطورهاي المجموعة صار في ادوية منهم فعالة ضد الجرام(+) بكتيريا.

• Levofloxacin: excellent activity against (S. pneumoniae→ g(+) infection)

Levofloxacin is now one of the important drugs that treat lung infections.

Quinolones

Antibacterial spectrum

• First-generation (nonfluorinated): nalidixic acid

narrow-spectrum → activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae.

• Second-generation: ciprofloxacin and norfloxacin

-gram-negative (pseudomonas, H.influenzae) and atypical , Neisseria spp., Chlamydia spp., and Legionella spp.

• Third-generation: levofloxacin → هون بلش يظهر تأثير على الجرام(+)

-gram-negative, atypical and gram-positive (including S. pneumoniae→community acquired pneumonia and MSSA).

• Fourth-generation: moxifloxacin, Gemifloxacin, delafloxacin

-*enhanced gram-positive effects* including staph and strep + coverage of gram-negative Enterobacteriaceae.

Staph and strep are common cause of lower respiratory tract infections.

-Homework: Which fourth-generation fluoroquinolone is effective against MRSA?

Delafloxacin has activity against methicillin resistant Staphylococcus aureus (MRSA).

Examples of Clinically Useful

Fluoroquinolones

Ciprofloxacin → 2nd generation.

• Effective against gram-negative including P. aeruginosa→(High dose for pseudomonal infections)

• Clinical indications:

1. Gastroenteritis e.g., traveler's diarrhea→ caused by g(-) bacteria transmitted by feco-oral rout

2. Typhoid fever

3. Anthrax (drug of choice)

- infectious disease caused by bacteria known as Bacillus anthracis.

- ciprofloxacin is the drug of choice for anthrax

4. Urinary tract infections

The main use of ciprofloxacin is for treatment of UTIs.

Examples of Clinically Useful Fluoroquinolones

Levofloxacin→ 3rd generation.

• Similar to cipro but also effective against gram-positive (strep not staph) + MSSA .

• Clinical indications:

First-line therapy for community acquired-pneumonia.--> خصوصا اذاكان في عندي مقاومة من البكتيريا للبينسيلين مثلا ..

-Can be used for UTIs.

Examples of Clinically Useful Fluoroquinolones

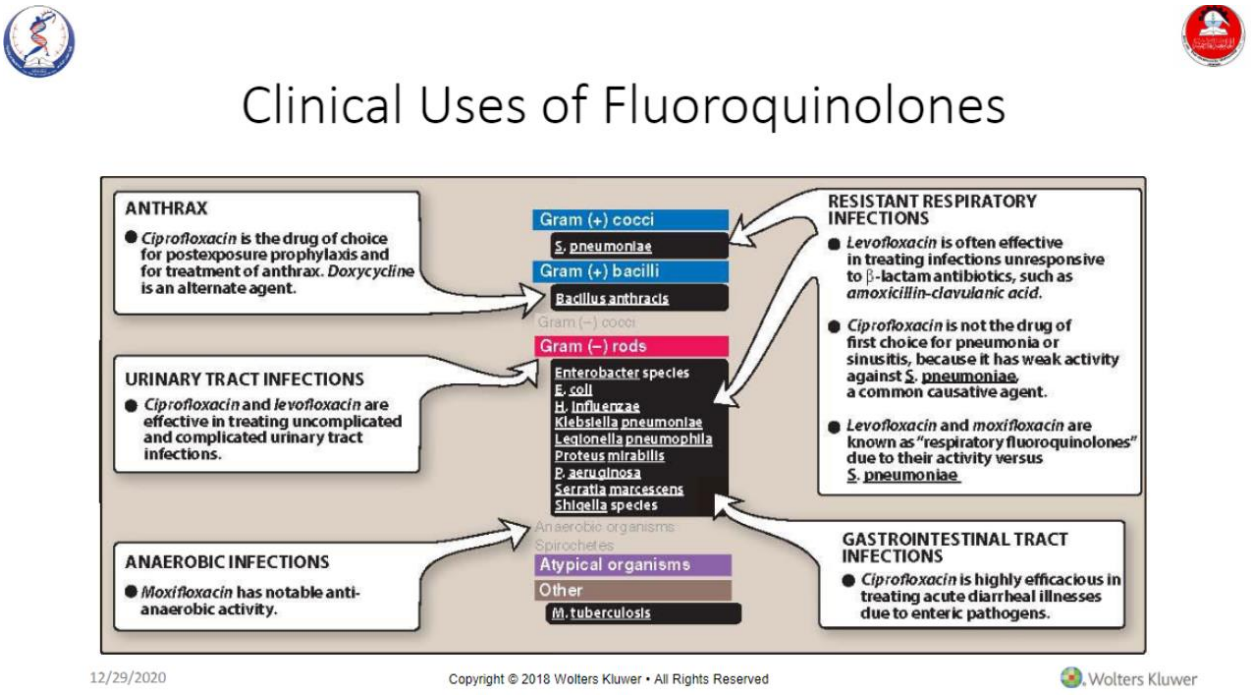
Moxifloxacin → 4th generation

• Effective against gram-negative, S. pneumonia and mycobacterium

• Clinical indications:

1. For community-acquired but not nosocomial pneumonia (weak against pseudomonas)

2. Second-line for TB



Fluoroquinolones and UTIs

"Fluoroquinolones (e.g., ofloxacin, ciprofloxacin, levofloxacin) are highly effective in UTIs, but these agents have a propensity for causing collateral damage and should be reserved for important uses other than acute uncomplicated cystitis. IDSA guidelines recommend that fluoroquinolones be used as second-line agents for acute uncomplicated cystitis and as first-line oral therapy for complicated cystitis". → to reduce superinfection risk and resistant

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases.

Fluoroquinolones

Mechanisms of resistance

-mainly chromosomal

- **Altered target:**

-mutations in *gyrA* or *parC*

- **Decreased accumulation**

-porin channels

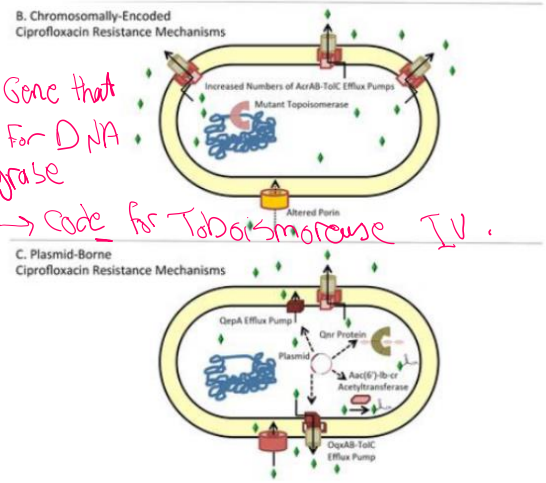
-efflux pumps

- **Fluoroquinolone degradation**
- Cross-resistance

main mechanism of Resistant.

*gyrA → Gene that code for DNA gyrase

*ParC → Code for Topoisomerase IV.



12/29/2020

Wolters Kluwer

Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases.

Fluoroquinolones

Pharmacokinetics

- **Absorption**

-mainly oral – IV/ophthalmic preps of cipro and levo

-food, Ca^{++}, Al^{+3} and Mg^{++} interfere with absorption → ↓ Absorption.

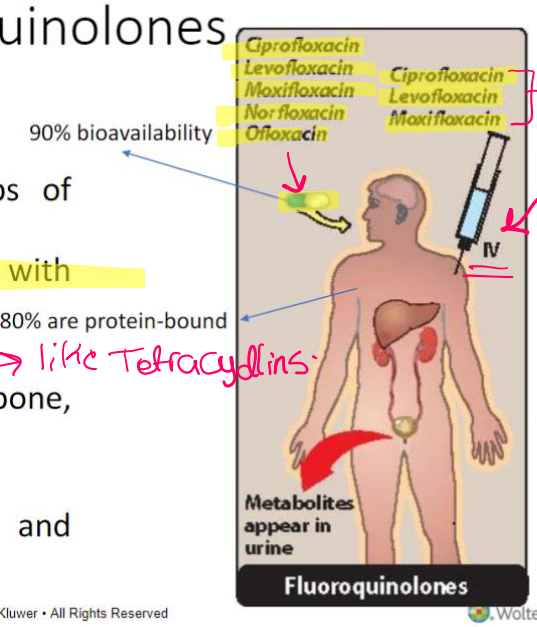
- **Distribution**

-very well distributed (high conc in bone, urine and lung)

-good CSF distribution

-concentrate in macrophages and neutrophils

well absorbed After oral administration.



can be given

→ like Tetracyclins.

- levofloxacin and moxifloxacin having a bioavailability that exceeds 90%
- Binding to plasma proteins ranges from 20% to 84%.
- Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and
- Mycobacterium.

Fluoroquinolones

Pharmacokinetics

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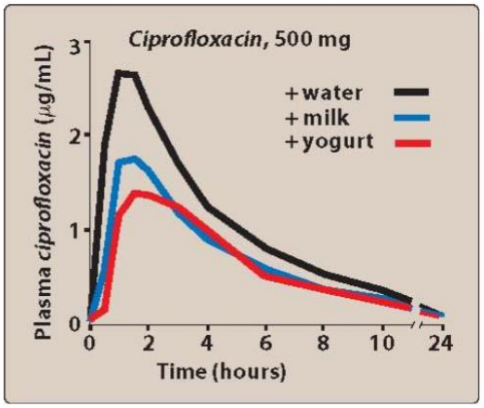


The graph show that the absorption of fluroquinolones If administrated With dietary food thus will interfere with the absorption of the drug.

Fluoroquinolones

Pharmacokinetics

- **Elimination**

-most fluoroquinolones are excreted renally

-Moxifloxacin is excreted by liver (can be used in patients with renal impairment)

Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction.

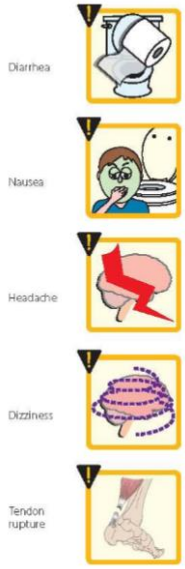
- Nausea
- Vomiting
- Dizziness.

Quinolones

Adverse effects

-generally well-tolerated

- **N/V/D**
- **Headache and dizziness**
- **Peripheral neuropathy and glucose dysregulation**
- **Phototoxicity** → As tetracyclins.
- **(boxed warning) Articular cartilage erosion, tendinitis, tendon rupture**
- **QT prolongation**



-Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light.

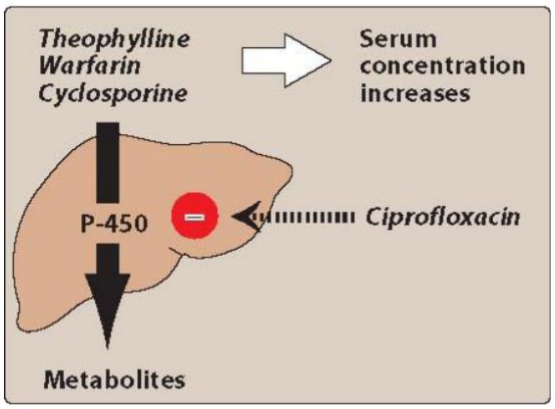
-blood glucose disturbances (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed.

These drugs should be avoided in patients predisposed to arrhythmias or heart problems because these drugs prolonged the QT.

Quinolones

Drug-drug interaction

- Cipro can inhibit metabolism of theophylline, others
- Quinolones can raise serum warfarin



CIPROFLOXACIN inhibit CYP450 leading to inhibit the metabolism of other drugs and increase their concentration in the blood ... such as warfarin so the serum warfarin will increase leading to bleeding.

Done by saja alnajjar .