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Review Article

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Insights on Fluoroquinolones as Anti-Bacterial Drugs

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Abstract

Fluoroquinolones are broad-spectrum antibacterial agents that have a novel mechanism of action. In this literature review, we will focus on the classification of these drugs, mechanism of action, development history, structure activity relationship, indications, contraindication, resistance, dosages, side effects, patient counseling, and their drug-drug interaction.

Keywords: Fluoroquinolones, Literature Review, Mechanism of Action, Structure Activity Relationship, Drug-Drug Interaction

Introduction

Fluoroquinolones are broad-spectrum antibacterial agents that have anovel mechanism of action. As synthetic compounds, these agents have been developed extensively to optimize anti-microbial activity, pharmacokinetic properties, and drug safety.

Although earlier quinolones were effective only in the genitourinary and only had activity against aerobic gram-negative bacteria, newer quinolones have wider potential applications and a broader spectrum of activity. However, there are many Food and Drug Administration approved indications for some of the newer quinolones, the quinolones are the drug of choice for only a few infections.

Quinolone – resistant bacteria are being increasingly identified and emerge under selective pressure created by extensive use.

Classification

The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favorable safety and tolerability profiles. Anew four-generation classification of the quinolone drug takes into account the expanded antimicrobial spectrum of the more recently introduced fluoroquinolones and their clinical indications [1].

• First generation drugs (e.g. Nalidixic acid) achieve minimal serum levels.
• Nalidixic acid structure (Figure 1) is related to quinolone as they are isosteres of each other. Quinolone has (CH) at position 8 but nalidixic acid which is naphthyridine structure has nitrogen atom at position 8.

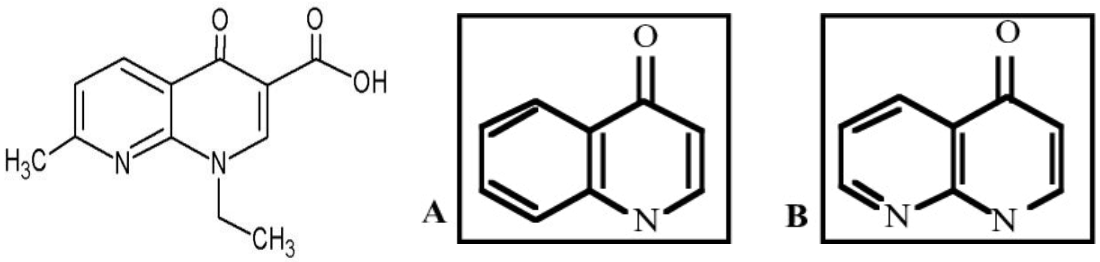


Figure 1: Nalidixic Acid and Quinoline Isosterism

• Second-generation quinolones (e.g., ciprofloxacin) have increased gram-negative and systemic activity.
• Third generation drugs (e.g. levofloxacin) have expanded activity against gram-positive bacteria and a typical pathogen.
• Fourth-generation quinolone drugs (currently only trovafloxacin) add significant activity against anaerobes. The quinolones can be differentiated within classes based on their pharmacokinetic properties. The new classification can help family physicians prescribe these drugs appropriately [2].

Generation	Drug names	Spectrum
1st	-Nalidixic acid -cinoxacin	Gram negative but not Psudomonous species
2nd	-Norfloxacin -Ciprofloxacin -Enoxacin -Ofloxacin	Gram negative (including psudomonous species), some gram positive (S.auteus) and some a typical.
3rd	-Levofloxxacin -Sparfloxacin -Moxifloxacin -Gemifloxxacin -Gatifloxacin	Same as 2nd generation with extended gram positive and atypical coverage
4th	Trovafloxacin	Same as 3rd generation with broad anaerobic coverage

Mechanism of Action

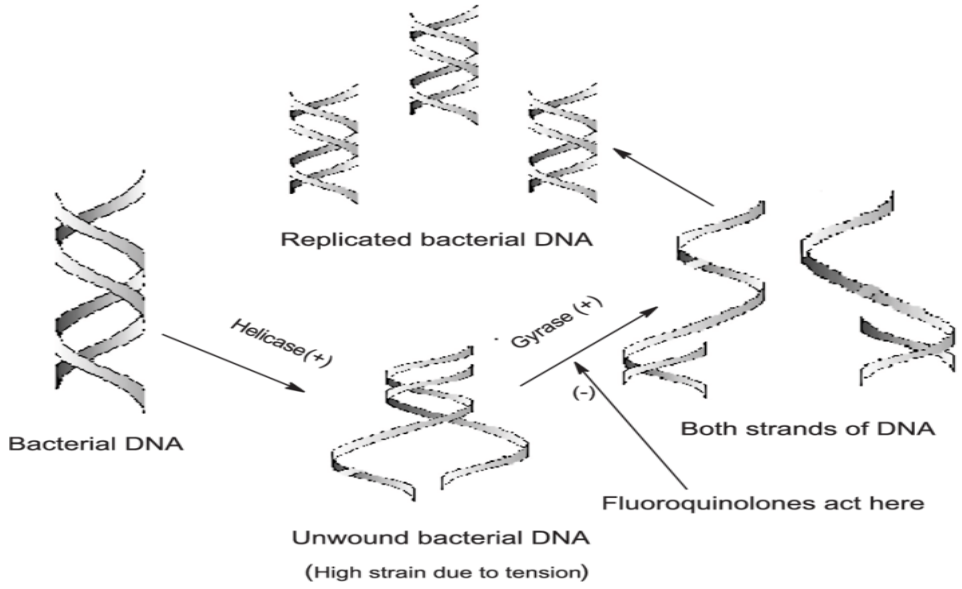


Figure 2: Mechanism of Action of Fluoroquinolones

Quinolones are chemo-therapeutic bactericidal drugs. They interfere with DNA- replication by preventing bacterial DNA from unwinding and duplicating. Specifically, they inhibit the ligase activity of the type-II topo- isomerases, DNA gyrase and topo-isomerase IV, which cut DNA to introduce super-coiling, while leaving nuclease activity unaffected. With the ligase activity disrupted, these enzymes release DNA with single-and double-strand breaks that lead to cell death [3].

Fluoroquinolones can enter cells easily via porins, so are often used to treat intracellular pathogens such as Legionella pneumophila and Myco- plasma pneumoniae. For many Gram-negative bacteria, DNA-gyrase is the target, whereas topo-isomerase IV is the target for many Gram- positive bacteria.

Eukaryotic cells are not believed to contain DNA-gyrase or topo-isomerase-IV. However, debate exists concerning whether the quinolones still have such an adverse effect on the DNA of healthy cell.

DNA gyrase, or simply gyrase, is an enzyme within the class of topo-isomerase and is a sub class of Type II topo-isomerases that reduces topological strain in an ATP dependent manner while double- stranded DNA is being unwound by elongating RNA-polymerase or by helicase in front of the progressing replication fork.

The enzyme Causes negative super-coiling of the DNA or relaxes positive super-coils. It does so by looping the template so as to form a crossing, then cutting one of the double helices and passing the other through it before releasing the break, changing the linking number by two in each enzymatic step. This process occurs in bacteria, whose single circular DNA is cut by DNA-gyrase and the two ends are then twisted around each other to form supercoils [4].

Development History

Since their discovery in the early 1960s, the quinolone group of anti-bacterial has generated considerable clinical and scientific interest. Nalidixic acid, the first quinolone to be developed, was obtained as an impurity during the manufacture of quinine.

Since this time, many derivatives have been synthesized and evaluated for their anti-bacterial potency.

Two major groups of compounds have been developed from the basic molecule:

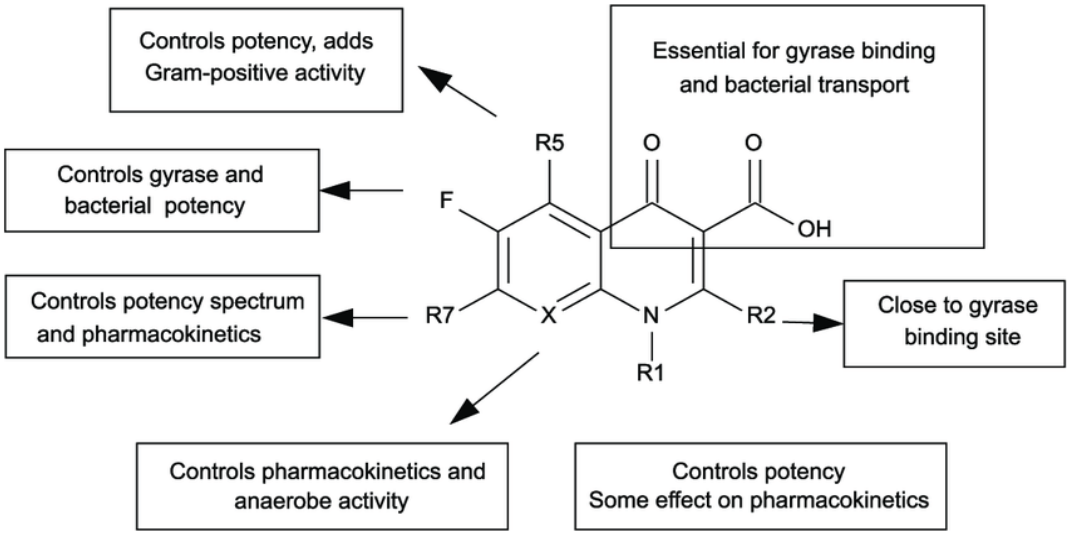
1) Naphthyridines
2) Quinolones

After development of nalidixic acid, took more than a decade before additional compounds, such as flumequin, norfloxacin and enoxacin became available for clinical use.

The main use for all these agents was the treatment of urinary tract infections. In the late 1980s more systemically active drugs, such as ciprofloxacin and ofloxacin, were marketed. Recently, there has been aconsider able increase in the number of agents that are in development, and to date over10000 molecules have been patented [4].

Structural Developments

Quinolones were derived from quinine. The Figure below shows basic fluoroquinolone molecule or 'pharmacophore'.



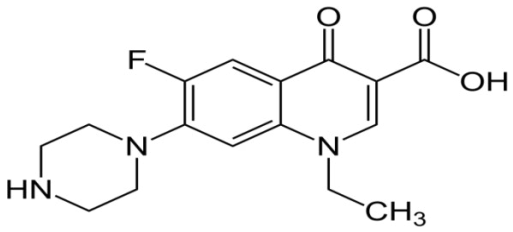
The addition of a fluorine molecule at position 6 was one of the earliest changes to the structure. This single alteration provides a more than10- fold increase in Gyrase inhibition and up to100-fold improvement in Minimum Inhibitory Concentration (MIC). The presence of a nitrogen at position 8 identifies naphthyridones, a carbon and associated group at position 8 identifies the quinolones.

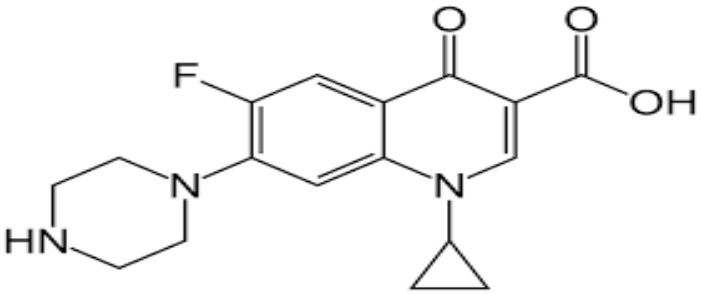
The quinolones and napththyridones were further enhanced by the addition of groups to the N1, C-5 and C-7 positions of their respective basic molecules. The addition of piperazine to the C-7 position (e.g.norfloxacin) improves activity against Gram-negative organisms.

There are data to suggest that a piperazine ring may play a role in inhibiting efflux mechanisms, thereby improving the potency of these drugs.

The structure of norfloxacin illustrates these developments and subsequent to this all quinolones (except garenoxacin) have a fluorine at position 6 and many have six-membered ring at position C-7.

The presence of a pyrrolodinyl group at position C-7 (e.g. clinafloxacin) improves activity against Gram-positive organisms. In addition to piperazine at the C-7 position, acyclopropyl group was introduced to the N1 position and is best exemplified by ciprofloxacin, which was first synthesized in 198.



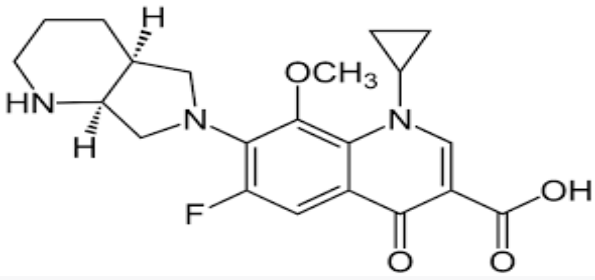


This increases the potency of the drug and many subsequent quino-

lones have a cyclopropyl group (e.g. grepafloxacin, moxifloxacin, gatifloxacin and garenoxacin).
The figure below shows moxifloxacin structure.

Some Modifications

A five membered ring or azabicyclic rings at position 7 are found in clinafloxacin and trovafloxacin (five- membered ring) or moxifloxacin and garenoxacin (aza bicyclorings). A methoxy group at position 8 is found in moxifloxacin and gatifloxacin. A di-fluoromethyl ether (OHF2) group is found at position 8 in garenoxacin [5].



The addition of a 2,4-di fluorophenyl group at position1 (e.g. trovafloxacin) also improves potency, especially in improving activity against anaerobes.

A number of other structural manipulations have been tried to improve the anti-Gram-positive activity of fluoroquinolones. One of the first additions was an NH2 group at position C-5, which resulted in a general increase in anti-Gram-positive activity.

This is seen with sparfloxacin which otherwise has a very similar structure to ciprofloxacin. Sparfloxacin also has a fluorine at position C-6, a piperazine at position C-7 and is alkylated. Grepafloxacin is also substituted at position C-5 but by a CH3 group and has improved anti-Gram-positive potency compared with ciprofloxacin.

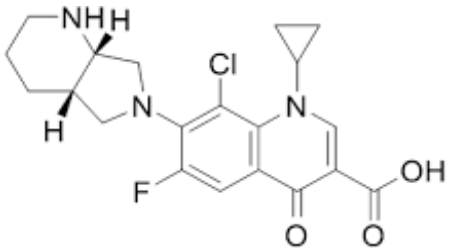
The substituents at position C-7 are associated with a number of key attributes, such as anti-bacterial spectrum, bioavailability and side- effects.

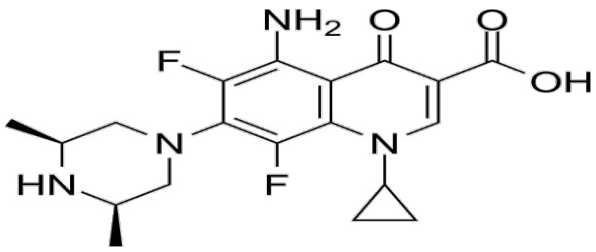
The most common substituents are cyclic amino groups, for example epiperazine or pyrrolidine rings; other groups have been less successful. Piperazine rings are particularly common (e.g.norfloxacin, enoxacin or ciprofloxacin) and confer potency against Gram-negative bacteria. The addition of methyl groups can improve both oral absorption and in vivo activity. However, the improved activity against Gram-positive bacteria can sometimes beat the expense of activity against Pseudomonas aeruginosa.

Pyrrolidinerings (five-membered) are also common substituents at position 7, and are associated with enhanced potency against Gram- positive bacteria. However, this group is associated with low water solubility and low oral bioavailability so in vivo activity may be compromised.

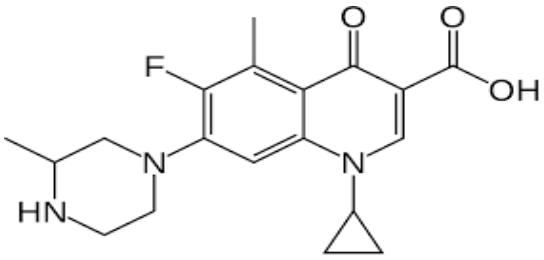
Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties. Gemifloxacin, an aphthyridone, is a good example of the advantages and disadvantages associated with a pyrrolidine ring at position 7.6 The addition of azabicyclo groups onto position 7 has resulted in agents (moxifloxacin and trovafloxacin) with significant anti-Gram positive activity, marked lipophilicity and half-lives of>10h.7,8.

Examples of adverse events associated with structural changes:
(A) The addition of fluorine or chlorine at position 8 being associated with photo-reactivity, e.g. Bay y 3118 and sparfloxacin.





(B) The substitution of an amine or a methyl group at position 5 having a potential role in QTc prolongation, e.g., sparfloxacin and grepafloxacin.



(C) Hemolytic uremic syndrome caused by temafloxacin.
(D) Hepatic eosinophilia caused by trovafloxacin.
(E) Pulmonary interstitial eosinophilia and other immunological side-effects caused by tosufloxacin and gemifloxacin, and the hypoglycaemia seen with temafloxacin and clinafloxacin.

Causes of These Adverse Events

There are powerful association between these events and 2,4-difluoro- phenyl group at position, as this is shared by trovafloxacin, temafloxacin and tosufloxacin1 but not by gemifloxacin. Another hypothesis suggests that their metabolites may be responsible for some of the immunologically mediated adverse events seen with these drugs.

Indication of Fluoroquinolones

They are broad-spectrum antibiotics that have a strong affinity for gram- negative bacteria, particularly Pseudomonas aeruginosa particularly cipro. These antibiotics are particularly useful for some diseases, such as pneumonia, since tissue and fluid concentrations often exceed serum drug concentrations. Their gram-positive activity has been expanded, which is particularly important because it includes strong activity against Streptococcus pneumoniae [6].

Fluoroquinolones are commonly used to treat genitourinary infections and are commonly used to treat hospital-acquired infections linked to urinary catheters. They are only used in community-acquired infection where there are risk factors for multi drug resistance or when conventional antibiotic regimens have failed.

They are suggested as first-line therapy for serious acute cases of pyelo- nephritis or bacterial prostatitis that may require hospitalization.

Because people with sickle-cell disease are more likely to get osteomyelitis from Salmonella, fluoroquinolones are the "drugs of choice" because they can reach bone tissue without chelating it like tetracyclines [7].

Fluoroquinolones can be used to treat the following conditions:
• Haemophilus influenzea
• Moraxella catarrhalis & Myco-plasma species
• Chlamydia species & Chlamydophila species
• Legionella species & Enterobacteriaceae
• Mycobacterium Tuberculosis & some a typical mycobacteria
• Some methicillin sensitive staphylococci

In the event of biological warfare, **ciprofloxacin** could be used to treat and prevent diseases like tularemia and anthrax of the skin and mouth that are purpose fully propagated and may be used to treat catscratch, legionnaires' disease, chancroid (genital sores caused by bacteria) [8].

Ofloxacin is used to treat infection caused by susceptible strains of specified bacteria that range from mild to moderate, *Chlamydia trachomatis, Citrobacter spp, Enterobacter spp, E.coli, Klebsiella.*

In the treatment of mild to severe CAP, a recent study found that intravenous or oral **levofloxacin** 750mg once day for 5 days is equally effective as 500mg once daily for 10 days. Exacerbations of chronic bronchitis and acute maxillary sinusitis benefit from levofloxacin treatment [8].

The newest fluoroquinolones exhibit better activity against gram-positive bacteria than ciprofloxacin (the first agent of the original fluoroquinolones), with only a minor loss inactivity against gram-negative bacteria.

Sparfloxacin has a broader spectrum of activity, including some anti-microbial activity against anaerobes and has even more potent Anti-mycoplasma action. We use sparfloxacin to treat blepharitis, conjunctivitis and corneal ulcers, Unsupervised prolonged use, on the other hand, is linked to the deposition of crystalline material in the cornea's epithelial and anterior stromal layers [9].

Grepafloxacin is considered third generation of this class and is used to Uncomplicated Neisseria gonorrhoeae which causes urethral gonorrhea in men and endocervical and rectal gonorrhea in women. Also, it used in Chlamydia trachomatis that causes non-gonococcal urethritis and cervicitis.

Trovafloxacin is the fluoroquinolone with the highest anaerobic activity, which includes activity against Bacteroides species. As a result, this drug has the greatest spectrum of activity among currently available quinolones, as well as abroad range of applications [10].

Contraindication

- Patients with a history of quinolone associated hypersensitivity reactions.
- Myasthenia gravis due to an increased risk of exacerbating existing muscle weakness. In pregnancy, it is suggested that quinolones should not be used as a first-line therapy during the first trimester [11].
- Patients with impairments of the CNS (e.g., epilepsy or arteriosclerosis).
- Patients with known prolongation of the QT interval or other risk factors for tachyarrhythmia.
- The risk for quinolone – associated tendinopathy is more pronounced among elderly persons, non-obese patients and individuals with concurrent use of glucocorticoids or chronic renal diseases.

- Quinolones are contraindicated in children because they cause destruction of the immature joint cartilage in animals. The use in pediatrics is restricted to life-threatening infections [12].
- The concurrent administration of tizanidine for muscle spasms contraindicated as the pharmacokinetics of tizanidine altered by CYP1A2 inhibition "Ciprofloxacin" leading to increasing levels of tizanidine and then decreased psychomotor activity, blood pressure, and heart rate [3].

Resistance

Fluoroquinolone resistance has increased as a result of increased usage of these antimicrobials, with rates of resistance varying by organism and geographic region. Fluoroquinolone resistance is usually caused by changes in the target enzymes (DNA gyrase and topoisomerase IV) as well as changes in drug entry and efflux.

The more susceptible target is chosen first: DNA gyrase in gram-negative bacteria or topoisomerase-IV in gram-positive bacteria. Resistance is developing among Enterobacteriaceae, Pseudomonas aeruginosa, S. nvestiga, and Neisseria species, particularly to earlier fluoroquinolones.

Because of rising resistance world-wide, they are no longer indicated for the treatment of gonorrhea [13].

Doses

Ciprofloxacin & Levofloxacin are available as oral suspension in many countries.

Agent	Usual adult dose	Usual children dose
Ciprofloxacin	500-750mg orally every 12 hours OR 400mg IV every 12 hours	10mg/kgorally or IV every 12 hours (Ciprofloxacin and levofloxacin are the only fluoroquinolones used in pediatrics and children
Norfloxacin	400-800mg orally every 12 hours	<18 years: safety and efficacy not established
Ofloxacin	200-400mg orally every 12 hours	<18 years: safety and efficacy not established
Levofloxacin	500-750mg orally/IV every 24 hours	8mg/kg orally/IV every 12 hours
Moxifloxacin	400mg orally/IV every 24 hours	<18 years; safety and efficacy not established
Gatifloxacin	200-400mg orally/IV every 24 hours	<18 years: safety and efficacy not established
Gemifloxacin	320mg orally every 24 hours	<18 years: safety and efficacy not established

- How to calculate the daily dose??

$$DO = \frac{Cl \times Breakpoint\ Index \times Targeted\ plasma\ concentration}{F\ \%}$$

DO:	Daily dose (mg/kg per day)
Cl:	Body Clearance (per h)
Breakpoint index:	Index for required effect (AUC_{24h}/MIC) (h)
Targeted plasma concentration:	MIC_{90} (µg/mL)
F%:	Bioavailability (from 0 to 1)

Side Effects

- Reactions of the gastrointestinal tract, the central nervous system (CNS) and the skin are the most often observed adverse effects. Occasionally major events such as phototoxicity, cardiotoxicity, arthropathy and tendinitis occur, leading to significant tolerability problems. Over the years, several structure-activity and side-effect relationships have been developed, in an effort to improve overall antimicrobial efficacy while reducing un desirable side-effects. In this article we review the toxicity of fluoroquinolones, including the newer derivatives such levofloxacin, sparfloxacin, graepafloxacin and the 7-aza bicycle derivatives, trovafloxacin and moxifloxacin.
- Several mechanisms are thought to be responsible. The involvement
- of g-aminobutyric acid (GABA) and excitatory amino-acid (EAA) neurotransmission and the kinetics of quinolones distribution in brain tissue are discussed [14].
- In addition, quinolones may interact with other drugs theoph-

ylline and nonsteroidal anti-inflammatory drugs (NSAID s) in producing CNS effects

- Prolongation of the QT interval, for example, is an adverse effect associated with the use of fluoroquinolones.
- Fluoroquinolones prolong the QT interval by blocking voltage-gated potassium channels, especially the rapid component of the delayed rectifier potassium current Ikr, expressed by HERG (the human ether-a-go go-related gene). According to the available case reports and clinical studies, moxifloxacin carries the greatest risk of QT prolongation from all available quinolones in clinical practice and it should be used with caution in patients with predisposing factors for Torsade de pointes (TdP).
- Although gemifloxacin, levofloxacin, and ofloxacin are associated with a lower risk of QT prolongation compared with moxifloxacin, they should also be used with caution in patients at risk for QT prolongation [15].
- Ciprofloxacin appears to be associated with the lowest risk for QT prolongation and the lowest TdP rate. The overall risk of TdP is small with the use of fluoroquinolones.

Patient Counseling

Before you take this medicine: For your safety, tell your doctor or pharmacist if:

-You are taking any other prescription or over-the-counter medicines.

-You have other health problems or you are pregnant or breastfeeding. You have had an allergic reaction to any medicine or food.

Tips for taking your medicine;

Take your medicine exactly as directed and with a full glass of water. Keep taking your medicine until the bottle is empty, even if you feel better

If you don't take it all, your symptoms may return and be harder to treat.

If you take enoxacin, norfloxacin, or ofloxacin, take it on an empty stomach —at least 30minutes beforeor2 hours after eating.

If you take 2 or more doses a day, take them at evenly spaced times, day and night. This keeps an even amount of medicine in your blood.

If you miss a dose, take it as soon as you remember — unless it is almost time for your next dose. If so, skip the missed dose.

Do not take a double dose.

Usage During Pregnancy and Breastfeeding

Fluoroquinolones have been shown to cause some danger in animal reproduction studies.

They should only be used during pregnancy if the clinical benefit outweighs the risk and there is no other option.

Fluoroquinolones make their way into breastmilk. It is not advised to use while breastfeeding [16].

Usage for Children

They are only permitted for use in children under very specific conditions in most countries, owing to significant rates of musculoskeletal adverse effects.

Fluoroquinolone prescribing indications for children are severely limited in the United Kingdom.

Due to persistent safety concerns, only inhalant anthrax and pseudomonal infections in cystic fibrosis infections are licensed indications in the United Kingdom. Serious adverse events occurred in 6% of those treated with levofloxacin and 4% of those treated with comparator antibiotics in a study comparing the safety and efficacy of levofloxacin to azithromycin or ceftriaxone in 712 children with community-acquired pneumonia. In comparison to other antibiotic classes, meta-analyses show that fluoroquinolones represent little or no increased risk to children.

For your Safety

Cover up if you have to go out in the sun. Do not use a sun lamp. This medicine makes your skin sensitive to the sun. When outside, wear a hat, sunglasses, and a sun-block of at least SPF15.Talk to your doctor or pharmacist before taking any other medicines. If you take any other medicines, take them at least 2 hours before or 4 hours after you take your antibiotic. This includes antacids, vitamins, or other supplements that contain iron, calcium, zinc, magnesium, or aluminum.

Drug-Drug Interaction

• Sucralfate

Several investigators examined the effect of sucralfate, which contains approximately 200 mg of aluminum per gram, on the absorption of fluoroquinolones. Eight healthy volunteers received norfloxacin 400 mg alone, simultaneously with sucralfate1g, or 2hours after sucralfate1 g. The relative bio-availability of norfloxacin was decreased 98% with the simultaneous sucralfate dose, and approximately 40% when sucralfate was given2 hours before norfloxacin.

• Calcium-Containing Antacids

When calcium carbonate (Titralac)30ml was given 5 minutes prior to norfloxacin 400mg, relative bioavailability, Cm in plasma, and urinary recovery were all reduced approximately 60% compared with control values.

A 5-ml dose of Titralac administered 2 hours before ofloxacin 400-mg orally resulted in no significant changes in absorption of the fluoroquinolones.

The interaction of fluoroquinolones with aluminum, magnesium, calcium, and iron should be considered severe. Absorption of the Fluoroquinolones are significantly impaired when they are administered in proximity to these compounds; this appears to occur with all drugs of this class equally, and interpatient variability is minimal.

Even though in several studies the interaction was minimized when the agents were dosed several hours apart.

One must keep in mind that these studies were conducted in healthy volunteers and frequently gave single doses of one or both agents.

Extra polation of the results to elderly, debilitated patients receiving long-term antacid, sucralfate, or iron therapy would be difficult. Therefore, it is prudent to avoid fluoroquinolones altogether unless the potentially interacting drugs could be discontinued temporarily or an alternative (e.g., an H2-antagonist such as ranitidine) could be administered.

Conclusion

Fluoroquinolones are antibacterial agents that have a novel mechanism of action. In this literature review, we shed the light on the classification of these drugs, mechanism of action, development history, structure activity relationship, indications, contraindication, resistance, dosages, side effects, patient counseling, and their drug-drug interaction.

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