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Fluoroquinolones

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Introduction

Antimicrobials are an important class of drugs largely used to treat bacterial diseases. Since discovery of oldest antimicrobial agent sulphanilamide, several antimicrobial agents have been developed due to their popular use in treatment of diseases. With the increasing awareness regarding efficacy of antibacterial and development of anti-microbial resistance, numerous new antibacterial have been synthesized for use in different diseases of farm animals. Quinolones represent an important category of antimicrobial agents. Among them, Fluoroquinolones constitute the most important group. Fluoroquinolones are increasingly employed in veterinary medicine to eradicate susceptible bacterial infection. Development of newer generation fluoroquinolones generated interest for their use in veterinary medicine. Fluoroquinolones present a wide range of activity against gram-positive and gram-negative bacteria.

Quinolones, also referred to as 4-quinolones, quinolone carboxylic acids and fluoroquinolones, comprise a large and expanding group of synthetic antimicrobial agents. Carboxylic acid at 3-position and keto group at 4-position are essential in structure of quinolones to maintain their antibacterial activity. The first drug of this class, nalidixic acid, was discovered in 1962 and was a modification of a compound isolated during the production of the anti-malarial drug, chloroquine. However, its antibacterial spectrum of activity was restricted to the Enterobacteriaceae and, because of limitations in absorption and distribution, the drug was effective solely for the treatment of urinary tract infections. In the 1980s, the addition both of a fluorine molecule at the 6-position of the basic quinolone structure and a piperazine substitution at the 7-position was found to enhance antibacterial activity, gaining

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efficacy against such organisms as *Pseudomonas aeruginosa* and Gram-positive cocci, and to increase the extent of oral drug absorption and tissue distribution.

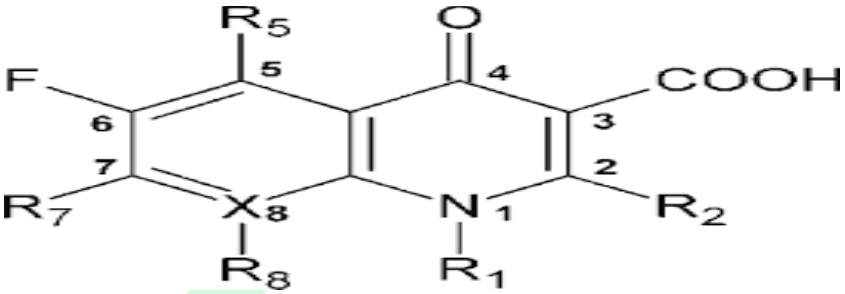

Fig. 1: General structure of Fluoroquinolones

The fluoroquinolones are characterized by concentration-dependent bactericidal activity and the ability to induce a post antibiotic effect against both Gram-positive and Gram-negative bacteria. Quinolones available for clinical use have been classified into four generations, mainly on the basis of their spectrum of activity.

Table 1: Classification of Fluoroquinolones

Generation	Examples	Characteristic Features
First	Nalidixic acid Oxolinic acid Pipemidic acid	Active against some Gram-negative bacteria. Highly protein bound drugs. Short half-life.
Second	Norfloxacin Enoxacin Ofloxacin Ciprofloxacin Lomefloxacin	Protein binding (50 per cent). Longer half-life than previous agents. Improved activity against Gram negative bacteria.
Third	Temafloxacin Sparfloxacin Grepafloxacin	Active against Gram negative bacteria. Also active against Gram positive bacteria
Fourth	Trovafloxacin Gatifloxacin Moxifloxacin Clinafloxacin	Show extended activity against both strains of bacteria. Active against anaerobes and atypical bacteria.

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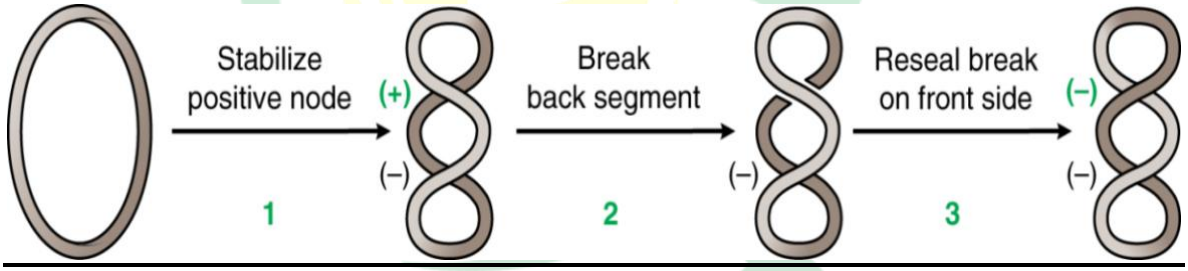
The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV. For many gram-positive bacteria (such as *S. aureus*), topoisomerase IV is the primary target site, inhibited by the quinolones. In contrast, for many gram-negative bacteria (such as *E. coli*), DNA gyrase is the primary quinolone target. The individual strands of double-helical DNA must be separated to permit DNA replication or transcription. However, anything that separates the strands results in "overwinding" or excessive positive supercoiling of the DNA in front of the point of separation. To combat this mechanical obstacle, the bacterial enzyme DNA gyrase is responsible for the continuous introduction of negative supercoils into DNA. This is an ATP-dependent reaction requiring that both strands of the DNA be cut to permit passage of a segment of DNA through the break; the break then is resealed. The DNA gyrase of *E. coli* is composed of two 105,000-dalton A subunits and two 95,000-dalton B subunits encoded by the gyrA and gyrB genes, respectively. The A subunits, which carry out the strand-cutting function of the gyrase, are the site of action of the quinolones. The drugs inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth (0.1 to 10 $\mu g.ml^{-1}$). Mutations of the gene that encodes the A subunit polypeptide can confer resistance to these drugs.



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gillman's The Pharmacological Basis of Therapeutics*, 12th Edition: http://www.accessmedicine.com

Model of the formation of negative DNA supercoils by DNA gyrase.

The enzyme binds to two segments of DNA (1), creating a node of positive (+) superhelix. The enzyme then introduces a double-strand break in the DNA and passes the front segment through the break (2). The break is then resealed (3), creating a negative (–) supercoil. Quinolones inhibit the nicking and closing activity of the gyrase and also block the decatenating activity of topoisomerase IV. (Reprinted from Cozzarelli, 1980, with permission.)

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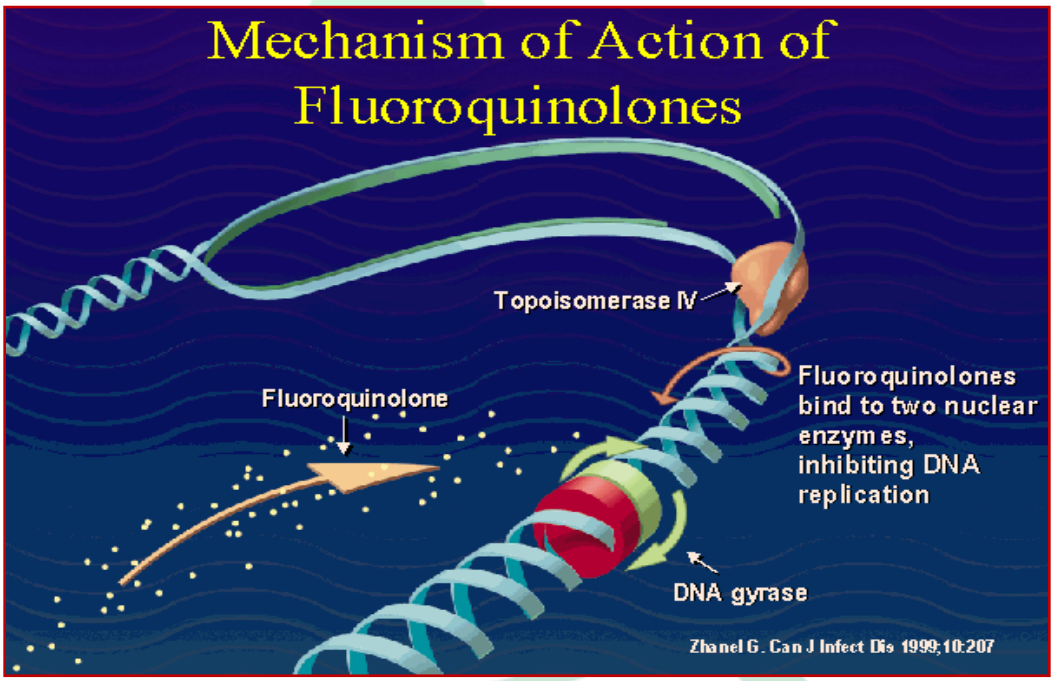
Fig.2: Mechanism of action of Fluoroquinolones

Topoisomerase IV also is composed of four subunits encoded by the parC and parE genes in *E. coli*. Topoisomerase IV separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication. Eukaryotic cells do not contain DNA gyrase. However, they do contain a conceptually and mechanistically similar type II DNA topoisomerase that removes positive supercoils from eukaryotic DNA to prevent its tangling during replication. Quinolones inhibit eukaryotic type II topoisomerase only at much higher concentrations (100 to 1000 $\mu g.ml^{-1}$).



Fluoroquinolones in general exhibit good activity against most gram-negative bacteria, especially those of the Enterobacteriaceae. *Escherichiacoli, Klebsiella* spp., *Proteus* spp., *Salmonella* spp., and *Enterobacter* spp. are usually susceptible. *Pseudomonasaeruginosa* is variably susceptible and, when it is susceptible, usually has a higher MIC than other susceptible organisms. Among fluoroquinolones, ciprofloxacin is the most active against *P. aeruginosa*. Gram-positive bacteria are variably susceptible. *Staphylococcusaureus, Staphylococcus pseudintermedius* and other *Staphylococcus* species usually are susceptible.

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However, the MIC values for staphylococci typically are higher than for gram-negative bacteria, and staphylococcal resistance to fluoroquinolones has been a problem in human patients. Methicillin-resistant strains of staphylococci (MRSA) are often resistant to fluoroquinolones. The use of the newest generation of fluoroquinolones has not yet been reported in veterinary medicine, except in experimental studies. These drugs, such as moxifloxacin, gatifloxacin, and the veterinary drug pradofloxacin have increased activity against gram-positive cocci and anaerobic bacteria and may have advantages for certain infections. Against gram-negative bacteria, such as the Enterobacteriaceae, they have equal or similar activity. Against *Pseudomonas aeruginosa*, these drugs are not as active as ciprofloxacin.

Fluoroquinolones are available for oral or intravenous administration. Both formulations are indicated for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, nosocomial pneumonia or uncomplicated skin and skin structure infections. In case of humans, moxifloxacin is mainly used to treat respiratory tract infections, cellulitis, anthrax, intra-abdominal infections, endocarditis, meningitis and tuberculosis.

Fluoroquinolones are used for the treatment of hospital acquired infections and also to be considered a drug of last remedy when all other drugs are failed.

Conclusion

Fluoroquinolones is an important group of antibiotics. They are highly useful in emergency conditions of animals and humans. Therefore, continuous use of these antibiotics should be avoided. So that we can use Fluoroquinolones in future days of emergency and life-threatening conditions.

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