The Pharma Innovation Journal 2018; 7(11): 413-417

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(11): 413-417

www.thepharmajournal.com
Received: 01-09-2018
Accepted: 03-10-2018

Dr. Arpita Shrivastav
College of Veterinary Science & Animal Husbandry, Rewa, Madhya Pradesh, India

Dr. Neeraj Shrivastav
College of Veterinary Science & Animal Husbandry, Rewa, Madhya Pradesh, India

Correspondence
Dr. Arpita Shrivastav
College of Veterinary Science & Animal Husbandry, Rewa, Madhya Pradesh, India

Fluoroquinolones: An old drug with new dimensions

Dr. Arpita Shrivastav and Dr. Neeraj Shrivastav

Abstract
The fluoroquinolones are a chain of synthetic antibacterial agents preferably used in the treatment of a variety of bacterial infections. These agents act through inhibition of the DNA gyrase, an important enzyme responsible for DNA replication by affecting DNA-rejoining reaction. The inhibition of the resealing leads to the liberation of fragments that are subsequently destroyed by the bacterial exonucleases. All fluoroquinolones accumulate within bacteria very rapidly, so that a steady-state intra bacterial concentration is obtained within a few minutes. Resistance develops slowly and is usually chromosomal and not plasmid mediated. However, development of resistance and transfer between animal and human pathogens has become a fervently argued issue among the microbiologists. Another concern regarding the use of new quinolones in the veterinary field is a possible detrimental effect on the environment. It still seems unlikely that the controlled use of veterinary quinolones will give rise to unfavorable effects on the environment.

Keywords: Ciprofloxacin, ofloxacin, quinolones, resistance, topoisomerase

Introduction
Fluoroquinolones constitute a very promising group of antimicrobial agents. These have become very popular during the last almost ten years as alternatives to treat bacterial isolates which are resistant to aminoglycosides, third generation cephalosporins, extended spectrum penicillins and other β lactam antibiotics, folic acid antagonists and macrolides [24,28]. These as a group are highly effective at extremely low concentrations compared to other groups of antibacterial agents. The minimum inhibitory concentration values (MIC) of fluoroquinolones range from 0.001 to 1.0 µg/ml against most of the susceptible microbes [22].

Some of the fluoroquinolone derivatives including Ofloxacin and ciprofloxacin have also been found to exhibit antibacterial activity against *Mycoplasma, Chlamydia, Legionella, Brucella* and *Mycobacterium* species [4, 28]. These are rapidly bactericidal *in vivo* and *in vitro* for susceptible microorganisms in a concentration-dependent manner. Newer fluoroquinolones (sparfloxacin, temafloxacin, tosulfoxacin etc.) have increased activity against *Streptococcus hemolyticus*, streptococci B, C, F and G, enterococci, staphylococci, *Corynebacterium* sp., *Listeria monocytogenes, and Bacillus* sp. [10]. These are also effective against anaerobic bacteria including *Clostridium perfringens, C. difficile, and Bacteroides fragilis* in addition to Gram-positive and Gram-negative bacteria [14]. Clinafloxacin, a newer quinolone, has improved activity against *Streptococcus pneumoniae* [33, 11]. Recently, pefloxacin, ofloxacin and ciprofloxacin have also been found to be active against *Plasmodium, Trypanosoma cruzi and Leishmania donovani.* A new fluoroquinolone trovafloxacin has been found to be useful against toxoplasmosis in human beings [20]. Prolonged post-antibiotic effect of fluoroquinolones against some of the susceptible microorganisms is one of the unique advantages of these antimicrobials.

Fluoroquinolones act on bacterial DNA gyrase. Resistance to fluoroquinolones does not develop rapidly as the resistance genes targeting the fluoroquinolones are seldom found on bacterial plasmids [6]. No plasmidic resistance against them has been documented [35]. Some of the anaerobic cocci like *Clostridium* sp. and *Bacteroides* are considered to be resistant to fluoroquinolones [24], however, resistant mutants have been seen on *in vitro* experimental selection [8], or clinical administration. These isolated mutants show cross reactivity for different quinolones and fluoroquinolones but no cross reactivity with other antimicrobial families.

Fluoroquinolones are more active in alkaline environments (pH > 7.4) against Gram-negative bacteria but susceptibility of Gram-positive bacteria is not affected by pH [9]. Quinolones have been used to treat a variety of microbial infections in humans - bronchitis, pneumonias [31],

lower urinary tract infections, *Salmonella typhi* infections, acute bacterial diarrhoeal diseases, intracellular infections (legionellosis, brucellosis, tularemia, *C. trachomitis* infections, skin and soft tissue infections, surgical prophylaxis (biliary cardiovascular and colorectal surgery), prophylaxis and therapy of infections in immunocompromised patients and malaria [31], otitis externa and opthalmitis [3].

Therapeutic use of fluoroquinolones is also becoming popular in veterinary medicine to treat infections of urinary tract, respiratory tract, gastro-intestinal tract, skin and soft tissue infections etc. Norfloxacin, enrofloxacin and ciprofloxacin are used for urinary tract infections [36], prostatitis and osteomyelitis. Danofloxacin is used for bovine respiratory diseases [15] and poultry mycoplasmosis [17]. Sarafloxacin is the first fluoroquinolone approved for food producing animals in US.

Fluoroquinolones have excellent oral bioavailability in all monogastric animals. High values of volume of distribution and low plasma protein binding allow them to cross the membranes and reach most parts of the body at concentrations much above the minimum inhibitory concentrations (MIC) against most of the susceptible pathogens [1].

With the few exceptions, adverse effects of fluoroquinolones are not of severe consequences if used judiciously compared to their beneficial features. Target sites are the juvenile cartilages of weight bearing joints in growing animals and cause lameness and pain [38].

Other adverse manifestations of fluoroquinolones include convulsions, dizziness [19], renal crystalluria in acidic urine, subcapsular cataracts skin eruptions, embryonic losses etc.

During the last one decade, lot of data has been generated on the pharmacokinetics of different fluoroquinolones in different species of animals including human beings, birds and aquatic fauna; enrofloxacin in sheep [23, 27].

Disposition kinetic profiles of different fluoroquinolones not only vary with the compounds but also between different species of animals. Therefore, it is Imperative that the pharmacokinetic studies should be conducted on all the agents in different species of animals and the environment(s) where these are to be used clinically.

To increase the productivity of animals, proper health cover should be provided by using the latest and most effective chemotherapeutic agents including ofloxacin and ciprofloxacin.

The history of fluoroquinolones dates back to the discovery of nalidixic acid in 1962 as an accidental byproduct during the synthesis of anti-malarial compound chloroquine. In 1970's, another group of quinolones was launched (oxolinic acid, pipemidic acid and cinoxacin) and these compounds were marginally better than nalidixic acid. A breakthrough was achieved in early 1980's with the development of fluorinated 4-quinolones such as norfloxacin and ciprofloxacin since these agents have broad antimicrobial activity, effective orally against a wide variety of infectious diseases, have fewer side effects and the microbial resistance does not develop rapidly.

Chemistry of fluoroquinolones

Fluoroquinolones (6-fluoroquinolones or 4-fluoroquinolones) are the synthetic antibacterial agents which are being extensively used in human and veterinary medicine [6]. These are the structural congeners of nalidixic acid as shown in Fig. 1:

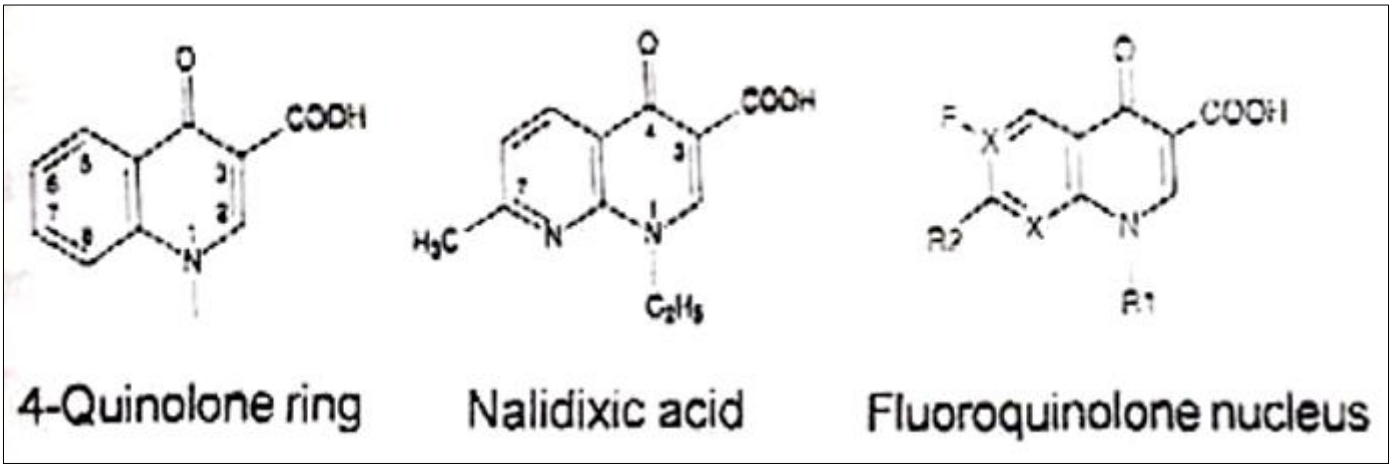

Fig 1: Chemical structures of Quinolone ring, nalidixic acid and fluoroquinolone nucleus

The basic structure of fluoroquinolones is a bicyclic aromatic ring structure with an alkyl group at nitrogen position (N_1) and carboxylic acid at position 3; and the keto group at C_4 is required for antibacterial activity. Quinolones bear both an acidic group (carboxylic acid) and a basic group (tertiary amine) and thus have amphoteric properties.

Lipid solubility of fluoroquinolones is generally low except between pH 6 and 8; within this range, these are less water soluble and are prone to precipitate under more acidic conditions [6] and apparently due to this property, crystalluria has been seen in man and animals [36].

Alterations in the ring structure largely enhance the antimicrobial activity and increase the volume of distribution of the molecule. Carboxylic acid attached at position 3 is necessary for DNA gyrase inhibition; similarly, keto-group at position 4 is also required for inhibition of DNA gyrase [35, 6]. Substitution at position 5 alters the pharmacokinetic properties of these antimicrobials. A fluorine atom at position 6 on the quinolone carboxylic acid nucleus increases the efficacy of these compounds against Gram-negative microbes and increases their spectrum against Gram-positive pathogens. Fluoroquinolones having 4-fluoro-phenyl moiety (difloxacin) have an increased spectrum of activity against anaerobes. A basic nitrogen containing moiety enhances tissue penetration and reduces central nervous system toxicity. The substitution of a piperazinyl ring at position 7 renders the molecule active against *Pseudomonas* [37]. The substitution of hydrogen atom by fluorine on 8th position of the ring and methyl group on the alkyl chain diminishes the rate of degradation and elimination.

Ofloxacin differs from other fluorinated quinolones by the presence of a ring linkage of the 1-nitrogen and 8-carbon of the quinolone nucleus [16]. At 3-carbon position of oxazine rings, a methyl group is attached whjch results in asymmetrical centre due to which ofloxacin has two optically active isomers the (-) and (+) form; the (-) form is 8-128 times more active than (+) form isomer against Gram-positive and Gram-negative bacteria [12, 16].

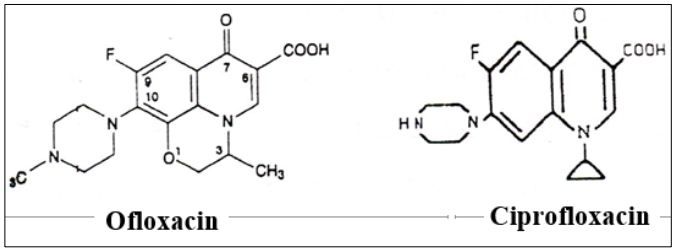

Fig 2: Chemical structures of ofloxacin and ciprofloxacin

Mechanism of action

Bacterial cells in a very small volume of cellular space (1-2 pm) normally contain large amounts of DNA (approx. one meter). Double stranded DNA undergoes an extensive compaction so that it can be compressed into the bacterial cells [35, 21] by the process termed as supercoiling of DNA. For replication of DNA, two strands must be separated; anything separating DNA strands results in positive supercoiling. Therefore, supercoiling of DNA molecule can occur by transient breaks in the DNA. In both, prokaryotes and eukaryotes, two enzymes topoisomerase I and II break the DNA strands and help in supercoiling. Topoisomerase I introduces breaks and unions only in one strand whereas topoisomerase II in both the strands of DNA. Bacteria possess a special topoisomerase II (DNA gyrase; E.C. 5.99.1.3) which continuously introduces negative supercoils into DNA by ATP-dependent reactions. [35]. Thus, aligns DNA into a relaxed form which has decreased susceptibility to fragmentation and increased ease of separation during strand replication [9]. The DNA is coiled around RNA core in a series of loopes i.e. negatively supercoiled by nicking both strands of DNA, passing broken strands behind the double strand and resealing both the nicks [4].

DNA gyrase is an intracellular enzyme. Fluoroquinolones enter the bacteria via pores [7] and rapidly accumulate within the bacteria with the steady state concentrations reaching within few minutes [25]. These inhibit replication of bacteria by an action on DNA gyrase. Fluoroquinolones bind in a cooperative manner to a pocket of single strand DNA created by DNA gyrase by an electrostatic interaction. Binding kinetics of these antimicrobials suggests that four molecules of these can stereo chemically fit into the pocket to inhibit DNA gyrase [14]. This enzyme, a type II isomerase, plays an important role in unwinding, cutting and consecutive resealing of DNA. The inhibition of resealing leads to liberation of fragments which subsequently are destroyed by bacterial exonucleases [5, 32].

Antimicrobial spectrum of fluoroquinolones

Fluoroquinolones are broad spectrum antimicrobial agents having high activity against Gram-negative aerobes [6, 21, 22]. These are rapidly bactericidal; primarily effective against Gram-negative bacteria and *Pseudomonas aeruginosa,* good to moderate activity against staphylococci, *mycobacteria, Chlamydia, mycoplasma* and *urea plasma;* little or no activity against streptococci (particularly group D streptococci), enterococci and anaerobic bacteria [6].

Antibacterial activity is often assessed on the basis of concentration of the agent required to inhibit the growth of bacterial isolates *in vitro* i.e. minimum inhibitory concentration (MIC). The MICs of fluoroquinolones are very dose to the concentrations needed to be bactericidal to the organisms or it may be only twice the inhibitory concentration [35, 22].

The MIC_{90} values of most of the fluoroquinolones is between 0.001 and 1.00 μg/ml for many Gram-negative bacteria including staphylococci and streptococci [2]; Prescott and Baggot, 1993; Spreng *et al.*, 1995) [26, 34].

In general fluoroquinolones are active against enteric Gram-negative bacilli and cocci (*E. coli*, *Klebsiella* sp., *Shigella* sp.). The MIC_{90} value against most of the *Enterobacteriaceae* range from 0.05 to 0.5 μg/ml [29, 2, 26, 35, 34, 6, 22].

Comparing the antibacterial activity of fluoroquinolone and non-quinolone antibacterial agents, it was found that ciprofloxacin had the broadest spectrum of activity against all Gram-negative and streptococci tested. For other bacteria like *Neisseria*, *Haemophilus influenza*, penicillinase producing *Neisseria gonorrhoea* [13, 29, 10, 35, 28], ciprofloxacin was twice as active as norfloxacin and rosoxacin against *Chlamydia trachomatis*, *Mycoplasma hominis, Ureaplasma urealyticum*, *Legionella, Brucella* and *Mycobacterium tuberculosis*.

Some newer fluoroquinolones e.g. sparfloxacin, temafloxacin, tosulfoxacin and several others have increased activities against staphylococci, streptococci, *Corynebacterium* sp., *Listeria* sp., *Bacillus* sp. etc. [10] and anaerobic bacteria (*Clostridium* sp., *Bacteroides fragilis* etc.) In addition to antibacterial activity, ofloxacin and ciprofloxacin are also active against *Plasmodium*, *Trypanosoma cruzi* and *Leishmania donovani* [10] and trovafloxacin (a new fluoroquinolone) against *Toxoplasma gondii* in humans [20].

Bacterial resistance

Antimicrobial resistance, the ultimate consequence of the use of any antimicrobial agent, is of great clinical concern not only in human but veterinary medicine too [6]. Due to synthetic nature and unique mode of action of fluoroquinolones, bacteria rarely develop spontaneous resistance to these antimicrobial agents [22].

Resistance primarily occurs by alterations in bacterial cell wall permeability while mutant forms of DNA gyrase occur rarely. Chromosomal mutations code for specific changes in microbial cell wall; increasing the lipophilicity of cell membranes or porin (hydrophilic pores), which result in decreased permeability of drug [35, 6, 22]. Permeability changes may also occur through alterations in active transport pump [18] thereby decreasing intracellular concentrations of fluoroquinolones. Such resistance can be overcome by increasing the concentration of drug [14]. Fluoroquinolone resistance is emerging in Gram-negative pathogens worldwide. Over the past 20 years, resistance to fluoroquinolones in Gram-negative bacilli has become common and widespread. Report from EARSS Program in Europe revealed a continued decrease in fluoroquinolone susceptibility. A decrease in the susceptibility rates of fluoroquinolones was also observed within the non-fermentative Gram-negative bacilli, including Pseudomonas aeruginosa and Acinetobacter spp. Traditionally, two mechanisms of resistance have been found to determine resistance to fluoroquinolones: the accumulation of mutations

in the targets (DNA gyrase and DNA topoisomerase IV) and upregulation of native efflux pumps either alone or together with decreased expression of outer membrane porins mediated by chromosome. The recent discovery of plasmid-mediated quinolone resistance by Qnr protein, AAC (6`)-Ib-cr and qepA pump provides us the new thought on the rapid increasing resistance. Plasmid-mediated resistance mechanisms provide low-level quinolone resistance that facilitates the emergence of higher-level resistance. The emerging of quinolone resistance has associated with resistance to other agents, such as beta-lactams and aminoglycosides. To screen for these genes at bedside for the clinical Gram-negative bacilli is needed. The ecologic relationship between fluoroquinolone use and resistance is complex and requires more study. Reducing fluoroquinolone use in food animials will impove human health. At the same time, we should advocate prudent use of fluoroquinolones in clinical practice worldwide.

Conclusion

Fluoroquinolones are one of the most useful classes of antimicrobial agents used in human and animal medicine today, both because of their spectrum and their physicochemical properties. As such, their popularity in clinical situations is increasing. Recently, however, concerns have been aroused over the possible emergence of quinolone-resistant strains and the effects on the environment if such drugs are overused. At present it appears that veterinarians can prolong their usefulness for many years if they use appropriate clinical judgment and proper dosing principles when they prescribe and administer these drugs to animals.

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