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# QUINOLONES AS ANTIMICROBIAL AGENTS A REVIEW

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**Abstract:**

*Quinolones are synthetic antibacterial agents used in the treatment of a variety of bacterial infections initially, quinolones were mostly used in the treatment of Gram-negative infections, but they were later modified in order to improve their pharmacokinetic properties and extend their antibacterial spectrum, becoming effective against a wide variety of Gram-negative and Gram-positive pathogens. They have a relatively simple nucleus, and structural modifications are quite easy. Consequent to their broad spectrum of antimicrobial effect and safety profile, there was significant hope and anticipation that this class of antibiotics would find an imperative place in therapeutics. In this paper an attempt is made to review prospects of different classes of quinolone antibacterials only for the purpose of comparison.*

**Keywords:** *Fluoroquinolones; Structural activity relationship; Resistance.*

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## INTRODUCTION:

The prototypical compound of the quinolones, nalidixic acid, was introduced into clinical use in 1962 to treat uncomplicated urinary tract infections (UTIs) and can be considered as the first generation of the quinolones[1,2,3]. However, the quinolones only became a widely used drug class in the 1980s with the development of a second generation of compounds, the fluoroquinolones, which displayed considerably improved activity, greater Gram-positive penetration and enhanced pharmacokinetic and pharmacodynamic properties[1,3,5]. The most important modifications to the quinolone structure were the introduction of fluorine at the sixth position and a major ring substituent at position seven. The first representative of this generation was norfloxacin; however, ciprofloxacin was the first fluoroquinolone that showed significant activity outside the urinary tract[4, 5]. After almost three decades in clinical use, ciprofloxacin remains one of the most commonly prescribed antimicrobial drugs, being listed by the World Health Organization (WHO) as an essential medicine and a critically important antibiotic[7].The clinical success of ciprofloxacin led to the development of a collection of newer-generation quinolones (levofloxacin, moxifloxacin, gatifloxacin, etc.) with an even broader and different spectrum of activity and pharmacokinetic characteristics[5, 6].

Due to their potency, broad activity spectrum, oral bioavailability and generally good safety profile, fluoroquinolones have been used extensively for multiple clinical indications worldwide[8,9]. Quinolones have been prescribed to treat UTIs, respiratory tract infections (e.g. community-acquired and nosocomial pneumonia, chronic bronchitis and tuberculosis), skin and soft tissue infections, bone and joint infections, intra-abdominal infections, sexually transmitted diseases, among others[5, 8]. However, due to the extensive use of these drugs in human and veterinary medicine, and despite prescribing guidelines now recommending reserving quinolone use, the number of quinolone-resistant strains has been growing steadily, being observed in all species treated by this antimicrobial class. Although still clinically valuable, quinolone use has been compromised by the emergence of resistance, having serious implications in some clinical settings[5,8,7].

**Mechanisms of Quinolone action:**

Quinolones act by inhibiting the activity of two essential bacterial type II topoisomerases, DNA gyrase and topoisomerase IV, which are involved in the modulation of the chromosomal supercoiling required for DNA synthesis, transcription and cell division. These enzymes modulate DNA topology by passing an intact double helix through a transient 4 bp staggered double-stranded break that they introduce in a separate segment. In order to preserve genomic integrity during this process, DNA gyrase and topoisomerase IV form covalent bonds between active site tyrosine residues and the 5¢-overhangs at the DNA break, forming enzyme-cleaved DNA complexes known as cleavage complexes. Quinolones interfere with this critical process by reversibly binding to these cleavage complexes at the enzyme–DNA interface in the cleavage–ligation active site, therefore increasing the steady-state concentration of cleavage complexes by physically blocking DNA strand religation. Quinolone–topoisomerase binding was recently demonstrated to occur through a water–metal ion bridge, where a noncatalytic Mg2+ ion coordinated with four water molecules forms a bridge for hydrogen bonding between the quinolone and the serine and acidic residues that act as anchor points to the enzyme[1,4,9,10].

DNA gyrase and topoisomerase IV are A2B2 heterotetrametric enzymes composed of two pairs of identical subunits, GyrA2 GyrB2 and ParC2ParE2 (or GrlA2GrlB2 ), respectively. Despite their general functional and structural similarities, DNA gyrase and topoisomerase IV have distinct physiological functions. DNA gyrase uses the energy of ATP hydrolysis to actively introduce negative supercoils into DNA which are essential for

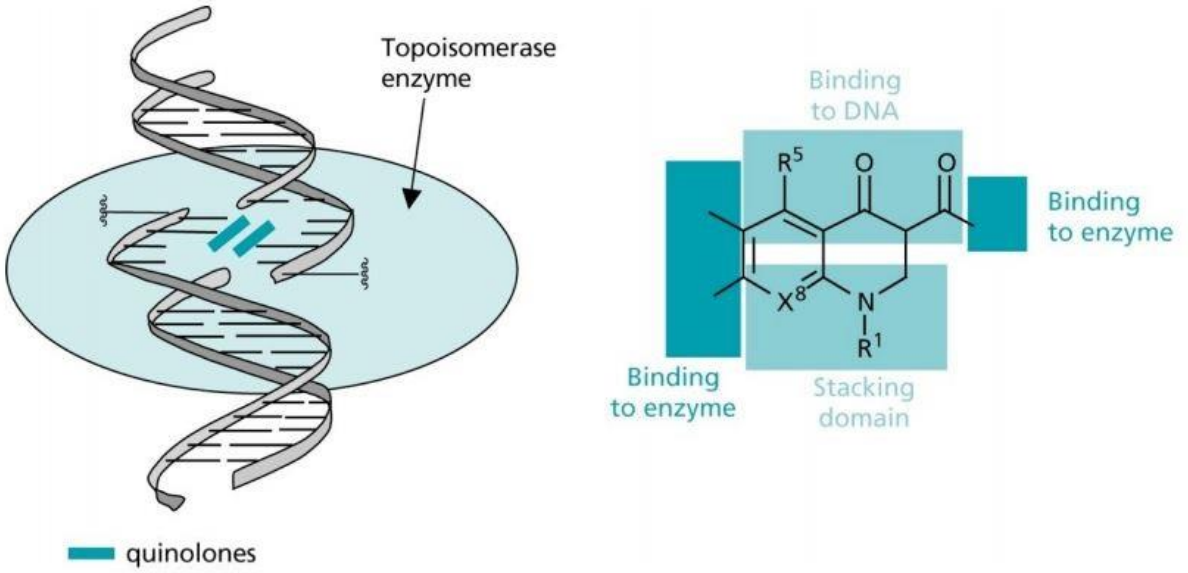
1. setting the super-helical density that allows chromosome condensation,
2. relieving the torsional stress that accumulates in front of replication forks and transcription complexes, and
3. promoting local melting for transcript initiation by RNA polymerase.

Topoisomerase IV also plays a role in maintaining chromosomal super-helical density and alleviating torsional stress, although to a lesser extent than DNA gyrase since it is only able to relax positive supercoils and unable to introduce further negative supercoiling. However, the major function of topoisomerase IV is decatenation of the interlocked daughter chromosomes at the end of replication [1,4,6,10].

Quinolones are known to target DNA gyrase and topoisomerase IV with varying efficiencies in different bacterial species. Generally, DNA gyrase is considered the primary target of quinolones in Gram-negative species and topoisomerase IV the primary target in Gram-positives. However, this has been proven to be untrue in many cases, with examples of

Gram-positive species where DNA gyrase is the primary target for quinolones and also cases of different quinolones having distinct primary targets in the same species or quinolones with similar potencies against both enzymes. Hence, the relative contribution of each topoisomerase to quinolone action still needs further investigation, on a species-by-species and drug-by-drug basis, in order to be fully elucidated [1,4,9].

The formation of quinolone–topoisomerase–DNA ternary complexes causes the DNA replication machinery to become arrested at blocked replication forks, resulting in an inhibition of DNA synthesis, which immediately leads to bacteriostatic (at low quinolone concentrations) and eventually to cell death (at lethal concentrations) [6,10]. Due to the positioning of DNA gyrase ahead of the DNA replication complex and of topoisomerase IV behind it, it appears that the interaction of quinolones with DNA gyrase results in a more rapid inhibition of DNA replication than with topoisomerase IV [911].Moreover, when DNA tracking systems (replication forks, transcription complexes, etc.) collide with these stabilized ternary complexes, permanent chromosomal breaks are generated [5,4].These double strand DNA breaks trigger the bacterial DNA stress response, in which the RecA protein is activated by DNA damage and promotes the self-cleavage of the LexA repressor, thus de-repressing the expression of SOS response genes such as DNA repair enzymes. The quinolone bactericidal activity therefore results from the overwhelming of these processes and the extent to which DNA repair is incomplete. Indeed, fluoroquinolone bactericidal activity has been shown to be enhanced when the induction of the SOS response is prevented. Although inhibition of protein synthesis does not seem to affect quinolone mediated inhibition of DNA replication, it has been proven to reduce the quinolone bactericidal activity, with varying magnitudes between different quinolones [9]. Hence, the primary effects of the formation of quinolone–topoisomerase–DNA complexes and the following bacterial response through stress-induced protein expression seem to have a clear association in determining quinolone bactericidal activity [10]. For instance, the contribution of reactive oxygen species to quinolone-mediated cell death has been recently shown to occur in a protein synthesis-dependent manner [12]. This suggests that, in addition to the inhibition of DNA replication, other events that may affect DNA or other cellular damage may also contribute to the bactericidal activity of quinolone drugs; however, the underlying molecular mechanisms are not yet fully understood[9]. Moreover, inhibition of the catalytic functions of DNA gyrase and topoisomerase IV due to quinolone stabilization of cleavage complexes results in a loss of enzyme activity that affects a number of nucleic acid processes and is therefore likely to contribute to the overall toxicity of quinolones [5].




**Quinolones: Mechanism of Action**

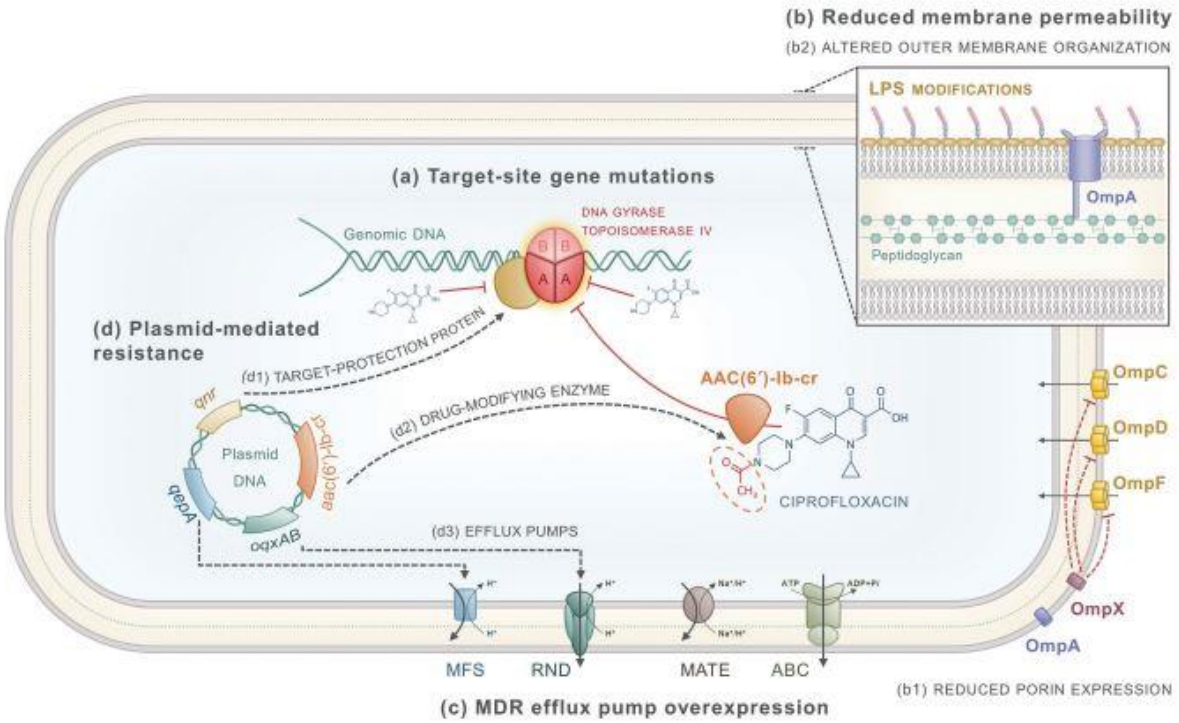
**Mechanisms of quinolone resistance:**

The acquisition of quinolone resistance may be associated with three types of mechanisms:

1. chromosomal mutations that alter the target enzymes and their drug-binding affinity;
2. chromosomal mutations leading to reduced drug

accumulation by either decreased uptake or increased efflux;

3. plasmid-acquired resistance genes producing either target protection proteins, drug modifying enzymes or drug efflux pumps [4,6]




**Mechanisms of quinolone resistance**

a) Chromosomal mutations within the QRDRs of the genes encoding the A and B subunits of DNA gyrase and topoisomerase IV structurally change the target protein, reducing its drug-binding affinity.

b) Chromosomal mutations leading to reduced outer membrane permeability, by either reduced porin expression (b1) or modifications in the outer membrane organization (b2), and also mutations leading to an increased expression of efflux pumps

c) contribute additively to resistance by decreasing cytoplasmic quinolone accumulation.

d) Plasmid-encoded quinolone resistance genes can produce Qnr target-protection proteins (d1), AAC(6¢)-Ib-cr acetyltransferase variants capable of modifying certain quinolones (d2) or QepA and OqxAB efflux pumps that actively extrude quinolones. LPS, lipopolysaccharide; MFS, major facilitator superfamily; RND, resistance–nodulation–division; MATE, multiple antibiotic and toxin extrusion; ABC, ATP-binding cassette; MDR, multidrug resistance [1,4,7].

**CLASSIFICATION:**

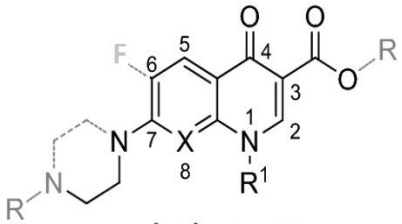
Presently, four generations of fluoroquinolone antibiotics exist as illustrated by the following table:

| | |
|---|---|
| First generation | Naldixic acid, Pipemidic acid, Oxolinic acid |
| Second generation | ciprofloxacin, levofloxacin, enoxacin, fleroxacin, ofloxacin, lomefloxacin, norfloxacin |
| Third generation | gatifloxacin, gemifloxacin, grepafloxacin, sparfloxacin |
| Fourth generation | moxifloxacin, trovafloxacin, Clinafloxacin, Gatifloxacin |

The newer quinolones have enhanced activity against staphylococci, streptococci and anaerobes. In general, the older generation compounds have more activity against gram negative bacteria and provide less gram positive coverage. The 3rd and 4th generation quinolones show an expanded spectrum of activity against gram positive organisms. In regards to their activity against *Mycobacterium tuberculosis*, moxifloxacin and gatifloxacin demonstrate more potent *in vitro* activity than ciprofloxacin or

levofloxacin.
Of these agents ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin. They have activity against a broad range of gram positive and negative organisms. The drugs in this class are uniformly active against the Enterobacteriaceae, and many strains of *Listeria*, *Chlamydia*, and mycobacteria [13,14,15].

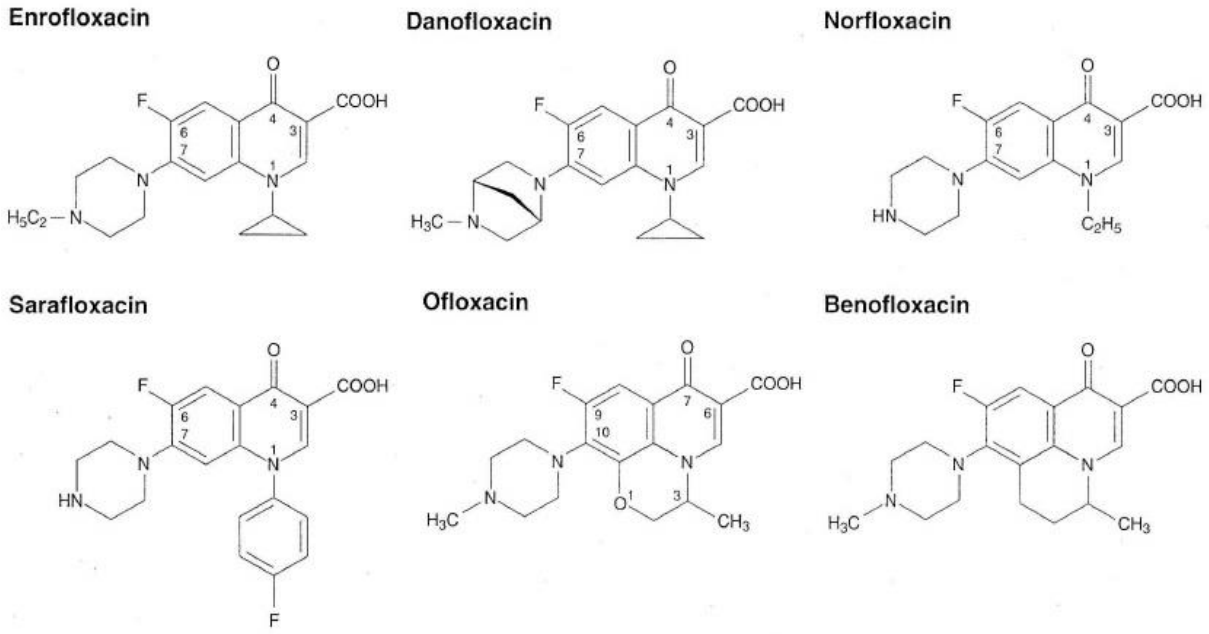
**Chemistry and Structure-activity relationships:**




quinolone core

Position 1 is nitrogen in the bicyclical aromatic ring structure, with an alkyl group (ethyl or perhaps cyclopropyl) often attached there. Carboxylic acid at position 3 is required for antimicrobial activity, similarly like a keto group at position 4. Many improvements on these early quinolone carboxylic acids have been made based in systematic structure-activity studies. A fluorine atom at position 6 on the quinolone carboxylic acid nucleus enhances the efficacy of these compounds against gramnegative pathogens and broadens the spectrum of activity against gram positive pathogens: a basic nitrogen-containing moiety enhances tissue penetration and reduces the central nervous system toxicity. Modifications of the basic structure at positions 2, 5 and 7 alter the pharmacokinetics of the compound. A carbon, nitrogen or oxygen atom occupies position 8 on the heterocyclic aromatic ring, depending on the quinolone. Nitrogen atoms at positions 1 and 8 produce naphthyridine carboxylic acids (e.g. enoxacin or nalidixic acid), whereas nitrogen atoms at positions 1, 6 and 8 are called pyridopyrimidine carboxylic acids, which are not fluorinated at position 6 (e.g. pipemidic acid). Because of the presence of carboxylic acid and one or several basic amine functional groups, these antibacterial agents are amphoteric and considered zwitterionic.

The structure of the ring has been largely modified to enhance the antimicrobial activity and to increase the volume of distribution of the molecule. The substitution of a piperazinyl ring at position 7 has rendered the molecule active against *Pseudomonas* and the presence of a fluorine atom at position 6 extends the activity of the molecule to some but not all gram-positive bacteria [16]. *Streptococcus* can be resistant [17]. Additions of alkyl chains to the para position of the piperazinyl ring, and to the nitrogen at position 1, increase the lipid solubility and the volume of distribution of the compounds. The substitution of hydrogen atoms by fluorines at position 8 of the ring and on the methyl of the alkyl chain diminishes the rate of degradation and decreases the rate of elimination. It was widely believed that 3-carboxylic acid and 4-carbonyl were necessary for the antimicrobial activity of the compounds. However, transformation of existing molecules in 2,3,4,9 tetrahydroisothiazolo [5,4-b] quinoline-3,4-diones produces a significant increase in their biological activity [18]. The quinolones bear both the acidic group (carboxylic acid) and the basic group (tertiary amine). This association gives them amphoteric properties. Their solubility is low, except between pH 6 and 8. Within this range, they have low water solubility and are prone to precipitate under more acidic conditions [19]. It is apparently due to this property that crystalluria has been observed in man and animals.




**General chemical structure of some fluoroquinolones**

**ANTIMICROBIAL ACTIVITY**

Until the introduction of newer analogs of quinolones, the more serious deficiency of the quinolones was their lack of anaerobic activity, limited anaerobic activity was also shown by the second generation of quinolones. The fluoroquinolones have an excellent activity against *Enterobacteriaceae*, fastidious gram-negative bacteria and *Pseudomonas aeruginosa*, good to moderate activity against staphylococci, mycobacteria, chlamydia, mycoplasma and ureaplasma: and little or no activity against streptococci (particularly group D streptococci), enterococci, and anaerobic bacteria. The postantibiotic effect of fluoroquinolones has been shown to be 4–8 h against *Escherichia coli*, *Klebsiella*, *Serratia*, and *Pseudomonas aeruginosa* [20]. Comparison of ciprofloxacin, norfloxacin, pefloxacin, pipemidic acid and a variety of nonquinolone antibacterial agents (nitrofurantoin, sulfamethoxazole, trimethoprim, cephradine and amoxicillin) demonstrated that ciprofloxacin had the broadest spectrum of activity against all gram-negative bacteria and streptococci tested, with the exception of *Enterococcus faecalis* and *Streptococcus pneumonia* [21].ompared with rosoxacin, norfloxacin, nalidixic acid and oxolinic acid the activity of ciprofloxacin against *Chlamydia trachomatis*, *Mycoplasma hominis* and *Ureaplasma urealyticum* was found to be at least twice as high [22]. Enrofloxacin has structural similarity to ciprofloxacin and has a similar antibacterial spectrum to ciprofloxacin against *Haemophilus* sp., *Pasteurella* sp. And *Actinomyces* sp. [23] Temafloxacin is more potent than either ciprofloxacin or ofloxacin against staphylococci and streptococci, but not against *Haemophylus influenzae*. Improved oral activity of temafloxacin is a function of both improved potency and better oral bioavailability [24].

Fluoroquinolones (either under development or already marketed) such as difloxacin, sparfloxacin, temafloxacin, tosufloxacin, and several other fluoroquinolones have increased activities against staphylococci, streptococci, enterococci, *Corynebacterium* sp., *Listeria monocytogenes* and *Bacillus* sp. These also show the activity against various anaerobic bacteria, including *Clostridium perfringens*, *Clostridium difficile*, and *Bacteroides fragilis*. Those containing a cyclopropyl group at position 1 show the activity against *Mycobacterium leprae* Recently, pefloxacin, ofloxacin, and ciprofloxacin were found to be active against *Plasmodium*, *Trypanosoma cruzi*, and *Leishmnia donovani* although *Toxoplasma gondii* was not susceptible. Many of the newer fluoroquinolones with increased activity against gram-positive bacteria have the lower activity against *Pseudomonas aeruginosa* than older fluoroquinolones [25]. Fluoroquinolones are more active in alkaline environments (pH > 7.4) for gram-negative bacteria [26], but susceptibility of gram-positive bacteria to fluoroquinolones is not affected by pH. Susceptibility is not affected by the inoculum size [27], but activity

is reduced by the presence of divalent cations [26]. In general, aminoglycosides, β-lactams, imidazoles, macrolides, and lincosamides infrequently show synergy with fluoroquinolones against Enterobacteriaceae, gram-positive bacteria and anaerobes: but rarely do they show antagonism. Antipseudomonal penicillins and imipenem are synergistic with fluoroquinolones in 20–50% of the *in vitro* and *in vivo* models. Antagonism in streptococci and enterococci occurs between fluoroquinolones and either macrolides or tetracyclines [20] in general, fluoroquinolones are antagonistic with chloramphenicol.

**Pharmacokinetics:**

Fluoroquinolone antibiotics are rapidly absorbed following oral administration, and generally demonstrate linear kinetics. Antibiotics eliminated by both renal and nonrenal routes offer advantages in patients with fluctuating renal function, while those with primarily renal elimination seem preferable in patients with complete renal failure because of the convenience of infrequent administration. Ofloxacin, ciprofloxacin, levofloxacin and gatifloxacin are mainly excreted in an unchanged form in the urine. There is a linear relationship between levofloxacin clearance and renal function, such that dose adjustment is needed in patients with moderate-to-severe renal impairment. Grepafloxacin is eliminated primarily through metabolism in the liver via the cytochrome P450 system and is excreted mainly in the faeces, either via bile or transmucosally[28]. Sparfloxacin is eliminated mostly by nonrenal processes, but some dosage adjustment is needed in patients with moderate-to severe renal dysfunction.

A factor contributing to fluoroquinolone activity is the tissue levels that they attain. The main barrier to antibiotic penetration is the no fenestrated capillary endothelium separating the capillaries from the submucosa [29]. To penetrate the alveolar space the antibiotic must also cross the alveolar membrane, which is rendered relatively impermeable by the presence of many tight junctions or zonulae occludens [30,31]. There is thus a significant barrier between the ELF and the capillary blood supply. Alveolar macrophages may take up antibiotics from the ELF or serum before migrating into the alveolar space. The activity of the newer macrolides and fluoroquinolones against intracellular respiratory pathogens has led to an increased interest in their penetration into macrophages and polymorphs. Most studies on tissue antibiotic levels are performed during the steady state, in uninfected individuals. ThisCould result in bias because the pharmacokinetics of antibiotics may be altered in individuals with an infection. It is also possible that tissue penetration at steady state differs from that after a single dose and so several doses may be needed to achieve steady state, which may also affect tissue penetration.

**Drug-Drug Interactions:**

Clinically important drug-drug interactions may occur with coadministration of a quinolone with an aluminum- or magnesium-containing antacid, theophylline, or caffeine. When coadministered with an aluminum- or magnesiumcontaining antacid, oral bioavailability of norfloxacin, ciprofloxacin [32,33], ofloxacin [34,35], and perhaps all quinolones is substantially diminished, possibly by binding of quinolone to antacid. Peak serum concentrations decreased 16-fold for ciprofloxacin and 4-fold for ofloxacin. Sucralfate also reduces the absorption of norfloxacin and likely other quinolones. Patients requiring antacid therapy might alternatively be given cimetidine, ranitidine, or a calcium-containing antacid, as these do not cause clinically important decreases in quinolone bioavailability.

Coadministration of enoxacin and to a lesser extent ciprofloxacin and pefloxacin with theophylline caused decreased hepatic clearance of theophylline, resulting in increased terminal half-life of elimination and elevated serum theophylline concentrations [36,37].

Evidence suggested that the mechanism of the drug-drug interaction was interference with demethylation of theophylline by the hepatic P450 enzymes by the 4-oxoquinolone metabolite. Notably, clinically important drug-drug interactions did not occur between theophylline and either norfloxacin or ofloxacin. Caffeine is structurally related to theophylline. With administration of a single dose of caffeine, serum caffeine concentrations were elevated 2- to 4-fold by concurrently administered enoxacin and 1.1- to 1.3-fold by ciprofloxacin or norfloxacin, while ofloxacin did not alter caffeine concentrations in serum [38,39,40,41].

**CONCLUSION:**

The fluoroquinolones inhibit the actions of the essential bacterial enzyme DNA gyrase. The details of the molecular interactions of these agents with DNA gyrase and DNA and the requirements for quinolone-mediated bacterial killing are, however, still being elucidated. The frequency of mutation to fluoroquinolone resistance is low for many gram-negative bacteria.

The fluoroquinolones are well absorbed orally and

generally achieve high concentrations in urine and stool. Serum and tissue levels of many agents are sufficiently high relative to activity to allow treatment of infections outside the urinary and gastrointestinal tracts. Although the relative contributions of renal and hepatic excretion vary among the fluoroquinolones, the half-lives of elimination are generally long, allowing twice-daily dosing.

Clinical experience with the newer fluoroquinolone antimicrobial agents is accumulating rapidly. These agents are likely to be used extensively as cost-effective and clinically efficacious alternatives to parenteral therapies in selected infections.

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