ARE ALL FLUOROQUINOLONES CREATED EQUAL

Review of Respiratory Quinolones

University of Texas Southwestern Medical Center, Dallas
Internal Medicine Grand Rounds
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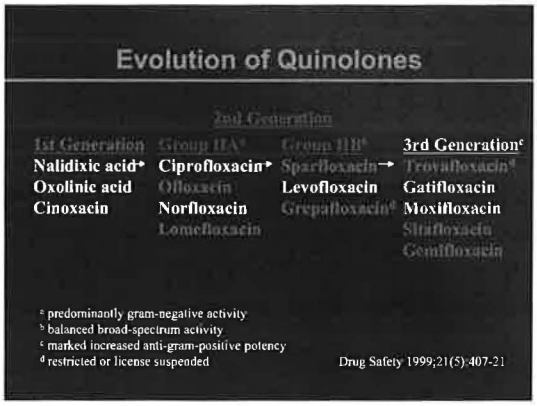
Naiel N. Nassar, MD, FACP

HISTORY

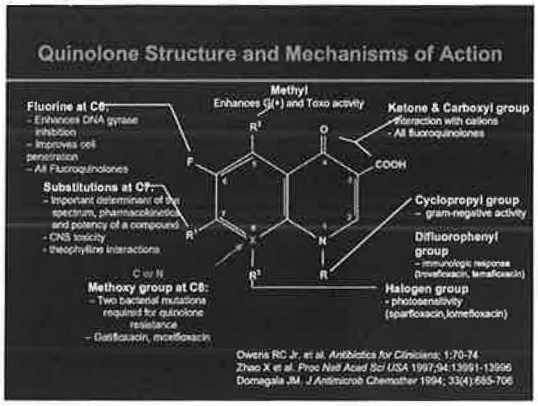


The discovery of the naphthyridine derivative nalidixic acid in the 1960s began the steady advancement of the development of quinolones. Two early first-generation quinolones, cinoxacin and oxolinic acid. had relatively limited spectra of activity but had more potent gram negative activity than nalidixic acid. A major step occurred with fluorination of quinolone compounds, led by norfloxacin in 1986. Ciprofloxacin, marketed in 1987, was the first widely administered quinolone with advanced systemic activity. Second-generation agents, now called fluoroquinolones, have excellent activity against many gram-negative aerobes. With the advent of this drug class, clinicians were able for the first time to treat a wide range of gram-negative aerobic infections orally; fluoroquinolones thus constituted a significant advance in the management of infectious diseases.

Throughout their evolution, quinolones have been modified to improve their pharmacokinetics, which led to less frequent dosing and higher bioavailability, and to widen their spectra of activity. The late 1990s saw development of third-generation agents, namely, sparfloxacin, levofloxacin, grepafloxacin, moxifloxacin, and gatifloxacin, which have increased gram-positive activity.

However, in 1999 sparfloxacin and grepafloxacin were withdrawn from the market due to toxicity concerns. Another third-generation drug, trovafloxacin, has substantial anaerobic activity in addition to gram-positive and gram-negative coverage, although, owing to safety issues, it is limited to treatment of severe, life-threatening infections in hospitalized patients.

QUINOLONE STRUCTURE AND MECHANISM OF ACTION



Position 1. This position is part of the enzyme-DNA binding complex, and has a hydrophobic interaction with the major grove of DNA. A cyclopropyl substituent is now considered the most potent modification here, followed by addition of a 2,4-difluorophenyl. Most other substituents, including one with only the wrong stearic position (*R*-ofloxacin) can presumably lower the number of molecules capable of binding to the enzyme-DNA pocket, and therefore reduce potency.

Position 2. This location is very close to the site for DNA gyrase (or topoisomerase IV) binding so it is believed that any added bulk inhibits access and results in a lower level of microbiological activity.

Positions 3 and 4. These two positions on the quinolone nucleus are considered critical for binding to cleaved or perturbed DNA, and no useful substitutions have yet been reported. Therefore, the 3-carboxylate and 4-carbonyl groups are considered essential for antimicrobial activity.

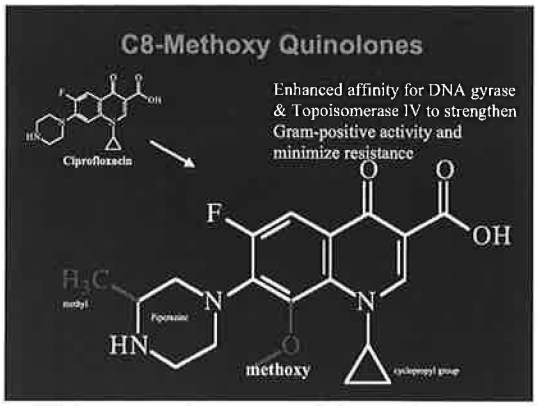
Position 5. Substituents at this position of the basic quinolone nucleus appear to have the capacity to alter overall stearic configuration of the molecule, which is how changes here are thought to affect activity. Modestly sized additions, such as an amino, hydroxyl, or methyl group can markedly increase in vitro activity against gram-positive bacteria, as well as enhance potency against *Toxoplasma gondii.*

Position 6. The addition of a fluorine molecule here markedly improved antimicrobial activity and gave rise to the now widely used and clinically successful fluoroquinolone compounds. New 6-Hquinolones are currently under development that appear very promising.

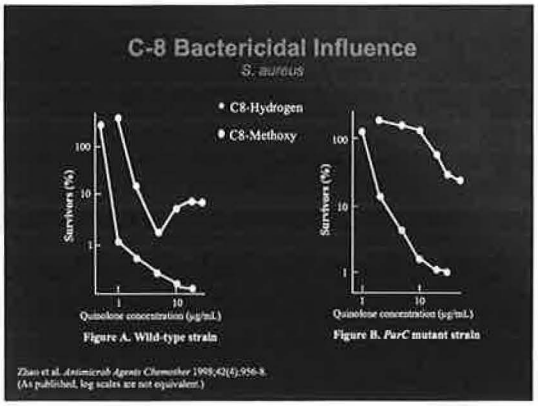
Position 7. This position is considered to be one that directly interacts with DNA gyrase, or topoisomerase IV. The optimal substituents at this position have been found to be groups that contain, at a minimum, a 5- or 6-membered nitrogen heterocycle. The most common of these are aminopyrrolidines and piperazines. Placement of a aminopyrrolidine improves gram-positive activity, whereas a piperazine generally enhances potency against gram-negative bacteria. Alkylation (-CH3) of the 5-membered or 6-membered heterocycle (pyrrolidines and piperazines, respectively) also enhances activity against gram-positive bacteria. New 2-pyridone additions to the 7-pyrrolidinyl ring have improved activity against staphylococci and anaerobes, but diminished effectiveness against important gram-negative bacilli, such as *P. aeruginosa*, compared to ciprofloxacin.

A recent interesting observation is that increased bulkiness here (R-7) appears to confer protection from the efflux exporter proteins of bacteria, and diminishes the likelihood of bacterial resistance in wild-type bacterial strains. Bulk here also increases anti-anaerobic activity. Moxifloxacin and trovafloxacin are the currently available agents with the greatest bulk at this position.

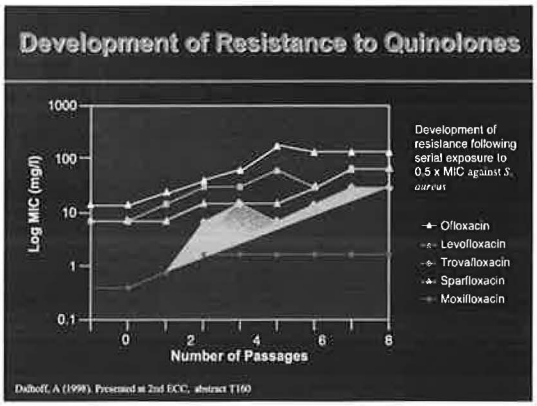
Position 8. This position is considered to affect overall molecular stearic configuration, similar to position 5. Therefore, changes made here affect target affinity, probably by altering drug access to the enzyme or DNA binding sites.



A free halogen (F or Cl) here may improve activity against anaerobes. Halogen substituents, as well as a methyl or methoxy also increase the in vitro activity against gram-positive cocci, even in those bacteria resistant to older fluoroquinolones. Interestingly, the R-8–substituted quinolones also exhibit enhanced bacteriostatic and lethal activities against GyrA mutants of both *E. coli* and *Mycobacterium* species. Furthermore, in *S. aureus* a substitution here created the most lethal agent for both wild type cells as well as those strains with a preexisting topoisomerase IV mutation. Of particular interest is the observation that specific changes here appear to dramatically alter the initial target in fluoroquinolones, at least in gram-positive cocci. A simple hydrogen as in ciprofloxacin, or even a fused ring (for example, ofloxacin, levofloxacin both have a benzoxazine bridge between C-8 and N-1) typically leads to high activity against topoisomerase IV, with little clinically useful activity against DNA gyrase. In contrast, a free halogen substituent shifts the initial target to that of DNA gyrase and markedly reduces anti-topoisomerase IV action. This was shown for the 8-fluoro-substituted quinolone, sparfloxacin.



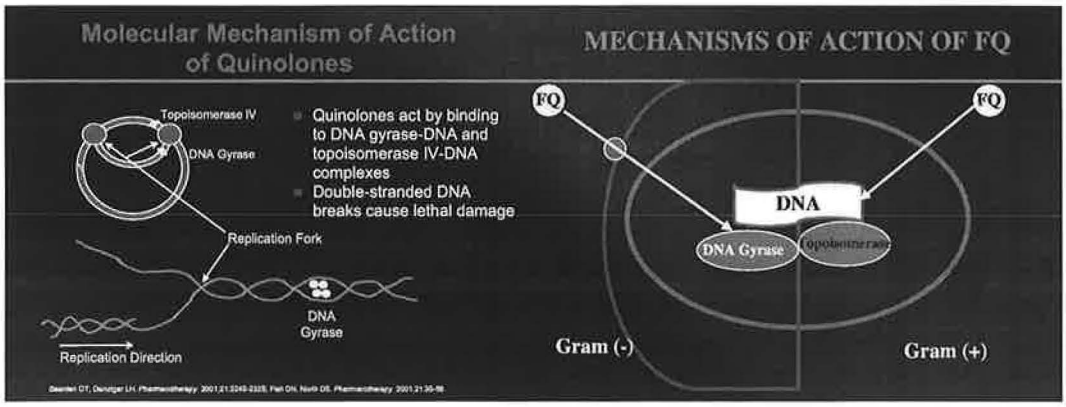
Replacement of the (C-8) carbon with a nitrogen, or adding a free methyl or methoxy substituent to C-8 improves activity and enhances antimicrobial potency. The benefit to potency from these changes is apparently due to the increase in clinically useful activity against both DNA gyrase and topoisomerase IV, so that 2 or more mutations in the QRDR regions of these enzymes are usually necessary for clinically relevant drug resistance to develop.



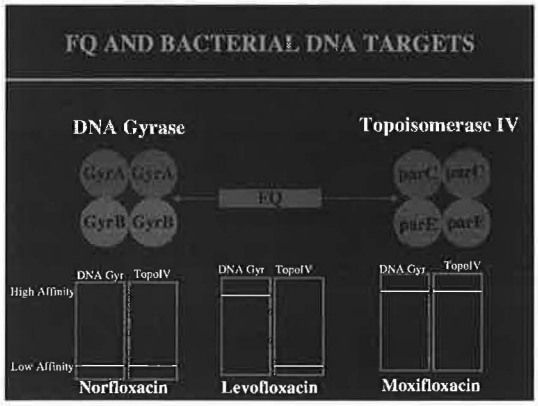
Trovafloxacin, with a nitrogen at ring position 8, demonstrated a reduction in activity associated with a single ParC mutation; however, the MIC still remained within a therapeutically useful range for most isolates. The unique effect of a free methoxy substituent here has been demonstrated for 2 new fluoroquinolones, gatifloxacin, and moxifloxacin. With this substituent, even a double ParC and GyrA mutation did not cause the MIC against *S. pneumoniae* to go above clinically attainable moxifloxacin concentrations. Recently, the optimal substituent placed here, combined with a bulky addition at the C-7 position, has also been shown to markedly reduce the development of fluoroquinolone resistance in *S. aureus*.

MECHANISM OF ACTION OF BACTERIAL TOPOISOMERASES

Two enzymes are the principal targets for the antibacterial activity of quinolones: DNA gyrase and topoisomerase IV. Bacterial DNA is a double-stranded, circular, supercoiled molecule;



efficient DNA replication requires systematic unwinding and preservation. Replication proceeds in a stepwise manner along the DNA circle, progressing along a continuously advancing point termed the replication fork. As the replication fork advances, it introduces detrimental helical stress, thereby creating unwanted positive or negative supercoils. If unresolved, stress renders the cell incapable of DNA replication. A mechanism must be in place to continuously restore the proper conformational structure of the DNA. DNA gyrase and topoisomerase IV aid in this process.

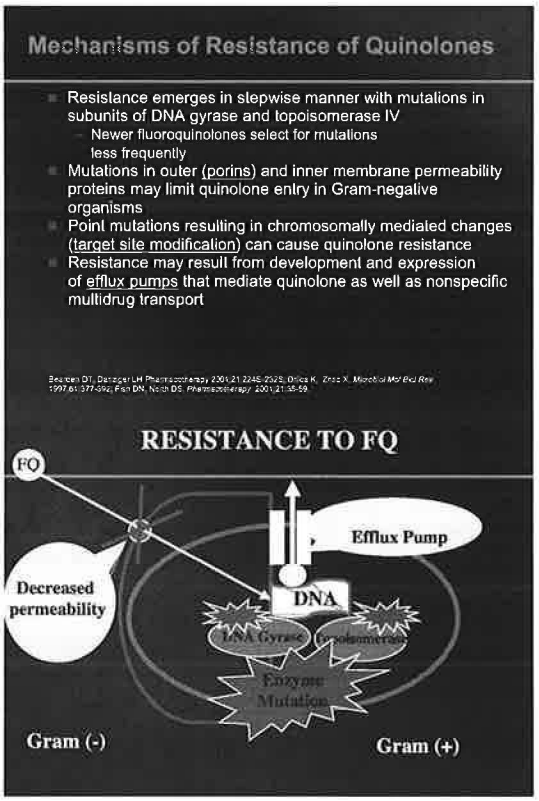


DNA gyrase is composed of two pairs of subunits, GyrA and GyrB. These subunits are encoded by genes *gyrA* and *gyrB,* respectively. The intact enzyme is responsible for introducing and removing DNA supercoils and for unlinking (decatenating) interlocked DNA circles. This action proceeds ahead of the actively moving replication fork. DNA gyrase safeguards against the occurrence of replication-induced structural changes before advancement of the replication fork.

Topoisomerase IV has two ParC and two ParE subunits, which are encoded by genes *parC* and *parE,* respectively. The major actions of topoisomerase IV are removal of DNA supercoils and separation of newly built daughter DNA after replication is complete. These actions occur primarily behind the advancing replication fork. The pair of type II topoisomerases thus work both before and behind the replication fork to provide a properly supercoiled environment for DNA synthesis and to release newly replicated DNA.

MECHANISMS OF FLUOROQUINOLONE RESISTANCE

Mechanisms of fluoroquinolone resistance include one or two of the three main mechanistic categories, alterations in the drug target, and alterations in the permeation of the drug to reach its target. No specific quinolone-modifying or -degrading enzymes have been found.



BACTERIAL TOPOISOMERASE MUTATIONS

Mutations in the genes that encode for DNA gyrase and topoisomerase IV can change the structure of one or more subunits of these enzymes. These mutations generally occur in a discrete sequence of the bacterial genes, called the quinolone resistance determinant region. Structural changes in type II topoisomerase subunits can inhibit the ability of quinolones to bind at these sites of action. Altered binding can decrease the drugs' effectiveness in inhibiting bacterial DNA replication and raise bacterial minimum inhibitory concentrations (MICs).

MEMBRANE PERMEABILITY AND EFFLUX PUMPS

Mutations occur in the outer and inner membrane proteins of bacteria. Quinolones must pass through cell membranes to reach their topoisomerase targets. The degree to which they cross cell membranes varies with bacterial species. The outer membranes of certain gram-negative organisms, including *Pseudomonas aeruginosa,* limit the uptake of fluoroquinolones. Altered expression of outer cell membrane channels (porins) may limit the agents' ability to permeate membranes of gram-negative bacteria. Other resistance mechanisms involve development and expression of efflux pumps that transport quinolones and other antibiotics out of the cell. A combination of intrinsic lack of permeability, alterations in porin expression, and efflux mechanisms is often involved in resistance.

ACQUISITION OF RESISTANCE

Chromosomally mediated changes caused by point mutations in genes are the greatest single cause of quinolone resistance. Plasmid-mediated mechanisms have been reported but are not well elucidated. Induction of resistance to a quinolone involves production of a gene mutation. Spontaneous mutations conferring various levels of resistance are thought to occur at a frequency of 10^6-10^{10} cell divisions. Mutations in *gyrA* and *gyrB* and *parC* and *parE* genes have variable effects on MICs in different species of bacteria. Mutations conferring resistance typically occur in a stepwise manner. Spontaneous mutations create a small mutant population with decreased susceptibility to quinolones. Exposure to intermediate quinolone concentrations can inhibit susceptible strains and allow overgrowth of a resistant first step mutant.

Second mutations then occur in first-step mutants, further raising MICs. This process can continue

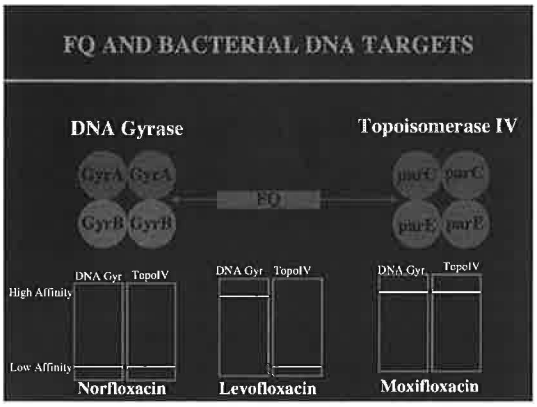
and augment other mechanisms, such as decreased permeability or efflux. Low-level resistance, with MICs in the intermediate breakpoint range, can be conferred by a number of single mutations. High-level resistance, with MICs above the established breakpoint, typically is seen with acquisition of multiple-resistance mechanisms.

ORGANISM-SPECIFIC RESISTANCE

Organism	Primary target	Secondary target
E. coli	*gyrA*	*gyrB, parC, parE*
S. typhimurium	*gyrA*	*gyrB*
P. aeruginosa	*gyrA*	*gyrB*
Klebsiella	*gyrA*	*parC*
S.aureus	*gyrA*	*gyrA, gyrB*
S. pneumoniae	Depends on the FQ molecule	

The general quinolone resistance mechanisms of target enzyme alteration, reduced permeability, and efflux apply to most bacteria; however, the specific mechanisms in each species have individual features and nomenclature. The order in which mutations occur and extent to which they alter MICs vary, depending on the bacterial species and on the quinolone.

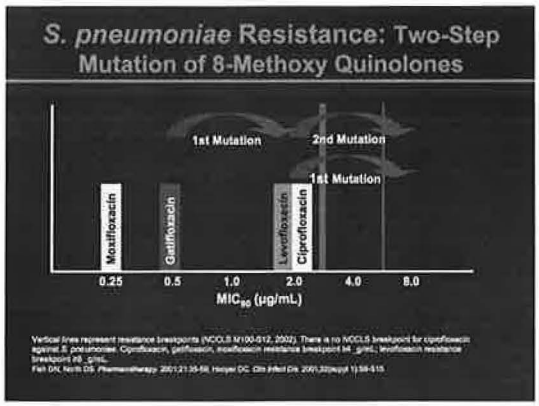
DIFFERENCES IN FLUOROQUINOLONE TARGETS AND RESISTANCE



The interaction of a fluoroquinolone with the complexes of either DNA gyrase or topoisomerase IV with DNA may block DNA synthesis and result in cell death. The antibacterial potency of a quinolone is defined in part by its potency against the two enzyme targets; the more sensitive of the two enzymes within a cell is the primary target. Many fluoroquinolones have differing potencies against DNA gyrase and topoisomerase IV.

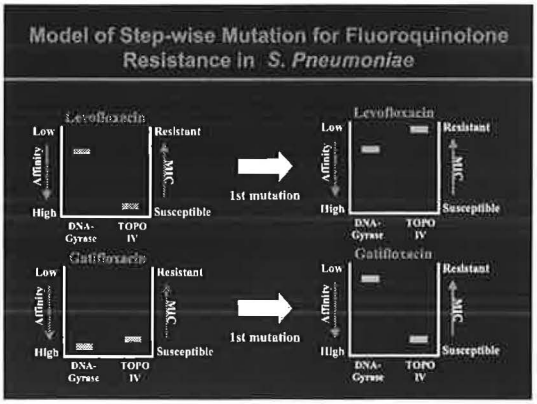
A general pattern for most quinolones has emerged: DNA gyrase is the primary drug target in gram-negative bacteria, and topoisomerase IV is the primary target in gram-positive bacteria. These differences correlate with relative drug sensitivities in several cases, the more sensitive of the two enzymes being the primary target defined by genetic tests. The first step in mutational resistance in the drug target usually occurs by an amino acid change in the primary enzyme target, with a rise in MIC of the cell predicted to be determined by the effect of the mutation itself or by the level of intrinsic sensitivity of the secondary drug target (whichever is lower). Higher levels of resistance may then occur by second mutational steps, in which amino acid changes are selected in the secondary target enzyme. Further mutations result in additional amino acid changes in either enzyme, depending on which was least resistant in the cell under

selection. On mechanistic grounds, this pattern of stepwise mutations in alternating target enzymes implies that both high intrinsic potency against the primary target and the similarity of potency against both targets will affect the likelihood of selection of first-step resistant mutants.



Thus, fluoroquinolones with a high therapeutic index (defined as the concentration of drug at the site of infection divided by the MIC of the drug for the target bacterium), in which drug concentration exceeds the MIC of a first-step mutant, are unlikely to select spontaneous first-step mutants present in the infecting bacterial population; such mutants are inhibited or killed by these concentrations. Furthermore, the greater the extent to which a fluoroquinolone has similar (and ultimately equal) potency against both enzyme targets, the lower the MIC increment for a first-step drug target mutant. Thus, for drugs with low increments in resistance for first-step mutants because of similar activities against both target enzymes, the extent to which drug concentrations can exceed the MIC of first-step mutants may be enhanced. These principles would predict that selection of fluoroquinolone resistance could occur readily with ciprofloxacin against species such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, organisms in which single mutations cause MICs of ciprofloxacin that approach or exceed achievable serum concentrations. This prediction has been borne out by surveillance data.

CLINICAL OCCURRENCE OF FLUOROQUINOLONE RESISTANCE



Fluoroquinolone resistance emerged shortly after these drugs were introduced; two species were particularly affected, *S. aureus* and *P. aeruginosa*. Ciprofloxacin and ofloxacin were the most extensively used fluoroquinolones during this early period. The emergence of resistance was predicted on molecular grounds because, in these species, single mutations, which raise the MIC of ciprofloxacin of these organisms 4- to 16-fold, produce a level of resistance at or above peak drug concentrations achievable in serum, providing an opportunity for spontaneous first-step mutants to survive and emerge when a patient is exposed to fluoroquinolones. In the case of *S. aureus* and coagulase-negative staphylococci, methicillin resistant strains developed fluoroquinolone resistance more rapidly than methicillin- susceptible strains.

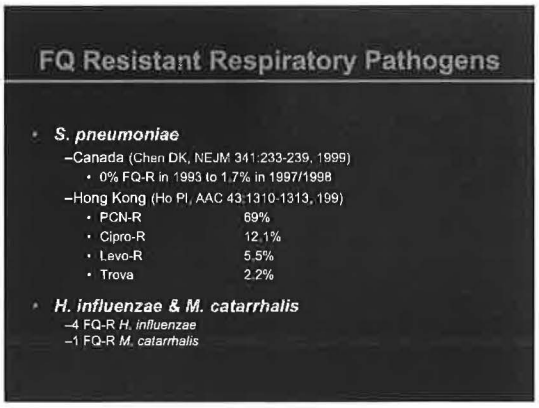
Case-control studies have identified fluoroquinolone use as a risk factor for resistance.

Fluoroquinolone resistance has also increased substantially in some settings in species in which multiple mutational events are required for resistance to occur (e.g., *Campylobacter jejuni*, *E. coli*, and *Neisseria gonorrhoeae*). Emergence in these species would not have been predicted on molecular grounds, suggesting that other epidemiologic factors may have come into play. For *C. jejuni*, resistance emerged in parallel in animal and human populations shortly after fluoroquinolones were introduced for use in humans and other quinolones were introduced in food animal production, particularly poultry, in parts of Europe. In the United States, where use of quinolones in food animals was introduced later, demonstrating a link between resistant *C. jejuni* strains from poultry and food products and those causing human disease was possible.

Fluoroquinolone resistance in *E. coli* has emerged in Europe, particularly in patients with urinary tract infections and neutropenic cancer patients with bacteremia that developed during fluoroquinolone prophylaxis. Fecal carriage of resistant *E. coli*, however, appears to be common in both healthy adults and children in Spain. Carriage of resistant strains by children, a group in which fluoroquinolones are rarely used, and in adults without prior quinolone exposures suggests acquisition of resistant strains by the population at large. This occurrence (in the context of documented high rates of fluoroquinolone resistance in *E. coli* isolated from poultry in Spain and, by analogy, to what has been documented with campylobacters) suggests that acquisition of resistant strains from food sources may have resulted in substantial colonization of the human population with resistant *E. coli*, creating a reservoir of resistant organisms.

Humans are the sole reservoir for infections with *N. gonorrhoeae*. In the United States, fluoroquinolone resistance in this organism has resulted largely from clonal outbreaks caused by human-to-human spread. Thus, for all three organisms in which fluoroquinolone resistance has become problematic despite a requirement for multiple mutations, other epidemiologic factors (of transmission and ongoing selection in reservoir populations of organisms) appear to be at work.

Only recently has fluoroquinolone resistance begun to emerge in *S. pneumoniae* albeit at low levels. In some cases, fluoroquinolone-resistant strains, like those resistant to beta-lactams, have emerged because of clonal spread. Because the newest fluoroquinolones are for treating patients with respiratory tract infections, increasing selection pressure for resistance is possible. This concern is especially great for drugs developed for use in children, who are a major reservoir of *S. pneumoniae*.



SPECTRUM OF ACTIVITY

Each fluoroquinolone has excellent in vitro activity against most Enterobacteriaceae. Ciprofloxacin, moxifloxacin, and gatifloxacin have the lowest MICs against various gram-negative pathogens such as *Escherichia coli* and *Klebsiella, Enterobacter, Citrobacter, Proteus, Salmonella,* and *Shigella sp.* Ciprofloxacin has the lowest MICs for *Pseudomonas aeruginosa* (range 0.5-4 μg/ml, median 2 μg/ml). The MICs of other fluoroquinolones against *P. aeruginosa* are at least 2 folds higher than those of ciprofloxacin. Trovafloxacin and moxifloxacin have the best in vitro activity against *Stenotrophomonas maltophilia* with an MIC of 2 μg/ml, whereas activity is limited for all of the other fluoroquinolones. In general, fluoroquinolones have excellent in vitro activity against *Haemophilus influenzae* and *Moraxella catarrhalis.*

Data suggest that fluoroquinolones preferentially target DNA gyrase in gram-negative bacteria, whereas topoisomerase IV is the primary target in gram-positive bacteria. The preferential topoisomerase

target within the cell also may be determined by fluoroquinolone structure.

Comparative In Vitro Activity of Fluoroquinolones Against Common Pathogens

Organism	Gati	Moxi	Levo	Gemi
S. aureus (MSSA)	0.16	0.21	0.49	0.04
E. coli	0.06	0.11	0.17	0.08
K. pneumoniae	0.43	0.63	0.23	0.24
E. cloacae	0.67	0.50	0.74	0.65
P. aeruginosa	12.99	16.44	11.54	9.17

Therefore, some fluoroquinolones have equal activity against both DNA gyrase and topoisomerase IV, and they would show activity against a broad range of gram-positive and -negative bacteria. A deficiency of ciprofloxacin, ofloxacin, levofloxacin, and other earlier fluoroquinolones is limited potency against gram-positive bacteria. The newer fluoroquinolones and others under development have improved activity against these organisms while retaining activity against gram-negative pathogens. Trovafloxacin, gatifloxacin, and moxifloxacin have greater in vitro activity than ciprofloxacin and ofloxacin against *Staphylococcus aureus* and *Staphylococcus epidermidis.* However, staphylococcal strains that are methicillin resistant usually are resistant to fluoroquinolones. Gatifloxacin and moxifloxacin have in vitro activity against methicillin-resistant strains of *S. epidermidis,* but clinical activity will depend on whether resistance develops during therapy.

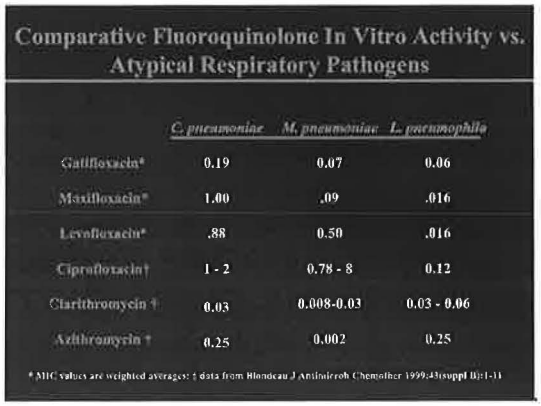
Most studies report MIC90s of ciprofloxacin between 2 and 4 μg/ml for *Enterococcus faecalis* and ≥4 μg/ml for *Enterococcus faecium.* Neither ofloxacin nor levofloxacin offers any advantage over ciprofloxacin for these bacterial strains. Trovafloxacin and moxifloxacin inhibit *E. faecalis* at concentrations of 0.5-1 μg/ml, but *E. faecium* tends to be more resistant.

Comparative Fluoroquinolone In Vitro Activity vs. Common Respiratory Pathogens*

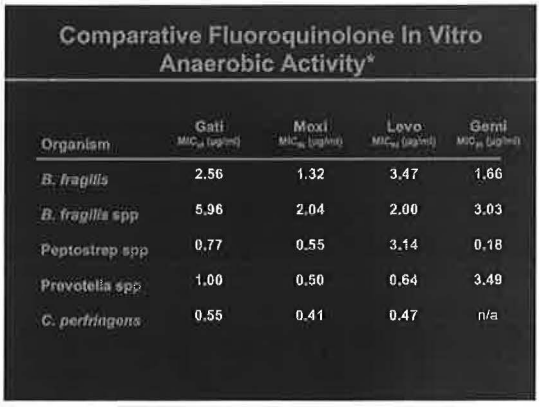
	S. pneumoniae	*M. catarrhalis*	*H. influenzae*†
Gatifloxacin			
MIC_{90} (μg/ml)	0.426	0.026	0.020
# isolates	7,035	2,266	5,471
Moxifloxacin			
MIC_{90} (μg/ml)	0.198	0.057	0.032
# isolates	8,151	4,184	8,613
Levofloxacin			
MIC_{90} (μg/ml)	1.526	0.090	0.049
# isolates	24,041	3,887	9,972
Gemifloxacin			
MIC_{90} (μg/ml)	0.05	0.004	0.004
# isolates	2,180	755	1,556

For *S. pneumoniae,* ciprofloxacin and ofloxacin MICs are ≥2 μg/ml compared with the other fluoroquinolones, 0.06-1 μg/ml. Strains resistant to, or with decreased susceptibility to, penicillin remain susceptible to the agents. Trovafloxacin, gatifloxacin, and moxifloxacin show excellent in vitro activity against *Streptococcus pyogenes* and *Streptococcus agalactiae.*

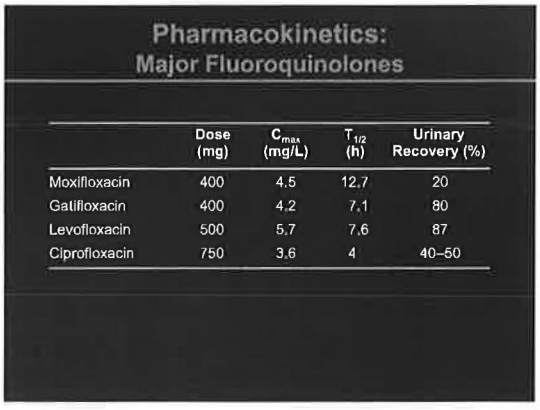
All drugs in this class are highly active against *Legionella sp,* but other atypical microorganisms exhibit variable susceptibility patterns. Several newer agents appear to be substantially more active than ciprofloxacin or ofloxacin against *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.* Gatifloxacin and moxifloxacin have the greatest in vitro activity against *C. pneumoniae and M. pneumoniae.*



Ciprofloxacin has relatively weak in vitro activity against most anaerobes. Whereas levofloxacin has somewhat lower MIC90s than ciprofloxacin to some anaerobic bacteria, it should not be considered clinically active against all anaerobes. Of currently available fluoroquinolones, trovafloxacin has considerably better in vitro activity against these pathogens. Gatifloxacin has lower MIC levels than trovafloxacin against *Peptostreptococcus, Clostridium perfringens,* and other clostridia spp. Moxifloxacin appears to have some anaerobic activity but less than trovafloxacin or gatifloxacin.



PHARMACOKINETICS



Although a microorganism's MIC90 is an important indicator of antibiotic activity, drugs must be compared based on achievable concentrations in vivo to determine clinical potency. Thus, pharmacokinetics must be considered when comparing and evaluating fluoroquinolones.

ABSORPTION AND DISTRIBUTION

Fluoroquinolones typically have excellent bioavailability, large volumes of distribution, extensive tissue penetration, and low plasma protein binding. Bioavailability of oral ofloxacin, levofloxacin, sparfloxacin, trovafloxacin, gatifloxacin, clinafloxacin, and moxifloxacin is in excess of 85%. bioavailability for oral ciprofloxacin and grepafloxacin is 70-80%.

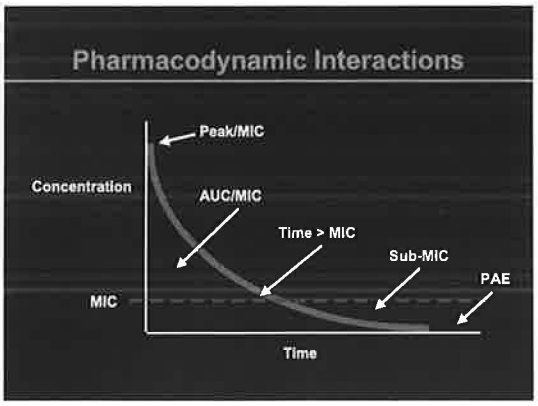
The maximum concentration (Cmax) varies significantly among new and investigational fluoroquinolones. In dose-ranging studies, Cmax and AUC increased in a linear, dose-proportional fashion. As indicated by their large volumes of distribution, most fluoroquinolones penetrate rapidly and efficiently through the body, achieving tissue and fluid concentrations that are generally higher than those in plasma. Most fluoroquinolones have low protein binding, ranging from 2-40%. Thus, any compromise of antimicrobial activity by changes in the extent of plasma protein binding should be minimal. The protein binding of trovafloxacin is 70%, which is high for a member of this class; values for grepafloxacin and moxifloxacin are 50% and 55%, respectively. The implications of the higher protein binding of these three agents are unclear as it is difficult to determine in vivo concentration changes.

METABOLISM AND ELIMINATION

Longer *beta*-half-lives of trovafloxacin, grepafloxacin, sparfloxacin, and moxifloxacin allow for once-daily dosing. The elimination half-lives of trovafloxacin, grepafloxacin, sparfloxacin, and moxifloxacin exceed 10 hours, whereas those of ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and clinafloxacin range between 5 and 8 hours. Although levofloxacin's elimination half-life compares with those of ciprofloxacin and ofloxacin, this drug is marketed for once-daily dosing.

Fluoroquinolones are removed from the body by both renal and nonrenal mechanisms. Ofloxacin, levofloxacin, and gatifloxacin undergo limited metabolism in humans, with >60% of unchanged drug found in urine after administration. A dosage adjustment should be made for levofloxacin when the patient's creatinine clearance is ≤50 ml/minute. Moxifloxacin does not require a decrease in dosage in patients with impaired renal function. Moxifloxacin undergoes conjugation to two metabolites that appear to have no major antimicrobial activity, and approximately 20% of the administered dose is excreted in urine. Ciprofloxacin has two routes of elimination; nonetheless, a decrease in dosage is recommended for patients with creatinine clearances ≤50 and ≤30 ml/minute, respectively.

PHARMACODYNAMICS

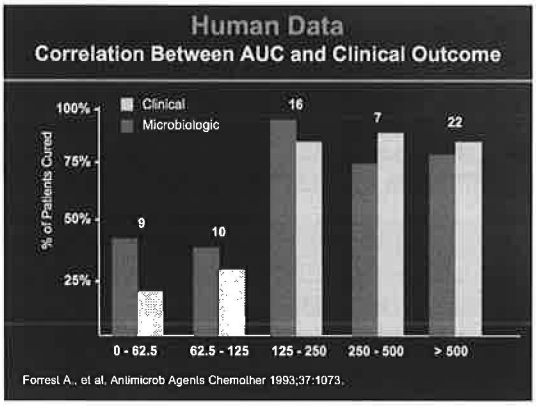


Pharmacodynamics integrate antimicrobial activity and pharmacokinetics of an antibiotic by focusing on inhibiting growth and killing bacteria. The value most often used to characterize antimicrobial activity is the MIC, which reflects the net drug effect after incubation of a standard inoculum of an organism with a fixed and constant concentration of drug for 18-24 hours. Since it does not account for the time course of antimicrobial activity, MIC cannot adequately characterize an antibiotic's pharmacodynamic properties.

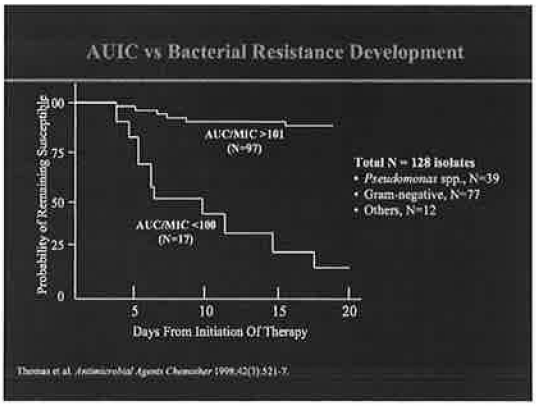
Fluoroquinolones have concentration-dependent killing, the peak:MIC or the AUC24:MIC (AUIC) would be most predictive of outcome. Animal and human models suggest that a peak:MIC ratio of ≥10 and an AUIC ratio of ≥125 optimize rapid bacterial killing and prevent regrowth of resistant gram-

negative bacterial subpopulations. Animal studies confirmed these findings. An AUIC of ≥100, peak:MIC ≥8, and serum levels above MIC 100% of the time predicted efficacy of fluoroquinolones in treating animal models of endocarditis; however, the AUIC showed the best linear correlation.

The question of whether a relationship exists between AUIC and development of bacterial resistance was examined in a population of patients, virtually all of whom were treated with ciprofloxacin for lower respiratory tract infections. An inverse relationship was found between the probability of developing bacterial resistance and AUIC. When the AUIC ratio was below 100, 82% of patients developed an infection with a resistant organism, most likely by selection of a subpopulation. However, when the AUIC ratio was above 100, only 9% of the patients developed a resistant infection.



This suggests that resistance can be avoided with attention to dosing, since regimens that provide an AUIC of at least 100 appear to reduce the rate of resistance. Therefore, an estimated AUIC of 125 or peak:MIC of 8-10:1 may result in optimal bacterial killing, minimize the potential for resistance, and improve clinical outcome against gram-negative pathogens.



DRUG-DRUG INTERACTIONS

ANTACIDS, MINERAL SUPPLEMENTS, SUCRALFATE, AND FOOD EFFECT

Without exception, all fluoroquinolones interact with multivalent cation-containing products, such as aluminum- or magnesium-containing antacids and products containing calcium, iron, or zinc. Concomitant use invariably results in marked reduction of oral absorption of the antimicrobial. The mechanism of this interaction is formation of insoluble chelation complexes in the gastrointestinal tract that inhibit drug absorption. Chelation of fluoroquinolones occurs to a greater degree with aluminum- and magnesium-containing products than with products containing calcium, iron, or zinc; however, the resulting decrease in fluoroquinolone absorption with all of these products is potentially significant and increases the possibility of therapeutic failure. Multivitamin preparations that contain minerals should be avoided. Similar adverse effects on fluoroquinolone absorption were observed with concomitant administration of ferrous sulfate, with decreases in bioavailability of the antibiotic of 19-66%. Although it is usually recommended that concomitant intake of calcium-rich foods (e.g., milk) be avoided because of

the potential for chelation effects, the actual influence of dairy products on fluoroquinolone absorption varies.

Sucralfate significantly interferes with oral absorption of fluoroquinolones. It decreased the bioavailability of these drugs by up to 98% when given within 2 hours of antibiotic administration. The mechanism of this interaction has been attributed to both the aluminum content of the sucralfate salt and direct binding of the fluoroquinolone by the sucralfate itself.

Antacids and other multivalent cation-containing products as well as sucralfate should be taken at least 2 hours before or 4-6 hours after the fluoroquinolone dose. The degree to which fluoroquinolones are absorbed is not significantly affected by food. Studies involving ciprofloxacin,

HISTAMINE2 RECEPTOR ANTAGONISTS AND PROTON PUMP INHIBITORS.

Concomitant administration of H2-blockers and proton pump inhibitors have no clinically significant effects on the absorption of the fluoroquinolones. Cimetidine can inhibit renal tubular secretion and therefore reduce systemic clearance of fluoroquinolones that are primarily excreted renally (levofloxacin, ciprofloxacin, gatifloxacin). The reduction in renal and total systemic clearance of fluoroquinolones, including moxifloxacin and gatifloxacin, caused by cimetidine is usually not clinically or statistically significant.

PROBENECID.

Like cimetidine, probenecid can inhibit renal tubular secretion of fluoroquinolones that are primarily eliminated through renal excretion. Approximate reductions in renal and total systemic clearance caused by probenecid are 24% for levofloxacin, 50% for ciprofloxacin, and 42% for gatifloxacin. Coadministration of moxifloxacin and probenecid did not alter the renal clearance of the fluoroquinolone. Although the decrease in renal clearance and increase in serum concentrations of most fluoroquinolones are not likely to be clinically significant, patients receiving probenecid concomitantly with fluoroquinolones that are primarily excreted renally should be monitored for adverse effects.

THEOPHYLLINE AND CAFFEINE.

Fluoroquinolones can inhibit clearance of xanthine derivatives, including theophylline and caffeine. This is not a class effect; the relative inhibitory capacity depends on the specific affinity of each fluoroquinolone or the cytochrome P450 (CYP) isozyme 1A2. Fluoroquinolones ranked in the approximate order in which they significantly interact with theophylline are as follows: ciprofloxacin >norfloxacin >levofloxacin, trovafloxacin, gatifloxacin, moxifloxacin. In numerous studies ciprofloxacin decreased theophylline clearance by 25-30%, and increased theophylline plasma concentrations by up to 308%. The effects of ciprofloxacin on caffeine metabolism is similar to effects on theophylline metabolism.

WARFARIN.

A number of anecdotal case reports describe possible interactions between fluoroquinolones and warfarin. Because certain fluoroquinolones inhibit hepatic CYP enzymes, it is conceivable that an interaction with warfarin could result in decreased warfarin metabolism and increased therapeutic response. However, prospective studies designed to elucidate fluoroquinolone - warfarin interactions generally failed to record pharmacokinetically or clinically significant interactions.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS.

Seizures were reported when enoxacin was given with fenbufen. The mechanism of this potential interaction appears to be potentiation by fenbufen of the competitive inhibition of GABA receptors by fluoroquinolones. Although this interaction between fenbufen and both enoxacin and ciprofloxacin produced convulsions in rats, a study in humans failed to find evidence of a significant interaction between ciprofloxacin and fenbufen.

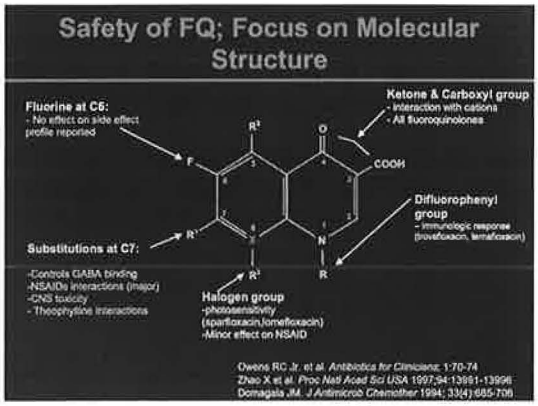
OTHER DRUGS.

Ciprofloxacin caused an increase in serum phenytoin concentrations when administered with phenytoin. Clinical evidence of toxicity also was reported when the agents were administered concurrently. Both ciprofloxacin and norfloxacin decreased clearance and increased serum concentrations of cyclosporine. Ciprofloxacin also enhanced cyclosporine-induced nephrotoxicity, possibly as a result of an increase in the concentration of cyclosporine; ciprofloxacin also was associated with increased rejection

rates in renal transplant recipients, the causes of which are unknown.

Although fluoroquinolones were occasionally implicated in causing increased serum concentrations of digoxin, studies of levofloxacin, trovafloxacin, and sparfloxacin all failed to find a significant alteration in digoxin pharmaco-kinetics. No clinically significant interactions were observed after coadministration of digoxin and moxifloxacin. However, concurrent digoxin and gatifloxacin led to modest increases in digoxin's Cmax and AUC values; significant increases in digoxin concentrations were observed for several patients. Although the clinical significance of this interaction is unclear, patients receiving the drugs together should be closely monitored.

The potential for a significant interaction between gatifloxacin and glyburide was evaluated in 34 patients with non-insulin dependent diabetes mellitus. No pharmacokinetic interactions and no adverse effects on patients' glucose tolerance or insulin concentrations were observed.



SPECIFIC ADVERSE EFFECTS

GASTROINTESTINAL

Gastrointestinal effects do not appear to be related to or affected by structural changes in the fluoroquinolone nucleus. They are thought to be caused by a combination of direct GI-irritation and CNS-mediated effects; thus some may occur when the drugs are administered intravenously. The estimated overall frequency of gastrointestinal effects is 2-20%, and these effects are the most frequently reported adverse effects of fluoroquinolones. Most common are nausea, anorexia, and dyspepsia; abdominal pain, vomiting, and diarrhea are less frequent but may be more severe.

Clostridium difficile-associated colitis uncommonly is associated with fluoroquinolones, perhaps because of the agents' minimal effect on gastrointestinal anaerobic flora. There is some concern that newer fluoroquinolones with enhanced anaerobic activity (trovafloxacin, moxifloxacin, gatifloxacin) may be associated with an increased risk of *C. difficile*-associated colitis, although this cannot be substantiated from data from clinical or surveillance studies.

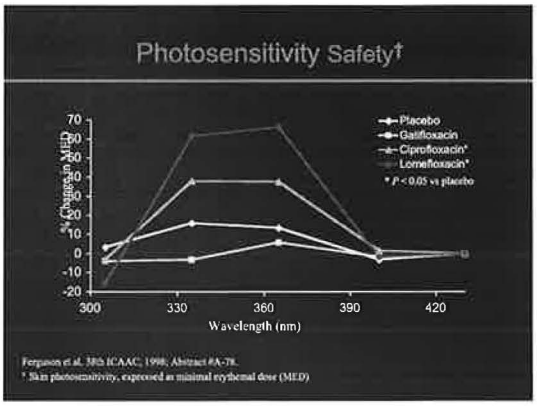
CENTRAL NERVOUS SYSTEM

Most common symptoms (0.2-11%) are headache, dizziness, and drowsiness; other less common effects are restlessness, insomnia and sleep disorders, agitation, and vision changes. Convulsions and seizures were rarely reported and usually occurred in patients with predisposing factors, such as seizure disorder, head trauma, anoxia, metabolic disturbances, or concomitant therapy with specific interacting drugs (theophylline, NSAIDs).

Adverse effects may be related to chemical structures of individual drugs. The side chain substituent in the R7 position of the fluoroquinolone nucleus appears to have the greatest influence on the degree of inhibition of g-aminobutyric acid (GABA) binding, which in turn may be related to CNS adverse effects. Bulky substituted side chains at the R7 position appear to lower binding affinity for the GABA receptor. Although the direct actions of fluoroquinolones in the CNS are thought to be associated with the drugs' ability to inhibit CNS-GABA receptors and their different binding potential to the N-methyl-D-aspartate receptor, correlation between inhibition of GABA receptors and clinically observed CNS adverse effects is poor. It is likely that penetration of individual agents across the blood-brain barrier plays an important role in determining the relative frequency and severity of CNS toxicity.

DERMATOLOGIC

Dermatologic adverse effects of fluoroquinolones occur at an overall rate of 0.5-3%. The most notable are phototoxic reactions. These may develop within just a few hours after administration of the drug and may occur in virtually any patient who has received a sufficient drug dosage and sufficient ultraviolet (UV) exposure. In contrast, photosensitivity reactions are immune mediated and require previous exposure to the offending agent; they usually require more than 1-2 days to develop. Immune mediated photosensitivity reactions are rare with fluoroquinolones; phototoxic reactions are far more common and appear to be a class effect. Most fluoroquinolones can produce phototoxic reactions given sufficient dosages and tissue concentrations; however, the drugs differ significantly in their phototoxicity potential at clinically relevant dosages and concentrations.



Drugs with the highest reactive potential are those that are halogenated at the 8 position of the quinolone nucleus. The presence of fluorine or chlorine atoms at this position seems to enhance the phototoxicity of these compounds; sparfloxacin and lomefloxacin have fluorine atoms at the 8 position, whereas the investigational clinafloxacin has a chlorine atom at the 8 position. A methoxy group at the 8 position appears to remove the phototoxicity risk; that is, gatifloxacin and moxifloxacin. The presence of an amino group at the 5 position also appears to enhance phototoxicity potential, as seen with sparfloxacin. In addition to chemical structure, pharmacokinetic variables such as extensive penetration into skin and long half-lives may influence the potential for phototoxicity of individual agents; sparfloxacin has both of these characteristics.

HEPATIC

The only marketed fluoroquinolone with known clinically significant hepatotoxicity is trovafloxacin. In premarketing studies, trovafloxacin was associated with low rates (< 1%) of elevated liver enzyme levels or hepatic abnormalities. However, long-term therapy (> 28 days) during a clinical study of chronic prostatitis was associated with asymptomatic increases in liver enzyme levels of 3 times or higher than normal values in 9% of 140 patients. Postmarketing surveillance data on trovafloxacin in the United States indicate that liver enzyme abnormalities may occur during shorter durations of therapy (< 28 days). Elevations in levels of hepatic transaminases usually resolved within 2 months of discontinuing therapy. However, post-marketing surveillance also detected nearly 150 cases of clinically symptomatic hepatic injury among approximately 2.5 million patients who had been treated with the drug. These cases included hepatitis and at least 14 cases of acute hepatic failure, as well as symptomatic pancreatitis. Four of these patients required liver transplantation, and five died as a result of liver-related illness.

URINARY TRACT

Nephrotoxic effects of the fluoroquinolones are uncommon, although rare cases of hematuria, interstitial nephritis, and acute renal failure were reported. The reported frequency of serum creatinine elevations during fluoroquinolone therapy is 0.2-1.3%, and the frequency of azotemia is similarly low. All nephrotoxic effects usually resolve promptly with discontinuation of the drug, and renal function return to normal within several weeks

MUSCULOSKELETAL

Arthropathy.

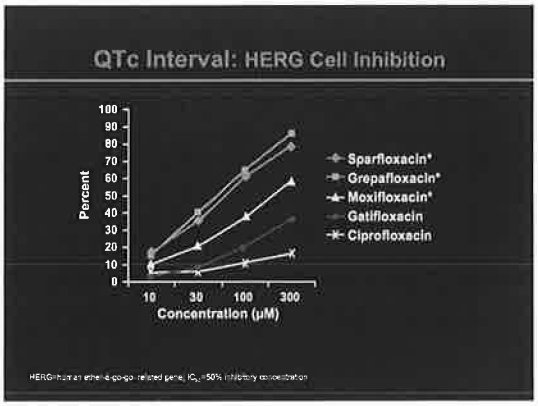
Fluoroquinolone-induced arthropathy is reported to occur in approximately 1% of all patients exposed to these agents. The most common manifestations were joint pain, stiffness, and swelling of weight-bearing joints, particularly knees. Symptom onset is usually within the first few days of therapy and is most common in patients <30 years old. Joint manifestations usually resolve within days to weeks after discontinuing the drug. Arthropathy was observed in animal studies, particularly in juvenile dogs, and was characterized by damage to chondrocytes, fissures in the extracellular matrix, and loss of collagens and glycosaminoglycans from immature articular cartilage. The risk of arthropathy appears to be a class effect that is not altered by structural changes of the drug. Several studies attempted to document bone or cartilage toxicities among children exposed to fluoroquinolones. In these studies, children received the drugs for 11-93 days, some for up to 600 days. Assessments were performed by clinical evaluation, magnetic resonance imaging, and/or histopathology after follow-up ranging from less than 6 months to 12 years. No evidence of fluoroquinolone-induced effects was found.

Tendinitis and Tendon Rupture.

Norfloxacin, ciprofloxacin, enoxacin, ofloxacin, and sparfloxacin are reported to cause either tendinitis or tendon rupture. Although not observed in clinical trials, patients receiving moxifloxacin or gatifloxacin are assumed to be at risk for tendon disorders because these disorders are considered to be a class effect. Tendon disorders most often involved the Achilles tendon, although the shoulder joint and hand also were affected; these disorders may occur either unilaterally or bilaterally. The relative risk of Achilles tendon rupture is 4-fold higher among individuals receiving a fluoroquinolone than in those not receiving the drugs. However, the overall frequency of this effect appears to be quite low. These patients are usually older than 50 years and are often on concomitant corticosteroid therapy; patients who are both older than 60 years and receiving corticosteroids may be at up to 14-fold greater risk of Achilles tendon rupture during fluoroquinolone therapy compared with individuals of all ages who are not receiving the antimicrobials. Men appear to be more commonly affected than women. Symptoms may occur within 2-42 days after starting therapy and usually resolve within 1-2 months after discontinuation of the drug. It is recommended that patients experiencing tendon pain or inflammation during fluoroquinolone therapy discontinue the drug and refrain from exercise until they can be adequately assessed for tendinitis.

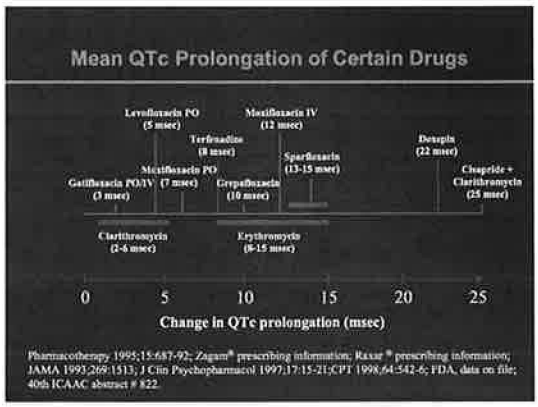
CARDIOVASCULAR

Administration of fluoroquinolones, most notably sparfloxacin and grepafloxacin, was associated with prolongation of QTc interval. Effects of the drugs on myocardial tissue are apparently related to the human ether-a-go-go gene (HERG), which encodes the rapidly activating delayed-rectifier potassium channel (IKr) in the heart.



Fluoroquinolone-induced inhibition of HERG/IKr can induce prolongation of the Qtc interval and, in turn, potentially lead to ventricular arrhythmias and sudden cardiac death. Studies of HERG-inhibiting effects of various fluoroquinolones showed that all drugs evaluated produce dose-dependent HERG blockade, although with markedly differing potencies. The HERG-inhibiting activity of grepafloxacin and

sparfloxacin occurs at clinically achievable plasma concentrations and may be associated, at least in part, with QTc interval prolongation. Gatifloxacin and ciprofloxacin had negligible effects on HERG at 30 μM, a concentration approximately 3- to 4-fold greater than the mean maximum concentration for these drugs in humans; the effects of moxifloxacin were slightly greater. Levofloxacin has apparently minimal effects on the QTc interval and was associated with a mean change of only 4.6 msec among 37 patients undergoing paired ECG. Cases of QTc prolongation and torsades de pointes were described, but considering the large numbers of patients who have been treated with levofloxacin, these appear to be very rare. Prolongation of the QTc interval (averaging ~ 2 msec) was reported with gatifloxacin; however, this was considered to be clinically insignificant, and the drug appears to have minimal effects on the QTc.



Data derived from clinical studies indicate that mean changes in QTc interval ranged from 1-7 msec during moxifloxacin therapy and was not associated with adverse cardiovascular events. Because of experience with older fluoroquinolones (grepafloxacin) and relative lack of experience with newer ones, the FDA recommends that package insert warnings for all new fluoroquinolones (including gatifloxacin and moxifloxacin) contain a statement suggesting that the risk of arrhythmias may be reduced by avoiding their use or administering them with caution in patients with known underlying cardiac conditions, those with known QTc interval prolongation or history of significant cardiac arrhythmias, those with uncorrected hypokalemia, and those receiving concomitant therapy with agents known to increase the QTc interval or to cause bradycardia. The FDA also has requested that all manufacturers of fluoroquinolones document the effects of their products on QTc prolongation.

IMMUNOLOGIC

Hypersensitivity reactions to fluoroquinolones occurred in 0.6-1.4% of patients in clinical studies. Skin manifestations such as erythema, pruritus, urticaria, and rash may be caused by either an allergic reaction or through release of histamine. Histamine release and hypotension were noted during rapid intravenous infusion of fluoroquinolones, and cutaneous erythema, itching, and a burning sensation were seen during intravenous administration of ciprofloxacin. A serum sickness-type reaction also occurred during ciprofloxacin therapy, and fatal hypersensitivity vasculitis was associated with both ciprofloxacin and ofloxacin. Anaphylactic reactions to fluoroquinolones are rare, with a frequency of 0.46-1.2 cases/100,000.

GLUCOSE HOMEOSTASIS

The FDA-approved prescribing information for gatifloxacin has been updated to include stronger precautions against possible disturbances of glucose homeostasis. Reports in the literature of possible drug-drug interactions between ciprofloxacin and glyburide suggest that the potential for a drug class effect exists that should be monitored. Package inserts for all marketed fluoroquinolones mention such potential interactions.

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