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Fluoroquinolones: Then and Now

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Abstract: *Fluoroquinolones were discovered in the 1960s as a derivative of the antimalarial drug chloroquine. Over the past 40 years, many fluoroquinolones have been developed for use in human and veterinary medicine. As with all classes of antibiotics, resistance to fluoroquinolones is a serious concern, and multiple avenues for resistance are being investigated. Resistance-associated point mutations in bacterial DNA and, more recently, plasmid-mediated resistance have been reported in both human and veterinary bacterial isolates. This article reviews the history and most current literature on fluoroquinolones approved for use in dogs and cats and the spectra of activity, mechanisms of action, resistance patterns, and recommendations for appropriate clinical use of these drugs.*

Quinolones were first discovered in 1962 as a result of alterations to a compound isolated from production of the antimalarial drug chloroquine.[1] The first drug in this class was nalidixic acid, which was approved for clinical use in 1965. Nalidixic acid was poorly absorbed in the gastrointestinal (GI) tract and had a narrow spectrum of activity. Its use was limited to treating urinary tract infections (UTIs) caused by Enterobacteriaceae spp. The structure of nalidixic acid was modified in the 1980s, improving its absorption and bioavailability and broadening its efficacy to include *Pseudomonas aeruginosa* and certain gram-positive cocci.[2] These changes included the addition of a fluorine molecule to the basic quinolone structure, resulting in what is now termed a *fluoroquinolone*.

The first fluoroquinolones approved for use in clinical medicine were norfloxacin and ciprofloxacin in the 1980s. In 1989, enrofloxacin was the first fluoroquinolone approved for use in dogs and cats, followed by orbifloxacin (1997), difloxacin (1997, for dogs only), and marbofloxacin (1999, approved for cats in 2001). Pradofloxacin is a recently discovered fluoroquinolone that appears to have enhanced bactericidal activity against pathogens that have reduced susceptibility to earlier fluoroquinolones.[3] Ciprofloxacin, although not approved for use in veterinary medicine, is frequently used off-label in dogs and cats, and is therefore included in this review.

Fluoroquinolones are divided into generations according to structural differences that change the spectra of activity. Nalidixic acid is considered a first-generation drug, with a limited spectrum of activity and poor tissue penetration. Second-generation drugs were designed with the addition of a fluorine at position 6 of the quinolone ring system, which improved both the spectrum of activity and tissue distribution. This category contains several structurally different compounds with different spectra of activity (**FIGURE 1**). Second-generation fluoroquinolones include enrofloxacin, difloxacin, marbofloxacin, and ciprofloxacin. Third-generation fluoroquinolones have increased activity against gram-positive bacteria and some anaerobic bacteria. Orbifloxacin is the only veterinary-approved product that falls into this category; however, it has minimal anaerobic activity in vivo.[4] Fourth-generation fluoroquinolones are also unique structurally, with a five-member pyrrolidine group replacing the six-member piperazine ring at position 7, resulting in improved activity against anaerobic and gram-positive organisms. Pradofloxacin, a recently developed veterinary fluoroquinolone, falls into this category.

Mechanism of Action and Pharmacokinetics

Fluoroquinolones impair DNA gyrase, one of several topoisomerase enzymes that are important to DNA replication.[5] Bacterial DNA is normally maintained in a supercoiled state. Bacteria must "uncoil" their DNA to replicate, which can lead to kinks and breaks throughout the strand. Bacterial DNA gyrase (also known as *topoisomerase II*) cuts, separates, and reseals the strands of DNA during replication (**FIGURE 2**, **A** through **E**). The exact mechanism by which fluoroquinolones induce DNA damage is unknown, but it is theorized that kinks and breaks left unrepaired as a result of the impaired DNA gyrase result in DNA destruction.[6,7] Although mammalian species also depend on topoisomerases for DNA repair, fluoroquinolones have a greater affinity for bacterial DNA gyrase than for mammalian DNA gyrase.[6] This difference allows fluoroquinolones to have rapid bactericidal activity without adverse effects on the host. In addition

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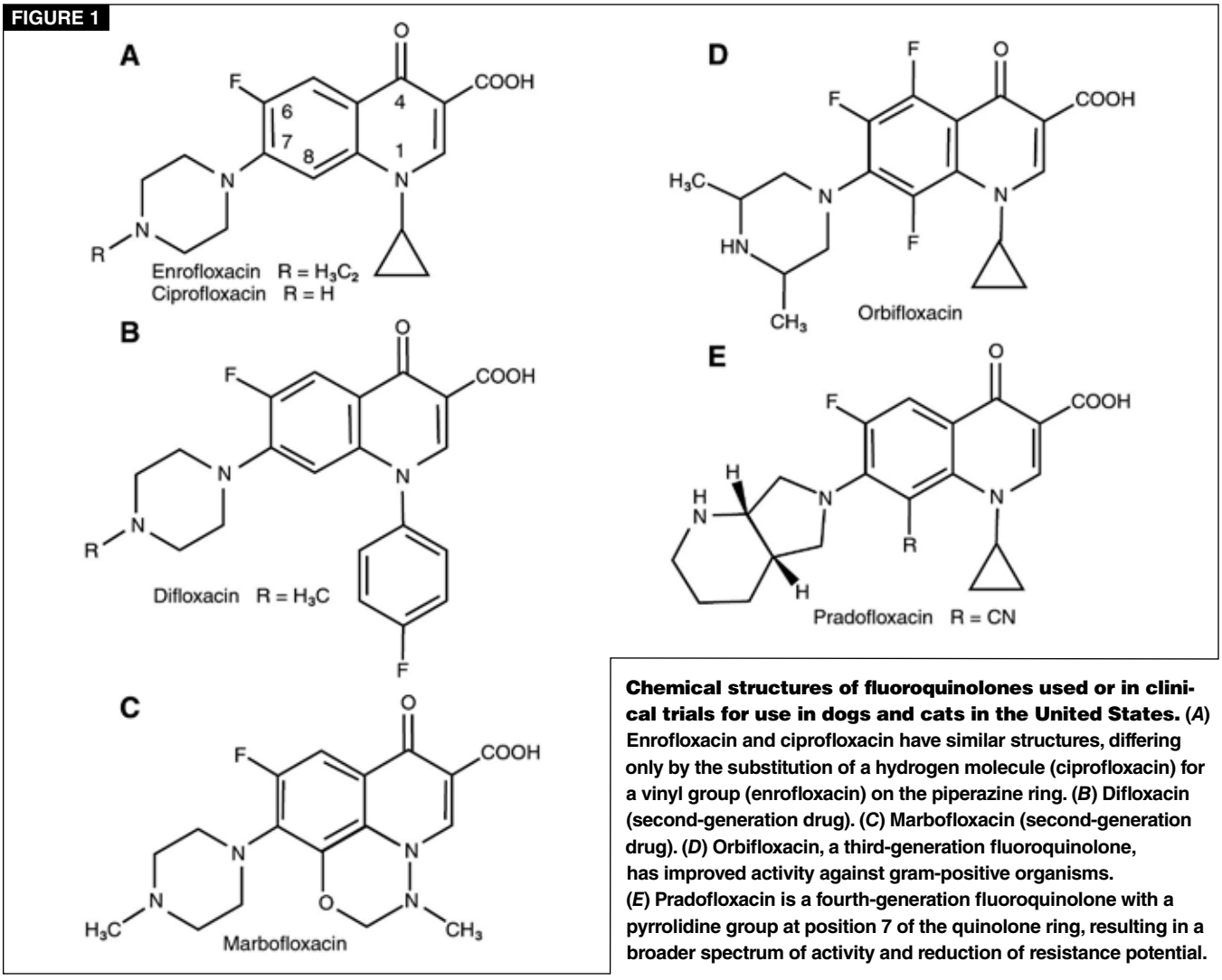
FIGURE 1



Chemical structures of fluoroquinolones used or in clinical trials for use in dogs and cats in the United States. (*A*) Enrofloxacin and ciprofloxacin have similar structures, differing only by the substitution of a hydrogen molecule (ciprofloxacin) for a vinyl group (enrofloxacin) on the piperazine ring. (*B*) Difloxacin (second-generation drug). (*C*) Marbofloxacin (second-generation drug). (*D*) Orbifloxacin, a third-generation fluoroquinolone, has improved activity against gram-positive organisms. (*E*) Pradofloxacin is a fourth-generation fluoroquinolone with a pyrrolidine group at position 7 of the quinolone ring, resulting in a broader spectrum of activity and reduction of resistance potential.

to DNA gyrase, fluoroquinolones have a secondary target, topoisomerase IV (**FIGURE 2**, **F** and **G**).[7,8] This enzyme mediates relaxation of DNA and is involved in the unlinking of daughter chromosomes after replication. Interruption of the action of this enzyme allows the bacterial DNA to be trapped after replication, leading to cell death. Inhibition of DNA gyrase is primarily associated with gram-negative bacteria, whereas inhibition of topoisomerase IV targets gram-positive bacteria.

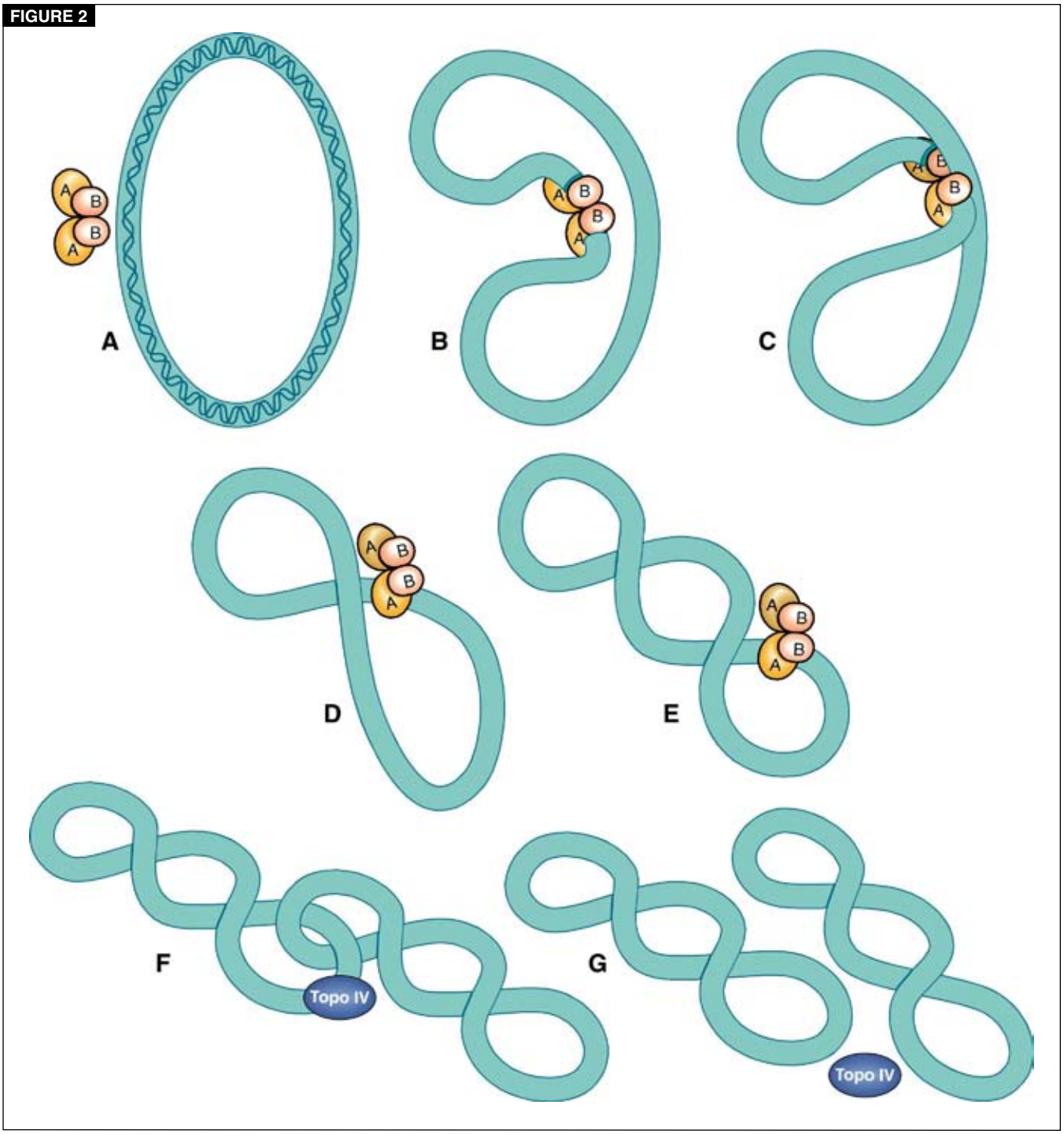
All fluoroquinolones have relatively similar pharmacokinetics. After oral administration, marbofloxacin, enrofloxacin, difloxacin, and orbifloxacin are more than 80% absorbed from the GI tract with 100% oral bioavailability.[6] Ciprofloxacin is also more than 80% absorbed, but it has only 40% bioavailability in dogs[9] and 33% in cats.[10] In addition, 10% to 40% of absorbed enrofloxacin is converted to ciprofloxacin in dogs and cats.[9] Therefore, given its pharmacokinetics, off-label use of ciprofloxacin in dogs and cats is poorly justified. The metabolic conversion of enrofloxacin to an active form of ciprofloxacin makes the use of ciprofloxacin redundant in veterinary medicine.

Drug and dose selection are based on several factors, including the animal's renal and hepatic function, simultaneous use of other medications, and the drug's metabolism and tissue penetration. Fluoroquinolones are known to achieve high concentrations at extravascular sites[11] and are, therefore, useful in the treatment of deep and superficial pyoderma. In addition, there is some evidence that fluoroquinolones accumulate in inflammatory cells, imparting even greater activity in areas with significant cellular inflammation.[12] Most fluoroquinolones are excreted unchanged in the urine, making them an excellent choice for the treatment of urogenital infections. Individual characteristics of specific drugs and their distribution and metabolism are reviewed later in this article.

Spectrum of Activity

Veterinary fluoroquinolones are often classified as "broad-

FIGURE 2



Targets of fluoroquinolones. (*A – E*): The primary target of the fluoroquinolone class of antibiotics is DNA gyrase, which relaxes and supercoils bacterial DNA during replication by cutting the DNA, passing it across another strand, and resealing it. (*F – G*): The secondary target is topoisomerase IV, which unlinks the newly replicated DNA strand from the parent strand.

spectrum" antibiotics and are used for the treatment of infections in many different body systems. This classification is not accurate for most veterinary fluoroquinolones, however. Historically, gram-negative bacteria such as *Escherichia coli, Klebsiella* spp, *Enterobacter cloacae, Proteus mirabilis, Citrobacter freundii, Serratia marcescens,* and (to some extent) *P. aeruginosa* are particularly sensitive to this class of antibiotics. Structural differences between different generations of fluoroquinolones result in activity against a wider spectrum of bacteria. Fluoroquinolones currently available in veterinary medicine (**TABLE 1**) have limited activity against gram-positive bacteria and almost no effect on anaerobic species.

TABLE 1 Common Fluoroquinolones Used in Dogs and Cats

Drug	Dose	Dog	Cat[a]	Spectrum	Trade Name	Available Forms
Ciprofloxacin	5–15 mg/kg PO q12h	Yes[b]	Yes[b]	Gram-negative	Cipro (Bayer Healthcare)	Oral tablets: 100, 250, 500, and 750 mg Oral suspension: 5 g/100 mL (5%), 10 g/100 mL (10%) Injection: 10 mg/mL
Difloxacin	Dog: 5–10 mg/kg/d PO q24h Not used in cats due to glucuronidation pathway	Yes	No	Gram-negative, some gram-positive	Dicural (Fort Dodge Animal Health)	Oral tablets: 11.4, 45.4, and 136 mg
Enrofloxacin	Dog: 5–20 mg/kg/d IM, IV, or PO q24h Cat: 5 mg/kg/d IM, IV, or PO q24h	Yes	Yes	Gram-negative, some gram-positive	Baytril (Bayer Animal Health)	Oral tablets: 22.7, 68, and 136 mg Injection: 22.7 mg/mL
Marbofloxacin	Dog: 2.75–5.5 mg/kg/d PO q24h Cat: 2.75–5.5 mg/kg/d PO q24h	Yes	Yes	Gram-negative	Zeniquin (Pfizer Animal Health)	Oral tablets: 25, 50, 100, and 200 mg
Orbifloxacin	Dog: 2.5–7.5 mg/kg/d PO q24h Cat: 2.5–7.5 mg/kg/d PO q24h	Yes	Yes	Gram-negative, some gram-positive	Orbax (Schering-Plough Animal Health)	Oral tablets: 5.7, 22.7, and 68 mg
Pradofloxacin[c]	Undetermined	Yes	Yes	Gram-negative, gram-positive, and anaerobic	Veraflox (Bayer Animal Health)	Oral tablets: 15, 60, and 120 mg Oral suspension: 2.5%

[a]Use with caution in cats due to the potential for severe acute retinal degeneration.
[b]Not approved for use in animals.
[c]In clinical trial; not commercially available in the United States.

Adverse Reactions

Adverse reactions to fluoroquinolones are limited, with GI upset (e.g., vomiting, diarrhea, anorexia) seen most commonly after oral administration. GI side effects are often self-limiting and resolve with discontinuation of the drug.

Seizures have also been reported in human patients treated with fluoroquinolones. Although the pathogenesis behind this effect is unclear, it is theorized that antagonistic effects of fluoroquinolones on γ-aminobutyric acid receptors may be involved.[13] Risk factors for seizures include concurrent epilepsy, high doses of the medication, and simultaneous use of NSAIDs.[4,6,14–18] To our knowledge, seizures associated with fluoroquinolone use have not been reported in the veterinary literature.

Cartilage deformities and joint growth disorders have been reported with all fluoroquinolones.[6,19–22] Generally, quinolone arthropathy is characterized by vesicle development on the articular surface, with subsequent erosion of cartilage. The exact mechanism is unknown, but it has been speculated that alterations in proteoglycan synthesis may play a role.[19] Additionally, alterations in chondrocyte DNA and inhibition of extracellular matrix components have been investigated.[19] Fluoroquinolones are not recommended for use in young, growing animals or pregnant animals because lesions can occur after as few as 1 to 2 days of treatment. If fluoroquinolones are the only viable option for certain infectious agents in this class of patients, owners should be advised thoroughly of the risks for future orthopedic disease.

Fluoroquinolones have also been shown to cause acute, diffuse retinal degeneration in cats. Although the mechanism has yet to be identified, it is suspected that this reaction is dose dependent, with higher doses resulting in more severe adverse effects.[23–25] In addition, rapid IV infusion, prolonged courses of treatment, patient age, and drug accumulation due to altered metabolism from concurrent dis-

ease may play a role.[25] Enrofloxacin has been specifically implicated,[23,24] but all fluoroquinolones should be used with caution in cats. Practitioners should not prescribe more than the label-recommended dose of 5 mg/kg/d. Although it is thought that only a small number of cats treated with fluoroquinolones experience retinal degeneration (0.0008%),[25] the risks associated with these antibiotics in cats should be discussed with owners before use. A small percentage of cats that become acutely blind regain some portion of their vision over time, but most cats remain blind for life.

Drug Interactions

Fluoroquinolones should be used with caution in patients receiving theophylline because the interaction between the drugs results in slower elimination of theophylline and can result in secondary toxicosis.[6] In addition, fluoroquinolones can be chelated by magnesium, calcium, and other cations, and therefore should not be administered orally with antacids or sucralfate. Chelation is not observed with parenteral preparations, which can be given safely with most common crystalloid fluids such as 0.9% sodium chloride, lactated Ringer's solution, and Normosol-R (Abbott Laboratories) electrolyte solution.

Fluoroquinolone Resistance

As mentioned above, fluoroquinolones kill bacteria through two known mechanisms. Amino acid substitutions that confer resistance appear to be localized to a specific topoisomerase subdomain, known as the *quinolone resistance–determining region*.[1,26] Mutations that result in resistance were previously thought to occur in a stepwise fashion so that some bacteria alter their DNA gyrase and other bacteria alter topoisomerase IV.[27] This concept led to the theory that bacterial resistance to fluoroquinolones would be slow to develop because these point mutations are rare, occurring in only a small population of bacteria. Despite this hypothesis, bacterial fluoroquinolone resistance has progressed considerably and has evolved to include plasmid-mediated resistance, long thought not to occur with fluoroquinolones.[28] In addition, bacteria can develop resistance through changes in membrane permeability and altered regulation of metabolite efflux channels. Bacteria that become resistant through these mechanisms are often resistant to other classes of antibiotics as well.

Research is now focusing on the development of fluoroquinolones that target both DNA gyrase and topoisomerase IV at different systemic concentrations. Such antibiotics would slow the development of resistance, requiring point mutations in both bacterial DNA gyrase and topoisomerase IV for resistance to develop. This would be extremely rare and, in turn, would make fluoroquinolones even more favorable for use against multidrug-resistant strains of bacteria. This research has led to the concept of mutant prevention concentrations (MPCs) of drugs. Minimal inhibitory concentration (MIC) is a well-known concept in microbiology that describes the concentration of an antibiotic that prevents the growth of a microorganism over a 24-hour incubation period. The MPC takes this concept one step further and is defined as the drug concentration that allows no residual visible growth. Consequently, bacteriostatic activity is exerted on even the most refractory or resistant variants.[27,29] The MPC would eliminate bacteria with mutations in both DNA gyrase and topoisomerase IV. However, MPC doses of currently available fluoroquinolones would likely result in toxicity to the patient. For example, the MPCs in vitro of enrofloxacin and pradofloxacin against a strain of *E. coli* and *Staphylococcus aureus* were 2.4 times and 6 times higher, respectively, than the MICs for these drugs.[27] Translation of in vitro studies to practical in vivo doses has not been reported, but it is theorized that the disparity between the MPC and the MIC in vivo would be quite significant. This is likely due to not only bioavailability but also the capacity to maintain the MPC for the period of time necessary to eliminate infection.[27]

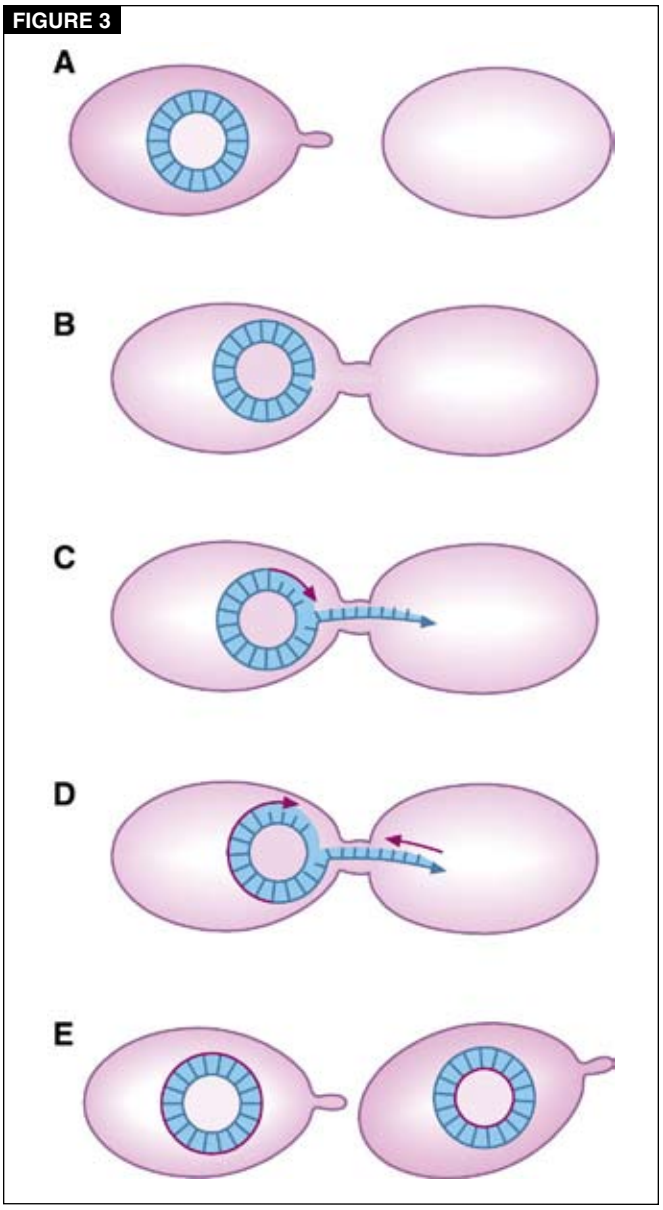
The development of new fluoroquinolones that close the gap between the MIC and the MPC has become a priority in pharmaceutical research.[27] Fourth-generation fluoroquinolones are created from simple structural changes to enrofloxacin at the C7 and C8 positions, resulting in retention of gram-negative activity, improved gram-positive activity, and—for the first time—antianaerobic activity as well.[30]

Other mechanisms of resistance to fluoroquinolones are also under investigation. Plasmid-mediated resistance results from the distribution of small strands of circular

Key Facts

- Fluoroquinolones exert their bactericidal effects through inhibition of bacterial DNA gyrase and topoisomerase IV.
- The fluoroquinolones difloxacin, enrofloxacin, marbofloxacin, and orbifloxacin are approved for use in veterinary medicine in the United States. No fluoroquinolones have been approved for use in food animals.
- Resistance to fluoroquinolones is primarily mediated through two mechanisms: DNA point mutations and plasmid transfer.
- Pradofloxacin is a new fluoroquinolone with broad-spectrum activity against gram-negative, gram-positive, and anaerobic bacteria that is designed to diminish mutation-mediated resistance.
- In dogs, up to 40% of enrofloxacin is converted to ciprofloxacin.

FIGURE 3



Plasmid-mediated resistance occurs via transfer of DNA between bacteria. (*A*) A conjugation bridge is established between two bacteria. (*B – D*) The circular DNA strand containing the genetic material conferring resistance is nicked and copied as it is transferred across the bridge. (*E*) The recipient bacterium now has the resistance genotype.

DNA, known as *plasmids* (**FIGURE 3**). Plasmid DNA can be duplicated independently from the bacteria's own DNA and can contain genes that encode for different mechanisms of resistance. In 2002, transmissible resistance was identified in an *E. coli* bacterial isolate, and the plasmid-encoded quinolone resistance gene (qnr) was identified.[28,31]

In 2006, plasmid-mediated resistance was identified in a multidrug-resistant *E. coli* bacteria isolated from dogs in a veterinary teaching hospital in Australia.[32] The emergence of plasmid-mediated resistance to fluoroquinolones in human and veterinary medicine raises important questions regarding the judicious use of these antibiotics in veterinary medicine. The FDA has identified the emergence of fluoroquinolone-resistant *Campylobacter*, *Salmonella*, and *E. coli* in the human population.[33,34] Interestingly, *Campylobacter* lacks topoisomerase IV, so a single mutation in its DNA gyrase results in significant resistance.[1] With plasmid-mediated resistance now becoming apparent, there is an even greater risk to the human and veterinary population for the development of multidrug-resistant bacteria in clinical situations.

Efforts to combat resistance originate in the clinical setting with appropriate antibiotic selection based on laboratory culture and sensitivity. Empirical use of antibiotics for suspected infections is common in both human and veterinary medicine. Financial constraints imposed by pet owners are often at the root of these clinical decisions in the veterinary setting. However, cost considerations should not outweigh concerns for public health. Fluoroquinolone resistance, specifically in *E. coli*, has already been reported in up to 40% of clinical isolates obtained from patients with UTIs.[9,35]

Studies of fluoroquinolone resistance in human urinary isolates reveal that up to 10% of all bacterial isolates in the United States and Canada have developed resistance to ciprofloxacin and levofloxacin.[36,37] Many of these same bacteria are also resistant to ampicillin (45.9%), sulfamethoxazole/trimethoprim (20.4%), and nitrofurantoin (14.3%). Investigation into typhoid and nontyphoid strains of *Salmonella* in Spain revealed multiple fluoroquinolone-resistant strains posing a significant health risk in this country.[38] *E. coli* strains isolated from UTIs in Turkey showed 17% resistance to ciprofloxacin in uncomplicated UTIs, and 38% resistance in complicated UTIs.[39] While a wide range of resistance has been identified in multiple classes of bacteria throughout the human literature, the underlying theme is the same: fluoroquinolone resistance is a growing problem in human medicine that poses a serious threat to the treatment of even simple infections. Future studies looking at other clinical isolates and resistance will be important to improving antibiotic use guidelines in both human and veterinary medicine.

Fluoroquinolone Agents

Ciprofloxacin

Ciprofloxacin is not approved for use in veterinary medicine, but it has been approved for human use since the 1980s. Ciprofloxacin is a product of the metabolism of enrofloxacin in dogs, and therefore the spectrum of activity for both drugs is similar; however, ciprofloxacin has no reported effect against gram-positive bacteria.

Pharmacokinetic studies suggest that ciprofloxacin is well absorbed after oral ingestion, but the oral bioavailabil-

ity is only 40% that of enrofloxacin in dogs and 33% of that in cats.[9,10,40,41] The reasons for the poor oral bioavailability of ciprofloxacin are not completely understood, but it is thought that metabolism by intestinal epithelial cells may be involved. In addition, the first-pass effect may also play a role because ciprofloxacin is partially metabolized by the liver. Despite its poor oral bioavailability, ciprofloxacin appears to achieve excellent serum and tissue concentrations that are above established MIC values.[40,41]

In humans, ciprofloxacin is 20% to 40% bound to serum proteins and appears to concentrate well in urine, prostatic secretions, saliva, nasal and bronchial secretions, skin, and bile. With the existence of approved veterinary products with similar spectra of activity, the off-label use of ciprofloxacin in dogs and cats is poorly justified. Arguments for its use have been based on bacterial culture and antimicrobial sensitivity testing demonstrating resistance to enrofloxacin but susceptibility to ciprofloxacin. With 10% to 40% of enrofloxacin being converted to ciprofloxacin in vivo,[9] it can be argued that bacteria susceptible to ciprofloxacin will likely be susceptible to enrofloxacin as well. Further in vivo studies are necessary to better evaluate the effects of ciprofloxacin in veterinary species.

Difloxacin

Difloxacin is rapidly and almost completely absorbed after oral administration, and approximately 50% is bound to circulating plasma proteins. It is primarily metabolized by hepatic glucuronidation and is secreted in bile.[42] Consequently, 80% of the drug is eliminated in the feces. In contrast to other fluoroquinolones, renal clearance accounts for only 5% of the removal of difloxacin from the canine system, which makes it an attractive choice for dogs with compromised renal function. The metabolism of difloxacin through glucuronidation prohibits the use of this drug in cats, because the lack of this enzymatic pathway in this species would likely result in toxicity. Due to its concentration in the liver and the bile, difloxacin is recommended for susceptible hepatobiliary infections. Despite its poor renal clearance, difloxacin is also labeled for use against susceptible UTIs and—as with other fluoroquinolones—susceptible skin and soft tissue infections. In addition, difloxacin appears to concentrate well in bone and is a good choice for treating susceptible osteomyelitis.

Enrofloxacin

Enrofloxacin is rapidly and almost completely absorbed when administered orally, and 27% is bound to plasma proteins. Highest concentrations are found in the bile, liver, kidney, lungs, and reproductive systems (including the prostate). Enrofloxacin is primarily metabolized by the liver and eliminated through the kidneys.[43] Because of its distribution, enrofloxacin is an excellent choice for susceptible UTIs, prostatitis, suppurative hepatitis, and pneumonia. Enrofloxacin also appears to have good penetration into bone and skin tissue and is considered a good choice for susceptible pyoderma and osteomyelitis. Enrofloxacin also concentrates well in the GI tract, and recent literature supports its use in antibiotic-responsive histiocytic ulcerative colitis (most commonly seen in boxer dogs).[44,45] These early studies are encouraging for future use of this drug in animals with ulcerative colitis that have been nonresponsive to traditional therapy.

Marbofloxacin

Marbofloxacin is rapidly and almost completely absorbed after oral administration, and appears to be only slightly protein bound (9% in dogs and 7% in cats). Marbofloxacin has a large volume of distribution and good penetration into body tissues. In dogs, approximately 40% is excreted unchanged in the urine (70% in cats); excretion through the feces is the other chief route of elimination. In addition, 10% to 15% of the drug is metabolized by the liver and excreted in the bile.[46] Due to its concentration in the urine, it is recommended for use against susceptible UTIs. Marbofloxacin is also labeled for use against susceptible skin and soft tissue infections.

Orbifloxacin

Orbifloxacin is rapidly and almost completely absorbed after oral administration and is mildly protein bound (8% in dogs and 15% in cats). Orbifloxacin has a large volume of distribution with good penetration into body tissues. Approximately 40% of the drug is excreted unchanged through the kidneys within 24 hours of oral administration.[47] Due to its significant concentration in the urine, orbifloxacin is recommended for use against susceptible UTIs. Orbifloxacin is also labeled for use against susceptible skin and soft tissue infections.

Pradofloxacin

Pradofloxacin is the newest fluoroquinolone antibiotic that is under development for use in dogs and cats. Pradofloxacin is intended for the treatment of wound infections, superficial and deep pyoderma, UTIs, gingival and periodontal infections, and acute upper respiratory infections.[39] Pradofloxacin was approved for use in Australia in April 2007, but it is still under review in Europe and in the United States. Because of its unique molecular structure, this fluoroquinolone has enhanced activity against gram-positive bacteria and anaerobes, while retaining broad-spectrum effects on gram-negative bacteria.[30] In vitro studies comparing the MIC and MPC of pradofloxacin with those of marbofloxacin, enrofloxacin, danofloxacin, sarafloxacin, orbifloxacin, and difloxacin demonstrate a significantly lower MPC for pradofloxacin than for other fluoroquinolones.[27] Further studies looking at in vivo effects of pradofloxacin at MPC levels in veterinary

patients will be critical in determining the usefulness of this drug in resistance prevention. MPCs have been determined in vitro for pradofloxacin against strains of *Mycobacterium bovis, S. aureus,*[29] *E. coli, Staphylococcus intermedius*,[27] and *Porphyromonas gingivalis*.[48] Pradofloxacin's success against *S. intermedius* prompted its experimental use for deep pyoderma in dogs.[30] In early studies, pradofloxacin appeared to be a safe and effective treatment for deep pyoderma in dogs and led to rapid clinical remission and a significantly lower recurrence rate compared with amoxicillin–clavulanic acid.[30] In addition to its role in resistance prevention, early studies using pradofloxacin in cats have shown no evidence that it causes fluoroquinolone-induced retinal changes.[3] Studies looking at other commonly associated fluoroquinolone side effects (e.g., cartilage defects, seizures) have not been reported at this time. The in vivo study of this drug is still in its infancy, and continued research is needed to evaluate its clinical effectiveness as well as its promising role in prevention of resistance.

Conclusion

The future clinical use of fluoroquinolones relies heavily on reducing the development of antibiotic resistance in human and veterinary bacterial infections. It is hoped that judicious use of fluoroquinolones, based on culture and susceptibility results, and considerations for tissue penetration and systemic therapeutic levels will result in effective clinical utility. Current research on MPCs and the discovery of new fluoroquinolones through structural alterations should lead to development of a group of antibiotics that are effective against a wider variety of gram-positive and anaerobic bacteria. Concerns about plasmid-mediated resistance are serious, and, even with promising new antibiotics on the horizon, off-label and empirical antibiotic use should be discouraged.

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1. The first fluoroquinolone to be approved for use in veterinary medicine was
a. nalidixic acid.
b. difloxacin.
c. enrofloxacin.
d. ciprofloxacin.

2. What is the primary mechanism of action for fluoroquinolones?
a. bacterial RNA inhibition
b. DNA gyrase inhibition
c. topoisomerase VII inhibition
d. bacterial cell wall lysis

3. Approximately 10% to 40% of enrofloxacin is metabolized to _____ in dogs.
a. difloxacin
b. orbifloxacin
c. marbofloxacin
d. ciprofloxacin

4. _____ is a potential adverse effect of fluoroquinolone administration in cats, but not in dogs.
a. Vomiting
b. Acute retinal degeneration
c. Anorexia
d. Diarrhea

5. What is the recommended dosage of enrofloxacin in cats?
a. 5 mg/kg/d
b. 12 mg/kg/d
c. 15 mg/kg/d
d. 20 mg/kg/d

6. Fluoroquinolones are most effective against _____ bacteria.
a. anaerobic
b. gram-negative
c. gram-positive
d. filamentous

7. _____ is metabolized via the glucuronidation pathway and therefore should not be used in cats.
a. Difloxacin
b. Enrofloxacin
c. Marbofloxacin
d. Orbifloxacin

8. The drug concentration defined as allowing no visible residual bacterial growth is known as the
a. MIC.
b. MPC.
c. bactericidal concentration.
d. resistance-prevention concentration.

9. What type of resistance, long thought to not occur with fluoroquinolones, has recently been discovered in clinical isolates?
a. DNA point mutations
b. membrane permeability changes
c. bacterial efflux channel regulation
d. plasmid-mediated resistance

10. In cats, retinal degeneration with fluoroquinolone use is associated with all of the following except
a. rapid IV infusion.
b. increased dose.
c. patient sex.
d. patient age.

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