Volume-3, Issue-2, April-2012
Available Online at www.ijppronline.com
International Journal Of Pharma Professional's Research
Review Article

ISSN NO:0976-6723

A REVIEW: PHARMACOKINETICS APPLICATION OF FLOUROQUINOLONS

Gupta Ritu[*1], Sharma K. K.[1], Sharma R D[1], Gupta D K[1], Tyagi Sachin [1], Yadav B.P.[2]
1. Department of pharmacy, B.I.T. Meerut, India
2.Department of Chemistry, Meerut college Meerut, India

Abstract
This review outlines some of pharmacokinetic parameters factors of fluoroquinolones antimicrobial agents. The oral absorption is not altered in human patients with disease. Plasma protein binding of the quinolones varies but newer quinolones less bound to plasma proteins. The serum concentration peak is reached rapidly. Most of the fluoroquinolone primary metabolites are active against bacteria: however, these metabolites have a shorter elimination half-life than their parent compound.

Keywords: - Fluoroquinolones; Pharmacokinetics; Resistance; Therapeutic use.

Introduction
The fluoroquinolones are a family of synthetic, broad-spectrum antibacterial agents with bactericidal activity. The parent of the group is nalidixic acid, discovered in 1962 by Lescher and colleagues. The first fluoroquinolones were widely used because they were the only orally administered agents available for the treatment of serious infections caused by gram-negative organisms, including Pseudomonas species. The newer fluoroquinolones have a wider clinical use and a broader spectrum of antibacterial activity including gram-positive and gram-negative aerobic and anaerobic organisms. Some of the newer fluoroquinolones have an important role in the treatment of community-acquired pneumonia and intra-abdominal infections.

2. PHARMACOKINETICS

2. a. ABSORPTION:
Oral absorption of fluoroquinolones depends on the specific agent administered with ofloxacin adsorbed better than ciprofloxacin, pefloxacin or enoxacin; all of these were more readily adsorbed than norfloxacin[1] with the absolute oral bioavailability of norfloxacin in dogs of approximately 35%.[2] Ciprofloxacin is absorbed primarily from the duodenum and jejunum when administered orally to monogastric animals.[3]

Correspondence Address:
Ritu Gupta,
Assistant professor, Department of pharmacy,
B I T campus, Meerut, India, 250103
E-mail:- ritukk@gmail.com
Phone no:- +91-9917778686

Bioavailability is lower in ruminants although the mechanism for this anecdotal observation has not been determined.

2. a.1. BIOAVAILABILITY
Bioavailability from parenteral injection sites is nearly 100% for all fluoroquinolones. Food generally inhibits the oral absorption of fluoroquinolones although there was no significant difference in enrofloxacin bioavailability in fed and fasted pigs[4] or in ciprofloxacin bioavailability in humans on various high fat/high calcium diets.[5] Overall, oral bioavailability of fluoroquinolones ranges from 30–90% in chickens[6] and pigs[4] although oral availability in donkeys was very low.[7]

2. a. 2. SERUM CONCENTRATION
The serum concentration peak is reached rapidly; the different fluoroquinolones display their maximum serum concentration peak within 1 and 2 hours after ingestion in man, and the times to the peak are similar in dogs, rodents and monkeys.[8] The time to serum peak concentrations after a single oral bolus administration of enrofloxacin is 2.5, 1.4, 0.9 and 0.5 hours, respectively, in the chicken, turkey, calf, dog and horse.[9]

The concomitant administration of magnesium and aluminium containing anti-acids decreases the oral bioavailability of fluoroquinolones. This action is attributed to the chelation of carboxylate groups by the bivalent cations.[10] The low serum concentration when administered with milk replacer may be due to the presence of minerals that could chelate the antimicrobial. Parenteral availability of most quinolones is approximately complete in pre-ruminant

and ruminant cattle[11] although norfloxacin nicotinate availability from intramuscular injection sites was 70–90%.[12] Supra-availability from extravascular route was observed in horses[13] and may be a result of the enterohepatic recycling known to occur with some fluoroquinolones. The possibility of enterohepatic recycling of fluoroquinolones potentially confounds many of the pharmacokinetic calculations that assume the dose proportionally and no recycling (i.e. classical one- and two-compartment open pharmacokinetic models).

2. b. DISTRIBUTION:

One of the most attractive pharmacokinetic characteristics of fluoroquinolones is their large volume of distribution. Distribution of fluoroquinolones to tissues is very good, owing to their physicochemical properties. Plasma protein binding of the quinolones varies, with the newer quinolones less bound to plasma proteins than nalidixic acid. The steady-state volume of distribution of the fluoroquinolones is large, being 2–3 l/kg for danofloxacin in cattle[11-14] and 3.45 ± 0.72 l/kg in horses[15], 1.47 l per kg for norfloxacin in dogs[2] and 0.75–0.96 l/kg for flumequine in calves.[16] In most species, this distribution volume is over 3 times greater than that for most β-lactam antibiotics and aminoglycosides, and probably represents intracellular sequestration of the drug in various tissues. Blister-fluid concentrations (indicative of interstitial fluid concentrations) equal serum concentrations within 2 h oral administration.[17] Furthermore, tissue cage fluid concentrations of norfloxacin or ciprofloxacin were somewhat, but not substantially, higher than concurrent plasma concentrations after 6 h oral administration, and they were lower than concurrent plasma concentrations from 0–6 h dosing in normal dogs.[18,19] The volume of distribution of enrofloxacin and ciprofloxacin increased in rabbits from 8 to 60 days of age, possibly due to changes in the body composition.[20]

High concentrations of fluoroquinolones are achieved in saliva, nasal secretions and nasal mucosa, and bronchial epithelium[17], although these are not substantially higher than concurrent plasma concentrations. In fact, nasopharyngeal concentrations of ciprofloxacin were much higher than the MIC90 for meningococci and *H. influenzae*, but they were below the MIC for methicillin-resistant *Staphylococcus aureus* in human patients.[21]

2.b.1. Enrofloxacin:

Enrofloxacin concentrations that were up to 3 times higher than the serum concentrations were observed in tissue homogenates from calves taken 1 h after dosing, with 12 h concentrations in tissue homogenates exceeding the concurrent serum concentrations.[22]

2.b.2. Danofloxacin:

These danofloxacin concentrations in lung homogenate appeared somewhat related to the regional blood flow although danofloxacin concentrations in consolidated lung homogenates were proportionally higher than in the blood flow.[23] Furthermore, the concentrations of danofloxacin in bronchial secretions reproduced concurrent plasma concentrations in swine in spite of higher concentrations in bronchial mucosa and whole lung homogenates;[24] similar relationships between bronchial secretion and lung tissue homogenate concentrations may apply to other species, including cattle. In the dog, enrofloxacin concentrations in bile and urine exceeded serum concentrations 10–20 times; tissue homogenate concentrations observed 1 h after drug administration in calves were in the following order: liver ≥ kidney > heart > lung ≥ spleen ≥ intestinal wall > serum = muscle = lymph nodes.[22]

2.b.3. Enoxacin:

Concentrations of enoxacin in the skin were almost equal to concurrent plasma concentrations after multiple oral dosing.[25] Semen concentrations were half of those observed in the serum shortly after ciprofloxacin administration, but they were 10 times higher than serum concentrations in 12 h and 24 h after dosing.26

2.b.4. Ciprofloxacin

Ciprofloxacin concentrations in expressed prostatic secretion after oral administration of 500 mg ciprofloxacin in human volunteers ranged from 0.9–15 μg/ml, indicating pronounced diffusion of ciprofloxacin into the prostatic fluid.[26] Enrofloxacin showed similar penetration into the prostatic fluid and tissue in dogs, that means both were higher than concurrent serum concentrations[27] and no differences were noted in the presence of chronic *Escherichia coli* prostatitis. Good penetration of enoxacin into myometrium, cervix, and Fallopian tubes was demonstrated in human beings.[28] In dogs, uterine and prostatic fluid concentrations were 2.2 and 1.4 μg/ml 1 h after an oral dose of 2.5 mg, whereas 1 h serum concentrations were 1.2 μg/ml after an oral dose of 5 mg enrofloxacin/kg.[22] In the cortical bone, enrofloxacin activity reached 29% of the concurrent serum activity[29] although it must be reminded that enrofloxacin and its dealkylated metabolite, ciprofloxacin, both contribute to *in vivo* activity.

The ratio of concentrations of ciprofloxacin

pefloxacin, and ofloxacin in amniotic fluid compared to plasma ranged from 0.35 to 0.5 within 2–6 hours after dosing; comparable milk to plasma ratios were 0.75 to 1.84.[3,30] There is approximately 16 times higher placental transfer of enrofloxacin than of ciprofloxacin in rabbits[31], suggesting some very profound compound-specific transport processes through the placenta.

In contrast, milk norfloxacin concentrations were up to 40 times higher than the corresponding serum concentrations after administration of norfloxacin nicotinate to ewes.[32] Enrofloxacin penetrates into milk to attain approximately twice the maximum concentration of ciprofloxacin at similar plasma concentrations, although the elimination of enrofloxacin from milk is approximately twice as fast as that for ciprofloxacin.[33] Penetration into the CNS is relatively good, and vitreous humor penetration is approximately 20%.[34] Apart from nasal secretions[35] and ejaculate, body fluid concentrations of fluoroquinolones rarely reach plasma concentrations.[36] Thus, the high tissue concentrations are a result of sequestration onto, or within, cells or cellular components of a tissue, although[37] found no specific subcellular structure affinity to pefloxacin. As an example, the intracellular concentrations of fluoroquinolones in polymorphonuclear leukocytes are 7–14 times higher than those found in the extracellular fluid.[38]

2. c. Metabolism:

The degree of the metabolism of fluoroquinolones varies widely. Biotransformation reactions involve predominantly the piperazinyl ring and its substituents. Most of the fluoroquinolone primary metabolites are active against bacteria: however, these metabolites have a shorter elimination half-life than their parent compound. In general, phase I metabolism occurs primarily through hydroxylation and oxidation to oxoquinolones. Ofloxacin is not metabolized whereas pefloxacin is nearly completely metabolized. Nalidixic acid is hydroxylated and then glucuronidated. Enrofloxacin and pefloxacin are Ndealkylated to form ciprofloxacin and norfloxacin, respectively, similarly like fleroxacin.[1,39] Other prominent metabolic pathways include oxidation to oxo-metabolites at the piperazine ring,[40] the major metabolites of ciprofloxacin, enoxacin, and norfloxacin.[1] Quite often, glucuronidation occurs, primarily on the carboxylic acid at position 3. The oxidized metabolites (like many of the N-desmethyl metabolites) have an antibacterial activity[39,41] whereas the glucuronide conjugates are devoid of any activity.[40,42] Other metabolic pathways include sulfoxidation and acetylation.[1]

2. d. EXCRETION

The excretion of fluoroquinolones is primarily via the kidney and secondarily via the liver. High urinary concentrations are achieved due to glomerular filtration and to probenecid-sensitive tubular secretion. Excretion is decreased in individuals suffering from the renal failure and fluoroquinolones should be used in such patients with caution. The percentage of elimination through the bile varies among the species. For example, biliary excretion of the pefloxacin glucuronoconjugate is high in dogs and rats relative to all other species.[43] Nearly a half of the intravenous dose of ciprofloxacin is eliminated in the feces, with slightly more than a half of the dose being eliminated in the urine, after an oral dose more than 90% is excreted in the feces. The glucuronide conjugates of the fluoroquinolones may be excreted in the urine or bile, depending on the fluoroquinolone and the species to which it was administered.[40] There are indications that the enterohepatic circulation of fluoroquinolones may occur, principally through the action of β-glucuronidases in the gastrointestinal tract that may liberate the parent agent or biologically active metabolites. Some studies also suggest that ciprofloxacin may be eliminated by active transepithelial elimination into the bowel lumen.[3,44]

2. d. 1. Renal Excretion:

The renal excretion of fluoroquinolones is also variable although glomerular filtration occurs for the unbound fraction of all fluoroquinolones. Active tubular secretion by the organic anion transport system also occurs to a more variable extent.[45] Probenecid blocks the renal tubular secretion of norfloxacin and ciprofloxacin but because of the other routes of excretion, no large drug accumulation occurs.[3] Renal excretion accounts for 100% of cinoxacin (a non-fluoroquinolone) in 24 h,[45] 60% of ciprofloxacin in 24 h in many species but only 30–40% in dogs[46] and 30–40% of norfloxacin and enrofloxacin in 24 h.

2. e. Biological Half-Life (*t*1/2)

In normal animals, the biological half-life (*t*1/2) of most fluoroquinolones ranges from 3 to 6 hours specifically, the *t*1/2 of flumequine is 6–7 in calves[16] ,3.5–4.5 h for danofloxacin (IM.SC. or IV) in calves,[11,14] 5.4 ±0.9 h for enrofloxacin in calves,[22] 2–4 h for ciprofloxacin in dogs [46] and horses,[15] 3.6 h for norfloxacin (IV) in dogs,[46] and 3 hours for enrofloxacin in laboratory Beagles compared to 5.0 ± 1.0 h in canine clinical patients.

2. e. 1. Elimination Half-Life

The interspecies differences are important: enrofloxacin has an elimination half-life of 7.3, 1.4, 1.2,2.1 and 3.3 hours in the chicken, turkey, calf, dog and horse, respectively.[9] Fleroxacin has an elimination half-life of 1.6 hours in the rabbit, 9.4 hours in the dog[48] and 10.8 in man.[49] Upon multiple dosing, ciprofloxacin, enoxacin and other fluoroquinolones have shown an increase in the *t*1/2 and increased *Vd* from the first dose;[40,50] however, this phenomenon was not observed for norfloxacin in dogs using a dosage regimen of 5 mg/ kg every 12 h for 14 days[2] nor for ciprofloxacin in other studies nor in dogs.[45,46,51]

2. f. AUC:

The area under the concentration time curve normalized to a 1 mg/kg dose decreased as the dose of norfloxacin increased from 5 mg/kg to 20 mg/kg in healthy dogs.[2] The multiple dose phenomenon described by Nix and Schentag[40] and the non-linearity of the AUC with increasing doses in dogs observed by Brown[2] may reflect a decreased absorption of fluoroquinolones at higher doses, or may be the result of complicated enterohepatic recycling that may occur after repeated doses. The pharmacokinetics seems to be independent of the gender[51] although individual fluoroquinolones may vary depending on the metabolic pathways and routes of excretion.

3.PHARMACOKINETIC OF FLUORO QUINOLONES IN DISEASES

3.1. Diarrohea

The oral absorption is not altered in human patients with diarrhea or in those with cutaeneous infections. In the cases of bacteriaemia, serum concentrations were still sufficient for effective treatment of gram-negative infections although differences and increased variability were observed.[3]

3.2. Hepatic Cirrhosis

Human beings with hepatic cirrhosis exhibited reduced metabolism of ciprofloxacin to oxociprofloxacin but not desethylene ciprofloxacin or sulfociprofloxacin, with no change in parent ciprofloxacin pharmacokinetics from that observed in healthy humans.[52]

3.3. Pneumonia

Danofloxacin pharmacokinetics and lung disposition were not altered dramatically in pneumonic calves compared with healthy ones although the volumes of distribution were somewhat larger in pneumonic calves.[53] Pneumonic and macroscopically normal lung homogenates had similarly high danofloxacin concentrations and similar depletion profiles. In pre-ruminant calves, the absorption from IM sites was not altered and elimination was not significantly slowed down by experimental pneumonic pasteurellosis.[54]

4. PHARMACOKINETIC PREDICTORS OF EFFICACY

The fluoroquinolones are classified as bactericidal compounds, and in fact they have shown concentration-dependent bacterial killing within a couple of orders of magnitude of the MBC. Unlike β-lactam antibiotics, the efficacy of fluoroquinolones is related to both the maximum concentration and the time above the MIC.[55]

In vitro pharmacokinetic systems have shown that peak concentrations exceeding 8 times the MIC were related with over 99% reduction in bacterial counts and prevention of bacterial regrowth for 24 h. The study did not separate peak concentrations from the time above the MIC by mimicking different pharmacokinetic profiles, precluding any definitive conclusions being
made regarding the best pharmacokinetic predictor of efficacy.

In Vivo Similar results were observed in an *in vivo* model of *Streptococcus pneumoniae* in mice with ciprofloxacin,[56] indicating that the peak concentration/MIC ratio had to reach a value of 10.6 for optimum protection in that model. Drusano[45] provided some additional insight by administering lomefloxacin to neutropenic rats with *Ps. aeruginosa* sepsis as a single daily dose which produced high peak concentration/MIC ratios (approximately 20/1) or as the same total daily dose fractionated into four daily injections, the latter producing a longer time above the MIC.

The single daily dose produced significantly higher survival than the more fractionated regimen, indicating that peak concentration and/or intensity of exposure is linked more closely with efficacy than the time above the MIC intensity of exposure that has been quantified as the ratio of the area under the concentration-time curve to the MIC (AUC/MIC), otherwise known as the area under the inhibitory concentration curve (AUIC). Forrest[57] noted that, for ciprofloxacin, the probability of clinical and microbiological cures was above 80% when the AUIC was higher than 125; when the AUIC was lower than 125, the probabilities for clinical and microbiological cures were 42% and 26%, respectively. The time to eradication of the infection was similarly related to the AUIC, with 125 and 250 the cut off points for moderate and rapid eradication of the infection.[57] The observation that the AUIC is closely related to efficacy may also be related to

increased coverage of more resistant strains whereas current expectations are that Cmax will be more closely related to reducing resistance. Optimizing one or both of these ratios may ultimately reduce the likelihood that the microbial flora will develop resistance. However, these are to date unproven hypotheses in the veterinary practice.

5. ADVERSE EFFECTS

With few exceptions, the adverse effects of fluoroquinolones are not of severe consequence when compared to the beneficial features they exhibit. The target tissues are the juvenile cartilage, central nervous system, urinary tract and digestive tract. Some skin eruptions were also observed in man.[58] Embryonic losses in female monkeys exposed to very high doses were described.[59] Toxicity of the fluoroquinolones is mild at therapeutic doses, and generally consists of gastrointestinal disturbances such as nausea, vomiting and diarrhea.[60]

At slightly higher doses, CNS signs of dizziness, restlessness, headache, depression, somnolence or insomnia may be seen.[61] High serum concentrations may produce immediate toxic reactions, possibly due to overwhelming histamine release. These immediate reactions are believed to be principally CNS in nature, and consist of convulsions, defecation, urination, and emesis within 2–3 min of rapid IV injection of norfloxacin solution.[2] These signs subsided within several minutes in the affected dogs, and slower infusion (for 2–3 minutes) did not produce such severe clinical signs. Others[62] reported that the epileptogenic activity of fluoroquinolones possibly relates to the γ-aminobutyric acid (GABA)-like structures of the substituents at position 7 of some of the fluoroquinolones, which may allow them to act as GABA-receptor antagonists. Furthermore, enrofloxacin has increased the frequency and intensity of seizures in epileptic dogs.[47]

Other fluoroquinolones need not be likely to produce these CNS effects. Crystalluria can occur in dogs and humans at high doses of norfloxacin although the occurrence is rare in human beings treated with ciprofloxacin and has not been reported with either danofloxacin or enrofloxacin. Non-inflammatory, erosive arthropathies can be observed in growing animals treated with fluoroquinolones. Lesions of the weight-bearing cartilage of juvenile rats and beagle puppies were observed after an experimental exposure to nalidixic acid or fluoroquinolones,[63] causing lameness and pain severe enough to impose humanitarian euthanasia.[63,64] They observed the first histological changes as early as 5 hours after a very high dose of ofloxacin.

It is apparently the reason why the manufacturer of enrofloxacin does not advocate the administration of this product to dogs younger than eight months of age. The articular cartilage forms vesicles after a single very high dose or after several moderately high doses, which can then progressively rupture and produce cartilaginous erosions. This observation is due to an early phase burst in oxidative metabolism in immature (but not mature) chondrocytes that may precipitate cell death.[65]

These erosions are preferentially located at weight bearing joints. For this reason, immature dogs, particularly those of large breeds, should not be treated with fluoroquinolones. In addition, most products labeled for human use state they should not be used in pregnancy although this warning may be precipitated by the lack of data. Furthermore, the use of fluoroquinolones in horses has not been recommended for similar reasons.[66] Although the basis for that recommendation has been made with very little published supporting information.

Photosensitization occurs with all marketed fluoroquinolones, especially pefloxacin, although it is rare for norfloxacin and ciprofloxacin.[60,61] Ocular cataracts have been seen with prolonged use in humans.[60] Enrofloxacin has not been shown to be mutagenic by the Ames test or by the Chinese hamster ovary-HGPRT forward mutation assay and unscheduled DNA synthesis test.[67]

In the pregnant laboratory animals given very high doses of fluoroquinolones, maternotoxicity has occurred and some embryonic deaths have been reported in laboratory animals; no such observations have been made in the target species treated with fluoroquinolones at therapeutic doses. Occasionally, laboratory tests may be altered in patients treated with fluoroquinolones, including increases in hepatocellular enzymes (alanine aminotransferase and aspartate aminotransferase), serum urea nitrogen and crystalluria, and decreases in haematocrit. These alterations may represent real perturbations of the organ systems of the animal or may be laboratory artifacts.

7. DRUG INTERACTIONS

The only possible drug interaction study that has been documented in animals is lack of effect of enrofloxacin on digoxin steady-state concentrations in dogs.[68] The following findings have been documented only in human studies.

- The oral absorption of fluoroquinolones is drastically decreased by antacids containing

magnesium and aluminium.[69] and other agents such as sucralfate also decrease the absorption of fluoroquino lones.

- Ranitidine did not alter the oral absorption of ciprofloxacin[69] but it decreased the oral bioavailability of enoxacin,[70] suggesting that gastric pH affects the oral absorption of some fluoroquinolones, perhaps through alterations in dissolution.
- After repeated administration the fluoroquinolones, including enrofloxacin, have been shown to decrease the hepatic clearance and to increase the elimination halflife of theophylline[71] and caffeine[72] reportedly by decreasing the demethylation of theophylline by the hepatic P450 enzymes, the 4-oxoquinolone metabolite.
- Ciprofloxacin administration over a period of 8–10 days prolonged the half-life of antipyrine from 9.45 to 14.9 h attributed to decreased clearance from 0.85 to 0.52 ml/min/kg in human patients.[73]
- However, others have stated that oral doses of ofloxacin, enoxacin and norfloxacin showed no significant effect on the content of cytochrome P450, cytochrome b5, NADPH- cytochrome P450 reductase, ethoxycoumarin O-deethylase, benzphetamine N-demethylase, or aniline hydroxylase in phenobarbital-responsive systems.[74]
- Furthermore, the clinically important drug-drug interactions between theophylline and ofloxacin were not shown in several instances.[3] Enoxacin decreases the hepatic clearance of the R-enantiomer of warfarin but not the S-enantiomer, and the anticoagulant effects of warfarin are increased by the concurrent administration of ofloxacin.[3]
- The concurrent administration of the non-steroidal anti-inflammatory agent fenbufen with enoxacin has been associated with seizures in human beings although patients given other fluoroquinolones concurrently with non-steroidal anti-inflammatory agents other than fenbufen did not develop seizures.[3] No drug-drug interaction studies have been published for danofloxacin.

8. THERAPEUTIC USES

The fluoroquinolones have shown efficacy against a variety of bacterial diseases and are indicated in the treatment of local and systemic diseases caused by a wide range of gram-positive and gram-negative bacteria, mycoplasma and chlamydia. Due to the wide array of spectrum the use of fluoroquinolones has been proposed in conditions such as deep-seated infections, prostatitis, CNS infections, bone and joint infections, and nosocomial infections resistant to other antibacterial agents.In human beings, the fluoroquinolones are used for the treatment of a variety of severe infections that are either located in tissues inaccessible to other antibacterial agents or caused by bacterial pathogens resistant to other antimicrobial agents. These include (but are not limited to) purulent exacerbations of chronic respiratory infections,[75] complicated and uncomplicated urinary tract infections, *Salmonella* spp. infections, and other infections, such as otitis externa and ophthalmitis, which are resistant to agents.[34]

Norfloxacin and ciprofloxacin have received the most extensive clinical trials. Norfloxacin has mostly been used for the treatment of urinary tract infections. In one study,[24] 408 out of 417 (98%) gram-negative isolates and 58 out of 62 (94%) gram-positive isolates were susceptible to norfloxacin. Norfloxacin is active against pathogens that often require parenteral therapy, and therefore, the entire spectrum of urinary pathogens can be treated with a single oral drug. Therefore many patients who once needed long-term hospitalization for parenteral therapy of difficult urinary tract infections can now be discharged earlier and treated with these oral fluoroquinolones. In animals, enrofloxacin, marbofloxacin, norfloxacin, norfloxacin nicotinate, difloxacin and danofloxacin are approved for use in animals. Enrofloxacin is used in dogs for complicated and uncomplicated urinary tract infections (e.g. doses up to 11 mg/kg every 12 h) and for a variety of other infections, such as mycobacterial infections;[76] prostatitis[27] and osteomyelitis[29] caused by susceptible bacteria. Higher recommended doses were calculated on the basis of an assumption that the concentrations of quinolones must exceed the MIC90 for the entire dosing interval,[77] this was later shown to be an incorrect assumption.[45,57] In dogs, a therapeutically equivalent dose of ciprofloxacin has been suggested to be 4–5 times the dose (on a mg/kg basis) of enrofloxacin which is 2.5 mg/kg twice a day; however, the scientific justification for this recommendation is questionable. Studies have been published indicating that enrofloxacin was effective in the treatment of acute salmonella infections in calves, and produced negative fecal cultures in salmonella carrier calves 5 and 12 days after treatment.[66] In swine, enrofloxacin is reported to eliminate the carrier state for *Salmonella* with an oral dose of 200 ppm in the feed for 10 days.[66] Clinical field studies were conducted with enrofloxacin and difloxacin in swine colibacillosis,

poultry colibacillosis, and other poultry bacterial and mycobacterial diseases, with therapeutic success.[66]

Danofloxacin has undergone extensive field efficacy studies in bovine respiratory diseases, indicating that a dose of 1.25 mg/kg every day for 3–5 days is effective under a variety of management systems.[76] Other efficacy studies with danofloxacin brought about promising results for poultry mycoplasmosis.[79] Parenteral enrofloxacin and oxytetracycline were both effective, and in terms of clinical efficacy, indistinguishable from each other, against *Actinobacillus pleuropneumoniae* in swine as determined by rectal temperature and lung weight.[80] Efficacy rates of enrofloxacin for treating pneumonia and diarrhea in cattle and swine are from 76% to 100%. Those of danofloxacin for cattle and swine pneumonia from 83% to 86%.[11,14] Enrofloxacin decreases mortality rates in poultry flocks with respiratory infections,[81] similarly like difloxacin, norfloxacin and danofloxacin. Danofloxacin may cause temporal sedentariness, and orbifloxacin may cause temporal walk failure.

The oral norfloxacin therapy of dogs suffering from acute enteritis removed the disease in 100%, and in another study the urinary tract infection.[82] The pharmaceutical formulations of new veterinary quinolones are solutions and powders. Enrofloxacin, danofloxacin, difloxacin and norfloxacin nicotinate are available as solutions for injection in cattle, and only enrofloxacin is available as a solution for oral use. For swine, all 4 drugs have been provided as solutions for injection. Danofloxacin, norfloxacin and norfloxacin nicotinate have been formulated as powder for feed and drinking water, and difloxacin, enrofloxacin, norfloxacin and danofloxacin as solutions for drinking water for swine. For poultry, danofloxacin, norfloxacin and norfloxacin nicotinate have been formulated as powder for adding to feed and drinking water, and difloxacin, enrofloxacin, norfloxacin and danofloxacin as solutions for adding to drinking water.

All drugs are administered for a maximum of 3 or 5 days. Injection sites should be changed when a large volume of drug is used, and the quinolones may cause indurations at the site of injection. Enrofloxacin should be used with caution because of its strong alkalinity.

9. INFLUENCE OF FLUOROQUINOLONES ON THE ENVIRONMENT

Further concern regarding the use of new quinolones in the veterinary field is a possible detrimental effect on the environment caused by the disposal of used drugs and from animal excreta. The first point to be considered is that new veterinary quinolones discarded into the environment are usually firmly adsorbed to soil and rarely pollute water. Furthermore, quinolones rapidly decompose when exposed to light. Finally, quinolones have virtually no effect on soil organisms such as protozoa and fungi or on insects and plants. It is therefore unlikely that the controlled use of veterinary quinolones will give rise to unfavorable effects on the environment. Although there are no definite data implicating the veterinary use of anti-infectives in the development of drug resistance in human pathogens or in worsening environmental pollution, an urgent need exists for more appropriate selection and use of antimicrobial drugs. To this end, there are 3 important restrictions on the use of new veterinary quinolones.

- First, new veterinary quinolones are indicated only when the first-choice drugs are ineffective.
- Second, they are administered only by, or under the direction of, veterinarians.
- Third, professional and public education should be improved in the area of infectious diseases and antimicrobials to reduce inappropriate use of these compounds.

The curriculum of health professional (medical, dental, nursing, and veterinary) schools and postgraduate educational programs should be updated in the areas of sterilization, disinfection, hazards of inappropriate antimicrobial drug use, appropriate diagnosis and treatment of infectious diseases, and antimicrobial resistance. These efforts should result in a reduction of the spread of infectious agents and more prudent use of antimicrobials.

Better guidelines should be established and enforced to reduce the spread of infectious agents and antimicrobial resistance in the hospital environment, nursing homes, day care facilities, and food production industries. Educational materials should be developed and widely distributed to patients and food producers. The need for partnerships in improving antimicrobial use for cost effective treatment of infections and to preserve the effectiveness of antimicrobial drugs for the future should be emphasized.

10. CONCLUSION

Fluoroquinolones are one of the most useful classes of antimicrobial agents used in human and animal medicine today, both because of their spectrum and their physicochemical properties. As such, their popularity in clinical situations is increasing. Recently, however, concerns have been aroused over the possible emergence of quinolone-resistant strains

and the effects on the environment if such drugs are overused. At present it appears that physicians and veterinarians can prolong their usefulness for many years if they use appropriate clinical judgment and proper dosing principles when they prescribe and administer these drugs to patients. If used in a well-controlled manner, quinolones will greatly contribute to stock farming management, without adversely influencing human chemotherapy.

REFERENCES

1. Lode H., Höffken G., Prinzig C., Glatzel P., Wiley R., Olschewski P., Sievers B., Reimnitz D., Borner K., Koeppe P. (1987): Comparative pharmacokinetics of new quinolones. Drugs, 34 (Suppl. 1), 21–25.

2. Brown S.A., Cooper J., Gauze J.J., Greco D.S., Weise D.W., Buck J.M. (1990): Pharmacokinetics of norfloxacin in dogs after a single intravenous and single and multiple oral administrations of the drug. Am. J. Vet. Res., 51, 1065–1070.

3. Wolfson J.S., Hooper D.C. (1991): Pharmacokinetics of quinolones: newer aspects. Eur. J. Clin. Microbiol. Infect. Dis., 10, 267–274.

4. Gyrd-Hansen N., Nielsen P. (1994): The influence of feed on the oral bioavailability of enrofloxacin, oxytetracycline, penicillin V and spiramycin in pigs. In: Proceedings of the Sixth Congress of the European Associassion for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 242–243.

5. Frost R.W., Carlson J.D., Dietz A.J.,Jr., Heyd A., Lettieri J.T. (1989a): Ciprofloxacin pharmacokinetics after a standard or high-fat/high-calcium breakfast. J. Clin. Pharmacol., 29,953–955.

6. Chen Z., Fung K.F., Fang B., Song Y. (1994): Antimicrobial and pharmacokinetic studies of fluoroquinolones in chickens. In: Proceedings of the Sixth Congress of the EuropeanAssociassion for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 209–210.

7. Lavy E., Ziv G., Glickman A. (1994): Pharmacokinetics of norfloxacin in the donkey (Equus asinus). In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 52–53.

8. Parpia S., Nix D., Hejmanowski H., Wilton J., Schentag J. (1989): Sucralfate reduces the gastrointetinal absorption of norfloxacin. Antimicrob. Agents Chemother., 33, 99– 102.

9. VanCutsem P.M., Babish J.G., Schwark W.S. (1990): The fluoroquinolone antimicrobials: Structure, antimicrobial activity, pharmacokinetics, clinical use in domestic animals and toxicity. Cornell Vet., 80, 173–186.

10. Gasser T., Graversen P., Madsen P. (1987): Treatment of complicated urinary tract infections with ciprofloxacin.Am. J. Med., 82 (Suppl. 4A), 278–281.

11. Giles C.J., Grimshaw W.T.R., Shanks D.J. et al. (1991): The efficacy of danofloxacin in the therapy of acute bacterial pneumonia in housed beef cattle. Vet. Rec., 128, 296–300.

12. Soback S., Gips M., Bialer M. (1994a): Norfloxacin nicotinate pharmacokinetics in unweaned and weaned calves. In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology, Edinburgh, Scotland. 63–64.

13. Pyörälä S., Panu S., Kaartinen L. (1994): Single-dose pharmacokinetics of enrofloxacin in horses. In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology, Edinburgh, Scotland. 45–46.

14. Grimshaw W.T.R., Magonigle R.A., Giles C.J., Tanner A.C., Risk J.E., Lynch M.J., Rice J.R. (1990a): The pharmacokinetics of danofloxacin in cattle. In: XVI World Buiatrics Congress, Salvador, Bahia, Brazil.

15. Dowling P.M., Wilson R.C., Tyler J.W., Duran S.H. (1995): Pharmacokinetics of ciprofloxacin in ponies. J. Vet. Pharmacol. Therap., 18, 7–12.

16. Mevius D.J., Breukink H.J., Guelen P.J.M., Jansen T., De Gréve B. (1990): Pharmacokinetics, metabolism and renal clearance of flumequine in veal calves. J. Vet. Pharmacol. Therap., 13, 159–169.

17. Neu H.C. (1988): Quinolones: A new class of antimicrobial agents with wide potential uses. Med. Clin. North Am., 72, 623–636.

18. Walker R.D., Stein G.E., Budsberg S.C., Rosser E.J.Jr., MacDonald K.H. (1989): Serum and tissue fluid norfloxacin concentrations after oral administration of the drug to healthy dogs. Am. J. Vet. Res., 50, 154–157.

19. Walker R.D., Stein G.E., Hauptman J.G., MacDonald K.H., Budsberg S.C., Rosser E.J.Jr. (1990): Serum and tissue cage fluid concentrations of ciprofloxacin after oral administration of the drug to healthy dogs. Am. J. Vet. Res.,51, 896–900.

20. Abadía A.R., Aramayona J.J., Fraile L., Martinez C., Garcia M.A., Bregante M.A. (1994a): Pharmacokinetics of enrofloxacin and ciprofloxacin during ontogeny in the rabbit. In: Proceedings of the Sixth Congress of the European Association for

Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 231.
21. Darouiche R., Perkins B., Musher D., Hamill R., Tsai S. (1990): Levels of rifampin and ciprofloxacin in nasal secretions: correlation with MIC90 and eradication of nasopharyngeal carriage of bacteria. J. Inf. Dis., 162, 1124–1127.
22. Sheer M. (1987): Concentrations of active ingredient in the serum and in tissues after oral and parenteral administration of Baytril. Vet. Med. Rev., 2, 104–118.
23. Apley M.D., Upson D.W. (1993a): Regional danafloxacin lung tissue concentrationsand their relationship to regional pulmonary blood flow in consolidated and nonconsolidated bovine lung. Am. J. Vet. Res., 54, 944–951.
24. Friis C. (1994): Penetration of danofloxacin into respiratory tract tissues and secretions in pigs. In: Proceedings of the Sixth Congress of the European Associassion for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 208–209.
25. Malmborg A.S., Rannikko S. (1988): Enoxacin distribution in human tissues after multiple oral administration. J. Antimicrob. Chemother., 21 (Suppl. B), 57–60.
26. Dalhoff A., Weidner W. (1984): Diffusion of ciprofloxacin into prostatic fluid. Eur. J. Clin. Microbiol., 3, 360–362.
27. Dorfman M., Barsanti J., Budsberg S. (1995): Enrofloxacin concentrations in dogs with the normal prostate and dogs with chronic bacterial prostatitis. Am. J. Vet. Res., 56, 386–390.
28. Bates S.A., Elder M.G. (1988): An evaluation of pelvic tissue concentrations after oral administration of enoxacin. J.Antimicrob. Chemother., 21 (Suppl. B), 79–85.
29. Duval J.M., Budsberg S.C. (1995): Cortical bone concentrations of enrofloxacin in dogs. Am. J. Vet. Res., 56, 188–192.
30.Giamarellou H., Kolokythas E., Petrikkos G., Gazis J., Aravantino D., Sfikakis P. (1989): Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am. J. Med., 87 (Suppl. 5A), 49–51
31. Aramayona J.J., Garcia M.A., Fraile L.J., Abadfa A.R., Bregante M.A. (1994): Placental transfer of enrofloxacin and ciprofloxacin in rabbits. Am. J. Vet. Res., 55, 1313–1318.
32. Soback S., Gips M., Bialer M., Bor A. (1994b): Effect of lactation on single-dose pharmacokinetics of norfloxacin nicotinate in ewes. Antimicrob. Agents Chemother., 38, 2336–2339.
33. Bregante M.A., Abadía A.R., Mora J., Aramayona J.J., Garcia M.A., Fraile L. (1994): Milk transfer of enrofloxacin and ciprofloxacin in the rabbit. In: Proceedings of the Sixth Congress of the European Associassion for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 231–232.
34. Barza M. (1991): Use of quinolones for treatment of ear and eye infections. Eur. J. Clin. Microbiol. Infect. Dis., 10,296–303.
35. Dobbs B.R., Gazeley L.R., Stewart I.A., Edwards I.R. (1988): Pharmacokinetics and sputum concentrations of enoxacin after twice daily oral dosing for seven days. J. Antimicrob. Chemother., 21 (Suppl. B), 61–66.
36. Sorgel F., Jaehde U., Naber K., Stephan U.(1989): Pharmacokinetic disposition of fluoroquinolones in human body fluids and tissues.Clin.Pharmacokin.,16 (Suppl. 1),5–24.
37. Carlier M.B., Scorneaux B., Zenebergh A., Desnottes J.F.,Tulkens P.M. (1990): Cellular uptake, localization and activity of fluoroquinolones in uninfected and infected macrophages. J. Antimicrob. Chemother., 26 (Suppl. B), 27–39.
38. Zweerink M.M., Edison A.M. (1988): The uptake of 3H-norfloxacin by human polymorphonuclear leukocytes. J. Antimicrob. Chemother., 21, 266–267.
39. Küng K., Riond J.L., Wolffram S., Wanner M. (1993): Comparison of an HPLC and bioassay method to determine antimicrobial concentrations after intravenous and oral administration of enrofloxacin in four dogs. Res. Vet. Sci., 54, 247–248.
40. Nix D.E., Schentag J.J. (1988): The quinolones: an overview and comparative appraisal of their pharmacokinetics and pharmacodynamics. J. Clin. Pharmacol., 28, 169–178
41. Prescott J.F., Yielding K.M. (1990): In vitro susceptibility of selected veterinary bacterial pathogens to ciprofloxacin, enrofloxacin and norfloxacin. Can. J. Vet. Res., 54, 195–197.
42. Venezia R.A., Prymas L.A., Shayegani A., Yocum D.M. (1989): In vitro activities of amifloxacin and two of its metabolites. Antimicrob. Agents. Chemother., 33, 762–766.
43. Montay G., Goueffon Y., Roquet F. (1984): Absorption, distribution,metabolic fate and elimination of pefloxacin mesylate in mice, rats, dogs, monkeys and humans. Antimicrob.Agents Chemother., 25, 463–472.
44. Ramon J., Dautrey S., Farinoti R., Carbón C., Rubenstein E. (1994): Intestinal elimination of ciprofloxacin in rabbits. Antimicrob. Agents Chemother., 38, 757–760.

45. Drusano G.L., Plaisance K.I., Forrest A., Standiford H.C. (1986): Dose ranging study and constant infusion evaluation of ciprofloxacin. Antimicrob. Agents Chemother., 30, 440–443.
46. Abadía A.R., Aramayona J.J., Muñoz M.J., Pla Delfina J.M.,Saez M.P., Bregante M.A. (1994b): Disposition of ciprofloxacin following intravenous administration in dogs. J. Vet. Pharmacol. Therap., 17, 384–388.
47. Sorgel F., Seelman R., Naber K., Metz R., Muth P. (1988): Metabolism of fleroxacin in man. J. Antimicrob. Agents Chemother., 22 (Suppl. D), 169–178.
48. Takayama S., Watanabe T., Akiyama Y. et al. (1986): Reproductive toxicity of ofloxacin. Arzneimittelforschung, 36, 1244–1248.
49. Chang T., Black A., Dunkey A., Wolf R., Sedman A., Latts J., Welling P.G. (1988): Pharmacokinetics of intravenous and oral enoxacin in healhy volunteers. J. Antimicrob.Chemother., 21 (Suppl. B.), 49–56.
50. Höffler D., Dalhoff A., Gau W., Beerman D., Michael A. (1984): Dose- and sex independent disposition of ciprofloxacin. Eur. J. Clin. Microbiol., 3, 363–366.
51. Frost R.W., Lettieri J.T., Krol G., Shamblen E.C., LasseterK.C. (1989b): The effects of cirrhosis on the steady-state pharmacokinetics of oral ciprofloxacin. Clin. Pharmacol. Therap., 45, 608–616.
52. Apley M.D., Upson D.W. (1993b): Lung tissue concentrations and plasma pharmacokinetics of danofloxacin in calves with acute pneumonia. Am. J. Vet. Res., 54, 937–943.
53. Thomas V., Deleforge J., Bolsramé B., Espinasse J. (1994b): Pharmacokinetics of marboflaxicin in healthy and sick pre-ruminant calves. In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology, Edinburgh, Scotland. 61.
54. Blaser J., Stone B.B., Groner M.C., Zinner S.H. (1987): Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. Antimicrob. Agents Chemother., 31, 1054–1060.
55. Sullivan M.C., Cooper B.W., Nightingale C.H., Quintiliani R., Lawlor M.T. (1993): Evaluation of the efficacy of cipro-floxacin against Streptococcus pneumoniae by using a mouse protection model. Antimicrob. Agents Chemother., 37, 234–239.
56. Forrest A., Nix D.E., Ballow C.H., Goss T.F., Birmingham M.C., Schentag J.J. (1993): Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob. Agents Chemother., 37, 1073–1081.
57.Ball P. (1986): Ciprofloxacin: an overview of adverse experiments.J. Antimicrob.Chemother., 18 (suppl. D), 187–193.
58. Neer T.M. (1988): Clinical pharmacologic features of fluoroquinolone antimicrobial drugs. J. Am. Vet. Med. Assoc.,193, 577–580.
59. Norrby S.R. (1991): Side effects of quinolones: Comparisons between quinolones and other antibiotics. Eur. J. Clin. Microbiol. Infect. Dis., 10, 378–383
60. Neu H.C. (1988): Quinolones: A new class of antimicrobial agents with wide potential uses. Med. Clin. North Am., 72, 623–636.
61. Akahane K., Segiguchi M., Une T., Osoda Y. (1989): Structure-epileptogenicity relationship of quinolones with special reference their interaction with γ-amino-butyric acid receptor sites. Antimicrob. Agents Chemother., 33, 1704–1708.
62. Kato M., Onedara T. (1988): Effect of ofloxacin on the uptake of (3H) thymidine by articular cartilage cells in rat. Toxicol. Lett., 44, 131–142.
63. Mc Queen C., Williams G. (1987): Effects of quinolone antibiotics in tests for genotoxicity. Am. J. Med., 82 (Suppl.4A), 94–96.
64.Hayem G., Petit P.X., LeVacher M., Gaudin C., Kahr M.F.,Pocidalo J.J. (1994): Cytofluorometric analysis of chondrotoxicity of fluoroquinolone antimicrobial agents. Antimicrob. Agents Chemother., 38, 243–247.
65. Berg J. (1988): Clinical indications for enrofloxacin in domestic animals and poultry. In: Quinolones: A new class of antimicrobial agents for use in veterinary medicine. In:Proc. West Vet. Conf, Las Vegas, Nevada: Mobay Corporation. Bhaumik A. (1997): Effect of norfloxacin treatment in acute enteritis in dogs. Indian Vet. J., 74, 246–247.
66. Althreuther P. (1987): Data on chemistry and toxicology of Baytril. Vet. Med. Rev., 2, 87–89.
67. Novotny M.J., Shaw D.H. (1991): Effect of enrofloxacin on digoxin clearance and steady-state serum concentrations in dogs. Can. J. Vet. Res., 55, 113–116.
68. Nix D.E., Watson W.A., Lener M.E., Frost R..W., Krol G.,Goldstein H., Lettieri J., Schentag J.J. (1989): Effects of aluminium and magnesium antacids and ranitidine on the absorption of ciprofloxacin. Clin. Pharmacol. Therap., 46, 700–705.
69. Grasela T.J.Jr., Schentag J.J., Sedman A.J.,

Wilton J.H., Thomas D.J., Schultz R.W., Lebsack M.E., Kinkel A.W. (1989): Inhibition of enoxacin absorption by antacids or ranitidine. Antimicrob. Agents Chemother., 33, 615–617.

70. Rybak M.J., Bowles S.K., Chandrasekar P.H., Edwards D.J. (1987): Increased theophylline concentration secondary to ciprofloxacin. Drug Intellig. Clin. Pharm., 21, 879–881.

71. Harder S., Staib A.H., Beer C., Papenburg A., Stille W., Shah P.M. (1988): 4-Quinolones inhibit biotransformation of caffeine. Eur. J. Clin. Pharmacol., 35, 651–656.

72. Ludwig E., Székely É., Csiba A., Graber H. (1988): The effect of ciprofloxacin on antipyrine metabolism. J. Antimicrob. Chemother., 22, 61–67.

73. Okazaki O., Kurata T., Tachizawa H. (1988): Effect of new quinolones on drugmetabolizing enzyme system of rat hepatic microsomes. Chemotherapy, 34, 149–154.

74. Maesen F.P.V., Davies B.I., Geraeds W.H., Baur C. (1987): The use of quinolones in respiratory tract infections. Drugs, 34 (Suppl 1), 74–79.

75. Studdert V.P., Hughes K.L. (1992): Treatment of opportunistic mycobacterial infections with enrofloxacin in cats. J. Am. Vet. Med. Assoc., 201, 1388–1390.

76.Walker R.D., Stein G.E., Budsberg S.C., Rosser E.J.Jr., MacDonald K.H. (1989): Serum and tissue fluid norfloxacin concentrations after oral administration of the drug to healthy dogs. Am. J. Vet. Res., 50, 154–157.

77. Jordan F.T.W., Horrocks B.K., Jones S.K., Cooper A.C., Giles C.J. (1993): A comparison of the efficacy of danofloxacin and tylosin in the control of Mycoplasma gallisepticum infection in broiler chicks. J. Vet. Pharmacol. Toxicol., 16, 79–86.78. Pijpers A., Vernooy J.C.M., Cruijsen A.L.M., Van Leengoed L.A.M.G., Koeman J., Hessels A.H., Vandenhoek J., Verheijden J.H.M. (1994): Efficacy of parenteral treatment with oxytetracycline and enrofloxacin against Actinobacillus pleuropneumoniae in swine. In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 93.

79. Hinz K.H., Rottmann S. (1990): Studies in vivo on the efficacy of enrofloxacin against Mycoplasma gallisepticum. Avian Pathol., 19, 511–522.

80. Patil V.K., Keskar D.V., Jagadish S., Bhalerao D.P., Sharma L.K. (1995): Clinicopathology of urinary tract infections in dogs. Indian Vet. J., 72, 374–377.