Enrofloxacin

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Enrofloxacin is a member of the family of 6-fluoro-7-piperazinyl-4-quinolones.[1] This antibiotic is highly lipophilic, and the addition of a carboxic acid and a tertiary amine contributes to the amphoteric properties of enrofloxacin.[2] Enrofloxacin is bactericidal and has excellent activity against both Gram-positive and Gram-negative pathogens.[1,3] This antibiotic has also been used to control certain intracellular pathogens. Modification of the 4-quinolone ring has enhanced the antimicrobial activity of this compound. Oral bioavailability of enrofloxacin is excellent in monogastric mammals and preruminant calves, with up to 80% of the ingested dose being absorbed into systemic circulation.[2] Oral absorption of enrofloxacin is rapid, with peak serum concentrations achieved 1 to 2 hours after administration.[4] Enrofloxacin does not readily complex with plasma proteins, which enables metabolites to readily cross cell membranes. In humans, approximately 10% to 40% of the fluoroquinolones are bound to plasma proteins.[2] As a group, the fluoroquinolones are widely distributed throughout the body, including the kidneys, liver, bile, prostate, uterus and fallopian tubes, bone, and inflammatory tissues.[5] Excretion of the fluoroquinolones is primarily through the kidneys, with secondary excretion through the liver.[2,5]

Enrofloxacin alters the action of bacterial DNA gyrase, a type II topoisomerase.[2] This enzyme is involved in unwinding, cutting, and resealing DNA. There are two subunits to DNA gyrase: subunit A and subunit B. Enrofloxacin acts on the nalA locus of subunit A. Inhibition of the gyrase leads to rapid cell death in bacteria. The concentration of fluoroquinolones required to alter the DNA of mammalian cells is two orders of magnitude higher than the concentration against bacterial DNA.[6,7]

The metabolism of enrofloxacin varies between species. Although enrofloxacin is an active antibiotic, biotransformation to ciprofloxacin may occur in some species. Biotransformation of enrofloxacin includes N-dealkylation, glucuronide conjugation to the nitrogen in the para position of the piperazinyl ring, oxidation in the ortho position to substituted amine, and the opening of the piperazinyl ring.[2]

The elimination half-life of enrofloxacin also varies between species. Chickens have a prolonged half-life (7.3 hours) in comparison with mammals, including canines (2.1 hours), calves (1.2 hours), and horses (3.3 hours).[2] The elimination half-life of enrofloxacin is much longer in ectotherms, such as reptiles.

Enrofloxacin has a biphasic concentration-response curve.[8] In the first phase, the proportion of bacteria killed increases as the concentration of enrofloxacin is increased. In the second phase, bacteria are killed at a lower rate as the concentration of enrofloxacin is increased.

Selection for resistance to enrofloxacin occurs from chromosomal mutations, the creation of gyrase modifications, or alterations in permeability.[9,10] No plasmid resistance has been demonstrated. Mutants may develop resistance to other fluoroquinolones and antimicrobials, including cephalosporins, chloramphenicol, and tetracyclines.[11,12]

The adverse effects associated with fluoroquinolones are primarily associated with abnormal development of immature cartilage, the urinary and gastrointestinal tracts, and the central nervous system. Arthropathies have been reported in immature rats, beagles, guinea pigs, and foals.[13-16] The cartilaginous surfaces of the femur, humerus, and tibial tarsal bone are the primary sites where fluoroquinolone-induced arthropathies occurred in beagle pups.[14] The most common histologic findings in quinolone-

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induced arthropathies are erosions of the articular cartilage.[13-15] Histologic lesions may be detected 2 days after treatment. Fluoroquinolones can achieve high concentrations in the urine, because the kidneys are the primary route of excretion for these drugs. Because fluoroquinolones have a low solubility in water, they can crystallizes in acidic urine.[2] Crystalluria could be a problem in carnivorous animals fed a high-protein diet. The adverse gastrointestinal effects associated with fluoroquinolones include nausea, vomiting, and abdominal cramping.[17] The descriptions of adverse effects associated with the central nervous system have been documented in human patients.[18] Changes in behavior, including psychosis, headaches, hallucinations, and seizures have been reported after treatment with 250 to 500 mg ciprofloxacin.

Fluoroquinolones are highly effective bactericidal compounds with relatively low minimum inhibitory concentrations (MIC). Clinical *Salmonella* Arizonae isolates evaluated at the University of California showed MIC values in 90% of the isolates, ranging between 0.128 μg/mL and 1.0 μg/mL.[2] Berg[16] reported that MICs demonstrated by 96% of *Salmonella* isolates from clinical samples were less than 0.125 μg/mL. *Salmonella* isolates from urinary tract infections also yielded low MIC levels for ciprofloxacin (0.06 μg/mL).[2] The systemic distributions of enrofloxacin and ciprofloxacin, in combination with the low MIC levels required to eradicate *Salmonella* and the levels of enrofloxacin achieved in the serum and tissues, suggest that these compounds would be beneficial for treating a prospective patient with a *Salmonella* infection.

Enrofloxacin has been evaluated as a method to eliminate *Salmonella* infections in cattle and poultry. Enrofloxacin administered to cattle at 5 mg/kg/d for 10 days eliminated *Salmonella* in more than half the subjects.[19] The *Salmonella* isolates from the cattle that remained infected after treatment were still sensitive to enrofloxacin. Calves experimentally infected with *Salmonella* Typhimurium were cleared of the infection after being treated with enrofloxacin at a dose of 5 mg/kg/d for 6 days.[20] Enrofloxacin administered to poultry in drinking water at 50 ppm for 5 to 10 days was effective against experimental *Salmonella* Typhimurium infection in broilers and turkeys.[20] Broilers reinfected with *Salmonella* Typhimurium 14 days after discontinuing treatment of 100 to 200 ppm enrofloxacin were reinfected at a similar rate.[20] Enrofloxacin, when administered under controlled conditions, was effective at eliminating *Salmonella* from domestic livestock and poultry.

Enrofloxacin has been used to treat bacterial infections in reptiles, because it is active against most of the Gram-positive and Gram-negative bacterial pathogens isolated from these species. Pharmacokinetic studies to detect the rates of absorption, metabolism, distribution, and excretion of enrofloxacin in reptiles are limited. Enrofloxacin administered either intramuscularly (IM) or *per os* (PO) at a dose of 10 mg/kg IM or PO at 5 mg/kg in Savannah monitors (*Varanus exanthematicus*) resulted in minimal conversion to ciprofloxacin.[21] The terminal elimination half-life was 40 hours for the IM and PO routes at 5 mg/kg, and 36 and 24 hours for IM and PO routes at 10 mg/kg. The peak plasma concentration for the IM and oral routes at 10 mg/kg were 10.5 μg/mL and 3.6 μg/mL, respectively. The peak serum concentrations recorded in the monitor lizard would be adequate to treat bacteria with high MIC values.

Enrofloxacin administered IM at 5 mg/kg to Burmese pythons (*Python molurus bivittatus*) resulted in a significant conversion to ciprofloxacin.[22] The peak serum concentration of enrofloxacin in the python was 1.66 μg/mL. The mean terminal half-life was 6.37 hours. The 5-mg/kg dose would be effective against bacteria with MIC values of 0.2 μg/mL.

In American alligators (*Alligator mississipiensis*), 5 mg/kg intravenously followed a 2-compartment model.[23] The extrapolated mean of enrofloxacin in alligators was 4.19 μg/mL, and the plasma drug levels remained above 1.0 μg/mL for approximately 36 hours. The levels measured in these animals were higher than the MIC (0.5 μg/mL) required for susceptible organisms, with the elimination half-life being slightly over 21 hours. An intravenous dose of 5 mg/kg every 36 hours should be appropriate for treating susceptible bacterial infections in American alligators. Oral dosing at 5 mg/kg was not found to produce effective MIC levels. Ciprofloxacin was detected in alligators after both oral and intravenous dosing, but the levels were below MIC for most bacteria.

In Indian star tortoises (*Geochelone elegans*), 5 mg/kg IM enrofloxacin produces mean maximal plasma concentrations of 3.59 μg/mL, with a half-life of 5.1 hours.[24] After a single IM injection, enrofloxacin could not be detected after 72 hours. The results of the study suggested that a dose of 5 mg/kg IM every 12 hours would be required to maintain MIC levels appropriate for susceptible infections. Ciprofloxacin is metabolized from enrofloxacin in Indian star tortoises.

The majority of the pharmacokinetic studies evaluating enrofloxacin in avian species are limited to

poultry, with only a few studies evaluating the efficacy of this drug in nonpoultry species. In African gray parrots (*Psittacus erithacus*), enrofloxacin can be administered via the drinking water. When African gray parrots are provided a range of doses in their drinking water (0.09-3.0 mg/mL), they tend to not consume as much water containing the higher doses.[25] From the study, the authors concluded that 0.19 to 0.75 mg/mL enrofloxacin in drinking water should provide appropriate MIC levels for susceptible infections.[25] African gray parrots do synthesize ciprofloxacin from the metabolism of enrofloxacin.[25]

The pharmacokinetics of enrofloxacin have been evaluated in two different species of raptors: red-tailed hawks (*Buteo jamaicensis*) and great-horned owls (*Bubo virginianus*).[26] In a crossover study, each bird (hawk and owl) was given enrofloxacin (15 mg/kg) orally, IM, or intravenously. Peak plasma levels were achieved between 4 to 8 hours for orally administered enrofloxacin and 0.5 to 2 hours for IM dosing. Intravenous dosing in the great-horned owls was associated with side effects, including bradycardia, weakness, and peripheral vasoconstriction. Although these signs were not observed in the hawks, special precautions should be taken, such as administering antiinflammatory agents, if enrofloxacin is administered intravenously in raptors. Plasma concentrations of enrofloxacin remained above acceptable MIC levels (1 μg/mL) for at least 15 hours for all three different dosing regimens. The authors concluded that enrofloxacin could be given with food (for example, prey) or IM, and that these dosing regimens would provide appropriate MIC levels for susceptible bacteria.

Enrofloxacin is used to manage many different bacterial diseases in lagomorphs, from *Pasteurella multocida* to *Mycoplasma* spp. Oral dosing with enrofloxacin does not appear to lead to the development of antibiotic dysbiosis, which is common with penicillins and cephalosporins. Enrofloxacin follows a 2-compartment model for oral and intravenous dosing, whereas it follows a 1-compartment model for subcutaneous (SC) dosing.[27] The elimination half-lives for enrofloxacin in rabbits are shortest for SC dosing (1.7 hours), followed by oral (2.41 hours), and intravenous dosing (2.5 hours). Maximal serum concentrations were achieved much quicker after SC dosing (0.9 hours) than oral dosing (2.3 hours). The bioavailability of enrofloxacin after SC dosing was higher (77%) than with oral dosing (61%). Enrofloxacin is well distributed through the tissues, including milk, and should be used cautiously in lactating rabbits.[27,28] Dosing rabbits with 5 mg/kg enrofloxacin PO or IM will achieve MIC levels appropriate for most bacterial pathogens.

To date, there have not been any pharmacokinetic studies for enrofloxacin performed on rodents or ferrets. A popular exotic animal formulary suggests a range of doses from 5 to 20 mg/kg PO, SC, or IM for these nontraditional mammals.[29] Although it is empirical, the author administers doses to rodents and ferrets at 5 to 10 mg/kg IM once, followed by oral administration. Higher doses are reserved for younger animals and smaller, more metabolically active patients.

Enrofloxacin remains an important antibiotic for treating bacterial infections. Veterinarians using this drug should reserve it for cases when a powerful bactericidal compound is required. Caution should be followed when administering this antibiotic to juvenile birds, reptiles, and mammals, where there is a paucity of information regarding the potential negative effects on the developing articular surfaces. Future research is necessary to determine the pharmacokinetics of the drug in species where data are lacking, and to ascertain the potential for side effects.

References

1. Hooper D, Wolfson J: The fluoroquinolones: structures, mechanisms of action and resistance and spectra of activity in vitro. Antimicrob Agents Chemotherap 28:581-586, 1985
2. Vancutsem PM, Babish JG, Schwark WS: The fluoroquinolone antimicrobials: structure, antimicrobial activity, pharmacokinetics, clinical use in domestic animals and toxicity. Cornell Vet 80:173-186, 1990
3. Scheer M: Studies on the antibacterial activity of Baytril®. Vet Med Review 2:90-98, 1987
4. Parpia S, Nix D, Hejmanowski H, et al: Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob Agents Chemotherap 33:99-102, 1989
5. Montay G, Goueffon Y, Roquet F: Absorption, distribution, metabolic fate, and elimination of pefloxacin mesylate in mice, rats, dogs, monkeys, and humans. Antimicrob Agents Chemotherp 25:463-472, 1984
6. Oomori Y, Yasue T, Aoyama H, et al: Effects of fleroxacin on HeLa cell functions and topoisomerase II. J Antimicrob Chemotherap 22:91-97, 1988 (suppl D)
7. Hussy P, Maass G, Tummler B, et al: Effect of 4-quinolones and novobiocin on calf thymus DNA polymerase alpha primase complex, topoisomerases I and II, and growth of mammalian lymphoblasts. Antimicrob Agents Chemotherap 29:1073-1078, 1986
8. Diver JM, Wise R: Morphological and biochemical changes in *Escherichia coli* after exposure to ciprofloxacin. J Antimicrob Chemotherap 18:31-41, 1986 (suppl D)
9. Easom CSF, Crane JP: Uptake of ciprofloxacin by

human neutrophils. J Antimicrob Chemotherap 23:284-288, 1983
10. Piddock L, Wise R: Mechanisms of resistance to quinolones and clinical perspectives. J Antimicrob Therap 23:475-481, 1989
11. Neu HC: Bacterial resistance to fluoroquinolones. Rev Infect Dis 10:57-63, 1988 (suppl D)
12. Bellido F, Pechere JC: Laboratory survey of fluoroquinolone activity. Rev Infect Dis 11:917-924, 1989 (suppl 5)
13. Kato M, Onodera T: Morphological investigation of cavity formation in articular cartilage induced by ofloxacin in rats. Fund Applied Toxicol 11:110-119, 1988
14. Burkhardt J, Hill MA, Carlton WW, et al: Histologic and histochemical changes in articular cartilages of immature beagle dogs dosed with difloxacin, a fluoroquinolone. Vet Pathol 27:162-170, 1990
15. Bendele AM, Hulman JF, Harvey AK, et al: Passive role of articular chondrocytes in quinolone induced arthropathy in guinea pigs. Toxicol Pathol 18:304-312, 1990
16. Berg J: Clinical indications for enrofloxacin in domestic animals and poultry, in Quinolones: A Symposium: A new class of antimicrobial agents for use in veterinary medicine. Shawnee, KS, Mobay Corporation, 1988, pp 25-34
17. Schluter G: Ciprofloxacin: review of potential toxicologic effects. Am J Med 82:91-93, 1987 (suppl 4A)
18. Ball P: Ciprofloxacin: An overview of adverse experiments. J Antimicrob Chemotherap 18:197-193, 1986 (suppl D)
19. Spiecker R: Untersuchungen zur Wirksamkeit des Chinoloncarbonsaure derivats. Bay Vp 2674 bei der Behandlung der latenten Salmonellen Infektion des Rindes. Dissertation. Hannover, West-Germany: Tierartzliche Hochschule. 1986
20. Bauditz R: Results of clinical studies with Baytril in calves and pigs. Vet Med Review 2:122-129, 1987
21. Hungerford C, Spelman L, Papich MG: Pharmacokinetics of enrofloxacin after oral and intramuscular administration in Savannah monitors (*Varanus exanthematicus*). Proceedings of the American Association of Zoo Veterinarians, October 28-30, 1997, Houston, TX, AAZV, 1997, pp 89-92
22. Young LA, Schumacher J, Jacobson E, et al: Disposition of enrofloxacin and its metabolite ciprofloxacin after IM injection in Burmese pythons (*Python molurus bivittatus*). J Zoo Wildl Med 28:71-79, 1997
23. Helmick KE, Papich MG, Vliet KA, et al: Pharmacokinetics of enrofloxacin after single-doe oral and intravenous administration in the American alligator (*Alligator mississipiensis*) J Zoo Wildl Med 35:333-340, 2004
24. Raphael BL, Papich M, Cook RA: Pharmacokinetics of enrofloxacin after a single intramuscular injection in Indian star tortoises (*Geochelone elegans*). J Zoo Wildl Med 25:88-94, 1994
25. Flammer K, Aucoin DP, Whitt DA, et al: Plasma concentrations of enrofloxacin in African grey parrots treated with medicated water. Avian Dis 34:1017-1022, 1990
26. Harrenstein LA, Tell LA, Vulliet R, et al: Disposition of enrofloxacin in red-tailed hawks (*Buteo jamaicensis*) and great-horned owls (*Bubo virginianus*) after a single oral, intramuscular, or intravenous dose. J Avian Med Surg 14:228-236, 2000
27. Broome RL, Brooks DL, Babish JG, et al: Pharmacokinetic properties of enrofloxacin in rabbits. Am J Vet Res 52:1835-1841, 1991
28. Aramayona JJ, Mora J, Fraile LJ, et al: Penetration of enrofloxacin and ciprofloxacin into breast milk, and pharmacokinetics of the drugs in lactating rabbits and neonatal offspring. Am J Vet Res 57:547-553, 1996
29. Carpenter JW: Exotic Animal Formulary (ed 3). St. Louis, MO, Elsevier Saunders, 2005