Azithromycin

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Azithromycin is a semisynthetic macrolide antibiotic representing the first of a subclass of macrolides classified as azalides. A relative newcomer to veterinary medicine azithromycin was first described in the late 1980s and differs from erythromycin by the insertion of a methyl-substituted nitrogen on the lactone ring at position 9a.[1] This addition creates a 15-membered macrolide. The alteration of the lactone ring provides a more stable compound in acidic environments and provides a larger spectrum of activity against Gram-negative bacteria.[2,3]

Azithromycin, like other macrolides, is a bacteriostatic antibiotic that inhibits protein synthesis by binding to the 50s ribosome. This drug has been found to be effective against a variety of different Gram-positive and Gram-negative bacterial pathogens, and has some activity against anaerobic bacteria.[2] In addition to its activity against bacteria, azithromycin has also been found to be effective against rickettsial organisms, spirochetes, and protozoa (eg, *Toxoplasma gondii*, *Giardia* spp., and *Cryptosporidium* spp.).

Azithromycin is highly bioavailable after being administered per os (PO) in dogs (97%), and only moderately bioavailable in cats (58%) and humans (37%).[4-7] In dogs, a single oral dose of 10 to 40 mg/kg provided tissue levels that were proportional to the dose.[4] Four- to 7-fold increases in tissue concentration were observed in dogs after being dosed with 20 mg/kg for 7 days.[4] In dogs, the elimination half-life after a 5-day treatment (30 mg/kg PO) for the liver was approximately 90 hours. More than 50% of the drug is excreted from mammals unchanged in the bile.[4,5]

Azithromycin can be concentrated in both polymorphonuclear cells and macrophages.[8] The ability of these cells to transport the antibiotic directly to a site of infection is an example of an endogenous system, the immune system, and an exogenous compound, the azithromycin, working together to control an infection. The direct delivery of the antibiotic by leukocytes undergoing diapedesis would also be expected to increase tissue concentrations of azithromycin when perfusion might be compromised. Mice (*Mus musculus*) and Mongolian gerbils (*Meriones unguiculatus*) experimentally infected with *Streptococcus pneumoniae* and *Haemophilus influenzae*, respectively, were found to have significantly higher concentrations of azithromycin within inflamed tissues (eg, middle ear and lung) compared with noninflamed tissues.[9] There was no difference in the serum levels of the antibiotic between infected and noninfected animals. Veterinarians working with small exotic rodents should consider these findings when selecting an antibiotic to treat a susceptible infection in these animals. Because this antibiotic can be delivered to inflamed tissues via the leukocytes, it has a distinct advantage over other classes of antibiotic agents.

Some macrolide antibiotics have been found to have antiinflammatory activity.[10] Although the exact mechanisms associated with this activity are unknown, it has been suggested that it is associated with their ability to inhibit the production of proinflammatory mediators and cytokines. Of the 4 macrolides tested (roxithromycin, clarithromycin, erythromycin, and azithromycin), azithromycin had the mildest effect on the antiinflammatory response.[10] Additional research is needed to determine the extent of the antiinflammatory effects of these drugs and evaluate the potential therapeutic benefit of these compounds.

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Azithromycin in Exotic Species

In rats (*Rattus norvegicus*), like dogs, a single oral dose of 10 to 40 mg/kg provided tissue levels that were proportional to the dose.[4] Two- to 4-fold increases in tissue concentration were observed in rats after being dosed with 20 mg/kg for 7 days.[4] However, canine tissue levels were 3- to 12-fold higher than rat tissue levels after multiple doses. The pharmacokinetics of azithromycin in rats followed a polyphasic pattern, with the drug being distributed rapidly into the tissues and then slowly redistributed from the tissues. This pattern resulted in persistent tissue levels. Overall, a high degree of tissue affinity for azithromycin was observed in the rats, as tissue-to-serum ratios were often 100 to 1. The tissues found to contain the highest levels of azithromycin included spleen, liver, kidney, lung, lymph nodes, and tonsils.[4] The findings of high concentrations of antibiotic in the lungs, in addition to azithromycin's spectrum of activity against *Mycoplasma* spp., suggest that it may be an important method of controlling *Mycoplasma pulmonis* infections in rats. Although muscle and fat azithromycin levels were 10-fold lower than those for the high-concentration tissues, they remained higher than those levels reported for the serum.[4] Azithromycin was also found to penetrate into the eye and brain and may be used to treat susceptible infections in these organs.

The specific activity of azithromycin against streptococcal experimental infections has been evaluated in several rodent species, including mice, rats, and gerbils.[11] Azithromycin was found to protect mice against a fatal streptococcal infection 5 days after inoculation. In addition to the increased survival associated with treatment, streptococci were eliminated from the lungs of mice treated with azithromycin at a dose of 12.5, 25, and 50 mg/kg PO. Gerbils treated orally with azithromycin at dosages of 12.5 or 50 mg/kg were cleared of *Streptococcus pneumoniae* infections in the middle ear. A higher dose of azithromycin (100 mg/kg twice per day for 3 days) was required to eliminate streptococcal endocarditis in rats.

To date, there has been only a single study evaluating the pharmacokinetics of azithromycin in a reptile, the ball python (*Python regius*).[12] Snakes were initially given azithromycin (10 mg/kg) via intracardiac administration. After a 4-week washout period, the same animals were given the same dose orally. The terminal half-life of azithromycin after intravenous and oral administration was 17 and 51 hours, respectively. Although the apparent volume of distribution for azithromycin in the snakes was low compared with mammals, it was greater than that reported for amikacin or piperacillin in pythons.[13,14] The authors suggested that the difference observed between the pythons and mammals might be attributed to a higher rate of drug metabolism, differences in cell anatomy, or differences in protein binding.

Azithromycin bioavailability in the ball pythons was 77%, which is lower than that in canines but greater than that reported in humans and cats.[4-7,12] The greater bioavailability observed in the snakes, when compared with humans and cats, was attributed to a potentially longer absorption rate or the intestinal variation that occurs in snakes during fasting periods and after ingesting a meal. Because the villi lining the intestine of a snake can change in size, it is thought that drug absorption may be increased during or after a recent meal as a result of the increased villi surface area. During periods of fasting, a lower concentration of the drug might be expected to be absorbed. In ball pythons, like other vertebrates, tissue levels of azithromycin were higher than levels in the plasma. Overall, tissue levels were 4 to 140 times greater than plasma levels. Fifteen metabolites of azithromycin have been identified in the ball python after treatment, 4 of which are unique to this particular species.[15] Because azithromycin can accumulate in the tissues and has a long half-life (oral dosing), the authors suggest dosing ball pythons with 10 mg/kg PO every 2 to 7 days. The dose and duration of treatment depend on which organ system is being treated, because antibiotic levels can vary between tissues.

As with reptiles, there have been few studies to evaluate the pharmacokinetics of azithromycin in captive psittacines. Mealy Amazons (*Amazona farinosa*) given 40 mg/kg of azithromycin directly into their crop had variable peak plasma concentrations (1.07 ± 0.86 fg/mL at 4.77 ± 3.59 hours), and the harmonic mean half-life was 13.5 hours.[16] The variability in the study was attributed to individual differences in crop emptying, and thus different rates of absorption from the lower gastrointestinal tract.[16] A second concentration peak was observed in some of the birds and was attributed to enterohepatic recycling of the drug.

A second study has been done to evaluate the pharmacokinetics of azithromycin in blue and gold macaws (*Ara ararauna*).[17] A crossover study was performed with 10 birds. Five of the birds received the drug PO, while the remaining 5 birds received it intravenously. After a 4-week washout period, the study was repeated with the route of administration being switched. The study only evaluated plasma concentrations of the drug. Based on the findings,

the authors suggested that 10 to 20 mg/kg PO every 48 hours for 5 treatments would be sufficient to manage nonintracellular infections, and that 40 mg/kg every 24 hours for 30 treatments would be sufficient to manage intracellular infections.[17]

To date, there have been no studies evaluating azithromycin in passerines; however, an anecdotal report of its use to treat avian mycobacteriosis does exist. Dorrenstein[18] has suggested that azithromycin can be used as part of a 3-drug cocktail to manage mycobacteriosis (tuberculostatica) in passerines. Combining the drug with rifabutin and ethambutol may limit the disease course associated with mycobacteriosis. However, because *Mycobacterium avium* is a zoonotic pathogen, the decision to treat an affected bird should only be considered if the health risks for humans in contact with the patient are assessed, and the owner understands the nature of this disease.

Conclusions

Azithromycin represents an important antibiotic from a new subclass of macrolides. The large spectrum of activity against not only Gram-positive and Gram-negative bacterial pathogens, but protozoa, rickettsia, and spirochetes, suggests that this antibiotic can play an important role in the veterinarian's pharmacologic arsenal. In addition to its wide coverage, this antibiotic can achieve exceptionally high concentrations in tissues, which may lend it to treating infectious diseases that would otherwise evade antibiotics. However, to know the true value of this antibiotic, additional research is needed to elaborate on its usefulness across species. Veterinarians considering the use of this antibiotic should base their decision on sound diagnostic testing, including culture and antimicrobial sensitivity.

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