Macrolides are a class of antibi-
otics that have been used
worldwide in human and vet-
erinary medicine. Because of their ac-
tivity against increasingly prevalent or-
ganisms in immunocompromised
patients and a better understanding of
their unique tissue-penetration prop-
erties, macrolides have attracted con-
siderable research interest in human
medicine. Veterinary-approved macro-
lides in the United States include ery-
thromycin, tilmicosin, and tylosin. Azithromycin, approved for human
use only, is the prototype of a new
subclass of macrolides called azalides.
Azithromycin shows promise for use
in veterinary medicine, particularly in
cats and certain avian and exotic
species.

Pharmacology
Azithromycin is derived from eryth-
romycin. It differs chemically from
erthyromycin in that a methyl-substi-
tuted nitrogen atom is incorporated
into the 14-membered lactone ring of
erthyromycin. This gives azithromycin
a more extensive spectrum of activity
with improved action against gram-
negative organisms, resistance to acid
degradation, improved tissue penetra-
tion, and a prolonged elimination half-
life.

Although usually classified as bacte-
riostatic, azithromycin may be bacte-
ricial in higher concentrations
against selected organisms. Like other
macrolides, it inhibits protein synthe-
sis in susceptible organisms.

The pharmacokinetic profile of
azithromycin is characterized by low
plasma drug concentrations but high
and persistent tissue concentrations.
The pharmacokinetic characteristics of
azithromycin have been used to sug-
gest that tissue concentrations may be
a more relevant parameter for this
drug. Following oral administration,
azithromycin is rapidly absorbed and
widely distributed into animal tissue.
Tissue concentrations generally exceed
plasma concentrations by 10- to 100-
fold after single-dose administration;
with multiple dosing, the tissue:plas-
tiun ratio increases, as does half-life.
High tissue levels are sustained long
after serum concentrations have de-
clined to very low levels. Although
high tissue concentrations are not usu-
ally equated with efficacy, especially
for extracellular organisms, studies
have demonstrated the clinical efficacy
of azithromycin in treating infections
caused by both intra- and extracellular
organisms when extravascular tissue
concentrations of azithromycin are
above the minimum inhibitory con-
centration (MIC) yet those of serum
are far below. Therefore azithromycin
appears to reach appreciable concen-
trations at extracellular sites of infec-
tion as well as within cells.

The serum half-life of azithromycin
in cats is 35 hours after a single intra-
venous injection of 5 mg/kg, the tis-
sue half-life ranges from 13 hours in
fat to 72 hours in cardiac muscle, and
the volume of drug distribution is 23
L/kg. In dogs, the plasma and tissue
half-lives are 29 and 90 hours, respecti-
vvely, and the volume of distribution
is 12 L/kg. Oral absorption is rapid
and high, with a bioavailability of
34% to 52% in humans, 58% in
cats, and 97% in dogs. Azithro-
mycin extensively penetrates cells,
including tissue fibroblasts, and appears
to be localized primarily in lysosomes.
It is also rapidly and extensively taken
up in vitro by phagocytic cells.
Azithromycin tissue and leukocyte
concentrations can be 100 and 200
times the serum concentration, re-
spectively. Concentrations up to 150
times blood levels occur in sputum,
lung, liver, tonsils, nasal sinuses, stom-
ach, kidneys, female genital tract, and
prostate. Although azithromycin levels
in the brain and eyes are lower than in
other tissues, they exceed blood lev-
els. Studies suggest that azithro-
mycin is delivered to sites of infection
by leukocytes as part of the body’s
normal response to infection and is
then released in response to phagocy-
tosis. The high tissue bioavailability
of azithromycin, particularly in in-
flamed foci, is thought to be due to its
affinity for phagocytic blood cells.
This may explain its persistently high
concentrations in areas of inflamma-
tion and better in vivo efficacy than that of comparable agents.\textsuperscript{11}

High tissue concentrations of antibiotic alone should not be interpreted as a quantitative measurement of clinical efficacy. A low pH environment may reduce the antimicrobial effectiveness of azithromycin because of ionization of the drug, but it is considerably more acid stable than erythromycin.\textsuperscript{4,6} Conversely, the extensive distribution of drug to tissues may be relevant to clinical activity.\textsuperscript{3}

After a single oral dose of azithromycin (20 mg/kg) in rabbits, drug levels peaked within the first 24 hours in all tissues and plasma assayed. The highest concentration was reached in the lacrimal gland, followed (in descending order) by Harder’s gland, conjunctiva, and plasma. Azithromycin levels measured throughout the 144-hour sampling period were consistently above the MIC for \textit{Chlamydia trachomatis} in the lacrimal glands; the conjunctiva maintained a concentration above the MIC for 96 hours and stayed within MIC levels for 144 hours. Of the ocular tissue examined, conjunctival tissue had the lowest azithromycin concentration; however, the levels maintained were 10 to 20 times higher than those of plasma concentrations. The azithromycin concentration in all tissues and plasma declined at approximately half the rate of the relative concentration every 24 hours. Other animal studies have demonstrated higher azithromycin concentrations in the iris and ciliary body with lower concentrations in the cornea and vitreous and aqueous humor, suggesting a relationship between drug concentration and tissue vascularity.\textsuperscript{11}

Azithromycin is eliminated primarily unchanged in the bile (>50% in both dogs and cats); metabolites are inactive. Urinary excretion is approximately 6% after oral administration.\textsuperscript{4,7,10}

\textbf{INDICATIONS}

Azithromycin may be indicated for the treatment of a variety of infectious diseases in animals (e.g., upper and lower respiratory tract infections, superficial and deep pyoderma, ophthalmic infections). Because azithromycin is not currently approved for veterinary use, it should be considered only when a veterinary-approved product is unavailable, the approved product has been proven clinically ineffective, or owner compliance is the limiting factor for treatment.\textsuperscript{12}

Azithromycin exhibits antimicrobial action in vitro against many gram-positive and gram-negative aerobic and anaerobic bacteria and protozoa. It is especially effective against intracellular pathogens.\textsuperscript{4}

Azithromycin has been studied in several animal species. The drug has shown effectiveness in treating infections caused by species of \textit{Streptococcus},\textsuperscript{13} \textit{Staphylococcus},\textsuperscript{13,14} \textit{Mycobacterium},\textsuperscript{16} \textit{Mycoplasma},\textsuperscript{9,10,13} \textit{Chlamydia},\textsuperscript{11,15} \textit{Babesia} (when combined with quinine or imidocarb),\textsuperscript{10,16} \textit{Cryptosporidium},\textsuperscript{10,13,17} \textit{Toxoplasma},\textsuperscript{11} \textit{Neopora},\textsuperscript{18} \textit{Borreliia},\textsuperscript{10} and \textit{Helicobacter}.\textsuperscript{19} Azithromycin has also been suggested for treating infec-
tions caused by susceptible species of *Nocardia*. The spectrum of activity for azithromycin includes other microorganisms (e.g., *Salmonella*, *Propionibacterium*, *Clostridium*, *Bacteroides*, *Pneumocystis*, *Legionella*, *Haemophilus*, *Bordetella*, *Shigella*). It is not inactivated by β-lactamase–producing bacteria and appears to have a postantibiotic inhibitory effect against susceptible gram-positive and gram-negative aerobic bacteria.

**CAUTIONS**

The most frequently observed side effects of macrolides in animals involve the gastrointestinal (GI) tract (e.g., nausea, inappetence, vomiting, diarrhea). Lacking the prokinetic (motilinlike) action of erythromycin, azithromycin appears to cause fewer GI side effects and is generally well tolerated after oral administration.

Cats appear to tolerate the drug particularly well. Other side effects may include hepatomegaly, cholestatic hepatitis, and increased liver enzymes.

Phospholipidosis has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin and has been demonstrated in numerous organ systems (e.g., eyes, dorsal root ganglia, liver, gallbladder, kidney, spleen, pancreas). Because this effect is reversible after discontinuing azithromycin therapy, the clinical significance of these findings is unknown.

Because arrhythmias have been reported (rarely) in human patients receiving azithromycin, animals with a history of arrhythmias should be monitored while receiving the drug. Some reduction in dose may be warranted in patients with hepatic or biliary dysfunction, although no reduction appears necessary in patients with renal dysfunction. Azithromycin should be avoided in patients with prior macrolide hypersensitivity.

**Use in Pregnancy and Lactation**

Animal reproduction studies conducted in rats and mice using oral azithromycin doses up to moderately maternally toxic levels (i.e., 200 mg/kg/day) showed no evidence of harm to fetuses. In human medicine, azithromycin is classified in Pregnancy Category B, which means that animal studies have failed to demonstrate fetal risk and there are no adequate and well-controlled studies in pregnant women. Azithromycin has been detected in human breast milk and the milk of lactating animals. Although no long-term animal studies have been conducted to evaluate carcinogenic potential, azithromycin has shown no mutagenic potential in standard laboratory tests. There is also no evidence of impaired fertility caused by azithromycin.

**Bacterial Resistance**

The main disadvantage of macrolides is their high rate of bacterial resistance. There is some cross-resistance among the macrolides, but erythromycin resistance does not necessarily translate into azithromycin resistance. It has been observed both in vitro and in vivo that bacterial resistance to azithromycin may not develop easily. However, resistance of *Staphylococcus aureus* to erythromycin is generally indicative of resistance to azithromycin. Streptococci are more susceptible than staphylococci to macrolides. Cross-resistance is seen, but resistant strains are unusual in

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**TABLE ONE**

Dosage and Administration of Azithromycin

<table>
<thead>
<tr>
<th>Species</th>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>Chlamydiosis, mycoplasmosis</td>
<td>5–10 mg/kg/day orally for 5 days, then every 48–72 hr&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidiosis</td>
<td>7–15 mg/kg orally every 12 hr for 5–7 days&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dog</td>
<td>Systemic infections</td>
<td>5–10 mg/kg orally every 12 hr for 5–7 days&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>10 mg/kg orally every 12–24 hr&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lyme borreliosis (early disease)</td>
<td>5 mg/kg intravenously every 12 hr for 10–20 days&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Avian (nonfood animal)</td>
<td>Chlamydiosis, mycoplasmosis, mycobacteriosis</td>
<td>1 drop/g orally every 12 hr, or 50–80 mg/kg/day orally (30-mg/ml suspension)</td>
</tr>
<tr>
<td></td>
<td>Chlamydiosis</td>
<td>Treat for 3 days, stop for 4 days; continue for 6 wk</td>
</tr>
<tr>
<td></td>
<td>Mycoplasmosis</td>
<td>Treat for 3 days, stop for 4 days; continue for 3 wk&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Mycobacteriosis</td>
<td>May require months of daily therapy as part of a multidrug regimen&lt;sup&gt;28&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tortoise</td>
<td>Upper respiratory disease</td>
<td>10 mg/kg (oral suspension) for 1 day, then 5 mg/kg once daily for 4 days&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Generally accepted dose among practitioners who use this drug.

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<sup>b</sup>March 2001

<sup>c</sup>Compendium
Client Counseling Information

General instructions for administering tablets or suspension:
- Azithromycin is an antibiotic used to treat infections.
- Give by mouth at regular intervals as directed by your veterinarian.
- Finish the entire course of therapy as prescribed even after signs of infection improve.
- Contact your veterinarian if your pet stops eating, vomits, has diarrhea, or its infection worsens.

Oral suspension (multidose):
- Store reconstituted suspension in the refrigerator; keep bottle tightly closed.
- Shake well before each use.
- Discard any unused portion after the expiration date on the prescription label.
- Do not give with food. You may give the drug 1 hour before or 2 hours after feeding your pet.

Tablets:
- Store in a cool, dark place out of reach of children and pets.
- May give with or without food (food may improve tolerability).

most countries. Cross-resistance to *Mycobacterium avium* complex organisms occurs between clarithromycin and azithromycin.

**Acute Toxicity**

The oral median lethal dose of azithromycin in mice or rats is 3000 to 4000 mg/kg.

**DRUG INTERACTIONS**

One of the limiting factors for macrolide use is the potential for a number of clinically significant drug interactions. Azithromycin, unlike erythromycin, does not inhibit hepatic microsomal enzyme CYP3A4 (formerly cytochrome P-450 IIIA4), thereby reducing the potential for drug interactions. Azithromycin decreases the antibacterial effects of chloramphenicol, other macrolides, and lincosamides because of competition for the same binding sites on the bacterial cell wall.

Transient decreases (80%) in theophylline levels were reported in a human patient receiving a sustained-release oral theophylline preparation (long-term therapy) and short-term oral azithromycin therapy after discontinuing use. The lowest theophylline levels occurred 72 hours after discontinuing azithromycin. Two rechallenges produced similar results, suggesting an unusual interaction between these two drugs. Because the mechanism for this interaction is unknown, respiratory signs should be monitored in patients receiving both theophylline and azithromycin after discontinuing azithromycin use.

Oral azithromycin should not be administered simultaneously with aluminum- or magnesium-containing antacids because the rate of absorption (but not the extent of azithromycin) may be decreased. If administered together, they should be separated by 2 hours.

**DOSE AND ADMINISTRATION**

Veterinary dosages for azithromycin are listed in Table One. Before choosing a dosage, practitioners should consider organism susceptibility to azithromycin, the drug concentration likely to be reached in the targeted tissue, and the patient’s physiologic condition.

REFERENCES

Azithromycin (continued from page 247)