Pharmacokinetics of Azithromycin in Foals

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Azithromycin given orally at a dosage of 10 mg/kg q 24 h should be appropriate for the treatment of Rhodococcus equi pneumonia and infections caused by other susceptible pathogens in foals. Authors’ address: Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, PO Box 100136, Gainesville, FL 32610-0136. © 2001 AAEP.

1. Introduction
Azithromycin is an azalide antimicrobial commonly used in human medicine. Azalides are similar to macrolides in that they both inhibit bacterial protein synthesis by binding to subunits of the 50S ribosome. Like erythromycin, azithromycin is mainly effective against Gram-positive aerobes. Studies in other species have shown that azithromycin has improved pharmacokinetics, is safer, and is slightly more effective against gram-negative and anaerobic bacteria when compared to erythromycin. The use of erythromycin in foals for the treatment of Rhodococcus equi pneumonia has been associated with several complications. Furthermore, erythromycin has an inconsistent absorption in foals when given orally and a growing number of resistant R. equi isolates have been identified. Because of its numerous advantages over erythromycin, azithromycin is an attractive alternative for the treatment of R. equi infections. The purpose of this study was to investigate the pharmacokinetics of azithromycin in foals and to determine its bioavailability and concentrations in serum, body fluids, and bronchoalveolar cells after repeated intragastric administration.

2. Materials and Methods
Azithromycin was administered to 6 non-neonate suckling foals at a dose of 10 mg/kg by both the intravenous (IV) and the intragastric (IG) route using a cross-over design. After the first IG dose, additional doses were administered at 24-h intervals. A microbiological assay was used to measure azithromycin concentrations in serum, peritoneal fluid, synovial fluid, pulmonary epithelial lining fluid (PELF), and bronchoalveolar (BAL) cells.

3. Results
Azithromycin had a long elimination half-life (t1/2) (median 20.32 h) and a large volume of distribution at steady state (median: 18.56 L/kg). After IG administration, the time to peak serum concentration (Tmax) ranged between 1.5 and 3 h, and bioavailability ranged between 31% and 86%. After repeated IG administration, Cmax ranged between 0.51 and 0.76 μg/ml. Peritoneal and synovial fluid concentrations were similar to serum concentrations. Bronchoalveolar cell and PELF azithromycin concentrations were 77- to 3285- and 6- to 130-fold higher than concurrent serum concentrations, respectively.
4. Discussion

The need for effective and potentially safer alternatives to erythromycin for the treatment of *R. equi* pneumonia has led us to investigate the pharmacokinetics of azithromycin in foals. The high and sustained intracellular and tissue concentrations achieved by azithromycin explain its in vivo efficacy against several intracellular pathogens despite in vitro minimal inhibitory concentrations (MIC) considerably higher than achievable peak serum concentrations. Because serum concentrations alone could not be used to determine the likelihood of clinical efficacy in the treatment of *R. equi* pneumonia of foals, azithromycin concentrations were also measured in PELF and BAL cells. In the present study, the majority of cells in BAL fluid were macrophages, the cell type in which *R. equi* survives and replicates. Concentrations of azithromycin in PELF and BAL cells considerably exceeded the MIC$_{90}$ of 60 *R. equi* isolates obtained from foals with pneumonia (1.0 µg/ml). Concentrations of azithromycin in PELF and BAL cells were still high 48 h after administration of the last oral dose. Side effects in people receiving azithromycin are rare and usually related to the gastrointestinal system with diarrhea, nausea, and abdominal pain being the most frequently reported. In the present study, a single intravenous bolus of azithromycin resulted in transient adverse effects characterized by yawning, trembling, ataxia, and weakness. No adverse reactions were noted during or after repeated intragastric administration. Based on the pharmacokinetic parameters, MIC of *Rhodococcus equi* isolates, and drug concentrations in PELF and BAL cells, a single daily oral dose of 10 mg/kg would likely be effective for the treatment of *R. equi* infections in foals. Additional studies are required to confirm the efficacy and safety of this dosage in a clinical setting.

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References