Erythromycin: Pharmacokinetics, Bioavailability, Nonantimicrobial Activity, and Possible Mechanisms Associated with Adverse Reactions

Jeffrey Lakritz, DVM, PhD and W. David Wilson, BVMS, MS, MRCVS

The oral administration of crushed enteric-coated tablets of erythromycin base to foals suppressed the pulmonary inflammatory response induced by bronchoalveolar lavage. The systemic bioavailability of erythromycin base was low and variable (19.8 ± 8.8%), likely as a result of degradation of a substantial portion of the administered dose to microbiologically inactive anhydroerythromycin in the stomach. Anhydroerythromycin may be capable of modulating inflammation and may be responsible for some of the adverse effects observed in foals treated with erythromycin. Erythromycin estolate appears to have a therapeutic advantage over erythromycin base in that its substantially higher bioavailability in foals results in higher plasma concentrations of active erythromycin and lower concentrations of the potentially harmful acid degradation product. Authors’ addresses: Depts. of Molecular Biosciences (Lakritz) and Medicine and Epidemiology (Wilson), School of Veterinary Medicine, University of California at Davis, Davis, CA 95616. © 1997 AAEP.

1. Introduction

Erythromycin is commonly used in foals, either alone or in combination with rifampin, to treat bacterial pneumonia caused by Rhodococcus equi and other susceptible bacteria. Almost all R. equi isolates are highly susceptible to erythromycin and the drug also possesses several properties that contribute to its effectiveness in treating foals with R. equi infection, including those with severe pyogranulomatous pulmonary lesions. Erythromycin is widely distributed in the body and is actively concentrated within neutrophils and alveolar macrophages, which makes it effective in killing susceptible facultative intracellular parasites such as R. equi.1 In addition, a number of dosage forms are available for oral administration, thus making treatment much easier than when injectable antimicrobials are used. Unfortunately, a substantial number of foals treated with erythromycin experience adverse reactions, particularly when erythromycin base is the oral dosage form used. Reported adverse reactions include diarrhea, hyperthermia, Pneumocystis carinii pneumonia, and acute respiratory distress syndrome, all of which may prove fatal.2-5

Plasma concentrations of erythromycin have been reported in foals and adult horses after the oral administration of several different oral formulations of erythromycin, including the estolate and ethylsuccinate esters, although the true bioavailability of the respective formulations was not determined.6,7 In addition, the use of a microbiological assay procedure to measure erythromycin concentrations in these studies precluded the detection of erythromycin metabolites or breakdown products that could
potentially be involved in the induction of adverse effects. The objectives of the studies reported in this paper were, therefore (a) to determine the pharmacokinetics and bioavailability of erythromycin base and erythromycin estolate administered orally to foals, (b) to measure plasma concentrations of erythromycin breakdown products and metabolites that may be responsible for adverse effects, and (c) to evaluate the effect of treatment with erythromycin on the pulmonary response to inflammatory stimuli.

2. Materials and Methods

A. Pharmacokinetic and Bioavailability Study

Eighteen healthy nursing foals between 2 and 4 months of age were used. Mares and foals were fed alfalfa hay the night before each phase of the crossover study but were held off feed until 2 h after administration of the drug the following morning. After placement of a jugular catheter, foals were given either erythromycin lactobionate (10 mg/kg) by rapid intravenous injection or erythromycin base (25 mg/kg) or estolate (25 mg/kg) by nasogastric tube. For intragastric administration, enteric-coated tablets of erythromycin base were crushed and suspended in water, or erythromycin estolate oral liquid (250 mg/ml) was used. Blood samples were collected into heparinized tubes at 0, 3, 6, 12, 18, 24, 30, 45, and 90 min and at 2, 3, 4, 5, 6, 8, 10, 12, and 24 h after drug administration. The harvested plasma samples were stored frozen in cryovials at −70°C until assayed.

Concentrations of microbiologically active erythromycin in plasma were determined by using a standard agar-gel diffusion method utilizing Micrococcus luteus (ATCC 9341) as the test organism. A rapid and sensitive high-performance liquid chromatography (HPLC)-EC method was also used to determine concentrations of erythromycin A and erythromycin degradation products in plasma. Plasma erythromycin concentration-time curves were analyzed by using commercial software (TOPFIT), and bioavailability was calculated by dividing the area under the respective curves for each oral formulation by the area under the curve for intravenously administered erythromycin lactobionate after correcting for dose.

B. Bronchoalveolar Lavage Study

Twelve healthy foals were anesthetized with xylazine and ketamine and positioned in left lateral recumbency. Bronchoalveolar lavage (BAL) was performed by using 250 ml of phosphate-buffered saline solution in 50-ml aliquots. Foals were monitored for the next 4 days, during which time erythromycin base (25 mg/kg of body weight) was given orally twice daily to six foals in the erythromycin treatment group but not to the six foals in the control group. Foals were reanesthetized 4 days after the initial BAL and the same area of the lung was relavaged. Cytologic examination and cell chemotaxis and adherence assays were performed on all BAL fluid samples. At 12 h after administration of the final dose, concentrations of erythromycin A and anhydroerythromycin A were determined in the plasma of treated foals.

3. Results

The microbiologic and HPLC assays for erythromycin gave similar results; thus the pharmacokinetic analysis was based on HPLC data. Following intravenous administration of erythromycin lactobionate the drug was rapidly eliminated, with an elimination half-life (t1/2) of 1.17 ± 0.24 h and a mean residence time (MRT) of 1.06 ± 0.39 h. The volume of distribution at steady state (Vdss) was 5.18 ± 4.3 L/kg, and body clearance (Clf) was 60 ± 21 (ml/kg)/h. Following oral dosing with erythromycin base, a mean maximum concentration of erythromycin (Cmax) of 1.09 ± 0.4 µg/ml was achieved 29 ± 6.9 min after dosing (Tmax). The apparent t1/2 (1.4 ± 0.3 h) and MRT (2.6 ± 0.4 h) were longer than observed after intravenous administration, and the mean systemic bioavailability was 19.8 ± 8.8% (range 8.0–30.0%). Concentration-time profiles for anhydroerythromycin A after oral dosing with erythromycin base indicated delayed absorption (Tmax = 1.1 ± 0.4 h) and a higher peak concentration (Cmax = 3.6 ± 1.3 µg/ml); a longer t1/2 (2.7 ± 0.5 h) and MRT (4.0 ± 0.8 h); and greater Vdss (16.4 ± 12 L/kg) and ClB (30 ± 10 (ml/kg)/h) compared with erythromycin A. Preliminary results indicate that the bioavailability of erythromycin estolate was substantially higher than that of erythromycin base and that much lower concentrations of anhydroerythromycin were detectable in plasma following administration of this formulation.

The BAL procedure induced marked changes in the differential cytologic features of BAL fluid (BALF) in healthy control foals but not in erythromycin-treated foals. There was a significant increase in the percentage of neutrophils in the second lavage sample in control foals (53 ± 38.0%) but not in erythromycin-treated foals (4.8 ± 3.66% p < 0.05). This effect was associated with an apparent decrease in the ability of BALF cells from erythromycin-treated foals to migrate toward a chemoattractant source. In addition, significantly fewer BALF cells adhered to a cell culture substratum after treatment with erythromycin. Erythromycin A was not detected in the plasma of any of the treated foals at the time of the second BAL performed 12 h after the oral administration of the final dose of erythromycin base. At that time, anhydroerythromycin A, a degradation product of erythromycin, was detected in the plasma of five of six foals at mean concentrations of 0.2 ± 0.06 µg/ml.

4. Discussion

These studies confirm the widespread distribution and rapid elimination of erythromycin after the intravenous administration of erythromycin lactobionate. Also noteworthy is the fact that a substan-
tial number of the experimental foals developed adverse reactions characterized by excitement and other signs during or shortly after rapid intravenous injection of erythromycin lactobionate, indicating that this formulation should be administered by slow intravenous infusion in the clinical setting.

The low bioavailability (19.8 ± 8.8%) of erythromycin base after intragastric administration of crushed enteric-coated tablets is at least partially due to conversion of a high proportion of the administered dose to microbiologically inactive anhydroerythromycin before absorption, presumably as a result of degradation induced by the acid conditions of the stomach. The superior bioavailability of erythromycin estolate, a more acid-resistant ester of erythromycin, resulted in higher plasma concentrations of erythromycin A and much lower concentrations of anhydroerythromycin. This finding suggests that lower daily doses of erythromycin estolate should achieve therapeutic results similar to those obtained with higher doses of erythromycin base. Enhanced bioavailability would also be expected if erythromycin base could be protected from acid degradation through the use of microencapsulated capsules rather than crushed enteric-coated tablets.

These studies indicate that bronchoalveolar lavage induces neutrophilic inflammation that persists for at least 4 days in the lungs of young horses.1 Erythromycin base given orally at a dose of 25 mg/kg twice daily markedly diminished this inflammatory response through a mechanism that may involve alteration of BALF cell function. Concentrations of erythromycin A in plasma were undetectable when this effect was observed, but measurable concentrations of anhydroerythromycin were present in the plasma of five of the six experimental foals, suggesting that this biologically active acid-degradation product may be involved. Alternatively, the presence of low concentrations of parent drug in pulmonary secretions may be responsible for the observed alterations in BALF cell chemotaxis and adherence. Regardless, erythromycin base administered orally to foals at clinically relevant doses appears to have non-antimicrobial effects that may interfere with host cell metabolism and decrease inflammatory responses in pulmonary airways.1 This anti-inflammatory effect may be detrimental in some circumstances in that it may promote pulmonary superinfection with erythromycin-resistant gram-negative bacteria or P. carinii. Conversely the inhibition of neutrophil migration into inflammatory sites during R. equi infection may have therapeutic benefits by reducing pyogranuloma formation.

The high plasma concentrations and widespread distribution of anhydroerythromycin achieved after the oral administration of erythromycin base suggest that anhydroerythromycin may be responsible for some of the adverse effects encountered in foals treated with erythromycin in the clinical setting. Anhydroerythromycin is known to be a potent inhibitor of oxidative metabolism.8 In humans and in other species, erythromycin treatment has been shown to inhibit IL-6 production by bronchial epithelial cells, to inhibit leukocyte chemotaxis, to disrupt calcium-dependent signaling pathways, to inhibit neutrophil membrane NADPH-oxidase, to suppress T-lymphocyte proliferation by impairing their response to IL-2, to decrease neutrophil elastolytic activity in bronchitis patients, and to stimulate proliferation and antitumor activity of macrophages. Erythromycin is also a motilin receptor agonist, stimulating gastrointestinal motility. Whether these reported effects were due to erythromycin or to anhydroerythromycin or another metabolite is not known because concentrations were not determined in these studies. Erythromycin and degradation products are actively accumulated within the intracellular compartment of neutrophils and macrophages. Intracellular concentrations of these drugs are 30–100 fold higher than plasma concentrations. High intracellular drug levels that produce inhibition of cytochrome P450 mediated drug metabolism may provide increased levels of substrate for other enzyme systems, resulting in biologically active mediators.8

Adverse reactions are frequently encountered in foals during courses of treatment with orally administered erythromycin. One possible mechanism involves the degradation of erythromycin in the stomach to anhydroerythromycin, which is a compound that does not have antimicrobial activity but appears capable of modulating inflammation and may have other biological effects. The oral administration of a suspension of crushed enteric-coated tablets of erythromycin base was characterized by low bioavailability and resulted in peak concentrations of anhydroerythromycin that were three times higher than those of erythromycin A. Erythromycin estolate may have a therapeutic advantage over erythromycin base in that its substantially higher bioavailability in foals results in higher plasma concentrations of active erythromycin and lower concentrations of potentially harmful degradation products. Erythromycin may produce non-antimicrobial effects by means of interaction with cellular binding proteins that influence cellular calcium levels and production of interleukins, CAMP, and prostaglandin E. Further studies are required to more clearly elucidate the mechanism through which erythromycin modulates pulmonary inflammation and induces adverse effects in the horse.

References


