Pharmacokinetics and Body Fluid and Endometrial Concentrations of Doxycycline after Oral Administration to Six Mares

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Doxycycline at a dose of 10 mg/kg of body weight PO q 12 h should be appropriate for the treatment of infections caused by susceptible gram-positive pathogens in horses. Authors’ address: Dept. of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, P. O. Box 100136, Gainesville, FL 32610-0136. © 1997 AAEP.

1. Introduction

Doxycycline, a structural isomer of tetracycline, is a broad-spectrum antimicrobial that has been studied in many species, including man, dog, cat, pig, cow, and goat. However, data on the oral use of doxycycline in the horse are lacking. The intravenous administration of doxycycline has been reported to be fatal in horses.1 The MIC90 for gram-positive pathogens isolated from horses is <0.25 µg/ml.2 In cattle and pigs, therapeutic plasma concentrations are considered between 0.06 and 1.0 µg/ml.3,4 Currently available oral antibiotics are limited in the horse, and the availability of a drug with a gram-positive spectrum would be a useful addition to current therapeutic options. The purpose of this study was to determine the pharmacokinetics and concentrations in the serum, synovial fluid, peritoneal fluid, cerebrospinal fluid (CSF), endometrium, and urine after the repeated intragastric administration of doxycycline.

2. Materials and Methods

Six healthy adult mares were given five doses of doxycycline hyclate1 (10 mg/kg of body weight, or BW) dissolved in water via a nasogastric tube at 12-h intervals. All horses were housed in box stalls and allowed ad libitum coastal hay and water. Blood samples were collected via venipuncture into clot tubes at times 0 (pretreatment), 5, 10, 15, 20, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 24, 24.5, 36, 36.5, 48, 48.08, 48.16, 48.25, 48.33, 48.5, 48.75, 49, 50, 52, 54, 56, 60, 64 and 72 h after the first dose. Synovial fluid was collected by means of arthrocentesis of the radiocarpal, intercarpal, and tibiotarsal joints at times 0, 48, 49, 50, 52 and 56 h. Peritoneal fluid was obtained via ventral abdominocentesis by using a teat cannula at the same time as synovial fluid collection. Cerebrospinal fluid was collected from the lumbosacral space, using a 17.7 cm × 17 g spinal needle 3 h after the last dose. Endometrial biopsy samples were collected at 1.5 and 3 h after the last dose. Urine samples were collected by catheterization of the bladder at 0, 12, 24, 36, 48, 49, 50, 52 and 60 h. Doxycycline concentrations were determined by a microbiological assay that used Bacillus cereus as the test organism.
3. Results
No adverse affects were seen in any of the mares treated in this study; feces remained normal throughout and beyond the study period. The mean peak serum concentration after the first dose was $0.32 \pm 0.16 \mu g/ml$ at 1 h postadministration. Mean trough serum concentrations were $\approx 0.16 \mu g/ml$. The mean peak serum concentration was $0.42 \pm 0.05 \mu g/ml$ 2 h after the last dose. The highest mean synovial concentration was $0.46 \pm 0.13 \mu g/ml$ and the highest mean peritoneal concentration was $0.43 \pm 0.07 \mu g/ml$, both at 2 h after the last dose. Synovial concentrations were higher than peritoneal concentrations at all times. The highest urine concentration was $145 \pm 25.4 \mu g/ml$ 2 h after the last dose. The highest endometrial concentration was $1.30 \pm 0.36 \mu g/ml$ 3 h after the last dose. Doxycycline was not detected in any of the CSF samples. The mean volume of distribution at steady state was 33.1 ± 6.7 L/kg. The mean elimination half-life was 8.7 ± 1.6 h. The mean serum clearance rate was 2.5 ± 0.4 (L/h)/kg.

4. Discussion
Except for CSF, the mean peak body fluid and endometrial concentrations were above previously reported MIC$_{90}$ (0.25 µg/ml) for pathogens susceptible to doxycycline in horses and other species. Because of previous reports of fatalities associated with the intravenous administration of doxycycline, we did not attempt this route. Therefore, the bioavailability of doxycycline was not determined. We were able to demonstrate that concentrations above previously reported MIC$_{90}$ were attainable. Previously recommended doses for doxycycline (3 mg/kg q 12 h) may not be adequate for clinical usage. In this study, we did not see any adverse affects with five consecutive doses of doxycycline. Doxycycline at a dose of 10 mg/kg PO q 12 h should be appropriate for the treatment of infections caused by susceptible gram-positive pathogens in horses.

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References and Footnotes

Halsey Drug Company Inc., Brooklyn NY 11233.