Long-Acting Oxytetracycline–Polyethylene Glycol in Horses: Pharmacokinetics and Tolerance

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A long-acting oxytetracycline in polyethylene glycol (PEG) was evaluated in a single dose study at 6.6 mg/kg IV and IM and in a long-term dose study at 20 mg/kg IM q 72 h. Pharmacokinetic results were typical for long-acting oxytetracycline formulation. The intramuscular injections caused local irritation, but oxytetracycline-PEG did not alter microbial flora or cause adverse gastrointestinal effects in any horses. Authors’ addresses: Dept. of Veterinary Physiological Sciences (Dowling) and Dept. of Veterinary Microbiology (Chirino-Trejo), Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Dr., Saskatoon, SK, Canada S7N 5B4. © 1999 AAEP.

1. Introduction
Oxytetracycline is a broad-spectrum antimicrobial infrequently used in horses because of concerns over potentially fatal adverse gastrointestinal effects. However, oxytetracycline has become the treatment of choice for suspected or known cases of equine monocytic ehrlichiosis (Potomac horse fever) and the emerging zoonotic disease equine granulocytic ehrlichiosis. Parenteral oxytetracycline is formulated as a hydrochloride salt combined with vehicles such as propylene glycol, polyvinyl pyrrolidone, 2-pyrrolidone or N,N-dimethylacetamide. Oxytetracycline hydrochloride with 2-pyrrolidone or N,N-dimethylacetamide produces prolonged serum and tissue concentrations, and is considered to be "long-acting." These oxytetracycline hydrochloride formulations can be administered to horses, but require administration by slow intravenous injection to avoid circulatory collapse. Long-acting oxytetracycline formulations are severely irritating when administered IM to horses; thus their use is avoided. These adverse effects have limited oxytetracycline therapy to intravenous administration by a skilled veterinarian. The oxytetracycline-PEG product is a recently developed long-acting oxytetracycline formulation in a PEG carrier. It is currently approved for use in cattle and swine in the treatment of respiratory tract diseases. The oxytetracycline-PEG formulation causes minimal tissue reactions with intramuscular or subcutaneous injection in cattle or intramuscular injection in swine.

2. Materials and Methods
In a pilot study, pharmacokinetics and tolerability of the oxytetracycline-PEG formulation administered intravenously and intramuscularly to horses was evaluated. Six American Quarter horses were used in the study. Initially, oxytetracycline-PEG was administered to the horses IV at a dose of 6.6 mg/kg and blood samples were drawn for 72 h. Seven days after the IV study, the horses were administered the same dose i.m. in the neck and blood samples collected as before. Plasma oxytetracycline concentrations were determined using a modification of the
agar well diffusion assay, using a *Bacillus cereus* strain sensitive to oxytetracycline. A second study was carried out to further evaluate the oxytetracycline-PEG formulation in horses, using a higher dose and a chronic dosing regimen. The dose was targeted to treat equine streptococcal respiratory tract pathogens. Nasal swabs were obtained from 22 feedlot horses from Fort MacLeod, Alberta, where streptococcal infections cause almost 100% morbidity. *Streptococcus zooepidemicus* and *Streptococcus equi* strains were isolated and tested for antimicrobial susceptibility to oxytetracycline. Based on minimum inhibitory concentrations (MIC), a dose of 20 mg/kg of oxytetracycline-PEG was calculated to maintain average serum concentrations above the MIC of streptococcal organisms during the treatment interval. Six yearling horses were given 20 mg/kg of oxytetracycline-PEG IM in the neck (alternating sides) every 72 h for 6 treatments. No more than 10 ml was injected into any one site. Blood samples were taken intensively during the first 72 h, then at peak and trough times during the rest of the study. The serum samples were analyzed for oxytetracycline by high-performance liquid chromatography. Fecal samples were collected per rectum from each yearling prior to each dose of oxytetracycline-PEG and 24 and 48 h after each dose. Fecal samples were cultured for *Clostridium* and *Salmonella* spp. and biochemical tests were run on suspected *Salmonella* isolates. Yearlings were monitored for adverse reactions during the dosing regimen.

3. Results

From the pilot study, the serum concentration vs. time curve describing the i.v. and i.m. disposition of oxytetracycline-PEG in horses was typical of a long-acting oxytetracycline formulation. After IV administration, the mean elimination rate constant (k) was 0.0019 min\(^{-1}\) and the mean elimination half life (t\(_{1/2,\text{elim}}\)) was 365 min (harmonic mean). The mean area under the curve to infinity (AUC) was 3045 µg min/ml, mean total body clearance (Cl) of oxytetracycline was 2.2 ml/min · kg and the mean residence time to infinity (MRT) was 436 min. The mean volume of distribution at steady-state (V\(_{\text{d,ss}}\)) of oxytetracycline-PEG was 0.95 L/kg. The apparent mean elimination rate constant (k) after intramuscular administration of oxytetracycline-PEG was 0.0005 min\(^{-1}\) with a t\(_{1/2,\text{elim}}\) of 1327 min (harmonic mean) or approximately 22 h. The mean AUC was 2518 µg min/ml, and the MRT was 2152 min. The mean maximum concentration (C\(_{\text{max}}\)) of oxytetracycline-PEG was 1.18 µg/ml, and the time to reach C\(_{\text{max}}\) (T\(_{\text{max}}\)) was 112 min. The mean bioavailability (F) of the oxytetracycline-PEG formulation in horses was 83%. No adverse gastrointestinal effects were observed in the horses at any time during the study. Nonpainful, mild subcutaneous swellings were observed at the IM injection sites in three horses. All injection sites were normal in appearance within 36 h of injection.

The higher, chronic dosing regimen produced serum concentrations approximately 3 times greater than seen in the pilot study. The higher dose of oxytetracycline-PEG was irritating, as there was considerable subcutaneous swelling following repeated injections. One yearling developed a sterile abscess from the sixty injection that required drainage. From the 118 fecal samples collected, no *Clostridium* spp. were isolated, but a single *Salmonella* spp. was isolated from one yearling that had received multiple doses of oxytetracycline-PEG. Using an E-test for determining susceptibility, the *Salmonella* isolate was susceptible to oxytetracycline. Diarrhea, colic or colitis did not occur in any yearling at any time during or after the study.

4. Discussion

The disposition of oxytetracycline hydrochloride in a propylene glycol or polyvinyl pyrrolidone vehicle has been described in horses. Intravenous administration of a long-acting oxytetracycline formulation negates the long-acting effect that is due to prolonged absorption, and the IV kinetics of oxytetracycline-PEG is similar to other IV-administered formulations. The IM kinetics of the oxytetracycline-PEG formulation is typical for a long-acting oxytetracycline formulation that is slowly absorbed from an extravascular site. Extravascularly administered long-acting or extended release drug formulations may have sufficiently slow absorption so that the drug absorption rate controls the apparent drug elimination rate resulting in different elimination half-life values for the two routes of administration.

The currently recommended treatment regimen for equine ehrlichial diseases is oxytetracycline hydrochloride in propylene glycol or polyvinyl pyrrolidone at a dose of 6.6 mg/kg IV q 24 h for 5–10 days. This dosage has been shown to be effective in clinical cases, however, pharmacokinetic evaluation of this dosage regimen has not been carried out or correlated to treatment efficacy. In vitro concentrations of oxytetracycline above 0.01 µg/ml effectively suppress growth of *Ehrlichia risticii.* In the pilot study, the mean C\(_{\text{max}}\) of oxytetracycline-PEG was 1.18 µg/ml after IM administration, with a mean concentration of 0.48 µg/ml at 36 h. The results of the pilot pharmacokinetic study indicate that oxytetracycline-PEG dosed at 6.6 mg/kg provides sufficient serum concentrations to inhibit the regrowth of *E. risticii* for at least 36 h.

The results of the chronic dosing study demonstrate that this formulation of oxytetracycline-PEG can be given to horses at 20 mg/kg IM on a long-term basis without causing adverse gastrointestinal effects. Colitis from oxytetracycline use in horses has been associated with overgrowth of oxytetracycline-resistant *Clostridium perfringens* and/or *difficile* and *Salmonella* spp. In this study, oxytetracycline-PEG did not have any effect on presence of clostridial organisms, and the single *Salmonella* isolated was less than expected, as *Salmonella* may be isolated from 70% of asymptomatic horses. The use of oxytet-
racycline-PEG did not have any effect on the susceptibility of the single isolate to oxytetracycline. Multiple intramuscular doses of oxytetracycline-PEG were irritating; however, it is not likely that such a long-term dosing regimen would be necessary in clinical practice. A two-dose regimen of 20 mg/kg q 72 h is currently used in the Alberta feedlot for treating streptococcal respiratory infections with good clinical efficacy.

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References and Footnotes

*Bio-Mycin 200, Boehringer Ingelheim (Canada) Ltd., 5180 South Service Rd., Burlington, Ontario, Canada L7L 5H4.*