



Original Research

Effects of Intrauterine Infusion of a Water-Based Suspension of Enrofloxacin on Mare Endometrium

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ABSTRACT

Intrauterine infusion of a commercial preparation of enrofloxacin has been shown to produce severe inflammation and irreversible deterioration of endometrial biopsy scores in mares. The aim of the present work was to evaluate the effect of intrauterine infusion of a water-based enrofloxacin suspension on mare reproductive tracts. Eight systemically healthy mares were used in the experiment. Each mare underwent a complete reproductive evaluation (ultrasonography, vaginal examination, endometrial cytology, endometrial culture, and endometrial biopsy) before treatment. Each mare received an infusion of 50 mL of a 2.5% water-based suspension of enrofloxacin daily for 3 days. To evaluate the acute effect of treatment, mares were examined daily by transrectal ultrasonography and vaginoscopy during the treatment and an endometrial biopsy was obtained 24 hours after the final infusion. To evaluate the chronic effect of treatment, a complete reproductive evaluation was performed on mares 21 days after initiation of treatment. Results of clinical evaluation showed a significant increase in intrauterine fluid accumulation during the treatment. A nonsignificant increase in endometrial biopsy grade was observed after the 3 days of treatment. There was no long-lasting effect of the infusion on clinical evaluation or endometrial histology. Endometrial concentrations of enrofloxacin and its metabolite ciprofloxacin were highly variable among mares yet were above the minimum inhibitory concentration in four of eight treated mares. We conclude that intrauterine infusion of a water-based enrofloxacin solution produced only a transient inflammatory response and may be useful for the treatment of bacterial endometritis sensitive to enrofloxacin without the deleterious effects seen with the administration of the commercial preparation.

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1. Introduction

Endometritis is considered the most common cause of infertility and early embryonic loss (<35 days) in mares [1–3]. Bacterial endometritis may be caused by a variety of Gram-positive and Gram-negative bacteria [3–5]. The most common organisms isolated by aerobic culture of an endometrial swab from the uterus of mares with bacterial endometritis are *Streptococcus equi* subsp *zoepidemicus*

and *Escherichia coli*, which account for 50% to 80% of all isolates [6]. Other common isolates include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Corynebacterium* spp., *Actinobacter* spp., *Proteus* spp., *Citrobacter* spp., *Enterobacteria cloaca*, and other β -hemolytic *Streptococcus* [3,4].

Infectious endometritis is commonly diagnosed by a combination of endometrial cytology and bacteriology [1,5]. Pregnancy and foaling rates are significantly lower in mares with positive uterine cytology and/or recovery of bacterial growth [5,7]. Mares with infectious endometritis may conceive but experience increased embryonic loss in the first trimester of pregnancy or abortion due to bacterial

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placentitis in late gestation [5,7]. In a recent study, positive endometrial cytology alone (>1% polymorphonuclear leukocytes [PMNs]) or positive bacteriology alone was associated with a decreased live foaling rate [7]. Culture of a single isolate is significantly associated with lower pregnancy rates at 28 days [5] and lower foaling rates [7]. Although isolation of two different organisms for cases of bacterial endometritis is possible, the presence of three or more organisms is generally considered the result of contamination [8].

In practice, treatment of bacterial endometritis commonly includes uterine lavage, followed by 3 to 5 days of intrauterine antibiotic infusions, which are selected based on culture, and sensitivity results, or based on the spectrum of antibiotic activity. Although guidelines for intrauterine antibiotic therapy are available in the literature, most treatment decisions are based on clinical experience [6].

Enrofloxacin, a second-generation fluoroquinolone, is a highly lipid soluble molecule that inhibits bacterial DNA gyrase, preventing DNA supercoiling and synthesis. Enrofloxacin is bactericidal, with a concentration dependent mechanism of action, making it an ideal choice for intrauterine infusion. Enrofloxacin has been shown to be effective against a variety of bacteria isolated from cases of equine endometritis such as *E. coli*, *P. aeruginosa*, *Klebsiella* spp., *Enterobacter*, *Proteus* and *Staphylococcus* spp. Most strains of *S. zooepidemicus* isolated from mares with endometritis were found to be susceptible to enrofloxacin [9].

The safety of intrauterine administration of commercial preparations of enrofloxacin has been evaluated in few studies. A study showed that a single intrauterine infusion at a dose of 2.5 mg/kg produced statistically nonsignificant histologic inflammatory changes [10]. However, in a more recent study, daily intrauterine administration of the same dose of an enrofloxacin commercial preparation (Baytril-100, Bayer HealthCare, Animal Health, Shawnee Mission, KS) during estrus resulted in a severe, acute, ulcerative, hemorrhagic endometritis [2]. Treated mares showed deterioration of the endometrial biopsy grade and development of intrauterine adhesions and fibrosis [2]. The authors speculated that the acute changes and fibrosis may be due to the caustic effect of the pH (10.4) of the enrofloxacin preparation or the excipients used.

The objective of the present study was to determine the effects of a 3-day course of daily intrauterine infusion of an alcohol-free, water-based enrofloxacin suspension, on clinical and histopathological characteristics of the endometrium.

2. Materials and Methods

2.1. Animals and Treatment Protocol

Eight healthy adult mares (two Quarter Horses, three Thoroughbreds, two Tennessee Walking Horses, and one American Saddlebred) aged 4 to 9 years weighing between 450 and 560 kg were used in this experiment. All mares were part of a herd of embryo transfer recipients. All mares had demonstrated normal cyclicity throughout the breeding season. All experimental procedures were

approved by the Institutional Animal Care Committee at Washington State University.

Mares were examined by transrectal ultrasonography until the preovulatory stage of estrus (i.e., day 0 of the experiment = dominant follicle >35 mm and edema grade 1). Each mare received an intrauterine infusion of 50 mL of a compounded alcohol-free, water-based 2.5% suspension of enrofloxacin (enrofloxacin 2.5% intrauterine suspension; Rood and Riddle Pharmacy, Lexington, KY) daily for 3 consecutive days (day 0, day 1, and day 2). To evaluate the effect of the treatment on the reproductive tract, all mares were subjected to pretreatment and posttreatment endometrial cytologic and biopsy evaluation as well as clinical evaluation as described below.

2.2. Clinical and Ultrasonographic Evaluation

Clinical evaluation of mares consisted of daily transrectal ultrasound examination using a 7- to 10-MHz linear transducer (Micromaxx machine, FUJIFILM Sonosite Inc, Bothell, WA) and vaginal speculum examination (sterile, disposable vaginal speculum 18"; Butler Animal Health Supply LLC, Dublin, OH) for the first 3 days and on day 21 of the experiment. Ultrasonographic evaluation of the reproductive tract at each examination point included the following: size of the largest follicle measured in millimeters, degree of edema graded from 0 to 4 (0, no edema; 1, slight edema; 2, mild; 3, moderate; and 4, severe), the largest amount of intraluminal fluid measured in centimeters in the dorsoventral plane and graded from 0 to 6 (0, no fluid; 1, ≤1 cm; 2, >2 cm; 3, >2–3 cm; 4, >3–4 cm; 5, >4–5 cm; and 6, >5–6 cm). The echogenicity of the fluid was also graded subjectively from 0 to 4 (0, no fluid; 1, anechoic; 2, slightly echogenic and/or hypoechoic relative to the uterine wall echogenicity; 3, moderate echogenicity and/or same echogenicity of uterine wall; and 4, very echogenic and/or hyperechoic relative to uterine wall).

Speculum examination of the cervix and vagina was performed at all four time points to note any changes associated with the treatment. Cervical examination findings were graded from 1 to 6 (1, normal pink, no discharge; 2, slightly hyperemic, no discharge; 3, slightly hyperemic, discharge present; 4, moderately hyperemic, no discharge; 5, very hyperemic, no discharge; and 6, very hyperemic, discharge present). Vaginal discharge was graded on a scale of 1 to 4 (1, clear and/or mucoid; 2, yellow; 3, white; and 4, brown).

2.3. Endometrial Culture and Cytology

Endometrial cytology and bacteriology were performed on all mares on day 0 and day 21 of the experiment. Samples were taken with a double-guarded uterine swab (Kalayjian culture instruments; Kalayjian Industries, Inc Signal Hill, CA) using the previously described method [5]. Swabs for bacteriology were immediately placed into a charcoal medium and submitted to the medical laboratory at Rood and Riddle Equine Hospital for aerobic culture. Cultures were plated on blood and Levine Eosin-Methylene Blue plates within 6 hours. Plates were incubated at 37°C and examined every 24 hours for 3 days. Bacteria were

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