How to Use a Buffered Chelator Solution for Mares With Chronic Endometritis

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1. Introduction

Endometritis is an important cause of infertility in the mare. Conventional therapy aimed at persistent post-mating endometritis and chronic endometritis can sometimes fail for a variety of reasons, including uncorrected anatomic abnormalities and the presence of biofilm in the uterus. Bacterial biofilms are complex populations of multiple microbial species embedded within a glycocalyx matrix, which allow for a 500-fold increase in bacterial resistance to antibiotics compared to traditional in vitro pure culture. With increasing frequency, bacteria with multiple resistance patterns are being recovered from the equine uterus. This highlights the need to find alternative methods to treat microbial infections rather than to continue to rely solely on traditional antibiotics.

A solution of 3.5 mM ethylenediaminetetraacetate dehydrate (EDTA) and 0.05 M tris(hydroxymethyl)amin (Tris) reduced the in vitro cellular viability and produced a strain-dependent increase in the susceptibility of genital strains of Pseudomonas aeruginosa. A third-generation buffered chelating agent, 8 mM EDTA, and a 20 mM 2-amino-2-hydroxymethyl-1,3-propanediol, potentiates antibiotics with fungal keratitis, presumably by altering cell wall integrity after removal of bivalent cations from the outer bacterial membrane.

The proposed therapeutic protocol is to lavage the uterus with lactated Ringer’s solution (LRS), instill a buffered chelator solution for 12 to 24 hours, and lavage the uterus on the subsequent days to remove potential exudate. Appropriate antimicrobial agents may be used in conjunction with the buffered chelator.

2. Safety in Reproductively Normal Mares

Preparation of the Buffered Chelator Solution

A buffered chelator solution for intrauterine infusion can be prepared by dissolving a 20-g packet of
pared using proportional odds modeling. The dif-
score between pre- and post-treatment was com-
pared with buffered chelator. Changes in
hypothesis being no difference in response to saline
buffered chelator on the endometrium were evalu-
ined for pregnancy 14 days after ovulation. Mares
inseminated on the subsequent estrus, and exam-
ined for endometrial edema, inflammation,
candine in pregnant percentage between groups was
evaluated by Fisher exact test. For all tests, signif-
icance was set at \( P < 0.05 \).

4. Study Results
There was no difference in pregnancy rates on the
estrous cycle immediately after treatment with the
buffered chelator or saline. There was no signifi-
cant difference in endometrial edema, inflammation,
and thickness of the mucus blanket before and after
treatment with either the buffered chelator or
saline.

5. Infertile Mares
Case 1 was a 12-year-old Thoroughbred mare with a
history of weak/septic foals in 2008 and 2009; both
foals died despite intensive treatment. Large-vol-
ume uterine lavage was performed during foal heat,
combined with oral trimethoprim-sulfadiazine. 
Escherichia coli was isolated 30 days postpartum,
and the mare was treated again with large-volume
lavage and intrauterine cefotiofur \( (2 \, \text{g}) \) for 4 days.
Re-culture of the mare on two subsequent estruses
determined that \( E. \, \text{coli} \) was still present, and treat-
ment was continued as before. Four months after
foaling, the mare was reevaluated with a low-vol-
ume uterine flush and endometrial biopsy. A
Staphylococcus aureus was isolated (sensitive to
amikacin and cefotiofur), and the endometrium was a
Kenney II due to moderate focal lymphocytic, plas-
mycotic endometritis with mild periglandular fibro-
sis and moderate edema. The mare’s uterus was
lavaged with 3 L saline on days 1 and 2, followed
each day by infusion of a buffered chelator \( b \) (500
mL). On days 3 to 5, gentamicin \( (2 \, \text{g}) \) was added to
the buffered chelator solution. Two months later,
no bacteria were isolated from a small-volume uter-
ine flush. In March of 2010, no bacteria were iso-
lated from a uterine small-volume flush; the mare
was bred and treated with uterine lavage and oxy-
tocin after breeding and cefotiofur \( (2 \, \text{g}) \) 24 hours after
mating. In February of 2011 she delivered a viable
foal.

Case 2 was a 14-year-old Thoroughbred mare that
foaled in 2010. She failed to become pregnant in
2010 and was treated extensively with intrauterine
antibiotics. In December of 2010, Candida parap-
silosis was isolated from the uterus, which was sen-
sitive to clotrimazole. She was treated in
December and January with intrauterine clotrim-
azole. In February 2011, she was re-cultured, and
the Candida was still present. Further diagnostics
included hysteroscopy to identify focal lesions (none
were identified) and endometrial biopsy (multifocal
lymphoplasmacytic, subacute, mild endometritis).
On the first estrus, she was treated with 2% acetic
acid solution for 5 minutes, followed by uterine la-
vage while awaiting repeat of the sensitivity testing
on the fungal isolate. On the second estrus, she
was treated with fluconazole \( (14 \, \text{mg/kg/d PO loading}
dose, 5 \, \text{mg/kg/d PO, 9 days}) \) and the buffered chela-
tor \( b \) on day 1 of estrus, followed by lavage on day 2
and infusion of clotrimazole \( (1000 \, \text{mg}) \), which was
repeated on day 4. Luteolysis was induced 5 days
after ovulation, \( c \) and an endometrial culture on the
subsequent estrus was negative for bacteria and
yeast. She was bred on two consecutive estrus cy-
cles to a fertile stallion but failed to become preg-
nant. On the third estrus, significant uterine fluid
was present, and she was again culture-positive for
Candida. The buffered chelator solution was not
available, so treatment with 2% acetic acid solution
and lavage as described above was repeated, fol-
lowed by intrauterine autologous plasma. She was bred on the subsequent cycle and was recently diagnosed pregnant (20 days).

6. Conclusions

Results of the study with reproductively normal mares suggest that contact with buffered chelators up to 24 hours is not deleterious to the equine endometrium or to the establishment of pregnancy. Only two clinical cases were available with a detailed history and complete follow-up. These results suggest that buffered chelators may be a useful adjunctive therapy with chronic endometritis due to either Gram-negative bacteria or fungi; however, treatment failures may still occur, especially when complicated by anatomic abnormalities such as cervical incompetence. The increasing frequency with which bacteria with multiple antibiotic resistance patterns are recovered from the equine uterus is of concern, and therapeutic regimes that can reduce the dependence on traditional intrauterine antibiotics are worthy of consideration.

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References and Footnotes


aTricideTM, Molecular Therapeutics, LLC, Athens, GA.
bTricide Solution (Tris/EDTA for Equine Use), Rood and Riddle Veterinary Pharmacy, Lexington, KY.
cLutalyse®, Pfizer Animal Health, New York, NY.
dLogistic procedure, SAS 9.1, Cary, NC.
eNaxcel, Pfizer Animal Health, New York, NY.