

Advanced Equine Reproduction Course

Domperidone- The Answer to Fescue Toxicity?

Fescue first appeared as a forage choice in the United States during the early 1940s. Widely considered a "wonder grass", it was easy to establish, tolerant, and tough. As it could adjust to heavy grazing and climatic change, the grass was planted widely, eventually covering some 35 million acres throughout the U.S.A. However, as more and more animals began to graze on the hearty pasture, more and more problems were reported. Cattle fed fescue appeared unthrifty and their milk production dropped. Horse breeders began having foaling problems with mares that were fed the grass. Mares fed fescue grass or hay might show a tendency to abort, prolonged gestation (and related dystocia), thickened and or retained placentas, and agalactia. Agalactia can cause major problems for the neonate. It can not receive essential colostrum if the mare is not producing milk. The foal then develops complications of failure of passive transfer unless treated.

In 1977, Charles Bacon, a plant pathologist at the Richard Russell Research Center in Athens, Georgia, discovered a fungal endophyte, *Acremonium coenophialum*, living within the fescue grass. Not visible to the naked eye, the fungus is transmitted only through the seed. In 1988, a study by J.L. Monroe et al. demonstrated the deleterious effects of allowing broodmares to graze infected fescue. In doing so, the researchers proved that *Acremonium* produces the toxin that causes fescue toxicity. Twenty-two mares were divided into two groups. One group grazed endophyte infected pasture from the end of their first trimester of pregnancy through parturition. The other group of mares was maintained on endophyte-free fescue. At the end of the study, no clinical problems were experienced by those mares kept on non-infected fescue. The group on *Acremonium coenophialum* fescue, however, experienced significant problems. Ten out of eleven mares experienced dystocias and prolonged gestation. Udder development and milk production were also reduced in these mares. In another study, fescue with the endophyte was found to contain ergot alkaloids, most notably ergovaline. Ergovaline is hypothesized to be the toxic principal of *Acremonium coenophialum*. Ergovaline apparently acts as a dopamine agonist in the pars distalis, suppressing prolactin secretion and leading to clinical problems.

Clearly, infected fescue should not be used a pasture grass. Unfortunately, tall fescue is the predominant forage grass in the United States. Of the over 35 million acres grown, over 58% contains the endophyte. This percentage is even higher east of the Mississippi River, where 70% of some pastures are contaminated.¹ Fescue itself is an excellent forage. As mentioned above, it is hearty and a good forage yielder. The endophyte itself doesn't cause problems for all horses, just mares in their last third of gestation. Endophyte-free pasture is expensive to establish and has not grown as well or been as hearty as the old fescue. Other options have been found so that fescue does not have to be avoided. One of the most promising is the development of a drug called domperidone.

Domperidone's use in pregnant mares was developed by Dee Cross, PhD, of Clemson University in South Carolina. When this drug is given as early as 15 days prior to foaling and continued up to 5 days after foaling, mares usually deliver normal foals without complications and have normal milk production. Domperidone is an anti-dopaminergic drug. It was developed in the 1980s to prevent nausea in cancer patients undergoing chemotherapy by blocking receptor sites to dopamine. Alkaloids in fescue mimic the function of dopamine.³ Dopamine inhibits ACTH secretion by binding with DA₂ receptors on corticotrophs. In a normal birth, fetal ACTH is released, triggering fetal release of cortisol. An increase in fetal cortisol increases the mare's progesterone and decreases her estrogen during the last 30 days of gestation. These hormonal changes are necessary for normal gestation duration and parturition. Mares on infected fescue have extra dopaminergic activity at these DA₂ sites, as ergovaline mimics the action of dopamine. Such mares have decreased levels of progesterone and increased levels of estrogen. The signal is not given for parturition to begin and pregnancy is prolonged.

Dopamine also affects milk production. Dopamine interacting with DA₂ receptors inhibit the secretion of prolactin. Prolactin stimulates milk production when it is released from the pituitary gland. Again, when broodmares graze endophyte infected fescue, the ergovaline acts like dopamine and inhibits prolactin production, leading to decreased mammary development and agalactia. This effect is intensified by the decreased levels of progesterone, as this hormone is needed for mammary tissue to develop.

By blocking dopamine receptors, domperidone decreases the effects of ergot alkaloids such as ergovaline. The dopaminergic toxin is prevented from binding the DA₂ receptors. The result is abnormal production of prolactin and progesterone. With normal production of these hormones, the domperidone-treated mare foals on time, with normal milk production and none of the fescue-induced problems expected. It is extremely rare for domperidone to fail if administered as prescribed.¹

In initial clinical trials, 27 Virginia mares in 1993 and 106 Kentucky, Ohio, South Carolina, and Virginia mares in 1994, received daily oral doses of domperidone paste during the last 25 days of pregnancy. Even though the mares were on infected fescue pasture at the time, all foaled on time and none of them experienced any fescue-associated difficulties.

Earlier research done at Clemson in 1990 also demonstrated domperidone's considerable potential as a treatment for fescue toxicosis in horses. Sixteen pregnant mares were assigned to 1 of 3 treatment groups: endophyte-infested control, 1.1 mg/kg of domperidone, and 3.3 mg/kg of sulpiride. Treatment began 30 days prior to expected foaling date and continued until parturition. Domperidone mares foaled closer to their expected date and had higher mammary gland scores than did control mares. In addition, serum prolactin and progesterone levels were higher and serum estradiol-17B was reduced in domperidone treated mares as compared to control mares.

In a subsequent study, Redmond et al. determined the minimum effective dose of domperidone for treating fescue toxicosis. The minimum effective oral dose was 1.1 mg/kg when administered 30 days before foaling. Subcutaneous administration of 0.44 mg/kg of domperidone for 10 days before the expected foaling date also provided recovery from tall fescue toxicoses. At all of these doses, no ill effects were noted. In other promising dopaminergic blockers, central nervous system effects could not be

controlled. They ranged from listlessness to constipation to excitation and incoordination. Domperidone does not affect the central nervous system because it can not cross the blood-brain barrier. In short, domperidone can be used as an effective treatment for fescue toxicity with no adverse side effects and relative safety.

Though domperidone is not yet approved by the FDA, it can be obtained by veterinarians on "experimental drug use". This means a veterinarian can administer the drug to horses known to have ingested infected fescue. The drug comes with a "clinical observations form" that must be completed and returned. The form is needed for submission to the FDA as part of the NADA for clearance of domperidone for equine fescue toxicosis.

The veterinarian should administer 5cc/500 kg mare body weight daily as an oral dose starting 10 days prior to expected foaling and up to parturition. If the mare remains on infected pasture up to foaling, treatments should begin 15 days before she is due. Mares showing no signs of udder development due to fescue intoxicosis should continue to be given domperidone up to 5 days after birth. Domperidone is given as a paste and costs about \$7.00 a treatment. To obtain the drug, veterinarians should contact Equi-Tox, Inc. at The Center for Applied Technology, Mailbox #2, 51 Westinghouse Rd., Pendleton, SC 29670. They can also contact Equi-Tox at (864)646-6443.

In the future, domperidone should become an important and useful drug in the treatment of fescue toxicosis. The drug's antidopaminergic properties block the adverse effects of ergovaline from *Acremonium*, while it has virtually no side effects. Though the preferred method of dealing with fescue is still to prevent consumption of the toxic grass or hay during the last 60-90 days of gestation, in those cases where this is impossible, domperidone is very useful, though expensive.

References

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