

## **Advanced Equine Reproduction Course**

by

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### **Domperidone and its use in the Broodmare**

Domperidone is a D2 receptor antagonist, that is unable to cross the blood brain barrier.<sup>1</sup> This is different from other dopamine antagonists, such as metoclopramide and phenothiazines which do cross the blood brain barrier. These drugs can result in neurologic side effects, such as restlessness and excitability, which are not seen with the use of domperidone.<sup>1</sup> In pregnant mares, domperidone indirectly acts to increase serum prolactin and progesterone levels that are decreased due to fescue toxicosis. There have been no reports of side effects with its use in pregnant mares. D.L. Cross has found that long term use in some cases has resulted in leaking of milk and colostrum.<sup>4</sup> This is only a problem if the mare does not foal within 24 hours. If this problem occurs the dose should be divided and given every twelve hours or reduced.

Fescue toxicity results from an endophytic fungus found in tall fescue grass. The endophyte is called *Acremonium coenophialum*. The endophyte contains an ergot alkaloid that acts as a D2 dopamine receptor agonist. It has been implicated as the cause of many reproductive problems in pregnant mares. Those mares that eat endophyte infected fescue tend to suffer higher rates of agalactia, increased gestation lengths, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, and decreased serum levels of prolactin and progesterone.<sup>2</sup> These problems are seen more often in mares eating the endophyte than mares who are not exposed.

It has been postulated that these mares have a prolonged gestation length due to the decreased levels of serum progesterone. In the normal pregnancy, progesterone levels rise about one month prior to parturition. This rise is stimulated by increased fetal cortisol levels that alter the progesterone metabolism of the placenta. When the pregnant mares are kept on endophyte infected fescue pastures this rise in progesterone does not occur. There has been no direct evidence to explain why this occurs, but it is suspected that the ergot alkaloid inhibits fetal cortisol releasing hormone activity which would lead to a suppression of the mares serum progesterone levels.<sup>2</sup> One study showed an average increase of 20 days in gestation in mares suffering from fescue toxicity.<sup>3</sup>

Those mares that are ingesting endophyte infected fescue are at a higher risk for dystocia. The dystocias are related to an inadequate preparation of the reproductive tract for parturition, prolonged gestation, and malpositioning of the foal.<sup>2</sup> These mares lack the progesterone priming necessary for normal foaling. The foals tend to be larger because of the extended gestational period and therefore they are more likely to have trouble fitting through the pelvic canal. When the foal does not properly align itself prior to parturition, the result is an abnormal presentation that will result in dystocia. These conditions result in a higher risk of mare and foal mortality. Studies have shown a significant difference in the incidence of dystocia in mares eating endophyte infected fescue versus those that are eating endophyte free fescue.<sup>3</sup> The recommendations for preventing these problems are to remove all pregnant mares from infected fescue six

weeks to three months prior to parturition. Even if the mare is removed only just prior to foaling there can be a reduction in the rate of foal mortality.<sup>2</sup>

The biggest problem in pregnant mares suffering from fescue toxicosis is agalactia. These mares can exhibit a complete lack of udder development prior to and after parturition. Horses rely on prolactin to stimulate prepartum lactogenesis.<sup>2</sup> In other species, there is a placental lactogen that allows for some udder development even in the absence of prolactin. This explains why other species do not experience the devastating consequences of complete agalactia that mares do when they are ingesting endophyte infected fescue. The ergot alkaloids found in the endophyte have a depressive effect on the secretion of prolactin. They act as dopamine agonists at the level of the pituitary.<sup>2</sup> The anterior pituitary controls the secretion of prolactin from the lactotrophs of the udder. This control is a result of the inhibition of dopamine. The ergot alkaloid binds to this receptor and inhibits the secretion is suppressed. Without prolactin, the udder can not develop prior to parturition. This is further complicated by the fact that prolactin is not the only hormone involved in lactogenesis. Both estrogen and progesterone work synergistically with prolactin to promote mammary tissue growth. Estrogen is necessary for ductal growth and progesterone is needed for lobulo-alveolar growth.<sup>2</sup> These hormones are required prior to parturition in order to get normal udder development. This explains why pregnant mares must be removed from infected fescue so far in advance of parturition, they require time for udder development as well as milk production. Normal mares begin mammary development two to six weeks prior to parturition, which coincides with the rising levels of progesterone in the serum.<sup>2</sup> The use of a dopamine antagonist like domperidone has been shown to reverse the clinical signs of fescue toxicosis and initiate lactogenesis.

The effect of endophyte ingestion by pregnant mares has also been shown to have severe affects on foal survivability. In one particular study only one foal survived the natal period. The foals that were born alive showed evidence of dysmaturity.<sup>3</sup> The pain and suffering that these mares and foals underwent led to the decision in later studies to remove the mares in control groups on endophyte infected fescue if their gestation length went beyond the expected date.<sup>1</sup>

At the present time there are two recommended treatments for fescue toxicity. The first method is also the means of prevention, removal from the source. All pregnant mares need to be removed from all sources of endophyte infected fescue prior to parturition. The endophyte is found in tall fescue grass, as well as hay cured from infected grasses. Fescue is one of the most widely used grass and hay types that are fed to horses. It is important to make sure that both the pasture and the hay are free of endophyte infected fescue. If the mare is showing signs of fescue toxicity prior to foaling, removal from the source will result in a rapid recovery.<sup>2</sup> The second therapy for these mares is to give them domperidone. It acts as an antagonist to the ergot alkaloid and reverses the effects of fescue toxicosis.

The treatment recommendations have been suggested by Dr. D.L. Cross from Clemson University.<sup>4</sup> The dose of domperidone is 5cc per 500kg of body weight daily as an oral treatment starting ten days prior to the expected foaling date up to foaling. The drug can also be used as soon as signs of fescue toxicity appear and given until foaling. Those mares that have already foaled and suffer from agalactia or low milk production are treated at the regular dose for at least five days. Domperidone can be used as both a

prevention and treatment of the consequences of fescue toxicosis. If a farm has a history of previous problems, mares can be put on domperidone up to fifteen days prior to the expected foaling date.

The results of a study by Redman and Cross et al on the efficacy of domperidone showed positive results to treatment. The pregnant mares that were put on endophyte infected fescue were put on domperidone therapy thirty days prior to their expected foaling date. The treated mares had shorter gestation lengths and no signs of agalactia when compared to control mares. The control mares suffered from agalactia until they were removed from the endophyte infected fescue. The mares on domperidone showed mammary development nine days after initiation of therapy.<sup>1</sup> Overall they found that the dopamine antagonistic effects of domperidone were effective in reversing the clinical signs of fescue toxicosis in pregnant mares.

Domperidone is considered an experimental drug by the U.S. Drug and Food Administration. Dr. D.L. Cross has been actively studying the effects of domperidone in the treatment of fescue toxicosis. The drug can only be obtained from [Equi-Tox](#), Inc. They will ship the drug to veterinarians for experimental use. A clinical observation form must be filled out by the owner and the veterinarian and returned to Dr. Cross. This information is being used to provide large scale clinical testing of the drug and its efficacy against fescue toxicosis.

## References:

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- 2 Cross, D.L., L.M. Redman, and J.R. Strickland Equine fescue toxicosis: signs and Solutions *Journal of Animal Science* 1995;73:899-908.
- 3 Putnam, M.R., D.I. Bransby, J. Schumacher et al, Effects of the fungal endophyte *Acremonium coenophialum* in fescue on pregnant mares and foal viability *American Journal of Veterinary Research*, 1991;52:2071-2074.
- 4 Cross, D.L. Domperidone for treatment of equine fescue toxicosis and agalactia, instructions to veterinarians *Clemson University, Clemson SC*.