

Clinical Effects of Domperidone on Fescue Toxicosis in Pregnant Mares

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Domperidone was administered (1.1 mg/kg body weight, PO, SID) to late gestation mares that were consuming or had recently consumed endophyte-infected fescue forage. Veterinarians and/or horse owners reported the drug to be 94.5% effective in prevention of the signs of fescue toxicosis. Mares consuming the treatment did not experience increased gestation length, dystocia, agalactia or lower than normal milk production, retained placentas, premature placental separations, dead, weak or dysmature foals that have been observed in control mares. Authors' addresses: Animal and Veterinary Sciences Dept., Clemson University, Clemson, SC 29634; Director of Regulatory Affairs, Equi-Tox, Inc., Center for Applied Technology, Pendleton, SC 29670; Experimental Statistics Dept., Clemson University, Clemson, SC 29634; Chappell Equine Clinic, Rock Hill, SC 29730. © 1999 AAEP.

1. Introduction

For many years, veterinarians and mare owners reported reproductive problems in mares grazing tall fescue.^{1,2,3} Bacon⁴ reported the first conclusive evidence of the presence of an endophytic fungus, later identified as *Neotyphodium coenophialum*. In cattle, the endophyte of tall fescue was found to be related to lower weight gains, increased body temperature, rough hair coats, gangrenous necrosis of tissue in feet, tail and ears, and reduced conception rates, as reviewed by Thompson and Stuedemann.⁵ Mares were exposed to either endophyte-infected or endophyte-free fescue grass in a controlled study at Clemson University.⁶ Increased gestation lengths, agalactia, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, and reduced serum prolactin and progesterone levels occurred in mares consuming endophyte-infected pasture, whereas horses on endophyte-free pasture appeared normal (Fig. 1).

Field testing of drugs under clinical conditions is required for FDA approval of drugs. This study was conducted following the guidelines of an FDA clinical trials protocol. All horses in the study received domperidone because owners are reluctant to leave mares untreated. The objective of this study was to evaluate the clinical safety and effectiveness of domperidone for prevention and treatment of fescue toxicosis in gravid mares, under field trial conditions.

2. Materials and Methods

Domperidone (Equidone[™])^a was used to treat fescue toxicosis in late gestation mares in field trials from 1993 through 1997. Each veterinarian or horse owner participating in the study was asked to complete a Clinical Observation Form. Fourteen hundred twenty-three (1423) Clinical Observation forms were returned from 33 different states in the United States. The veterinarian was asked to diagnose fescue toxicosis on the farm before treatment was

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REPRODUCTION

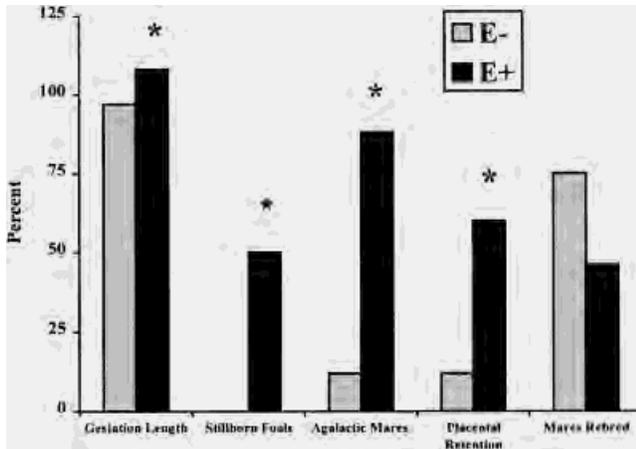


Fig. 1. Effect of endophyte-infected fescue (E+) versus endophyte-free (E-) fescue on gestation length, foal mortality, agalactia, incidence of placental retention, and rebreeding response in mares (adapted from Monroe et al., 1988). Stars indicate difference between treatments ($P < 0.05$).

initiated. A journal article describing the signs of fescue toxicosis was included in each packet sent to veterinarians,⁷ along with complete dosing instructions. The oral dose was administered once daily in a molasses based carrier in a single dose syringe at 1.1 mg/kg of body weight. Some mares were dosed in a preventative mode (dosing initiated 10 or more days before expected foaling date). However, many mares were treated only shortly before expected foaling and many were past expected foaling before dosing was initiated. Also, many of the mares had foaled and were agalactic or milking at a very low level whenever dosing was initiated. Most of the observations on the clinical report were subjective. An FDA clinical trials protocol was followed in the conduct of the study.

3. Results

A. Initiation of Treatment Relative to Expected and Actual Foaling Dates

To determine when domperidone therapy was initiated in relation to the expected foaling dates, mares were grouped according to the initiation of treatment relative to the expected foaling dates. A summary of these results can be seen in Fig. 2.

When studying trends in the initiation of domperidone therapy in mares relative to the expected foaling date, there appear to be two (02) normal distributions around time periods where the number of mares initiated peaked. The primary peak was between 10–15 days before the expected foaling date, which is the recommended initiation period. The secondary peak was between 5–10 days after the expected foaling date. This was probably the time period when mare owners began to worry about their late-foaling mares and called their veterinarian.

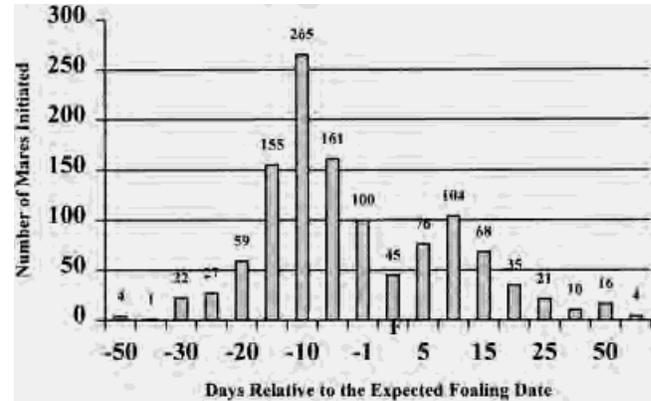


Fig. 2. The initiation of domperidone therapy in mares relative to the expected foaling date.

B. Gestation Data

Mares dosed ≥ 10 –15 days before the expected foaling date are considered to be in a “preventative mode” of therapy. Mares dosed from < 10 days before the expected foaling date to the expected foaling date are considered to be in a “treatment mode” of therapy.

In this study, mares that were dosed from 30–16 days before the expected foaling date foaled an average of 2.97 (± 1.21) days before the expected foaling date (Fig. 3).

Mares that were dosed from 15–10 days before the expected foaling date foaled an average of 3.26 (± 1.08) days after the expected foaling date (Fig. 3).

Mares that were dosed from 9–1 days before the expected foaling date foaled an average of 6.59 (± 0.97) days after the expected foaling date (Fig. 3).

In a control study by Monroe,⁶ gravid mares grazing endophyte-infected tall fescue had gestation lengths 27 days longer than mares grazing endophyte-free fescue (360 days versus 333 days; $P < 0.01$). In a control study by Putnam,⁸ gravid mares grazing endophyte-infected tall fescue had gestation lengths that were 20 days longer than mares grazing endophyte-free tall fescue (356 days versus 336 days; $P < 0.05$). Seven control mares grazing endophyte-infected tall fescue from a study by Earle⁹ had gestation lengths of 360 days (Fig. 3).

C. Udder Development Before Treatment

Question: What was mare’s udder development before initiation of treatment?

Udder development prior to domperidone therapy was observed and recorded for 1211 mares. Comments were ranked subjectively into one of five categories depending on the amount of development.

Approximately 88% of mares had little to no udder development prior to the initiation of domperidone therapy. In the study by Monroe,⁶ 87.5% of mares grazing endophyte-infected fescue were agalactic, compared with agalactia noted in 12.5% of mares grazing uninfected fescue ($p < 0.01$).

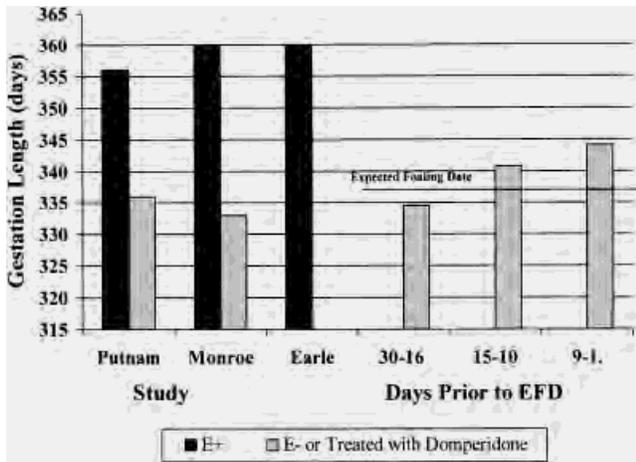


Fig. 3. Gestation lengths for mares consuming endophyte-infected tall fescue (E+) and mares consuming endophyte-free tall fescue (E-) in three separate control studies; and mares consuming endophyte-infected tall fescue in this study, receiving domperidone at different days prior to the expected foaling date (EFD). Please note that the expected foaling date for this study is based on a 337.5 day gestation length.

D. Udder Development During Treatment

Question: What was mare's udder development during treatment and up to foaling?

Udder development during domperidone therapy was observed and recorded for 1238 mares. Approximately 80% of mares had normally or rapidly developing udders after the initiation of domperidone therapy, with an additional 13% having a "good" udder at foaling (93% total). These data suggest a marked improvement in udder development after initiation of domperidone therapy when compared to udder development before domperidone therapy.

E. Mares' Lactation After Foaling

Question: Did mare appear to be lactating normally after foaling?

Mare lactation after foaling was observed and recorded for 1340 mares. It should be noted that not all of these mares received treatment before foaling; two hundred sixty-one (261) mares did not begin treatment until after the actual foaling date. A majority (76.4%) of mares were reported to have normal lactation after foaling, while 23.28% of mares did not have normal lactation after foaling. Most of these mares had not received previous domperidone therapy.

More than 83% of veterinarians and/or mare owners reporting abnormal lactation postfoaling felt domperidone therapy to be effective in the treatment/prevention of fescue toxicosis.

F. Foal Viability and Mortality

Question: Did mare have a live foal?

Of 1423 mares, data on foal births was submitted for 1369 mares. More than 98% of mares (1343)

treated with domperidone had live foal births. A summary of these results can be found in Table 1.

In the study by Earle,⁹ 86% of foals delivered on endophyte-infected fescue pasture died. In the study by Monroe,⁶ 50% of mares on endophyte-infected fescue pastures had stillborn foals. In the study reported herein, 1.9% of mares did not have live foals.

When grouped by initiation of treatment relative to expected foaling date, a higher rate of stillborn foals was observed in mares which were treated after their expected foaling date than in mares treated before their expected foaling date.

G. Placental Retention in Mares

Question: Did mare have a retained placenta?

Of 1423 mares, data on placental retention was submitted for 1322 mares. Approximately 93% of mares (1236) treated with domperidone did not have retained placentas.

When grouped by initiation of treatment relative to expected foaling date, a higher rate of placental retention was observed in mares which were treated after their expected foaling date than in those mares treated before their expected foaling date.

H. Effectiveness of Domperidone Therapy in the Treatment and Prevention of Fescue Toxicosis

Question: Do you feel that the domperidone therapy was effective in treating Fescue Toxicosis in this mare?

Of 849 mares for which data were received, 94.5% of veterinarians and/or mare owners felt domperidone therapy was effective. A summary of results can be found in Table 2.

I. Effectiveness of Domperidone Therapy in the Prevention of Fescue Toxicosis

The raw data from this question are summarized in Table 3.

Domperidone therapy was felt to be effective in the prevention of fescue toxicosis in 95.2% of mares treated.

4. Discussion

Data from this and previous work that we conducted indicate that domperidone is effective in the prevention and treatment of fescue toxicosis in periparturient mares.

Although the recommended method for preventing fescue toxicosis in periparturient mares is removal from fescue feed-sources 60-90 days prior to the expected foaling date, only 2.7% of the mares in this

Table 1. Birth Status of Foals From Mares Receiving Domperidone Therapy.

Response	Number of Foals
Live Birth	1343 (98.10%)
Stillborn	26 (1.90%)

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Table 2. A Summary of the Effectiveness Data for Mares Receiving Domperidone Therapy for Treatment of Fescue Toxicosis

Response	Number of Mares
Effective	802 (94.47%)
Not Effective	40 (4.71%)
Not Certain	7 (0.82%)

study were so removed. Approximately 36% of the mares were removed from fescue at some point, before or after foaling. These and other data indicate that removal from fescue may not be a *practical* option for the majority of mare owners.

Mares dosed in a preventative mode foaled near to their expected foaling date, avoiding the very long gestation times and the very dramatic detrimental effects associated therewith and reported in control studies for mares on toxic fescue.

Little to no udder development was reported in 88% of the mares before the initiation of domperidone therapy. After receiving domperidone therapy, 93% of mares had a "good" udder at foaling.

Over 76% of the mares were reported to have normal lactation after foaling compared to only 9% of the mares in the Putnam⁸ control study and approximately 12% of the mares in the Monroe⁶ control study. Of those mares lactating *abnormally* post-foaling, 75% did not receive domperidone therapy until after foaling. Of those abnormally lactating mares, 83% of their owners and/or veterinarians felt that domperidone therapy was effective. This may be due to the fact that in many of these cases, domperidone therapy was utilized for postfoaling, fescue-related agalactia.

A live foal birth was reported for over 98% of the mares in this study, compared to 27% of the mares in the Putnam control study, 50% in the Monroe control study, and 14% in the Earle⁹ control study. There was a higher rate of stillborn foals in mares whose treatment was initiated after their expected foaling

Table 3. A Summary of the Effectiveness Data for Mares Receiving Domperidone Therapy for the Prevention of Fescue Toxicosis.

Response	Number of Mares
Effective	790 (93.3%)
Not Effective	40 (4.7%)
Not Certain	7 (0.8%)
Not Applicable	10 (1.2%)

date. There was no placental retention in 93% of the mares, compared with approximately 40% of the mares in the Monroe⁶ control study. There was a higher rate of placental retention in mares whose treatment was initiated after their expected foaling date.

Of abnormal observations, the majority were related to milk and/or colostrum production levels. Prefoaling milk leakage should be listed as a precaution for the use of the drug. Also, domperidone may stimulate gastrointestinal motility since it is a gastrointestinal prokinetic drug. Therefore, some precaution should be exercised in the use of domperidone in mares that are suffering from colic where intestinal blockage is suspected.

Approximately 95% of veterinarians and/or mare owners felt that domperidone therapy was effective in the treatment and prevention of fescue toxicosis.

This study provides evidence that domperidone is safe and efficacious for the prevention and treatment of fescue toxicosis in periparturient mares under field conditions.

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