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Efficacy of domperidone gel in an induced model of fescue toxicosis in periparturient mares

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Abstract

The objective was to evaluate the efficacy of domperidone in the prevention of reproductive complications of fescue toxicosis in periparturient mares. Pregnant mares at ≤310 days of gestation were fed ≥200 μg ergovaline per kg diet daily in endophyte-infected fescue hay and seed, starting ≥30 days before their expected foaling date (EFD: 340 days after breeding). Thirty-five mares were randomized to a treatment group to receive either domperidone gel (n = 20, 1.1 mg/kg, PO, once daily) or placebo (n = 15). Treatment was initiated 10 to 15 days before the EFD and continued for 5 days after foaling. "Treatment success" was defined as foaling within 14 days of the EFD, adequate mammary development on the day of foaling, and adequate lactation for 5 days postpartum. Twenty-seven mares were included in the effectiveness analysis. More mares in the domperidone group (12/13, $P < 0.0001$) were treatment successes than in the control group (1/14). Gestation length was shorter ($P = 0.0011$), and lactation at foaling ($P = 0.0011$) was better for the domperidone-group mares. Foals from two control mares were born dead and four others died or were euthanized within a few days after birth, compared with one foal death (an autolyzed twin) from a domperidone-treated mare. Plasma IgG concentrations were evaluated in 24 foals. Failure of passive transfer of immunoglobulins (IgG <800 mg/dL) occurred in 13/16 (81%) foals of domperidone-group mares and 7/8 (88%) foals of control mares. In conclusion, the reproductive complications of fescue toxicosis in periparturient mares induced by a fescue seed/hay model were prevented by treatment with domperidone.

Keywords: Domperidone; Fescue; Horse; Endophyte; Pregnancy; Neonate

1. Introduction

Tall fescue, *Schedonorus phoenix* (formerly *Lolium arundinacea*, and *Festuca arundinacea* [1]) is a hardy perennial grass adapted to humid, temperate areas. Between 58 and 63 percent of tall fescue sampled from over half of the continental USA was infected with the endophyte *Neotyphodium coenophialum* [2,3], (formerly *Acremonium coenophialum, Sphacelia typhina* and *Epichloë Typhina* [4]) the causative agent of fescue toxicosis (*N. coenophialum* infected *S. Phoenix* is referred to as toxic fescue).

The clinical signs of fescue toxicosis in pregnant mares were first reported in 1980 when mares grazing

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fescue pastures had an incidence of agalactia twelve times that of the general population of mares grazing other pastures [5]. Clinical signs of fescue toxicosis include prolonged gestation [6–8], reduced mammary development [8], reduced milk production [7–10], premature allantochorionic separation [11], retained placenta [7], prolonged gestation [7,9], a heavy, tough placenta [12], thickened amnion [13], stillbirth [9–11], dystocia (secondary to foals having large, poorly muscled skeletons), and foals born with overlong hooves [6,9].

The *N. coenophialum* produces ergot alkaloids, including ergovaline, ergosine, ergocryptine, ergocrystine and ergonine [14], of which ergovaline and ergocryptine have been identified in the plasma of mares with fescue toxicosis [15], and lysergic acid [16], identified in the plasma of geldings fed toxic fescue [17]. The most abundant ergot alkaloid in toxic fescue is ergovaline [14,18,19].

The effects of ergovaline on prolactin secretion [20] suggest that dopamine antagonists may prevent fescue toxicosis. In mares, plasma prolactin concentrations increase in the week prior to foaling, coinciding with mammary development and physiological preparation for parturition [21]. Plasma prolactin concentrations in mares with fescue toxicosis are significantly lower in early pregnancy [22], late pregnancy [8], and at foaling [7], compared with normal mares, but increase in pregnant mares following removal from toxic fescue pasture [8,23].

Secretion of prolactin by lactotropes in the anterior pituitary is tonically inhibited by dopamine acting at dopamine-2 (D_2) receptors; consequently, D_2 receptor antagonism increases prolactin secretion [24]. *In vitro*, domperidone reverses the inhibitory effects of low concentrations of ergovaline on prolactin secretion [20], and, at a daily dosage of 1.1 mg/kg body weight, can prevent fescue toxicosis in mares [8]. Domperidone, a selective D_2 receptor antagonist, is unlike other D_2 receptor antagonists in that it does not cross the blood–brain barrier [25]. Neuroleptic effects in other dopamine antagonists (e.g., metoclopramide, fluphenazine) preclude their long-term use. Treatment of mares with the ergot derivative bromocriptine, a D_2 receptor agonist, elicited clinical signs as seen in fescue toxicosis, and decreased plasma prolactin concentrations on the day prior to foaling [26].

Ineffective treatments for equine fescue toxicosis include feeding a high caloric diet [27], intramuscular selenium supplementation [7,10], and administering phenothiazine [28]. Removal of mares from infected pasture at 300 days of gestation resulted in foaling events similar to those experienced by mares not exposed to toxic fescue [6].

This study comprised two parts: 1) a pilot study to validate a model for inducing fescue toxicosis in periparturient mares fed tall fescue seed and hay providing $\geq$200 μg ergovaline per kg of total daily ration; and 2) a controlled study, using this model, to investigate the efficacy of a domperidone gel at 1.1 mg/kg for preventing fescue toxicosis in periparturient mares.

2. Materials and methods

2.1. Pilot study

2.1.1. Mares and husbandry

Pregnant mares with a known breeding date were enrolled into the study. Mares were acclimated to the facility for approximately 2 wk before initial treatment, during which time water, housing conditions, and feeding were identical to those provided during the treatment phase of the study. Mares were housed individually in 3.7 $\times$ 7.3 m stalls within a building with open sides until approximately 2 wk before the expected foaling date (EFD), when they were moved to enclosed 3.7 $\times$ 7.3 m foaling stalls. After foaling, mares and foals either remained in the foaling stalls, or were returned to individual stalls in the same facility (used for acclimation). Water was supplied by a local utility and was available *ad libitum*.

Within 12 to 24 h after initial suckling, plasma samples were collected from each foal and Immunoglobulin G (IgG) concentrations were analyzed using a commercial kit (SNAP Foal IgG Test, Idexx Laboratories, Westbrook, ME). Foals with failure of passive of IgG (FPT), defined as plasma IgG $<$800 mg/dL, were given one unit (1 L) of equine plasma (Hi-Gamm Equi, Lake Immunogenics, Ontario, NY, USA) iv. Foal IgG concentrations were rechecked as needed, and additional plasma was administered if indicated. Standard foaling management procedures (e.g., administration of tetanus antitoxin, phosphate enemas, and dipping the navel in iodine) were conducted. Neither colostrum nor milk were analyzed. Foals of mares with poor or inadequate mammary gland development were bottle-fed milk replacer for foals (Foal-Lac Powder, PetAg, Inc., Hampshire, IL, USA).

2.1.2. Induction of toxicosis

Ergovaline concentrations in endophyte-infected tall fescue hay and seed were determined by HPLC assay, conducted at University of Missouri Veterinary Medi-