

Equine Fescue Toxicosis: Signs and Solutions¹

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ABSTRACT: Gravid mares grazing endophyte-infested (E+) tall fescue exhibit increased gestation lengths, agalactia, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, increased sweating during warm weather, reduced serum prolactin and progesterone, and increased serum estradiol-17 β levels. Also, E+ tall fescue hay is less digestible than endophyte-free (E-) hay. Unlike many other species, horses consuming E+ tall fescue do not exhibit increased body temperature. Young horses consuming only E+ pasture do not gain as well as those consuming E- pasture. There is little

difference in gain when the pasture is supplemented with enough concentrate to meet NRC requirements for growth. Neither selenium injections nor supplementing with corn at 50% of the NRC requirements for energy reduces the effects of toxic tall fescue on reproduction and lactation in gravid mares. It seems that the alkaloids of E+ tall fescue are serving as D2 dopamine receptor antagonist. Domperidone, a dopamine receptor antagonist, is effective in preventing the signs of tall fescue toxicosis in horses without neuroleptic side effects.

Key Words: Horses, *Festuca arundinacea*, Toxinogenic Fungi, Dopamine, Receptors, *Acremonium Coenophialum*.

Introduction

Approximately 688,000 horses in the United States are kept on tall fescue (Hoveland, 1993), and for many years veterinarians and horse owners have reported reproductive problems in mares that consume tall fescue (Garrett et al., 1980; Poppenga et al., 1984; Villahoz et al., 1984). Bacon et al. (1977) reported the first conclusive evidence of the presence of an endophytic fungus in tall fescue. The fungus was later identified as *Acremonium coenophialum* (Morgan-Jones and Gams, 1982). 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 (1993). Monroe et al. (1988) provided the first conclusive evidence that the endophyte of tall fescue (*Acremonium coenophialum*) was the causative agent for reproductive abnormalities in gravid mares (Figure 1). They reported increased gestation lengths, agalactia, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, and reduced serum prolactin and progesterone levels in mares consuming endophyte-infested (E+) pasture, whereas horses on endophyte-free (E-) pasture appeared normal.

Clinical Signs

Physiological Effects

Body Temperature and Blood Flow. In cattle and sheep, blood flow to the peripheral tissues decreased and body temperature increased when tall fescue seed was included in the diet (Rhodes et al., 1991). The reduction in blood flow to the peripheral tissues is probably related to the increased body temperature because the animal is less efficient in cooling itself. Unlike cattle and sheep, pregnant mares exhibit no

increase in body temperature when they are exposed to the endophytic toxins (Monroe et al., 1988; Putnam et al., 1991). However, horses sweat more freely than cattle and are more capable of cooling themselves by sweating. Putnam et al. (1991) observed an increase in sweating in gravid mares grazing E+ tall fescue.

In cattle, it seems that peripheral vasoconstriction caused by the alkaloids of E+ tall fescue is related to "fescue foot" (Solomons et al., 1989). There have been no reports of a similar malady in horses.

Figure 1. Effect of endophyte-infested tall fescue on gestation length (percentage of expected parturition date), foal mortality, agalactia, incidence of placental retention, and rebreeding response in mares (adapted from Monroe et al., 1988). Difference ($P < .05$) between treatments is indicated by an asterisk.

Gestation Length. Mares consuming E+ tall fescue have been shown to have gestation lengths in excess of the normal range of 335 to 345 d (Monroe et al., 1988; Putnam et al., 1991; Redmond et al., 1991a). Progesterone is an essential hormone required for pregnancy maintenance in gravid mares

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(Squires, 1993). Secretion from the primary corpus luteum (CL) results in an increase in serum progesterone levels during the 1st wk after conception, then a gradual decrease until about the end of the 1st month. Concentrations of progesterone then increase dramatically between d 30 and 40. This rise in progesterone occurs at approximately the same time as the formation of endometrial cups and secretion of equine chorionic gonadotrophin, which stimulates secretion of progesterone from secondary CL. Progesterone concentrations peak at 2 to 3 months after conception. By the 6th month, progesterone levels are very low and remain low until approximately 1 month before parturition, when the levels again begin to rise up to the point of parturition (Pashen, 1984). Additionally, a non-ovarian source of progesterone, possibly the placenta, is maintaining pregnancy during the later stages of pregnancy (Squires, 1993). Pashen (1984) suggested that the rise in progesterone and other progestogens observed during late pregnancy is a result of altered progesterone metabolism by the placenta, and that this alteration of progesterone metabolism is a result of increased fetal cortisol levels. Monroe et al. (1988), Redmond et al. (1993), and Taylor (1993) have documented reduced serum progesterone levels in gravid mares consuming E+ tall fescue during late gestation (Figure 2). Also, ergot alkaloids have been shown to block cortisol-releasing hormone (CRH)-stimulated adenylate cyclase activity in rat *pars intermedia* cells in vitro (Labrie et al., 1983). Additionally, Giguere et al. (1982) found that CRH stimulates adrenocorticotrophic hormone release from anterior pituitary cells via a cyclic adenosine monophosphate (cAMP)-dependent mechanism. Therefore, it is possible that the ergot alkaloids of tall fescue may cause prolonged gestation in mares by inhibiting fetal CRH activity. However, direct evidence for this theory does not exist.

reproductive tract for foaling, prolonged gestation, and fetal malpresentation. Foals usually have larger than normal skeletal frames due to the prolonged gestation, increasing the difficulty of expelling a fetus through an unprepared tract (Monroe et al., 1988; Putnam et al., 1991; Redmond et al., 1991a). Additionally, foals are often rotated 90 to 180 degrees from the normal position for delivery (Taylor et al., 1985; Monroe et al., 1988; Redmond et al., 1991a). The failure of the mare, or the foal, to initiate the events that prepare for and result in normal parturition results in the subsequent catastrophic events of dystocia, as well as mare and foal mortality in many instances.

Milk Production and Agalactia. The effects of endophyte consumption on milk production depend on the species of animal in question. Cattle (Strahan et al., 1987; Porter and Thompson, 1992; Schmidt and Osborn, 1993), sheep (Stidham et al., 1982), and mice (Zavos et al., 1988) have been shown to have reduced milk yields, whereas horses (Monroe et al., 1988, figure 2) and rabbits (Daniels et al., 1984) exhibit complete agalactia. The connection between tall fescue toxicosis and lactogenesis seems to be through the effects of the ergot alkaloids on lactogenic hormones. Cattle, sheep, and mice have both placental lactogen and prolactin (Forsyth, 1986). In contrast, horses and rabbits rely on prolactin to stimulate prepartum lactogenesis (Forsyth, 1986). The depressive effects of ergot alkaloids on prolactin secretion may suppress prolactin's effect on lactogenesis in cattle, sheep, and mice but have no effect on placental lactogen. As a result, the placental lactogen and the small level of pituitary prolactin may be sufficient to initiate prepartum lactogenesis in these species and would allow lactation to begin after parturition. In the horse, it seems that the reduced prolactin secretion from the pituitary lactotrophic cells results in agalactia. Apparently, the alkaloids of tall fescue are serving as D2 dopamine receptor agonists at the pituitary level (Strickland et al., 1992). Also, unlike ruminants, the horse does not benefit from pre-gastric metabolism of alkaloids and would be subject to larger doses of the alkaloids from E+ tall fescue (Wachenheim et al., 1992).

Figure 2. Effect of endophyte-infested tall fescue and domperidone treatment on serum progesterone levels in gravid mares. First detectable differences ($P < .05$) from pretreatment levels are indicated by an asterisk. Unless otherwise indicated, data points represent four mares per treatment (dagger indicates number of mares in E- group). Mares that were not prepared for parturition 7d after the calculated date of parturition (as determined by veterinary examination) were relocated to endophyte-free pasture (from Redmond, 1994).

Dystocia. The incidence of dystocia in horses is increased by endophyte consumption (Monroe et al., 1988, figure 2; Green et al., 1991; Putnam et al., 1991; Redmond et al., 1991a). The dystocia seems to be a result of inadequate preparation of the

Figure 3. Effect of endophyte-infested tall fescue and domperidone treatment on serum prolactin levels in gravid mares. First detectable differences ($P < .05$) from pretreatment levels are indicated by an asterisk. Unless otherwise indicated, data points represent four mares per treatment. Mares that were not prepared for parturition 7d after the calculated date of parturition (as determined by veterinary examination) were relocated to endophyte-free pasture (from Redmond, 1994)

Prolactin. One of the most consistent signs of tall fescue toxicosis is decreased serum prolactin levels in animals consuming E+ tall fescue (Neal and Schmidt, 1985; Bond and Bolt, 1986; Elsasser and Bolt, 1987; Earle et al., 1990; Redmond, 1994; figure 3).

For an in-depth study of the control of prolactin secretion in mammals, the reader is referred to a review by Ben-Jonathan et al. (1989). Only a brief explanation of control of prolactin secretion will be presented herein; however, it is felt that prolactin and dopamine receptors are of such importance in the equine tall fescue toxicosis malady that they warrant some discussion. Control of prolactin secretion from lactotrophs of the anterior pituitary is primarily through tonic inhibition by dopamine, produced in the hypothalamus or posterior pituitary (Peters et al., 1981; Ben-Jonathan et al., 1989). Dopamine is transported to the anterior pituitary via the hypothalamic/hypophysial portal system (Guyton, 1986). Dopamine exerts its inhibitory action on prolactin secretion through interaction with the D2 dopamine receptor located on the lactotrophic cell. Interaction with this receptor is thought to activate a pertussis-sensitive G protein (Boyd et al., 1988), which in turn may cause a decrease in cAMP and calcium concentrations in the lactotroph as well as a hyperpolarization of the cell membrane (Ben-Jonathan et al., 1989). Compounds interacting with this receptor as agonists will cause a suppression in prolactin secretion.

Although primary control of prolactin secretion in mammals is through tonic inhibition, stimulatory mechanisms are also involved in the control of prolactin secretion (Ben-Jonathan et al., 1989; Jones et al., 1989; Sortino, et al., 1989; Mori et al., 1990).

The involvement of prolactin in mammary development and in the initiation of lactation has been well documented (Houdebine et al., 1985). However, prolactin has been reported to have receptors in other tissues as well. These include liver, kidney, cerebral cortex, and seminal vesicles (Turkington and Frantz, 1972). The location of saturable binding sites for prolactin in tissues other than mammary tissue indicates its importance in other processes besides lactation. Prolactin affects the circadian rhythm of lipogenesis and insulin receptor numbers in hepatic tissue of hamsters (Cincotta and Meier, 1985a, 1989). Prolactin treatment of *in vitro* hamster hepatocytes increased the lipogenic rate in relation to untreated hepatocytes (Cincotta and Meier, 1989). Additionally, Cincotta and Meier (1985b) reported that inhibition of prolactin secretion in hamsters decreased hepatic lipogenic rates. Therefore, a reduction in serum prolactin levels in animals receiving a diet of E+ tall fescue may partially explain the reduced body weight gains seen in these animals, should prolactin elicit similar effects on lipogenesis in animals other than hamsters. Additionally, prolactin has been reported to increase feed intake in female rats in a dose-related manner (Gettens et al., 1989). Because reductions in feed intake and serum prolactin are signs of animals grazing E+ tall fescue, it is possible that the lowered serum prolactin levels are involved in the reduction of feed intake.

Prolactin has been reported to act as an immunomodulator (Hiestand and Mekler, 1986; Mukherjee et al., 1990; O'Neal and Yu-Lee, 1991; Yu-Lee et al., 1991). A recent report by Gay et al. (1990) indicated that mice and rats given a diet of E+ tall fescue seed exhibited impaired immune function. However, cattle did not show a similar response. Other effects

of prolactin in mammals include synergistic effects with steroid hormones on male and female gonads, water and electrolyte balance, effects on male sex accessory glands (conditioning effect), and temperature regulation (Nicoll and Bryant, 1972; Faichney and Barry, 1986).

Although prolactin is necessary to initiate lactogenesis, the involvement of progesterone and estrogen in lactation is significant. Estrogen and progesterone stimulate development of ductal and secretory structures when mammary tissue is primed with insulin, aldosterone, and prolactin (Forsyth, 1983). Estrogen is necessary for the cell division in terminal end buds that leads to ductal growth, and progesterone stimulates lobulo-alveolar growth. Prolactin is necessary to prime mammary tissue and apparently acts synergistically with estrogen and progesterone to promote mammary tissue growth (Forsyth, 1983). Mammary development in the horse begins 2 to 6 wk before parturition (Evans, 1990), but Worthy et al. (1986) have shown that the large increase in prolactin levels occurs only 5 to 10 d before parturition. Progesterone levels in normal gravid mares rise during the last 30 to 40 d of gestation and estrogen levels decrease (Pashen, 1984). Research by Redmond et al. (1993), Redmond (1994), and Taylor (1993) show opposite patterns for prolactin, progesterone, and estradiol-17 β (Figures 2, 3, and 4). Mares grazing E+ pastures have lower serum progesterone and prolactin and higher estradiol-17 β than normal mares during the latter stages of gestation. The alteration in the levels of these hormones in gravid mares grazing E+ pastures and their interaction in mammary tissue development and subsequent lactation is significant in explaining the agalactia seen in these mares.

Figure 4. Effect of endophyte-infested tall fescue and domperidone treatment on serum estradiol-17 β levels in gravid mares. First detectable differences ($P < .05$) from pretreatment levels are indicated by an asterisk. Unless otherwise indicated, data points represent four mares per treatment (dagger indicates number of mares in endophyte-free group; ** represents number of mares in 1.65 and 2.2 mg of domperidone/kg BW groups). Mares that were not prepared for parturition 7d after the calculated date of parturition (as determined by veterinary examination) were relocated to endophyte-free pasture (from Redmond, 1994).

Effects of Growth Rate and Digestibility.

Consumption of E+ tall fescue or treatment with its extract causes a reduction in rate of gain and feed intake in cattle (Schmidt et al., 1982; Hoveland et al., 1983; Bond and Bolt, 1986), rats (Neal and Schmidt, 1985), and rabbits (Daniels et

al., 1984). No reduction in growth rate was observed in yearling horses when corn-based concentrates were used to supplement E+ or E- hay (McCann et al., 1992). Also, Pendergraft and Arns (1993) observed similar gains in yearling horses consuming E+ or E- hay with concentrate supplementation to meet NRC requirements for growth. However, average daily gains were reduced by 57% (.24 and .56 kg for high- and low- endophyte treatments, respectively) in yearling horses grazing E+ pasture without supplementation (Aiken et al., 1993). These researchers observed a similar reduction in gain in steers in the same study.

Redmond et al. (1991b) and McCann et al. (1992) observed lower intake and digestibility for E+ hay fed to mature geldings and yearling horses, respectively. McCann et al. (1993) and Pendergraft and Arns (1993) found no differences in digestibility due to the presence of the endophyte in hay when yearling horses were fed concentrate with hay. Concentrate supplementation was used in both studies to meet NRC requirements for growth for yearling horses.

These results suggest that the effects of endophyte consumption on digestibility and growth rate may be lessened by the inclusion of concentrates in the diet. In contrast, energy supplementation has no beneficial effects for alleviating the lactation and reproductive problems seen in gravid mares that graze E+ pasture (Earle et al., 1990).

Dopamine Receptors: Possible Involvement in Tall Fescue Toxicosis

Evidence of Dopamine Receptor Involvement

The consistent observation of decreased serum prolactin levels in animals receiving diets of E+ tall fescue (Porter et al., 1985; Bond and Bolt, 1986; Elsasser and Bolt, 1987; Evans et al., 1988; Monroe et al., 1988; Redmond et al., 1991a,b) indicates the involvement of dopamine receptors in tall fescue toxicosis. This conclusion, based on reduced serum prolactin levels, is derived from dopamine's involvement in the control of prolactin secretion *in vivo*. Also, several recent studies provide further evidence of dopamine receptor involvement in tall fescue toxicosis. Strickland et al. (1992) used isolated pituitary cell preparations and provided evidence that the alkaloids of tall fescue are acting as dopamine agonists to effect a reduction in prolactin production from the lactotroph cells. Ireland et al. (1991) demonstrated that the selective dopamine agonist bromocriptine (Fluckiger, 1975) could cause signs of equine fescue toxicosis. Redmond et al. (1992) demonstrated that a selective D2 dopamine receptor antagonist, domperidone (Stoof and Keabian, 1984), was capable of eliminating the signs of equine tall fescue toxicosis. Kitzman et al. (1986) and Lipham et al. (1989) also reported that a dopamine antagonist, metoclopramide, reversed signs of tall fescue toxicosis in cattle. These studies strongly support the involvement of dopaminergic mechanisms in tall fescue toxicosis.

Dopamine Receptors, Locations, and Action

Five different subclasses of the dopamine receptor have been identified on the basis of biochemical, molecular, and pharmacological properties. The subclasses are D1 and D2 (Keabian and Calne, 1979), D3 (Sokoloff et al., 1990), D4 (Van Tol et al., 1991), and D5 (Sunahara et al., 1991). Dopamine receptors are dispersed throughout the body and

seem to affect the function of several tissues (Hosgood, 1990). Tissues listed as having D1 and D2 dopamine receptors include renal and mesenteric vascular smooth muscle (vasodilatory effect, D1 receptor), the striatum (inhibit acetylcholine and dopamine release, D2 receptor), bovine parathyroid gland (increase parathyroid hormone release, D1 receptor), carotid body (depression of chemosensory activity, D2 receptor), sympathetic nerve terminals (inhibit norepinephrine release, D2 receptor), and the anterior and intermediate lobes of the pituitary gland (prolactin and α -melanocyte-stimulating hormone, D2 receptor), as well as others (Cooper et al., 1991). The D3, D4, and D5 receptors have only recently been identified; therefore, studies of the biochemical and pharmacological activities of these receptors are just beginning. Some of the aforementioned receptor activities listed for the D1 and D2 receptor subtypes may actually be mediated through these newly discovered dopamine receptor subtypes. It should also be noted that the pharmacological activity of the ergot alkaloid group of tall fescue toxins is different for the D1 and D2 receptors. These alkaloids interact with the D2 receptor in an agonistic fashion, whereas interaction with the D1 dopamine receptor is in an antagonistic fashion (Siegel et al., 1989).

Again, reduction in prolactin secretion is most likely caused by agonistic interaction of tall fescue toxins with the D2 receptor on the lactotroph. As previously mentioned, feed intake seems to be reduced when animals consume tall fescue toxins. Feed intake may be affected by toxin interaction with dopaminergic mechanisms. Several reports indicate that dopamine is capable of modifying gut motility (Sorraing et al., 1984; King and Gerring, 1988; Stafford and Leek, 1988; Clark and Moore, 1989). Likewise, dopamine is known to stimulate the feeding center of the hypothalamus (Newsholme and Leech, 1983) and have effects on mesenteric blood vessels (Gilman et al., 1990). Therefore, compounds interacting with dopamine receptors, such as the ergot alkaloids, might have an effect on gut motility, gut perfusion, and digestion kinetics, thus possibly altering nutrient availability as well as feed intake. The distribution and wide range of physiological activities of the dopamine receptors suggest that these receptors should receive more attention in the future as sites of action for the tall fescue toxins.

Approaches to Solving Fescue Toxicosis

Selenium

Early studies with horses indicated that administration of selenium might alleviate the effects of E+ tall fescue on pregnant mares (Heimann et al., 1981). However, a subsequent study by Taylor et al. (1985) found that selenium had no effect. Also, Monroe et al. (1988) injected mares on E- and E+ tall fescue pasture with selenium intramuscularly (2.5 mg/kg body weight) at 28-d intervals. Monroe et al. (1988) confirmed the findings of Taylor et al. (1985) by showing that there were no beneficial effects in relieving the signs of tall fescue toxicosis attributed to selenium therapy. Additionally, Monroe et al. (1988) demonstrated conclusively that the problems associated with consumption of tall fescue are due to presence of the endophyte by showing that mares grazing E-tall fescue exhibited none of the problems observed in mares consuming E+ tall fescue.

Dilution of Toxin Intake

Earle et al. (1990) fed gravid mares 50% of the NRC requirement for energy as cracked corn for the last 90 d of gestation. There were no beneficial effects as a result of grain feeding. Foal mortality was 66 and 100% for the energy and no energy supplement treatments, respectively. Mare mortality was 66 and 50% for the energy and no energy supplement treatments, respectively. This study also confirmed the severity of the problems under the conditions in South Carolina.

Withdrawal from Pasture

A survey of equine veterinary practitioners in the tall fescue growing regions of the United States (Cross et al., unpublished data) indicated that most veterinarians are recommending that gravid mares be withdrawn from E+ pastures from 6 wk up to 3 mo before expected parturition. Many times selenium and vitamin E injections were combined with the recommendation. Personal communications with private horse owners indicate that some gravid mares exhibit tall fescue toxicosis even though toxic sources of tall fescue have been withdrawn from them at least 60 d before expected foaling date. These observations are somewhat inconsistent with the data of Earle et al. (1990), Redmond et al. (1991a), and Taylor (1993), showing rapid recovery of mares that are withdrawn from E+ pastures and moved to either E- pastures or other feed sources at or near foaling. Taylor (1993) withdrew mares grazing E+ tall fescue 10, 20, or 30 d before expected foaling date. Other than having more retained placentas, mares withdrawn 30 d before expected foaling date were similar to mares grazing E-tall fescue with respect to lactation, foaling, and hormone patterns. Mares withdrawn either 20 or 10 d before expected foaling date had more agalactia and altered hormone patterns with only one dead foal (10 d group).

Phenothiazine

Redmond et al. (1991a) administered phenothiazine orally (2 g·mare⁻¹·d⁻¹) for 40 d before expected foaling date. Phenothiazine was ineffective in relieving any of the signs associated with tall fescue toxicosis in gravid mares.

Dopamine Antagonists

Although not present in tall fescue, bromocriptine is an ergot alkaloid and a dopamine receptor agonist. Ireland et al. (1991) administered bromocriptine to gravid pony mares and observed signs that were similar to those seen in mares grazing E+ tall fescue. Administration of perphenazine, a dopamine receptor antagonist and a phenothiazine derivative, provided some relief in the signs seen with bromocriptine administration. In non-pregnant pony mares, administration of perphenazine at 1.0 mg/kg body weight increased plasma prolactin but resulted in hyperesthesia (Loch et al., 1990). Metoclopramide has been used to increase plasma prolactin levels and decrease body temperature in calves grazing E+ pasture (Lipham et al., 1989). In rats, fluphenazine and trifluoperazine had mammotrophic effects (Ben-David et al., 1965). Other drugs such as chlorpromazine and acepromazine have some potential for dopamine antagonist activity, but all of the aforementioned drugs can have considerable neuroleptic activity because all cross the blood-brain barrier and have central nervous system activity. The potential for secondary

neuroleptic effects negates these drugs from serious consideration as treatments for tall fescue toxicosis. Redmond et al. (1992) administered domperidone orally (1.10 mg/kg body weight) to gravid mares grazing E+ tall fescue. Domperidone increased serum prolactin and progesterone and provided what seemed to be nearly complete recovery of gravid mares from tall fescue toxicosis without side effects of the drug. Treated mares had milk, live foals, and gestation length. Subsequently, Redmond et al. (1993) conducted a dose titration study to determine the minimum effective dose of domperidone for treating tall fescue toxicosis. Again, domperidone provided recovery from tall fescue toxicosis in gravid mares and the minimum effective oral dose was 1.1 mg/kg body weight when administered daily for 30 d before foaling. Subcutaneous administration of .44 mg/kg body weight of domperidone for 10 d before expected foaling date provided recovery from tall fescue toxicosis in a recent study (E.K. Altom, Clemson University, unpublished data). During the 1993 foaling season this author, under a U.S. Food and Drug Administration "Investigational New Animal Drug" number, supervised the administration of domperidone by three different veterinary groups to 15 gravid mares in Virginia. These mares had been diagnosed as having signs of tall fescue toxicosis. All mares appeared to foal normally and lactated. In all cases, domperidone therapy was terminated at foaling.

Implications

The alkaloids of endophyte-infested tall fescue are highly toxic to gravid mares, causing increased gestation lengths, agalactia, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, increased sweating during warm weather, reduced serum prolactin and progesterone, and increased serum estradiol-17B levels. Daily dosing of gravid mares with domperidone will prevent these signs of toxicity without side effects. Therefore, treatment with domperidone could be of considerable value for preventing pain and suffering and in reducing the economic losses associated with equine fescue toxicosis.

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