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Induction and maintenance of gastric ulceration in horses in simulated race training

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Summary

Gastric ulceration is a prevalent condition of racehorses. A number of models of gastric ulceration have been described, but none mimic the conditions of a horse in training. The objectives of this study were to determine whether gastric ulcers could be induced and maintained in a group of horses in simulated race training. In addition, serum cortisol was measured on a weekly basis to investigate the possibility that stress may be important in the pathogenesis of gastric ulceration. Thirty horses used in the trial were fed Bermuda grass hay and 6 kg of a concentrate diet, and exercised 6 days/week at speed over a distance of 1.6–2.4 km. Serum was collected and gastroendoscopic examinations performed on a weekly basis for the duration of the trial. All horses developed moderate to severe ulceration, and ulcers were maintained for the 56 day period of the trial. Only one horse had signs of abdominal discomfort, which resolved with minimal symptomatic treatment and without the use of anti-ulcer medications. Serum cortisol remained within reference ranges for the duration of the trial. Although there was some variation between the weekly examinations, serum cortisol concentrations were decreased from values obtained at the start of the trial. In this study ulcers developed without the administration of nonsteroidal anti-inflammatory agents or withholding of feed. This model provides a method to study the condition, and to investigate the effects of medications on the healing of ulcers in racehorses.

Introduction

Gastric ulcers have been identified relatively frequently in foals (Traub *et al.* 1983; Becht and Byars 1986; Murray *et al.* 1990) and adult horses (Acland *et al.* 1983; Murray *et al.* 1989; Vatistas *et al.* 1994a,b; Murray *et al.* 1996). Endoscopic surveys of the stomachs of Thoroughbreds in active race training have identified gastric ulceration in 81–89% horses (Murray *et al.* 1989; Vatistas *et al.* 1994a,b; Vatistas 1998). Gastric ulceration in mature horses has been associated with clinical evidence of abdominal discomfort (Murray *et al.* 1989). Colic was attributed to the presence of gastric ulceration in 31 horses on the basis of a lack of lesions at exploratory laparotomy and an alleviation of abdominal discomfort following anti-ulcer therapy (Murray *et al.* 1989). However, other studies have suggested that overt abdominal pain may be a less common sequelae to the development of gastric ulceration (Vatistas *et al.* 1994a,b).

Although commonly observed in Thoroughbreds, the aetiology of gastric ulceration in horses remains to be elucidated due, in part, to the lack of a suitable model and the difficulties involved in performing research on client-owned horses. Gastric ulceration may be induced by alternately feeding and fasting horses (Murray 1994). However, ulcers had healed in the majority of animals which were examined endoscopically 7 days following the final period of fasting (Murray 1994). Spontaneous resolution of ulcers is uncommon clinically in horses maintained in active training. Models have also used nonsteroidal anti-inflammatory medications (NSAIDs) to produce ulcers in ponies (Jones 1983; MacAllister and Sangiah 1993). Ulcers induced by the administration of NSAIDs may have a dissimilar endoscopic appearance to naturally occurring ulcers (D.R. Thompson, personal communication) and gastric ulceration in horses in race training is rarely associated with the administration of NSAIDs (Vatistas *et al.* 1994b; Murray *et al.* 1996; Vatistas 1998). In addition, ulcers caused by NSAID administration frequently affected the glandular mucosa (Furr and Murray 1989; Kumaran and Bhuvanakumar 1994) and tended to heal spontaneously (Jones 1983; MacAllister and Sangiah 1993), both of which occurrences are infrequent in the clinical setting (Vatistas and Snyder 1997; Vatistas 1998). Spontaneous healing of ulcers, following induction of ulceration by either fasting or NSAID administration, precludes the evaluation of anti-ulcer medication. Clinical studies conducted at the race track designed to determine the effectiveness or the appropriate dosage of anti-ulcer medication are hampered by the lack of client compliance, the use of concurrent medications, and differences in quantity of feed given, training regimes and racing schedules. Consequently, a model that maintains gastric ulcers and mimics the situation on the race track, but in which exercise, feeding and management may be precisely controlled, may be useful in the investigation of anti-ulcer therapies.

Stress in man has been documented as a cause of peptic ulcer disease (Yoshitomi *et al.* 1986). By extrapolation from human studies, stress has been suggested as a cause of gastric ulceration in horses (Murray 1993). Stress, due to concurrent disease, has been documented to increase the prevalence of peptic ulcer disease in neonatal foals (Furr *et al.* 1992). Difficulties exist in defining stress objectively, but several studies in man and horses have used serum cortisol concentrations (McCall *et al.* 1987; Alexander *et al.* 1988; Taylor 1989; Mal *et al.* 1991; Taylor 1991;

Covalesky *et al.* 1992; Taylor and Watkins 1992; Taylor *et al.* 1992; Clark *et al.* 1993; Kaciuba-Uscilko *et al.* 1994; Ockenfels *et al.* 1995; Hydbring *et al.* 1996; Smith *et al.* 1996; Pollard 1997). There is a popularly held belief that horses in race training are in a stressful environment and, consequently, may be prone to conditions such as gastric ulceration. However, a study measuring serum cortisol concentrations in racing Thoroughbreds and horses at pasture found no significant differences between the 2 groups (Irvine and Alexander 1994).

From studies at the race track, we have determined a typical feeding, environmental and training regime that was associated with the presence of gastric ulceration in horses (Vatistas 1998). In general, horses are fed large quantities of concentrates (grain) and enter an increasing exercise programme of progressively faster galloping work. The aims of this study were to determine whether ulcers could be induced and maintained in a population of horses fed a concentrate diet, maintained in fast work and fasted before exercise. In addition, by measuring serum cortisol, the study aimed to determine if horses were stressed by race training and whether gastric ulceration induced signs of acute abdominal discomfort.

Materials and methods

Study design

Thirty mature Thoroughbred horses were used, including 10 females, 16 geldings and 4 intact males age 2–13 years, weighing 408–560 kg. Fifteen horses were accustomed to the training regime for at least 2 weeks before endoscopic examination (*Group 1*), while the remaining 15 horses were maintained at pasture immediately before the trial (*Group 2*). All horses entered a simulated training regime on the same day (Day 0) and were maintained in training for 56 days. They were examined gastroendoscopically and venous blood was collected every week for the duration of the trial. The start of the trial was defined as the time the unfit (*Group 2*) horses entered into the exercise and feeding protocol.

Exercise

Horses were exercised 6 times/week. Horses were walked for approximately 0.4 km, were trotted for a additional 0.4 km and then galloped for 1.6–3.4 km on a 0.8 km oval training track. One day/week, horses were 'breezed' for an additional 0.8 km. Following completion of exercise, horses were walked for approximately 0.4 km, washed down, and 'cooled off' on a 'hot walker' for 30 min.

Feeding

Horses were fed coastal Bermuda hay twice daily, in the morning and evening. Horses also received 6 kg of a concentrate ration[1] (Heavy Duty '14' Horse Feed) containing 14% crude protein, 3% fat, 7.5% fibre, 0.4–0.8% calcium, 0.4% phosphorus, 10 ppm copper, 0.1 ppm selenium and 0.5 ppm zinc.Water was available *ad libitum* throughout the trial, but was withheld for 4 h before gastroendoscopy.

Gastroendoscopy

Gastroendoscopic examinations were performed 2 days before the trial (Days -2 and -1), and on Days 7, 14, 21, 28, 34, 42, 49 and 56. Twelve hours before gastroendoscopic examination, feed was withheld, horses were muzzled and bedding removed. Gastroendoscopy was performed on days when the horses were not exercised. Horses were sedated with xylazine hydrochloride (X-Ject E)[2] (0.3 mg/kg bwt i.v.) and acepromazine maleate (0.02 mg/kg bwt i.v.), and restrained with a twitch. A 3 m gastroendoscope[3] was passed using the left or right nostril into the stomach. The stomach was insufflated, and systematically searched. The period of fasting allowed visualisation of the entire squamous portion of the stomach, and a portion of the glandular mucosa. The worst gastric lesions were recorded using the following grading system:

0 Intact mucosal epithelium (may have reddening and/or hyperkeratosis).
1 Small single or small multifocal ulcers: ulcers extended through the mucosa to the submucosa and were <2 cm diameter, as judged by the marks on the endoscope.
2 Large single or large multifocal ulcers: ulcers extended through the mucosa to the submucosa and were >2 cm diameter, as judged by the marks on the endoscope.
3 Extensive and coalescing ulcers with areas of apparent deep ulceration: ulcers extended through the mucosa to the submucosa. Ulcers appeared as *grade 2* ulcers, but would coalesce, producing areas of extensive ulceration.

Housing

All horses were kept in individual stalls and their health monitored at least twice daily.

Serum cortisol

Venous blood samples were collected in the morning on the same days that endoscopy was performed into plain (without anticoagulant) vacutainer tubes. Samples were allowed to clot and separated at 2000 ***g***. The serum was separated and sent for determination of serum cortisol concentrations at Texas A & M Veterinary Diagnostic Laboratories. Samples were collected before endoscopic examinations, whilst the horse was resting in its stall.

Statistical analysis

ANOVA (repeated measures) was used to determine whether there was a temporal effect for the severity of ulceration or the values of serum cortisol concentration for either *Group 1* or *Group 2* horses. Significance was set at $P \leq 0.05$.

Results

Of the horses in *Group 1* (Table 1), all had ulceration at the beginning of the trial and the grade of ulceration was not altered for the duration of the ($P = 0.17$). Of *Group 2* horses, 13 had no evidence of ulcers and 2 had mild (*grade 1*) gastric ulceration on the first examination, but ulcers had developed in the majority of horses by 7 days and were present in all horses by 14 days. There was a significant increase in the severity of ulceration from baseline ($P = 0.02$). Although the grade of ulceration varied in some horses between examinations, there was no change in the severity of ulceration from Day 28 to the end of the trial. In both groups, ulcers were located within the squamous mucosa, adjacent to the *margo plicatus*.

At the start of the trial, mean ± s.e. serum cortisol concentration for *groups 1* and *2* were 150.42 ± 27.05 nmol/l and 178.85 ± 65.69

TABLE 1: Mean ± s.e. values for ulcer severity and serum cortisol concentrations (nmol/l) of 30 horses maintained in simulated race training

	Days -2 to -1	Day 7	Day 114	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56
Ulcer score[1]									
Group 1 horses (Conditioned):	57.13 ± 24.28	55.20 ± 23.46	51.61 ± 25.39	57.13 ± 22.08	62.65 ± 22.08	66.24 ± 20.42	64.31 ± 22.63	55.20 ± 23.46	75.35 ± 12.70
Group 2 horses (unfit):	3.59 ± 9.66	33.12 ± 21.25	47.75 ± 22.08	62.65 ± 24.29	68.17 ± 22.91	69.82 ± 20.42	69.83 ± 17.66	58.79 ± 20.42	71.00 ± 21.25
Serum cortisol nmol/l									
Group 1 horses (Conditioned):	150.40 ± 27.05	102.40 ± 36.16	169.19 ± 30.36	183.82 ± 37.54	162.56 ± 47.20	157.04 ± 24.84	153.73 ± 32.84	154.84 ± 31.46	119.51 ± 26.50
Group 2 horses (unfit):	178.85 ± 65.69	110.68 ± 40.57	174.43 ± 34.50	181.33 ± 32.57	141.04 ± 35.60	135.24 ± 26.50	156.50 ± 37.26	151.00 ± 31.46	130.55 ± 32.57

[1]See Materials and methods.

nmol/l, respectively; and by the end of the trial, 130.55 ± 32.57 nmol/l and 119.51 ± 26.50 nmol/l, respectively. Although serum cortisol concentrations varied from one week to the next (Table 1), there was a significant downward trend over the course of the study ($P<0.0001$).

During the course of the trial, 8 horses were given topical treatment with dimethylsulphoxide[4] for soreness of the metacarpophalangeal joints, 2 horses were treated for a cough, one for an abscess with penicillin (20,000 iu/kg i.m. b.i.d. for 5 days) and one was treated topically with polymixin B, bacitracin, neomycin for superficial skin abrasions. One horse had a mild bout of colic treated with mineral oil (2 litres *per os*) and xylazine hydrochloride (300 mg, i.v.), and one horse, which refused food on one occasion, was administered mineral oil (2 litres *per os*).

Discussion

In our study, all horses had developed gastric ulcers within 2 weeks of entering simulated race training. This is similar to Thoroughbreds in active race training, in which gastric ulceration has a prevalence of 80–90% and an incidence of 100% (Lind *et al.* 1983). In developing the present model, the aim was to simulate conditions during race training. Studies of therapeutic regimes using client-owned horses at the race track may be hampered by owner compliance, the lack of control of the horses' feeding, concurrent medication administration and exercise schedule. To avoid these potential complications, various models have been described (Jones 1983; MacAllister and Sangiah 1993; Murray 1994). These have been hampered by the need to administer NSAIDs or the spontaneous healing of ulcers (Jones 1983; MacAllister and Sangiah 1993; Murray 1994). In developing the present model, we used information gained in a previous cohort study of horses entering race training (Vatistas 1998). Significant factors for the development of gastric ulceration included the feeding of concentrates and faster exercise (Vatistas 1998). In addition, withholding feed before exercise was a modifying factor that, although not causing gastric ulceration, may have decreased time of onset. In our study, we incorporated the feeding of a high concentrate diet and periods of galloping exercise. Our model appeared similar to the clinical situation, in that ulcers developed and were maintained.

Although a common condition of racing Thoroughbred horses, the aetiology of gastric ulceration remains to be elucidated. Early reviews of equine gastric ulcers have implicated some of the potential causes in man, including age, (Kato *et al.* 1992) occupation (Pfeiffer 1992), stress (Yoshitomi *et al.* 1986), diet (Yoshitomi *et al.* 1986; Rachmilewitz *et al.* 1994) and NSAIDs (Vakil *et al.* 1994). However, comparisons between ulceration in mature horses and man are not valid due to the differing gastric anatomy between the two species. In an attempt to determine the effects of individual factors in the feeding and management of horses responsible, several studies have attempted to address the effects of withholding feed, feeding concentrates and stabling (Murray 1994; Murray and Eichorn 1996). Murray determined that alternately withholding feed for 24 h followed by feeding for 24 h induced ulceration of the squamous mucosa that appeared endoscopically similar to naturally occurring ulcers (Murray 1994). However, such a severe form of feed deprivation does not occur in horses in training, in which horses may be fasted for 4 h before training exercise, although the period of feed withdrawal may be longer prior to a race. The results of our study tend to support the concept from other studies that feed deprivation is not necessary for the development of gastric ulceration (Vatistas 1998). The stabling of horses from pasture has been documented to increase the severity of gastric ulceration (Murray and Eichorn, 1996). All horses in the present study were stabled and this may have had some influence on the development of gastric ulceration. Evidence for the role grain is predominantly anecdotal, but there has been one study that demonstrated an increased prevalence of gastric ulceration in ponies fed a concentrate diet compared to ponies fed hay alone. Owing to the design of the present study, it was not possible to separate the effects of feeding, exercise and stabling. Further studies using this model are required to separate these factors to determine which are important in the aetiology of gastric ulceration or whether all are required.

It has been suggested that NSAIDs are a cause of gastric ulceration in horses in race training. However, ulcers of the squamous mucosa developed in all the horses in the present trial without the use of NSAIDs. Further evidence that the administration of NSAIDs are not important contributors to the formation of gastric ulceration within the squamous mucosa has been provided by several studies of horses in active race training

(Murray *et al.* 1996; Vatistas *et al.* 1994a,b; Vatistas 1998). However, the effects of the administration of NSAIDs on the development of naturally occurring ulcers of the glandular mucosa have yet to be determined.

The stress of race training has been suggested as a cause of gastric ulceration in Thoroughbred racehorses. A potential cause of the high prevalence of ulcers in racing Thoroughbreds may be the stress of the race track in association with feeding practices of horses in training. Rodents, which share a similar gastric anatomy to horses, develop mild ulceration of the squamous mucosa following feed deprivation or stress (Hinton 1980; Ossenkopp and Mazmanian 1985; Ostensen *et al.* 1985a,b; Rydning and Berstad 1985; Lindell *et al.* 1994). When feed deprivation and stress were combined in the same animal, more severe ulceration of the squamous mucosa was induced than expected from a simple additive effect of feed deprivation and stress. In our study, we attempted to determine stress by measurement of serum cortisol. In horses, serum cortisol has been shown to have a diurnal rhythm, being highest in the morning and lowest in the evening (Bottoms *et al.* 1972; Larsson *et al.* 1979). In man, serum cortisol concentrations have been shown to be altered by physiological stress (Kaciuba-Uscilko *et al.* 1994; Ockenfels *et al.* 1995). Serum cortisol concentration has been used as a measure of stress in horses (Flisinska-Bojanowska *et al.* 1974; Lucke and Hall 1980; McCall *et al.* 1987; Alexander *et al.* 1988; Martinez *et al.* 1988; Taylor 1989; Mal *et al.* 1991; Covalesky *et al.* 1992; Furr *et al.* 1992; Clark *et al.* 1993; Irvine and Alexander 1994; Hydbring *et al.* 1996; Smith *et al.* 1996). Serum cortisol concentrations were increased with road transport, anaesthesia, exposure to a new environment, disease, restraint, nasogastric intubation, and abrupt weaning of foals (McCall *et al.* 1987; Taylor 1989; Covalesky *et al.* 1992; Furr *et al.* 1992; Clark *et al.* 1993; Irvine and Alexander 1994; Hydbring *et al.* 1996). Serum cortisol concentrations were not altered by isolation, different diets or shoeing (Alexander *et al.* 1988; Martinez *et al.* 1988; Stull and Rodiek 1988; Ma *et al.* 1991). The values determined in our study declined during the period of study, suggesting that horses became acclimatised to their environment. Other studies that have shown that the values of serum cortisol concentration are the same in Thoroughbreds in training and horses at pasture (Irvine and Alexander 1994). The results of our study suggest that, rather than training itself, the most stressful event may have been when horses entered their new environment. Compared to pastured animals, an increase in cortisol values and a loss of the normal diurnal rhythm has been documented in horses within 48 h of stabling (Irvine and Alexander 1994). However, as horses become acclimatised to new environments, cortisol concentrations return to baseline and the diurnal rhythm returns (Covalesky *et al.* 1992; Irvine and Alexander 1994).

In a number of studies, ulcers have been implicated as a cause of abdominal pain, poor performance and death due to gastric perforation (Murray *et al.* 1989; Murray 1992; Vatistas *et al.* 1994a,b). Increasing severity of gastric ulceration was greater in horses displaying clinical signs of recurrent, acute or chronic colic, diminished appetite and poor body condition than in a similar group of horses free from signs of abdominal discomfort (Murray *et al.* 1989). In addition, colic was attributed to the presence of gastric ulceration in 31 horses on the basis of a lack of lesions at exploratory laparotomy, and an alleviation of abdominal discomfort following anti-ulcer therapy (Murray 1992). In this study, only one horse showed signs of colic, and another had a diminished appetite. These signs resolved with minimal symptomatic treatment, and without treatment with anti-ulcer medications. The results of this and other studies suggest that colic may be an uncommon sequelae to gastric ulceration (Vatistas *et al.* 1994b; Vatistas 1998). Other studies have suggested that signs of gastric ulceration are associated with performance, appetite and body condition (Murray *et al.* 1989; Vatistas *et al.* 1994b). Other studies, in which sensitive measures of body condition, appetite, performance and abdominal pain are taken, are required to determine the effects of gastric ulceration on the horses' health.

Manufacturers' addresses

[1]Texas Farm Products Co., Nacogdoches, Texas, USA.
[2]Burns Veterinary Supply, Rockville Center, New York, USA.
[3]Pentax Precision Instruments, Precision Medical Instruments, Chandler, North Carolina, USA.
[4]SFB, Wichita, Kansas, USA.

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