

THE EFFECTIVENESS OF ONCE DAILY ULCERGUARD® (RANITIDINE) ADMINISTRATION FOR THE TREATMENT OF EQUINE GASTRIC ULCER SYNDROME (EGUS)

P.J. SPENDLOVE¹

¹ Ranvet Pty Ltd 10-12 Green St Botany NSW 2019 AUSTRALIA

AIMS

To determine the efficacy of once daily Ulcerguard® (ranitidine hydrochloride) administration for the treatment of equine gastric ulceration in Thoroughbred horses in a stable environment, performing intense work/exercise.

OBJECTIVES

- ❖ Determine the effectiveness of once daily administration (45mL/8,865mg ranitidine daily) and (30mL/8,865mg ranitidine daily).
- ❖ Assess (objectively) the relative improvement in gastric ulceration severity (grade) and distribution over 14 consecutive days of treatment.
- ❖ Assess (subjectively) resolution of clinical signs if present before commencement of treatment.

MATERIALS AND METHODS

A total of 50 horses (mean age=3.8 years, 18 female and 32 male) participated in this study, whereby horses were examined via gastroscopy and subsequently assessed on Day 0 for objective gastric ulceration scores, subjective assessment of clinical/sub-clinical signs of gastric ulceration and sites of ulceration. All feed was withheld for a minimum of 12 hours prior to gastroscopy and hay access restricted during this time period. All horses participated in morning work prior to gastroscopy and were manually restrained with a lip twitch and sedated with 0.5mL Calmant® IV (detomidine hydrochloride) for the procedure.

Horses were administered 45mL Ulcerguard® (ranitidine 197mg/mL) (n=15) or 30mL Ulcerguard® (ranitidine 295.5mg/mL) (n=35) for 14 consecutive days and re-assessed with a repeat of the aforementioned procedures on Day 14. During the trial period, horses were fed standard full racing grain based diets and worked as per normal.

On each occasion, video images were taken of the gastric squamous epithelium from the right side of the stomach along the margo plicatus, the dorsal part of the fundus, the greater curvature along the margo plicatus (MPGC), the lesser curvature along the margo plicatus (MPLC) and the glandular mucosa along the greater surface. Images were later still-framed and assessed for lesion scores based on the degree of erosion/ulceration at each site in the stomach.

Lesion scores ranged from 0-5 (0=intact epithelium; 1=generalized reddening or hyperkeratosis/superficial erosion; 2=superficial erosion with isolated areas of submucosal lesion/isolated deep haemorrhaging; 3=Deep isolated haemorrhaging lesions/linear haemorrhaging encircled with hyperkeratotic squamous mucosa; 4=Advanced linear haemorrhaging lesions; 5=Deep submucosal lesions and extensive haemorrhaging/entire squamous mucosa eroded).

It is noteworthy to consider that no individual scoping system has been universally accepted for the diagnosis of gastric ulceration in horses (*MacAllister et al, 1997*) however, recently, the Equine Gastric Ulcer Council (EGUC) suggested a uniform scoring system which grades gastric ulcers based on a 5 point scoring system (0-5) point scale, with 0 being normal and grade 5 being extensive, deep lesions (*Anonymous, 1999*).

RESULTS

The highest prevalence of lesions (94%) were located along the margo plicatus, with diffuse distribution over the greater curvature wall and dorsal areas of the fundus being apparent in 11% of horses examined. Lesions were most commonly found over the greater curvature of the margo plicatus (97%), with 14% of horses presenting with lesions of the lesser curvature margo plicatus region.

Ulcer severity was objectively graded (Grade 0 being normal and Grade 5 being the most severe) of lesions with an **average grading at Day 0 being a Grade 3 ulcer lesion score.**

Between Day 0 and Day 14, 42 horses (84%) were followed through time to Day 14 of treatment, while eight horses (16%) were lost to the trial for various reasons such as being spelled, being sold or other confounding injury/concurrent treatment ie; phenylbutazone administration. Of the 42 horses re-examined, 38 horses (90.5%) were found to be sub-clinical, of which 30 horses (71%) were graded as clinical cases at trial commencement due to exhibiting one or more of the characteristic clinical signs associated with gastric ulceration (ie; dull coat, poor appetite, poor body condition, unfavourable temperament, failure to finish, poor performance).

Ulcer severity was objectively graded (Grade 0 being normal and Grade 5 being the most severe) of lesions with an **average grading at Day 14 being a Grade 1 ulcer lesion score.**

Of these horses, 7 horses (17%) were further followed through time to Day 38 of treatment, whereby they had received 3 weeks (21 days) once daily administration followed by 3 times per week administration (maintenance dose). Of the re-examined horses, 6/7 (86%) presented with a zero ulcer lesion score and all horses (7/7=100%) were free from clinical signs.

Additionally, no significant difference ($P>0.05$) between 45mL and 30mL/day treatment regimens was found.

In conclusion, 14 days of treatment consisting of once daily Ulcerguard® treatment resulted in an **average comparative ulcer lesion grading decrease/improvement of 2 lesion scores.**

Figure 1; Average Response to treatment (14 days therapy)

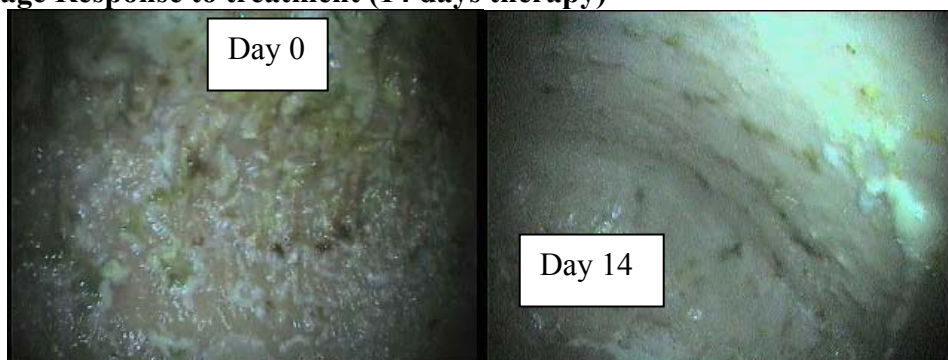


Figure 2; Average Response to treatment focal distribution (14 days therapy)



Figure 3; Average Response to treatment diffuse distribution (14 days therapy)

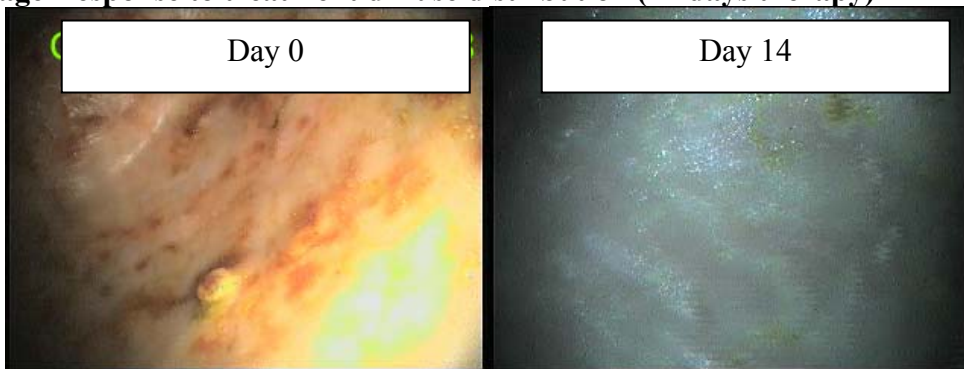
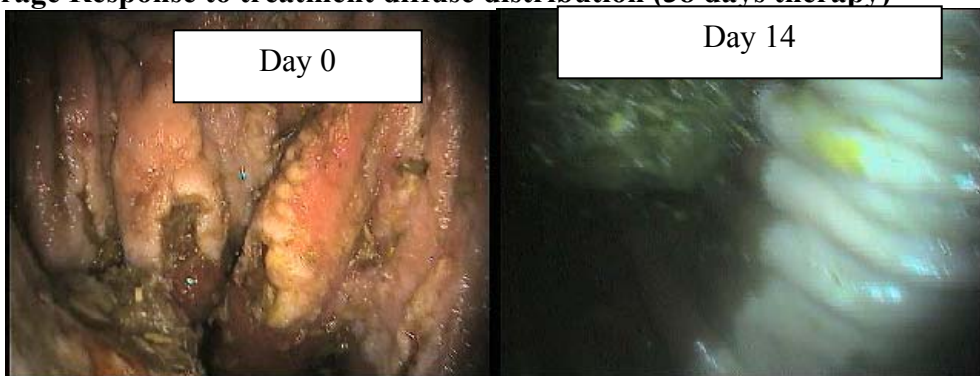


Figure 4; Average Response to treatment diffuse distribution (38 days therapy)



REVIEW OF THE LITERATURE

A Brief Outline of Gastric Ulceration/Definition & Clinical Signs

Gastric ulceration has been recognized as a common, performance-limiting ailment of performance horses and due to its complicated and multifactorial nature, the term Equine Gastric Ulcer Syndrome (EGUS) has been used to describe the disease.

Clinical signs may or may not be present and are often non-specific, including loss of appetite, weight loss/poor body condition, poorly formed faeces, dull coat and stereotypies such as wind-sucking.

Prevalence of Equine Gastric Ulcers

Equine Gastric Ulcer Syndrome has been reported to effect between 58-100% of adult Thoroughbred and Standardbred horses in training (*Ferrucci et al, 2003; Bell et al, 2007; Begg and O'Sullivan, 2003*), with 75-80% of lesions being found in the squamous portion of the stomach, particularly along the margo plicatus.

Gastric ulceration is also a highly prevalent disorder in foals (*Murray et al, 1990*) and non-performance adult horses (*Murray et al, 1989*). The equine gastric squamous epithelial mucosa is highly susceptible to peptic injury, because it has minimal intrinsic mucosal protective mechanisms and is frequently exposed to a highly acidic environment (*Murray and Schusser, 1993*). Further studies have revealed that gastric lesions can occur in as little as 48 hours with deprivation of feed due to feed deprivation resulting in increase gastric acidity (*Murray and Schusser, 1993*).

Equine Stomach Anatomy & Function

The equine stomach secretes hydrochloric acid continuously under the influence of vagus nerve stimulation, gastrin and histamine, even when the horse is not eating (*Campbell-Thompson and Merritt, 1990*). Hydrochloric acid is secreted by parietal cells, with histamine being the most potent stimulus of gastric acid secretion in the horse (*Kitchen et al, 1998*). Gastric acidity is lowest during mastication, as eating stimulates the secretion of bicarbonate-rich saliva which acts to neutralize gastric acid. Once a horse ceases chewing, gastric pH can rapidly increase, with the pH falling to below 2.0 and acidity remaining for the duration of time the horse does not eat (*Murray and Schusser, 1993*).

Protection of the equine gastric squamous mucosa from peptic injury is dependent upon limited exposure to gastric secretions, as there is no surface barrier to hydrochloric acid and these epithelia have limited properties to prevent peptic injury. The continuous secretion of hydrochloric acid by the equine stomach makes horses particularly susceptible to damage of the gastric squamous mucosa.

Causes of Gastric Ulceration

The development of gastric ulcers can be viewed as an imbalance between aggressive and protective factors on the mucosa (*Andrews and Nadeau, 1999*). The squamous mucosa bordered by the margo plicatus is the most common region for ulcer development due to being constantly exposed to gastric acid (*Murray, 1994*). Continued exposure of the squamous mucosa to hydrochloric acid results in loss of the superficial epithelial layers, with severity of lesions being associated with the duration of exposure to hydrochloric acid (*Furr et al, 1992*).

Despite the condition being highly prevalent, no reports to date have demonstrated a definite relationship between ulcer score and severity of clinical signs (*MacAllister et al, 1997; Dionne et al, 2003*).

Pharmaceutical Treatment of Equine Gastric Ulcers

The goals of clinical treatment are to eliminate clinical signs, promote healing of ulcers and prevent recurrence (*MacAllister, 1999*). Currently, pharmaceutical treatment of gastric ulcers relies upon the use of H₂ receptor antagonist drugs (ie; ranitidine) and proton pump inhibitors (ie; omeprazole). In addition to pharmacological therapy, dietary and environmental modification has also been shown to assist healing (*Buchanan and Andrews, 2003*), particularly sufficient roughage in the diet which aids to absorb gastric secretions so they do not contact the susceptible mucosal lining.

Importantly it should be noted that treatment requirements may vary between individuals (*Murray 1994*) and thus treatment should be tailored for each horse. Treatment focuses on pharmacologic inhibition of gastric acid secretion and treatment is advised to be continual whilst horses are in training, to prevent recurrence.

Ranitidine/H₂ Receptor Antagonists

The histamine H₂ receptor antagonists inhibit hydrochloric acid secretion by competing with histamine for receptor sites on the parietal cell (*Katz, 1991*). Histamine is the most potent stimulus for hydrochloric acid secretion, and because occupation of the receptor site is by competitive inhibition, the greater the concentration of H₂ antagonist at the receptor site, the greater and more prolonged the degree of suppression of hydrochloric acid secretion.

Several studies to date have examined the effects of histamine H₂ antagonists on gastric acid secretion and gastric acidity in horses. In the first such study, comparison of two variable doses of ranitidine (4.4mg/kg and 6.6mg/kg) administered by nasogastric tube, on gastric fluid pH revealed that the higher dose rate increased gastric fluid pH to a greater degree than the lower dose rate during the 6 hours post administration (*Murray and Grodinsky, 1992*). In another study in which an indwelling pH electrode was used to measure gastric pH in horses fed grass hay, oral ranitidine 6.6mg/kg three times daily resulted in a median 24 hour pH of 4.8 compared with a median 24 hour pH of 3.2 in horses fed hay without treatment (*Murray and Schusser, 1993*). Further studies conducted by *Sanchez et al (1998)* revealed 6.6mg/kg oral ranitidine significantly decreased gastric pH for 8 hours post administration compared with 2.2mg/kg IV ranitidine which maintained an increased gastric pH for 5 hours post administration.

However, there is conflicting evidence regarding the effect of H₂ antagonists on the healing of gastric ulcers. In clinical reports where there were no control horses, oral administration of ranitidine (6.6mg/kg) for three weeks was associated with complete ulcer healing in up to 90% of horses (*Furr and Murray 1998*). Additionally, cessation of clinical signs attributed to gastric ulceration was reported to occur within a few days of beginning treatment. In another study, ranitidine (6.6mg/kg) three times daily prevented the induction of ulcers in a feed-deprivation model (*Murray and Eichorn, 1996*). Based on the current body of research, it is the general consensus that to be effective, H₂ antagonists must be administered at doses that can be expected to increase gastric pH for 4-8 hours, with an oral dosage of ranitidine (6.6mg/kg three times daily) being supported as the recommended dosage regimen by several studies (*Murray and Eichorn, 1996; Murray and Grodinsky, 1992; Murray and Schusser, 1993*).

Research has also ascertained that horses have individually characteristic gastric pH responses to oral ranitidine, with three patterns being generally observed, namely; a ***complete response*** (gastric fluid pH increases to >7 and remains >6 for 4-10 hours), an ***intermediate response*** (biphasic increase in pH by increase, decrease and increase), ***poor response*** (gastric fluid pH increases minimally for a short period) observed by *Murray and Grodinsky (1992)*.

Finally, concurrent consumption of roughage appears to enhance the effect of ranitidine on increasing gastric pH (*Murray and Schusser, 1993*).

Healing of Gastric Ulceration

The rate of gastric healing is affected by both the size and depth of lesions, with depth being the more important determinant. Superficial lesions in the squamous mucosa may take as little as seven days to heal when compared to deeper lesions (requiring the removal of tissue debris and wound healing, make take as long as three months (*Murray et al, 1989*). A similar study using H₂ receptor antagonists to promote ulcer healing, found significant differences in regional healing times. With lesions in the saccus caecus and cardia healing more rapidly than those at the margo plicatus (*Furr and Murray, 1998*).

Investigation into the spontaneous healing of gastric ulcers in horses in training has also been conducted. A study by *Murray et al (1996)* revealed that only 6/35 (17%) of horses had improved over three months and none had healed completely, with the trend being toward worsening with continued training.

Conclusions

Many studies have been conducted on the effects of ranitidine on healing experimentally induced ulcers however, minimal research has been conducted into investigating the effectiveness of ranitidine on the healing of naturally occurring gastric ulceration in a non-simulated environment and such information may be beneficial to clinicians. Furthermore, to date, treatment efficacy evidence for ranitidine has been largely based on anecdotal evidence and extrapolation from human studies.

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