Original Research

A Comparison Between Omeprazole and a Dietary Supplement for the Management of Squamous Gastric Ulceration in Horses

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A R T I C L E   I N F O

A B S T R A C T

Although several studies have assessed the short-term effect of dietary supplements on the treatment and prevention of gastric ulceration in horses, few have assessed the response over a duration of more than 30 days. A blinded randomized noninferiority clinical trial was conducted using 42 Thoroughbred horses in race training with squamous ulceration of $\geq$ grade 2/4, randomly assigned to one of two treatment groups for a period of 90 days: omeprazole at the full label dose of 4 mg/kg or the Succeed digestive conditioning supplement. Noninferiority analyses and Wilcoxon sign rank tests were used to analyze the data. At day 90, Succeed was noninferior to 4 mg/kg omeprazole administered daily in terms of the proportion of horses with complete resolution of squamous ulceration. At day 30, Succeed was found to be inferior to omeprazole in terms of the proportion of horses with grade $\leq$1/4 squamous ulceration. The proportion of horses with reducing squamous ulcer score (compared with day 0) was statistically significant for both treatments at days 30 and 60. At day 90 of the 17 horses on Succeed, nine had a reducing squamous ulcer score (P value = .049), and of the 19 horses on omeprazole, 10 had a reducing squamous ulcer score at day 90 (P value = .091). The noninferiority of Succeed compared to omeprazole at 90 days for the complete resolution of squamous ulceration and the reduced efficacy of omeprazole following 90 days of treatment are likely to be of interest to practitioners managing gastric ulceration in performance horses.

1. Introduction

The prevalence of squamous ulceration in racing Thoroughbreds has been reported as >70% in several studies [1–9]. Equine gastric ulcer syndrome (EGUS) is detrimental to horse health and performance due to associated pain and discomfort [10,11]. Omeprazole, a proton pump inhibitor, is the most commonly used treatment for gastric ulceration in horses and is the only product licensed for this purpose in most countries. Omeprazole has been shown to be efficacious in the short term in four previous studies with healing rates of 73% to 80% and improvement rates of up to 92% following 25 to 56 days of treatment [12–15]. The bioavailability of oral enteric coated omeprazole is variable but unaffected by feeding or fasting [16]. Withdrawal of omeprazole after 56 days of treatment has been reported as resulting in a rapid return of gastric ulceration [15]. However, another study showed only a 20% recurrence rate following withdrawal of omeprazole following 56 days

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treatment [13]. To the authors' knowledge, the efficacy of omeprazole over a period of greater than 60 days in horses maintained in race training has not been reported.

Nutraceutical approaches for dealing with EGUS are being developed and tested. Hellings and Larsen [17] administered a mixture of B vitamins and salts of organic acids to performance horses presenting with EGUS for up to 7 weeks and concluded that this may promote healing of gastric ulcers. A pectin and lecithin mixture, supplemented with an antacid, reduced the severity of gastric ulceration over a 35-day period [18], but pectin–lecithin may be ineffective when given without an antacid [19]. A dietary supplement comprised of sea buckthorn berries reduced the severity of glandular, but not squamous, ulceration in Thoroughbred horses [20]. Sykes et al [21] reported that a combination of pectin–lecithin complex (Apolectol), live yeast, and magnesium hydroxide, when supplemented for 24 to 27 days reduced the severity of glandular and squamous gastric ulcers in Thoroughbred horses in race training. Andrews et al [22] reported that a supplement containing a number of ingredients, including pectin, lecithin, sea buckthorn, and L-Glutamine, may result in less severe recurrence of squamous ulceration following omeprazole treatment.

Succeed Digestive Conditioning Program (Succeed) is a daily supplement designed to support gastrointestinal health of horses. Succeed is a nutraceutical supplement containing oat oil rich in polar lipids, oat flour rich in oat Beta Glucan, L-Glutamine, and L-Threonine and extracts of the cell wall of *Saccharomyces cerevisiae,* one containing beta glucan and the other a mannan oligosaccharide. Anecdotally, this product is used in the management of gastric ulceration. However, it has not previously been evaluated in a blinded clinical trial.

The aim of the present study was to examine the hypothesis that Succeed is not inferior to omeprazole for the treatment of squamous ulceration in horses in race training over the course of 90 days.

2. Materials and Methods

2.1. Study Design

A blinded randomized clinical trial was conducted to compare the efficacy of 4 mg/kg orally administered omeprazole (Gastrogard) (Merial Animal Health Ltd, Harlow UK) with a dietary supplement (Succeed) (Freedom Health LLC, Ohio) for the management of squamous gastric ulceration over a period of 90 days. A sample size calculation was conducted which determined that 28 horses in each group would be required to provide 80% power, assuming 90% efficacy of both treatments and that a 20% difference in efficacy is not clinically important. Ethical approval for this trial was provided by Health Products Regulatory Authority in Ireland. To meet the trial inclusion criteria, horses had to be in full-time race training for a minimum period of 2 weeks, not receiving any dietary supplements or medication and being in good health, according to the veterinary surgeon and trainer at the time of initiation of the trial. Recruitment was from two racing yards in Ireland, and all horses on each yard which met the inclusion criteria were subjected to gastroscopy. Both flat and National Hunt yards were included in this study to represent a broad spectrum of racehorses in the UK and Ireland. Within each yard, the management of horses was standardized with regards to exercise, training, and nutrition although owing to inherent differences in training regimens and timing within the respective seasons, it was not possible to standardize management between the two yards. No changes were instituted in the management of horses in either treatment group in response to a diagnosis of gastric ulceration.

2.2. Gastroscopic Examination

Before gastroscopic examination, the horses were fasted for 12 hours and water was removed 1 hour before the procedure. Horses were identified by means of microchip number. Before gastroscopic examination, 0.5 mg/kg xylazine (Chanazine, Chanelle UK, Hungerford, Berkshire, UK) was administered intravenously with an additional 0.5 mg/kg administered if adequate sedation was not achieved. Gastroscopy was performed using a 3-m endoscope (Pentax VSB 2900- Pentax Medical, Slough, UK); after nasogastric passage, a standardized examination protocol was performed including insufflation of the stomach and flushing the mucosal surface with water [23]. The entire examination was recorded on video and saved with the horse's microchip number as identification. The glandular mucosa was inadequately observed in the majority of horses. Consequently, further analysis of glandular lesions was not included in the study.

2.3. Treatment Allocation and Repeat Examination

If grade $\geq$2/4 ulceration was present, the horse was randomly allocated to one of two treatment groups. Randomization was performed by drawing cards on each of which one of the two treatment groups was stated. Treatment group A received omeprazole at the recommended dose of 4 mg/kg PO q24 hours for a 90-day period. Those in treatment group B received Succeed at the manufacturer's recommended dose of 27g total dose PO q24 hours for 90 days. Treatment was administered in the morning, before feeding and work. Gastroscopy was repeated at 30-day intervals throughout the 90-day trial period, resulting in horses that completed the trial undergoing four examinations. It was recommended that horses that were racing during the trial had omeprazole withheld for 5 days before each racing date, based on a British Horseracing Authority detection time of 72 hours (3 days), with an additional safety margin added. (Detection Times- British Horseracing Authority http://www.britishhorseracing.com/resources/equine-science-and-welfare/medication-control.asp.) Veterinary surgeons undertaking the gastroscopies, reviewing and assessing the videos, and performing the statistical analysis were all blinded to treatment group; hence, the study was triple blinded. It was not possible to blind the trainer to treatment group due to differing appearance of the formulations of product and the need to withdraw omeprazole before racing.

2.4. Review of Ulceration Scores

A panel of three diplomates of either the European College of Equine Internal Medicine or the American College of Veterinary Internal Medicine reviewed videos (authors H.B.C., R.C.C., and D.G.M.S.). Each video was graded for both squamous and glandular ulceration; the median value of the three reviewers was used as the definitive ulcer grade. The grading system chosen was in accordance with the recent consensus statement from the European College of Equine Internal Medicine [24] (Table 1) due to the highest level of interoperator agreement [25]. Reviewers were also asked to state if they believed the video was nondiagnostic. If one reviewer stated a video to be nondiagnostic, the mean of the remaining two grades was used as the definitive grade. If more than one reviewer stated the video was nondiagnostic, this video was removed from further analysis.

2.5. Statistical Analysis

Interobserver agreement was assessed for squamous ulceration using a weighted kappa, the kappa weighting is detailed in Table 2. The agreement between each pair of reviewers was assessed. Degrees of interobserver agreement were as suggested by Landis and Koch [26]: $\kappa < 0.20$ = poor agreement, κ 0.21–0.40 = fair agreement, κ 0.41–0.60 = moderate agreement, κ 0.61–0.80 = substantial agreement, and κ 0.81–1.00 = excellent agreement.

A Wilcoxon-rank sum test was performed to assess the difference in squamous ulceration scores, for both treatment groups, at day 0 of the trial. Noninferiority was assessed using a one-sided upper 90% confidence interval of the difference in treatment failure percentage between the two treatment groups [27] for the healing of squamous gastric ulcers at each time point. Data are presented as the difference in treatments for each of the three measures of success (omeprazole–Succeed) with 90% confidence intervals. A 20% difference in clinical outcome was defined as the point at which treatments would be considered different, this margin is based on a previous noninferiority study in gastric ulceration in horses [28] which established the a priori noninferiority margin of 20% based on similar human studies assessing gastrointestinal injury. For the purposes of noninferiority analysis, three different measures of success were used:

Table 1
Grading system for equine squamous gastric disease (adapted from the 1999 EGUS Council scoring system) [24].

Grade of Ulcer	Description of Lesion
0	The epithelium is intact, and there is no appearance of hyperemia (reddening) or hyperkeratosis (yellow appearance to the squamous mucosa)
1	The mucosa is intact, but there are areas of reddening or hyperkeratosis (squamous)
2	Small, single, or multifocal lesions
3	Large, single, or multifocal lesions or extensive superficial lesions
4	Extensive lesions with areas of apparent deep ulceration

Abbreviation: EGUS, equine gastric ulcer syndrome.

Table 2
Weighting matrix used to calculate paired weighted kappa statistics.

	Grade of Ulceration	Clinician 1				
		0	1	2	3	4
Clinician 2	0	1	0.8	0.4	0	0
	1	—	1	0.8	0.4	0
	2	—	—	1	0.8	0.4
	3	—	—	—	1	0.8
	4	—	—	—	—	1

- Improvement of squamous mucosal grade by two or more since day 0.
- Squamous ulcer grade of 1/4 or less at the time point of interest.
- Complete resolution of ulceration (i.e., grade 0/4 at the time point of interest).

Wilcoxon sign rank tests were used to assess the change in squamous ulcer score (from day 0) for horses on the two treatments, at days 30, 60, and 90. Two commercially available statistical software packages were used (Minitab version 12.1.2 [Minitab Inc, USA, http://www.minitab.com] and Stata version 13.1 [StataCorp LP, College Station, Texas]).

3. Results

Sixty-six horses underwent an initial gastroscopy; the retention of horses at various stages of the trial is described in Fig. 1, showing the percentage of horses with squamous gastric ulceration of grade $\geq 2/4$ from the initial group presented and the percentage of horses remaining in each treatment group at each time point.

Interobserver agreement for grading of squamous gastric ulceration was found to be substantial [26] ranging from K = 0.65 to K = 0.73 for the three paired estimates of agreement between reviewers. At day 0, there was no significant difference between treatment groups for squamous gastric ulcer score ($P = .29$). The distribution of grades at day 0 is shown in Fig. 2.

Of the 36 horses with four diagnostic gastroscopies, 13 were from a flat racing yard, of which six horses received omeprazole and seven horses received Succeed. There were 23 horses from a National Hunt yard, of which 12 received omeprazole and 11 received Succeed. One horse from the Succeed group was not included in statistical analysis as all the gastroscopies from this horse were deemed to be nondiagnostic due to the presence of gastric contents, suggesting this horse had delayed gastric emptying compared to its cohort. Fig. 3 shows the changes in grade for each treatment at each time point, a zero on the y-axis indicates no change in ulcer score from day 0.

3.1. Noninferiority Analysis

Noninferiority analysis (Table 3 and Fig. 4) showed that at day 90, Succeed was noninferior to omeprazole for complete resolution of squamous ulceration. At day 90, noninferiority was close to being shown for an
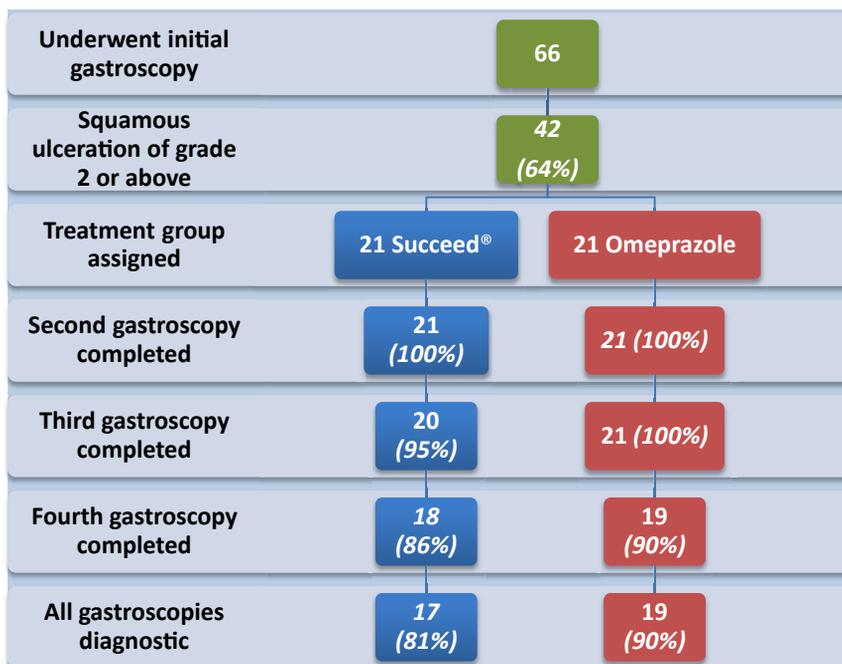
Underwent initial gastroscopy	66	
Squamous ulceration of grade 2 or above	42 (64%)	
Treatment group assigned	21 Succeed®	21 Omeprazole
Second gastroscopy completed	21 (100%)	21 (100%)
Third gastroscopy completed	20 (95%)	21 (100%)
Fourth gastroscopy completed	18 (86%)	19 (90%)
All gastroscopies diagnostic	17 (81%)	19 (90%)

Fig. 1. Flow chart showing the number of horses at each stage of the trial.

improvement in squamous ulcer score by two of more grades (upper 90% confidence interval = 20.4). At day 30, Succeed was shown to be inferior to omeprazole in terms of squamous ulcer grade one or less and close to inferior in terms of improvement by two or more grades (lower 90% confidence interval = 18.4). For all other measures of success and time points (improvement in squamous ulcer score by two or more grades at day 60; squamous ulcer grade one or less at days 60 and 90; complete resolution of squamous ulceration at days 30 and 60), noninferiority analysis was inconclusive.

3.2. Treatments Efficacy

The number of horses with a positive, negative, or no change in squamous ulcer score from day 0 to day 30, 60
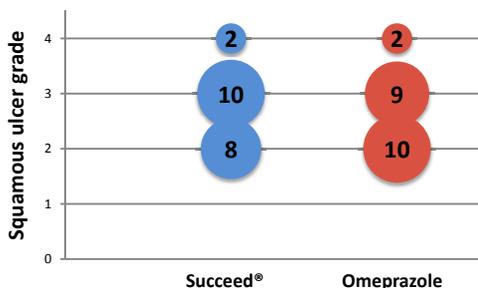

Fig. 2. Bubble plot showing the distribution of grades at day 0 (note that although 21 horses were assigned to the Succeed group, grades were available from only 20 horses as one horse had gastroscopies deemed to be nondiagnostic, on review, throughout the trial period).

and 90, on each treatment is given in Table 4. Both treatments showed statistically significantly greater numbers of horses with reducing squamous ulcer score (than increasing squamous ulcer score) at days 30 and 60. Of those horses on omeprazole, 14 of 21 (66.7%) and 16 of 21 (76.2%) at days 30 and 60, respectively, had a positive change in squamous ulcer score, from day 0. Of those horses on Succeed, nine of 20 (45%) and 11 of 19 (57.9%) at days 30 and 60, respectively, had a positive change in squamous ulcer score, from day 0. The equivalent analysis for day 90 was more marginal: Of the 17 horses on Succeed, nine had a reducing squamous ulcer score at day 90 (P value = .049), and of the 19 horses on omeprazole, 10 had a reducing squamous ulcer score at day 90 (P value = .091).

3.3. Withdrawal Periods for Horse on Omeprazole

Of 19 horses that completed the trial on omeprazole, 12 had withdrawal periods applied during the trial. Of these, one horse had one withdrawal, one horse had two withdrawals, four horses had three withdrawals, three horses had four withdrawals, and three horses had five withdrawals. The mean total withdrawal period and longest consecutive withdrawal period during the 90-day trial was: for all horses on omeprazole—total 13 days (range 0–38 days), consecutive 4.6 days (0–14 days) and those subject to withdrawal—total 18 days (4–38 days), consecutive 6.5 days (4–14 days).

4. Discussion

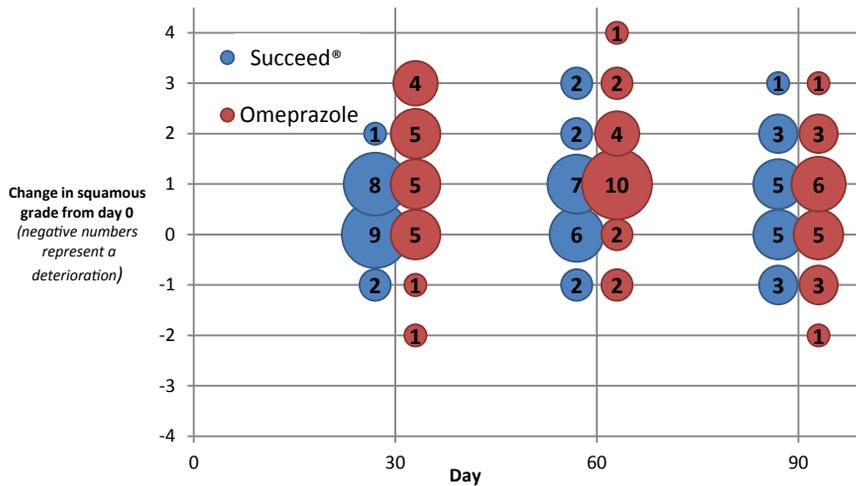The present study is the first to demonstrate that a nutraceutical supplement that provides a number of

Fig. 3. Bubble plot showing the number of horses in each treatment group with four diagnostic gastroscopies representing each change in squamous ulcer grade over time; the size of the bubble is reflective of the number of horses in each group with a squamous ulcer score which changed by the number of grades on the y axis.

ingredients targeted to support gastrointestinal health is noninferior to omeprazole in terms of its ability to ameliorate squamous ulceration in the horse when provided in the diet for at least 90 days. When used at a dosage of 27g po q24 hours, the Succeed Digestive Conditioning Program supplement was found to be noninferior to 4 mg/kg omeprazole administered q24 hours at the end of a 90-day course of treatment when complete resolution of ulceration was used as the measure of success. Noninferiority was close to being shown at day 90 for an improvement in squamous ulcer score by two or more grades. Fig. 4 clearly shows a trend, regardless of the measure of success used, in that any difference in the efficacy of the two treatments reduces as duration of treatment increases, with noninferiority achieved or almost achieved in two cases.

Noninferiority analysis has the advantage of providing a comprehensive measure of a difference between two treatments by including direction of effect and an estimation of whether this is of clinical significance by including a predefined margin of difference [27]. As such it is also interesting to note that for two measures of success, at day

30, Succeed was inferior or almost inferior to omeprazole. Viewed together these analyses suggest that omeprazole is more efficacious in the short term (less than 60 days), but that by day 90 there is little, if any difference between the two treatments. Indeed, compared with day 0, at days 30 and 60, significantly more horses showed a reducing rather than increasing squamous ulcer score on both treatments. However, at day 90, the equivalent analysis for omeprazole was no longer statistically significant (P value = .091), whereas that for Succeed remained (marginally) statistically significant (P value = .049). The percentage of horses showing improvement on omeprazole compared with Succeed was higher at days 30 and 60. But at day 90, there was no difference between the two treatments on this measure (52.6% of horses on omeprazole and 52.9% of horses on Succeed). It is important to note that this study was not designed to measure the efficacy of each treatment per se, and for that reason, it is likely that these findings may in part be due to a lack of statistical power.

The findings relating to the efficacy of omeprazole at day 30 concur with previous work [13,14,29–31]. However, this is the first study, to the author's knowledge, that has

Table 3
Noninferiority analysis of the effect of Succeed digestive conditioning supplement, compared to omeprazole in the healing of squamous ulceration.

Measure of Success	Day	Treatment Group Succeed	Treatment Group Omeprazole	Difference in % Success (Omeprazole−Succeed)	90% CI x(Lower–Upper)
		% Success (Number With Successful Outcome/Number of Horses)			
Improvement by two or more grades	30	5 (1/20)	43 (9/21)	37.9	(18.4, 57.3)
	60	21 (4/19)	33.3 (7/21)	12.3	(−10.6, 35.1)
	90	23.5 (4/17)	21 (4/19)	−2.5	(−25.3, −20.4)
Squamous grade of ≤1	30	10 (2/20)	52.4 (11/21)	42.4	(21.3, 63.4)
	60	31.6 (6/19)	52.4 (11/21)	20.8	(−4.3, 45.9)
	90	23.5 (4/17)	26.3 (5/19)	2.8	(−20.9, −26.5)
Complete resolution of squamous pathology	30	0 (0/20)	28.8 (6/21)	28.6	(12.4, 44.8)
	60	15.8 (3/19)	19 (4/21)	3.3	(−16.4, 23.0)
	90	17.6 (3/17)	10.6 (2/19)	−7.1	(−26.2, 12.0)

Abbreviation: CI, confidence interval.

Table 4
The number of horses in each treatment group, at each time point, that showed a positive change (i.e., improving), negative change (i.e., worsening), or no change in squamous ulcer score from day 0.

	Change in Squamous Ulcer Score (Positive, Negative, or No Change From Day 0) on Succeed or Omeprazole at the Three Different Time Points					
	Day 30		Day 60		Day 90	
	Succeed (n = 20)	Omeprazole (n = 21)	Succeed (n = 19)	Omeprazole (n = 21)	Succeed (n = 17)	Omeprazole (n = 19)
Positive (i.e., reducing squamous ulcer score)	9	14	11	16	9	10
Negative (i.e., increasing squamous ulcer score)	2	2	2	2	3	4
No change in squamous ulcer score	9	5	6	3	5	5
Wilcoxon sign rank test P value	.032	.003	.009	.001	.049	.091

identified a reduced efficacy of omeprazole after more than 2 months of treatment. This along with the finding of noninferiority at day 90 for Succeed compared with omeprazole raises the question of whether omeprazole continues to result in acid suppression over a prolonged period of time. However, there is very limited strong evidence of rebound acid hypersecretion in humans following cessation of treatment with proton pump inhibitors for periods of longer than 8 weeks [32]. It is possible that a rebound gastric acidosis occurs in horses subjected to intermittent withdrawal for reasons of competitive activity. In this study, a mandatory withdrawal period of 5 days was applied to those in the omeprazole group before a racing commitment. This was not prevented as the investigators

felt it was important to compare these two products in true "field conditions." Indeed, the authors believe that the maintenance of horses in full race training is an advantage in this study to reflect normal usage of both omeprazole and the dietary supplement. However, the authors also recognize that given more than half of the horses on omeprazole had at least one period of withdrawal of treatment at some point during the trial (indeed 10 of 21 horses had at least three withdrawal periods), it is likely that the reduced efficacy of omeprazole at day 90 is associated with these enforced withdrawals that were required to allow horses to race. The physiological mechanism associated with this reduced efficacy may be contended, but the outcome of intermittent withdrawal has not
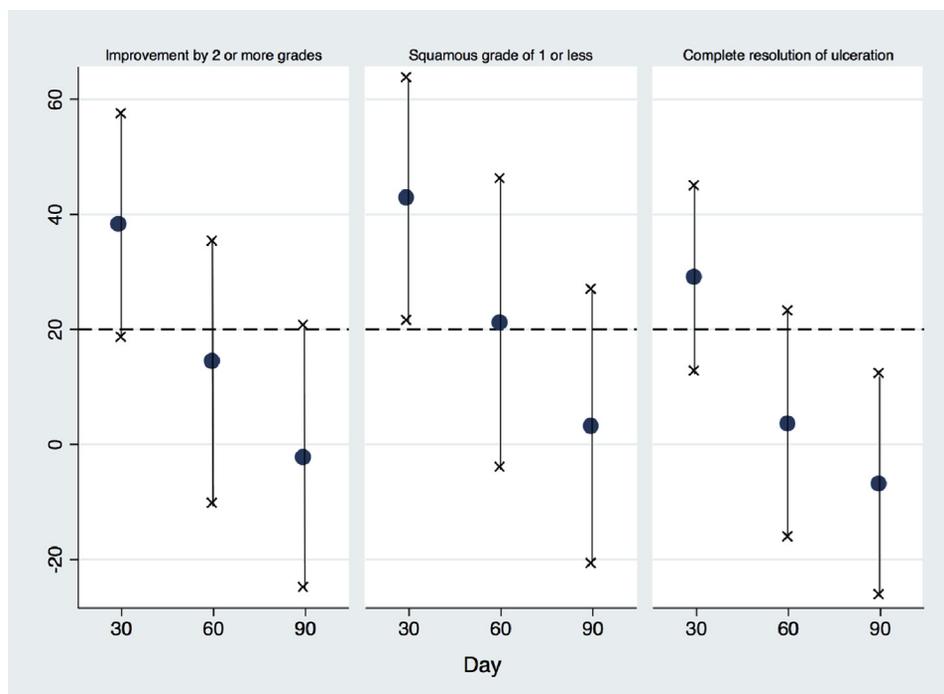

Fig. 4. Treatment differences for different measures of success with 90% confidence intervals shown. The clinically significant treatment difference of 20% is marked by a dashed line. When the 90% confidence interval crosses this dashed line, the result is inconclusive for noninferiority. When the upper 90% confidence limit is below the dashed line, the experimental treatment (i.e., Succeed) is noninferior to omeprazole. When the lower 90% confidence limit is above the dashed line, the experimental treatment (i.e., Succeed) is inferior to omeprazole.

previously been investigated and given the prevalence of gastric ulceration in performance horses this would be a useful area to pursue.

4.1. Limitations of the Study

It is also possible that the number of inconclusive findings is a result of the lower than expected efficacy of both treatments, and with noninferiority analysis, there is a risk of declaring noninferiority in error as a result of the investigational drug being less effective than was anticipated [33]. Further studies are required to investigate the effect of prolonged administration of omeprazole, especially as this drug is frequently administered to performance horses for the duration of an athletic season.

The large number of inconclusive comparisons on the noninferiority analysis may be due to a lack of statistical power. Although a sample size calculation was performed before commencement of the study, there were a higher number of horses lost from the study than was anticipated and the initial prevalence of gastric ulceration was lower than estimated.

5. Conclusions

To the author's knowledge, this is the first study to report the efficacy of treatments for gastric ulceration over a period of greater than 2 months. Succeed was shown to be noninferior to omeprazole following 90 days of treatment. Given the often-prolonged use of treatments for gastric ulceration over a racing season, the authors believe this to be a notable finding. Additionally, the finding that prolonged administration of omeprazole did not result in a statistically significant resolution of squamous ulceration warrants further investigations which also account for periods of withdrawal.

Acknowledgments

References

[1] Begg LM, O'Sullivan CB. The prevalence and distribution of gastric ulceration in 345 racehorses. Aust Vet J 2003;81:199–201.

[2] Bell R, Kingston J, Mogg T, Perkins N. The prevalence of gastric ulceration in racehorses in New Zealand. N Z Vet J 2007;55:13–8.

[3] Hammond CJ, Mason DK, Watkins KL. Gastric ulceration in mature Thoroughbred horses. Equine Vet J 1986;18:284–7.

[4] Marqués FJ, Epp T, Wilson D, Ruiz AJ, Tokateloff N, Manning S. The prevalence and risk factors of oesophageal and nonglandular gastric lesions in Thoroughbred racehorses in Saskatchewan: equine gastric ulcer syndrome (EGUS). Equine Vet Educ 2011;23:249–54.

[5] Murray MJ, Nout YS, Ward DL. Endoscopic findings of the gastric antrum and pylorus in horses: 162 cases (1996–2000). J Vet Intern Med 2001;15:401–6.

[6] Murray MJ, Schusser G, Pipers FS, Gross SJ. Factors associated with gastric lesions in Thoroughbred racehorses. Equine Vet J 1996; 28(5):368–74.

[7] Murray MJ, Grodinsky C, Anderson CW, Radue PF, Schmidt GR. Gastric ulcers in horses: a comparison of endoscopic findings in horses with and without clinical signs. Equine Vet J 1989;21(S7):68–72.

[8] Rabuffo TS, Orsini JA, Sullivan Eileen K, Engiles J, Norman T, Boston R. Associations between age or sex and prevalence of gastric ulceration in Standardbred racehorses in training. J Am Vet Med Assoc 2002;221:1156–9.

[9] Vatistas NJ, Snyder JR, Carlson G, Johnson B, Arthur RM, Thurmond M, et al. Cross-sectional study of gastric ulcers of the squamous mucosa in Thoroughbred racehorses. Equine Vet J 1999; 31:34–9.

[10] Videla R, Andrews FM. New perspectives in equine gastric ulcer syndrome. Vet Clin North Am Equine Pract 2009;25:283–301.

[11] Nieto JE, Snyder JR, Vatistas NJ, Jones JH. Effect of gastric ulceration on physiologic responses to exercise in horses. Am J Vet Res 2009; 70:787–95.

[12] Sykes BW, Sykes KM, Hallowell GD. A comparison between pre- and post exercise administration of omeprazole in the treatment of equine gastric ulcer syndrome: a blinded, randomised, clinical trial: pre- vs. post exercise omeprazole for equine gastric ulcer syndrome. Equine Vet J 2014;46:422–6.

[13] Doucet M, Vrins A, Dionne R, Alva R, Ericsson G. Efficacy of a paste formulation of omeprazole for the treatment of naturally occurring gastric ulcers in training standardbred racehorses in Canada. Can Vet J 2003;44:581–5.

[14] Murray MJ, Haven ML, Eichorn ES, Zhang D, Eagleson J, Hickey GJ. Effects of omeprazole on healing of naturally-occurring gastric ulcers in Thoroughbred racehorses. Equine Vet J 1997;29:425–9.

[15] Andrews FM, Sifferman RL, Bernard W, Hughes FE, Holste JE, Daurio CP, et al. Efficacy of omeprazole paste in the treatment and prevention of gastric ulcers in horses. Equine Vet J 1999;31:81–6.

[16] Sykes BW, Underwood C, McGowan CM, Mills PC. Pharmacokinetics of intravenous, plain oral and enteric-coated oral omeprazole in the horse. J Vet Pharmacol Ther 2015;38:130–6.

[17] Hellings IR, Larsen S. ImproWin® in the treatment of gastric ulceration of the squamous mucosa in trotting racehorses. Acta Vet Scand 2014;56:13.

[18] Woodward MC, Huff NK, Garza F, Keowen ML, Kearney MT, Andrews FM. Effect of pectin, lecithin, and antacid feed supplements (Egusin®) on gastric ulcer scores, gastric fluid pH and blood gas values in horses. BMC Vet Res 2014;10:S4.

[19] Sanz MG, Viljoen A, Saulez MN, Olorunju S, Andrews FM. Efficacy of a pectin-lecithin complex for treatment and prevention of gastric ulcers in horses. Vet Rec 2014;175:147.

[20] Huff NK, Auer AD, Garza F, Keowen ML, Kearney MT, McMullin RB, et al. Effect of sea buckthorn berries and pulp in a liquid emulsion on gastric ulcer scores and gastric juice pH in horses. J Vet Intern Med 2012;26:1186–91.

[21] Sykes BW, Sykes KM, Hallowell GD. Efficacy of a combination of apolectol, live yeast (Saccharomyces cerevisiae [CNCM I-1077]), and magnesium hydroxide in the management of equine gastric ulcer syndrome in Thoroughbred racehorses: a blinded, randomized, placebo-controlled clinical trial. J Equine Vet Sci 2014;34:1274–8.

[22] Andrews FM, Camacho-Luna P, Loftin PG, Gaymon G, Garza F, Keowen ML, et al. Effect of a pelleted supplement fed during and after omeprazole treatment on nonglandular gastric ulcer scores and gastric juice pH in horses. Equine Vet Educ 2015;28:196–202.

[23] Murray M. How to perfrom gastroduodenoscopy. Proc. Annu. Conv. AAEP 2002, vol. 48. Veranda Communications Inc.: Lexington, KY: 2002. p. 282–286.

[24] Sykes BW, Hewetson M, Hepburn RJ, Luthersson N, Tamzali Y. European College of Equine Internal Medicine Consensus Statement—equine gastric ulcer syndrome in adult horses. J Vet Intern Med 2015;29:1288–99.

[25] Bell R, Kingston J, Mogg T. A comparison of two scoring systems for endoscopic grading of gastric ulceration in horses. N Z Vet J 2007; 55:19–22.

[26] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

[27] Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJV. Reporting of noninferiority and equivalence randomized trials. J Am Med Assoc 2006;295:1152–60.

[28] Sykes BW, Sykes KM, Hallowell GD. A comparison of three doses of omeprazole in the treatment of equine gastric ulcer syndrome: a blinded, randomised, dose-response clinical trial. Equine Vet J 2015; 47:285–90.

[29] Lester GD, Smith RL, Robertson ID. Effects of treatment with omeprazole or ranitidine on gastric squamous ulceration in racing Thoroughbreds. J Am Vet Med Assoc 2005;227:1636–9.

[30] MacAllister CG, Sifferman RL, McClure SR, White GW, Vatistas NJ, Holste JE, et al. Effects of omeprazole paste on healing of spontaneous gastric ulcers in horses and foals: a field trial. Equine Vet J 1999;31:77–80.

[31] Sykes BW, Sykes KM, Hallowell GD. A comparison of two doses of omeprazole in the treatment of equine gastric ulcer syndrome: a blinded, randomised, clinical trial. Equine Vet J 2014;46:416–21.

[32] Hunfeld NGM, Geus WP, Kuipers EJ. Systematic review: rebound acid hypersecretion after therapy with proton pump inhibitors. Aliment Pharmacol Ther 2007;25:39–46.

[33] Bermingham EC, del Castillo JRE, Radecki SV. The use of the noninferiority analysis in clinical studies: the use of the non-inferiority analysis in clinical studies. Equine Vet J 2014;46:399–401.