Evaluation of the Effects of Omeprazole on Physiological Indices of Performance of Horses During Incremental Treadmill Exercise

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ABSTRACT

Omeprazole is a proton-pump inhibitor recently approved in the United States for the treatment of gastric ulcer disease in horses. A study was designed to determine the effects of omeprazole treatment on the physiological indices of performance of horses during incremental treadmill exercise. In a crossover-design study carried out over 2 weeks, five horses completed standardized incremental exercise tests on a high-speed treadmill either with no treatment or treatment with omeprazole. No statistically significant effects of omeprazole were found on the mean maximum responses for specific oxygen consumption, specific carbon dioxide production, number of steps completed, concentration of plasma lactate, heart rate achieved, or total run time during the standardized incremental exercise protocol. The results indicate omeprazole treatment is unlikely to be associated with marked enhancement of athletic performance.

INTRODUCTION

The prevalence of gastric ulcer disease (GUD) in racehorses has been shown to be exceedingly high. Some estimates indicate that as many as 80% of horses in race training suffer from the disease with the severity ranging from mild to severe. Recently, results of a survey conducted in other types of performance horses such as cutting, three-day event, and hunter-jumpers indicate that GUD may be common in all types of performance horses. Although the prevalence of GUD has been well described, the etiology in horses has not been determined despite numerous studies.

While ongoing research efforts seek to understand the pathogenesis of GUD in horses, the current clinical focus has been on developing effective therapies to treat and prevent ulcer formation. Treatment recommendations for GUD in horses have included a diverse array of medications including antacids, cytoprotective agents, and H₂ receptor antagonists.
such as cimetidine and ranitidine. Most of these agents are not approved for use in horses in the United States, and their efficacies in the treatment of GUD in horses are not well established. Recently, omeprazole (Gastrogard®, Merial, Duluth, GA) was approved in the United States for the treatment of GUD in horses. Omeprazole, a proton-pump inhibitor, decreases acid production in the stomach, which promotes healing of formed ulcers and prevents new ulcer formation. The recommended treatment regimen for omeprazole is oral administration once daily, initially at 4 mg/kg for 4 weeks, followed by a maintenance dose of 2 mg/kg for at least another 4 weeks.

The need for long-term therapy to effectively treat GUD presents difficulties for the owners of horses participating in athletic competitions. Most regulatory agencies do not allow the administration of foreign substances, including therapeutic medications, within 24 to 48 hours of competition. These policies were implemented to protect the integrity of equine sports and the welfare of the horses. The goal was to prevent horses from competing under the influence of performance-enhancing drugs. Unfortunately, in the case of GUD, these regulations can interfere with appropriate veterinary care of affected horses. If it can be shown that a therapeutic medication does not increase a horse’s performance, regulatory agencies may allow their use during competitions. Therefore, the objective of this study was to determine whether omeprazole affects the physiological indices of performance of horses in a standardized incremental exercise test.

**MATERIALS AND METHODS**

**Horses**

Six horses, including four thoroughbreds, one standardbred, and one warmblood, 3 to 7 years of age, weighing 490 to 516 kg each, free of clinically detectable disease, were used in this study. For at least 8 weeks prior to the study, the horses were exercised 3 days a week on a high-speed equine treadmill. The exercise protocol consisted of 3 minutes of walking at 1.9 meters per second (m/s), 3 minutes of trotting at 3.0 m/s, and 6 minutes of galloping. Initially the horses were galloped at 7 m/s for the 6 minutes, but over the conditioning period the galloping speed was gradually increased; the week before the test, horses were galloping 3 minutes at 7 m/s followed by 3 minutes at 12 m/s. The standardbred followed the same basic protocol but paced at the higher speeds instead of galloping. During the conditioning period, the horses were also acclimated to wearing a facemask which was placed over their muzzles and connected to their halters. Horses were housed in box stalls and fed a mixture of oat and alfalfa hay with free access to water at all times. On the days the horses were not exercised on the treadmill, they were either turned out in round corrals or hand walked. The Institutional Animal Care and Use Committee at the University of California, Davis approved all procedures in the study.

**Gastroscopic Examination**

Within 1 week of initiating the study, all horses were evaluated for the presence of GUD. For this purpose, the horses were fasted at least 12 hours and sedated with 150 mg xylazine by intravenous injection. Immediately following sedation, a fiberoptic videoendoscope (11 mm × 3 m) was passed into the stomach for evaluation of the gastric mucosa for the presence of ulcers.

**Treatments**

A crossover design was used with horses randomized into two groups, one receiving omeprazole and the other receiving no treat-
The study was conducted over the course of 2 weeks. During the first week, three horses received omeprazole and three received no treatment; during the second week, the groups were reversed. Omeprazole treatment consisted of oral administration of omeprazole at 4 mg/kg once per day for a total of 7 days. Incremental exercise measurements were performed on Tuesday and Thursday of each week, corresponding to Days 5 and 7 following omeprazole treatment.

**Standardized Incremental Exercise Test**

Horses were equipped with instrumentation prior to being led onto the treadmill. A 14-gauge, 5.25-inch Teflon® (DuPont, Wilmington, DE) catheter was percutaneously placed in the jugular vein using sterile technique. Three electrodes were affixed to shaved patches on the dorsal and ventral thorax for measurement of electrocardiograms (ECGs) during the experiments. The horses were secured to an overhead safety support by a nylon surcingle, cross-tied to the side rails at the front of the treadmill, and hand held by a lead rope attached to their halters during the runs.

To begin the study, the horses were walked individually onto the treadmill; the catheters and tubing were connected and checked for patency; the ECG wires were connected to a bioelectric amplifier; and the treadmill was started. The horse initially walked at a speed of 1.9 m/s for 3 to 5 minutes while all connections were checked, signals adjusted, and the gas collection mask placed over the horse’s nose and attached to its halter. The treadmill speed was increased to 3 m/s for 4 minutes, 7 m/s for 2 minutes (canter), and then run for 90-second intervals at speeds of approximately 11, 12, 13, 14, and 15 m/s. The standardbred walked at a speed of 1.9 m/s for 3 to 5 minutes, paced for 4 minutes at 4.5 m/s, and then paced the remainder of the exercise at the speeds and times as described previously. The test was stopped when the horse could no longer maintain its position on the treadmill despite energetic encouragement from laboratory personnel. At that time, the treadmill was slowed to 1.9 m/s and the horse was allowed to recover for several minutes before it was taken off the treadmill and cooled out by hand. The galloping phase of the run, from the time the treadmill speed was increased to 11 m/s until the time it was slowed to walk speed, was recorded as the total run time. Treadmill speed was monitored at all times with an optical tachometer reading from the unpowered passive (no slippage) drum of the treadmill. Experiments on all but one day were recorded on videotape to allow later analysis of events that occurred during the experiment, such as reassessment of run duration, as needed.

Once the treadmill speed was increased to 11 m/s, blood samples were drawn at 30-second intervals to measure the rate of plasma lactate accumulation. Whole-blood samples (6 ml) were drawn into syringes containing heparin as an anticoagulant and stored in crushed ice until they were centrifuged and the plasma collected. Plasma lactate concentrations were determined within 4 hours of completion of the run using a commercial lactate analyzer.

The gas collection mask was a polyvinyl chloride (PVC) cone that tapered from a diameter of 25 cm at the opening to 20 cm at the point it connected to a flexible PVC tube in series with a rigid PVC duct 25 cm in diameter. A bias flow of gas was drawn through the mask and ductwork by a 5-hp turbine. The bias flow rate was monitored by an electronic mass flow meter connected in parallel with the bias flow line via a PVC pipe 5 cm in diameter; a butterfly valve allowed the division of flow to be regulated so the output of
the mass flow meter was near full scale (1500 l/min) when bias flow was maximized (approximately 10,000 l/min). During experiments, bias flow was approximately 8,000 to 9,000 l (at ambient temperature and pressure)/min. Additionally, the static pressure inside the bias flow tubing was measured with one arm of a differential pressure transducer. Bias flow rate and static pressure were measured and recorded during all runs and calibrations.

Temperature and relative humidity of the bias flow gas was monitored with an electronic thermohygrometer. Samples of expired gas were drawn from the bias flow line by a diaphragm pump and passed through a 2-meter length of Nafion™ (DuPont) tubing with a countercurrent flow of dry air (containing calcium sulfate, CaSO₄) to remove all water vapor from the gas sample. The sample was passed through a carbon dioxide (CO₂) analyzer and then split, half passing directly through one cell of an oxygen analyzer and the other half passing through a column of sodium hydroxide-coated nonfibrous silicate and CaSO₄ before entering a second cell of the oxygen analyzer.

All electrical outputs described above were recorded on a PC computer using WinDaq (DATAQ Instruments, Inc., Akron, OH) hardware and WinDaq/Pro+ software at sampling rates ranging from 500 Hz (ECG and static line pressure, with fluctuations caused by ventilation) to 2 Hz (tachometer, temperature, humidity, foot switch). Data were analyzed using WinDaq Waveform Browser software. Steady-state values for heart rate (HR), oxygen consumption (VO₂), and carbon dioxide production (VCO₂) were measured during the final 30 seconds at each speed, after the horses had been allowed 60 seconds to come to steady state. Frequencies were measured using fast Fourier transform of the ECG and static line pressure recordings.

Oxygen consumption and CO₂ production were calculated as described by Pascoe and coworkers using the technique developed by Fedak and coworkers. In essence, the changes in CO₂ and oxygen concentrations caused by the horse while exercising are approximately matched by calibration flows of CO₂ (raising its concentration to mimic the horse’s CO₂ production) and nitrogen (diluting oxygen to mimic consumption of oxygen by the horse’s metabolism). These calibration flows (CO₂ and nitrogen) were measured by two electronic mass flowmeters each. The outputs of the flowmeters, as well as the other transducers, were recorded by the WinDaq hardware/software. Each horse’s actual metabolic production or consumption of gas could then be calculated by multiplying the calibration gas flow (at standard temperature and pressure with water vapor removed) by the ratio of the change in gas concentration caused by the horse versus the flow of calibration gas. The derivation of these calculations to preserve mass balance is described in detail elsewhere. Additional corrections were applied for slight differences in bias flow that existed between horse measurements and calibrations, as well as slight differences in bias line static pressure that systematically bias the oxygen concentration measured by the analyzer’s electrochemical cell.

Statistical Analysis

Repeated measures analysis of variance (ANOVA) was used to test for differences in peak specific oxygen consumption (VO₂peak), peak specific CO₂ production (CO₂peak), maximum number of steps completed (STEPmax), peak concentration of plasma lactate (lactatepeak), maximum heart rate achieved (heart ratemax), and total run time in the absence and presence of omeprazole using desktop statisti-
cal software (SAS/STAT, SAS Institute, Cary, NC). Differences were considered significant if $P < .05$.

## RESULTS

Four of the six horses completed the study as designed, participating in two control and two omeprazole-treated standardized incremental exercise tests. One horse suffered from intermittent lameness due to fetlock arthritis and was able to complete only one control and one omeprazole-treated test. During the first week of the study, one horse sustained a mild tear of the superficial digital tendon in the course of the second run and was eliminated from the study.

### Gastroscopic Examination

The results of the gastroscopic examinations revealed the presence of GUD in four of the six horses at the start of the study. The severity of GUD was considered moderate for two horses and mild for the other two. In all cases, the ulcers were confined to the squamous portion of the stomach and the margo plicatus. The remaining two horses, one of which was the one eliminated from the study at the end of the first week, had no evidence of ulcer disease.

### Standardized Incremental Exercise Measurements

No statistically significant effect of omeprazole was found on the mean responses for $\text{VO}_{2\text{peak}}, \text{CO}_{2\text{peak}}, \text{STEP}_{\text{max}}, \text{lactate}_{\text{peak}}, \text{heart rate}_{\text{max}}$, or total run time during the standardized incremental exercise protocol (Table 1). The mean mass specific oxygen consumption and $\text{CO}_2$ production at the intermediate steps of the test were also not significantly different between the control and omeprazole treatment (Figure 1). In addition, the effect of omeprazole on oxygen consumption and $\text{CO}_2$ production was not consistent in any individual horse (Figure 2). The variability in fractional changes in lactate accumulation rate is high because the absolute numbers for that variable tend to be small (i.e., $< 20 \text{ mM/min}$), so small changes in the absolute numbers represent large fractional changes. In a similar manner, there was no consistent effect of omeprazole on heart rate or lactate accumulation rate in individual horses at any step of the protocol (Figure 3). Finally, omeprazole had no consistent effect on the total run times (Figure 4). For example, three of the horses ran longer with omeprazole treatment, but two horses ran longer under control conditions (Figure 4).

<p>| TABLE 1. Treadmill Exercise Measurements (Mean ± SD) for Five Horses Treated With Omeprazole or Given No Treatment Before Treadmill Exercise |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>No Treatment</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak specific oxygen consumption (ml [STPD]/s kg)</td>
<td>2.38 ± 0.36</td>
<td>2.29 ± 0.22</td>
</tr>
<tr>
<td>Peak specific $\text{CO}_2$ production (ml [STPD]/s kg)</td>
<td>2.78 ± 0.44</td>
<td>2.71 ± 0.40</td>
</tr>
<tr>
<td>Maximum steps completed</td>
<td>3.2 ± 0.7</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>Peak plasma lactate (mM)</td>
<td>19.5 ± 6.7</td>
<td>19.4 ± 5.0</td>
</tr>
<tr>
<td>Maximum heart rate (beats per minute)</td>
<td>208.3 ± 8.4</td>
<td>208.8 ± 13.9</td>
</tr>
<tr>
<td>Total run time (seconds)</td>
<td>293 ± 82</td>
<td>277 ± 102</td>
</tr>
</tbody>
</table>

STPD = standard temperature and pressure with water vapor removed.
DISCUSSION

The administration of omeprazole was not associated with significant increases in physiological indices of performance (VO$_{2\text{peak}}$, CO$_{2\text{peak}}$, STEP$_{\text{max}}$, lactate$_{\text{peak}}$, heart rate$_{\text{max}}$) measured during standardized incremental exercise protocols in five horses. The lack of demonstrable effects of omeprazole in this study has significant clinical implications. For example, although omeprazole has been shown to be safe and effective in the treatment of GUD, many drug and medication rules forbid its administration to horses during competition. The commendable objectives of these rules are to protect the welfare of the horses and the integrity the sport. Nevertheless, when one considers the high prevalence of GUD, along with the lack of evidence of effect of omeprazole on performance, consideration should be given to allowing therapeutic administration of omeprazole to performance horses during competition.

The effects of GUD on physiological indices of performance measured in standardized incremental exercise protocols were not determined in this study. Although four of the five horses completing the study did have mild to moderate GUD, the duration of treatment (i.e., 7 days) with omeprazole was not sufficient to cause a significant degree of healing of the ulcers.$^9,18$ None of the horses in the study displayed any clinical signs often associated with GUD, such as poor appetite, mild to severe colic, changes in attitude, or weight loss.

![Figure 1. Mean mass-specific rates of oxygen consumption (top panel) and CO$_2$ production (bottom panel) as a function of treadmill speed for omeprazole-treated and untreated control horses. Data include one horse that paced at 4.5 m/s while the other four horses trotted at 3.0 m/s. Values are mean ± SD. STPD = at standard temperature and pressure with water vapor removed.](image-url)
Several studies have demonstrated that superior athletic capacity correlates with physiological variables such as VO$_{2peak}$.

In addition, peak plasma lactate concentrations have also been correlated with athletic performance in thoroughbred horses undergoing a maximal exercise test.

The type of incremental exercise procedure used in the present study has the added advantage that variables may be measured and compared at maximal and submaximal exercise intensities. This is important because, although racing performance is generally considered to involve maximal efforts, most other forms of equine athletic competitions involve submaximal exercise. Taken together, the results of these studies indicate that the measurements made during incremental exercise procedures correlate with aerobic and anaerobic capacities in horses. Therefore, evaluation of the effects of drugs or medications in horses undergoing incremental exercise protocols may be an appropriate method to determine whether those agents affect athletic performance.

Although the results of this study indicate that omeprazole does not enhance performance in an incremental exercise protocol, the question remains as to whether this type of test is an adequate reflection of performance in a race or other type of athletic competition.

![Figure 2](image)

**Figure 2.** Fractional changes from untreated control in mass-specific rates of oxygen consumption (top panel) and CO$_2$ production (bottom panel) recorded during incremental exercise for each of five horses treated with omeprazole. Values for each horse are calculated by dividing measurements made with omeprazole treatment by measurement under untreated control conditions.
ical indices of performance measured during an incremental treadmill exercise protocol. It must be recognized, however, that the statistical power of the current study may have been inadequate to detect very small changes associated with omeprazole therapy. Nevertheless, the results do support the conclusion that omeprazole does not exert a great effect on these parameters. Therefore, the results of this study should provide regulators with some confidence that if omeprazole is used during equine competitions for a horse that suffers from GUD, it is unlikely to be associated with any marked enhancement of athletic performance.

**REFERENCES**


