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Effect of sucralfate on total carbon dioxide concentration in horses subjected to a simulated race test

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ABSTRACT

The purpose of this study was to test the hypothesis that sucralfate, a gastric ulcer medication, would alter plasma concentrations of total carbon dioxide (tCO_2), lactate (LA), sodium (Na^+), potassium (K^+), chloride (Cl^-) and total protein (TP), as well as calculated plasma strong ion difference (SID) and packed cell volume (PCV) in horses subjected to a simulated race test (SRT). Six unfit Standardbred mares (~520 kg, 9–18 years) were used in a randomized crossover design with the investigators blinded to the treatment given. The horses were assigned to either a control (40–50 mL apple sauce administered orally (PO)) or a sucralfate (20 mg/kg bodyweight dissolved in 40–50 mL apple sauce administered PO) group. Each horse completed a series of SRTs during which blood samples were taken via jugular venipuncture at five sampling intervals (prior to receiving treatment, prior to SRT, immediately following exercise, and at 60 and 90 min post-SRT). During the SRTs, each horse ran on a treadmill fixed on a 6% grade for 2 min at a warm-up speed (4 m/s) and then for 2 min at a velocity predetermined to produce $VO_{2max.}$ Each horse then walked at 4 m/s for 2 min to complete the SRT. Plasma tCO_2, electrolytes, LA, and blood PCV and TP were analysed at all intervals.

No differences ($P > 0.05$) were detected between control and sucralfate for any of the measured variables. There were differences ($P < 0.05$) in tCO_2, SID, PCV, TP, LA and electrolyte concentrations relative to sampling time. However, these differences were attributable to the physiological pressures associated with acute exercise and were not an effect of the medication. It was concluded that sucralfate did not alter plasma tCO_2 concentration in this study.

Introduction

Equine gastric ulcer syndrome (EGUS) is very prevalent in athletic horses, especially young racehorses, where clinical signs can range from no overt symptoms to substantial pain (Hammond et al., 1986; Vatistas et al., 1994; MacAllister, 1999). This condition, observed in ~93% of racehorses, is thought to be induced by a combination of practices associated with racehorses in training (Murray et al., 1989). In particular, frequent treatments with non-steroidal anti-inflammatory drugs (NSAIDs), such as phenylbutazone and flunixin meglumine (Jones, 1983; Vatistas, 1999), and high-energy concentrate diets with minimal forage availability contribute to gastrointestinal disturbances (Feige et al., 2002; Gordon et al., 2006). Long-term box stall housing, an unnatural environment for horses, may also play a role in ulcer development (Dionne et al., 2003; McClure et al., 2005).

A variety of treatments may be used to treat gastric ulcers in humans and horses. Bismuth compounds and antacids are commonly used to treat acute disorders in humans, but are not effective in altering pH of the equine stomach due to the much larger size of the horse (Clark et al., 1996). Histamine H_2 receptor antagonists, such as ranitidine, work at the parietal cell level inhibiting gastric acid secretions by blocking interactions of histamine (Brunton, 1996). These medications, though effective in humans, would also require extremely large doses and are therefore impractical in horses. The efficacy of proton pump inhibitors have been documented and have shown to be quite effective in treating ulcers in horses (Campbell-Thompson et al., 1988; MacAllister et al., 1999). Omeprazole, a popular proton pump inhibiting medication, is a highly potent and highly specific inhibitor of hydrogen-potassium adenosine triphosphatase (H^+, K^+ ATPase), although this medication is expensive. One less costly alternative is sucralfate.

Sucralfate (a salt of sucrose octasulfate) is a hydroxy-aluminum compound used in horses and humans to treat gastric ulcerations (McCarthy, 1991; Jensen et al., 1992; MacAllister et al., 1993; Brunton, 1996). Sucralfate forms a sticky, viscid gel at a pH of <4.0 that adheres to epithelial cells lining the stomach and protects them from further degradation. The medication also lessens the activity of pepsin in the stomach and bile acids in the small intestine, and elevates pH in the gastrointestinal tract by stimulating endogenous buffers in the stomach such bicarbonate (HCO_3^-). The coating and

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buffering mechanisms work in concert to create an environment that is supportive for ulcer healing (MacAllister et al., 1999).

The pharmacological effects of sucralfate have been well documented in the resting horse (Geor et al., 1989; Pepich, 1993). However, a paucity of information exists concerning sucralfate and its implications for the acid–base status of the exercising horse. This may have relevance if sucralfate administration elevates whole body pH in addition to stomach pH. This may then inadvertently elevate the threshold plasma total carbon dioxide (tCO_2) concentration – a parameter used by regulators to determine if a racing (or competition) horse has been administered an alkalinising agent.

Alkalinizing agents are administered prior to a race with the intent of delaying the onset of fatigue caused by the acidosis associated with intense anaerobic work during the race etc. (Lloyd et al., 1992; Lloyd and Rose, 1992; Rose and Lloyd, 1992; Lloyd and Rose, 1995). The alkalinising action of a variety of substances may be ergogenic for racehorses, but the practice is damaging to the integrity of the sport, and more importantly, to the welfare of the horse due to potential adverse effects. A 'milkshake', consisting of baking soda ($NaHCO_3$), water, sugar, and other ingredients, can be administered via nasogastric tube, although the ergogenic benefits are debatable (Lawrence et al., 1990; Irvine, 1992; Lloyd et al., 1992; Lloyd and Rose, 1992; Rose and Lloyd, 1992; Lloyd and Rose, 1995) and the administration of alkalinising agents may infringe racing rules during competition.

Horses use HCO_3^- to buffer the metabolic acidosis and to increase muscle cell pH resulting from intense exercise. In aqueous solution, carbon dioxide largely exists as carbonic acid, which dissociates into H^+ and HCO_3^- ion in transportation (Martin, 1981). With respect to the Henderson–Hasslebalch equation, HCO_3^- concentration can be measured through analysis of tCO_2 concentration in blood plasma (Lloyd et al., 1992; Lloyd and Rose, 1992). These indices are the basis for pre- and post-race testing for the administration of alkalinising agents that has been implemented in many racing jurisdictions across the United States and around the world. The purpose of the present study was to test the hypothesis that the gastric ulcer medication, sucralfate, would alter plasma concentration of tCO_2, lactate, and total protein (TP), as well as packed cell volume (PCV), in horses subjected to a simulated race test (SRT).

Materials and methods

Six clinically healthy, unfit and ulcer-free Standardbred mares (~520 kg bodyweight [BW]; 9–18 years old) were used. All horses were trained to run on a high-speed equine treadmill (Sato I; Equine Dynamics) and familiarized with equipment present in the exercise physiology laboratory prior to beginning the experiment. The mares were housed as a group on a dry lot paddock and each mare was fed approximately ~12 kg/day of mixed alfalfa-grass hay, and provided ~6 kg/day of a commercially available grain divided into two feed per 24 h period. Water and trace-mineral blocks were available ad libitum. The Rutgers University Institutional Animal Care and Use Committee approved all methods and procedures of this investigation.

The experiment was conducted using a crossover design where the horses were randomly assigned to one of two treatments, either control (40–50 mL apple sauce orally (PO)) or sucralfate (20 mg/kg BW dissolved in 40–50 mL apple sauce PO). The dose of sucralfate was based on the amount and frequency of administration used by veterinarians treating Standardbred racehorses in New Jersey.

In preparation, each horse performed a graded incremental exercise test (GXT) approximately 1 month prior to the start of the first round of drug administration and first SRT. The GXTs were used to determine the velocity to produce maximal oxygen uptake (VO_{2max}) of each horse (Kearns and McKeever, 2002; McKeever et al., 2006). In this way, each high intensity SRT exercise test was specific to the exercise ability of each horse. The SRT was designed to be analogous to the warm-up, high intensity run, and cool down seen in most Standardbred races (Szucsik et al., 2006). The sequence for treatment and SRT testing followed the same pattern for the first and second tests. For each of the rounds of testing, the horses were administered the treatment (either control or sucralfate) three times a day for a period of 24 h and finally 1 h prior to commencing the SRT. During each SRT, the horses ran on the equine treadmill (fixed 6% incline) for 2 min at a warm-up speed of 4 m/s, 2 min at the velocity required to reach VO_{2max}, and 2 min at a cool-down speed of 4 m/s.

Blood samples (21 mL) were collected at five intervals throughout the course of each mare's SRT via jugular venepuncture and stored in three, pre-chilled lithium heparinized, 7 mL tubes (Vacutainer; Becton–Dickinson). Sampling intervals were defined as: prior to treatment (Pre-Tx), 5 min before SRT (Pre-Ex), immediately following SRT (Post-0), and 60 and 90 min following exercise (Post-60 and Post-90, respectively). All blood samples were obtained using a 20 gauge needle and stored on ice prior to instrumental analysis. After completion of the first SRT, the mares were returned to their group pastures where they underwent a 1 month washout period. This was followed by administration of the opposite treatment and the second SRT in the same pattern as detailed above. All horses had free access to water, but were fed limited hay on the morning of SRT. Grain feeding was discontinued on the morning of the SRT to limit confounding factors in our investigation.

Two of the 7 mL tubes per each sampling interval were centrifuged (TJ-6R; Beckman–Coulter) at a 1500*g* at 4 °C for 15 min. Plasma was harvested from each tube for strong ion difference (SID) calculation (mmol/L) and tCO_2 analysis (mmol/L) (Synchron EL-ISE; Beckman–Coulter). Plasma tCO_2 concentration was measured, in duplicate, at the New Jersey State Police Equine Drug Testing Laboratory at the Meadowlands Racetrack. That instrument is used to test all samples from the surrounding New Jersey racetracks (Szucsik et al., 2006). Concentrations of sodium (Na^+), potassium (K^+), and chloride ions (Cl^-; mmol/L) were measured via a portable clinical analyzer (i-STAT, Heska). Plasma lactate concentrations (mmol/L) were measured in duplicate using a lactate analyzer (1500 Sport; Yellow Springs Instrument Company) (McKeever et al., 2006). Plasma SID was calculated as SID (mmol/L) = $[Na^+] + [K^+] - [Cl^-] - [Lactate^-]$ (Szucsik et al., 2006).

The third 7 mL tube of blood collected during each sampling interval was used to determine packed cell volume (PCV), via microhematocrit technique, and total plasma protein (TP) (mg/dL), via refractometry, measured in duplicate for each sample. The PCV and TP concentrations were analysed to assess compartmental fluid shifts during the exercise test.

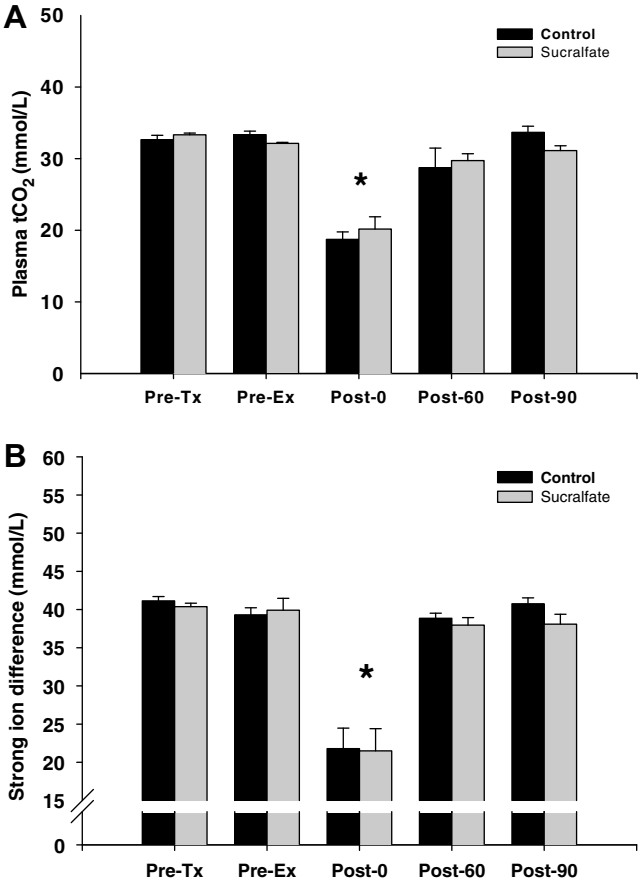

Fig. 1. Data showing the effect of sucralfate and exercise on (A) plasma tCO_2 concentration and (B) plasma SID (means ± standard error). No difference ($P > 0.05$) was detected between treatments across each of the five sampling intervals. An asterisk (*) indicates plasma tCO_2 concentration and SID decreased ($P < 0.05$) for both treatment groups from the Pre-Ex to Post-0 intervals and returned to pre-exercise levels by 60 min post-exercise.