

Effects of two intravenous dose levels of omeprazole on the gastric juice pH of healthy horses[□]

Efecto de dos niveles de dosis intravenosas de omeprazol sobre el pH del jugo gástrico de caballos sanos

Efeito de dois níveis de doses intravenosas de omeprazol no suco gástrico pH cavalos saudáveis

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Summary

Background: omeprazole suppresses gastric acid secretion and increases gastric juice pH by blocking the H⁺, K⁺ ATPase in the secretory membrane of parietal cells. Gastric juice pH below 4, long periods of no feed intake and stress are factors predisposing to gastric ulcers in horses. **Objective:** to determine the effect of 1 and 2 mg/Kg intravenous (IV) omeprazole on the gastric juice pH of Colombian Creole horses. **Methods:** seven horses were treated with two IV levels of omeprazole (1, and 2 mg/Kg body weight (BW)) in a crossover design. The omeprazole dose for each animal was reconstituted with 100 ml 0.9% NaCl. Gastric pH was measured using a portable pH-meter in stomach samples collected at time 0 (just before treatment), and 1, 2, 3, 5, 7, 9, 11, and 24 hours post-treatment. **Results:** the gastric pH at time 0 fluctuated from 1.6 to 3.2 in all horses. Both omeprazole doses (1 and 2 mg/Kg) significantly increased the gastric pH (pH>4.6) from 1 to 11 hours after the treatment. At 24 hours post-treatment, pH of the group treated with 1.0 mg/Kg significantly decreased to 2.8 ± 0.3, but remained elevated at 5.7 ± 0.87 for the group treated with 2 mg/Kg. **Conclusion:** the study demonstrated that a single IV omeprazole dose of 2 mg/Kg, but not 1 mg/Kg, maintained gastric pH above 4 during 24 hours.

Keywords: *equine, stomach, ulcer.*

Resumen

Antecedentes: el omeprazole disminuye la secreción de ácido gástrico e incrementa el pH del jugo gástrico al bloquear la enzima H⁺, K⁺ ATPasa en la membrana secretora de la célula parietal. El estrés y el pH gástrico por debajo de 4 durante largos periodos de ayuno predisponen a las úlceras gástricas en caballos. **Objetivo:** determinar el efecto de dos dosis diferentes de omeprazol intravenoso (IV) sobre el pH gástrico en caballos Criollos Colombianos. **Métodos:** siete caballos fueron tratados con una o dos dosis de omeprazol IV (1 vs.

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2 mg/Kg de peso corporal (PC)) en un diseño cruzado. La dosis de omeprazol para cada animal fue reconstituida con 100 ml de NaCl 0,9%. El pH del jugo gástrico se determinó con un medidor portátil a las: 0 (antes del tratamiento), 1, 2, 3, 5, 7, 9, 11 y 24 horas post-tratamiento. **Resultados:** el pH gástrico a la hora 0 varió de 1,6 a 3,2 en todos los caballos. Ambas dosis de omeprazol (1 y 2 mg/Kg) incrementaron significativamente el pH gástrico ($\text{pH} > 4,6$) de 1 hora hasta 11 horas después del tratamiento. A las 24 horas pos-tratamiento el pH en el grupo tratado con 1 mg/Kg IV disminuyó significativamente a $2,8 \pm 0,3$, pero se mantuvo elevado a $5,7 \pm 0,87$ en el grupo tratado con 2 mg/Kg. **Conclusión:** el estudio demostró que una sola aplicación intravenosa de 2 mg/Kg de omeprazol, pero no de 1 mg/Kg, mantuvo el pH gástrico por encima de 4 durante 24 horas.

Palabras clave: equino, estómago, úlcera.

Resumo

Antecedentes: o omeprazol diminui a secreção de ácido gástrico e aumenta o pH do suco gástrico através do bloqueio da enzima H^+ , K^+ ATPase na membrana secretora da célula parietal. O pH do suco gástrico inferior a 4 por longos períodos de jejum e estresse pode causar úlceras gástricas em equinos. **Objetivo:** determinar o efeito de 1 mg/Kg e 2 mg/Kg de omeprazol intravenoso (IV) sobre o pH do suco gástrico do cavalo Criollo Colombiano. **Métodos:** sete cavalos foram tratados com omeprazol (1 mg/Kg e 2 mg/Kg de peso corporal, IV), em um desenho cruzado. Uma dose de omeprazole de cada animal fue reconstituida com 100 ml de NaCl a 0,9% e foi administrada por via intravenosa. O pH do suco gástrico foi medido, usando um medidor de pH portátil nas amostras estomacais nas 0 horas (antes do tratamento), 1, 2, 3, 5, 7, 9, 11 e 24 horas pós-tratamiento. **Resultado:** o pH do suco gástrico quando 0 variou de 1,6 a 3,2 em todos os cavalos. Ambas as doses de omeprazol (1 e 2 mg/Kg) induziram um aumento significativo no pH do suco gástrico ($\text{pH} > 4,6$), a partir de 1 hora até 11 horas pós-tratamiento. Às 24 horas pós-tratamiento, o pH médio \pm desvio padrão (DP) no grupo tratado com 1 mg/Kg IV, diminuiu significativamente para $2,8 \pm 0,3$ mas manteve-se elevado a $5,7 \pm 0,87$ no grupo tratado com 2 mg/Kg IV. **Conclusão:** o estudo demonstra que uma única aplicação intravenosa de omeprazol a 2 mg/Kg IV, mas não a 1 mg/Kg em equinos, manteve o $\text{pH} > 4$ no suco gástrico por 24 horas.

Palavras-chave: equino, estômago, úlcera.

Introduction

Equine gastric ulcer syndrome (EGUS) is highly prevalent in all ages and affects horse performance and fitness (Andrews and Nadeau, 1999; Doucet *et al.*, 2003). Large numbers of stabled horses undergo intense work routines, which can predispose to gastrointestinal problems such as gastric ulcers. EGUS is usually associated with changes in attitude, poor appetite, weight loss, decreased physical performance, diarrhea, abdominal discomfort or recurrent colic episodes (Murray *et al.*, 1996; Birkmann *et al.*, 2014), and is a common pathology in horses (Videla and Andrews, 2009). Anti-ulcer treatments generally consist in neutralizing stomach acidity using antacids or to reduce acid secretion with antisecretory drugs, aiming to provide a favorable environment for healing. Proton-pump inhibitors such as omeprazole are commonly used to suppress gastric acid secretion (Daurio *et al.*, 1999; Ruiz JD *et al.*, 2012). Histamine-2 (H_2) antagonists such as ranitidine or cimetidine (Campbell-Thompson and Merritt, 1987) are also commonly used for this purpose. Ranitidine (6.6 mg/Kg, orally administered) tended to increase

gastric fluid $\text{pH} > 6$ for a longer time (166 \pm 106 mins) compared with famotidine (98 \pm 110 mins), and higher doses are necessary in horses than those recommended in humans (Murray and Grodinsky, 1992). Omeprazole blocks H^+ secretion from parietal cell membranes by irreversibly joining the H^+ , K^+ ATPase proton pump (Holt and Howden, 1991). Pharmaceutical preparations for oral administration of omeprazole range from tablets to enteric-coated granules developed to release the drug in the intestine, thus preventing it from being degraded by the acidic environment of the stomach (Daurio *et al.*, 1999; Ruiz JD *et al.*, 2012). Oral administration of 4 mg/Kg omeprazole once daily is highly effective for healing gastric ulcers in horses (Doucet *et al.*, 2003; McClure *et al.*, 2005; McKeever *et al.*, 2006; Sykes *et al.*, 2014). However, oral administration of medications in horses with gastrointestinal disorders such as gastric reflux or dysphagia is contraindicated, so intravenous (IV) administration of omeprazole is an alternative route to increase gastric pH (Rand *et al.*, 2014). Andrews *et al.* (2006) administered 0.5 mg/Kg IV omeprazole once daily for five days to six adult horses, and observed that gastric pH increased from 2 to 4.35 one hour after

administration on the first day of the treatment. They also reported a pH of 5.27 ± 1.74 before omeprazole was administered 23 hours after the 4th daily dose was given. However, pH was very different among horses and time, whereas only 3 out of 6 horses had gastric pH above 4.0 one hour after omeprazole administration on the first day of the treatment, and it was above 4.0 in 5 of the 6 animals on day five (Andrews *et al.*, 2006).

The objective of this study was to determine the effect of a single IV dose of 1 or 2 mg/Kg omeprazole on gastric pH in Colombian Creole horses.

Materials and methods

Ethical considerations

All experimental procedures were approved by the Institutional Committee for the Care and Use of Animals of CES University (Medellin, Colombia; Act No 3-2013).

Animals

Seven healthy Colombian Creole horses (four males and three females) averaging seven years of age (range 4-10 years) and weighing 292 ± 63 Kg were used in the study. The horses were part of a herd used for training practices with CES University veterinary students and were kept on grazing pastures. Animals underwent physical examination and were dewormed one month before the start of the study. Blood work parameters before the study (complete blood count, creatinine, blood urea nitrogen, and alkaline phosphatase) were within the normal range for horses. Food was withheld 12 h before administering the drug. The animals were fasted throughout the 24 h duration of the study and water was provided *ad libitum* at all times.

Treatments

Each horse received all three IV treatments (control, 1, and 2 mg/Kg omeprazole) with a 7-day interval between treatments. Lyophilized omeprazole powder (Omezol Iyo[®] BEST, S. A. laboratories, Bogotá, Colombia) was diluted in 100 ml 0.9% NaCl and IV administered between 7:00 and 8:00 a.m on the day of the treatment using an 18-gauge x 1.5-inch needle.

Gastric juice samples for pH measurements were collected in glass bottles through a nasogastric tube and pH was measured immediately after collection using a portable pH-meter at time 0 (before injection) and at 1, 2, 3, 5, 7, 9, 11, and 24 hours post-injection. The pH-meter was calibrated using standard solutions (pH 4.0 and 7.0) before each collection time.

Statistic analysis

Data on gastric pH before injection and 1, 2, 3, 5, 7, 9, 11, and 24 hours post-injection were analyzed with STATGRAPHICS software (Statpoint Technologies, Inc. VA, USA). Results are presented as the mean \pm SD, but plotted as mean \pm standard error of the mean (SEM) for the ease of graphical illustration. Statistical differences between pH values were determined by analysis of variance (ANOVA) blocked by horse, with repeated measurements of pH. Significance was considered when $p \leq 0.05$.

Results

Gastric juice pH was low in all horses before omeprazole administration, ranging from 1.6 to 3.2. One hour after injecting 1 mg/Kg omeprazole, gastric pH increased significantly ($p \leq 0.05$) from 2.4 ± 0.4 to 6.5 ± 1 (range 4.6 to 7.5). Similarly, horses injected with 2 mg/Kg omeprazole had a significant increase in gastric pH from 2.2 ± 0.5 before injection to 6.9 ± 0.3 (range 6.3 to 7.1) one hour after the injection ($p \leq 0.05$). Figure 1 shows that no significant difference was observed between both omeprazole doses ($p > 0.05$). The control group showed no statistical difference at any time after the injection compared with time 0 (pre-treatment values; $p > 0.05$).

As shown in Figure 1, both 1 and 2 mg/Kg omeprazole induced significant increase in gastric pH (pH > 4.6 in all horses) from 1 to 11 hours after the injection, compared with the control group and pre-treatment values ($p \leq 0.05$). Gastric pH between horses treated with 1 and 2 mg/Kg omeprazole did not differ significantly from 1 to 11 hours post-administration ($p > 0.05$).

Whereas gastric pH of horses injected with 1 mg/Kg omeprazole decreased to 2.8 ± 0.3 at 24 h post-injection,

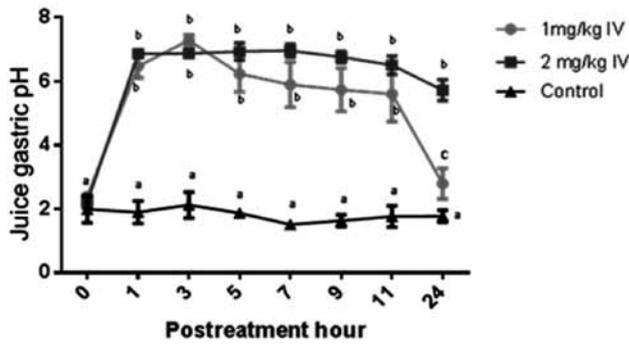


Figure 1. Mean \pm standard error of the mean (SEM) of gastric pH in adult horses after IV omeprazole dosages of 1 or 2 mg/Kg body weight (BW) and control. Values with different letters indicate significant differences ($p \leq 0.05$). Omeprazole was administered immediately after the first collection of gastric juice at 0 h.

it remained elevated at 5.7 ± 0.87 for the group treated with 2 mg/Kg. At 24 hours post-administration, a significant difference was found between both omeprazole groups ($p \leq 0.05$, Figure 1).

No adverse reactions related to omeprazole administration or the nasogastric intubation procedures were observed throughout the study.

Discussion

No significant differences were observed in gastric pH baseline (pH fluctuated from 1.6 to 3.2) at time 0 prior to omeprazole administration. This is consistent with some reports of minimal inter-individual variability in baseline gastric pH (Tellez *et al.*, 2005; Andrews *et al.*, 2006). Nevertheless, other studies have reported significant inter-horse variations (Daurio *et al.*, 1999; JD Ruiz *et al.*, 2012).

Both omeprazole injections (1 and 2 mg/Kg) increased gastric pH after one hour of injection, with values above 4 for all horses (range 4.6 to 7.5). Other researchers found gastric pH increased above 4 during the first hour only in three out of six horses treated with 0.5 mg/Kg IV omeprazole (Andrews *et al.*, 2006). In the present study, pH remained above 4 for up to 11 hours after injection of either 1 or 2 mg/Kg omeprazole; which is the minimum pH that should be maintained for as long as possible in order to improve

the healing rate of gastric lesions (Armstrong, 2004). However, only the highest omeprazole dose in our study (2 mg/Kg) was able to maintain the pH above 4 for 24 h after injection in every horse treated; which is similar to results reported by other researchers using 4 mg/Kg orally (Daurio *et al.*, 1999). Our results clearly indicate that a single dosage of 2 mg/Kg IV omeprazole inhibits gastric acid secretion for 24 hours. After absorption, omeprazole is transferred from the plasma to the acid secretory canaliculi of parietal cells (Holt and Howden, 1991) and covalently binds to H⁺, K⁺ ATPase (Bays and Finch, 1990), so the anti-secretory effect of omeprazole on parietal cells persists long after plasma concentrations have decreased (Holt and Howden, 1991).

Previous reports have shown that sedating agents can modify the solid and liquid phase of gastric emptying in horses, with possible effects on gastric pH (Doherty *et al.*, 1999; Sutton *et al.*, 2002). In the present study, the effect on gastric pH could only be attributed to omeprazole, since alpha-2 agonist tranquilizers—commonly administered for horse manipulation—were not used.

This study demonstrates that administering a single dosage of 1 mg/Kg IV omeprazole is not enough to increase gastric pH above 4 for 24 hours. However, a dose of 2 mg/Kg IV omeprazole produced a sustained increase of gastric pH above 4 during 24 hours, which is considered essential for gastric ulcer healing. Since the effect of omeprazole on gastric pH is not only dose but also time dependent, a limitation of this study was whether repeated daily administration of 1 mg/Kg IV, or even lower doses, could achieve and maintain steady states of gastric juice pH above 4 during few days after starting the therapy.

In summary, a dose-time-response relationship exists between omeprazole and gastric pH in horses, confirming that treatment with 1 or 2 mg/Kg IV omeprazole is effective to increase gastric pH.

Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

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