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Hypothesis Article

A free ride: Is long-term omeprazole therapy safe and effective?

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Summary

Omeprazole has been widely used in the horse for nearly 20 years. Yet, to date, few studies have evaluated its safety with specific regards to the adverse effects reported in human medicine. Recent studies on omeprazole in the horse have highlighted the potential for rebound gastric hyperacidity at the time of discontinuation of therapy, for decreased calcium absorption during administration and for disruption to hindgut function when administered alongside non-steroidal anti-inflammatory drugs. Unlike human medicine, no clear evidence exists for a link between omeprazole administrations and an increased risk of fractures in the horse. However, evidence exists that the proposed pathophysiological pathways for increased fracture risk which are present in human medicine are also present in the horse. Limited evidence suggests that decreased efficacy may occur over time with long-term omeprazole administration.

Introduction

Omeprazole is a commonly used medication in equine practice, and it is widely believed that administration of omeprazole is safe in the horse, both in the short term and the long term. However, a recent study that demonstrated an increased risk of phenylbutazone-induced gastrointestinal disease associated with the concurrent administration of omeprazole has challenged the notion that it is universally safe (Ricord *et al*. 2020). Similarly, omeprazole is widely believed to be effective for long-term administration as a preventative for equine gastric ulcer syndrome (EGUS) and it is registered for this purpose. However, little systematic evaluation has been performed on the efficacy of long-term (>60–90 days) dosing. Omeprazole is known to upregulate its own metabolism via the cytostome p450 pathway in other species and a 50% decrease in bioavailability has been reported after 28 days of dosing in the horse (Di Salvo *et al*. 2017). Whether this decreased bioavailability affects long-term efficacy in the horse is poorly described.

The purpose of this article is to review the current literature with a focus on specific safety aspects of omeprazole in the horse including rebound gastric hyperacidity, changes in faecal microbiota richness and diversity, interactions with non-steroidal anti-inflammatory drugs and increased fracture risk. Evidence supporting the efficacy of long-term administration is also reviewed. The author hypothesises that the commonly held belief that long-term administration of omeprazole is universally safe and effective should be challenged, and that further investigations are required to document both the safety and efficacy of long-term administration in the horse.

Rebound gastric hyperacidity

Rebound gastric hyperacidity, which manifests as severe heartburn, is a well-recognised adverse effect of abrupt discontinuation of proton pump inhibitor (PPI) therapy in humans (Haastrup *et al*. 2018). Up to 44% of healthy human volunteers receiving a 4-week course of a PPI experienced symptoms consistent with rebound gastric hyperacidity in one study (Niklasson *et al*. 2010). In another study, approximately 22% of healthy human volunteers experienced symptoms consistent with rebound gastric hyperacidity after 8 weeks of PPI therapy (Reimer *et al*. 2009). The most commonly agreed hypothesis to explain rebound gastric hyperacidity is through increases in serum gastrin concentrations. Gastrin is produced by the epithelial G-cells of the pyloric antrum, pancreas and duodenum in response to a range of stimuli associated with feeding (**Fig 1**). Its production is inhibited in a negative feedback loop by decreased intragastric pH via somatostatin release from D-cells (Helgadottir and Bjornsson 2019). Gastrin stimulates intragastric acid secretion directly via the parietal cell, and indirectly via enterochromaffin-like (ECL) cell activation, which, in turn, causes release of histamine, another potent stimulator of the parietal cell (Waldum *et al*. 2019). The ECL-cell/histamine pathway is the dominant signalling mechanism for gastric acid production (Helgadottir and Bjornsson 2019). Acid suppression, when induced by drugs such as the PPIs, increases intragastric pH and results in loss of this negative feedback on gastrin production which subsequently causes hypergastrinemia (**Fig 2**). Gastrin also has trophic effects on a range of gastric mucosa cells with prolonged hypergastrinemia resulting in proliferation of the ECL-cell population (Waldum *et al*. 2004). When acid-suppressive therapy is discontinued, a rebound hyperacidity is observed because of both the hypergastrinemia and increased ECL-cell population (**Fig 3**).

- It has recently been demonstrated that oral omeprazole therapy induces an increase in serum gastrin in the horse over a 2-week treatment period. Serum gastrin levels doubled over a 14-day period when omeprazole was administered at approximately 4 mg/kg q. 24 h (Pagan *et al*. 2020).

The clinical implications of rebound gastric hyperacidity have not been systematically investigated in the horse to date. Pilot studies have demonstrated the rapid development of grade III/IV Equine Squamous Gastric Disease (ESGD) ≤76 h after the last dose of omeprazole (Sykes, unpublished data). Although the development of ESGD lesions within 72 h using a 24 h on/off fed/fasted model has previously been reported (Murray 1994), the severity of the lesions observed by the

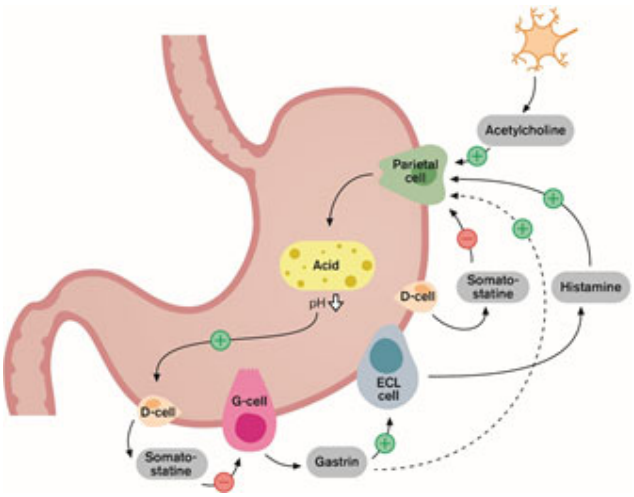

Fig 1: Feeding stimulates gastrin release from G-cells, which has direct stimulatory effects on the parietal cell as well as stimulating histamine release from ECL-cells, which, in turn, stimulates the parietal cell. The later, indirect pathway, via the ECL-cell and histamine, is the dominant signalling mechanism for HCl acid production. As a negative feedback mechanism, decreasing intragastric pH stimulates release of somatostatin from D-cells which, in turn, suppresses G-cell function and gastrin release. Figure reproduced from Helgadottir and Bjornsson (2019).

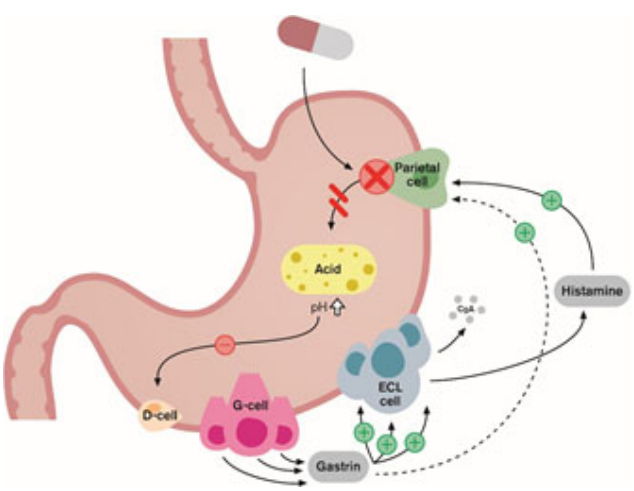

Fig 2: Proton pump inhibitors (PPIs) inhibit acid production at the common, terminal pathway of the parietal cell. The consequent rise in intragastric pH results in inhibition of the negative feedback loop, normally mediated via the D-cell, leading to hypergastrinemia which in turn causes hyperplasia of ECL-cell. Figure reproduced from Helgadottir and Bjornsson (2019).

author is more severe than previously described, especially in horses that were allowed ongoing access to feed during the omeprazole withdrawal period. This suggests that rebound gastric hyperacidity may play a role in the rapid recurrence of disease in some patients. Further, it suggests that moderate to severe ESGD can recur within the current racing withdrawal periods for omeprazole, a finding which warrants further investigation as it would have significant implications for the regulations surrounding the use of omeprazole in racehorses.

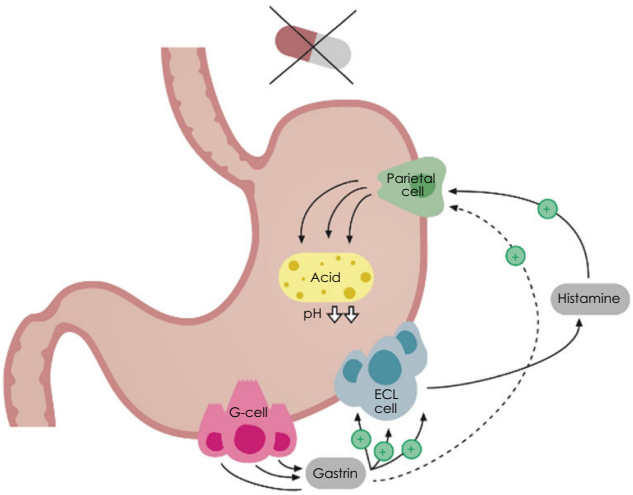

Fig 3: The recovery of acid production can be exaggerated following PPI discontinuation due to a direct effect of hypergastrinemia, and an indirect effect of ECL-cell hyperplasia causing exaggerated release of histamine, both of which stimulate the parietal cell. Figure reproduced from Helgadottir and Bjornsson (2019).

Impact on faecal microbiota richness and diversity

An increased risk of antimicrobial-associated diarrhoea is a well-recognised side effect of omeprazole in humans (Sheen and Triadafilopoulos 2011), and omeprazole has been shown to increase the risk of non-specific diarrhoea in neonatal foals (Furr *et al*. 2012). A rich and diverse microflora is believed to be associated with a decreased risk of gastrointestinal disease (Schoster *et al*. 2017). Established methods for the determination of faecal microbiota richness and diversity are relatively new, and to date, there has been limited research into the potential for omeprazole to induce dysbiosis. Two studies in the peer-reviewed literature found no effect of short-term (7 day [Cerri *et al*. 2020] and 28 day [Tyma *et al*. 2019]) omeprazole administration on the faecal microbiota, but to date, the effects of long-term administration have not been evaluated.

Concurrent administration with non-steroidal anti-inflammatory drugs

It has recently been demonstrated that concurrent administration of omeprazole increases the risk of phenylbutazone-induced gastrointestinal toxicity, over that of administration of phenylbutazone alone (Ricord *et al*. 2020). Reported complications in that study were impactions (small colon, n = 1; and large colon, n = 1) in 2/8 horses in the phenylbutazone only group and impactions (small colon, n = 1; and large colon, n = 1), non-specific colic (n = 1), and diarrhoea or colitis (n = 3) in 6/8 horses in the omeprazole/phenylbutazone group (Ricord *et al*. 2020). Complications included two fatalities from colitis in the omeprazole/phenylbutazone group (Ricord *et al*. 2020). The occurrence of inflammatory lesions is consistent with findings in dogs where concurrent omeprazole administration exacerbates intestinal inflammation associated with administration of

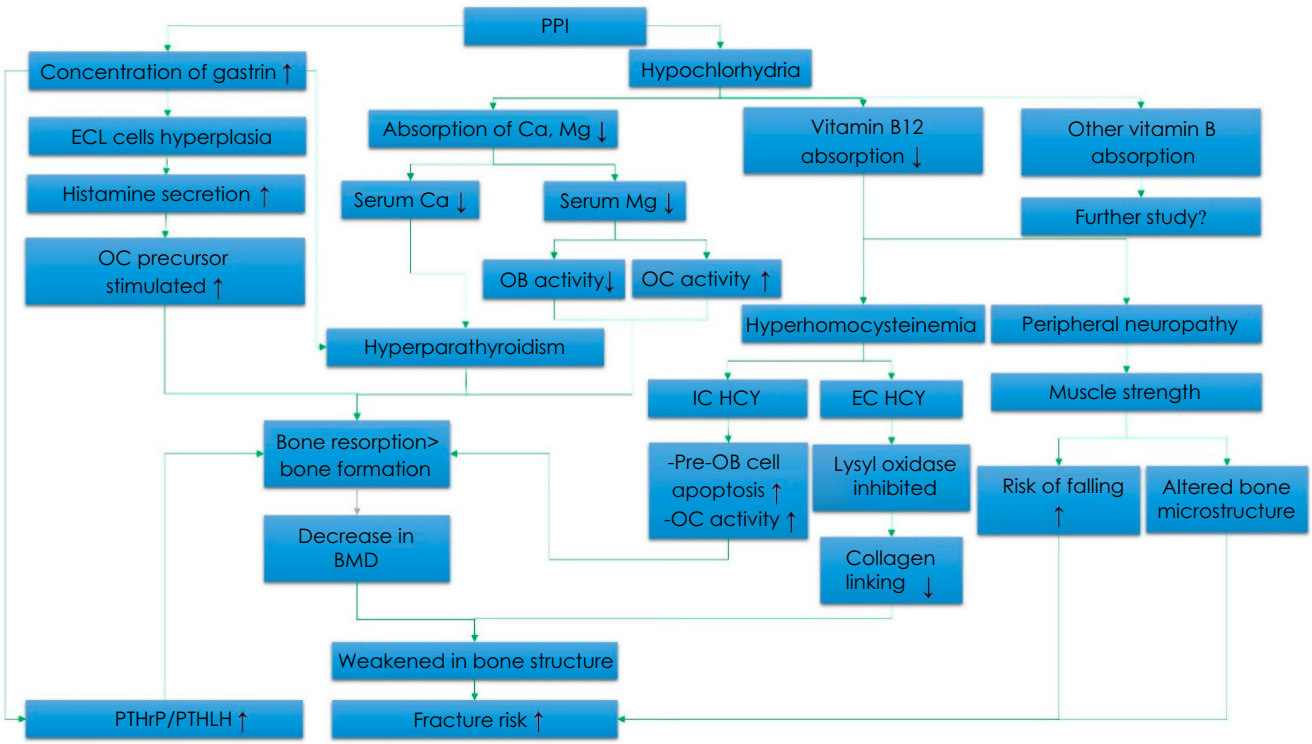

Fig 4: Summary of the systemic effects of proton pump inhibitors (PPIs) in increasing fracture risk. Abbreviations: IC HCY, intracellular homocysteine; EC HCY, extracellular homocysteine; ECL cells, enterochromaffin-like cells; Ca, calcium; Mg, magnesium; BMD, bone mineral density; PTHrP, parathyroid hormone-related peptide; PTHLH, parathyroid hormone-like hormone; OB, osteoblast; OC, osteoclast; ↑, increase; ↓, decrease. Figure reproduced from Thong* et al. *(2019).

carprofen (Jones *et al*. 2020). Collectively these findings suggest that, although omeprazole's site of action is the stomach, deleterious effects of administration may be observed elsewhere in the gastrointestinal tract. This is likely to be particularly important in the horse as a hindgut fermenter and warrants further investigation.

Fracture risk in racehorses

In human medicine, the use of omeprazole, and related proton pump inhibitors, is associated with an increased risk of fractures in geriatric patients (Sheen and Triadafilopoulos 2011), infants (<1-year-old) (Malchodi *et al*. 2019), children (4–18 years old) (Freedberg *et al*. 2015) and young adults (18–29 years old) (Freedberg *et al*. 2015). In human infants, an increase in fracture risk was observed after the administration of treatment courses as little as <30 days and the increased risk remained for at least 12 years after discontinuation of therapy (Malchodi *et al*. 2019).

The potential impact of omeprazole on fracture risk in the horse is especially relevant to the racing industry. Although uncommon (Parkin *et al*. 2004; Georgopoulos and Parkin 2017) fractures are a high-impact event that result in significant negative publicity, especially, when they occur during high-profile events (Matthey 2020). Increased awareness of the adverse effects of PPIs has resulted in concerns over their widespread use in humans being raised in both the scientific and lay press (Bakalar 2019). Similarly, concerns have been raised in equine industry publications as to a potential link between omeprazole administration and increased fracture risk (Pietrzak 2020). In the author's opinion, growing awareness of the existence of a potential link between omeprazole administration and increased fracture risk poses a significant threat to the social licence under which racing operates. It is important that the equine industry develop a deeper understanding of whether such a link exists, and if it does, what factors contribute to it.

The mechanism of increased fracture risk in humans remains poorly understood, but it is believed to be related to several factors including changes in mineral absorption and direct effects of the drugs on bone remodelling at the cellular level. **Figure 4** outlines the currently hypothesised mechanisms of action. The three key proposed mechanisms include the induction of hypergastrinemia, decreased absorption of calcium and magnesium, and decreased absorption of vitamin B12. It is considered unlikely that decreased absorption of vitamin B12 would be a significant factor in the horse as it primarily absorbs vitamin B12 via its large intestine as a hindgut fermenter, which is less expected to be impacted by omeprazole therapy. However, a recent study suggested that the first two mechanisms, namely hypergastrinemia and decreased absorption of calcium occur in the horse with omeprazole therapy (Pagan *et al*. 2020). This contrasts with an early study that found no effect on serum calcium, bone mineral content or bone mineral density (Caston *et al*. 2015), although the use of compounded omeprazole in that study raises concerns over the validity of the negative findings. The recent findings demonstrating omeprazole's capacity to impact upon serum gastrin and calcium absorption emphasise the need for further research to understand any potential relationship between omeprazole administration and increased fracture risk.

Upregulation of omeprazole metabolism and decreased efficacy over time

The efficacy of omeprazole for the prevention of ESGD at either 1 (McClure *et al*. 2005) or 2 (Andrews *et al*. 1999; Doucet *et al*. 2003) mg/kg q. 24 h following 27–28 days treatment at 4 mg/kg q. 24 h has been evaluated. In all three studies, 16–20% of horses experienced either the development of new lesions or worsening of ulcer severity between Days 27–28 and 54–59. In a fourth study (Kerbyson *et al*. 2016), omeprazole was continued at 4 mg/kg q. 24 h for 90 days. No difference was observed in the percentage of horses healing to ESGD grade ≤ I/IV between 30 and 60 days, but the percentage of responders halved between 60 and 90 days. When complete healing was assessed the percentage of responders dropped from 28.8% at 30 days, to 19% and 10.6% at 60 and 90 days, respectively (Kerbyson *et al*. 2016). To the author's knowledge, there are no peer-reviewed studies to support the use of long-term omeprazole therapy for the prevention of equine glandular gastric disease (EGGD).

Potential reasons for the drop in response over time include a reduction in dose in the first three studies, decreasing owner compliance with time or upregulation of omeprazole metabolism reducing systemic bioavailability over time. The plausibility of the later mechanism is supported by a recent study that demonstrated reductions of 50 and 62% in Area-Under-the-Curve (AUC) and Maximal Concentration (C_{max}), respectively, between Days 1 and 29 in horses administered oral omeprazole at 4 mg/kg once per day (Di Salvo *et al*. 2017). As AUC is the primary determinant of efficacy in other species (Lind *et al*. 1983), a decrease in AUC over time would be expected to be associated with decreased efficacy over time. Considering this, the author believes that the validity and efficacy of long-term (>60−90 days) prophylactic treatment warrants further investigation.

Conclusions

Omeprazole remains an important medication for the treatment of EGUS. To date, its use appears to be well tolerated overall based on the absence of overt adverse effects being recognised despite its widespread use over an extended period. However, a recent study demonstrating increased complications associated with its use alongside phenylbutazone (Ricord *et al*. 2020), a practice that has been assumed to be safe for years, highlights that lack of evidence for an adverse effect does not preclude the possibility of an adverse effect being present. Instead, specific studies should be performed to investigate any potential adverse effects. Likewise, in the absence of specific studies to document long-term (>60–90 days) efficacy for ESGD prevention, efficacy should not be assumed. Further studies documenting both the efficacy and specific safety of long-term omeprazole are warranted.

Author's declaration of interests

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Ethical animal research

Not applicable to this review article.

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