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This review accompanies the relevant episode of the Cutting Edge veterinary podcast. In each episode of this podcast, 3rd year students in the University of Calgary's veterinary medicine program fill you in on the most up-to-date literature and evidence-based practices on topics that matter to you, the practising veterinarian.

Is the Extended-Release Injectable Formulation of Omeprazole a Reasonable Alternative to the Oral Product for the Treatment of Equine Gastric Ulcers?

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Introduction to Equine Gastric Ulcers

Equine Gastric Ulcer Syndrome (EGUS) encompasses erosions, ulcerations, and mucosal lesions that occur between the terminal esophagus and the proximal duodenum in the horse.[1,2,3] Ulcers in the stomach can further be divided into two distinct syndromes: equine squamous gastric disease (ESGD), which targets the non-glandular stomach, and equine glandular gastric disease (EGGD), which targets the glandular stomach.[2,3] The reason for this distinction are the different etiologies and risk factors for these syndromes. Equine gastric ulcers are a common issue for both adults and foals, with an estimated prevalence of 50-90%.[2,3,4]

Equine Squamous Gastric Disease

ESGD occurs when the squamous gastric mucosa experiences sustained exposure to acid.[1,5] The squamous mucosa is more susceptible to pH-related injury due to its poor blood supply and lack of a mucus-bicarbonate protective layer.[5] Repeated exposure to acid causes loss of the tissue's protective barrier and results first in erosions that ultimately ulcerate.[1,5] Key risk factors for the development of ESGD include: high concentrate diet, fasting, stress, stereotypies, and anything that causes a pressure increase inside the abdomen (such as exercise).[1,4]

Equine Glandular Gastric Disease

EGGD differs in its pathophysiology from ESGD and our understanding of it is still evolving.[6] However, it is thought that EGGD develops as a result of compromise in the mucosal defense mechanisms.[1,7] The glandular mucosal defense mechanisms rely heavily on prostaglandins, which play a critical role in maintaining the mucosal barrier through promoting

mucus and bicarbonate secretion, sustaining blood flow, and inhibiting acid secretion.[8] Any compromise in the mucosal barrier allows the mucosa to be exposed to gastric acid.[2,7] Risk factors include treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and stress.[1] As mentioned, prostaglandins are very important for mucosal integrity in the gastrointestinal tract; NSAIDs reduce the production of prostaglandins leading to disruption in mucosal blood flow.[1]

Treatment

Omeprazole is the treatment most reached for when addressing EGUS. Thus far, treatment of ESGD has been more successful than treatment of EGGD.[6] This is due to the pathophysiology of ulcer formation in EGGD, which is not directly related to acid exposure and instead is more the result of a breakdown of the mucosal barrier.[8] This is a potential explanation for the difference in efficacy of treatment. The ultimate goal of omeprazole treatment is to reduce the production of hydrochloric acid in the stomach to prevent further development of ulcers and give the mucosa time to heal.[2,6]

All medical treatment of gastric ulcers must be accompanied by management changes. This is due to the risk factors that lead to EGGD and ESGD. Increasing pasture turnout and reducing concentrate in their diet is a good starting point.[1,8] Stress, although challenging to judge in horses, is important to reduce.[8] Exercise is another risk factor that needs to be changed, this includes reducing duration and frequency.[8]

Mechanism of Action

Proton pumps are the final common step in the pathway leading to hydrochloric acid secretion from gastric parietal cells into the stomach lumen.[9] Gastric acid secretion requires the activation of proton pumps that exchange H+ and K+ across the cell membrane via the enzyme H+/K+-ATPase.[10] Hydrogen and chloride ions are secreted into the stomach lumen via a symport carrier.[10] Proton pump inhibitors (PPIs) target this final common pathway by working in the secretory membrane of active parietal cells on the H+/K+-ATPase enzyme.[2,9] PPIs inhibit this enzyme and stop the production of hydrochloric acid.[1,11] Acid secretion can only recur once new proton pumps are made resulting in the prolonged effect seen after administration;[9] however, acid production is not completely suspended due to the presence of dormant parietal cells that become active post PPI administration.[9] The maximum inhibitory effect is achieved roughly 2-4 days after administration.[11] Omeprazole is the only PPI licensed for use in horses.[12]

Oral Omeprazole

Oral omeprazole has long been the treatment of choice for EGUS by clinicians. The dose of 4 mg/kg orally once daily of Gastrogard (the most popular oral omeprazole on the market) has been evaluated thoroughly and its efficacy proven by numerous studies.[13] However, the recent availability of extended-release injectable omeprazole has prompted comparisons

between the injectable and oral omeprazole-containing products, in particular, because numerous studies have demonstrated that many variables, including the presence of food in the GI tract, type of diet, and formulation (plain or buffered) impact the absorption and utilization of oral omeprazole. These are important to consider when contemplating whether oral omeprazole is the best treatment for certain EGUS patients.

Oral Omeprazole Formulations

Exposure of oral omeprazole to acid in the stomach followed by alkalinisation in the small intestine can cause the drug to become inactive prior to its absorption.[13] Additionally, the acid labile nature of the drug also predisposes it to degradation in highly acidic environments.[14] This necessitates specific formulations to protect the drug from changes in pH and thus degradation. Protection comes in the form of the addition of a highly alkaline medium mixed with the omeprazole or enteric coated granules suspended within the omeprazole paste.[15] Other, unbuffered, forms of oral omeprazole (i.e. no alkaline medium present) have recently been introduced to the U.K. market. However, plain unbuffered omeprazole has been shown to have reduced bioavailability when compared to enteric-coated and buffered omeprazole when administered orally.[15] Although a buffer is required for optimal absorption of oral omeprazole, a study conducted by Meritt et al found that not all formulations of buffered omeprazole (especially compounded formulas) offer the same protection.[16] The compounded solutions studied contained different suspension vehicles for the omeprazole, which resulted in different pHs of the final products. It was found that Gastrogard (vehicle suspension pH of 10.2) and one other compounded oral omeprazole product (vehicle suspension pH of 8.7) were the only products that resulted in a mean hourly gastric pH >4.0 after administration.[16] The lower pHs (5.1 and 5.7) of the other compounded oral omeprazole solutions likely resulted in decreased effectiveness in the delivery of omeprazole and thus reduced efficacy in increasing gastric pH to aid in ulcer healing.[16] This is important to consider when administering compounded oral omeprazole, as formulations may individually differ in the amount and type of alkaline medium incorporated and thus not contain appropriate amounts of a buffer solution.

Diet & Fasting

It has been shown that feeding horses ad libitum before the administration of a buffered oral omeprazole reduced its bioavailability to 50-60% of that in horses held off feed overnight prior to administration[17] Thus, it is often recommended to administer oral omeprazole after a fasting period.[6] In contrast, a second study found that the bioavailability of enteric-coated omeprazole differed minimally between fasted and non-fasted groups.[15] This raises the question: does fasting actually affect the bioavailability of omeprazole?

It has also been suggested that high forage diets should be fed to EGUS patients to reduce overall decreases in gastric pH.[14] This recommendation is made to prevent the

alternative of feeding high grain diets containing lots of starch. This is based on the theory that high starch diets promote a gastrointestinal environment that can contribute to the development of EGUS.[18] However, a study conducted by Sykes et al[19] demonstrated that horses who were fed a high grain/ low forage diet spent a greater percentage of time with their gastric pH >4 than those who were on a hay diet when treated with either 4 mg/kg or 1 mg/kg of Gastrogard. Although investigating diet composition was the aim of this study, the researchers suspected that the horses on the high grain/low forage diet may have naturally finished their timed meals sooner than their hay fed counterparts resulting in an artificially longer "fasting time" prior to oral omeprazole administration.[19] This confounding factor warrants further investigation of the true effect of diet on the absorption of oral omeprazole. However, it further exhibits how numerous variables (such as type of diet and fasting), both individually and collectively, affect the bioavailability of oral omeprazole.

Injectable Omeprazole

Alternatives to oral administration of omeprazole include intravenous and intramuscular injections, which address complications associated with feeding and individual variations impacting bioavailability.[7] Opting for an extended-release intramuscular injectable form of omeprazole offers advantages such as enhanced owner and patient compliance due to reduced dosing frequency, in contrast with the daily administration required for oral omeprazole.[7]

Efficacy

It has been shown that intramuscular injectable omeprazole produces comparable or better increases in gastric pH when compared with the oral formulation.[20] The duration and magnitude of acid suppression are crucial factors in gastric ulcer healing.[20] In human studies, effective healing rates for gastroesophageal reflux disease (GERD) align with the percentage of time gastric pH remained above 4 (%tpH>4), with values exceeding 66% considered effective.[20] Similar benchmarks have been applied in evaluating intramuscular injectable omeprazole in horses, where %tpH>4 surpassed that of the oral formulation on days 1-7, demonstrating sustained acid suppression for at least 7 days.[20]

Dosing

The extended-release injectable form of omeprazole has gained prominence as a favorable alternative to its oral counterpart. In a study done by Sykes et al[20], utilizing a dose of 20 mL of a 100 mg/mL formulation, it was shown that administering two doses at 7-day intervals led to healing rates of 100% and 75% for Thoroughbred racehorses with ESGD and EGGD, respectively. The rationale behind the 7-day dosing regimen stems from a pilot study in which a single 20 mL dose maintained intragastric pH levels above 4 for up to 7 days– an established benchmark for evaluating omeprazole treatment effectiveness.[20] However, recent

research proposes a 5-day dosing interval, citing suboptimal acid suppression in horses between days 4 and 7.[21] Sykes et al's[20] study, involving intramuscular injectable omeprazole administered to horses with pH probes inserted into their stomachs, demonstrated a decline in mean %tpH>4 from over 66% on days 1-4 to approximately 40% on day 5, plummeting to around 15% by day 7. Given the criterion of %tpH>4 needing to exceed 66%, the observed decline after day 4 indicated inadequate acid suppression. Thus, a dosing interval of 5 days between doses may increase efficacy by preventing the decline in gastric pH between days 4 and 7.[21]

For the treatment of ESGD, the current protocol involves assessing lesion improvement after 2 weeks, with continued treatment for another 2 weeks if lesions persist.[7,22] This approach is grounded in the significant improvement of ESGD lesions by day 14, which tends to plateau from days 14-28.[7] On the other hand, horses with EGGD lesions may require a minimum of 4 weeks of treatment, irrespective of the medication type administered.[20] However, studies suggested that EGGD healing rates as high as 93% may be achieved in just 21 days with dosing occurring four times at 5-day intervals.[21]

Pharmacokinetics

The intramuscular injectable formulation exhibits heightened stability at room temperatures over prolonged periods, surpassing the performance of its intravenous counterpart.[23] In contrast, intravenous omeprazole usage faced challenges related to owner compliance and reliability, primarily attributed to its short half-life, susceptibility after reconstitution, and the necessity of daily administration.[23]

A study of the pharmacokinetics of an extended-release, injectable compounded formulation of omeprazole revealed that the maximum serum concentration (Cmax) ranged from 21.9 ng/mL to 65 ng/mL, with a mean of 46.2 ng/mL.[7] Impressively, the mean plasma concentration of omeprazole remained stable at approximately 9.6 ng/mL for a full 7 days following each dose. The time taken to reach Cmax (Tmax) for all horses was consistently 6 hours post-injection, and the calculated area under the curve (AUC) varied between 933.7 ng/ml*h to 2732 ng/ml*h.[7]

The pharmacokinetics of the injectable intramuscular formulation differ when compared to the oral formulation. The Cmax of Gastrogard (oral omeprazole), as demonstrated in a study by Sykes et al,[13] was notably higher than that of the injectable omeprazole. However, the maximal drug concentration of proton pump inhibitors in the plasma (Cmax) are poorly correlated with acid suppression[24,25,26]. This is because omeprazole accumulates and irreversibly binds to its site of action in the parietal cells of the stomach and is not required to be in the plasma for an effect to occur. Therefore, these numbers offer little insight into the realistic effects of each omeprazole formulation. Currently, no bioequivalence studies

comparing extended-release injectable and oral formulations of omeprazole exist and thus further research on this topic would be beneficial.

Adverse Effects

The most frequently reported adverse reactions with the extended-release injectable omeprazole formulation are edema, heat, pain, and abscessation, occurring in 0.01% to 8% of cases.[7,13,17,20,21] A majority of these complications necessitated no intervention, being inherently self-limiting and typically resolving within 3 days post-injection.[20] An exception was noted in a singular instance where a horse developed a small abscess on the neck following injection, requiring lancing but subsequently healing without further complications.[21]

Conclusion

Whether the diagnosis is EGGD or ESGD the long standing treatment of choice for EGUS is omeprazole. The choice of oral vs extended-release injectable treatment ultimately comes down to individual patient factors. As described above, the extended-release injectable formulation is an alternative to the oral formulation with comparable efficacy. Patient factors that influence this decision include ease of drug administration (oral vs injectable), type of ulcer, and owner compliance (including the ability to administer daily medication and to fast the patient before oral administration). Economic considerations may also play a role in decision making. As well, as emphasized above, management must be changed to make any treatment effective. The introduction of the extended-release injectable formulation of omeprazole provides veterinarians with a new option for the treatment of equine gastric ulcers.

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