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Aspirin Induced Gastric Ulcer: Review Article

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Abstract

Gastric diseases range from mild, temporary upsets to life-threatening emergencies that require immediate intervention. Gastric ulcers in animals arise from a breakdown in the stomach's protective mucosal barrier, caused by an imbalance between corrosive stomach acids and natural defense mechanisms. These ulcers are broadly categorized into non-infectious (the majority of cases) and infectious origins across various species. The excessive use of (NSAIDs), The Non-Steroidal Anti-inflammatory Drugs such as (aspirin, flunixin meglumine, or carprofen) and corticosteroids significantly reduces the production of protective stomach prostaglandins (PGs), directly damaging the mucosa.

NSAIDS like aspirin hinders the cyclooxygenase (COX) activities which causes a decrease in prostaglandins leading to several key associations: -

- Bicarbonate secretion and reduced mucus.
- Weakened platelet aggregation.
- Damage of epithelia due to microvascular structures being altered.
- An increase in adhesion of leukocytes, lipid peroxidation and neutrophil infiltration.
- A decrease in the antioxidant enzymes like Catalase, Superoxide Dismutase, Glutathione Peroxidase, Glutathione S- Transferase and Glutathione (GSH).
- Uncoupling of oxidative phosphorylation.
- Drug being trapped inside epithelial cells.
- Gastric injury pathogenesis due to lipid peroxidation and superoxide generation.

Gastric Injury is to be diagnosed by the endoscopy procedure and most of the time, treatment will require medication administration to reduce the secretion of gastric acid and facilitate mucosal protection. H2 receptor blockers that has ranitidine, cimetidine, and famotidine are the most typical used drugs to decrease the secretion of acid. Omeprazole, a widely used proton pump inhibitors (PPI) are also used to decrease stomach acid.

Keywords: Gastric Ulcer, Cyclooxygenase (COX), Proton Pump Inhibitors (PPI)

Introduction

In mammals and birds, the stomach is a big part in the gastrointestinal tract, it stores the food and transports it to the duodenum (Treuting, *et al.*, 2018) [37], the stomach regions consist of pyloric, fundic and cardiac regions where as historically, its composition is determined by layers; the mucosa, the submucosa, the muscularis, and the serosa. (Mescher AL, *et al*, 2013) [21]. The mucosa layer, has gastric glands and columnar epithelium meets with the central cavity (lumen) through gastric pits. The submucosa layer consists of lymph and blood cells and connective tissue. The muscularis layer is composed of muscles and finally the serosa layer which is a thin layer covers the outer area of the stomach. (Bancroft JD, *et al*., 2008).

Common gastric diseases range from mild, temporary upsets to life-threatening emergencies that require immediate intervention (Parrah, *et al*., 2013) [24]. Most Common Gastric Conditions include *acute gastritis:* sudden inflammation of the stomach lining. It is often triggered by eating spoiled food, toxic plants, or foreign objects; *Gastric Dilatation-Volvulus:* a progressive disease which is life-threatening where the stomach is filled with gas (bloating) and twists on itself (volvulus), eventually leading to the cutting off the blood supply and requires immediate surgery; *Gastroenteritis:* inflammation of both the stomach and the intestines. It can be caused by viral infections, bacterial infections (like *Salmonella*), or internal parasites; *Gastric Ulcers:* open sores in the stomach lining, frequently caused by prolonged use of NSAID medications or underlying diseases; *Gastric Tumors:* rare, but can occur, with gastric carcinoma being the most common type in older dogs. (Daure, *et al.,* 2017) [9]

Gastric ulcers in animals arise from a breakdown in the stomach's protective mucosal barrier, caused by an imbalance between corrosive stomach acids and natural defense mechanisms. These ulcers are broadly categorized into non-infectious (the majority of cases) and infectious origins across various species (Neubert, S. *et al*., 2022) [23].

Gastric ulcer

Gastric ulcers come down to a defect caused in the mucosa penetrating the muscularis mucosa (Stanton M, *et al*., 1989) [31]. In reality, the gastroduodenal and gastric ulceration clinical findings requires specific medical diagnosis where ulcers aren't exactly caused by just one thing, and cases differ from one to another, besides the overuse of NSAIDS it could be caused from bacterial infections, an overproduction of stomach acid due to weakened mucus barrier and lifestyle key factors like smoking or alcohol usage or stress. (Johns Hopkins Medicine, n.d.) which means that ulcers cause is likely to be multifactorial and is different from one case to another and are clearly defined as an open sore in the mucosal lining of the digestive tract. (Pen Medicine, Eisner, 2025) Ulcers, also called peptic ulcers, as the ulcers are being exposed to gastric acid and the secretion of pepsin. (Schaer M, *et al*., 2003) [28]. Injuries to the gastric mucosa is a frequently encountered disorder in the gastrointestinal system, this condition is driven by complex interplay where the mucosal barrier's protection such as adequate mucosal blood flow and protective alkaline layer- mucosal bicarbonate barrier, cellular repair mechanism and prostaglandin activity is overwhelmed by aggressive factors such as pepsin, gastric acid and reactive oxygen species, the imbalance triggers and facilitates ulceration. (Karakaya *et al*., 2009) [14]. (Li *et al*., 2006) [18].

Classification of gastric ulcers

Knowing the classification of stomach ulcers is crucial for clinicians because each class has a completely different treatment plan. Gastric ulcers are categorized based on the severity of the clinical presentation, the anatomical placement within the gastrointestinal region, and the depth of the ulcer in the gastrointestinal mucosa. Focal duodenal ulceration, duodenal erosions, duodenitis, glandular mucosal ulceration, and widespread gastritis are examples of gastrodudenal ulcers (Murray, 1991). Gastric ulcers can range from basic epithelial erosion to full thickness bleeding or perforating ulcers, depending on their depth. Additionally, ulcers can be either acute or chronic based on clinical presentation (Bao Y., 2010) [2].

Incidence of gastric ulcerations

Both young and adult animals can develop gastric ulcers, but mature animals are more likely to do so. Similarly, stomach ulcers is more common in athletes than in dogs. According to endoscope studies, 48.5% of canine athletes have stomach ulcers. According to reports, foals have a 25–50% frequency of stomach ulcers, while older horses have a greater incidence of 60% (Bao Y., 2010) [2].

The occurrence of stomach ulceration in relation to the inciting cause differs greatly between species. Gastroendoscopy has shown gastric ulceration in horses as well as in animals with related symptoms including poor appetite, poor body conditions, or signals of abdominal discomfort. (Bottero *et al*, 2022) [4]

Unlike humans with renal failure in whom gastric ulcer predominates, gastric necrosis and ulceration appear to be uncommon in dogs with renal failure-3.6% (Peters R. M, *et al*., 2005).

Pathophysiology of gastric ulceration

The development of ulcers is caused by several pathophysiological processes. However, suppression of the stomach mucosal barrier characteristics and promotion of gastric acid secretion are the common underlying pathophysiological mechanisms. Mucosal barrier diseases are prevalent in animals, although acid secretory disorders are rare (Parrah *et al*., 2013) [24]. The multifactorial pathophysiological mechanism of gastric ulceration in dogs is caused by a variety of factors, such as physical harm to the gastrointestinal mucosa, compromised mucosal defense, and chemical changes to the mucosa and its healing process (Lacy ER., 1987) [16]. Only in cases of severe trauma, such as gastric foreign bodies or surgical implants, do ulcers result from physical disruption (Ader P., 1979) [1].

Numerous defensive mechanisms that preserve and safeguard epithelial integrity are present in the gastric mucosa. The gastric epithelium layer is constantly renewing; deeper neck mucous cells take seven days to renew, while surface mucous cells do so in three days (Strombeck, D. R. *et al*., 1990) [32]. If the basal lamina is intact, surface mucous cells cover the minor abnormalities in the stomach epithelial lining within 30 to 60 minutes. In order to sustain digesting and defensive activities, the mucosa receives at least 70% of the stomach blood flow (Alan Barkun *et al*., 2010) [3].

Maintaining sufficient blood flow during streaming may depend on physiological corticosteroid levels. Prostaglandin also promotes blood flow and enhances the generation of mucus and bicarbonate. According to (Duan SY *et al*. (2006) [11], mucous has a high viscosity, is sticky, and easily forms a film that covers the epithelium. This mucous layer possesses selective permeability, traps alkaline fluid, and is not broken down by pepsin, forming a buffer zone against an acidic or toxic environment (Kauffman *et al*., 1989) [15].

Oxyntic cells actively secrete bicarbonate ions into the luminal surface, which also serve as a chemical buffer. The cycloxygenase pathway (COX-1 and COX-2), which produces prostaglandins from arachidonic acid, is typically inhibited by non-steroidal anti-inflammatory medicines, which can compromise the mucosal defense mechanism. The COX-1 pathway produces prostaglandins that are good for the stomach (Parrah *et al*., 2013) [24].

Shock decreases the amount of blood that reaches the stomach in animals, which leads to acidosis due to inadequate perfusion and decreased bicarbonate ion transport to the surface cells. Corticosteroids decrease the creation of PG and enhance the generation of stomach acid. Gastric ulcers will develop and persist in the absence of these beneficial PG's blood flow and gastric mucus and bicarbonate production (Rohrer CR *et al*., 1999) [27].

Causes of gastric ulceration

Non-infectious causes of gastric ulcer

A number of non-steroidal anti-inflammatory medications, including piroxicam, have been shown to cause ulcers in horses, dogs, and rodents (Lanza, F. L. *et al*., 2009) [17].

The most frequent causes of stomach ulcers in domestic animals are non-infectious reasons. Medication: excessive use of NSAIDs (non-steroidal anti-inflammatory drugs) such as carprofen, aspirin, or flunixin meglumine (Spee LA.,

2010) [30]. and corticosteroids directly harm the mucosa by drastically lowering the synthesis of protective stomach prostaglandins (Grainek I. M, *et al*., 2008).
Systemic and metabolic diseases: Shock, liver disease, and kidney failure (uremia) change mucosal blood flow and enhance stomach acid output (Björklund C, 2014).
When administered orally at varying dosage rates, a lead salt mixture (Chloride Br, Sulfate) caused stomach ulcers (Parrah *et al*., 2013) [24].
As a potential strategy to prevent obesity in ovariectomized bitches, gastric ulceration has been documented as a complication after auto-transplantation of the ovaries to the portal vein drainage (Davis MS *et al*., 2003) [10].
Stress and lifestyle, horses: Transport, stall confinement, high-intensity activity, and irregular feeding are common causes of Equine Gastric Ulcer Syndrome; Pigs: High stomach acidity is brought on by finely ground pelleted feed, sudden fasting (empty feeders), and stressful environmental changes; Neoplasia (Cancer): tumors that cause severe ulceration, often in dogs and cats, include mast cell tumors (which release histamine) and gastronomies (which induce excess stomach acid output); food factors: severe acute gastritis and consequent ulceration are caused by indiscretion, foreign body intake, and abrupt food changes (Swaby H *et al*., 2012) [33].

Infectious causes of gastric ulcer
Certain bacterial, parasite, and fungal diseases can directly or indirectly cause stomach sores, however they are less prevalent than non-infectious causes. Helicobacter species: The stomachs of dogs, cats, and people are frequently colonized by species like H. pylori, H. felis, and H. heilmannii. Their direct function as the main cause of ulceration is still hotly contested in veterinary medicine, despite the fact that they cause varied degrees of stomach inflammation (gastritis). (Pavlova and others, 2021) [25]
Clostridium species: Overgrowth of these bacteria can cause tissue damage and mucosal ulcers in certain ruminants and foals.
Internal parasites that cause physical erosion and ulcer formation include Ollulanus tricuspis in cats, Gasterophilus larvae (botflies) in horses, and Trichostrongylus in cattle and sheep. Fungal Infections: In dogs, cats, and horses, profound fungal infections (such as gastric pythiosis or candidiasis) can penetrate the stomach walls and cause severe, persistent ulcerations (C. De Witte *et al*., 2018).

Aspirin, as a common cause of gastric ulcer
Acetylsalicylic acid, or aspirin, is a potent nonsteroidal anti-inflammatory medication (NSAID) that is frequently used to treat pain, fever, and inflammation (D.L. Simmons *et al*., 2004 and M. Fornai *et al*., 2005 [12]). Aspirin is frequently used to avoid cardiovascular thrombosis and to treat inflammatory conditions such rheumatoid arthritis (Z. Wang *et al*., 2011) [39]. However, long-term NSAID use is typically linked to bleeding, perforation, ulceration, and erosion of the stomach mucosa (M. Fornai *et al*., 2005 [12] and J.L. Wallace 2001 [38]).
Aspirin side effects most frequently occur in the gastrointestinal tract. Damage to the gastrointestinal mucosa, worsening of stress ulcers, and aggravation of preexisting gastric ulcers are the main, dangerous adverse effects.(Yomna and others, 2019) [40] These may be brought on by its topical irritating effect, neutrophil activation, elevated reactive oxygen species (ROS), decrease in microcirculation, and decrease in prostaglandin E2 (PGE2) production in the mucosa, which is necessary for homeostatic processes like maintaining mucosal integrity and mucosal blood flow (Carvalho, C. A *et al*., 2011) [6].
A person exposed to aspirin has three to four times the risk of upper gastrointestinal bleeding, perforation, or both compared to a non-aspirin user, according to several studies. Its clinical applicability is severely limited as a result of these side effects. Adding antioxidants was one of the novel ways to prevent aspirin-induced stomach mucosal damage (Seleem, H. S *et al*., 2010) [29].
By preventing the production of endogenous prostaglandins (PGs), NSAIDs damage the stomach. Two isoforms of cyclooxygenase (COX) create PGs from arachidonic acid, which shield the stomach mucosa from a range of stressors (K. Takeuchi *et al*., 2018) [34].
PGs implicated in mucosal protection are produced by COX-1, which is typically expressed in the stomach. PGs important in the healing of stomach ulcers are produced by COX-2, which is inducible in inflammation (K. Takeuchi *et al*., 2018) [34].

Pathogenesis of aspirin induced gastric ulceration
Reduced mucus and bicarbonate secretion, decreased mucosal blood flow, impaired platelet aggregation, altered microvascular structures resulting in epithelia damage, increased leukocyte adherence and increased production of reactive oxygen species (ROS), increased lipid peroxidation and neutrophil infiltration, and decreased antioxidant enzymes are all linked to aspirin's inhibition of cyclooxygenase (Laine L 1996 and Benjamin Scally *et al*., 2018).
The development of gastric damage is also influenced by PG-independent processes that include drug entrapment in epithelial cells, uncoupling of mitochondrial phosphorylation, lipid peroxidation, and superoxide production (Laine L 1996). Aspirin causes the mucous layer that serves as a barrier for the stomach wall to fail and increases the release of hydrochloric acid (HCL), which ultimately results in gastric ulcers (Benjamin Scally *et al*., 2018).

Diagnosis of gastric ulcer
Gastric ulcers are definitively diagnosed by visualizing the ulcer, typically through endoscopic examination or gastrotomy. When there are no other risk factors for stomach ulcers, the ability to biopsy tissue in and around the ulcer to look for primary gastric illnesses, particularly neoplasia, is an advantage of endoscopic or surgical diagnosis. Abdominal ultrasonography or contrast radiography can produce strongly supportive results for ulcers. (Chung and others, 2015) [8]
Some, but not all, individuals with gastric ulcers may exhibit filling deficiencies, thickening of the stomach wall, and extended retention of contrast material in the stomach during contrast radiography. stomach wall thickening, which is frequently focal, the identification of a mucosal crater that may contain microscopic bubbles, disturbance of the usual layering of the stomach wall, and gastric hypomotility are all ultrasonographic findings suggestive of gastric ulcers. Many of these ultrasonographic features are not unique to gastric ulcers and can be observed with other gastric

disorders (such as gastric neoplasia) (Liptak JM *et al*., 2002 [19], Penninck D *et al*., 1997 [26]).

Management and treatment of gastric ulcers

PGE2 analogs may help lower the risk of stomach ulcers in patients with unavoidable risk factors. Misoprostol treatment has been shown to protect dogs from NSAID-induced ulcers in numerous investigations. In order to prevent stomach ulcers, patients with mast cell malignancies, renal failure, or hepatic illness are frequently prescribed H2 blockers (Bytzer *et al*., 2001) [5], because cimetidine typically needs to be used every eight hours and can change how other medications are metabolized. In small animal practice, prevention of glucocorticoid-induced ulcers is still a challenge. H2 blockers have not been shown to stop dogs or cats from developing stomach ulcers, despite the fact that they are frequently given to patients on high-dose glucocorticoids (Schubert ML *et al*., 2005).

Finding and getting rid of underlying illnesses or risk factors is the main treatment for stomach ulcers. Drugs that lower stomach acid secretion and preserve the mucosa in the event of an ulcer must be administered as part of treatment for most patients (Chey *et al*., 2007). The H2 receptor blockers, which include famotidine, ranitidine, and cimetidine, are the most widely used class of medications to lower acid secretion. Gastric ulcers can also be treated with proton pump inhibitors like omeprazole.

However, individuals with challenging ulcers or challenging primary causes (such as certain gastrinomas) have been given preference (Pilotto *et al*., 2010). Misoprostol and other synthetic PGE2 analogs can also be beneficial, especially for patients with ulcers brought on by NSAIDs. Patients with confirmed or suspected ulcers should be given sucralfate. Sucralfate takes on a gel-like consistency in an acidic environment, which promotes medication binding to ulcer beds and shields them from further acid damage. Additionally, sucralfate can increase the protective qualities of mucus and stimulate the local synthesis of prostaglandins (Fox LE 1990).

Conclusion

NSAIDs are widely used worldwide, however a number of studies have shown how they affect the gastrointestinal, cardiovascular, renal, biliary, and hematological systems, among other body systems. Acetylsalicylic acid, or aspirin, is a potent nonsteroidal anti-inflammatory medication (NSAID) that is frequently used to treat pain, fever, and inflammation. However, long-term NSAID use is typically linked to bleeding, perforation, ulceration, and erosion of the stomach mucosa. Gastric ulcer risk can be decreased by administering PGE2 analogs. Misoprostol treatment has been shown to protect dogs from NSAID-induced ulcers in numerous investigations. To avoid stomach ulcers, individuals with mast cell malignancies, renal insufficiency, or hepatic illness are frequently prescribed H2 blockers. Finding and getting rid of underlying illnesses or risk factors is the main treatment for stomach ulcers. Drugs that lower gastric acid secretion and protect the mucosa from ulcers will also be administered to most patients as part of their treatment.

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