pH-independent effects of acid suppressants in dogs and cats: a One Health perspective and case for further investigation

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ABSTRACT
Our understanding of the use of acid-suppressant drugs (ASDs) in companion animals is largely centered around the treatment of acid-related disorders including gastroesophageal reflux and gastrointestinal ulceration. The companion article by Grady et al, JAVMA, October 2024, summarizes our current knowledge of the efficacy of and indications for ASDs for the treatment of acid-related disorders. Far less is understood about both the benefits of and potential for adverse effects of ASDs outside of the parietal cell including those directed toward inflammation and immunomodulation, tumorigenesis, fibrosis, and oxidative stress. In this Currents in One Health article, we summarize the pH-independent properties of ASDs as demonstrated in studies conducted largely in humans and rodents. The objective of this review is to highlight and increase awareness of the pH-independent effects of ASDs to elucidate the need for further veterinary research in this area.

Keywords: histamine-2 receptor antagonist, proton pump inhibitor, famotidine, omeprazole, esomeprazole

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and disease. Key cytokines and chemokines important to effector cell function include IL-1β, IL-2, and IL-6, tumor necrosis factor-α (TNF-α), and chemokine receptor ligand 8 (CXCL8). A balance of these molecules is necessary for an appropriate immune response to pathogens and allergens. Imbalances contribute to the development of autoimmune- or immune-mediated inflammatory disorders.

Neutrophils are one of the most important “first-line” defender cells in the innate immune response. These granulocytes predominantly kill pathogens via 3 main pathways: (1) phagocytosis, (2) degranulation, and (3) formation of neutrophil extracellular traps. Successful phagocytosis depends on the ability of neutrophils to migrate from the circulation to local tissues and the appropriate local cytokine and leukocyte milieu for neutrophil activation. Chemokine receptor ligand 8, CXCL2, and CXCL5, chemokines that are directly affected by ASDs as discussed below, play a prominent role in neutrophil activation and neutrophil-macrophage communication.

Macrophages and mast cells are also regulators of inflammation and pathogen defense. Like neutrophils, macrophages may suppress or stimulate inflammation, depending on the surrounding cytokine and chemokine environment. A proinflammatory macrophage phenotype may be promoted by interferon-γ, granulocyte-macrophage colony-stimulating factor, and lipopolysaccharide. Mast cells are best known for responses in allergic and infectious disorders. Interleukin-4 plays an instrumental role in general mast cell function and vascular endothelial adhesion responses. An acidic intracellular pH is also important for mast cell granule homeostasis and mast cell degranulation.

Both innate and adaptive immune cells possess histamine-2 receptors. The histamine-2 receptor regulates the synthesis and secretion of proinflammatory cytokines and chemokines from healthy and neoplastic cells. This may be in part how H2RAs exert some of the adverse effects described below.

Effect of ASDs on Inflammation and Immunomodulation

Many studies have demonstrated the anti-inflammatory effects of ASDs. The PPIs exert the most robust effect on inflammatory pathways. The select mechanisms by which PPIs exert anti-inflammatory effects are summarized including (1) inhibiting the nuclear factor-κB (NF-κB)...

Figure 1—Major mechanisms by which proton pump inhibitors impact granulocytes. AhR = Aryl hydrocarbon receptor. CXCL = Chemokine receptor ligand. CXCR = Chemokine receptor. NF-κB = Nuclear factor-κB. TNF-α = Tumor necrosis factor-α. V-ATPase = Vacuolar-ATPase. Image created with BioRender.com in June 2024.
pathway with subsequent downstream effects such as decreased proinflammatory cytokine production, (2) decreasing the release of the granulocytic intracellular contents including neutrophils and mast cells, and (3) modifying inflammatory cell trafficking between the circulation and local tissue sites in part due to altered adhesion proteins.14–17

The ASDs may reduce inflammation (eg, lowered CXCL8, IL-1β, TNF-α, and decreased mortality rate) not only in acid-related disorders such as eosinophilic esophagitis18–21 but also in states of severe inflammation and inappropriate immune cell activation such as sepsis,22 autoinflammatory diseases,23 acute pancreatitis,24 and a variety of neoplastic diseases. For example, omeprazole reduced proinflammatory cytokine secretion in murine bone marrow–derived mast cells and inhibited mast cell function in a murine model of food allergy.25 In a second example, in the presence of various PPIs evaluated, anti-inflammatory effects against human monocyte cultures occurred in a concentration-dependent manner.22 As a third example, esomeprazole was observed to significantly reduce the mortality rate in mice with lipopolysaccharide-induced septicemia compared to control and similar to a variety of noninfectious septicemia. 

In addition, ASDs may impact leukocyte number and extravascular trafficking.22,25 For example, oral ranitidine administration decreased serum cytokines, number of circulating B cells, and IL-2 receptor expression in healthy humans following 6 weeks of therapy.27 As another example, cimetidine, but not famotidine, successfully inhibited human neutrophil-endothelial adhesion,28 attesting to the fact that different types of H2RAs exhibit varying immunomodulatory properties. Less evidence exists for a direct impact of PPIs on leukocyte trafficking, although omeprazole has been observed to impact polymorphonuclear neutrophil leukocyte migration and reduce neutrophil chemotaxis.29

Multiple PPIs (ie, lansoprazole, rabeprazole, and esomeprazole) improved endothelial integrity and hypertension in preeclampsia models,30 most likely by way of modulation of nitric oxide and endothelial adhesion protein expression. If ASDs do, in fact, influence endothelial integrity, then this would represent another mechanism by which ASDs impact inflammatory response.

Very few veterinary studies have been conducted on these same effects. One study31 found no differences in blood cytokines in Alaskan racing sled dogs following 3 days of oral omeprazole therapy; however, the study did not include a control group, and the high-intensity exercise regimen of the dogs may have affected these results. In a retrospective study32 of dogs with cutaneous mast cell tumors, dogs treated with famotidine had a significant increase in the neutrophil-to-lymphocyte ratio compared to those treated with a PPI or with no ASD, suggesting that H2RAs could also impact circulating canine leukocyte numbers or trafficking.

The mechanisms responsible for the collective anti-inflammatory effects of ASDs are likely multifactorial and remain poorly explored in veterinary medicine. Additional research is called for, given the widespread use of ASDs in veterinary medicine.

**Tumorigenesis**

Many receptors and pathways govern normal and abnormal signaling between innate immune cells and the development and progression of cancer. Important tumorigenic pathways include the development of a favorable tumor microenvironment (TME), the recruitment of tumor-associated neutrophils and macrophages (TANS and TAMs) and natural killer cells, and the blockade of the vacuolar-ATPase (V-ATPase) pump and the aryl hydrocarbon receptor (AhR). Cancer cells require a TME to proliferate successfully, metastasize, and, in some cases, resist chemotherapy.33,34 One component of the TME is a proinflammatory neutrophil and macrophage phenotype. The TANS and TAMs, which function in concert to degrade the extracellular matrix integrity of the host, promote tumor angiogenesis and facilitate metastasis.4,33,35,36

A hallmark feature of nearly every complex TME ecosystem is an acidic milieu that surrounds neoplastic cells and facilitates the upregulation of proangiogenic factors, tissue invasion, and the sabotage of chemotherapeutic efficacy. Tumor cells create an acidic environment through the upregulation of V-ATPase pumps. The V-ATPase pumps are responsible for hydrogen ion transport out of healthy and neoplastic cells, helping to maintain membrane homeostasis and many effector functions.37,38 While V-ATPases are important for cells in health, many tumors also use these pumps to their advantage.39–40 More malignant neoplasms use these pumps to create neutral intracellular, but acidic luminal and extracellular, compartments. This pH gradient then results in the “trapping” of chemotherapeutic agents in spaces where they are unable to penetrate and kill neoplastic cells.

Disruption or blockade of these pumps by selective V-ATPase pump inhibitors, such as bafilomycin A, induces tumor cell apoptosis and reduces the metastatic potential of certain tumors.41 This creates an acidic TME, which recruits proinflammatory mediators and also upregulates proangiogenic factors (eg, vascular endothelial growth factor and CXCL8) critical for metastasis.42–44

There is an interplay between select leukocyte populations and the development and proliferation of certain neoplasms. Chemokine receptor ligand 8 is a key regulator in the transformation of inflammation to cancer in multiple species.45 Because of this, research efforts focused on the inhibition of pathways that upregulate CXCL8, such as the NF-κB pathway, have been and will likely continue to be a fruitful avenue of investigation. Select leukocyte populations are also cytotoxic to tumors and have a key relationship with inflammatory cytokines for
successful anticancer effects. One example would be natural killer cells and IL-2 working together to inhibit metastasis, which also involves other compounds such as histamine.46

Aryl hydrocarbon receptor dysfunction has also been implicated in many immune and inflammatory disorders in humans and in rodents.47 Aryl hydrocarbon receptor-deficient immune cells deficient produce higher than desired amounts of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-18, interferon-γ, and TNF-α. Part of the reason for this might be that many ligands can bind the AhR, and the AhR itself seems to exhibit plasticity in its effector function depending on the local microenvironment, resulting in many places for under or overstimulation. Similar to V-ATPase pumps, a variety of neoplasms upregulate the AhR for help with tumorigenesis and metastasis. Some of the most compelling evidence for the cancer “promoting” properties of the AhR would be increased nuclear AhRs in neoplasms with higher amounts of genes known to enhance growth factors, angiogenesis, proinflammatory cytokines, and the NF-κB pathway.48

**Effect of ASDs on Tumorigenesis**

Acid-suppressant drugs may induce cytotoxicity not only in healthy immune cells but also in various types of neoplastic cells. For example, in addition to direct effects on viability, PPIs improve the survival times of patients with select neoplasms by improving chemotherapeutic effectiveness.49–54 Vacular-ATPase pump blockade is one known mechanism by which PPIs might induce cytotoxic and anti-inflammatory effects. Specific V-ATPase pump inhibitors, such as bafilomycin A, successfully reduce chemotherapy resistance for multiple types of cancers in people.55,56 Bafilomycin, however, is highly toxic to healthy cells, and therefore, higher doses of PPIs, which are generally better tolerated at the higher doses needed to target neoplastic V-ATPases, might be a more attractive therapy than bafilomycin.

While there is a large body of evidence that V-ATPase blockade is pivotal in the promotion of PPI anticancer effects, multiple mechanisms are at play depending on the type of neoplasm. For example, omeprazole and esomeprazole induced apoptosis of human B-cell lymphoma cells both in vitro and ex vivo and improved sensitivity of cell cultures to vinblastine. Significantly, this suggests a mechanism independent from V-ATPase inhibition because, unlike granulocytic cells and select neoplasms (carcinomas and sarcomas),57,58 lymphoma cells have not been reported to upregulate these pumps to improve survival and metastasis. In the same study,52 immunodeficient mice had reduced tumor growth following omeprazole treatment compared to control. Investigators concluded that multiple mechanisms contributed to PPI-induced cell death and reduced chemotherapy resistance. Another study demonstrated that low-dose PPI therapy resulted in neoplastic cell apoptosis via down-regulation of proinflammatory cytokine production in vitro59 and in vivo.60 In addition, another study showed that omeprazole is capable of inhibiting pancreatic cancer cell invasion in experimental studies via blockade of the AhR and subsequent inhibition of the chemokine receptor type 4. AhRs are critical for the successful proliferation and metastatic ability of multiple malignant neoplasms, which can also help to promote immune-mediated inflammatory disorders (Figure 1).62–64 The AhRs promote the production of proinflammatory cytokines and chemokines helpful for a chronic inflammatory environment. In vivo, high-dose PPI therapy resulted in an improved clinical outcome for adults with colonic and rectal cancer.55

Fewer studies examining the effects of H2RAs on tumorigenesis exist. A recent study concluded that both lansoprazole and famotidine had collective antitumor effects, as both drugs reduced select inflammatory cytokines and circulating free radicals and increased the proapoptotic marker caspase-3 in the blood of patients with diffuse large B-cell lymphoma. The collective mechanisms by which ASDs achieve these effects are poorly understood, and caution is advised in making any definitive conclusions without further study as Hellstrand et al found that H2RAs accelerated melanoma metastasis via inhibition of natural killer cell-mediated function.

One comprehensive review summarizes current veterinary medical knowledge of the anticancer effects of ASDs. Only 2 studies68,69 have explored the benefits of ASDs in the treatment of spontaneously occurring tumors in both dogs and cats. One study68 compared 27 dogs and 7 cats with chemoresistant neoplasia receiving high-dose lansoprazole in conjunction with chemotherapy and found that, in comparison to a control population (10 dogs, 7 cats), nearly 70% of those receiving lansoprazole had either partial or complete responses. This was in contrast to the control population, where only 17% had short-lived responses to chemotherapy alone. The same group later reported that 75% of companion animals (22 dogs, 2 cats) achieved partial or complete remission, in comparison to only 1 dog (10%) achieving complete remission from a historical group (10 dogs) treated with metronomic chemotherapy alone. While there are inherent limitations to these studies, such as a variety of neoplasms and chemotherapy protocols, the results provide an illuminating foundation for the further study of these properties in companion animal patients. In Gould et al,69 we investigated the impact of famotidine and esomeprazole compared to vehicle control on healthy and neoplastic in vitro mast cell (rodent, human, and canine) viability, structure, and function. We found that only esomeprazole, in a concentration-dependent manner, induced mast cell apoptosis and altered degranulation patterns. In contrast, even the highest concentration of PPI lacked cytotoxicity to an agranulocytic, canine lymphoma cell line. Further investigation of the specific mechanisms responsible for the impact on mast cells is warranted, along with a broader look at the impact on innate immune and neoplastic cell function in vivo in veterinary species.
**Oxidative Stress**

Important contributors to excess free radicals and oxidative stress from a broad standpoint include overproduction of reactive oxygen species, reduced antioxidants in the body, or a combination of both. Stimulation of reactive oxygen species can be endogenous from a multitude of disease processes, or exogenous, because of drug exposure or chemical toxicity. Excess reactive oxygen species and depletion of antioxidant capacity have been recognized as driving factors in the pathogenesis of gastritis and gastrointestinal (GI) ulceration.71–73

**Effect of ASDs on Oxidative Stress**

Acid-suppressant drugs exhibit antioxidant properties and, therefore, might have beneficial effects for the treatment of GI ulceration beyond their acid-suppressing effect. Several in vitro studies assessing the comparative total free radical scavenging ability between H2RAs74 and PPIs75 demonstrated that ASDs of the same class possess differing antioxidant activity. In a model of murine hepatotoxicity, ranitidine had the strongest total free radical scavenging ability compared to cimetidine and famotidine.74 Cimetidine reduced production of certain hydroxyl free radicals (ie, pentane and methane) secondary to ethanol-induced acute liver injury in rats.76 Considering that other H2RAs (eg, cimetidine and ranitidine) are rarely used in veterinary patients due to their weak gastric acid-reducing properties,77 further research in veterinary patients might better identify scenarios where H2RAs other than famotidine might be beneficial. Finally, investigators78 found an increase in natural gastric antioxidants, along with a reduction in prooxidants, following both H2RA and PPI therapy in an in vivo rodent model of acetylsalicylic acid-induced gastritis. This study is one of the few head-to-head investigations comparing the antioxidant properties of H2RAs and PPIs in the same model.

To the authors’ knowledge, no published studies exist evaluating the antioxidant properties of ASDs in companion animals with naturally occurring diseases. While controlled studies are needed, if ASDs exert similar free radical scavenging effects as seen in rodents and humans, there are extra-GI disease processes that occur commonly in veterinary patients for which PPIs and H2RAs might be of benefit. These investigations are particularly needed because, in studies52,79 of cultivated gastric epithelial cells and B lymphocytes, ASDs demonstrated prooxidant properties. One mechanism identified is that V-ATPase blockade can cause cell membrane destabilization and overproduction of free radicals.

**Fibrosis**

Injury to resident cells with secondary inflammation is one of the main contributors to fibrosis. Scarring and collagen deposition are considered hallmarks of fibrosis and represent the product of persistent, ongoing inflammation of various etiologies (eg, infectious, immune-mediated, chemical, or allergic insult).80 One of the most important collagen-promoting cells is the myofibroblast, which receives signals via various proinflammatory cytokines and chemokines (eg, IL-13, IL-21, and TGF-β).

**Effect of ASDs on Fibrosis**

A handful of studies in human patients and murine models attest to the antifibrotic effects of PPIs (Supplementary Table S1). Esomeprazole suppressed fibroblast proliferation and reduced profibrotic protein in a model of pulmonary fibrosis.81 This same study82 also demonstrated the antifibrotic benefits of the PPI in a murine model of acute lung injury, which was mirrored in a retrospective analysis of PPI-treated human patients with acute lung injury adults compared to placebo control. Proton pump inhibitors have also been touted to reduce morbidity and mortality in humans with idiopathic pulmonary fibrosis, although evidence is mixed on the beneficial effects of PPIs in this disease state.82,83 Endoscopic esophageal fibrosis scores in patients with eosinophilic esophagitis were also reduced following monotherapy with standard or high-dose PPI therapy in comparison to a group treated with topical corticosteroids84; however, the group receiving steroids had a higher proportion of subjects with esophageal strictures compared to the PPI group before the initiation of therapy.

While some studies would suggest beneficial, antifibrotic effects of PPIs, others show a possible profibrotic effect. For example, pantoprazole altered the intestinal microbiota and Toll-like receptor signaling profiles and increased hepatic steatosis and fibrosis in a murine model.85 The mechanisms of action for some of the identified deleterious effects of ASDs remain unexamined, particularly in naturally occurring disease states in both humans and animals.

**pH-Independent Adverse Effects of Acid Suppressants in Human and Veterinary Medicine**

**Short-term adverse effects**

**Histamine-2 receptor antagonists**

Although H2RAs are generally well tolerated, several short-term pH-independent adverse effects have been reported in humans, including hematologic, cardiovascular, renal, and central nervous system disturbances. Specifically, famotidine has been linked with the development of thrombocytopenia,86 and cimetidine has been linked with neutropenia87 and pancytopenia.88 The most common clinical sequelae of famotidine in humans are headache (approx 4.7% of patients), confusion in elderly patients,88 and constipation.86 Most of the cardiovascular and renal adverse effects have been linked to cimetidine,89–91 which is not typically prescribed to veterinary patients.
**Proton pump inhibitors**

Short-term pH-independent adverse effects related to PPI use are not as commonly documented as longer term side effects (see the next section). Some similarities exist between PPI use and H2RA use and the development of various cytopenias (eg, platelets, erythrocytes, and neutrophils). Thrombocytopenia has been well documented in patients receiving less than or equal to 2 months of therapy with varying PPIs (ie, pantoprazole, lansoprazole, omeprazole).92–95 One case report96 describes development of both immune-mediated hemolytic anemia and thrombocytopenia 5 weeks after initiation of oral omeprazole therapy. Conversely, some reports suggest that at least some non-immune-mediated mechanisms are at play, given reports97,98 in which patients are described as having responded to withdrawal of the PPI alone and were not dependent on corticosteroids for improvement. While a single report99 hypothesizes that esomeprazole might have been responsible for development of thrombocytopenia, the patient was receiving concurrent therapies. Thus far in humans, pantoprazole is the most reported PPI linked to causation of thrombocytopenia.100–102

Concern exists for various cytopenias developing secondary to short-term, concurrent chemotherapeutic and PPI administration. There is enough literature to support the continued investigation of coadministration of PPIs with ASDs because of the previously discussed decrease in chemotherapy resistance; however, interactions between select chemotherapeutics may be lethal and should be carefully considered. For example, pancytopenia has been repeatedly documented following less than or equal to 2 weeks of dual methotrexate and PPI therapy.103 No reports of short-term pH-independent adverse effects secondary to PPIs have been documented in dogs and cats.

**Long-term adverse effects**

**Histamine-2 receptor antagonists**

Compared to the study of adverse effects resulting from chronic use of PPIs, there is a dearth of information on the long-term adverse effects of H2RAs. Most of the side effects reported for H2RAs have been related to hematologic disturbances from peripheral destruction or reduced bone marrow production of platelets, RBCs, and WBCs.

**Proton pump inhibitors**

The pH-independent adverse events related to chronic PPI use are more well documented and involve a multitude of organs. Organ systems most frequently reported as negatively impacted include the renal, cardiovascular, and central nervous systems.

For example, one of the most widely reported adverse effects associated with chronic PPI use is the development or accelerated progression of chronic kidney disease. One study104 that looked at a large cohort of patients receiving long-term PPIs (up to 5 years) found that in comparison to non-PPI users including those receiving H2RAs, the risk for chronic kidney disease development was increased. Reports105–109 have also demonstrated the development of acute kidney injury, likely from acute interstitial nephritis, compared to age-matched controls. A link between long-term PPI use and development or progression of dementia has also been suggested. The V-ATPase blockade is one mechanism believed to be of importance, as V-ATPase pumps have a critical role in degradation of amyloid-β plaque buildup. Two studies, both in German adults, concluded that elderly individuals chronically and consistently receiving PPIs had between a 36%110 and 44%111 increased risk of development of dementia, compared to 12% in sporadic users.111 In one of these retrospective studies,111 consistent PPI users also had higher rates of depression and stroke. This supports many other reports112,113 of cardiovascular complications secondary to long-term PPI use, namely myocardial infarction. As discussed earlier in this review, PPIs have an impact on vascular tone by way of nitric oxide synthase blockade, which might play a role in the development of myocardial infarction or other cardiac adverse effects, but associations and responsible mechanisms require further exploration.

A poorly understood but newly emerging adverse effect from long-term PPIs is its impact on GI permeability, likely via disruption of epithelial tight junction integrity. One study114 using multiple disease models (cell culture, organoids, and in vivo murine intestinal bowel disease) found an acceleration in experimentally induced enterocolitis secondary to chronic omeprazole administration. As many disease processes for which PPIs are indicated involve the GI tract, this is an important future area of investigation for both humans and animals. Another important area of study in humans is PPI use in patients with primary infections. This makes sense given the impact PPIs have on immune cell function covered earlier in this review. Patients with COVID-19 receiving PPIs were more likely to have severe clinical outcomes compared to ASD naïve patients in 2 studies115,116 whereas another study117 found no link between PPI use and increased mortality from COVID-19. The specific mechanisms for many of these associations remain unknown and should be investigated with prospective, controlled studies.

Chronic PPI administration has also been linked to other adverse effects resulting from pH-dependent properties (eg, secondary pneumonia, risk of bone fracture), which are discussed more in the companion article by Grady et al, JAVMA, October 2024. While multiple mechanisms are likely responsible for the increased development of fractures, including pH-dependent sequelae (eg, malabsorption of calcium and cobalamin), pH-independent effects such as osteoclast V-ATPase pump inhibition are likely important contributors.108

The authors are aware of no studies in veterinary medicine that assess the impact of pH-independent effects in cats and dogs. While several studies118,119 have assessed for adverse effects following 2 months of therapy in companion animals, the focus was on
pH-dependent effects (covered in the companion article by Grady et al., JAVMA, October 2024). We can report that in a crossover study, healthy cats received 2 months of either placebo or oral omeprazole, no decreases in leukocyte populations were identified between treatments or pre- and postadministration (unpublished data).

Conclusions

Acid-suppressant drugs are commonly prescribed, but their pH-independent effects are poorly understood. Further exploration into these pH-independent effects would allow clinicians to tailor ASD treatment for disease processes and to monitor for and detect possible adverse effects. While the body of human medical evidence on these issues is more robust, many of these studies focus on healthy or artificially induced models of disease. Therefore, both human and veterinary medicine could benefit from a One Health approach to investigation of these pH-independent effects of ASDs in naturally occurring diseases in veterinary companion animals.

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