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ANTI-EMETICS AND ANTIULCERS DRUGS: WHEN ARE THEY USEFUL?

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Emesis is found in a wide range of clinical disease processes. Protracted vomiting is physically exhausting and can cause dehydration, acid-base and electrolyte disturbances, and aspiration pneumonia. Antiemetic drugs are used to control excessive vomiting once an etiological diagnosis has been made, to prevent motion sickness and psychogenic vomiting, and to control emesis from radiation and chemotherapy.

Antiemetics may act peripherally to reduce afferent input from receptors or to inhibit efferent components of the vomiting reflex response. They may also act centrally to block stimulation of the CRTZ and emetic center.

Emesis is thought to be regulated by a series of nuclei located in the brainstem, within the reticular formation of the medulla oblongata and including the Nucleus tractus solitarius (NTS), collectively referred to as the emetic center. The emetic center receives inputs via a number of afferent pathways from the cerebral cortex, vestibular apparatus, and Chemoreceptor trigger zone (CTZ) located in the area postrema as well as vagal or sympathetic afferents from peripheral sensory receptors in the stomach, intestinal tract, other abdominal organs (eg, uterus, bladder, and kidneys), and peritoneum.

Within the emetic center, key neurotransmitter receptors include 5-hydroxytryptamine 5-HT_3 (serotonin), α2-adrenergic (norepinephrine), and Neurokinin-1 (NK1) (sensitive to substance P) receptors. Other neurotransmitter receptors found in those regions of the brain involved with the emetic response include D_2 (dopaminergic), H_1 and H_2 (histaminergic), 5-HT_{1A} (serotoninergic), μ- and δ-opioid (endorphin), and M_1 and M_2 (cholinergic) receptors.

Key neurotransmitter receptors thought to play an important role in the final part of the efferent pathway to the gastrointestinal musculature include 5-HT_4, M_2, and dopaminergic receptors. Convergence of the stimulant pathways through the emetic center means that abolition of activity at this level has the potential to prevent emesis, whether generated peripherally or centrally. This concept has been confirmed in studies in which NK1 receptor antagonists binding to NK1 receptors within the NTS provided broad-spectrum antiemetic activity.

Metoclopramide antagonizes primarily dopaminergic (D_2) and to a lesser extent 5-hydroxytryptamine (HT) serotonergic receptors, thereby preventing stimulation of the chemoreceptor trigger zone. As a 5-HT_4 serotonergic receptor agonist, metoclopramide also has an antiemetic effect by stimulating gastrointestinal motility; because of this property, metoclopramide must be used with caution in dogs that are at risk of intussusception. Another well-recognized adverse effect of metoclopramide is the development of muscle fasciculation and tremors.

Review of the medical records indicated that the second most commonly used antiemetic in the dogs was prochlorperazine, which is a phenothiazine derivative. In addition to α-adrenergic receptor antagonism, the antiemetic properties of prochlorperazine are mediated through antagonism of dopaminergic, histaminergic, and cholinergic receptors; antagonism of these receptors limits stimulation of the chemoreceptor trigger zone. In dogs, prochlorperazine can cause hypotension and sedation; both of these adverse effects may lead to complications such as shock and increased risk of aspiration of vomitus. Similar to the adverse effects associated with metoclopramide, prochlorperazine has been reported to cause muscle fasciculations, tremors, and release of prolactin.

Ondansetron is a highly specific antagonist of the 5- HT_3 serotonergic receptors in visceral and vagal afferent neurons; through this action, ondansetron prevents stimulation of the chemoreceptor trigger zone. In children, ondansetron has been shown to be more effective than metoclopramide in control of chemotherapy induced emesis. In a study in dogs, ondansetron was effective in decreasing the frequency of chemotherapy induced emesis. Although ondansetron-associated adverse reactions appear to be rare, administration of this drug is often cost prohibitive.

All these antiemetics did not completely control vomiting in dogs. Maropitant is a novel NK1 receptor antagonist with potential for use as a general antiemetic in dogs and may be able to inhibit the emesis arising either centrally or peripherally.
Preliminary Maropitant dose-response investigations have indicated that the standard dosage regimen, for either treatment or prevention of emesis, should be 1 mg/kg by SC injection or 2 mg/kg as oral tablets, with the dose being given once every 24 hours for up to 5 days as required. This is supported by pharmacokinetic data demonstrating that in dogs, these maropitant dosage regimens provide similar peak plasma concentrations (with means of 92.0 ng/mL delivered by 1 mg/kg, SC, and 81.0 ng/mL from 2 mg/kg, PO). However, as might be expected, the time taken to achieve maximum plasma concentrations is shorter following SC administration (with means of 0.75 hours for 1 mg/kg, SC and 1.9 hours for 2 mg/kg, PO). Furthermore, no apparent adverse clinical observations were recorded that related to the administration of maropitant.
Although the parenteral route may be preferred for the treatment of acute emesis, the oral route is probably more appropriate for owners administering the product at home for the prevention of emesis, such as might arise from motion sickness or prior to planned chemotherapy.

Anti-ulcers drugs
Famotidine is a competitive inhibitor of histamine type 2 (H_2) receptors, used for the treatment of nausea, vomiting, and esophagitis. Famotidine is generally considered to be safe in most veterinary patients. However, famotidine has been anecdotally associated with intravascular hemolysis after IV administration to cats.
Sucralfate is an anti-ulcer drug that has a cytoprotective effect on gastrointestinal mucosa. Sucralfate disassociates in the acid environment of the stomach to sucrose octasulfate and aluminum hydroxide. Sucrose octasulfate polymerizes to a viscous substance that protect the ulcerated mucosa. It prevents back diffusion of hydrogen ions, inactivates pepsin, and adsorbs bile acid. Additionally, sucralfate increases the mucosal synthesis of prostaglandins, which have a cytoprotective role. Because sucralfate is not absorbed, it is virtually free of side effects. The dosage for cats is 2 to 5 ml, and for dogs is 3 to 15 ml/8-12 hours.
Omeprazole, a proton pump inhibitor, decreases gastric acid secretion by blocking the final step in the production of hydrochloric acid in the parietal cell. In dogs, omeprazole decreased aspirin-related gastritis but had no effect on ulcer healing. A single dose inhibits acid secretion for 3-4 days, despite a relatively short plasma half life. The recommended dosage in dogs and cats is 0.7 mg/kg/day.
Misoprostol, a synthetic prostaglandin E_1 analog, inhibits gastric acid production and has a cytoprotective effect. Several studies have shown the protective effect of misoprostol in preventing GI mucosal lesions in humans as well as in dogs treated with nonsteroidal anti-inflammatory drugs, but is less efficacious than H_2 blockers to treat ulcers. However, the use of misoprostol recently was observed to not be effective in preventing GI hemorrhage in dogs receiving high doses of methylprednisolone and undergoing spinal surgery.
Misoprostol has a cytoprotective effect from stimulation of bicarbonate and mucus secretion, increased mucosal blood flow, decreased vascular permeability and increased cellular proliferation and migration. Side effects of misoprostol are mainly limited to diarrhea and flatulence, and is contraindicated in pregnant dogs as it can induce abortion. It is dosed at 2-5 µg/kg PO BID-TID.

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