Clinical Applications of Substance P (Neurokinin-1 Receptor) Antagonist in Canine Medicine

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Abstract

Substance P binds to the Neurokinin-1 (NK-1) receptors found in the emetic center of the CNS to induce emesis. Maropitant is a selective NK-1 receptor antagonist that inhibits the binding of Substance P to NK-1 receptors. It is commonly used for the prevention and treatment of vomiting in dogs. This review aims to discuss and analyze the therapeutic potential of Substance P (Neurokinin-1 receptor) antagonist with a particular focus on the drug maropitant in canine medicine. A systematic literature review was performed to identify literature during the past 20 years (2001-2021) using databases, such as ScienceDirect, PubMed, Scopus, and Google Scholar. The initial search identified 173 articles. Based on the specific inclusion and exclusion criteria, 41 articles were selected for further analysis. Studies have already confirmed the role of Substance P and NK-1 receptors in central pain processing, intestinal smooth muscle contraction, vasodilation, and neurogenic inflammation. Maropitant is considered one of the most effective veterinary antiemetic drugs that are currently in use. It works well against peripheral and central stimuli that trigger the vomiting center. It has already demonstrated therapeutic efficacy in dogs for managing acute vomiting associated with pancreatitis, gastritis, and parvoviral enteritis. It can also prevent and treat chemotherapy-induced emesis and can delay the signs of nausea and adverse gastrointestinal effects. Since maropitant has broad-spectrum antiemetic activity, they can be recommended for managing uremic vomiting in dogs. In addition, it has also exhibited an anesthetic sparing effect since the dogs treated with maropitant require a slightly lower percent of isoflurane as an inhalational anesthetic. NK-1 receptors are also identified in different areas of the pain pathways. Therefore, NK-1 receptor antagonists might be effective for managing visceral pain. However, further studies are required to establish the broad therapeutic potential of NK-1 receptor antagonist drugs such as maropitant in canine medicine. The pain associated with the subcutaneous administration of maropitant is due to metacresol, a preservative used in some
formulations. Therefore, the side effects can be eliminated by developing novel maropitant formulations specifically for dogs.

**Keywords**: Neurokinin-1 receptor antagonist, maropitant, renal failure, antiemetic, canine medicine

1. **Context**

   Substance P is the first neuropeptide discovered in mammals (1931) (1). It binds to Neurokinin-1 (NK-1) receptors found in the emetic center of the CNS, thereby inducing emesis (2). Therefore, selective Substance P antagonists can act as potent broad-spectrum antiemetics in dogs and cats against various emetic stimuli (2). Neurokinin 1 receptor antagonists are widely used in CINV (Chemotherapy-Induced Nausea and Vomiting) and PONV (Postoperative Nausea and Vomiting) (3,4). The brain stem regions, viz., area postrema, and nucleus solitaries are concerned with vomiting reflexes (5).

   Recently developed NK1 receptor antagonists like aprepitant can cross the blood-brain barrier, making them useful in a wide range of CNS disorders (6). Furthermore, NK1 antagonists play a role in tumor treatment (7). Apart from this, substance P and its derivatives are also used in targeted radionucleotide tumor diagnosis (8). However, the action of substance P-derived medical preparations is limited as endogenous substance P is a potent vasodilator mediated by nitric oxide (9).

   Neurokinin 1 is present not only in the central nervous system but peripheral tissues as well. Where, it plays a role in the transmission of pain, the transition of inflammatory response at peripheral sites viz. gastrointestinal and respiratory tract, stress and anxiety (10). Maropitant is a selective NK-1 receptor antagonist approved for the prevention and treatment of vomiting in dogs. It is available in both injectable and tablet formulations and can be used for managing motion sickness (10).

   Maropitant is a strong antiemetic and has also been used as pre-anaesthetic because of its antiemetic property and capacity to alleviate visceral pain, i.e., the one originating from abdominal and thoracic organs (11). It also helps in a quick return to food intake in the postoperative phase of canine patients (12). Upon release of the neuropeptides from endings of sensory nerves, there is vasodilation and enhanced vasculature permeability. These functions are blocked by the NK1 receptor antagonists when they are administered intra-arterially. Also in animals, iontophoretic, i.e., the transdermal application reduces the pulpal pain by blocking substance P induced pulpal blood flow in dental treatments (15).
The recent drug rolapitant is a highly potent, sensitive, orally active, and long-acting NK1 receptor antagonist with a half-life of 180 hours (14). Another drug netupitant demonstrated synergistic action with palonosetron by inhibiting substance P response (15). The longer half-life overcomes the problem of repeated administration in cases of acute and delayed emesis (16). The pool of options thus helps in choosing the optimal regimen that best suits the animal in various aspects, viz., cost, tolerability, availability, and safety.

2. Evidence Acquisition

This review aims to discuss and analyze the therapeutic potential of Substance P (Neurokinin-1 receptor) antagonist with a particular focus on the drug maropitant in canine medicine. A systematic literature review was performed to identify literature during the past 20 years (2001-2021) using databases, such as ScienceDirect, PubMed, Scopus, and Google Scholar. The search keywords include Substance P, Neurokinin-1 receptor antagonist, maropitant, antiemetic, uremic gastritis, canine medicine. The following inclusion criteria were used for literature selection: availability of information on Substance P (NK-1) receptor antagonists, their properties, side effects, and therapeutic potential focusing on canine medicine. The results did not include articles written in languages other than English.

3. Results

The initial search identified 173 articles. Relevant, critical, and most recent literature was given preference. Based on the specific inclusion and exclusion criteria, 41 articles were selected for further analysis. The obtained data were used for developing this review.

3.1. Substance P (Neurokinin-1 receptor) antagonist

Substance P is a neuropeptide (11 amino acids) that belongs to the tachykinin family (17). Substance P (NK-1) receptor antagonist inhibits the binding of Substance P to NK-1 receptors (Figure 1) (2). Preliminary studies have confirmed the role of Substance P and NK-1 receptors in central pain processing, intestinal smooth muscle contraction, vasodilation, and neurogenic inflammation (10, 17). In addition, substance P is involved in the physiological functions of the gastrointestinal tract, such as fluid and electrolyte secretion, motility, and immunoinflammatory response regulation (18).

Maropitant is the first NK-1 receptor antagonist used in veterinary practice (2, 19). It is also considered one of the most effective veterinary antiemetic drugs that are currently in use. They work well against peripheral and central emetogens (20, 21). On the contrary, other antiemetics prevented vomiting caused by either peripheral (ondansetron) or central (chlorpromazine and metoclopramide) stimulation but not both (20). Other examples of NK-1 receptor inhibitor are aprepitant, casopitant, fosaprepitant netupitant, and rolapitant (22). Higher expression of NK-1 receptors in muscle and mucosal immune cells of inflamed tissues could be
considered a rationale for using NK-1 receptor antagonist drugs for treating intestinal inflammation (18).

3.2. Broad-spectrum antiemetic drug

Emesis is one of the most common presenting signs of gastrointestinal dysfunction in small animal practice (21). If not controlled at the early stages, vomiting can cause severe dehydration, reflux esophagitis, weight loss, and aspiration pneumonia (2). An antiemetic is indicated when vomiting is severe and/or persistent (2, 23). They can help reduce the frequency of vomiting and prevent further aggravation of acid-base and electrolyte imbalance (2). Several pathways constituting multiple inputs and the involvement of co-transmitters contribute to different arms of the vomiting reflex. Therefore, antiemetic drugs have to be selected based on the triggered pathway of the vomiting reflex (21). An ideal antiemetic drug will prevent both central and peripheral stimuli that trigger the vomiting center (21).

Maropitant has already demonstrated therapeutic efficacy in dogs for managing acute vomiting associated with pancreatitis, gastritis, and parvoviral enteritis (24-26). Promising results were obtained after administering one or two doses of maropitant, indicating very high efficacy (24). In addition, a single daily dose protocol of maropitant was found to be more effective than metoclopramide that is administered twice or thrice daily for treating emesis associated with various etiologies in dogs (27). Maropitant can also be used to prevent and treat chemotherapy-induced emesis in dogs (28). They also delay chemotherapy-induced signs of nausea and adverse gastrointestinal effects in dogs (28, 29). Maropitant is combined with loperamide to prevent paclitaxel-induced adverse gastrointestinal effects (29). It has similar efficacy to ondansetron for controlling the clinical signs (vomiting) associated with parvoviral enteritis in dogs (26).

The standard antiemetic dose of maropitant in dogs is 1 mg/kg q24h indicating a 24-hour duration of effect (21). It is administered via the subcutaneous route and has an elimination half-life ranging from 4 to 8 hours in dogs (2). However, a higher dose is recommended (8 mg/kg PO q24h) for managing motion sickness in dogs. In addition, the animal has to be fasted for 1 hour before the oral administration of maropitant at this dosage (2, 21). The absolute bioavailability of maropitant is low after oral administration (23.7% at 2 mg/kg) but higher (90.7%) when administered subcutaneously. The lower bioavailability following oral administration is due to the first-pass metabolism (19). Experimental studies conducted in healthy adult Beagle dogs confirmed that maropitant does not have any prokinetic effect (30). Therefore, the use of maropitant as an antiemetic drug will not affect the process of gastric emptying.

3.3. Maropitant for uremic gastritis

Uremic gastritis is defined as the histopathologic changes and gastrointestinal signs that occur due to renal failure in dogs (31). It is commonly associated with acute renal failure or end-
stage chronic renal failure (23). Renal failure-induced uremia can disrupt the integrity of epithelial tight junctions of the stomach, jejunum, ileum, and colon (32). The histopathological changes associated with uremic gastritis include glandular atrophy, fibroplasia, mast cell infiltration, edema of the lamina propria, submucosal arteritis, and mineralization (31, 33). The classical uremic signs such as vomiting, nausea, and anorexia develop only when azotemia worsens. In addition, such clinical signs are also induced by the effect of uremic toxins on the chemoreceptor trigger zone (CRTZ) (33). The uremic toxins generated in renal failure patients are sensed by the CRTZ of the area postrema. The ablation of this area in dogs prevented uremic vomiting in dogs (34).

One of the possible mechanisms that contribute to gastrointestinal pathology is linked to the high blood concentrations of gastrin as a result of decreased renal catabolism and loss of inhibitory control over gastrin secretion (23, 35). Therefore, high levels of gastrin in the circulation can increases gastric acid secretion. Another proposed mechanism involves the back-diffusion of hydrochloric acid and pepsin into the stomach resulting in inflammation and release of histamine, which further stimulate acid secretion. This mechanism is facilitated by the loss of integrity of the gastric mucosal barrier (pre-epithelial, epithelial, and post-epithelial elements) (32, 36). Canine uremic gastropathy affects mucosal lamina propria, and the lesions produced can be linked to diffuse vascular injury and altered parietal cell function (37). Therefore, efforts have to be directed to correcting dehydration, acid-base, and electrolyte imbalance. In addition, antiemetics, prokinetic agents, H2-receptor antagonists, antacids, gastric protectants, and adsorbents are commonly used for managing the gastrointestinal dysfunction associated with renal failure (23).

In addition to managing acute vomiting, maropitant has also demonstrated therapeutic efficacy for managing chronic vomiting in cats with chronic kidney disease (25). Therefore, maropitant is ideal for the nutritional management of patients with chronic kidney disease. Since maropitant has a broad-spectrum antiemetic activity covering both peripheral and central emetogens (20), they can be recommended for managing uremic vomiting in dogs. They are the ideal choice for managing emesis associated with uremia since it has already demonstrated efficacy against xylazine induced vomiting in cats (38), both of which are mediated to act via the area postrema (34, 38, 39).

3.4. **Perioperative use of maropitant**

Morphine is commonly administered in the epidural space to obtain long-lasting analgesia during the postoperative period (40). However, the use of epidural opioids can induce emesis in dogs (41). Maropitant can prevent vomiting induced by morphine administration (postoperative analgesia) in dogs (40, 42). Subcutaneous administration of maropitant (1 mg/kg) 30 minutes before the intramuscular administration of morphine reduced the frequency of emesis (70% decrease) in dogs undergoing ovariohysterectomy (42). Similar results were obtained when
Maropitant was used with epidural administration of morphine in dogs (40). Maropitant can be used as a pre-anesthetic agent for ovariohysterectomy in dogs since it was found to minimize the systolic arterial pressure and heart rate response to surgical stimulation (43). It also offered better recovery quality, and the animals are more likely to eat within 3 hours post-recovery period (43).

Maropitant has better antiemetic efficacy than metoclopramide for preventing morphine-induced vomiting in dogs (41). In addition, maropitant also prevented hydromorphone-induced vomiting in dogs when administered 30-45 min before the opioid (12, 44). However, the significant decrease in the incidence of vomiting was not associated with an improvement in the signs of nausea and ptyalism (44). Dogs treated with maropitant require a slightly lower percent of isoflurane as an inhalational anesthetic (43). In addition, intravenous administration of maropitant decreases the minimum alveolar concentration (MAC) of sevoflurane in dogs (45). However, epidural administration did not affect the MAC value (45). The administration of maropitant also reduced the MAC for blunting adrenergic response (MAC-BAR) of sevoflurane, indicating a sparing effect on the anesthetic requirement in dogs (46). It decreases the anesthetic requirement during visceral stimulation of the ovary and ovarian ligament. Therefore, NK-1 receptor antagonists play a major role in managing ovarian and visceral pain in dogs (47). NK-1 receptors are identified in different areas of the pain pathways, such as the dorsal horn, dorsal root ganglia, sensory afferents, ascending projections of the spinal cord. Therefore, NK-1 receptor antagonists might be effective for managing visceral pain (10).

3.5. Side effects of maropitant

Subcutaneous administration of maropitant is associated with pain and discomfort in dogs and cats (41, 48). The pain is due to the presence of metacresol, a preservative used in some of the formulations (Cerenia, Zoetis) (48). Therefore, another formulation (Prevomax, Le Vet. Pharma) was developed, containing benzyl alcohol as the preservative. Maropitant formulations with benzyl alcohol were significantly less painful due to the local anesthetic properties of benzyl alcohol (48). In addition, subcutaneous injection of refrigerated maropitant (Cerenia) may significantly reduce the pain associated with it (49).

4. Conclusions

Gastrointestinal dysfunction associated with renal failure is considered the major challenge during medical management in canine patients. Therefore, specific nutritional and medical management strategies have to be developed to control and treat such dysfunctions. Substance P (Neurokinin-1 receptor) antagonist such as maropitant has become the standard antiemetic of choice in veterinary patients to prevent chemotherapy-induced vomiting. In addition, maropitant can be considered an ideal antiemetic in dogs and cats due to its broad-spectrum activity against various emetic stimuli. Therefore, the current evidence indicates the potential use of maropitant for managing emesis associated with canine uremic gastropathy. In
addition, the NK1 receptor antagonists may also prove beneficial for chemotherapy-induced nausea and vomiting in dogs. Furthermore, since NK-1 receptors are identified in different areas of the pain pathways, NK-1 receptor antagonists might effectively manage visceral pain. However, further studies are required to establish the therapeutic potential of NK-1 receptor antagonist drugs such as maropitant in canine medicine.

Authors' Contribution

Study concept and design: K. S. and S. K. D.
Acquisition of data: K. S. and K. J.
Analysis and interpretation of data: K. S. and K. J.
Drafting of the manuscript: K. S. and K. J.
Critical revision of the manuscript for important intellectual content: M. A., Aakanksha, S. N. C., P. K. P., S. K. D. and K. D.
Administrative, technical, and material support: P. K. P., S. K. D. and K. D.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

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Declaration of Interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

References


Figure 1: Schematic representation of Neurokinin-1 (NK-1) receptor (long isoform-full length with 407 amino acids) containing an extracellular N-terminus, three extracellular loops (E1, E2, and E3), four intracellular loops (C1, C2, C3, and C4), and seven transmembrane domains. Reproduced from Garcia-Recio and Gascón (2015) (5) under Creative Commons Attribution License (CC-BY).
Figure 2: Illustrates the mechanism of action and indications of maropitant, a substance P (neurokinin-1) receptor antagonist used as antiemetic in dogs.