Archives of Razi Institute

DOI: 10.22092/ARI.2021.356171.1797

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

Sharun, K[1*], Jambagi, K[2], Arya, M[1], Aakanksha[1], Chaithra, S. N[1], Patel, P. K[2], Dixit, S. K[2], Dhama, K[3]

1. Division of Surgery, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh-243122, India
2. Division of Medicine, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh-243122, India
3. Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh-243122, India

Corresponding Author: sharunkhansk@gmail.com

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.

Acknowledgments

The authors are thankful to the Director, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India, for providing the necessary research facilities. The figure is designed using BioRender.com

Funding

The authors did not receive support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript.

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

1. Palma C. Tachykinins and their receptors in human malignancies. Curr Drug Targets. 2006 Aug;7(8):1043-52.

2. Trepanier LA. Maropitant: Novel Antiemetic. Available at: https://www.cliniciansbrief.com/article/maropitant-novel-antiemetic (Accessed on August 31, 2021)
3. Aapro MS, Walko CM. Aprepitant: drug-drug interactions in perspective. Ann Oncol. 2010 Dec;21(12):2316-2323.
4. Majumdar AK, Howard L, Goldberg MR, Hickey L, Constanzer M, Rothenberg PL, Crumley TM, Panebianco D, Bradstreet TE, Bergman AJ, Waldman SA, Greenberg HE, Butler K, Knops A, De Lepeleire I, Michiels N, Petty KJ. Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. J Clin Pharmacol. 2006 Mar;46(3):291-300.
5. Garcia-Recio S, Gascón P. Biological and Pharmacological Aspects of the NK1-Receptor. Biomed Res Int. 2015;2015:495704.
6. Johnson MB, Young AD, Marriott I. The Therapeutic Potential of Targeting Substance P/NK-1R Interactions in Inflammatory CNS Disorders. Front Cell Neurosci. 2017 Jan 4;10:296.
7. Muñoz M, Rosso M, González A, Saenz J, Coveñas R. The broad-spectrum antitumor action of cyclosporin A is due to its tachykinin receptor antagonist pharmacological profile. Peptides. 2010 Sep;31(9):1643-8.
8. Baum, R.P. Therapeutic Nuclear Medicine; Springer Publisher: Heidelberg, Germany, 2014.
9. Hoover DB, Chang Y, Hancock JC, Zhang L. Actions of tachykinins within the heart and their relevance to cardiovascular disease. Jpn J Pharmacol. 2000 Dec;84(4):367-73.
10. Hay Kraus BL. Spotlight on the perioperative use of maropitant citrate. Vet Med (Auckl). 2017 Aug 24;8:41-51.
11. Morris R, Cheunsuang O, Stewart A, Maxwell D. Spinal dorsal horn neurone targets for nociceptive primary afferents: do single neurone morphological characteristics suggest how nociceptive information is processed at the spinal level. Brain Res Brain Res Rev. 2004 Oct;46(2):173-90.
12. Hay Kraus BL. Effect of dosing interval on efficacy of maropitant for prevention of hydromorphone-induced vomiting and signs of nausea in dogs. J Am Vet Med Assoc. 2014 Nov 1;245(9):1015-20.
13. Kim YK, Chu WS, Lee HJ, Ahn DK, Kim SK. Effect of iontophoretical application of NK1 receptor antagonists on pulpal blood flow in cats. J Endod. 2005 Sep;31(9):647-51.
14. Rapoport B, Schwartzberg L, Chasen M, Powers D, Arora S, Navari R, Schnadig I. Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting over multiple cycles of moderately or highly emetogenic chemotherapy. Eur J Cancer. 2016 Apr;57:23-30.
15. Poma A, Christensen J, Davis J, Kansra V, Martell RE, Hedley ML. Phase 1 positron emission tomography (PET) study of the receptor occupancy of rolapitant, a novel NK-1 receptor antagonist. J Clin Oncol. 2014;32(15_suppl): e20690-e20690.

16. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2014 Feb;22(2):469-77.
17. Schank JR, Heilig M. Substance P and the Neurokinin-1 Receptor: The New CRF. Int Rev Neurobiol. 2017;136:151-175.
18. Polidoro G, Giancola F, Fracassi F, Pietra M, Bettini G, Asti M, Chiocchetti R. Substance P and the neurokinin-1 receptor expression in dog ileum with and without inflammation. Res Vet Sci. 2017 Oct;114:297-307.
19. Benchaoui HA, Cox SR, Schneider RP, Boucher JF, Clemence RG. The pharmacokinetics of maropitant, a novel neurokinin type-1 receptor antagonist, in dogs. J Vet Pharmacol Ther. 2007 Aug;30(4):336-44.
20. Sedlacek HS, Ramsey DS, Boucher JF, Eagleson JS, Conder GA, Clemence RG. Comparative efficacy of maropitant and selected drugs in preventing emesis induced by centrally or peripherally acting emetogens in dogs. J Vet Pharmacol Ther. 2008 Dec;31(6):533-7.
21. Elwood C, Devauchelle P, Elliott J, Freiche V, German AJ, Gualtieri M, Hall E, den Hertog E, Neiger R, Peeters D, Roura X, Savary-Bataille K. Emesis in dogs: a review. J Small Anim Pract. 2010 Jan;51(1):4-22.
22. Ibrahim MA, Preuss CV. Antiemetic Neurokinin-1 Receptor Blockers. [Updated 2021 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470394/
23. Lefebvre HP, Ferré JP, Watson ADJ. Effect of Renal Failure on Gastrointestinal Physiology in Dogs. Last updated on 2002. Available at: https://www.vin.com/apputil/content/defaultadv1.aspx?id=3846282&pid=11147 (Accessed on August 31, 2021)
24. Ramsey DS, Kincaid K, Watkins JA, Boucher JF, Conder GA, Eagleson JS, Clemence RG. Safety and efficacy of injectable and oral maropitant, a selective neurokinin 1 receptor antagonist, in a randomized clinical trial for treatment of vomiting in dogs. J Vet Pharmacol Ther. 2008 Dec;31(6):538-43.
25. Quimby JM, Brock WT, Moses K, Bolotin D, Patricelli K. Chronic use of maropitant for the management of vomiting and inappetence in cats with chronic kidney disease: a blinded, placebo-controlled clinical trial. J Feline Med Surg. 2015 Aug;17(8):692-7.
26. Sullivan LA, Lenberg JP, Boscan P, Hackett TB, Twedt DC. Assessing the Efficacy of Maropitant Versus Ondansetron in the Treatment of Dogs with Parvoviral Enteritis. J Am Anim Hosp Assoc. 2018 Nov/Dec;54(6):338-343.
27. de la Puente-Redondo VA, Siedek EM, Benchaoui HA, Tilt N, Rowan TG, Clemence RG. The antiemetic efficacy of maropitant (Cerenia) in the treatment of ongoing emesis caused by a wide range of underlying clinical aetiologies in canine patients in Europe. J Small Anim Pract. 2007a Feb;48(2):93-8.

28. de la Puente-Redondo VA, Tilt N, Rowan TG, Clemence RG. Efficacy of maropitant for treatment and prevention of emesis caused by intravenous infusion of cisplatin in dogs. Am J Vet Res. 2007b Jan;68(1):48-56.
29. Cartagena-Albertus JC, Engel Manchado J, Moise A, Moya García S, Montoya Alonso JA. Assessment of the administration of maropitant and loperamide to dogs with cancer for the prevention and reduction of adverse effects associated with the administration of paclitaxel. Am J Vet Res. 2019 Jun;80(6):601-606.
30. Schmitz S, Fink T, Failing K, Borsch C, Kunz C, Clemence R, Savary-Bataille K, Neiger R. Effects of the neurokinin-1 antagonist maropitant on canine gastric emptying assessed by radioscintigraphy and breath test. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2016 Jun 16;44(3):163-9.
31. Peters RM, Goldstein RE, Erb HN, Njaa BL. Histopathologic features of canine uremic gastropathy: a retrospective study. J Vet Intern Med. 2005 May-Jun;19(3):315-20.
32. Vaziri ND, Yuan J, Nazertehrani S, Ni Z, Liu S. Chronic kidney disease causes disruption of gastric and small intestinal epithelial tight junction. Am J Nephrol. 2013;38(2):99-103.
33. Sanderson S. Current concepts for management of chronic renal failure in dogs: early diagnosis and supportive care. Last updated on October 1, 2008. Available at: https://www.dvm360.com/view/current-concepts-management-chronic-renal-failure-dogs-early-diagnosis-and-supportive-care-proceedin (Accessed on August 31, 2021).
34. Borison HL, Hebertson LM. Role of medullary emetic chemoreceptor trigger zone (CT zone) in postnephrectomy vomiting in dogs. Am J Physiol. 1959 Oct;197:850-2.
35. Goldstein RE, Marks SL, Kass PH, Cowgill LD. Gastrin concentrations in plasma of cats with chronic renal failure. J Am Vet Med Assoc. 1998 Sep 15;213(6):826-8.
36. Quintero E, Kaunitz J, Nishizaki Y, De Giorgio R, Sternini C, Guth PH. Uremia increases gastric mucosal permeability and acid back-diffusion injury in the rat. Gastroenterology. 1992 Dec;103(6):1762-8.
37. Cheville NF. Uremic gastropathy in the dog. Vet Pathol. 1979 May;16(3):292-309.
38. Hickman MA, Cox SR, Mahabir S, Miskell C, Lin J, Bunger A, McCall RB. Safety, pharmacokinetics and use of the novel NK-1 receptor antagonist maropitant (Cerenia) for the prevention of emesis and motion sickness in cats. J Vet Pharmacol Ther. 2008 Jun;31(3):220-9.
39. Colby ED, McCarthy LE, Borison HL. Emetic action of xylazine on the chemoreceptor trigger zone for vomiting in cats. J Vet Pharmacol Ther. 1981 Jun;4(2):93-6.
40. Mathis A, Lee K, Alibhai HI. The use of maropitant to prevent vomiting induced by epidural administration of preservative free morphine through an epidural catheter in a dog. Vet Anaesth Analg. 2011 Sep;38(5):516-7.
41. Lorenzutti AM, Martín-Flores M, Litterio NJ, Himelfarb MA, Invaldi SH, Zarazaga MP. A comparison between maropitant and metoclopramide for the prevention of morphine-induced nausea and vomiting in dogs. Can Vet J. 2017 Jan;58(1):35-38.

42. Lorenzutti AM, Martín-Flores M, Litterio NJ, Himelfarb MA, Zarazaga MP. Evaluation of the antiemetic efficacy of maropitant in dogs medicated with morphine and acepromazine. Vet Anaesth Analg. 2016 Mar;43(2):195-8.
43. Marquez M, Boscan P, Weir H, Vogel P, Twedt DC. Comparison of NK-1 Receptor Antagonist (Maropitant) to Morphine as a Pre-Anaesthetic Agent for Canine Ovariohysterectomy. PLoS One. 2015 Oct 29;10(10):e0140734.
44. Claude AK, Dedeaux A, Chiavaccini L, Hinz S. Effects of maropitant citrate or acepromazine on the incidence of adverse events associated with hydromorphone premedication in dogs. J Vet Intern Med. 2014 Sep-Oct;28(5):1414-7.
45. Alvillar BM, Boscan P, Mama KR, Ferreira TH, Congdon J, Twedt DC. Effect of epidural and intravenous use of the neurokinin-1 (NK-1) receptor antagonist maropitant on the sevoflurane minimum alveolar concentration (MAC) in dogs. Vet Anaesth Analg. 2012 Mar;39(2):201-5.
46. Fukui S, Ooyama N, Tamura J, Umar MA, Ishizuka T, Itami T, Miyoshi K, Sano T, Yamashita K. Interaction between maropitant and carprofen on sparing of the minimum alveolar concentration for blunting adrenergic response (MAC-BAR) of sevoflurane in dogs. J Vet Med Sci. 2017 Mar 18;79(3):502-508.
47. Boscan P, Monnet E, Mama K, Twedt DC, Congdon J, Steffey EP. Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. Am J Vet Res. 2011 Dec;72(12):1576-9.
48. Deckers N, Ruigrok CA, Verhoeve HP, Lourens N. Comparison of pain response after subcutaneous injection of two maropitant formulations to beagle dogs. Vet Rec Open. 2018 Feb 17;5(1):e000262.
49. Narishetty ST, Galvan B, Coscarelli E, Aleo M, Fleck T, Humphrey W, McCall RB. Effect of refrigeration of the antiemetic Cerenia (maropitant) on pain on injection. Vet Ther. 2009 Fall;10(3):93-102.

Figures

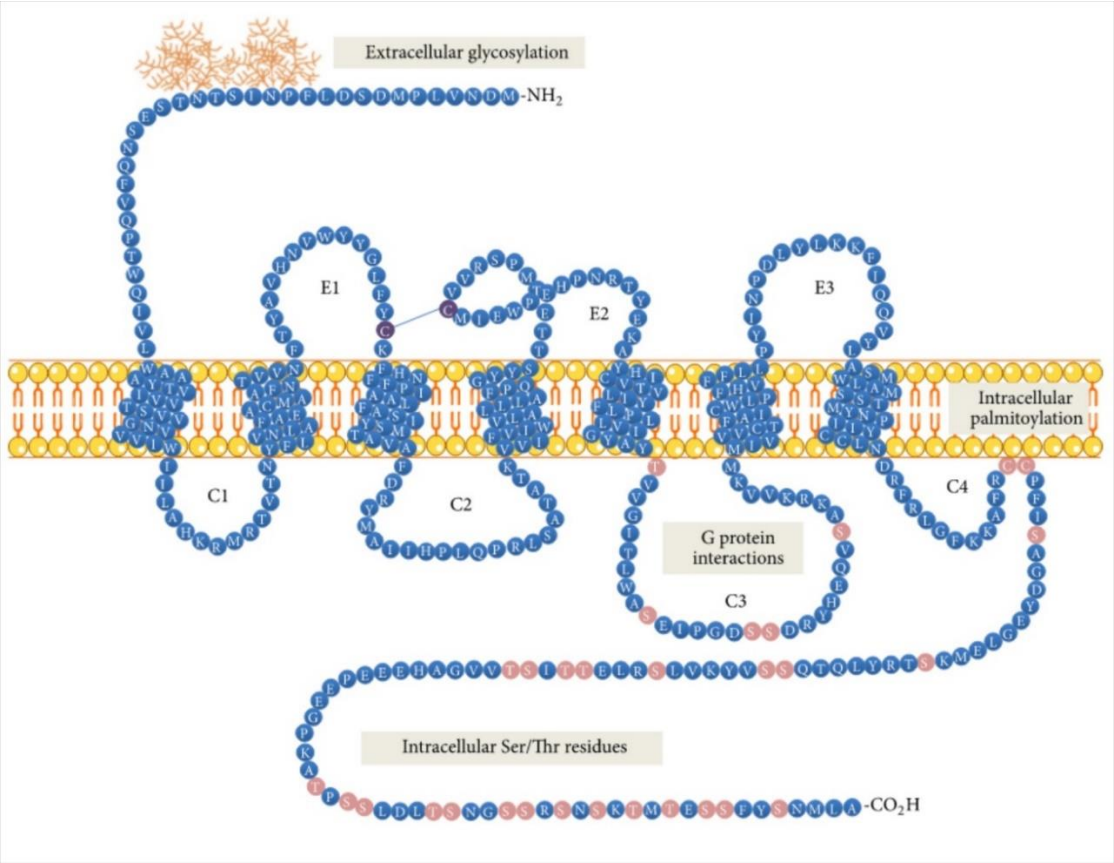

Figure 1: Schematic representation of Neurokinin-1 (NK-1) receptor (long isoform-full length with 407 amino acids) containing an extracellular N-terminus, three extracellular loops (E1, E2, and E3), four intracellular loops (C1, C2, C3, and C4), and seven transmembrane domains. Reproduced from Garcia-Recio and Gascón (2015) (5) under Creative Commons Attribution License (CC-BY).

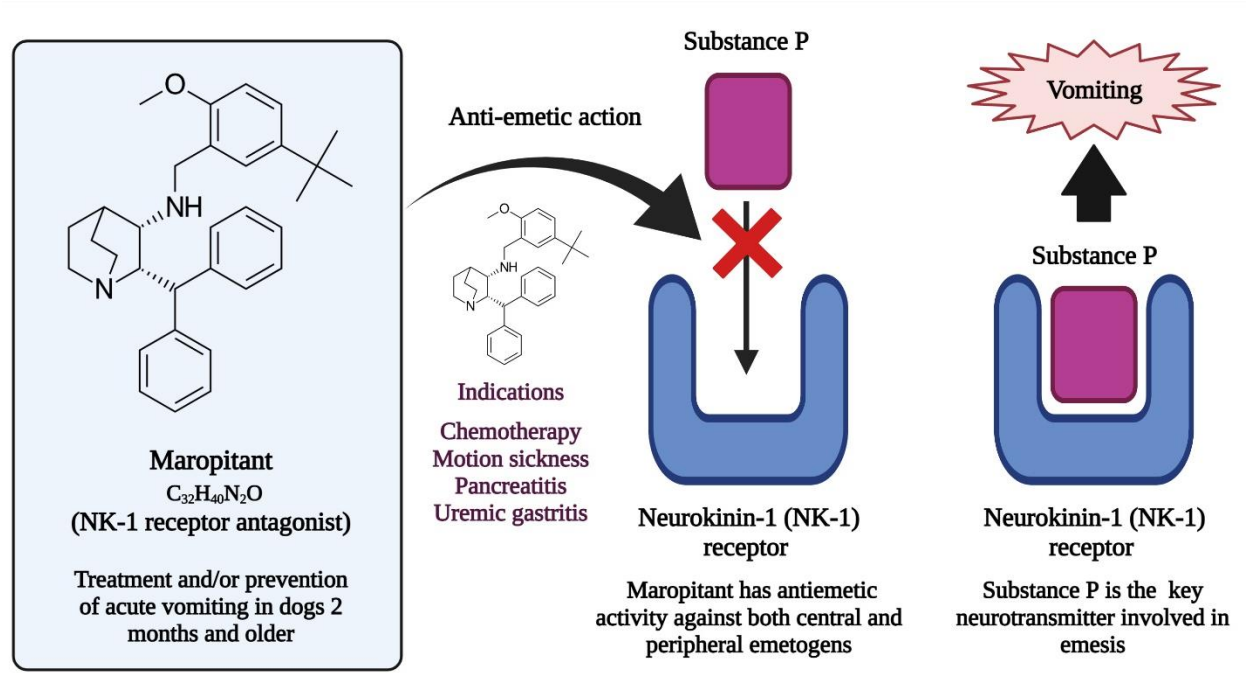

Figure 2: Illustrates the mechanism of action and indications of maropitant, a substance P (neurokinin-1) receptor antagonist used as antiemetic in dogs.