Archives of Razi Institute, Vol. 76, No. 5 (2021) 1175-1182

DOI: 10.22092/ari.2021.356171.1797

Mini Review

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

Received 19 September 2021; Accepted 9 October 2021
Corresponding Author: sharunkhansk@gmail.com

Abstract

Substance P binds to the Neurokinin-1 (NK-1) receptors found in the emetic center of the central nervous system (CNS) to induce emesis. Maropitant is a selective NK-1 receptor antagonist that inhibits the binding of substance P to NK-1 receptors and is commonly used to prevent and treat vomiting in dogs. This review study aimed 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 the existing literature on the subject during the past 20 years (2001-2021) using such databases as ScienceDirect, PubMed, Scopus, and Google Scholar. The initial search identified 173 articles; however, 41 articles were selected for further analysis, based on the specific inclusion and exclusion criteria. 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 one of the most effective veterinary antiemetic drugs that work well against peripheral and central stimuli that trigger the vomiting center. It has been already demonstrated that the therapeutic efficacy of maropitant for managing acute vomiting in dogs is associated with pancreatitis, gastritis, and parvoviral enteritis. It can also prevent and treat chemotherapy-induced emesis and delay the signs of nausea and adverse gastrointestinal effects. Regarding the broad-spectrum antiemetic activity of maropitant, it 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 percentage of isoflurane as an inhalational anesthetic. The 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. It has been shown that 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: Antiemetic, Canine medicine, Maropitant, Neurokinin-1 receptor antagonist, Renal failure

1. Context

Substance P is the first neuropeptide discovered in mammals in 1931(1). It binds to Neurokinin-1 (NK-1) receptors found in the emetic center of the CNS and induces emesis as a result (2). Therefore, selective substance P antagonists can act as potent broad-spectrum antiemetics in dogs and cats against various emetic stimuli (2). The NK-1 receptor antagonists are widely used in chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting (3, 4). The brain stem regions (i.e., area postrema and nucleus solitaries) are concerned with vomiting reflexes (5).

Recently developed NK1 receptor antagonists, such as aprepitant can cross the blood-brain barrier, which makes 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 diagnosis of tumors (8). However, the application of substance P-derived medical products is limited since endogenous substance P is a potent vasodilator mediated by nitric oxide (9).

It should be noted that NK11 is present in both the central nervous system and peripheral tissues, where it plays a role in the transmission of pain, the transition of inflammatory response at peripheral sites (e.g., gastrointestinal and respiratory tract), stress, and anxiety (10). As a selective NK-1 receptor antagonist, maropitant is approved to prevent and treat vomiting in dogs. It is also 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-anesthetic due to its antiemetic property and capacity to alleviate visceral pain originating from abdominal and thoracic organs (11). It also helps canine patients to resume food intake more quickly in the postoperative phase (12). Vasodilation and increase in vasculature permeability occur upon release of the neuropeptides from endings of the sensory nerves. These functions are blocked by the NK1 receptor antagonists when administered intra-arterially. Transdermal application of iontophoretic in animals reduces pulpal pain by blocking substance P induced pulpal blood flow in dental treatments (13).

The drug rolapitant is a highly potent, sensitive, orally active, and long-acting NK1 receptor antagonist with a half-life of 180 h (14). Another drug netupitant demonstrated synergistic effects of palonosetron through the inhibition of substance P response (13). The longer half-life overcomes the problem of repeated administration in cases of acute and delayed emesis (15). The pool of options thus helps choose the optimal regimen that best suits the animal in various aspects (e.g., cost, tolerability, availability, and safety).

2. Evidence Acquisition

This review aimed 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 the related literature in the past 20 years (2001-2021) using such databases as ScienceDirect, PubMed, Scopus, and Google Scholar. The search keywords included “substance P”, “Neurokinin-1 receptor antagonist”, “maropitant”, “antiemetic”, “uremic gastritis”, and “canine medicine”. The inclusion criteria used for selecting the related literature included the availability of information on substance P (NK-1) receptor antagonists, 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, and the relevant, critical, and most recent studies were 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) belonging to the tachykinin family (16). 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, 16). 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 (17).

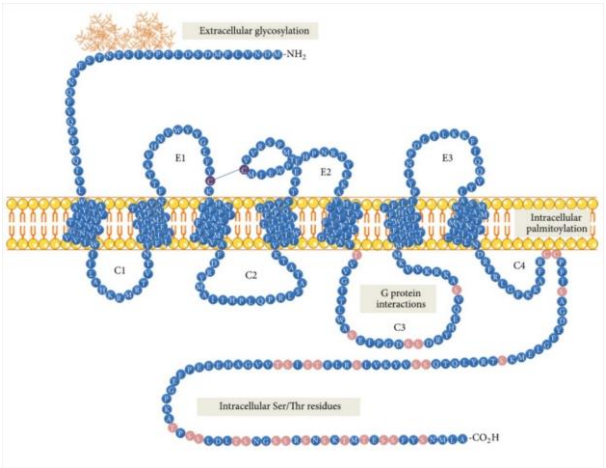

Figure 1. Schematic presentation of Neurokinin-1 (NK-1) receptor (long isoform-full length with 407 amino acids) containing an extracellular N-terminus, three extracellular loops (E1, E2, and E3), four intracellular loops (C1, C2, C3, and C4), and seven transmembrane domains. Reproduced by Garcia-Recio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

Maropitant is the first NK-1 receptor antagonist used in veterinary practice (2, 18). It is also one of the most effective veterinary antiemetic drugs that are currently in use. They work well against peripheral and central emetogens (19, 20). On the contrary, other antiemetics prevented vomiting caused by either peripheral (ondansetron) or central (chlorpromazine and metoclopramide) stimulation, not both (20). Other examples of NK-1 receptor inhibitor include aprepitant, casopitant, fosaprepitant netupitant, and rolapitant (21). 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 (17).

3.2. Broad-Spectrum Antiemetic Drug

Emesis is one of the most common signs of gastrointestinal dysfunction in small animals (19). Vomiting can cause severe dehydration, reflux esophagitis, weight loss, and aspiration pneumonia if not controlled at the early stages (2). An antiemetic is indicated when vomiting is severe and/or persistent (2, 22). They can help reduce the frequency of vomiting and prevent further aggravation of acid-base and electrolyte imbalance (2). Several pathways constitute multiple inputs, and the involvement of co-transmitters contributes to different arms of the vomiting reflex. Therefore, antiemetic drugs have to be selected based on the triggered pathway of the vomiting reflex (19). An ideal antiemetic drug will prevent both central and peripheral stimuli that trigger the vomiting center (19).

Maropitant has already demonstrated therapeutic efficacy in dogs for managing acute vomiting associated with pancreatitis, gastritis, and parvoviral enteritis (23-25). Promising results were obtained after the administration of 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 administered twice or thrice daily for the treatment of emesis associated with various etiologies in dogs (26). Maropitant can also be used to prevent and treat chemotherapy-induced emesis in dogs (27). These also delay chemotherapy-induced signs of nausea and adverse gastrointestinal effects in dogs (27, 28). Maropitant is combined with loperamide to prevent paclitaxel-induced adverse gastrointestinal effects (28). It has shown similar efficacy to ondansetron for controlling the clinical signs (e.g., vomiting) associated with parvoviral enteritis in dogs (25).

The standard antiemetic dose of maropitant for dogs is 1 mg/kg q 24h, indicating a 24-h duration of the effects (19). It is administered subcutaneously and has an elimination half-life of 4 to 8 h 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 fast for 1 h before the oral administration of maropitant at this dosage (2, 19). The absolute bioavailability of maropitant is low after oral administration (23.7% at 2 mg/kg) and higher (90.7%) when administered subcutaneously. The lower bioavailability following oral administration is due to the first-pass metabolism (18). Experimental studies

conducted in healthy adult Beagle dogs confirmed that maropitant does not have any prokinetic effect (29). Therefore, the use of maropitant as an antiemetic drug does 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 (30). This condition is commonly associated with acute renal failure or end-stage chronic renal failure (22). Renal failure-induced uremia can disrupt the integrity of epithelial tight junctions of the stomach, jejunum, ileum, and colon (31). The histopathological changes associated with uremic gastritis include glandular atrophy, fibroplasia, mast cell infiltration, edema of the lamina propria, submucosal arteritis, and mineralization (30, 32). 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) (32). 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 (33).

The high blood concentrations of gastrin are one of the possible mechanisms contributing to gastrointestinal pathology as a result of decreased renal catabolism and loss of inhibitory control over gastrin secretion (22, 34). Therefore, high levels of gastrin in the circulation can increase 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, 35). Canine uremic gastropathy affects mucosal lamina propria, and the lesions produced can be linked to diffuse vascular injury and altered parietal cell function (36). 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 to manage the gastrointestinal dysfunction associated with renal failure (22).

Maropitant has also been demonstrated to have therapeutic efficacy in managing chronic vomiting, other than acute vomiting, in cats with chronic kidney disease (23). Therefore, maropitant is ideal for the nutritional management of patients with chronic kidney disease. Regarding the broad-spectrum antiemetic activity of maropitant covering both peripheral and central emetogens (20), it can be recommended for managing uremic vomiting in dogs. Moreover, maropitant is the ideal choice for managing emesis associated with uremia since it has already demonstrated efficacy against xylazine-induced vomiting in cats (35), both of which act via the area postrema (33, 35, 37).

3.4. Perioperative Use of Maropitant

Morphine is commonly administered in the epidural space to obtain long-lasting analgesia during the postoperative period (38). However, the use of epidural opioids can induce emesis in dogs (39). Maropitant can prevent vomiting induced by morphine administration (postoperative analgesia) in dogs (38, 40). Subcutaneous administration of maropitant (1 mg/kg) 30 min before the intramuscular administration of morphine reduced the frequency of emesis (70% decrease) in dogs undergoing ovariohysterectomy (40). Similar results were obtained when maropitant was used with epidural administration of morphine in dogs (38). Maropitant can be used as a pre-anesthetic agent for ovariohysterectomy in dogs since it has been found to minimize the systolic arterial pressure and heart rate response to surgical stimulation (41). It also offered better recovery quality, and the animals are more likely to eat within 3 h post-recovery period (41).

The result of previous studies revealed that maropitant had better antiemetic efficacy than metoclopramide for preventing morphine-induced vomiting in dogs (39). In addition, maropitant also prevented hydromorphone-induced vomiting in dogs

when administered 30-45 min before the opioid (12, 42). However, the significant decrease in the incidence of vomiting was not associated with an improvement in the signs of nausea and ptyalism (42). Dogs treated with maropitant require a slightly lower percentage of isoflurane as an inhalational anesthetic (41). In addition, although intravenous administration of maropitant decreased the minimum alveolar concentration (MAC) of sevoflurane in dogs (43), epidural administration did not affect the MAC value (43). The administration of maropitant also reduced the MAC for blunting adrenergic response of sevoflurane, indicating a sparing effect on the anesthetic requirement in dogs (44). 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 (45). NK-1 receptors are identified in different areas of the pain pathways, including 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 (39, 46) (Figure 2). The pain is due to the presence of metacresol, a preservative used in some formulations (Cerenia, Zoetis) (46). Therefore, another formulation (Prevomax, Le Vet.) was developed that contained benzyl alcohol as the preservative. Maropitant formulations with benzyl alcohol were significantly less painful due to the local anesthetic properties of benzyl alcohol (46). In addition, subcutaneous injection of refrigerated maropitant (Cerenia) may significantly reduce the pain associated with it (47).

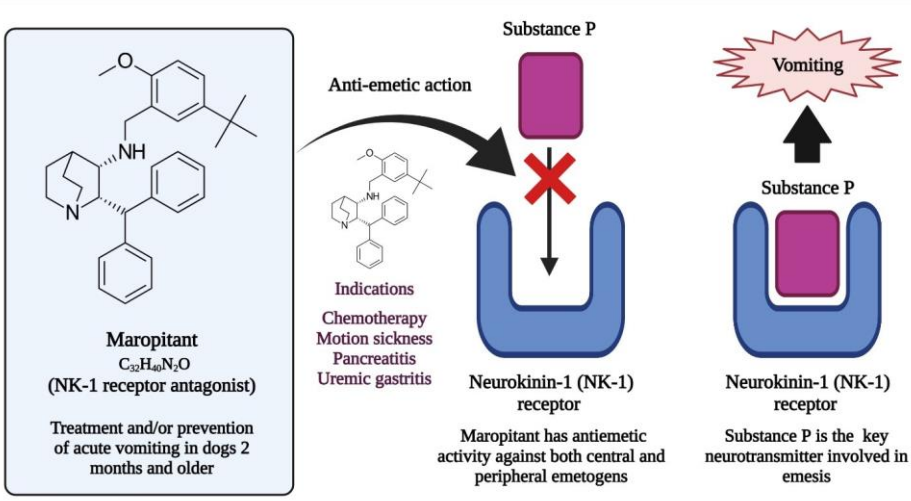

Figure 2. The mechanism of action and indications of maropitant, a substance P (neurokinin-1) receptor antagonist used as antiemetic in dogs.

4. Conclusion

Gastrointestinal dysfunction associated with renal failure is considered the major challenge during the medical management of 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 antiemetic of choice in veterinary patients for the prevention of 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 indicated 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 confirm 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.

Conflict of Interest

Authors declare that there exist no commercial or financial relationships among them that could, in any way, lead to a potential conflict of interest regarding the publication of the present study.

Grant Support

The authors did not receive any support from any ornamental, public, or non for profit organization or institutes for the present study. No funding was received to assist researchers with the preparation of this manuscript.

Acknowledgment

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

References

1. Palma C. Tachykinins and their receptors in human malignancies. Curr Drug Targets. 2006;7(8):1043-52.
2. Trepanier L. Maropitant:Novel Antiemetic .Available from: https://www.cliniciansbrief.com/article/maropitant-novel-antiemetic.
3. Aapro MS, Walko CM. Aprepitant: drug-drug interactions in perspective. Ann Oncol. 2010;21(12):2316-23.
4. Majumdar AK, Howard L, Goldberg MR, Hickey L, Constanzer M, Rothenberg PL, et al. Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. J Clin Pharmacol. 2006;46(3):291-300.
5. Garcia-Recio S, Gascon 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. 2016;10:296.
7. Munoz M, Rosso M, Gonzalez A, Saenz J, Covenas R. The broad-spectrum antitumor action of cyclosporin A is due to its tachykinin receptor antagonist pharmacological profile. Peptides. 2010;31(9):1643-8.
8. Baum RP. Therapeutic Nuclear Medicine. Heidelberg, Germany: Springer; 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;84(4):367-73.
10. Hay Kraus BL. Spotlight on the perioperative use of maropitant citrate. Vet Med (Auckl). 2017;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;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;245(9):1015-20.
13. 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. Am J Clin Oncol. 2014;32(15):20690.

14. Rapoport B, Schwartzberg L, Chasen M, Powers D, Arora S, Navari R, et al. 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;57:23-30.
15. 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). SCC. 2014;22(2):469-77.
16. Schank JR, Heilig M. Substance P and the Neurokinin-1 Receptor: The New CRF. Int Rev Neurobiol. 2017;136:151-75.
17. Polidoro G, Giancola F, Fracassi F, Pietra M, Bettini G, Asti M, et al. Substance P and the neurokinin-1 receptor expression in dog ileum with and without inflammation. Res Vet Sci. 2017;114:297-307.
18. 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;30(4):336-44.
19. Elwood C, Devauchelle P, Elliott J, Freiche V, German AJ, Gualtieri M, et al. Emesis in dogs: a review. J Small Anim Pract. 2010;51(1):4-22.
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;31(6):533-7.
21. Ibrahim MA, Preuss CV. Antiemetic Neurokinin-1 Receptor Blockers. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
22. Lefebvre H, Ferré J, Watson A. Effect of Renal Failure on Gastrointestinal Physiology in Dogs Available from : https://www.vin.com/apputil/content/defaultadv1.aspx?id=3846282&pid=11147.
23. 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;17(8):692-7.
24. Ramsey DS, Kincaid K, Watkins JA, Boucher JF, Conder GA, Eagleson JS, et al. 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;31(6):538-43.
25. 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;54(6):338-43.
26. de la Puente-Redondo VA, Siedek EM, Benchaoui HA, Tilt N, Rowan TG, Clemence RG. The anti-emetic 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. 2007;48(2):93-8.
27. 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. 2007;68(1):48-56.
28. Cartagena-Albertus JC, Engel Manchado J, Moise A, Moya Garcia 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;80(6):601-6.
29. Schmitz S, Fink T, Failing K, Borsch C, Kunz C, Clemence R, et al. Effects of the neurokinin-1 antagonist maropitant on canine gastric emptying assessed by radioscintigraphy and breath test. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2016;44(3):163-9.
30. Peters RM, Goldstein RE, Erb HN, Njaa BL. Histopathologic features of canine uremic gastropathy: a retrospective study. J Vet Intern Med. 2005;19(3):315-20.
31. 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.
32. Sanderson S. Current concepts for management of chronic renal failure in dogs: early diagnosis and supportive care. [updated 2008. Available from: https://www.dvm360.com/view/current-concepts-management-chronic-renal-failure-dogs-early-diagnosis-and-supportive-care-proceeding.
33. Borison HL, Hebertson LM. Role of medullary emetic chemoreceptor trigger zone (CT zone) in postnephrectomy vomiting in dogs. Am J Physiol. 1959;197:850-2.
34. Goldstein R, Marks S, Kass P, Cowgill L. Gastrin concentrations in plasma of cats with chronic renal failure.

J Am Vet Med Assoc. 1998;213(6):826-8.
35. Hickman MA, Cox SR, Mahabir S, Miskell C, Lin J, Bunger A, et al. 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;31(3):220-9.
36. Cheville NF. Uremic gastropathy in the dog. Vet Pathol. 1979;16(3):292-309.
37. Colby ED, McCarthy LE, Borison HL. Emetic action of xylazine on the chemoreceptor trigger zone for vomiting in cats. J Vet Pharmacol Ther. 1981;4(2):93-6.
38. 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;38(5):516-7.
39. Lorenzutti A, Martín-Flores M, Litterio N, Himelfarb M, Invaldi S, Zarazaga M. A comparison between maropitant and metoclopramide for the prevention of morphine-induced nausea and vomiting in dogs. Can Vet J. 2017;58(1):35-8.
40. Lorenzutti AM, Martin-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;43(2):195-8.
41. 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;10(10):0140734.
42. 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;28(5):1414-7.
43. 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;39(2):201-5.
44. Fukui S, Ooyama N, Tamura J, Umar MA, Ishizuka T, Itami T, et al. 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;79(3):502-8.
45. 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;72(12):1576-9.
46. 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;5(1):000262.
47. Narishetty S, Galvan B, Coscarelli E, Aleo M, Fleck T, Humphrey W, et al. Effect of refrigeration of the antiemetic Cerenia (maropitant) on pain on injection. Vet Ther. 2009;10(3):93-102.