Original Article

jfms Journal of Feline Medicine and Surgery

Maropitant administered orally 2–2.5 h prior to morphine and dexmedetomidine reduces the incidence of emesis in cats

Journal of Feline Medicine and Surgery
2017, Vol. 19(8) 876–879

DOI: 10.1177/1098612X16663595
journals.sagepub.com/home/jfms

This paper was handled and processed by the American Editorial Office (AAFP) for publication in *JFMS*

SAGE

Manuel Martin-Flores[1], Alicia Mastrocco[1], Augusto M Lorenzutti[2], Luis Campoy[1], Pati Kirch[1], Marisa Stone[1], McKenzie M Learn[1] and Jordyn M Boesch[1]

Abstract

Objectives The main goal of this study was to test the antiemetic effects of maropitant administered orally 2–2.5 h prior to morphine and dexmedetomidine in cats.

Methods Eighty-three healthy female cats were randomized to receive maropitant (8 mg orally; n = 39) or no treatment (control; n = 44), 2–2.5 h prior to morphine 0.1 mg/kg and dexmedetomidine 20 µg/kg intramuscularly. The incidence of sialorrhea, lip licking, retching and vomiting were recorded after morphine/dexmedetomidine injection.

Results There were no differences between groups in terms of age or weight. The treated group received a mean ± SD dose of maropitant of 2.9 ± 0.6 mg/kg. The incidence of sialorrhea and lip licking was no different between groups. The incidence of retching (control 36% vs maropitant 13%; $P = 0.012$) and emesis (control 32% vs maropitant 13%; $P = 0.03$) was significantly reduced in cats treated with maropitant.

Conclusions and relevance Maropitant 8 mg (total dose) administered orally 2–2.5 h prior to morphine and dexmedetomidine significantly reduced, but did not eliminate, the incidence of retching and vomiting. Maropitant did not decrease the occurrence of sialorrhea and lip licking, signs that may be indicative of nausea. Maropitant might be useful for morning administration to prevent emesis in outpatient cats requiring sedation or anesthesia; however, dose regimens or interval of administration might require improvement.

Accepted: 17 July 2016

Introduction

Maropitant is a neurokinin-1 (NK_1) receptor antagonist and a potent antiemetic agent. Its efficacy has been demonstrated in dogs receiving opioids,[1,2] and in cats receiving opioids and α_2-agonist agents.[3,4] Maropitant might therefore be a useful agent for preanesthetic medication, as both opioids and α_2-agonist agents are commonly used for sedation and prior to general anesthesia in cats, and both can induce emesis. Subcutaneous (SC) administration of maropitant (1 mg/kg) effectively prevented emesis triggered by a combination of morphine and dexmedetomidine administered intramuscularly (IM) in cats. However, SC injection of maropitant resulted in substantial discomfort in most cats.[4]

Maropitant is approved for oral (PO) administration (2 mg/kg) in dogs but not in cats.[5] Nevertheless, it was also demonstrated that PO administration of 8 mg to cats reduced morphine and dexmedetomidine-induced emesis 10-fold. In that study, maropitant was administered PO approximately 18 h prior to injection with the emetogenic agents, and it was concluded that oral maropitant could be suitable for administration the evening

[1]Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA
[2]Department of Pharmacology and Toxicology, Catholic University of Córdoba, Córdoba, Argentina

Corresponding author:
Manuel Martin-Flores MV, DACVAA, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, 930 Campus Road, Box 32, Ithaca, NY 14850, USA
Email: martinflores@cornell.edu

prior to elective procedures, to decrease the incidence of emesis without causing discomfort from SC injection.

As antiemetic medication cannot always be administered the evening prior to a procedure, in this investigation we evaluated the efficacy of oral maropitant administered shortly before injection of morphine and dexmedetomidine in cats. We hypothesized that maropitant 8 mg administered orally 2–2.5 h in advance would reduce the incidence of retching and emesis caused by morphine and dexmedetomidine in healthy female cats.

Materials and methods

This investigation was approved by the local Institutional Animal Care and Use Committee of Cornell University. After obtaining owners' informed consent, 92 female domestic shorthair cats scheduled for elective ovariohysterectomy entered this study. All cats were considered as being of American Society of Anesthesiologists physical status I, based on physical examination and blood analysis consisting of hematocrit, plasma protein, blood urea nitrogen and blood glucose concentrations. All cats were housed individually and fasted from solid food, but not water, for at least 12 h prior to inclusion in the study. Cats with a history of vomiting, inappetence, diarrhea, or those with sialorrhea or abdominal pain observed during physical examination were excluded.

Study design

This study was conducted over a 3 week period, where 8–9 cats were scheduled for ovariohysterectomy each day. On the day of surgery, each cat was randomly assigned (by removing labels from an opaque envelope) to receive maropitant (Cerenia; Zoetis) 8 mg PO, or no antiemetic treatment (control). Treatment allocation and maropitant administration were performed by three of the authors (AM, PK and MS), none of whom participated in data collection. Cats were left undisturbed after administration of maropitant until they received morphine and dexmedetomidine.

Two hours later, physical examination was completed and morphine (Morphine sulfate; Baxter Healthcare) 0.1 mg/kg and dexmedetomidine (Dexdomitor; Zoetis) 20 µg/kg (mixed in the same syringe) were administered IM by second-year veterinary medicine students, and supervised by faculty and licensed veterinary technicians. Cats were then observed for the following 30 mins for sialorrhea, lip licking, retching or emesis. Sialorrhea (collection of clear or frothy fluid around the lips, with or without dripping) and licking of the lips were documented as individual signs and recorded as yes/no variables. Retching was defined as the rhythmic contraction of diaphragmatic and abdominal muscles without expulsion of contents, regardless of whether it was followed by emesis. Emesis was defined as the forceful expulsion of gastric contents. Episodes of emesis separated by ⩾5 s were considered individual events. The time to first retch and first vomit (relative to morphine and dexmedetomidine injection), and the total number of emetic events were recorded for each cat.

Statistical analysis

Distribution of the results were evaluated with the D'Agostino–Pearson test. The significance of differences between groups for age and weight were tested with Student's *t*-tests for parametric data and the Mann–Whitney tests for non-parametric data. The significance of differences in the incidence of sialorrhea, lip licking, retching and emesis (considered all-or-none events) was measured with one-tailed Fisher's exact tests. Significance was set at 0.05, and results are summarized as mean ± SD or median (minimum–maximum) for parametric and non-parametric data, respectively. All statistical analyses were performed with computer software (GraphPad Prism 6).

Results

Six cats were excluded owing to signs of pain elicited upon abdominal palpation, or owing to sialorrhea, retching or vomiting observed prior to the administration of any agents. An additional two cats were excluded owing to violations in the sedative protocol. One additional individual was excluded because it could not be examined owing to its fractious behavior. Therefore, a total of 83 cats completed the study; 39 received maropitant and 44 did not. In one cat per group, the presence or absence of sialorrhea following the administration of the premedication was not documented. Morphine and dexmedetomidine were administered between 2 h and 10 mins, to 2 h and 30 mins after maropitant. The mean ± SD dose of maropitant was 2.9 ± 0.6 mg/kg PO.

There were no differences for age (control 8 months [range 3–36 months]; maropitant 8 months [range 2–48 months]; $P = 0.8$) or weight (control 2.9 ± 0.5 kg; maropitant 2.9 ± 0.5 kg; $P = 0.6$) between groups.

The incidences of sialorrhea, lip licking, retching and vomiting are summarized in Table 1. There were no differences between groups for sialorrhea or lip licking; however, maropitant reduced retching and emesis. Time to first retch was 3 mins (range 2–6 mins) for control and 3 mins (1–4 mins) for maropitant ($P = 0.28$), and the time to first vomit was 3 mins (range 2–5 mins) for control and 3 mins (range 1–5 mins) for maropitant ($P = 0.35$). When emesis occurred, the number of emetic events was 1 (range 1–2) for control and 1 (range 1–3) for maropitant ($P = 0.2$).

Discussion

The main finding of our investigation was that the incidences of retching and emesis caused by morphine and dexmedetomidine administration were significantly reduced, but not eliminated, when maropitant 8 mg was administered PO approximately 2 h prior to premedication with an opioid (morphine) and an α_2-agonist (dexmedetomidine).

Table 1 Incidence of sialorrhea, lip licking, retching and emesis in cats receiving maropitant 8 mg orally administered 2–2.5 h prior to dexmedetomidine 20 µg/kg and morphine 0.1 mg/kg intramuscularly, and in cats not treated with antiemetic (control)

	Sialorrhea	Lip licking	Retch	Emesis
Control	4/43 (9%)	17/44 (39%)	16/44 (36%)	14/44 (32%)
Maropitant	8/38 (21%)	11/39 (28%)	5/39 (13%)	5/39 (13%)
P value	0.12	0.22	0.012	0.03

Previous work with maropitant in cats showed that SC administration (1 mg/kg) was highly efficacious at preventing emesis induced by the administration of morphine and dexmedetomidine; the incidence of emesis was decreased from 59% in the control group to 3% in the maropitant group.[4] However, the authors reported substantial discomfort in several individuals following the injection of maropitant into the SC space. A similar observation regarding discomfort from SC injections was also reported in dogs receiving maropitant.[6] As an alternative, oral administration of maropitant was studied in cats receiving morphine and dexmedetomidine.[3] In that study, oral administration of maropitant 8 mg (total dose) ~18 h prior to anesthetic premedication, reduced the incidence of emesis from 40% to 4%; only one cat in the treated group vomited. Those results suggested that maropitant 8 mg PO could be administered the evening prior to a scheduled procedure in order to reduce the incidence of emesis from α_2-agonists and opioids. This route of administration, albeit not currently licensed for cats, appears as a good alternative under those circumstances, to replace the less comfortable SC injection.

In the present investigation, we evaluated the effects of maropitant when administered approximately 2 h prior to morphine and dexmedetomidine; as it is not always possible to medicate cats with an antiemetic agent the evening prior to a scheduled procedure, administration of maropitant close to the time of premedication could be used to reduce the risks of emesis in outpatient cats. We selected a period of approximately 2 h for two reasons. First, information in dogs suggest that peak plasma concentration after oral administration of 2 mg/kg occurs in an average of 2 h.[5] In cats, oral maropitant 1 mg/kg produced peak plasma levels between 2 and 3 h[7]; moreover, maropitant 1 mg/kg orally administered 2 h prior to xylazine reduced the emetic events by 90%.[7] Therefore, we considered that 2 h might be the shortest potential interval. Second, a period of 2 h to administer an antiemetic prior to sedation would still be practical in our service, given the time intervals between admission and sedation. The actual time interval between maropitant administration and morphine and dexmedetomidine injection in our cats exceeded 2 h by 10–30 mins. At the dose administered, maropitant reduced the incidence of retching and emesis significantly; however, this effect was less than previously reported.[3,4,7]

Considering that xylazine-induced emesis was reduced by 90% when maropitant 1 mg/kg was administered orally 2 h in advance,[7] we expected that our dose (2.9 mg/kg in average) would have resulted in higher antiemetic efficacy. Moreover, maropitant 2.5 mg/kg administered orally 18 h prior to morphine and dexmedetomidine almost completely prevented emesis.[3] There are several possible explanations for the apparent reduced efficacy in this study. It is possible that in some cats, plasma concentrations of maropitant might have been insufficient to prevent emesis. Peak plasma concentration is expected to occur 2–3 h postadministration,[7] and hence a longer interval might have been required in some animals before peak concentrations were reached. It is also possible that an even longer period is required before sufficient effector-site concentrations are reached, as further passage is required for the drug to reach the NK_1 receptors. In other words, it might be possible that plasma concentration is not directly related to clinical effect. In addition, the emetic potential of morphine and dexmedetomidine might differ from that of xylazine, which could, at least in part, explain the discrepancies between our results and those reported by Hickman et al.[7] It is expected that more effective antiemesis could be achieved by allowing longer time between maropitant administration and injection of sedatives.

The incidences of sialorrhea and lip licking were not reduced by maropitant administration. This observation has been previously reported in cats, and in dogs.[8,9] Sialorrhea and lip licking are commonly considered signs associated with nausea; however, assessment of nausea remains subjective. The results of this work, and those from prior reports suggest that, if sialorrhea and lip-licking do, in fact, represent nausea, the antinausea effect of maropitant might not be as effective as its antiemetic effect. Emesis is a complex response to a variety of stimuli. In people, it can be divided into three phases; nausea (an inclination to vomit), retching (involuntary effort to vomit) and vomiting (ejection of gastric contents).[10] It is unclear why treatment with maropitant reduced the incidence of emesis but did not appear to reduce the incidence of nausea in cats and dogs. Several possibilities can be speculated, including our inability to diagnose nausea in animals, the possibility of nausea being triggered by the activation of NK_1 receptors by a mechanisms other than substance P (and hence not prevented by maropitant), or, alternatively, the variable

effect of maropitant at different sites through the emesis pathway; namely, the area postrema, the nucleus tractus solitarius and the dorsal motor nucleus of the vagus.[10] For example, it has been reported that the activity of NK_1 antagonists appears to be more intense at the nucleus tractus solitarius than at the area postrema.[11] In other words, maropitant may not prevent the agonist activity of substance P in all areas with similar efficacy.

In the current study, the incidence of retching and emesis in the control group was noticeably lower than in previous reports,[3,4] when similar populations of cats received the same opioid and α_2-agonist combinations. Previously, the incidence of retching and emesis after morphine 0.1 mg/kg and dexmedetomidine 20 µg/kg ranged between 40% and 59%, whereas in this current study the incidences of retching and emesis were 36% and 32%, respectively. We cannot speculate on the reason for this decrease in the incidence of emesis, considering that the same agents and doses were administered to healthy female cats in every study.

Prolonged PO maropitant treatment has been studied previously in cats with chronic kidney disease. In that study, 4 mg was administered daily to affected cats for 14 days.[12] No adverse effects were attributed to maropitant administration. The apparent safety of maropitant for oral administration in cats, combined with the data demonstrated its efficacy to prevent opioid and α_2-induced emesis, suggest that maropitant could be used to increase the comfort of cats requiring sedation or anesthesia that include those emetogenic agents. While the use of antiemetic agents is clearly indicated in animals in which retching or vomiting could have serious consequences (eg, increased intraocular or intracranial pressure), perioperative emesis might not represent a major risk to healthy animals undergoing elective procedures. Nonetheless, nausea, retching and emesis are commonly considered uncomfortable, and antiemetic medication might enhance the overall quality of the procedure. It was recently reported that the majority of dog owners are concerned about the negative impact of nausea and vomiting, and the majority of these owners (99%) would probably (48%) or definitely (51%) choose treatment to prevent nausea and vomiting.[13] Moreover, the average amount that owners were willing to pay for antinausea/emetic treatment was US$ 75.[13] At the time of writing, the acquisition cost for maropitant 16 mg at our institution was US$ 1.88. These values might be relevant when deciding whether to offer perioperative antiemetic treatment to healthy cats.

Conclusions

Maropitant 8 mg PO (average of 2.9 mg/kg) significantly reduced the incidence of retching and emesis in cats receiving morphine and dexmedetomidine as part of preanesthetic medication. It is likely that a longer interval between maropitant administration and preanesthetic medication might result in higher antiemetic efficacy. These results suggest that maropitant might be useful for morning administration to prevent emesis in outpatient cats requiring sedation or anesthesia; however, dose regimens or interval of administration might require improvement.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

References

1 Hay Kraus BL. **Efficacy of maropitant in preventing vomiting in dogs premedicated with hydromorphone**. *Vet Anaesth Analg* 2013; 40: 28–34.
2 Claude AK, Dedeaux A, Chiavaccini L, et al. **Effects of maropitant citrate or acepromazine on the incidence of adverse events associated with hydromorphone premedication in dogs**. *J Vet Intern Med* 2014; 28: 1414–1417.
3 Martin-Flores M, Sakai DM, Mastrocco A, et al. **Evaluation of oral maropitant as an antiemetic in cats receiving morphine and dexmedetomidine**. *J Feline Med Surg* 2016; 18: 921–924.
4 Martin-Flores M, Sakai DM, Learn MM, et al. **Effects of maropitant in cats receiving dexmedetomidine and morphine**. *J Am Vet Med Assoc* 2016; 248: 1257–1261.
5 Cerenia (maropitant citrate) [package insert]. Zoetis, Kalamazoo, MI.
6 Lorenzutti AM, Martin-Flores M, Litterio NJ, et al. **A comparison between maropitant and metoclopramide for the prevention of morphine-induced nausea and vomiting in dogs**. *Can Vet J* 2017; 58: 35–38.
7 Hickman MA, Cox SR, Mahabir S, 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: 220–229.
8 Hay Kraus BL. **Efficacy of orally administered maropitant citrate in preventing vomiting associated wuth hydromorphone administration in dogs**. *J Am Vet Med Assoc* 2014; 244: 1164–1169.
9 Lorenzutti AM, Martin-Flores M, Litterio NJ, et al. **Evaluation of the antiemetic efficacy of maropitant in dogs medicated with morphine and acepromazine**. *Vet Anaesth Analg* 2016; 43: 195–198.
10 Gan TJ. **Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy**. *CNS Drugs* 2007; 21: 813–833.
11 Saito R, Takano Y and Kamiya H. **Roles of substance P and NK_1 receptor in the brainstem in the development of emesis**. *J Pharmacol Sci* 2003; 91: 87–94.
12 Quimby JM, Brock WT, Moses K, et al. **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: 692–697.
13 Kraus B and Cazlan C. **Assessment of dog owner concern regarding perioperative nausea and vomiting and willingness to pay for antiemetic treatment**. *Vet Anaesth Analg* 2015; 42: A58.