Article

A comparison between maropitant and metoclopramide for the prevention of morphine-induced nausea and vomiting in dogs

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Abstract — Morphine is widely used as a preanesthetic agent in dogs, but it often produces signs of nausea and vomiting. Maropitant (MRP) and metoclopramide (MCP) prevent emesis attributable to the opioid agent apomorphine in dogs. We evaluated the antiemetic efficacy and the discomfort in response to SQ injection of MRP [1 mg/kg body weight (BW)], MCP (0.5 mg/kg BW), and normal saline (SAL; 0.1 mL/kg BW) administered to 63 dogs, 45 minutes prior to morphine (0.5 mg/kg BW) and acepromazine (0.05 mg/kg BW). Dogs were observed for signs of nausea (ptyalism, lip licking, and increased swallowing) and vomiting for 30 minutes after morphine/acepromazine. The incidence of emesis was 0% for MRP, 38% for MCP, and 71% for SAL ($P < 0.001$). The incidence of signs of nausea was not different between groups. Discomfort due to injection was higher after MRP (48%), than after MCP (9.8%) and SAL (4.8%) ($P < 0.001$).

Résumé — Comparaison entre le maropitant et la métoclopramide pour la prévention de nausée et des vomissements induits par la morphine chez les chiens. La morphine est largement utilisée comme agent préanesthésique chez les chiens, mais elle produit souvent des symptômes de nausée et de vomissements. Le maropitant (MRP) et la métoclopramide (MCP) préviennent le vomissement causé par l'agent opioïde apomorphine chez les chiens. Nous avons évalué l'efficacité antiémétique et l'inconfort en réponse à une injection SC de MRP [1 mg/kg de poids corporel (PC)], de MCP (0,5 mg/kg PC) et d'une solution saline normale (SAL; 0,1 mL/kg PC) administrée à 63 chiens, 45 minutes avant la morphine (0,5 mg/kg PC) et l'acépromazine (0,05 mg/kg PC). Les chiens ont été observés pour détecter des signes de nausée (ptyalisme, lèchement des lèvres et déglutition accrue) et le vomissement pendant 30 minutes après l'administration de morphine/acépromazine. L'incidence du vomissement était de 0 % pour MRP, de 38 % pour MCP et de 71 % pour SAL ($P < 0{,}001$). L'incidence des signes de nausée n'était pas différente entre les groupes. L'inconfort attribuable à l'injection était supérieur après MRP (48 %) par rapport à celui après MCP (9,8 %) et SAL (4,8 %) ($P < 0{,}001$).

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Introduction

Morphine and acepromazine are widely used as preanesthetic agents in dogs. However, morphine produces gastrointestinal disturbances including constipation, salivation, signs of nausea, and vomiting (1), the latter two being particularly important as they not only produce discomfort, but may also increase the risk for aspiration of the vomitus (2,3). Morphine is a potent emetogenic agent; the incidence of emesis ranges between 50% and 75% after IM administration of 0.5 mg/kg body weight (BW) (4,5). Acepromazine is commonly administered with morphine, and while it has antiemetic effects *via* dopamine D2 receptor antagonism, its use reduces, but does not eliminate the incidence of morphine-induced emesis when administered simultaneously with morphine (4).

Additional antiemetic agents might be used to prevent signs of nausea and vomiting and improve the overall quality and comfort of the peri-anesthetic period. Maropitant (MRP) is a neurokinin-1 receptor antagonist that inhibits substance P and has potent anti-emetic effects (6). Maropitant completely prevented morphine-induced vomiting when administered SQ 30 to 45 min prior to an opioid (7,8). Administration of MRP, however, does not consistently reduce signs of nausea (7,9) or the incidence of gastroesophageal reflux (10), and causes pain at the injection site (5,8,11).

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Table 1. Age, weight [median (minimum – maximum)] and gender distribution in groups MRP, MCP, and SAL

	Group			
Variable	MRP (n = 21)	MCP (n = 21)	SAL (n = 21)	P-value
Age (years)	3.0 (1.5 to 10.0)	3.0 (0.5 to 7.0)	3.0 (0.5 to 8.5)	0.852
Weight (kg)	13.7 (7.9 to 33.0)	13.8 (4.0 to 27.0)	14.0 (5.0 to 26.0)	0.801
Gender (males)	7/21	9/21	8/21	0.817

MRP — maropitant; MCP — metoclopramide; SAL — saline.

Table 2. Incidence of nausea, retching, and vomiting in dogs administered maropitant (MRP; 1 mg/kg BW), metoclopramide (MCP; 0.5 mg/kg BW), or normal saline (SAL; 0.1 mL/kg BW) SQ, 45 min prior to morphine (0.5 mg/kg BW) and acepromazine (0.05 mg/kg BW). The time to first emetic event, number of emetic events per dog [median (minimum – maximum)] and the incidence of pain after injection are also reported. Different superscript letters indicate significant differences between groups

Variable	MRP (n = 21)	MCP (n = 21)	SAL (n = 21)	P-value
Nausea	16/21 (76%)[a]	15/21 (71%)[a]	17/21 (81%)[a]	0.769
Retching	1/21 (4.8%)[a]	6/21 (29%)[b]	9/21 (43%)[b]	0.016
Vomiting	0/21 (0%)[a]	8/21 (38%)[b]	15/21 (71%)[c]	< 0.001
Emetic events	—	1.0 (1.0 to 3.0)[a]	1.0 (1.0 to 3.0)[a]	0.591
Time to first emesis (min)	—	3.9 (2.0 to 11.5)[a]	7.1 (3.8 to 10.2)[a]	0.093
Pain	10/21 (48%)[a]	2/21 (9.5%)[b]	1/21 (4.8%)[b]	< 0.001

MRP — maropitant; MCP — metoclopramide; SAL — saline.

Metoclopramide (MCP) exerts its antiemetic effects *via* dopamine D2 and serotonin 5-HT3 antagonism. Additionally, it has a prokinetic effect in the upper segment of the gastrointestinal tract *via* serotonin 5-HT4 agonism; it increases the tone of the lower esophageal sphincter, and increases gastric and duodenal motility (12). The antiemetic efficacy of subcutaneous MCP for apomorphine-induced emesis in dogs is similar to that of MRP (13). Moreover, MCP reduces the incidence of gastroesophageal reflux in anesthetized dogs (14). To our knowledge, it has not been reported that MCP injection results in pain. Providing similar efficacies in preventing opioid-induced emesis, there might be advantages to the use of MCP in the perianesthetic period in dogs.

In this investigation we evaluated the anti-nausea and antiemetic effects of MRP and MCP, administered 45 min prior to morphine/acepromazine to healthy dogs. Our null hypothesis was that the incidences of signs of nausea and vomiting would be equal for both agents. In addition, we evaluated signs of discomfort after subcutaneous administration of either antiemetic agent.

Materials and methods

This study was approved by the Committee on Bioethics and Animal Welfare of Universidad Católica de Córdoba. We enrolled 63 adult mixed-breed dogs, American Society of Anesthesiology (ASA) classification I (based on physical examination, complete blood cell count and basic serum biochemistry consisting of total serum protein, blood urea nitrogen, and blood glucose), and scheduled for orchiectomy or ovariohysterectomy as part of a canine population control program. Owner's consent was requested prior to the inclusion of the animals in the study. Solid food was withheld overnight but dogs had access to water until 1 h prior to the beginning of the study. Dogs with a history of vomiting, inappetence, diarrhea, abdominal pain, or concurrent treatment with drugs that affect gastrointestinal motility or produce signs of nausea and vomiting in the last month were excluded. This study was designed as a randomized, blinded, prospective controlled trial, and was completed within a period of 1 mo. The experiments were carried out 3 days a week, in groups of 4 to 6 animals. Dogs were weighed prior to the beginning of the experiment, as part of the pre-surgical physical examination. All dogs received morphine 1% (Amidiaz; Laboratorios Richmond, Buenos Aires, Argentina), 0.5 mg/kg BW, IM, and acepromazine 1% (Acedan; Laboratorios Hollyday, Buenos Aires, Argentina), 0.05 mg/kg BW, IM, in the middle gluteal muscle at time zero, as part of their preanesthetic medication. Dogs were randomly assigned to 1 of 3 treatment groups of 21 animals each by extracting labels from an opaque envelope: MRP 1% (Cerenia; Pfizer PGM, Pocé sur Cisse, France), 1 mg/kg BW; MCP 0.5% (Pileran; Laboratorios Hollyday), 0.5 mg/kg BW; and a control group receiving normal saline (SAL; 0.1 mL/kg BW). MRP, MCP or SAL was administered SQ between the shoulders 45 min before morphine and acepromazine by 1 investigator (MAH) who was unaware of treatment allocation. The dogs were observed for signs of discomfort after injection of the treatment solutions. Discomfort to injection was considered to occur when the dogs vocalized and/or attempted to bite the skin at the site of injection, immediately after administration of either solution. After the administration of morphine/acepromazine, each dog was observed continuously for 30 min for signs of nausea (ptyalism, lip licking, and increased swallowing), retching, or vomiting. Vomiting was recorded when there was expulsion of gastric contents through forceful contractions of the abdominal muscles, and retching was considered as a nonproductive act of vomiting. In dogs that vomited, the time to the first emesis and the number of emetic events per dog were recorded. Dogs were observed for signs of nausea, retching, and vomiting by 5th-year

veterinary medicine students who registered each event. All students were supervised by 3 of the authors (NJL, MPZ, SHI); the students and supervisors were unaware of treatment allocation.

Statistical analysis

Data were analyzed using commercial software (InfoStat 2008; Grupo InfoStat, FCA, Argentina). Nonparametric distribution of all continuous variables was confirmed with the Shapiro-Wilk test. Age, body weight, and distribution of gender were compared between groups with the Kruskal-Wallis test by ranks. The incidence of signs of nausea, retching, and vomiting, and the incidence of discomfort to treatment administration were compared between groups with Chi-square tests. Time to first emesis and the number of emetic events per dog were also compared between groups with the Kruskal-Wallis test by ranks. Results are reported as median (minimum-maximum). Significance was set at 5% throughout.

Results

All animals completed the study. No differences were observed between groups for age, body weight, and gender (Table 1). The incidence of signs of nausea was not different between the 3 groups (Table 2). Retching occurred less frequently with MRP than in the 2 other groups, and was not different between MCP and SAL. Maropitant prevented emesis, and MCP reduced its incidence compared with SAL (Table 2). When emesis occurred, the number of emetic events per dog and the time to first emetic event were not different between MCP and SAL.

Discomfort following injection was observed more frequently with MRP than in the 2 other groups (Table 2).

Discussion

The main findings of this study are that MRP (1 mg/kg BW) administered SQ 45 min prior to morphine and acepromazine prevented vomiting and substantially reduced the incidence of retching, but did not reduce the incidence of signs of nausea in dogs. The efficacy of MCP as an antiemetic was less than that of MRP; it reduced the incidence of vomiting by ~50% compared with saline, and it did not produce a noticeable reduction of signs of nausea.

The high efficacy of MRP to prevent opioid-induced emesis is in accord with previous findings. MRP (1 mg/kg BW, SQ) abolished emesis induced by hydromorphone when administered 30 to 45 min prior to the opioid (7,8). MRP (1 mg/kg BW, SQ) was also evaluated in dogs receiving morphine; in that study, it reduced morphine-induced emesis by 70% when administered 30 min in advance (9). The apparent lower efficacy between both studies might be the result of insufficient time for MRP to peak, or differences in the emetogenic potencies of the 2 opioids: the incidence of emesis after IM administration of morphine (0.5 mg/kg BW) was 75% while that of hydromorphone (0.1 mg/kg BW) was 44% (4). In our study, we increased the interval between MRP and morphine administration to 45 min, and this resulted in 100% reduction of emesis in that group. Taken together, these data suggest that when used to prevent emesis from morphine, >30 min are necessary for MRP to exert its maximal effect.

In the present study, MCP (0.5 mg/kg BW, SQ) reduced the incidence of emesis by 53%, which was significantly lower than that produced by MRP. This observation is at odds with previous findings showing that MCP (0.5 mg/kg BW) prevented apomorphine-induced emesis in dogs. Apomorphine is typically considered a potent emetogenic agent, and it shares with morphine the mechanisms for producing vomiting. This discrepancy between the results of that study and ours highlights the limitations of extrapolating data when different emetogenic agents are used. In closer agreement with our current results, the antiemetic efficacy of MCP was less than that of MRP when emesis was the result of various disease processes, including gastroenteritis, pancreatitis, uremia, and poisoning (11).

Signs associated with nausea were not reduced by the administration of either MRP or MCP. These findings are in agreement with previous reports showing a limited effect of MRP (1 mg/kg BW, SQ) (7,8,15) and MCP (0.55 mg/kg BW, IM) (15) as anti-nausea medication against other emetogenic agents, such as lycorine (2 mg/kg BW, SQ) and hydromorphone (0.1 to 0.2 mg/kg BW, IM). Only MRP (1 mg/kg BW) prevented signs of nausea when administered SQ 60 min before administration of hydromorphone (0.1 mg/kg BW, IM) (8).

The number of emetic events and time to first emesis in those dogs that vomited was not different between groups MCP and SAL. Most dogs vomited before 10 min in both groups, with only 1 dog in group MCP and 2 dogs in group SAL vomiting after 10 min. We saw no evidence that MCP (0.5 mg/kg BW, SQ) either reduced the number of emetic events per dog, or delayed the onset of emesis; it appears that emesis is either prevented or not in each individual dog, as an all-or-none phenomenon.

In the present study, 48% of the dogs receiving MRP (1 mg/kg BW) showed signs of discomfort after SQ injection, and this was significantly higher than the 9.5% in those receiving MCP (0.5 mg/kg) or the 4.8% receiving SAL (0.1 mL/kg BW). Behavioral signs of discomfort were transient, and resolved quickly. The incidence of this adverse reaction in our study was higher than that reported by the manufacturer (4%) or other authors (4 to 11%) (8,5,11). The discrepancy between our results and those from other authors is likely due to different criteria for evaluating the dogs' responses to injections. A study in cats reported a high incidence of adverse reactions to SQ administration of MRP (1 mg/kg BW) (16). Moreover, those authors suggested that the responses were often severe.

In summary, our results show that MRP prevents vomiting, and that MCP has a moderate antiemetic efficacy, when either antiemetic agent was administered 45 min prior to morphine and acepromazine. Neither agent was effective in preventing signs of nausea. Injection of MRP was associated with signs of discomfort more frequently than occurred with MCP or saline.

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References

1. Lamont LA, Mathews KA. Opiods, nonsteroidal anti-inflammatories and analgesic adjuvants. In: Tranquilli WJ, Thurmon JC, Grimm KA, eds. Lumb & Jones' Veterinary Anesthesia and Analgesia. 4th ed. Oxford, United Kingdom: Blackwell Publishing, 2007:241–271.
2. Alwood AJ, Brainard BM, LaFond E, Drovatz KJ, King LG. Postoperative pulmonary complications in dogs undergoing laparotomy: Frequency, characterization and disease related risk factors. J Vet Emerg Crit Care 2006;16:176–183.
3. Tart KM, Babski DM, Lee JA. Potential risks, prognostic indicators, and diagnostic and treatment modalities affecting survival in dogs with presumptive aspiration pneumonia: 125 cases (2005–2008). J Vet Emerg Crit Care 2010;20:319–329.
4. Valverde A, Cantwell S, Hernández J, Brotherson C. Effects of acepromacine on the incidence of vomiting associated with opioid administration in dogs. Vet Anaesth Analg 2004;31:40–45.
5. Koh RB, Isaza N, Xie H, Cooke K, Robertson SA. Effects of maropitant, acepromazine, and electroacupuncture on vomiting associated with administration of morphine in dogs. J Am Vet Med Assoc 2014; 244:820–829.
6. 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 Therap 2007;0:336–344.
7. 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;28:1414–1417.
8. 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;245:1015–1020.
9. 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;43:195–198.
10. Johnson RA. Maropitant prevented vomiting but not gastroesophageal reflux in anesthetized dogs premedicated with acepromazine-hydromorphone. Vet Anaesth Analg 2014;41:406–410.
11. de la Puente-Rendondo 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;48:93–98.
12. Papich MG. Drugs affecting gastrointestinal function. In: Riviere JE, Papich MG, eds. Veterinary Pharmacology & Therapeutics. 9th ed. Ames, Iowa: Blackwell Publishing, 2009:1247–1272.
13. 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 Therap 2008;31:533–537.
14. Wilson DV, Evans TA, Mauer WA. Influence of metoclopramide on gastroesophageal reflux in anesthetized dogs. Am J Vet Res 2006;67:26–31.
15. Kretzing S, Abraham G, Seiwert B, et al. In vivo assessment of antiemetic drugs and mechanism of lycorine-induced nausea and emesis. Arch Toxicol 2011;85:1565–1573.
16. Martín-Flores M, Sakai DM, McKenzie LM, et al. Maropitant reduces the incidence of emesis, but produces discomfort after injection, in cats receiving dexmedetomidine and morphine. J Am Vet Med Assoc 2015. In press.