Comparative evaluation of the antiemetic and propofol-sparing effects of acepromazine and maropitant in female dogs undergoing elective ovariohysterectomy

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Abstract

Nausea and vomiting are frequent adverse effects associated with opioid administration, potentially leading to discomfort, risk of aspiration, and reduced postoperative appetite. This study aimed to compare the efficacy of acepromazine and maropitant in preventing morphine-induced nausea and vomiting, to evaluate their propofol-sparing effects, and to assess postoperative appetite in female dogs undergoing elective ovariohysterectomy (OHE). Twenty-four young, healthy female dogs (mean age 32.7 ± 26 months; mean body weight 6.8 ± 3 kg) were included. The animals received an intravenous injection of maropitant (1 mg/kg; GM), acepromazine (0.02 mg/kg; GA), or saline (GS), 30 minutes before the intramuscular administration of morphine (0.5 mg/kg). The incidence of nausea and vomiting was recorded over 30 minutes following morphine administration. Sedation scores, propofol requirements for anaesthetic induction, and postoperative appetite were also evaluated. Compared to saline, maropitant and acepromazine reduced the incidence of vomiting in 100% and 37.5% of the animals, respectively. None of the treatments prevented nausea. Acepromazine induced greater sedation and reduced the propofol dose required for anaesthetic induction in comparison to maropitant and saline. Postoperative appetite recovery did not differ significantly among groups. Despite the small sample size and the limited observation period, it is concluded that maropitant effectively prevents morphine-induced vomiting without sedative or propofol-sparing effects. Conversely, acepromazine does not prevent emesis but provides deeper sedation and reduces the requirement for propofol. Neither drug demonstrated efficacy in managing nausea or enhancing postoperative appetite in healthy female dogs undergoing elective OHE.

Keywords: emesis; NK-1 receptor antagonist; opioids; phenothiazines; preanaesthetic medication.

Avaliação comparativa dos efeitos antieméticos e poupadores de propofol da acepromazina e do maropitant em cadelas submetidas à ovariohisterectomia eletiva

Resumo

Náuseas e vômitos são efeitos adversos frequentes associados à administração de opioides, podendo levar a desconforto, risco de aspiração e redução do apetite pós-operatório. Este estudo teve como objetivo comparar a eficácia da acepromazina e do maropitant na prevenção de náuseas e vômitos induzidos por morfina, avaliar seus efeitos poupadores de propofol e avaliar o apetite pós-operatório em cadelas submetidas à ovariohisterectomia eletiva (OHE). Vinte e quatro cadelas jovens e saudáveis (idade média de 32,7 ± 26 meses; peso corporal médio de 6,8 ± 3 kg) foram incluídas. Os animais receberam uma injeção intravenosa de maropitant (1 mg/kg; GM), acepromazina (0,02 mg/kg; GA) ou solução salina (GS), 30 minutos antes da administração intramuscular de morfina (0,5 mg/kg). A incidência de náuseas e vômitos foi registrada ao longo de 30 minutos após a administração de morfina. Os escores de sedação, a necessidade de propofol para indução anestésica e o apetite pós-operatório também foram avaliados. Comparados à solução salina, o maropitant e a acepromazina reduziram a incidência de vômitos em 100% e 37,5% dos animais, respectivamente. Nenhum dos tratamentos preveniu náuseas. A acepromazina induziu maior sedação e reduziu a dose de propofol necessária para a indução anestésica em comparação ao maropitant e à solução salina. A recuperação do apetite pós-operatória não diferiu significativamente entre os grupos. Apesar do pequeno tamanho da amostra e do período de observação limitado, conclui-se que o maropitant previne efetivamente o vômito induzido por morfina sem efeitos sedativos ou poupadores de propofol.

Por outro lado, a acepromazina não previne a êmese, mas proporciona sedação mais profunda e reduz a necessidade de propofol. Nenhum dos dois medicamentos demonstrou eficácia no controle da náusea ou na melhora do apetite pós-operatório em cadelas saudáveis submetidas à OHE eletiva.
Palavras-chave: *antagonista do receptor NK-1; êmese; fenotiazinas; medicação pré-anestésica; opioides.*

1 Introduction

Opioids are frequently administered during the preoperative period due to their analgesic and sedative properties (Valverde *et al*., 2004). Among these, morphine is commonly used in canine patients (Marquez *et al*., 2015), although its use is associated with adverse effects such as nausea and vomiting (Lorenzutti *et al*., 2016; Valverde *et al*., 2004). These effects may result from the direct stimulation of the chemoreceptor trigger zone (CTZ) of vomiting, located in the fourth ventricle of the brainstem, through interactions with dopamine, histamine, and neurokinin-1 (NK1) receptors (Blancquaert *et al*., 1986; Mallick-Searle; Fillman, 2017).

The prevention of nausea and vomiting is essential to ensure patient comfort and safety, as emesis may impair central venous return and increase intraocular and intracranial pressures (Cunningham; Barry, 1986), and may also predispose patients to aspiration pneumonia (Claude *et al*., 2014). Therefore, effective strategies are required to mitigate the incidence of vomiting induced by emetogenic agents, such as opioids and alpha-2 adrenergic agonists (Claude *et al*., 2014; Lorenzutti *et al*., 2016).

Although antiemetic drugs such as ondansetron and metoclopramide are effective in various contexts, they are not consistently successful in preventing morphine-induced emesis (Lorenzutti *et al*., 2017). Acepromazine, a phenothiazine derivative, has been shown to reduce the incidence of vomiting and to enhance sedation, thereby reducing the need for general anesthetics. However, its antiemetic efficacy is limited to approximately 70% (Claude *et al*., 2014; Smith *et al*., 2001; Valverde *et al*., 2004).

More recently, maropitant has gained attention for its potent antiemetic properties through NK-1 receptor antagonism. This pharmacological profile confers efficacy against a broad range of emetogenic stimuli, including opioids (Claude *et al*., 2014; Kenward *et al*., 2016). Furthermore, maropitant has been reported to reduce anesthetic requirements (Fukui *et al*., 2017; Okano *et al*., 2015; Swallow *et al*., 2017), possibly through central or peripheral NK-1 receptor blockade (Alvillar *et al*., 2012).

Postoperative appetite recovery is a key component of Enhanced Recovery After Surgery (ERAS) protocols, which aim to minimize surgical stress, support the early restoration of physiological function, and reduce hospitalization time. Early voluntary food intake contributes to improved gastrointestinal recovery, decreases postoperative complications, and is associated with earlier discharge (Melnyk et al., 2011). In this context, Carcéles et al. (2025) reported that the preoperative administration of maropitant at 1 mg/kg in dogs indirectly facilitated the earlier recovery of spontaneous oral intake, potentially contributing to postoperative recovery and earlier hospital discharge.

Given the limited number of studies directly comparing the effects of maropitant and acepromazine on the prevention of vomiting (Claude et al., 2014), as well as the scarcity of data regarding their impact on nausea and postoperative appetite recovery, further investigation is warranted. Moreover, the potential anesthetic-sparing effects of these drugs, particularly during induction with propofol, remain underexplored. Therefore, the objective of the present study was to compare the efficacy of acepromazine and maropitant in preventing morphine-induced nausea and vomiting, as well as to evaluate their propofol-sparing effects during anesthesia induction and their influence on postoperative appetite recovery in female dogs undergoing elective ovariohysterectomy.

2 Material and methods

This prospective, randomized clinical trial was approved by the Ethics Committee on Animal Use of the Universidade Federal do Paraná (protocol number 30/2017). Informed consent was obtained from the owners of all animals before enrollment.

Twenty-four client-owned, mixed-breed female dogs, weighing 6.8 ± 3 kg and aged 32.7 ± 26 months, presented for elective ovariohysterectomy and were enrolled in the study. Inclusion criteria included female dogs weighing more than 2 kg and classified as American Society of Anesthesiologists (ASA) physical status I or II (ASA, 2020), based on physical examination and laboratory tests (complete blood count, platelet count, and renal and hepatic biochemical profiles). Female dogs displaying aggressive behavior or abnormalities in screening tests were excluded.

The animals were admitted to the hospital 24 hours prior to surgery, housed individually in padded cages within a quiet environment, maintained under controlled temperature, and provided with commercial food and water ad libitum. They were subjected to an 8-hour fasting period before the study. Before administration of any treatment (Tbaseline), heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were recorded by the same observers. After intravenous catheter placement, the animals were randomly assigned to one of three treatment groups (n = 8): acepromazine 0.02 mg/kg (GA), maropitant 1 mg/kg (GM), or 0.9% NaCl saline solution (GS). All treatments were administered intravenously in a standardized volume of 2 mL per animal, delivered as a bolus over 30 seconds by a researcher who was not involved in subsequent evaluations.

Thirty minutes after treatment administration (T0), physiological parameters were reassessed, and morphine (0.5 mg/kg) was administered intramuscularly. Physiological parameters were measured again at 10 (T10), 20 (T20), and 30 (T30) minutes after morphine injection. A trained evaluator, blinded to the treatment groups, assessed the occurrence of emesis and nausea. Clinical signs of nausea included drooling, increased swallowing frequency, and lip licking. The onset (TON) and ending (TOF) of these signs were timed in minutes using a digital stopwatch, beginning at the moment of morphine administration. Emesis was defined as retching with attempted or successful expulsion of gastric contents.

At T30, two independent evaluators, blinded to the treatments, assessed the degree of sedation using the scale proposed by Gurney et al. (2009), which ranges from 0 (no sedation) to 15 (maximum sedation observed). Following the T30 evaluation, anesthesia was induced by an experienced anesthesiologist using a continuous infusion of propofol at a rate of 1 mg/kg/min. The infusion was interrupted once the animal reached the surgical plane of anesthesia (Stage III, Plane 2), as described by Guedel (1936), characterized by rotation of the eyeballs, mandibular relaxation, and absence of palpebral and cough reflexes during intubation. The total dose of propofol required for induction was recorded. Anesthesia was then maintained with isoflurane, and the animals underwent elective ovariohysterectomy (OHE).

Postoperative appetite was assessed by a blinded evaluator, who did not participate in the evaluation of nausea or emesis, during the two hours following extubation. Cooked chicken (prepared in water without salt or seasoning) was offered every five minutes, starting as soon as the animal assumed sternal recumbency. Appetite was considered present when voluntary food ingestion occurred within this observation period.

Statistical analysis was performed using GraphPad Prism 8. Sedation scores were compared using the Mann-Whitney test. Parametric variables (HR, RR, RT, weight, age, propofol dose, and nausea onset and resolution times) were subjected to the Shapiro-Wilk normality test and analyzed using analysis of variance (ANOVA), followed by Dunnett's test. Appetite data were analyzed using Fisher's exact test. A significance level of 5% was adopted for all statistical tests.

3 Results

Normally distributed continuous data were summarized as mean ± standard deviation (SD), while ordinal data were summarized as median, minimum, and maximum values. Animals were evenly distributed across treatment groups ($p > 0.05$). Heart rate (HR) decreased earlier over time at T10 in groups GM (maropitant) and GS (saline solution) compared to GA (T20), although no statistically significant difference was observed between groups (Table 1).

Table 1 – Mean values (mean ± SD) of heart rate (HR), respiratory rate (RR), and rectal temperature (RT) in female dogs premedicated with maropitant (1 mg/kg; GM, *n* = 8), acepromazine (0.02mg/kg; GA, *n* = 8), or saline solution (GS)(*n* = 8), followed by morphine (0.5mg/kg)

	Groups	Baseline	T0	T10	T20	T30	*p* value*
HR (bpm)	GM	129 ± 28	113 ± 32	98 ± 21*	89 ± 17*	78 ± 19*	0.0020
	GA	97 ± 23	82 ± 21	85 ± 23	72 ± 19	68 ± 17*	0.0202
	GS	129 ± 25	110 ± 26	95 ± 19*	88 ± 23*	90 ± 19	0.0084
p* value*		0.8425	0.5340	0.9203	0.7151	0.9605	
RR (mpm)	GM	54 ± 31	50 ± 28	69 ± 55	52 ± 23	51 ± 20[b]	0.5856
	GA	57 ± 45	44 ± 25	53 ± 33	43 ± 27	32 ± 15[a]	0.3673
	GS	46 ± 13	43 ± 10	90 ± 32*	73 ± 58	70 ± 52[b]	0.0673
p* value*		0.7696	0.8056	0.2290	0.2034	0.0468	
RT (ºC)	GM	38.2± 0.4	38.1 ± 0.6	37.7 ± 0.6	37.7 ±0.6	37.6 ± 0.6	0.065
	GA	38.0± 0.4	37.9 ± 0.4	38.1 ± 0.9	37.8 ± 0.5	37.6 ±0.4	0.1927
	GS	38.4± 0.4	38.6 ± 0.3	38.3 ± 0.3	38.3 ± 0.6	38.0 ± 0.3	0.0535
p* value*		0.1045	0.0545	0.1720	0.0963	0.0793	

Baseline = before treatment administration.
T0, T10, T20, and T30 correspond to the time points before, and 10, 20, and 30 minutes after morphine administration, respectively.
*Within-group comparisons over time. Significantly different from Baseline ($p < 0.05$).
**Between-groups comparisons. Different letters within the same row indicate significate differences ($p < 0.05$).
Source: research data

Respiratory rate (RR) increased in the GS group 10 minutes after morphine administration (T10), although this change was not statistically significant. Acepromazine (GA) significantly reduced RR at T30 compared to saline (GS) and maropitant (GM). Rectal temperature (RT) did not decrease significantly in any treatment group (Table 1).

All animals in group GS (8/8) exhibited emesis, while the incidence was reduced by 37.5% in GA (5/8) and eliminated (100% reduction) in GM (0/8) (Table 2). Nausea was observed in all animals throughout the experiment (Table 2).

Table 2 – Frequency of emesis, nausea after morphine administration, and food intake after extubation in female dogs premedicated with maropitant (1 mg/kg; GM, *n* = 8), acepromazine (0.02 mg/kg; GA, *n* = 8), or saline solution (GS) (*n* = 8), followed by morphine (0.5 mg/kg)

	GM	GA	GS
Emesis	0/8 (0%)[a]	5/8 (62.5%)[b]	8/8 (100%)[b]
Nausea	8/8 (100%)	8/8 (100%)	8/8 (100%)
Appetite	4/8 (50%)	1/8 (12.5%)	2/8 (25%)

Different letters in the same row indicate significant differences among groups ($p < 0.05$)
Source: research data

Regarding the time to onset of nausea signs, GM exhibited the earliest onset (1.6 ± 1.1), whereas GS presented the latest onset (2.7 ± 1.1); however, no statistically significant differences were observed between the groups (Table 3).

Table 3 – Mean values (mean ± SD), in minutes, of the onset and resolution of nausea signs following intramuscular administration of morphine (0.5 mg/kg) in female dogs premedicated with maropitant (1 mg/kg; GM, *n* = 8), acepromazine (0.02 mg/kg; GA, *n* = 8), or saline solution (GS) (*n* = 8)

	GM	GA	GS
Onset time	1.6 ± 1.1	2.1 ± 0.9	2.7 ± 1.1

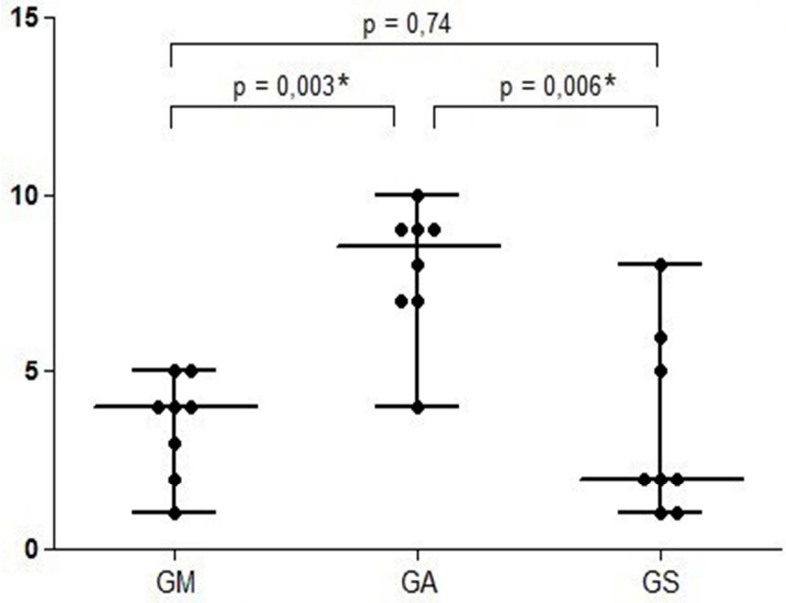
Ending time	9.9 ± 5.6	11 ± 8.8	10.0 ± 8.3

Source: research data

Regarding appetite, a higher proportion of animals in GM accepted food within two hours postoperatively. However, no statistically significant difference was found among the groups (Table 2).

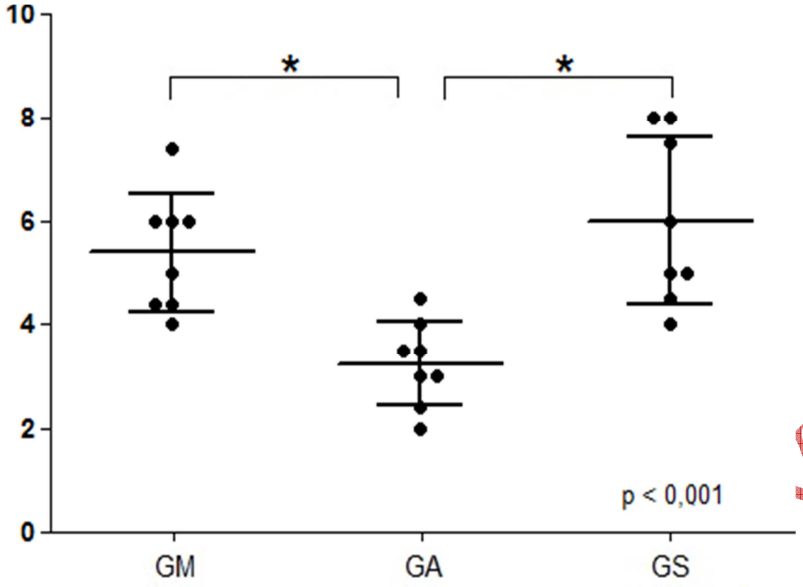
Sedation scores were higher in GA, ranging from 4 to 10, compared with GM (1 to 5) and GS (1 to 8) (Figure 1). The required dose of propofol for induction was lower in GA (3.2 ± 0.8) than in GM (5.4 ± 1.14) and GS (6 ± 1.6) (Figure 2), consistent with the principle that greater sedation reduces the dose of propofol required for induction.

Figure 1 – Sedation scores (median, minimum, and maximum) 30 minutes after administration of maropitant (1 mg/kg; GM, *n* = 8), acepromazine (0.02 mg/kg; GA, *n* = 8), or saline solution (GS) (*n* = 8), followed by morphine (0.5 mg/kg)



Groups differ significantly. *p*-value determined by the Mann-Whitney test
Source: research data

Figure 2 – Mean values (mean ± SD) of the propofol dose required for anesthetic induction in dogs sedated with morphine (0.5 mg/kg), 30 minutes after the administration of maropitant (1 mg/kg; GM, *n* = 8), acepromazine (0.02 mg/kg; GA, *n* = 8), or saline solution (GS) (*n* = 8)



Groups differ significantly. *p*-value determined by the Mann-Whitney test
Source: research data

4 Discussion

This randomized, blinded clinical trial investigated the antiemetic effects of acepromazine and maropitant in female dogs premedicated with morphine. The primary objective was to evaluate the efficacy of maropitant in preventing morphine-induced emesis.

Ovariohysterectomy was selected as the experimental model because it is one of the most commonly performed surgical procedures in small animal practice, providing a clinically relevant context. Furthermore, its standardized and predictable nature allows for improved control of variables and more reliable statistical comparisons between treatment groups.

Concerning the physiological parameters, the observed reduction in heart rate (HR) was anticipated and attributed to the pharmacological action of morphine (Henao-Guerrero *et al*., 2009), not to the administered treatments. This conclusion is supported by the absence of differences between baseline and post-treatment timepoints, as well as among the experimental groups.

An increase in RR may be related to a side effect of morphine, resulting from its interaction with the thermoregulatory center in the hypothalamus and subsequent panting (Lascelles, 2000; Pascoe, 2000). Previous studies have reported a mitigating effect on this response when acepromazine or maropitant is administered (Claude *et al*., 2014; Koh *et al*., 2014; Smith *et al*, 2001). These findings are consistent with the present study, in which the control group (GS) exhibited a significant increase in RR 10 minutes after morphine administration, whereas the groups receiving acepromazine (GA) or maropitant (GM) demonstrated a reduction. The significant reduction in RR observed in GA at T30 compared with saline (GS) and maropitant (GM) may be attributed to a potentiating effect of the morphine–acepromazine combination.

Despite previous reports of rectal temperature (RT) reduction with acepromazine (Monteiro *et al*., 2019), no significant temperature variation was observed in the current experiment. This discrepancy may be due to environmental temperature control or the short evaluation period. An alternative explanation involves the action of μ-opioids in the thermoregulatory gray matter center (Clark, 1979; Cristina-Silva *et al*., 2017), which could mask potential treatment-induced changes

The mechanism of opioid-induced vomiting is multifactorial, involving central stimulation of the chemoreceptor trigger zone by neurotransmitters such as dopamine, serotonin, histamine, and substance P (Mallick-Searle; Fillman, 2017). In particular, substance P binds to NK-1 receptors in this zone (Saito; Takano; Kamiya, 2003) and plays a role in activating abdominal and diaphragmatic muscle contractions that culminate in emesis (Lorenzutti *et al*., 2017). Hence, NK-1 receptor antagonists, such as maropitant, and substances that inhibit the release of substance P have

demonstrated effective antiemetic action (Darmani; Belkacemi; Zhong, 2019; Lorenzutti *et al*., 2017). In the present study, maropitant effectively prevented emesis induced by morphine, consistent with previous findings using acepromazine at 0.03 mg/kg administered intramuscularly 30 to 45 minutes before opioid administration (Claude *et al*., 2014).

Notably, an even greater antiemetic effect (approximately 70% efficacy) has been achieved using higher doses of acepromazine (0.05 mg/kg, intramuscular), given 15 minutes before opioid administration (Valverde *et al*., 2004). However, this effect was not replicated with simultaneous administration of both agents, suggesting that the antiemetic action of acepromazine is dose- and timing-dependent (Claude *et al*., 2014; Valverde *et al*., 2004). It may be necessary to extend the interval between acepromazine administration and opioid delivery to achieve optimal antiemetic efficacy.

Similarly, the present study did not observe a reduction in the incidence of nausea with maropitant or acepromazine when administered 30 minutes before morphine, which corroborates previous studies (Claude *et al*., 2014; Hay-Kraus, 2014; Lorenzutti *et al*., 2016). Conversely, anti-nausea efficacy has been reported with a 60-minute pre-treatment interval (Hay-Kraus, 2014), reinforcing the notion that a longer latency period may be required for maropitant to be effective against nausea. One possible limitation of the present study is the absence of a validated nausea scoring system, which might have allowed the detection of more subtle differences in the severity or frequency of nausea signs between treatment groups.

As expected, sedation scores were higher in the acepromazine group (GA), reflecting its tranquilizing effect (Varga *et al*., 2017), especially when combined with opioids, which can act synergistically (Monteiro *et al*., 2019; Smith *et al*., 2001). This enhanced sedation corresponded with a reduced requirement for propofol during anesthesia induction in GA (3.0 ± 0.7 mg/kg) compared to GS (5.8 ± 1.8 mg/kg) and GM (5.1 ± 0.9 mg/kg). These results align with earlier studies reporting reductions of 6 to 17% in propofol doses when maropitant was used as a premedication (Fukui *et al*., 2017; Okano *et al*., 2015; Swallow *et al*., 2017).

Although previous research has indicated an earlier return to spontaneous feeding (within 3 hours) in dogs premedicated with maropitant (Lotti *et al*., 2018), the present study found no statistically significant differences among the groups. It should be noted that appetite was only assessed during the first two postoperative hours. Longer monitoring periods may be necessary to fully evaluate the impact of these medications on postoperative food intake.

The limitations of this study include the use of a fixed 30-minute interval between antiemetic administration and opioid injection, which may have been insufficient to prevent nausea; the limited postoperative appetite observation period; the relatively small sample size; and the absence of a treatment group receiving both maropitant and acepromazine, which could reveal additive or synergistic effects.

5 Conclusions

Maropitant was effective in preventing morphine-induced emesis but did not influence sedation or the propofol-sparing effect. Conversely, acepromazine failed to prevent emesis but promoted deeper sedation and reduced the propofol dose required during anesthetic induction, likely due to its sedative properties, particularly when combined with morphine. These findings suggest a potential clinical indication for maropitant in patients for whom vomiting is contraindicated and morphine is the only available opioid.

However, neither drug was effective in preventing nausea or restoring appetite postoperatively, which may be partly explained by the short postoperative observation window and the absence of a validated nausea scoring system. Future studies should consider extending the evaluation period, employing validated tools to assess nausea, and investigating the effects of combining acepromazine and maropitant. Additionally, exploring these drugs in different surgical models or in patients with varying clinical conditions could provide a broader understanding of their potential applications.

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Conflict of interest
The authors declare no conflict of interest.

Bioethics and biosecurity committee approval
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Authors' contributions
LOPES, D. M.: data collection, analysis, and/or interpretation; manuscript drafting; critical review with significant intellectual input; overall supervision and coordination of the study. **DEBIAGE, R. R.; WOLFRAN, L.:** data collection, analysis, and/or interpretation; manuscript drafting. **FUKUSHIMA, F. B.:** Study conception and/or design; data collection, analysis, and/or interpretation; manuscript drafting; critical review with significant intellectual input; general supervision and coordination of the study. All authors contributed to the writing, discussion, reading, and final approval of the manuscript.

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