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Evaluation of oral maropitant as an antiemetic in cats receiving morphine and dexmedetomidine

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Abstract

Objectives The aim of the study was to evaluate the antiemetic effects of maropitant, after oral administration, in cats receiving morphine and dexmedetomidine.

Methods This prospective, blinded, randomized controlled trial involved 98 healthy female domestic shorthair cats. Cats were randomly assigned to receive maropitant PO 8 mg total (group M) administered 18 h prior to sedation with intramuscular dexmedetomidine 20 µg/kg and morphine 0.1 mg/kg, or no antiemetic treatment (group C). The occurrence of signs of nausea (sialorrhea and lip-licking), retching and emesis during the 30 mins following administration of dexmedetomidine and morphine was measured for each group.

Results Two cats were excluded from the investigation. Cats in group M (n = 46) received an average of 2.5 mg/kg of maropitant PO. Compared with group C (n = 50), cats in group M had lower incidences of emesis (M: 4% vs C: 40%), retching (M: 8% vs C: 40%) and lip-licking (M: 30% vs C: 52%) (all $P < 0.05$). The incidence of sialorrhea was not different between groups (M: 21% vs C: 22%).

Conclusions and relevance Maropitant 8 mg total PO was effective in reducing morphine and dexmedetomidine-induced emesis by 10-fold, when administered as early as 18 h in advance to healthy cats. Maropitant PO could be useful for administration the evening prior to a scheduled procedure requiring sedation/anesthesia to decrease the incidence of emesis.

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Introduction

Opioid analgesics and α2-agonist agents are commonly used in cats prior to general anesthesia for their sedative, analgesic and minimum alveolar concentration (MAC)-sparing effects. Unfortunately, several of these agents often result in emesis. The incidence of emesis from α2-agonists and/or opioids can be very high, depending on the agent and dose used. Santos et al reported an incidence of 78% when dexmedetomidine and buprenorphine were administered to healthy cats.[1] More recently, the incidence of emesis from a combination of dexmedetomidine and morphine administered preoperatively to healthy cats was 59%.[2] That incidence was reduced to 3% when maropitant, a neurokinin-1 receptor antagonist, was administered subcutaneously (SC) prior to medication with morphine and dexmedetomidine.[2]

When used in dogs, maropitant has shown to be very effective for the prevention of opioid-induced emesis.[3,4] There is, however, a paucity of reports regarding the use of maropitant for this purpose in cats. Based on a recent investigation,[2] and our clinical observations, the effectiveness of maropitant appears to be superior to other antiemetic agents, such as ondansetron,[1] and hence, it may be a useful antiemetic agent to cats receiving either opioids or α2-agonists, or both. However, in that investigation it was noted that pain from subcutaneous injection of maropitant was substantial. In this investigation

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we evaluated maropitant administered orally to cats that were receiving a combination of morphine and dexmedetomidine prior to general anesthesia. We hypothesized that maropitant would significantly reduce the incidence of behavior associated to nausea, retching and vomiting, compared with a control group not receiving the antiemetic agent.

Materials and methods

This investigation was reviewed and approved by the Institutional Animal Care and Use Committee of Cornell University. Ninety-eight female domestic shorthair cats scheduled for elective ovariohysterectomy as part of the institutions' spay and neuter program were included in this prospective, blinded and randomized controlled trial. All cats were considered American Society of Anesthesiologists (ASA) physical status I based on physical examination and blood analysis consisting of hematocrit, plasma protein concentration, blood urea and glucose concentrations. Cats presenting with a history of vomiting, inappetence, diarrhea or abdominal pain elicited during physical examination were excluded from this investigation. All cats were housed individually and fasted from solid food, but not water, for 12 h prior to general anesthesia.

Study design

This study was conducted over a 3 week period, where seven to nine cats were scheduled for ovariohisterectomy each day. The day prior to surgery, each cat was randomly assigned to receive either maropitant (Cerenia; Pfizer Animal Health) (group M) 8 mg PO or no treatment (group C), by removing labels from an opaque envelope. Maropitant was always administered at 6 pm the evening before anesthesia, 18 h prior to medication with morphine and dexmedetomidine and data collection (see below). Treatment allocation and maropitant administration were performed by one of the authors (AM) and a licensed veterinary technician, neither of whom participated in data collection. Cats were left undisturbed after administration of maropitant until the following day.

On the day of surgery, and after physical examination was completed, each cat received a combination of morphine 0.1 mg/kg (morphine sulfate; Baxter Healthcare Corporation) and dexmedetomidine 20 µg/kg (Dexdomitor; Pfizer Animal Health) intramuscularly (IM). Cats were then observed for the following 30 mins for signs of nausea (sialorrhea and lip-licking), retching or emesis. After that interval, an intravenous (IV) catheter was placed and general anesthesia induced. No further observations were recorded as part of this investigation. All injections of morphine and dexmedetomidine were performed by second year veterinary medicine students, under the supervision of faculty and licensed veterinary technicians.

Emesis and signs of nausea

Cats were observed during the 15 mins prior to, and for 30 mins after the administration of morphine and dexmedetomidine. Veterinary students assigned to each cat – and unaware of treatment allocation – documented the presence of signs of nausea, retching or vomiting. Signs of nausea included sialorrhea (collection of clear or frothy fluid around the lips, with or without dripping) or licking of the lips.[1] Retching was defined as the rhythmic contraction of diaphragmatic and abdominal musculature without expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents though the mouth. The time to first retch and vomit, relative to morphine and dexmedetomidine administration, was recorded for each cat. The total number of emetic events per cat was documented (episodes of emesis were considered individual events when they were separated by $\geqslant$5 s).

Statistical analysis

Based on our previous results,[2] two groups of at least 26 individuals each were necessary to detect a decrease in the incidence of emesis by 75% assuming $\alpha = 0.05$ and a statistical power of 95%. The non-parametric distribution of the results was confirmed with the D'Agostino–Pearson test. Significance of differences between groups in age and weight were tested with the Mann–Whitney U-test. Presence of siaorrhea and lip-licking, emesis and retching events, were considered all-or-none events, and the significance of differences in their incidences were measured with the Fisher's exact test. Significance was set at 0.05 throughout. All statistical analyses were performed with computer software (GraphPad Prism 6). All results are non-parametric data and summarized as median (minimum–maximum).

Results

Two cats were excluded from the investigation because vomiting and abdominal pain were observed the day prior to general anesthesia. A total of 96 cats completed the investigation; 46 cats were randomly allocated to group M, and 50 cats to group C. Cats in group M received an average of 2.5 mg/kg (SD 0.35, range 1.7–3.3) of maropitant PO.

There were no significant differences between groups M and C for age (12 months [5.5–84] vs 11.5 [6–73]), respectively ($P = 0.13$); however, body weight was higher for M than for C (3.2 [2.4–4.6]vs 3.0 [1.5–6.6] kg, respectively [$P = 0.02$]).

Prior to morphine and dexmedetomidine administration, sialorrhea was observed in one cat in M and none in C ($P = 1.0$), and lip-licking was observed in three cats in each group ($P = 1.0$). The incidences of sialorrhea and lip-licking, emesis or retching, in the 30 mins following morphine and dexmedetomidine injection are summarized in Table 1. The incidence of lip-licking was significantly

Table 1 Incidence of emesis, retching, sialorrhea and lip-licking in cats receiving maropitant 8 mg PO administered 18 h prior to dexmedetomidine 20 µg/kg and morphine 0.1 mg/kg IM, or no antiemetic treatment (control)

	Incidence of emesis	Incidence of retching	Incidence of sialorrhea	Incidence of lip-licking
Maropitant	4% (2/46)	8% (4/46)	21% (10/46)	30% (14/46)
Control	40% (20/50)	40% (20/50)	22% (11/50)	52% (26/50)
P value	0.0002	0.0003	1.0	0.04

reduced in cats treated with maropitant ($P = 0.04$). Significantly fewer cats retched and vomited in group M. Four cats retched in group M and 20 cats retched in group C. Retching was first observed at 4.0 (range 3.0–9.0) mins in group M and 3.0 (range 2.0–14.0) mins in group C.

Two cats vomited in group M whereas 20 cats vomited in the control group (90% reduction). Emesis first occurred at 4 and 9 mins in the two individuals that vomited in group M, respectively, and 3.0 (range 1.0–11.0) mins in group C. Each cat that vomited in the M group did it only once whereas in the control group (C) the number of emetic events per cat was 1.0 (range 1.0–5.0). The time to first vomit, number of emetic events per cat and time to first retch, were not compared between groups due to the low incidence of retching and vomiting in group M.

Discussion

The primary finding of our investigation is the high efficacy of oral maropitant to prevent morphine and dexmedetomidine-induced emesis in healthy cats. The low incidence of emesis in cats treated with maropitant found in this investigation is similar to the value previously reported when maropitant was administered by subcutaneous injection in cats that also received morphine and dexmedetomidine (4% and 3%, respectively).[2]

Several antiemetic agents have been previously evaluated in cats: metoclopramide, dexamethasone and promethazine have been studied.[5–7] In those studies, these agents reduced, but did not eliminate, the incidence of emesis that was induced by the administration of xylazine.[5–7] In addition to having used a different emetogenic agent than in our investigation, those studies evaluated a small number of cats (six to eight animals), making comparisons between the efficacy of those agents and that of maropitant virtually impossible. Ondansetron has also been evaluated for its antiemetic effects after administration of dexmedetomidine and buprenorphine in groups of approximately 30 cats each.[1] In that study, administration of ondansetron decreased the incidence of emesis from 78% to 33%.[1] The low incidence of emesis observed in the present investigation in cats treated with maropitant (4%) and that observed previously when maropitant was administered SC (3%)[2] suggests that this agent is a superior antiemetic drug for cats, at least when emesis is triggered by the co-administration of opioids and α2-agonists.

In accordance with previous findings,[2] the incidence of retching was also decreased in cats receiving maropitant. However, signs that may indicate nausea, such as sialorrhea and excessive licking of the lips, were not both consistently reduced with maropitant. In the current study, while the incidence of sialorrhea was equal between groups, the incidence of lip-licking was reduced in treated cats. Also, of interest, more cats were observed to lick their lips than to salivate excessively. There are two potential explanations of these findings: (1) It is possible that excessive licking of the lips occurs more frequently or more consistently with nausea than sialorrhea, and hence, that it might be a more sensitive sign to detect nausea in cats; (2) it is also possible that lip-licking is simply easier to observe than sialorrhea, especially if sialorrhea does not include dripping of fluids. In that case, licking of the lips may simply be reported more frequently that sialorrhea, even if they occur at the same frequency. Further research is necessary to confirm whether lip-licking in fact occurs more often than sialorrhea in cats receiving emetogenic agents. It should also be noted that the evaluation of nausea is, by nature, subjective. While salivating and lip-licking are commonly accepted as indicators of nausea, it is impossible to say if an animal not displaying those signs may in fact feel nauseated or not. However, in an effort to advocate for improved comfort for our patients, it is probably the safer position to assume that the presence of sialorrhea or lip-licking in animals receiving emetogenic substances and presenting with vomiting indicates nausea.

We administered maropitant orally 18 h prior to the injection of morphine and dexmedetomidine; the emetogenic agents. The injectable formulation of maropitant is administered once a day, suggesting its effects might last for 24 h. Indeed, maropitant was very effective for emesis prevention when injected SC 20 h prior to morphine and dexmedetomidine in our previous work.[2] The decision to investigate the use of maropitant when administered orally 18 h prior to sedatives was motivated in part by the possibility of administering this antiemetic agent the evening prior to a scheduled procedure that requires general anesthesia. Our results suggest that this practice could be useful. The safety and

efficacy of maropitant has previously been investigated in a small number of cats. In those animals, PO maropitant reduced xylazine induced emesis by 90% when administered only 2 h prior to the emetogenic agent.[8] When maropitant was administered PO 24 h prior to xylazine, it reduced emesis by only 66%. It should be noted that in that study, maropitant was used at a 1 mg/kg dose, while we administered a higher dose (2.5 mg/kg on average). This difference in dose, and the fact that we used a different emetogenic trigger, might explain the higher efficacy of our results.

In the present investigation, we decided to evaluate an oral formulation of maropitant motivated in part by the aversive behavioral response observed in cats that received the injectable formulation of maropitant.[2] Injection of maropitant resulted in substantial discomfort after SC injection.[2] In addition, it has also been reported that SC injection can result in mild to moderate red foci at the site of injection, and hemorrhage and inflammation of the subcutis in cats that receive at least 1.5 mg/kg of the injectable formulation.[8] Maropitant is approved for use in cats only in its injectable form; the oral formulation is currently only approved for use in dogs. Considering the positive results of this investigation, and the evidently painful responses to injectable maropitant observed in the past,[2] we believe that pursuing approval for an oral formulation in cats would be advantageous for pets, owners and veterinarians.

Conclusions

Oral maropitant at a dose of 8 mg total (average of 2.5 mg/kg) was effective in reducing morphine and dexmedetomidine-induced emesis by 10-fold, when administered as early as 18 h in advance to healthy cats. These results suggest that maropitant could be administered the evening prior to a scheduled procedure requiring sedation or anesthesia in order to decrease the incidence of vomiting and therefore provide a more pleasant experience.

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