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ORIGINAL ARTICLE

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Comparative efficacy of metoclopramide, ondansetron and maropitant in preventing parvoviral enteritis-induced emesis in dogs

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The aim of the study was to evaluate the efficiencies of selected anti-emetic drugs (metoclopramide, ondansetron and maropitant) in preventing vomiting in the treatment of canine parvoviral enteritis. We designed a randomized, prospective clinical study. PVE quick ELISA test-positive dogs between 4 and 12 months of age were included in the study. Each of metoclopramide, ondansetron, maropitant and control group had 8 dogs. Metoclopramide and ondansetron were administered as 0.5 mg/kg doses three times a day via intravenous route, and maropitant was administered as 1 mg/kg doses once a day subcutaneously. The number and severity of daily vomitings were recorded. All dogs were treated and monitored for five days; treatments were continued until all animals healed. Metoclopramide, ondansetron and maropitant decreased the severity of vomiting from the first day and the vomiting numbers from the third day in PVE treatment. Obtained results showed that maropitant can be used successfully such as metoclopramide and ondansetron, which are frequently used for PVE treatment. At the same time, it was discovered that metoclopramide, ondansetron and maropitant were equally effective in reducing the frequency and severity of vomiting.

1 | INTRODUCTION

Parvoviral enteritis (PVE) is a disease caused by parvovirus-2 (CPV-2) in dogs, which is a single-chain, nonenveloped DNA virus (Crawford & Sellon, 2010). PVE is a viral disease that most commonly affects young, unvaccinated dogs younger than 6 months (Macintire & Smith-Carr, 1997). Canine parvovirus-2 (CPV-2) is responsible for classic PVE, and there now are at least three identified strains (CPV-2a, CPV-2b, CPV 2c) (Willard, 2009). Rottweiler, Doberman pincher, American bull terrier, Labrador retriever and German shepherd dogs are known to be more sensitive (Crawford & Sellon, 2010). Dogs with PVE may either be asymptomatic or may die with severe clinical signs shortly. Virus attacks rapidly dividing cells (especially) the GI tract and bone marrow. Clinical signs often start with anorexia, lethargy, fever and progress within 1–2 days to vomitus and diarrhoea, which may be yellow, mucoid or haemorrhagic (Crawford & Sellon, 2010). Vomiting is usually prominent and may be severe enough to mimic foreign body obstruction and/or cause esophagitis (Willard, 2009). Large fluid and protein losses from vomiting and diarrhoea can cause severe dehydration and hypovolemic shock (Crawford & Sellon, 2010).

Fluid infusion is performed to prevent dehydration, antibacterial agent administration is performed to prevent secondary infections, and anti-emetic agents are used to prevent vomiting. Dopaminergic D_2 antagonist metoclopramide, serotonin antagonist ondansetron and NK-1 receptor antagonist maropitant may be used for preventing vomiting in dogs (Lenberg, Sullivan, Boscan, Hackett, & Twedt, 2012; Mantione & Otto, 2005; Willard, 2009). Metoclopramide is able to pass the blood–brain barrier and prevents vomiting by its effect in the medulla

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spinalis region of the brain. Additionally, it has a prokinetic effect. Metoclopramide inhibits gastric relaxation induced by dopamine, thus enhancing the cholinergic responses of gastric smooth muscle to increase motility (Papich, 2011). It is commonly used in prevention of vomiting due to chemotherapy or PVE, and postoperatively in ileus. If gastrointestinal obstruction is considered, it should not be used as it increases gastric and intestinal motility (De La Puente-Redondo et al., 2007; Elwood et al., 2010; Lamm & Rezabek, 2008; Willard, 2009). Ondansetron inhibits serotonin 5-HT_3 receptors and is used to prevent chemotherapy-related nausea and vomiting by blocking emetic stimuli that release serotonin (Papich, 2011). It shows efficacy on the enteric neurons of the gastrointestinal system (GIS) and shows anti-emetic effect via the chemoreceptor trigger zone of the brain. It also has been used to treat vomiting from other forms of gastroenteritis, pancreatitis and inflammatory bowel disease (Papich, 2011). It has no gastric or intestinal peristaltic increasing effect (Mantione & Otto, 2005; Prittie, 2004; Washabau & Elie, 1995).

Neurokinin-1 (NK_1) receptors within the nucleus tractus solitarius, the area postrema and the dorsal motor vagal nucleus play a significant role in emesis (Gardner et al., 1996), and it has been established that the neuropeptide substance P, a potent agonist of the NK_1 receptor, is a fundamental neurotransmitter in the pathophysiology of emesis (Gardner et al., 1995, 1996). Maropitant is a potent and selective neurokinin-1 receptor antagonist, which acts in a dose-dependent manner as an anti-emetic by inhibiting the binding of substance P; therefore, it is effective against neural and humoral (central and peripheral) causes of vomiting.

In dogs, maropitant is rapidly absorbed after both oral and subcutaneous administration with plasma concentration peaks (T_{max}) between 1 and 2 hr (Food & Drug Administration, 2007). Recommended parenteral dose of maropitant is 1 mg/kg for emesis in dogs.

In a study performed in Europe on vomiting dogs with different aetiologies, such as PVE, gastroenteritis resulting from dietary indiscretion, and pancreatitis, emesis-reducing effects of maropitant have been reported (Lamm & Rezabek, 2008). Vail, Rodabaugh, Conder, Boucher, and Mathur (2007) have reported that it was also effective in preventing cisplatin-related vomiting in chemotherapy. Maropitant should be administered one hour before travelling to prevent travelling-related vomiting (Benchaoui et al., 2007; Conder, Sedlacek, Boucher, & Clemence, 2008). Maropitant is not recommended in dogs younger than 8–16 weeks due to the risk of causing bone marrow hypoplasia (Benchaoui et al., 2007; Food and Drug Administration, 2007; Willard, 2009).

Sedlacek et al. (2008) compared the effects of maropitant, metoclopramide, chlorpromazine and ondansetron in patients with apomorphine- and ipecac syrup-induced vomiting. They have reported that maropitant, metoclopramide and chlorpromazine were significantly superior to ondansetron in apomorphine-related central vomiting, whereas maropitant and ondansetron were superior to metoclopramide and chlorpromazine in prevention of ipecac syrup-related vomiting in dogs.

In this study, we compared the anti-emetic effects of metoclopramide, ondansetron and maropitant in PVE-induced vomiting.

2 | MATERIALS AND METHODS

2.1 | Study population

Thirty-two, client-owned dogs of 4–12 months of age presented to the Small Animal Clinics of the Veterinary Teaching Hospital, Uludag University, with clinical signs indicative of canine PVE and tested positive at SNAP test for canine parvovirus–canine coronavirus–giardia antigen[1] were included in the study. Giardiasis was excluded in all dogs by the absence of trophozoites on a faecal wet mounted slide examined at admission and two consecutive negative zinc sulphate flotation tests. None of dogs were vaccinated against any disease.

The dogs were of various weights (mean 4.7 ± 0.2 kg), breeds (23 mixed breeds, three German shepherd dogs, three Anatolian shepherd dogs, three Rottweilers), gender (17 males and 15 females) and ages (between four and twelve months; mean 5.1 ± 0.1 months). There were no significant differences regarding the age, body weight and gender among the groups.

All dogs received a physical examination and were severely depressed, anorexic; had watery, bloody diarrhoea; and vomited frequently (≥ four times per 12 hr). The clinical examinations included the examinations of mucosa and lymph nodes, and measurement of heart and respiratory frequency, body temperature and capillary filling time. Blood samples were collected for haematological and biochemical analyses. All clinical examinations were repeated every 24 hr for five days. The study proposal was reviewed and approved by the Ethics Committee of Uludag University (2010-06/03).

2.2 | Study procedure

All dogs were hospitalized in individual cages in the infectious disease isolation unit for five days, and the cages were cleaned every eight hours to prevent reinfection. To determine the frequency and severity of vomiting, the dogs were monitored via a video-recording system throughout the study. To provide a blinded-approach, one researcher treated the animals and gave the drugs (GOK) and the other (EY) only observed the animals. Frequency (0 to >3) and severity (mild, moderate, severe) of vomiting were scored as previously described by De La Puente-Redondo et al. (2007). In short, severity of vomiting was classified as: mild: animals with nonproductive retching; moderate: animals with vomiting without bile; and severe: animals with vomiting containing bile. Any losses (n = 4) occurring during the first three days of the treatment were excluded from the study.

All dogs, on the day of admission, were rehydrated over six hours using lactated Ringer's solution with 5% dextrose[2] and potassium chloride[2] (20 mEq/L) added to it. The antibiotic therapy consisted of ampicillin[3] (22 mg/kg, q8h, iv, five days, followed by 30 mg/kg, q12h, orally, 10 days), gentamicin[4] (2 mg/kg, q12h, iv, five days, initiated after rehydration) and metronidazole[5] (25 mg/kg, q12h, iv, five days). Treatment protocol was adapted from Macintire and Smith-Carr (1997) and Prittie (2004). No anti-emetic drug was performed during the first 8 hr.

Dogs were randomized to receive either metoclopramide[6], ondansetron[7], maropitant[8] as a primary anti-emetic. Randomly selected animals

TABLE 1 The dose, administration route and frequency of the anti-emetic drugs used in treatment groups

Group no	Anti-emetic drug	Dose and route	Frequency
1	Metoclopramide	0.5 mg/kg, intravenous	Once in 8 hr
2	Ondansetron	0.5 mg/kg, intravenous	Once in 8 hr
3	Maropitant	1 mg/kg, subcutaneous	Once in 24 hr
4	Control	No treatment	–

in the control group did not receive any anti-emetic drug. Treatments and monitoring were performed for five days; treatments were continued thereafter until all animals healed. Table 1 shows the dose, route and frequency of administration of the anti-emetic drugs used.

2.3 | Statistical analysis

The results are given as mean ± standard deviation. Variance analysis (ANOVA) and Kruskal–Wallis tests were used for repetitive measures[9]. Student's *t*-test was used for the comparison of two groups; nonparametric (Friedman repeated-measures ANOVA on ranks) tests were used in determining the number and severity of vomiting. The data were confirmed to be normally distributed before starting ANOVA. $p < .05$ was accepted as statistical significance.

3 | RESULTS

3.1 | The frequency and severity of vomiting

When the frequency of vomiting was compared between the groups and treatment days, no difference was observed on day 0. The in-group comparison of the groups according to treatment days revealed no difference between day 0 and days 3 and 5 in metoclopramide, ondansetron and maropitant groups ($p < .05$). On days 3 and 5, the frequency of vomiting decreased in metoclopramide, ondansetron and maropitant groups when compared with the control group ($p < .05$). Also in the control group, the frequency and severity of vomiting were less on day 5 when compared with days 0 and 1 ($p < .05$).

The severity of vomiting was decreased on days 1, 3 and 5 when compared to day 0 in all treatment groups when compared with the control group ($p < .05$). No difference was detected regarding the vomiting severity among days 1, 3 and 5 in these groups. Statistically significant difference was detected between days 0 and 1, and day 5 of the control group ($p < .05$). Figure 1 compares the number and severity of vomiting according to the treatment day in all the groups.

4 | DISCUSSION

Anti-emetics are very common in the treatment of PVE in addition to fluid replacement and antibacterial drug use. Anti-emetic drugs

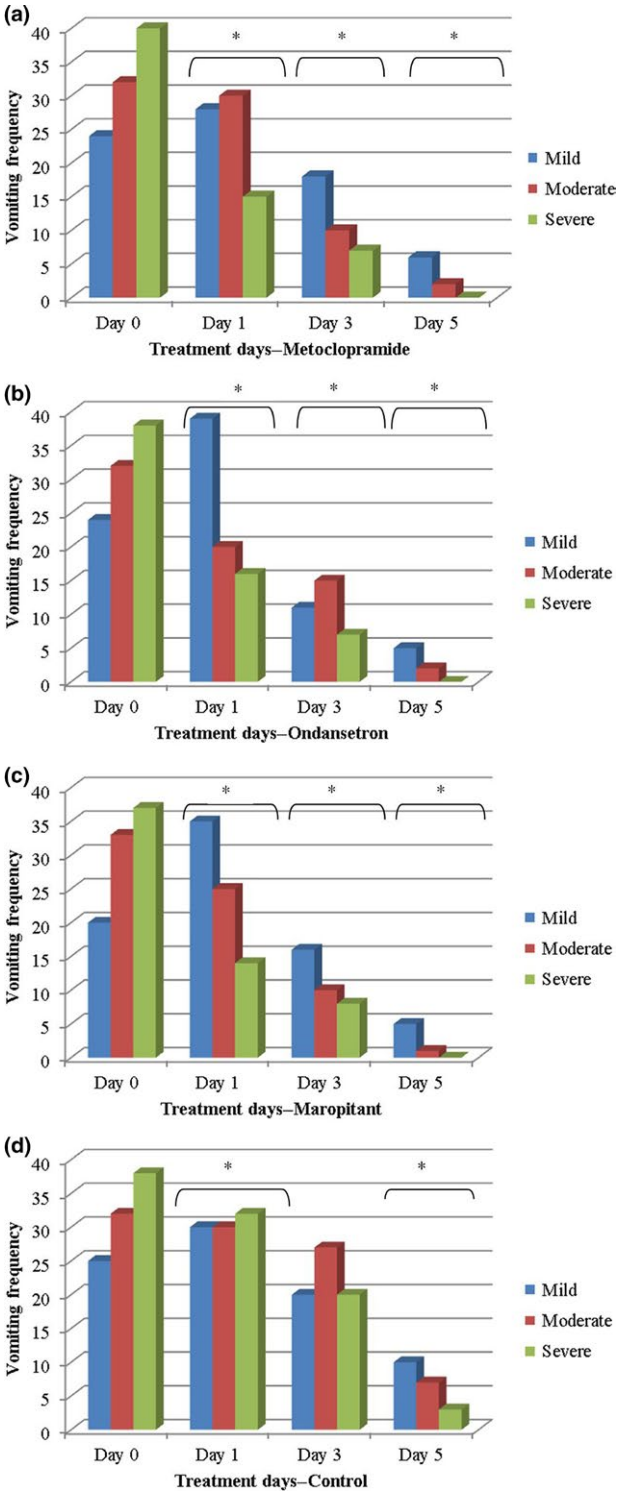

FIGURE 1 Comparison of vomiting frequency in metoclopramide ($n = 8$)-, ondansetron ($n = 8$)- and maropitant ($n = 8$)-treated dogs and control dogs ($n = 8$) with parvoviral enteritis (PVE). Metoclopramide (a) and ondansetron (b) were administered as 0.5 mg/kg doses three times a day via intravenous route, and maropitant (c) was administered as 1 mg/kg doses once a day subcutaneously. Randomly selected animals in the control group (d) did not receive any antiemetic drug. All dogs were treated and monitored for five days. *denotes statistical difference compared with Day 0 ($p < .05$). [Colour figure can be viewed at wileyonlinelibrary.com]

enable oral feeding of the patient shortly and minimize the fluid loss that triggers dehydration. Metoclopramide responds well as an anti-emetic drug and is used conventionally, but it should be used every eight hours (Mantione & Otto, 2005; Willard, 2009; Prittie, 2004). Metoclopramide has both anti-emetic and prokinetic properties, and this limits its usage in patients with invagination risk. Ondansetron, which is preferred in resistant vomiting and postchemotherapy by the veterinarians, is used 2–3 times a day. Its usage is limited as it may only be used intravenously. Maropitant, which is more recent in the market as oral and injectable (subcutaneous and recently licensed for intravenous administration), is used once a day effectively, but its efficacy in PVE is not known yet (Mantione & Otto, 2005; Ramsey et al., 2008; Vail et al., 2007; Watson et al., 1995). Use of maropitant may be limited due to its moderate bone marrow-suppressive effect in dogs younger than 8 weeks (Food and Drug Administration, 2007) and less cost-effective price than the other drugs. However, sufficient effect in once a day usage is its major advantage.

Frequency of vomiting decreased on days 3 and 5 when compared with day 0 in all treatment groups, and on day 5 when compared with days 0 and 1 in the control group ($p < .05$). On days 3 and 5, the frequency of vomiting decreased in metoclopramide, ondansetron and maropitant groups when compared with the control group ($p < .05$). This shows that metoclopramide, ondansetron and maropitant reduced the frequency of vomiting starting with day 3 compared with the control group. None of the three drugs was superior to one another with regard to the frequency of vomiting.

Sedlacek et al. (2008) used 0.9% NaCl, maropitant, metoclopramide and chlorpromazine to prevent vomiting in patients that were administered apomorphine and ipecac syrup. They reported that maropitant has a similar effect to metoclopramide and chlorpromazine in preventing apomorphine-induced central vomiting, and this effect is significantly superior to ondansetron. They determined that maropitant was as effective as ondansetron in the prevention of ipecac syrup-related vomiting and that it was superior to metoclopramide and chlorpromazine. Lenberg et al. (2012) compared maropitant and ondansetron in dogs with PVE. They reported that both drugs were similar regarding the number and severity of vomiting and the time to recovery. During hospitalization, the dogs were compared according to live weight, and maropitant was detected to induce weight gain and ondansetron was detected to induce weight loss. De La Puente-Redondo et al. (2007) reported a single daily dose of maropitant to be more effective than metoclopramide administered two or three times daily in the treatment of emesis caused by various aetiologies in dogs; however, the number of PVE-induced cases was very limited (two out of 183 cases) in that study. In other studies, maropitant was found to be effective in morphine- (Koh, Isaza, Xie, Cooke, & Robertson, 2014) or hydromorphone (Hay Kraus, 2014)-induced vomiting.

Severity of vomiting decreased on days 1, 3 and 5 when compared with day 0 in all treatment groups, and on day 5 when compared with days 0 and 1 in the control group ($p < .05$). No difference was detected among metoclopramide, ondansetron and maropitant groups on days 1, 3 and 5. This showed that metoclopramide, ondansetron and maropitant reduced the severity of vomiting starting with day 1 of treatment compared with the control group. None of the three drugs was superior to one another and had similar effect on the number and severity of vomiting.

As a conclusion, metoclopramide, ondansetron and maropitant used as anti-emetic drugs in the treatment of PVE reduced the severity of vomiting starting with the first day of treatment and reduced the number of vomiting starting with day 3 of treatment. These results indicate that maropitant may successfully be used besides metoclopramide and ondansetron, which are conventionally used. Furthermore, it was detected that metoclopramide, ondansetron or maropitant was not superior to one another in reducing the number or severity of vomiting. This study is the first to investigate the effect of three different anti-emetics in treatment of parvoviral enteritis-induced emesis.

NOTES

[1]Anigen Rapid, Bionote Inc., South Korea

[2]Eczacibasi-Baxter Ltd, Turkey

[3]Mustafa Nevzat, Turkey

[4]Fako, Turkey

[5]I.E. Ulagay, Turkey

[6]Metpamid, Yeni, Turkey

[7]Zofran, Glaxo SmithKline, UK

[8]Cerenia, Pfizer, France

[9]SigmaStat 3.5, Systat Software

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