RESEARCH PAPER

Efficacy of maropitant in preventing vomiting in dogs premedicated with hydromorphone

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Abstract

Objective The goal of this study was to evaluate the effectiveness of maropitant (Cerenia) in preventing vomiting after pre-medication with hydromorphone.

Study design Randomized, blinded, prospective clinical study.

Animals Eighteen dogs ASA I/II admitted for elective orthopedic surgical procedures. The dogs were a mixed population of males and females, purebreds and mixed breeds, 1.0–10.2 years of age, weighing 3–49.5 kg.

Methods Dogs were admitted to the study if they were greater than 1 year of age, healthy and scheduled to undergo elective orthopedic surgery. Dogs were randomly selected to receive one of two treatments administered by subcutaneous injection. Group M received 1.0 mg kg^{-1} of maropitant, Group S received 0.1 mL kg^{-1} of saline 1 hour prior to anesthesia premedication. Dogs were premedicated with 0.1 mg kg^{-1} of hydromorphone intramuscularly. A blinded observer documented the presence of vomiting, retching and/or signs of nausea for 30 minutes after premedication.

Results All dogs in S vomited (6/9), retched (1/9) or displayed signs of nausea (2/9). None (0/9) of the dogs in M vomited, retched or displayed signs of nausea. Dogs in M had significantly fewer incidences of vomiting ($p = 0.0090$), vomiting and retching ($p = 0.0023$) and vomiting, retching and nausea ($p < 0.0001$) when compared to S.

Conclusion and clinical relevance Maropitant prevents vomiting, retching and nausea associated with intramuscular hydromorphone administration in dogs.

Keywords dogs, hydromorphone, maropitant, vomiting.

Introduction

Opioids are commonly used for chemical restraint and as preanesthetic medications in veterinary medicine. Full mu-agonists offer dose dependent sedation and analgesia and are used to treat moderate to severe pain. They may also be used as induction agents and as intra- and post-operative analgesics in veterinary patients. Adverse side effects may include respiratory depression, bradycardia, behavioral changes including sedation, dysphoria or excitement, urine retention and decreased urine production and gastrointestinal effects including salivation, nausea, vomiting and defecation (Wilson 1992; Branson & Gross 2001; Lamont & Mathews 2007).

Hydromorphone is approximately five to seven times more potent than morphine, exhibits similar efficacy, and at equianalgesic doses, produces a similar adverse effect profile as morphine (Mahler & Forrest 1975; Coda et al.1997). However, neither hydromorphone nor oxymorphone were found to increase plasma histamine concentrations after intra-venous administration (Smith et al. 2001) as is seen with morphine (Doenicke et al. 1995). Oxymorphone also causes less vomiting than either morphine or hydromorphone in dogs (Valverde

V A A 7 8 8 B
Journal Name Manuscript No.
Dispatch: 26.9.12 Journal: VAA CE: Sindhuja R.
Author Received: No. of pages: 7 PE: Priyadharshini

et al. 2004) however, it is significantly more expensive (Pettifer & Dyson 2000). The ability to give hydromorphone intravenously (IV), without the risk of histamine release, and the decreased cost, contribute to its widespread use as an analgesic drug in veterinary medicine.

The incidence of vomiting in dogs given opioids as anesthetic pre-medications is 50–75% with morphine (Valverde et al. 2004; Wilson et al. 2007), 44–100% with hydromorphone (Valverde et al. 2004; KuKanich et al. 2008) and 33% with oxymorphone (Valverde et al. 2004). The incidence of vomiting is affected by the specific drug and its lipid solubility profile, the dose and route of administration and concomitant drug administration. Decreasing incidence of vomiting is observed with higher opioid doses, higher lipid solubility and prior administration of acepromazine (Blancquaert et al. 1986; Hersom & Mackenzie 1987; Gross 2001; Valverde et al. 2004; KuKanich et al. 2008).

Vomiting and regurgitation, especially when associated with anesthesia have been documented as risk factors for development of aspiration pneumonia (Fransson et al. 2001; Alwood et al. 2006; Tart et al. 2010). Additional risk factors for aspiration include underlying esophageal, laryngeal and neurological disease, prolonged anesthesia, cervical disc lesions and the use of hydromorphone as an intra-operative analgesic; all of which can be commonly encountered in clinical anesthesia practice (Fransson et al. 2001; Alwood et al. 2006; Kogan et al. 2008; Tart et al. 2010). In addition, vomiting may be particularly undesirable in certain cases such as penetrating eye wounds, intra-ocular surgery and patients with head trauma or a brain tumor where increasing intraocular or intracranial pressure caused by vomiting may lead to increased patient morbidity (Cunningham & Barry 1986; Yusufu 2002; Slettedal & Bragad 2005; Eberhart et al. 2007).

Maropitant (Cerenia, Pfizer, NY, USA) is a neurokinin-1 receptor (NK1) antagonist that has been approved to prevent and treat vomiting in dogs. It has been shown to be highly effective in preventing vomiting secondary to a broad spectrum of emetic stimuli including cisplatin, apomorphine, copper sulfate, motion sickness and a wide range of clinical causes of vomiting (Benchaoui et al. 2007; De La Puente-Rendondo et al. 2007a,b; Vail et al. 2007; Conder et al. 2008; Ramsey et al. 2008). The goal of this study was to evaluate the effectiveness of maropitant in preventing vomiting after pre-medication with hydromorphone.

Materials and methods

Study population

This study was approved by the Iowa State University Institutional Animal Care and Use Committee. Dogs presented to the Lloyd Veterinary Medical Center at Iowa State University College of Veterinary Medicine for elective orthopedic surgery were included in the study. The owners' gave consent for each animal to be included in the study. The study population included 18 dogs, classified as ASA status 1 or 2 based on complete physical examination and normal routine blood chemistry and complete blood count. There were 13 spayed females, 4 castrated males and one intact male, aged 1–11.2 years and weighing 3.0–49.5 kg. Ten different breeds of dog were represented in the study including two mixed breed dogs, four Labrador Retrievers, four Golden Retrievers, and single representatives of Boxer, Mastiff, Pomeranian, Brussells Griffon, Newfoundland, Blue Heeler, German Shepherd, Miniature Pinscher.

Study protocol

On entry into the study, dogs were randomly assigned to receive one of two treatments prior to preanesthetic medication. Group M received 1.0 mg kg^{-1} (0.1 mL kg^{-1}) of maropitant and Group S received saline 0.1 mL kg^{-1} subcutaneously 1 hour prior to anesthesia premedication. The dose of saline was selected to parallel the volume of maropitant needed to deliver a 1.0 mg kg^{-1} dose. All subcutaneous injections were administered in the loose skin on the midline between the scapulae to allow monitoring of subsequent injection reaction at the site. Dogs were premedicated with 0.1 mg kg^{-1} of hydromorphone intra-muscularly in the lumbar epaxial muscles. A trained observer blinded to treatment group documented the emetic events and the presence of signs of nausea for each dog for 30 minutes after premedication. Vomiting was defined by expulsion of stomach contents from the mouth. Retching was defined as forceful contraction of abdominal muscles without expulsion of stomach contents from the mouth. Signs interpreted as nausea included salivation, increased frequency of or exaggerated swallowing motions and licking of lips. Each discrete emetic event was recorded. All dogs were evaluated the following day for pain and swelling at the injection site.

Statistical analysis

The primary variable used in the analysis of efficacy was whether the dog experienced one or more vomiting episodes. A two-tailed Fisher exact test was performed between the treatment and control group. The Fisher exact test was repeated with the inclusion of retching and nausea in addition to vomiting. Statistical significance was assessed at $p \leq 0.05$. A *t*-test was used to detect incidental differences that may have occurred between the groups for age and weight. A Fisher exact test was run for the incidence of vomiting in the saline group between males and females.

Results

There was no significant difference in age or weight between dogs in Group M and S

Six of nine dogs (6/9, 66%) that received saline vomited at least once after hydromorphone (Table 1). Three dogs (3/9, 33%) vomited only once and three dogs (3/9, 33%) vomited more than once after hydromorphone. One dog (1/9, 11%) in the saline group retched but did not vomit. Two dogs (2/9, 22%) exhibited signs of nausea including profuse salivation and lip licking but did not vomit or retch. Therefore, all dogs in the saline group vomited, retched or displayed signs of nausea. There was no significant difference in the incidence of vomiting between males and females in the saline group.

None (0/9) of the dogs that received maropitant vomited, retched or displayed signs of nausea. Dogs receiving maropitant had significantly fewer incidences of vomiting ($p = 0.0090$), vomiting and retching ($p = 0.0023$) and vomiting, retching and nausea ($p < 0.0001$) when compared to saline.

Table 1 Age, weight and sex distribution of dogs receiving maropitant (Group M) and saline (Group S)

			Sex	
Group	**Age (years)*†**	**Weight (kg)*‡**	**Male**	**Female**
M	5.98 ± 2.75	31.7 ± 14.0	2	7
S	5.35 ± 2.75	27.0 ± 16.5	3	6

*Values expressed as mean ± SD; †$p = 0.6317$; ‡$p = 0.5249$

In Group M, one dog exhibited pain on injection of maropitant. On the day following surgery, there was no evidence of pain or swelling at the injection site in dogs receiving either saline or maropitant as evidenced by observation and palpation.

Discussion

Vomiting involves three stages: nausea, retching and vomiting (Andrews 1992; Twedt 2000). Nausea is a sensation that precedes vomiting and may or may not lead to vomiting. Signs of nausea in animals may include depression, salivation, licking of lips and increased swallowing. Next, there are retrograde contractions of the proximal small intestine and pylorus and relaxation of the fundus (Twedt 2000; Elwood et al. 2010). Retching is the second phase and consists of forceful contractions of the expiratory intercostal muscles, diaphragm and abdominal muscles with elevation of the larynx and closure of the glottis (Andrews et al. 1990; Elwood et al. 2010). Decreased tone in the cervical esophagus, pharyngeal and lower esophageal sphincter, production of negative intra-thoracic and positive intra-abdominal pressures and contraction of the pylorus and antrum of the stomach, are associated with the movement of gastric contents into the esophagus (Andrews & Hawthorne 1988; Twedt 2000; Elwood et al. 2010). Vomiting occurs when gastric contents are expelled from the mouth. Respiration is inhibited and the nasopharynx and glottis close as the vomit passes through the pharyngeal cavity to prevent aspiration (Twedt 2000; Elwood et al. 2010).

Central neurologic control of vomiting involves a complex set of activities. There are two anatomically and functionally separate units: the vomiting or emetic center which consists of the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus which are located in the medulla oblongata (Elwood et al. 2010) and the chemoreceptor trigger zone (CTZ) which has been identified as the area postrema and is located on the dorsal surface of the medulla oblongata adjacent to the fourth ventricle (Elwood et al. 2010). The CTZ lies outside the blood brain barrier (BBB) and is responsive to circulating emetogens (Elwood et al. 2010). Emetogenic signals from the CTZ stimulate neurons of the nucleus tractus solitarius and from there the central pattern generator (CPG) of the vomiting reflex which triggers the motor response (Carpenter et al. 1988; Koga & Fukuda 1992). The vomiting center,

which lies within the BBB, integrates efferent input from a number of sources including the cerebral cortex (psychogenic vomiting), vestibular input arising from the semi-circular canals (vomiting associated with motion sickness or vestibular disorders), vagal and sympathetic afferents from the gastrointestinal system and other abdominal organs and the CTZ (Carpenter et al. 1983; Tattersall et al. 1996). Convergence of information from the CTZ and higher centers in the nucleus tractus solitarius leads to stimulation of the central pattern generator (CPG) for vomiting, located in the reticular area, eliciting the motor act of vomiting (Koga & Fukuda 1992; Fukuda et al. 1999).

Substance P, a neuropeptide in the tachykinin family and a potent agonist at the NK_1 receptor, is found in high concentrations in areas of the brain stem involved in emesis including the nucleus tractus solitarius, the area postrema and the dorsal motor nucleus of the vagus (Ariumi et al. 2000; Hargreaves 2002) and is considered to be the key neurotransmitter involved in vomiting (Diemunsch & Grelot 2000). Injection of substance P into the brainstem of ferrets rapidly causes vomiting (Gardner et al. 1995). Vomiting induced by emetogens such as apomorphine, copper sulfate and cisplatin can be prevented in dogs by inhibiting NK1 receptors for substance P (Watson et al. 1995). Confirmation of the role of NK_1 receptors in the final common pathway in vomiting in dogs came by selective antagonism of NK_1 receptors in decerebrate dogs exposed to abdominal vagal stimulation (Fukuda et al. 1999). The proposed site of antiemetic action of NK_1 receptor antagonists is located in the CPG or in the pathway connecting the nucleus tractus solitarius to the CPG (Fukuda et al. 1999; Andrews et al. 2001). NK_1 receptor antagonists, by acting at the center coordinating the vomiting response to various central (neural) and peripheral (humeral) stimuli, can provide broad-spectrum inhibition of vomiting (Gardner et al. 1996; Fukuda et al. 1999).

Maropitant, a selective NK_1 receptor antagonist has been shown to be effective for prevention of vomiting caused by stimulation of both central and peripheral pathways (De La Puente-Rendondo et al. 2007c, Sedlacek et al. 2008). Maropitant has been shown to significantly reduce vomiting relative to a saline negative control for both apomorphine (centrally acting emetogen) and syrup of ipecac (peripherally acting emetogen). When compared to metoclopramide, chlorpromazine and ondansetron, it was the only antiemetic effective against both centrally (apomorphine) and peripherally (syrup of ipecac) acting emetogens (Sedlacek et al. 2008).

Hydromorphone has physicochemical properties very similar to those of morphine (Pettifer & Dyson 2000; Sarhill et al. 2001). Morphine can have both emetic and anti-emetic effects. The emetic effects are the result of stimulation of delta receptors outside the blood/brain barrier (CTZ) whereas the anti-emetic effects can be attributed to mu-and/or kappa-mediated mechanisms on the vomiting/emetic center (Blancquaert et al. 1986; Hersom & Mackenzie 1987). At low doses (0.3 mg kg^{-1} IV), morphine caused vomiting in 6/6 dogs whereas doses of 1 and 2 mg kg^{-1} resulted in 3/5 and 0/28 incidence of vomiting respectively (Blancquaert et al. 1986). The higher doses of morphine also prevented vomiting induced by apomorphine; 3/5 and 0/23 for doses of 1 and 2 mg kg^{-1} respectively. It is postulated that the lower dose of morphine reaches the CTZ but not the vomiting center, therefore resulting in emesis, whereas the higher dose can reach the VC and block the effects on the CTZ (Blancquaert et al. 1986). Highly lipid soluble opioids have an anti-emetic effect due to their effect on the VC. Fentanyl, at doses of 5 and 10 μg kg^{-1} IV did not cause vomiting in 6/6 and 12/12 dogs respectively, and 10 μg kg^{-1} prevented the emetic effect of apomorphine and copper sulfate in 4/7 and 4/5 dogs respectively (Blancquaert et al. 1986). Methadone and sufentanil, also highly lipid soluble, did not cause vomiting in dogs (Blancquaert et al. 1986; Hersom & Mackenzie 1987).

The incidence of vomiting in the saline group was 6/9 (66%). This is slightly higher than previously reported by Valverde et al. (2004) who found an incidence of 7/16 (44%) in a group of dogs receiving hydromorphone (0.1 mg kg^{-1}) intra-muscularly 15 minutes prior to administration of acepromazine. This discrepancy may be due to the relatively low numbers of dogs in each study or differences in administration site. All dogs in the present study were injected in the lumbar epaxial muscles. Absorption of drugs given in non-postural muscles is slower than in postural muscles (Self et al. 2009). Slower absorption may have an effect similar to lower opioid doses on the CTZ, leading to a more pronounced emetic effect. The site of intra-muscular injection was not specified in the Valverde et al. (2004) study. The incidence of vomiting after intramuscular administration is higher than when hydromorphone is administered intravenously at

doses of 0.1 mg kg^{-1} (3/9, 33%) 0.5 mg kg^{-1} (0/7, 0%) but lower than when administration is by subcutaneous injection at doses of 0.1 mg kg^{-1} (6/8, 75%) and 0.5 mg kg^{-1} (8/8, 100%) (KuKanich et al. 2008).

When additional prodromal signs of vomiting such as retching and nausea were included, a 100% incidence was observed in the saline group. In Valverde et al.'s (2004) study, inclusion of retching and salivation increased the incidence of signs of vomiting to 28/40 (70%) dogs. However, it was not indicated whether these dogs received oxymorphone, morphine or hydromorphone. However, it is clear that the incidence of prodromal signs is higher than overt vomiting.

Acepromazine, when administered at a dose of 0.05 mg kg^{-1} IM 15 minutes prior to hydromorphone, decreased the incidence of vomiting from 7/16 (44%) to 5/21 (24%), which is thought to be due to blockade of dopamine receptors in the chemoreceptor trigger zone (Valverde et al. 2004). Maropitant decreased the incidence of vomiting after hydromorphone to 0/9, making it a more effective, reliable anti-emetic.

In human anesthetic patients, satisfaction with their anesthesia experience is closely tied to the ability to avoid peri-operative nausea and vomiting. This issue ranks ahead of pain, death and myocardial infarction as a patient concern. In a recent interview study of 12,276 patients, 3652 (30%) reported at least one perioperative complaint, of these 1705 (46%) were related to perioperative nausea and vomiting (Lehmann et al. 2010). Avoiding the discomfort associated with peri-operative nausea and vomiting may also be a consideration for veterinary patients.

Maropitant was completely effective in preventing vomiting, retching and nausea associated with administration of the opioid analgesic hydromorphone in this study. The standard dosage recommendations for treatment or prevention of vomiting are 1.0 mg kg^{-1} by SC injection or 2.0 mg kg^{-1} as oral tablets (De La Puente-Rendondo et al. 2007b). The pharmacokinetic data demonstrate that in dogs, these two maropitant doses provide similar peak plasma concentrations (92 ng mL^{-1} for 1 mg kg^{-1} SC, 81 ng mL^{-1} for 2 mg kg^{-1} PO) (De La Puente-Rendondo et al. 2007b). However, the time taken to achieve maximum plasma concentration is shorter following SC administration (0.75 hours for 1 mg kg^{-1} SC and 1.9 hours for 2 mg kg^{-1} PO), thus making it the preferred route of administration in a clinic setting (De La Puente-Rendondo et al. 2007b). Oral dosing of 2 mg kg^{-1}at least 2 hours prior to administration of hydromorphone may provide a more appropriate route for owners administering the product at home for the prevention of emesis prior to a planned elective surgery where use of hydromorphone or other opioid drugs that are known to elicit vomiting will be administered.

The randomized clinical study reported here demonstrated that maropitant was effective in the prevention of vomiting after administration of hydromorphone 0.1 mg kg^{-1} intra-muscularly when given 1 hour prior to anesthetic premedication. Avoidance of peri-operative nausea and vomiting may decrease patient discomfort, risk of perioperative aspiration pneumonia and morbidity associated with increased intra-ocular or intracranial pressures.

Acknowledgements

The author wishes to thank Amanda Jirak Ayers for technical assistance with this project. Maropitant was provided by Pfizer Animal Health, New York, NY.

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Received 2 September 2011; Accepted 3 October 2011.