In dogs undergoing anaesthesia do pre-anaesthetic gastroprotectants reduce gastro-oesophageal reflux?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In dogs undergoing anaesthesia do pre-anaesthetic gastroprotectants reduce gastro-oesophageal reflux?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

Five papers were critically reviewed. There was a randomised prospective study, two randomised blinded prospective studies, randomised non-blinded prospective study and a randomised, double blinded and placebo-controlled prospective study

Strength of evidence

Moderate

Outcomes reported

Evidence of high quality suggests omeprazole or cisapride with esomeprazole decrease the incidence of gastro-oesophageal reflux (GOR) in the anaesthetised dog. In addition, a study of lower quality showed that continuous infusion of metoclopramide at a higher than normal dose rate decreased the incidence of GOR

Conclusion

Omeprazole or cisapride with esomeprazole decreases the incidence of GOR in the anaesthetised dog

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision-making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care

Clinical Scenario

A 5-year-old Labrador undergoing elective arthroscopy under general anaesthesia developed regurgitation and nausea following recovery from anaesthesia. The dog was otherwise healthy with no history of vomiting or regurgitation. The dog developed oesophagitis as a complication of this. Does the administration of pre-anaesthetic gastroprotectants reduce the risk of GOR?

The evidence

There is evidence to support that pre-anaesthetic gastroprotectants prevent GOR. The peer-reviewed studies are generally prospective studies. There is no consistency between the trials of patient sex, breed, depth of anaesthesia, surgery being performed and position during surgery. The choice of anaesthetic drugs can also influence the risk of GOR.

Panti et al. (2009) studied the effects of omeprazole administration pre-operatively on 47 dogs undergoing orthopaedic surgery. Compared to the control group, the dogs that received pre-operative omeprazole had a significant decrease in the occurrence of GOR. In contrast, Zacuto et al. (2012) found that esomeprazole (an isomer of omeprazole) had no effect on GOR. However, cisapride with esomeprazole decreased reflux events. The study by Favarato et al. (2012) evaluated metoclopramide or ranitidine on 90 anaesthetised dogs and concluded that there was no influence on the effect of GOR. However, Wilson et al. (2006) concluded that whilst a low dose of metoclopramide had no effect on the incidence of GOR, administering a higher than normal dose of metoclopramide as a continuous infusion resulted in a 54% reduction in relative risk of developing GOR. Although the same dose rates of metoclopramide were used for both studies they produced conflicting results. In the study by Johnson (2014) the administration of maropitant in 26 dogs undergoing surgery showed that it prevented vomiting but not the occurrence of GOR.

The gastroprotectant used should be tailored to the patient and the clinical scenario presented (Marks et al., 2018).

Summary of the evidence

Favarato et al. (2012)	
Population:	• Healthy female dogs undergoing general anaesthesia for ovariosalpingohysterectomy. • Age range 0.5–9 years. • Weight range 1.5–34 kg.
Sample size:	90 dogs
Intervention details:	• 30 dogs were the control group – received only the anaesthetic protocol. • 30 dogs received metoclopramide – an intravenous bolus of 1 mg/kg 5 minutes before induction, and continuous infusion (1 mg/kg/h intravenously) immediately after anaesthetic induction. • 30 dogs received ranitidine – intravenous bolus of 2 mg/kg, 6 hours before anaesthesia. • All dogs received acepromazine (0.1 mg/kg), propofol (6 mg/kg) and isoflurane for anaesthetic protocol. • All received a 12 hour food and water fast. • Dogs were randomly assigned to groups.
Study design:	Randomised prospective study
Outcome studied:	• Evaluation of metoclopramide or ranitidine on the number of acid and non-acid reflux events during anaesthesia in dogs. Oesophageal pH values were monitored using intraluminal oesophageal pHmetry placed cranially to the oesophagogastric junction and recorded throughout the procedure.

	• pH values lower than 4 was considered an acid reflux episode. A non-acid reflux was confirmed by oesophagoscopy immediately after surgery. • Chi-squared test was used to compare the frequency of GOR events between groups.

Main findings: (relevant to PICO question):	• Reflux episodes were presented in seven dogs:
	  ○ Control group – 4/30 dogs;
	  ○ Ranitidine group – 2/30 dogs;
	  ○ Metoclopramide group – 1/30 dog.
	• Pre-anaesthetic metoclopramide and ranitidine did not reduce GOR.
	• No difference of reflux episodes ($p>0.05$) was found between the groups.

Limitations:	• Study was not stated to be blinded. • Low reflux events in the control group made it difficult to determine a difference compared to the treatment groups – a larger sample size could determine a different result. • Higher doses (more than normally used) of metoclopramide were used in the study.

Johnson (2014)	
Population:	• Dogs undergoing general anaesthesia for elective soft tissue or orthopaedic surgery. • Average age 3.1 years (range 6 months to 10 years). • Average weight 20.5 kg (range 3.6–49.8 kg). • No history of vomiting. • Mix of 18 purebred dogs and eight mixed breed dogs. • 18 females and eight males.
Sample size:	26 dogs
Intervention details:	• Treatment Group (n= 13 dogs) received maropitant (1 mg/kg^{-1}) intravenously (5–7 minutes) 45–60 minutes before premedication. • Control Group (n= 13 dogs) received saline 0.9% (0.1 mL/kg^{-1}) intravenously (5–7 minutes) 45–60 minutes before premedication. • Premedication consisted of hydromorphone (0.1 mg/kg^{-1}) and acepromazine (0.03 mg/kg^{-1}) intramuscularly followed by propofol (2–6 mg/kg^{-1}) and isoflurane (19 dogs) and sevoflurane (seven dogs) for anaesthesia. • Food, not water was withheld for 12 hours before anaesthesia. • Dogs were randomly assigned to groups. • Observer blinded to treatment monitored for retching or vomiting before induction.
Study design:	Randomised and blinded prospective study

Outcome studied:	Objective study to evaluate the efficacy of maropitant for prevention of vomiting and GOR in dogs undergoing anaesthesia measuring oesophageal pH • Flexible oesophageal pH probe placed into distal oesophagus (measured to assume tip was near gastro-oesophageal junction) detected for GOR. • Measurements were taken using a pH recorder and uploaded at study completion. • GOR defined as a pH less than 4 for gastric acid reflux or more than 7.5 pH for bile reflux for around 30 seconds. • Initial pH values were measured immediately on probe placement. • The Fisher Exact test was used to compare GOR in the groups.
Main findings: (relevant to PICO question):	• Vomiting and retching was prevented in the maropitant group (Treatment Group – 0 dogs and Control Group – 6/13 dogs retched or vomited). • GOR was not prevented as no difference in frequency between the groups (Treatment Group – 4/13 dogs and Control Group – 6/13 dogs had a reflux event).
Limitations:	Small sample size – a larger group could have shown a difference between the control group and the treatment group.

Panti et al. (2009)	
Population:	• Dogs (ASA Risk 1–2, American Society of Anesthesiologists Classification) undergoing general anaesthesia for pelvic limb orthopaedic surgery. • Weight range 9–85 kg. • No history of reflux, regurgitation, vomiting or gastrointestinal disturbances.
Sample size:	47 dogs
Intervention details:	• Treatment Group – 22 dogs were given 1 mg/kg omeprazole orally (p.o) at least 4 hours before anaesthesia. • Control Group – 25 dogs received only premedication. • Pre-anaesthetic – acepromazine (0.03 mg/kg) and methadone (0.2 mg/kg) intramuscularly followed by approximately 4 mg/kg propofol intravenously 1 hour later and maintained on isoflurane. • Each dog received an epidural – 37 dogs received preservative free morphine and a local anaesthetic and 10 dogs received preservative free morphine and sterile normal saline. • 31 dogs breathed spontaneously, and 16 dogs breathed with a ventilator. • Clinician (not involved in probe placement or anaesthetic) allocated patient to treatment group using a random number generator.

	• Food, not water, withheld for 12 hours.
	• Patient positioning:
	  ○ in dorsal recumbency was in 16/22 dogs in the Treatment Group and 15/25 dogs in the Control Group;
	  ○ in lateral recumbency was in 6/22 dogs in the Treatment Group and in 10/25 dogs in the Control Group.
	• Mechanical ventilation was performed in the Treatment Group on 5/22 dogs and in the Control Group on 11/25 dogs; the remainder breathed spontaneously.
	• pH probe placed into distal oesophagus after induction by the same operator using a set measurement. It was placed once adequate depth of anaesthesia was reached (15 to 20 minutes) to prevent GOR on placement.
	• Parameters were recorded every 5 minutes during anaesthesia by an anaesthetist unaware of the group the patient was in.
	• If regurgitation occurred (food up into the mouth) probe was washed with water.
	• Anaesthesia duration was between 120 and 330 minutes.
	• The Fisher Exact test was used to compare GOR in the groups.

Study design:	Randomised and blinded prospective study
Outcome studied:	• Investigate the effect of pre-operative administration of omeprazole on oesophageal pH. • GOR is defined as an abrupt decrease in pH below 4.
Main findings: (relevant to PICO question):	• GOR was decreased in dogs with the addition of omeprazole. • Treatment Group – 4/22 (18%) dogs less than 4 pH. • Control Group – 13/25 (52%) less than 4 pH. • GOR was 4.7 times more likely in the control group compared to the treatment groups (logistic regression, 95% CI 1.1 to 24.7, P = 0.032). • The number needed to treat with omeprazole to prevent GOR was 2.95 (95% CI 1.69 to 11.83).
Limitations:	• Long duration between each anaesthesia. • Large weight range between dogs.

Wilson et al. (2006)	
Population:	• Healthy dogs undergoing elective orthopaedic surgery. • Weight > 4.4 kg. • Age over 6 months. • Any dogs with a history of dysphagia, regurgitation or vomiting were excluded.
Sample size:	52 dogs
Intervention details:	• Control Group – 18 dogs received a saline (0.9% sodium chloride (NaCl)) infusion before and during anaesthesia. • Treatment Group 1 – 16 dogs received a low dose metoclopramide – bolus of 0.4 mg/kg intravenously followed by a continuous rate infusion of 0.3 mg/kg/hr before and during anaesthesia. • Treatment Group 2 – 18 dogs received a high dose metoclopramide – bolus of 1mg/kg intravenously followed by a continuous infusion of 1 mg/kg/hr before and during anaesthesia. • Premedication of acepromazine (0.044 mg/kg and morphine (0.66 mg/kg) intramuscularly, followed by thiopental to effect and maintained by isoflurane. • Food was withheld overnight (11–23.5 hours) but water was available. • Dogs were randomly assigned into groups however personnel knew their treatment status. • If vomiting occurred (54%), it was recorded following premedication. • All patients were placed into dorsal recumbency. • Patients breathed spontaneously. • Flexible pH probe taped to oesophageal stethoscope was inserted into oesophagus to measure GOR by 1 of 3 trained people using a standardised placement system. • Placement was near to gastroesophageal junction and data continually collected by a computer. • GOR was defined as a pH less than 4 or more than 7.5 for more than 30 seconds. • The Fisher Exact test was used to compare GOR in the groups.
Study design:	Randomised, non-blinded prospective trial
Outcome studied:	The effect of two doses of metoclopramide on the incidence of GOR in anaesthetised dogs measuring oesophageal pH.

Main findings: (relevant to PICO question):	• Higher doses of metoclopramide was associated with a 54% reduction in relative risk of developing GOR.
	• Dogs that had a GOR episode during anaesthesia:
	  ○ Control Group – 12/18 dogs;
	  ○ Treatment Group 1 – 7/16 dogs;
	  ○ Treatment Group 2 – 6/18.

Limitations:	• Morphine was used which could result in increased GOR. • Study was not blinded.

	• Higher doses (more than normally used – normal range of 0.5 mg to 1 mg/kg once daily (NOAH, 2020)) of metoclopramide were used in the study.

Zacuto et al. (2012)	
Population:	• Healthy dogs undergoing elective orthopaedic surgery. • Age range 0.5–12 years. • Weight range 3.6–52 kg. • Pure breeds and mixed breeds. • All dogs with a history of GOR, regurgitation, vomiting, oesophagitis or coughing were excluded.
Sample size:	61 dogs
Intervention details:	• Control Group – 21 dogs received saline (0.9% NaCl) 10ml over 3 minutes intravenously. • Treatment Group 1 – 22 dogs received esomeprazole (1 mg/kg) over 3 minutes intravenously. • Treatment Group 2 – 18 dogs received a combination of esomeprazole (1 mg/kg) over 3 minutes intravenously and cisapride (1 mg/kg diluted with sterile saline to a total of 100 ml) over 15 minutes intravenously • All were given 12–18 hours and 1–1.5 hours before anaesthetic induction. • Premedication of hydromorphone (0.05 mg/kg) and atropine (0.02 mg/kg) subcutaneously followed by propofol (4 mg/kg) and diazepam (0.3 mg/kg) intravenously and maintained on isoflurane. • Each dog received a loading dose of fentanyl (5 µg/kg) followed by a constant rate infusion (0.4 µg/kg/min) intravenously for analgesia. • All dogs were fasted for 12 hours. • Patients were randomly assigned to groups using a random number generator. • Anaesthetist was blinded to treatment group of patients. • Patients did not have a standard positioning. • Oesophageal pH/impedance probe was placed into oesophagus and external reference pad placed in axillary region to measure GOR. The probe was placed by 1 of 2 persons proximally to the gastroesophageal junction. • A one-way analysis of variance (ANOVA) and nonparametric Mann-Whitney U test to evaluate statistical differences.
Study design:	Randomised, double blinded and placebo-controlled prospective study
Outcome studied:	• The influence of esomeprazole and cisapride on gastroesophageal reflux during anaesthesia in dogs. • The data was collected via a computer and GOR defined when the pH was less than 4.

Main findings: (relevant to PICO question):	• Preanesthetic administration of cisapride and esomeprazole decreases the number of reflux events (per dog) in anesthetised dogs compared to placebo but esomeprazole alone does not.
	• The proportion of dogs having a GOR episode did not differ significantly among groups. Dogs that showed reflux episodes in each group:
	  ○ Control Group 8/21 dogs;
	  ○ Treatment Group 1 8/22 dogs;
	  ○ Treatment Group 2 2/18.

Limitations:	Small group of participants.

Appraisal, application and reflection

GOR is common in dogs and studies have shown a range of 12% to 78.5% incidences occur under general anaesthesia in studies in referral hospitals (Rodríguez-Alarcón et al., 2015).

The patients in all the studies were fasted of food overnight or for at least 12 hours for consistency and is compatible with a normal clinical setting (Favarato et al., 2012; Johnson, 2014; Panti et al., 2009; Wilson et al., 2006; and Zacuto et al., 2012). The Johnson (2014) study concluded pre-anaesthetic maropitant can assist in reducing vomiting but not the incidence of GOR as the two groups showed a similar GOR event rate. Further studies of a larger group would be required to prove this because the study was underpowered.

A study of preoperative omeprazole was performed by Panti et al. (2009). Results show a significant difference between the control group and the treatment group showing that omeprazole decreases GOR events in the anaesthetised dog. The study uniquely looked at the number needed to treat, showing three dogs would be given omeprazole prophylactically to prevent one of them from having GOR. This study therefore provides a good argument for the prophylactic treatment of all dogs undergoing general anaesthesia.

Morphine was used as an epidural in Panti et al. (2009) and Wilson et al. (2006) used it as a premedication. Morphine has been known to increase GOR when given intramuscularly and so should be avoided in patients undergoing anaesthesia (Wilson et al., 2005).

High doses of metoclopramide trialed by Wilson et al. (2006) in dogs undergoing anaesthesia was associated with a 54% reduction in relative risk of developing GOR. The study consisted of neutered male dogs and a mixture of spayed and entire female dogs. Although the trial was randomised the study was not blinded. The results do not show a significant difference in low dose metoclopramide. Conversely, a trial by Favarato et al. (2012) using pre-anaesthetic metoclopramide (same dose as Wilson et al. (2006)) or ranitidine concluded no influence in incidence of GOR. The difference between studies was that Wilson et al. (2006) used morphine as a premedication and that could have increased the incidence of GOR showing a discrepancy between the findings. Had morphine been used in Favarato et al. (2012) there is a possibility that a higher GOR event would be present in the control group and may have increased the chances in finding the beneficial effects of metoclopramide or ranitidine. In addition, Favarato et al. (2012) could have been underpowered compared to the Wilson et al. (2006) trial and that could have determined different results.

Esomeprazole with the addition of cisapride (prokinetic drug) has resulted in a decrease in GOR (Zacuto et al., 2012). The trial was randomised with a placebo-control. The difference to the other studies was that it was given 12–18 hours and 1–1.5 hours before anaesthesia. Esomeprazole itself increased the pH significantly but a noticeable difference with cisapride decreased GOR. The patients were not exposed to morphine as per previous studies but were similarly starved for 12 hours.

A limitation of the studies evaluated is the inclusion of all breeds. Brachycephalic breeds are more susceptible to GOR due to the increase in negative intrathoracic pressure as a result of overcoming upper respiratory tract obstruction associated with brachycephalic obstructive airway syndrome (Downing and Gibson, 2018). Therefore, the inclusion of brachycephalic breeds, which is unknown in these studies may bias the results. It would be prudent for future studies into GOR to consider this breed disposition. Another limitation is that dogs in each study were undergoing either soft tissue or orthopaedic surgery. Patients that undergo abdominal and orthopaedic surgeries are thought to be at higher risk of developing GOR (Rodríguez-Alarcón et al., 2015). Furthermore, other factors to consider that can increase the incidence of GOR include; the anaesthetic drugs given, patient signalment (breed, sex, age and weight) and positioning of the patient (Rodríguez-Alarcón et al., 2015). Finally, if there was mucosal abutment at the probe tip then this could potentially cause a false negative (Wilson et al., 2006).

In conclusion, studies suggest that high doses of metoclopramide, or omeprazole, or a combination of esomeprazole and cisapride have an effect on reducing GOR episodes in the anaesthetised dog. However, further trials would be beneficial. A new study factoring in trial number, patient positioning, sex, breed and type of surgery being performed could result in supporting previous studies.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on CAB Direct 1973 – 2020 Week 18 PubMed on NCBI interface 1920 – May 2020
Search terms:	CAB Abstracts: 1 (canine or canines or dog or dogs) 2 (anaesthe* or anesthe*) 3 (gastroprotectant* or gastro-protectant* or protectant* or omeprazole or esomeprazole or cisapride or maropitant or metoclopramide or ranitidine) 4 (((gastro* or gastric) and reflux) or GOR or GER) 5 1 and 2 and 3 and 4 PubMed: 1. (canine or canines or dog or dogs) 2. (anaesthesia or anesthesia or anaesthetic or anesthetic) 3. (gastroprotectant or gastro-protectant or protectant or omeprazole or esomeprazole or cisapride or maropitant or metoclopramide or ranitidine) 4. ((gastro or gastric) and reflux) or GOR or GER 5. 1 and 2 and 3 and 4
Dates searches performed:	14 May 2020

Exclusion / Inclusion Criteria	
Exclusion:	Studies that did not include anaesthesia, were not English, wrong species or were not related to PICO
Inclusion:	Peer-reviewed journals, veterinary journals, full papers, dogs

Search Outcome						
Database	**Number of results**	**Excluded – Not peer-reviewed**	**Excluded – Did not answer the PICO question**	**Excluded – Anything other than veterinary journals**	**Excluded – Not in English**	**Total relevant papers**
CAB Abstracts	9	1	3	0	0	5
PubMed	10	0	6	0	0	4
Total relevant papers when duplicates removed						**5**

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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