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**The effect of premedication with butorphanol or methadone on ease of endoscopic duodenal intubation in dogs.**

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**Running Head**

Opioid premedication in dogs prior to endoscopy

## **ABSTRACT**

### **Objective**

The effect of premedication with butorphanol or methadone on ease of endoscopic duodenal intubation.

### **Study Design**

Prospective, randomized, blinded clinical trial

### **Animals or Animal population**

Twenty client owned dogs

### **Methods**

Dogs were randomly assigned to receive intravenous (IV) premedication with either butorphanol ( $0.4 \text{ mg kg}^{-1}$ ) or methadone ( $0.3 \text{ mg kg}^{-1}$ ). General anaesthesia was induced with propofol to effect, and maintained with isoflurane in 100% oxygen. Sedation score 20 minutes after administering premedication, and induction dose of propofol were recorded. Heart rate (HR), mean arterial pressure (MAP), haemoglobin oxygen saturation ( $\text{SaO}_2$ ), respiratory rate ( $f_R$ ) and end-tidal isoflurane concentration ( $\text{Fe}'\text{Iso}$ ) were recorded every five minutes. Spontaneous lower oesophageal and pyloric sphincter opening, presence of gastro-oesophageal and duodeno-gastric reflux, antral peristaltic contractions and response to endoscopy were recorded as Yes / No. Ease of duodenal intubation (EDI) was graded on a four point scale. Time (seconds) from the start of pyloric intubation to successfully entering the duodenum was recorded.

### **Results**

Median EDI score ( $2.5 \pm 1.1$  Butorphanol,  $4.0 \pm 1.0$  Methadone,  $p = 0.035$ ), time ( $65 \pm 35.5$  s Butorphanol,  $120 \pm 38.1$  s Methadone,  $p = 0.028$ ) and spontaneous pyloric sphincter opening (7/10 Butorphanol, 2/10 Methadone,  $p = 0.035$ ) significantly differed between groups. No other significant differences were found.

### **Conclusions and clinical relevance**

In these clinical cases duodenal intubation was performed with greater ease, shorter time and more frequent spontaneous opening of the pyloric sphincter after premedication with butorphanol in comparison to methadone. The use of butorphanol facilitated the passage of the endoscope and is therefore recommended for premedication prior to upper gastrointestinal tract endoscopy.

### **Keywords:**

Canine; Methadone; Butorphanol; Endoscopy; Pylorus

## Introduction

Endoscopic examination of the gastrointestinal tract is a commonly performed procedure in dogs. The ability to obtain biopsies and to visualise the mucosal surface of the intestines without the need for an exploratory laparotomy has advantages in potentially already compromised patients (Zoran 2001; Simpson 2005). General anaesthesia for these cases however is still a necessity, not only for both the safety and comfort of the patient and operator, but also for protection of the equipment (Zoran 2001).

The pyloric sphincter can impede passage of an endoscope from the stomach into the duodenum (Donaldson et al. 1993). The aim of pharmacological manipulation of pyloric sphincter tone is to optimise conditions to allow easy passage of the endoscope into the duodenum. The use of morphine ( $0.5 \text{ mg kg}^{-1}$ ) in combination with atropine ( $0.04 \text{ mg kg}^{-1}$ ) given intramuscularly (IM) results in conditions that make the passage of an endoscope through the canine pyloric sphincter more difficult (Donaldson et al. 1993). It is therefore often recommended that opioids be avoided as part of the premedication prior to general anaesthesia for endoscopy (Zoran 2001; Hall 2008). No studies currently compare the use of methadone and butorphanol for premedication prior to upper gastrointestinal tract endoscopy despite the recommendation that  $\mu$  opioid agonists be avoided and butorphanol be used for this indication (Kerr 2016).

Butorphanol is a synthetic opioid partial agonist, its low efficacy at  $\mu$  opioid receptors leads to its classification as a  $\kappa$  opioid receptor agonist and a  $\mu$  opioid receptor antagonist (WHO 2006). Butorphanol produces mild sedation when used alone and analgesia inferior to that of the full  $\mu$  agonists (Kerr, 2016). It is therefore best reserved for minor elective surgical and diagnostic procedures.

Methadone is a synthetic opioid agonist with a high affinity for  $\mu$  opioid receptors and a similar potency to morphine. The dextrorotatory enantiomer of methadone is an NMDA receptor antagonist, an additional property that is not possessed by other  $\mu$  opioid receptor agonists or butorphanol. When used alone for sedation methadone produces only mild sedation and is associated with a high prevalence of panting, but less vomiting than morphine (Monteiro et al. 2008; Monteiro et al. 2009). The lower prevalence of retching and vomiting in dogs premedicated with methadone compared to morphine makes it a good choice for gastrointestinal endoscopy.

The purpose of this study was to compare the influence of butorphanol and methadone on the ease of passing an endoscope from the stomach through the pyloric sphincter into the duodenum of dogs anaesthetised with propofol and isoflurane. We hypothesised that butorphanol would result in conditions that better facilitated the passing of the endoscope than methadone.

## **Materials and methods**

Ethical approval was obtained from the Animal and Welfare Ethical Review Board of the ?, UK (VIN/15/021). Informed owner consent was obtained for each dog recruited to the study. Based on previously published work (Donaldson et al. 1993) it was calculated that we would require 10 dogs per group to detect a difference of one, using the scale published by Matz et al. (1991) on the ease of performing endoscopic duodenal intubation, at a 95% confidence level with 80% power.

### **Animals**

Twenty dogs scheduled for upper gastrointestinal endoscopy involving examination of the duodenum were enrolled in this study. All dogs considered eligible for the anaesthetic protocol were included. Exclusion criteria included dogs that were

unsuitable for the anaesthetic protocol and dogs suspected of having gastric or lower gastrointestinal tract disease alone and therefore not scheduled for examination of the duodenum.

### Study Protocol

A prospective, randomized, blinded clinical trial was designed. Patients enrolled in the study were randomly assigned to one of two groups using an online randomisation programme ([www.sealedenvelope.com](http://www.sealedenvelope.com)). Group M (n=10) were to receive methadone and Group B (n=10) butorphanol as intravenous premedication.

All dogs underwent physical examination by the same anaesthetist on the day of the scheduled procedure and were judged to be suitable for the anaesthetic protocol. Dogs were assigned an American Society of Anaesthesiologists (ASA) score (I-V) and a body condition score (BCS) using a nine point scale. Food but not water was withheld for 24 to 48 hours prior to general anaesthesia, dependent on whether lower gastrointestinal endoscopy would be performed. If required, dogs were given three peroral doses of a bowel cleansing agent (25 ml/kg/dose, KleanPrep; Norgine, UK) with the last dose  $\geq 12$  hours before, and a warm water enema two hours before general anaesthesia. A 20Ga catheter (Jelco; Smiths Medical, UK) was placed into either cephalic vein. Group M received methadone  $0.3 \text{ mg kg}^{-1}$  (Comfortan; Dechra, UK) and Group B butorphanol  $0.4 \text{ mg kg}^{-1}$  (Alvegesic; Dechra, UK) intravenously (IV) as premedication. Treatments were prepared by a second anaesthetist to ensure the anaesthetist performing the study remained blinded to group allocations. All treatments were diluted to a total volume of  $0.05 \text{ ml kg}^{-1}$  using sterile water for injection (Water for Injection; Hameln Pharmaceuticals, Germany).

Dogs were taken to a quiet room and allowed to acclimatize for 10 minutes before administration of treatments. Dogs were kept in the same room and monitored throughout for any signs of adverse reaction to the treatments. After 20 minutes the level of sedation was assessed using a composite sedation scale ranging from 0) no sedation to 15) well sedated (Gurney et al. 2009). Dogs were then moved to the room where endoscopy was to be performed. Anaesthesia was induced with Propofol (PropoFlo; Abbott,UK) IV given to effect to allow endotracheal intubation. General anaesthesia was maintained with Isoflurane (Iso-Vet; Chanelle, Primal Healthcare, UK) vaporised in 100% oxygen, given at a variable concentration to maintain an adequate depth of anaesthesia, delivered via a Mapleson-D or circle breathing system. Dogs were positioned in left lateral recumbency and connected to a multiparameter monitor (PM-9000Vet; Mindray, China). When the relevant monitoring was attached, endoscopy was started. Heart rate (HR), oscillometric mean arterial pressure (MAP), haemoglobin oxygen saturation (SaO<sub>2</sub>), respiratory rate (*f*R) and end-tidal isoflurane concentration (Fe' Iso) were recorded every five minutes throughout the test period. Upper gastrointestinal tract endoscopy was performed first if lower gastrointestinal tract endoscopy was also required. If a response of purposeful movement or swallowing was seen during either passage of the endoscope into the stomach or through the pyloric sphincter, this was recorded and a 1 mg kg<sup>-1</sup> propofol bolus given IV. If an increase of greater than 20% in either HR, *f*R or MAP was seen, this was recorded and the inspired concentration of isoflurane increased by 0.25% on the vaporiser setting. If evident, the presence of gastro-oesophageal reflux was recorded and when the lower oesophageal sphincter was visualised it was examined for spontaneous opening. Once through the lower oesophageal sphincter and into the stomach the movement of the antrum was examined. The endoscope was positioned to clearly visualise the pyloric sphincter and if



present, reflux from the duodenum into the stomach was recorded. The pyloric sphincter was also examined for spontaneous opening. When the pyloric sphincter had been visualised a stopwatch was started and the endoscopist advanced the endoscope through the pyloric sphincter into the duodenum. The stopwatch was stopped when positive confirmation of entering the duodenum could be made. The ease of passing the endoscope through the pyloric sphincter was also graded using a four point scale (Matz et al. 1991). 1 = immediate entry with minimal manoeuvring required, 2 = rapid entry with moderate manoeuvring, 3 = difficult entry with multiple attempts required and 4 = no entry after two minutes. Once the duodenum had been entered the study period was finished and the general anaesthetic monitored and maintained as deemed appropriate for the remainder of the endoscopic examination. At the end of general anaesthesia, dogs were disconnected from the anaesthetic machine and recovered in a quiet room.

#### Statistical analysis

Descriptive results of parametric continuous variables are given as the mean  $\pm$  standard deviation (SD) and non-parametric continuous plus categorical variables as the median (interquartile range). Computer software (SPSS version 23; IBM Corp, USA) was used for statistical analysis. Data was tested for normality using the Shapiro-Wilk test. Variables that were normally distributed were tested using Students t-test for differences between treatments. Non-normally distributed variables were tested for differences between treatments using the Mann-Whitney U test. For categorical variables a Fishers exact test was used. Statistical significance was set as a p-value  $<0.05$ .

#### **Results**

There was no statistical difference for sex, weight, age, ASA classification and BCS between the dogs in either group (Table 1).

No significant differences were found for sedation scores 20 minutes after drug administration, or the dose of propofol required for induction of general anaesthesia, or the physiological parameters or the Fe' Iso between groups at the time of passage of the scope through the pyloric sphincter (Table 2).

No significant differences between groups was found for response to passing of the endoscope, presence of oesophageal reflux, spontaneous opening of the lower oesophageal sphincter, presence of duodenal reflux, and presence of antral movement. Spontaneous opening of the pyloric sphincter was significantly different between the two groups. Of dogs in Group B 7/10 showed spontaneous opening of the pyloric sphincter compared to 2/10 dogs in Group M ( $p = 0.035$ ) (Table 3).

The ease of passing the endoscope through the pyloric sphincter differed significantly between groups, with significantly greater ease shown for Group B ( $p = 0.035$ ). The time taken to pass the endoscope through the pyloric sphincter also differed significantly between groups with 65 (65) seconds for Group B and 120 (44) seconds for Group M ( $p = 0.028$ ). (Table 4)

## **Discussion**

Compared to methadone at a dose of  $0.3 \text{ mg kg}^{-1}$  IV, premedication with butorphanol at a dose of  $0.4 \text{ mg kg}^{-1}$  IV prior to upper gastrointestinal tract endoscopy, resulted in conditions that allowed for easier and quicker passage of the endoscope through the canine pyloric sphincter.

Endogenous opioid peptides are released by neurons of the myenteric plexus, in particular neurons that project to circular muscle (Sternini et al. 2004). Opioid receptors

are found both pre- and post-synaptically on excitatory and inhibitory enteric neurons (Holzer 2009). This wide distribution of opioid receptors means that effects of exogenous opioids can lead to pyloric muscle spasm or relaxation dependent on which pathway is interrupted. Effects on excitatory pathways is via inhibition of acetylcholine release, and on inhibitory pathways via inhibition of nitric oxide release (Holzer 2009). The distribution of opioid receptor type varies between species and location along the gastrointestinal tract (Sternini et al. 2004). Despite this, recommendations to avoid opioids prior to endoscopy often do not differentiate between classes of opioid drugs (Zoran 2001; Hall 2008). This may mean that the use of opioid drugs that facilitate endoscopy and also provide additional comfort for the patient are being overlooked.

In this study, the use of methadone was associated with significantly longer times and reduced ease of passing the endoscope through the pyloric sphincter. This finding is consistent with a study of Donaldson et al. (1993) where the use of three premedication combinations containing morphine resulted in the most difficulty for passage of an endoscope through the pyloric sphincter, compared to nine other premedication combinations. Although methadone and not morphine was used in this study, their similar activity at opioid receptors should allow for transposition of results. Premedication with methadone resulting in more difficult passage of an endoscope through the pyloric sphincter is likely due to increased tone of the circular muscles (Holzer 2009). Our study supports this view as spontaneous pyloric sphincter opening was found to be less frequent in dogs that had received methadone. Increases in sphincter muscle tone following  $\mu$  opioid receptor agonists is supported by the administration of the  $\mu$  opioid receptor antagonist naloxone causing a reduction in pyloric sphincter tone and reversing opioid induced constipation (Reynolds et al. 1984; Jurna et al. 1992). This finding in dogs is in contrast to that found when hydromorphone

at a dose of 0.1 mg kg<sup>-1</sup> was compared to butorphanol at 0.4 mg kg<sup>-1</sup> in cats, where no significant difference in ease or time taken to pass the endoscope through the cardiac and pyloric sphincters was found (Smith et al. 2004). This shows the importance of species variations when thinking about the effect of opioid drugs on gastrointestinal activity.

In contrast to methadone, butorphanol's intrinsic partial  $\mu$  opioid receptor agonist activity causes only slight increases in gastrointestinal smooth muscle activity (WHO 2006). Antagonism of endogenous opioid receptor ligands is another possible mechanism to explain the findings seen. Peristaltic activity in the rat intestine is inhibited by  $\mu$  and  $\delta$  opioid receptor agonists but not  $\kappa$  opioid receptor agonists (Holzer 2009). If the dog's intestine shows a similar response to  $\kappa$  opioid receptor agonists this may explain the higher incidence of spontaneous opening of the pyloric sphincter in the group receiving butorphanol.

The reason for no difference in the incidence of lower oesophageal sphincter opening is likely due to a difference in the distribution of opioid receptors in comparison to the pyloric sphincter (Holzer 2009). The tone of the lower oesophageal sphincter is unlikely to have a significant impact on the speed and ease of performing endoscopy due to the fact that minimal manipulation of the endoscope is required for orientation and passage of the endoscope into the stomach.

Both groups of dogs in the present study required 1x MAC of isoflurane, this is lower than the concentration of inhalation agent required in previous studies where 1.2 – 1.5x MAC has been required (Lieb et al. 1990; Donaldson et al. 1993). A response to passage of the endoscope in this study was defined as either purposeful movement or swallowing requiring additional propofol, or changes of greater than 20% in monitored

physiological variables. Although 6 dogs in the methadone group and 4 dogs in the butorphanol group showed a response to passage of the endoscope, this was primarily as a transient increase in the heart rate and did not require intervention. Only one dog in each group required additional propofol. It can therefore be concluded that a Fe'Iso of 1x MAC is sufficient to facilitate upper gastrointestinal tract endoscopy following either premedication used in this study.

Although the doses of butorphanol and methadone selected for this study may not be considered equipotent, they were selected based on the average dose of each drug when used as the sole premedication prior to general anaesthesia at the institution in which the study was conducted. This approach, rather than simply using the same dose of each drug, makes the doses used clinically relevant. Given that this study investigated the effects of the premedication it can be said that the doses used were equi-efficacious as there was no difference between groups for the sedation score, induction dose of propofol ( $\text{mg kg}^{-1}$ ) or Fe'Iso (%). The doses of butorphanol  $0.4 \text{ mg kg}^{-1}$  and methadone  $0.3 \text{ mg kg}^{-1}$  could therefore be considered equipotent in the context of this study.

The 15 point sedation scale used in this study (Gurney et al. 2009) is an adapted version of a previously published 20 point scale (Kuusela et al. 2000). This adapted version removes the need to assess relaxation of the jaw tone. The original scale and another simplified version that has previously been used to assess sedation in cats (Grint et al. 2009), have been found to have good intra- and inter-rater reliability (Wagner et al. 2016). Variability was kept to a minimum by one observer assessing sedation level in all dogs. An improvement would be the use of a clicker to produce a repeatable noise to assess the response to sound rather than a hand clap (Wagner et al. 2016).

A limitation of the study is that due to the constraints of a teaching hospital environment, the endoscopic procedures were performed by seven different endoscopists. It has been previously suggested that experience of the person performing the endoscopy has a significant effect on the ease of passing the scope through the pylorus (Matz et al. 1991). All users performing endoscopy during this study had been trained in the use of an endoscope for upper gastrointestinal tract endoscopy and none of the endoscopists were novice to the technique or equipment used. The effect of the operator performing the endoscopy was investigated, data not presented here, and it was found that endoscopist experience was not significantly correlated with either time taken or ease of passing the endoscope through the pyloric sphincter in this study.

This study reports for the first time the use of either butorphanol or methadone, and their comparison, for premedication prior to upper gastrointestinal tract endoscopy in the dog. It uses updated anaesthetic protocols in comparison to previous studies and in clinical rather than experimental animals. Both methadone and butorphanol resulted in adequate anaesthesia at 1x MAC of isoflurane, without any difference in sedation score. Improved conditions for endoscopy were found for the butorphanol group and might result in a better experience for both the patient and endoscopist. In conclusion, in these clinical cases duodenal intubation was performed with greater ease, shorter time and more frequent spontaneous opening of the pyloric sphincter after premedication with butorphanol in comparison to methadone, showing that the use of opioids should not necessarily be avoided in patients undergoing endoscopy.

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<b>Parameter</b>	<b>Group B</b>	<b>Group M</b>	<b>p value</b>
Weight	20.0 ± 12.9	14.2 ± 8.4	0.247
Age	80 ± 49	64 ± 47	0.453
ASA	2 ± 1	2 ± 1	0.303
BCS	4 ± 5	3 ± 2	0.155
Gender	6 M / 4 F	7 M / 3 F	0.500

**Table 1** Weight (kg), age (months), ASA classification (I-V), body condition score (BCS, 1-9) and gender (M male, F female) of dogs premedicated with either 0.4 mg kg<sup>-1</sup> butorphanol (Group B) or 0.4 mg kg<sup>-1</sup> methadone (Group M) intravenously



<b>Parameter</b>	<b>Group B</b>	<b>Group M</b>	<b>p value</b>
Sedation Score	5.3 ± 2	7.2 ± 2.5	0.082
Induction Dose	4.3 ± 1.2	5.8 ± 1.9	0.056
HR	98 ± 27	86 ± 20	0.274
<i>f</i> R	13 ± 8	16 ± 10	0.405
SpO <sub>2</sub>	98 ± 1	98 ± 0.5	0.631
MAP	67 ± 4	66 ± 10	0.856
Fe' Iso	1.22 ± 0.21	1.28 ± 0.22	0.531

**Table 2** Sedation score (/15, 0) no sedation to 15) well sedated, induction dose of propofol (mg/kg), heart rate (HR), respiratory rate (*f*R), haemoglobin-oxygen saturation (SpO<sub>2</sub>) %, mean arterial pressure (MAP) mmHg and end-tidal isoflurane concentration (Fe' Iso) % at time of passage of an endoscope through the pyloric sphincter in dogs premedicated with either 0.4 mg kg<sup>-1</sup> butorphanol (Group B) or 0.4 mg kg<sup>-1</sup> methadone (Group M) intravenously.

	Group	Yes	No	p value
Response to passing the Endoscope	B	4	6	0.328
	M	6	4	
Oesophageal reflux present	B	2	8	0.500
	M	1	9	
Spontaneous opening of the lower oesophageal sphincter	B	5	5	0.500
	M	4	6	
Duodenal reflux present	B	6	4	0.085
	M	2	8	
Spontaneous opening of the pyloric sphincter	B	7	3	0.035*
	M	2	8	
Antral movement present	B	2	8	0.314
	M	4	6	

**Table 3** Observations made during upper gastrointestinal tract endoscopy in dogs after premedication with either 0.4 mg kg<sup>-1</sup> butorphanol (Group B) or 0.4 mg kg<sup>-1</sup> methadone (Group M) intravenously. \* indicates a significant difference between the groups (p < 0.05).

	Ease of passing the endoscope through the pyloric sphincter			
Score	1	2	3	4
B (n =10)	4	1	4	1
M (n = 10)	1	0	4	5

**Table 4** Ease of passing the endoscope through the pyloric sphincter grade (1-4) in dogs after premedication with either 0.4 mg kg<sup>-1</sup> butorphanol (Group B) or 0.4 mg kg<sup>-1</sup> methadone (Group M) intravenously.

Scoring 1 = immediate entry with minimal manoeuvring required, 2 = rapid entry with moderate manoeuvring, 3 = difficult entry with multiple attempts required and 4 = no entry after two minutes. (Matz et al. 1991).