Evaluation of the effects of premedication on gastroduodenoscopy in cats

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Objective—To evaluate the effects of hydromorphone, hydromorphone and glycopyrrolate, medetomidine, and butorphanol premedication on the difficulty and time required to pass an endoscope into the stomach and duodenum of cats anesthetized with ketamine and isoflurane.

Design—Randomized complete block crossover study.

Animals—8 purpose-bred adult female cats.

Procedures—Each cat was premedicated and anesthetized 4 times with an interval of at least 7 days between procedures. Cats were premedicated with hydromorphone, hydromorphone and glycopyrrolate, medetomidine, or butorphanol administered IM. Twenty minutes after premedication, sedation was assessed by use of a subjective ordinal scale. Cats received ketamine administered IM, and 10 minutes later a cuffed orotracheal tube was placed and anesthesia maintained with isoflurane. Cats breathed spontaneously throughout the procedure. When end-tidal isoflurane concentration was stable at 1.4% for 15 minutes, endoscopy was begun. The times required to pass the endoscope through the cardiac and pyloric sphincters were recorded, and the difficulty of endoscope passage was scored by use of a subjective ordinal scale.

Results—No significant differences in difficulty or time required to pass the endoscope through the cardiac and pyloric sphincters were found among premedicant groups. Premedication with medetomidine resulted in the greatest degree of sedation and longest time to return to sternal recumbency.

Conclusions and Clinical Relevance—Results suggest that hydromorphone, hydromorphone and glycopyrrolate, medetomidine, and butorphanol at the doses tested can be used satisfactorily to premedicate cats prior to general anesthesia for gastroduodenoscopy. (*J Am Vet Med Assoc* 2004;225:540–544)

Gastroduodenoscopy is a procedure commonly used in cats to aid in the diagnosis of diseases of the stomach and small intestine.[1-4] The procedure is less invasive than exploratory celiotomy and is therefore associated with lower morbidity and mortality rates; it is often preferred to surgery. Nevertheless, gastroduodenoscopy in cats requires general anesthesia.

The cardiac and pyloric sphincters can impede passage of an endoscope.[1,5] Pyloric sphincter tone in the cat is the result of action of 2 circumferential bands of smooth muscle[6,7] that are regulated by a complex pathway affected by both neural and hormonal stimuli. Both contraction and relaxation of the pyloric sphincter have been linked to vagal stimulation.[6,8] Several drugs commonly used as premedicants prior to general anesthesia may increase tone of the sphincters of the gastrointestinal tract and therefore hinder gastroduodenoscopy.

Glycopyrrolate is a synthetic anticholinergic drug commonly administered as a premedicant to decrease salivary secretion, increase gastric pH, minimize bradycardia associated with concurrent administration of opioids,[9] and prevent vagal reflexes associated with gastrointestinal insufflation. Although administration of glycopyrrolate to humans decreases cardiac sphincter tone,[10] anticholinergic drugs may increase pyloric sphincter tone, making passage of an endoscope into the duodenum more difficult; for this reason, their use is contraindicated for gastroduodenoscopy.[4,11]

Hydromorphone is a semisynthetic, pure μ-opioid agonist commonly used as a premedicant in cats because of its analgesic and sedative properties.[12] Endogenous opioid agonists and exogenous morphine increase pyloric sphincter tone in cats, whereas naloxone, a μ-opioid antagonist, decreases pyloric sphincter tone in cats.[8,13] When an anticholinergic drug was administered with a μ-opioid agonist to dogs, the difficulty of passing an endoscope through the pyloric sphincter increased[5]; therefore, some endoscopists have suggested that opioids be avoided altogether in small animals undergoing gastroduodenoscopy.[4,14]

Butorphanol is a synthetic opioid and is considered an agonist of the κ receptor and an antagonist of the μ receptor.[15,16] Although it provides less analgesia and sedation than pure μ-opioid agonists,[17] butorphanol is often used as a premedicant in cats. The effect of butorphanol on the tone of the cardiac and pyloric sphincters is not known.

Medetomidine is an α_2 adrenergic agonist that provides both profound sedation and analgesia in cats.[18] When given as a premedicant to dogs, medetomidine does not influence the degree of difficulty of passage of an endoscope through the pyloric sphincter.[14]

The purpose of the study reported here was to evaluate the effects of hydromorphone, hydromorphone and glycopyrrolate, medetomidine, and butor-

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phanol premedication on the difficulty and time required to pass an endoscope into the stomach and duodenum of cats anesthetized with ketamine and isoflurane. We hypothesized that the order in which these drugs would affect the difficulty and time required to pass an endoscope into the stomach and duodenum (from most difficult and longest time to least difficult and shortest time) would be hydromorphone and glycopyrrolate, hydromorphone, butorphanol, and medetomidine.

Materials and Methods

Animals—The study was approved by the Cornell University Institutional Animal Care and Use Committee. Eight purpose-bred adult female cats aged 1 to 10 years (median age, 6.5 years) and weighing 2.6 to 4.5 kg (5.7 to 9.9 lb; median weight, 3.3 kg [7.3 lb]) were used. Seven cats had been infected with *Helicobacter pylori* during a previous study; however, none of these cats had clinical signs attributable to infection. One cat died between procedures (after receiving hydromorphone and butorphanol) as a result of an unrelated disease. All cats were healthy (on the basis of history and physical examination), had normal appetites, and had no evidence of diarrhea or vomiting. In this crossover study, the order in which cats were premedicated was determined by a restricted lottery to assure that there were only 2 cats in each premedicant group per day; there was an interval of at least 7 days between procedures.

Experimental protocol—Food was withheld from cats for at least 12 hours before each procedure. Hydromorphone[a] (0.1 mg/kg [0.045 mg/lb]), hydromorphone and glycopyrrolate[b] (0.1 and 0.01 mg/kg [0.005 mg/lb], respectively), medetomidine[c] (0.03 mg/kg [0.014 mg/lb]), and butorphanol[d] (0.4 mg/kg [0.18 mg/lb]) were administered IM. The doses were chosen on the basis of those commonly used in cats at the Cornell University Hospital for Animals. Twenty minutes after administration of premedicants, the degree of sedation was scored by the same nonblinded, experienced evaluator (AAS; 0 = no effect; 1 = impaired or prancing gait, some excitement; 2 = head lowered, braced stance with hindquarter weakness; 3 = sternal or lateral recumbency, unable to stand, some response to positioning; and 4 = sternal or lateral recumbency, no response to positioning).[19]

General anesthesia was induced with ketamine[e] (10 mg/kg [4.5 mg/lb], IM). Cats lay on a circulating warm-water blanket throughout the entire anesthetic period. Ten minutes after ketamine administration, orotracheal intubation was attempted; in cats that were insufficiently anesthetized to allow orotracheal intubation, isoflurane[f] was provided via a face mask until intubation could be performed. The time of intubation was considered the start time of anesthesia (time 0). Anesthesia was maintained with isoflurane in oxygen by use of a pediatric circle-rebreathing system, and cats were allowed to breathe spontaneously. End-tidal carbon dioxide partial pressure and isoflurane concentration were monitored[g] and recorded every 5 minutes, beginning at time 0. When end-tidal isoflurane concentration was stable at 1.4% for 15 minutes, endoscopy was initiated. The highest end-tidal carbon dioxide partial pressure attained by each cat was recorded.

Endoscopy was performed by use of a gastrointestinal videoscope[h] with an 8.5-mm insertion tube diameter and 103-cm working length. An expert endoscopist (REG) was blinded to the premedication administered. The time required to pass the endoscope from the upper esophageal sphincter through the cardiac sphincter and into the stomach was recorded. The time required to pass the endoscope from the upper esophageal sphincter through the cardiac and pyloric sphincters and into the duodenum was also recorded. The stomach was not explored. The time required to pass the endoscope was recorded by 2 observers (AAS and LPP), and the mean time was calculated. Transit time between the stomach and duodenum was calculated by subtracting the time required to pass the endoscope from the mouth to the stomach from the time required to pass the endoscope from the mouth to the duodenum. Anatomic location of the endoscope was verified via visual identification by the endoscopist.

The difficulty of passing the endoscope from the esophagus to the duodenum was evaluated subjectively by the endoscopist (0 = no difficulty with no or little endoscope manipulation required, 1 = moderate difficulty with a moderate amount of endoscope manipulation required, 2 = marked difficulty with numerous endoscope manipulations required, and 3 = no entry gained into the duodenum after 10 minutes).

Anesthesia was discontinued after removal of the endoscope from the cat. Cats were observed during recovery from anesthesia, and time from the end of anesthesia to the cat's return to sternal recumbency was recorded.

Statistical analyses—Data were analyzed by use of statistical software.[i] Because this was a crossover study, data were blocked on cat and analyzed by use of a Friedman test. To confirm that absence of 1 cat from 2 procedures did not affect the final results, complete data from the hydromorphone and butorphanol groups were analyzed by use of the Wilcoxon signed-rank test. The ability of premedicants to induce sedation was evaluated within treatments by use of the 1-tailed Wilcoxon rank sum test. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

Compared with state prior to premedication (nonsedated cats), premedication induced sedation in all groups (hydromorphone, $P = 0.002$; hydromorphone and glycopyrrolate, $P = 0.035$; medetomidine, $P < 0.001$; butorphanol, $P = 0.035$). Medetomidine induced a significantly ($P = 0.001$) greater degree of sedation than the other 3 premedicants (**Table 1**). The delivery of isoflurane by use of a mask to facilitate orotracheal intubation was required in 21 of 30 procedures. Only 1 cat that was given medetomidine required isoflurane to facilitate intubation. All cats given hydromorphone and glycopyrrolate required isoflurane to aid intubation. One cat given butorphanol and 2 cats given hydromorphone were intubated without isoflurane.

Passage of the endoscope from the mouth through the cardiac sphincter to the stomach and from the stomach through the pyloric sphincter to the duodenum took approximately 10 and 20 seconds, respectively (Table 1). No significant differences were found among premedicant groups or individual cats. No significant differences in difficulty of passing the endoscope were found among premedicant groups or individual cats. No significant differences among premedicant groups or individual cats were found for the maximum end-tidal carbon dioxide partial pressure. No significant differences in time from start of anesthesia (time 0) to start of endoscopy were found among premedicant groups. Duration of anesthesia ranged from 18 to 43 minutes (median, 26 minutes) and was not significantly different among premedicant groups.

Table 1—Median (range) values for variables assessed in a study that evaluated the effects of hydromorphone, hydromorphone and glycopyrrolate, medetomidine, and butorphanol premedication on difficulty and time required to pass an endoscope into the stomach and duodenum of cats anesthetized with ketamine and isoflurane.

Variable	Hydromorphone (n = 8 cats)	Hydromorphone and glycopyrrolate (7)	Medetomidine (7)	Butorphanol (8)
Sedation score*	1 (0–2)	1 (0–1)	3 (2–4)‡	0.5 (0–1)
Time from mouth to stomach (s)	9 (5–16)	7 (5–12)	8 (6–16)	8 (5–15)
Time from stomach to duodenum (s)	20 (14–41)	18 (10–40)	20 (16–119)	22 (12–84)
Difficulty of passing endoscope†	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)
Maximum end-tidal CO_2 partial pressure (mm Hg)	57 (46–68)	57 (44–60)	55 (32–67)	54 (46–68)
Time to return to sternal recumbency (min)	10 (4–35)	16 (7–72)	82 (68–222)‡	14 (3–34)
Time from start of anesthesia (time = 0) to start of endoscopy (min)	21 (18–30)	24 (17–25)	20 (17–27)	22 (18–26)

*Sedation scores were defined as 0 = no effect; 1 = impaired or prancing gait, some excitement; 2 = head lowered, braced stance with hindquarter weakness; 3 = sternal or lateral recumbency, unable to stand, some response to positioning; and 4 = sternal or lateral recumbency, no response to positioning. †Difficulty of passing the endoscope from the esophagus to the duodenum was defined as 0 = no difficulty, with no or little endoscope manipulation required; 1 = moderate difficulty, with a moderate amount of endoscope manipulation required; 2 = marked difficulty, with numerous endoscope manipulations required; and 3 = no entry gained into duodenum after 10 minutes. ‡Significantly ($P < 0.05$) greater value than for other premedicants.

Time to return to sternal recumbency was longer for cats given medetomidine than for cats given the other 3 premedicants ($P = 0.004$; Table 1). Time to return to sternal recumbency was also influenced by the individual cat; 2 cats had significantly ($P = 0.04$) longer recovery times than other cats, irrespective of premedicant group.

Discussion

No significant differences in difficulty or time required to pass an endoscope into the stomach and duodenum were found among cats given hydromorphone, hydromorphone and glycopyrrolate, medetomidine, and butorphanol. The gastroduodenoscopy procedure was remarkably short in almost all cats; the time required to enter the stomach never exceeded 16 seconds, and the time taken to pass the endoscope from the stomach into the duodenum was approximately 20 seconds and always < 2 minutes.

Glycopyrrolate did not affect the duration or difficulty of passage of the endoscope through either sphincter when it was administered with hydromorphone. Atropine (another anticholinergic drug) induces relaxation of the cardiac sphincter in cats,[20] which may facilitate passage of the endoscope into the stomach; however, little is known about the effects of glycopyrrolate on sphincter tone in cats. Because glycopyrrolate is the anticholinergic drug used routinely as a premedicant at the Cornell University Hospital for Animals, it was used in our study.

We found no evidence to suggest that use of hydromorphone makes gastroduodenoscopy more difficult than use of any of the other premedicants tested; the longest time required to enter the duodenum in cats given hydromorphone was < 1 minute. Use of a μ-opioid agonist and an anticholinergic drug increased the difficulty of gastroduodenoscopy in dogs[5]; however, this combination does not appear to have the same effect in cats.

Recommendations to avoid opioids before gastroduodenoscopy do not differentiate between κ and μ-opioid agonists.[4,14] Because butorphanol is an antagonist of μ-opioid receptors, we expected that it would impede gastroduodenoscopy to a lesser degree than hydromorphone; however, both the ease and speed of passing the endoscope were indistinguishable.

Sap and Hellebrekers[14] suggested that medetomidine may prevent pyloric sphincter spasm, facilitating endoscope passage into the duodenum in dogs. No differences in difficulty or duration of endoscope passage were found between cats given medetomidine and cats given the other premedicants.

The controversy regarding the relationship between anesthetic drugs and difficulty of endoscopy has centered on premedicants rather than on induction agents and volatile anesthetics.[4,5,11,14,21] Ketamine is an induction agent that is commonly used in small animal practice and has been used as an anesthetic in studies[13,22] that evaluated the effects of other drugs on pyloric sphincter tone; however, the effects of ketamine on pyloric sphincter tone are not known. Ketamine causes relaxation of the cardiac sphincter of rabbits in vitro.[23] Volatile anesthetics administered via a cuffed orotracheal tube are recommended for maintenance of anesthesia during gastroduodenoscopy to prevent aspiration of gastric contents.[1] Isoflurane anesthesia does not affect the difficulty of gastroduodenoscopy in dogs[j]; however, its effects have not been evaluated in cats. We did not evaluate the effect of ketamine or isoflurane alone on gastroduodenoscopy; however, it is possible that either agent or the combination attenuated an increase in sphincter tone that may have been induced by the premedicants.

We intentionally chose a single expert endoscopist to minimize the effects that individual variation and lack of experience have on gastroduodenoscopy; this strategy also decreased variability associated with learning by the endoscopist. It is possible, therefore, that subtle changes in pyloric tone that would be a barrier to an inexperienced endoscopist were not apparent in our study. The stomach is occasionally distended

with air during gastroscopic examination, and this may initiate a reflex increase in pyloric tone and therefore impede duodenoscopy.[1] The stomach was minimally distended in our study; therefore, pyloric tone may have been somewhat less than if a gastric examination involving greater gastric distension had been attempted prior to passage of the endoscope through the pylorus. Most cats used in our study were infected with *H pylori*. Although these cats had no clinical signs attributable to infection and the data obtained from the noninfected cat was not exceptional, we cannot completely exclude the possibility that *H pylori* infection may have affected sphincter tone. It is also possible that cats with preexisting gastrointestinal tract disease may have responded differently.

Medetomidine induced the most profound and long-lasting sedation of all the premedicants. Medetomidine induces its dose-dependent sedation by acting on centrally located α_2 receptors. Adverse effects associated with administration of medetomidine to cats include bradycardia, emesis, apnea, and cyanosis.[18] The dose of medetomidine used in our study induced greater CNS depression than the other premedicants. If the dose of medetomidine had been decreased to induce CNS depression similar to that caused by the other premedicants, it is possible that endoscopy may have been easier and taken less time. Nevertheless, the times we recorded were short and passage of the endoscope was easy; any improvement caused by decreasing the dose of medetomidine would probably be minimal and unlikely to influence the choice of premedicant.

Hydromorphone and glycopyrrolate, hydromorphone, and butorphanol provided less sedation than medetomidine. Hydromorphone and butorphanol are primarily administered for their analgesic effects; however, both may also induce sedation via μ and κ receptors, respectively.[17] Effects of hydromorphone on the CNS range from profound sedation to excitation, depending on the physical status of the animal and its level of pain; animals with signs of pain tend to be less excited and more sedated.[12] The cats used in our study had no signs of pain when hydromorphone or butorphanol were administered, which may account for the low sedation scores.

In our study, glycopyrrolate administered at a moderate dose did not affect sedation scores. Administration of high doses of atropine to humans results in dysphoria and CNS excitement; a similar effect has not been observed after administration of glycopyrrolate.[24]

Hydromorphone, medetomidine, butorphanol, ketamine, and isoflurane all cause respiratory depression in cats.[12,18,22,25,26] Not surprisingly, most cats had end-tidal carbon dioxide partial pressures greater than the upper limit of the reference range (35 to 45 mm Hg),[27] but none of the cats had end-tidal carbon dioxide partial pressures > 68 mm Hg, and there were no differences in the end-tidal carbon dioxide partial pressures among premedicant groups.

The ability to intubate the trachea of cats in our study without the use of isoflurane appeared to parallel the degree of sedation observed in the cats. Cats given medetomidine rarely required isoflurane, whereas cats that received the other premedicants routinely required isoflurane to facilitate orotracheal intubation.

All cats recovered from anesthesia without stimulation; however, the cats that received medetomidine took longer (> 1 hour) to return to sternal recumbency. The duration of action of medetomidine is dose-dependent and can last up to 90 minutes in cats.[18] When medetomidine is combined with ketamine, cats have a lack of awareness of their surroundings for up to 2 hours.[26] Butorphanol and hydromorphone have durations of analgesia in cats of 3 to 6 hours and 4 to 6 hours, respectively, which suggests that their effects were still present at recovery from anesthesia.[12,16,28] To hasten recovery time, a lower dose of medetomidine could be used or its effects could be reversed via administration of atipamezole, an α_2 adrenergic antagonist.[18,29,30]

[a] Hydromorphone, Elkins-Sinn Inc, Cherry Hill, NJ.
[b] Robinul injectable, Baxter Healthcare Corp, Richmond, Va.
[c] Domitor, kindly provided by Pfizer Animal Health, Exton, Pa.
[d] Torbugesic-SA, kindly provided by Fort Dodge Animal Health, Fort Dodge, Iowa.
[e] KetaFlo, Abbott Laboratories, North Chicago, Ill.
[f] Isoflurane, Abbott Laboratories, North Chicago, Ill.
[g] Datex-Engstrom AS/3 Compact Monitor, Datex-Engstrom, Helsinki, Finland.
[h] P-140 gastrointestinal videoscope, Olympus America Inc, Melville, NY.
[i] Statistix 7, Analytical Software, Tallahassee, Fla.
[j] Leib MS, Clutton E, Zajac A, et al. The effects of volatile anesthetics on endoscopic intubation of the duodenum of dogs (abstr). *J Vet Intern Med* 1990;4:123.

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