

Cerenia Prevents Perioperative Nausea and Vomiting and Improves Recovery in Dogs Undergoing Routine Surgery

Deborah Ramsey

Tim Fleck

Thomas Berg

Steve Nederveld

Donald DeLong

Jezaniah-Kira Tena

Michelle Aleo

Robert McCall

VMRD-Global Therapeutics Research, Zoetis, Inc. Kalamazoo, MI

Corresponding Author: Robert B. McCall, robert.b.mccall@zoetis.com

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ABSTRACT

Cerenia is a selective neurokinin-1 receptor antagonist used to treat nausea and vomiting in dogs. The present study investigated the effects of Cerenia (maropitant) injectable solution (1.0 mg/kg) on post-operative nausea and vomiting in dogs pre-medicated with morphine or buprenorphine and undergoing an ovariohysterectomy or a routine castration. Improvement in the quality and speed of recovery were also assessed. Forty eight dogs were randomized to treatment with Cerenia or placebo that were administered 45 minutes prior to the opioid pre-medication. Surgery was performed under general anesthesia using isoflurane. Study participants collecting clinical assessment data were masked to treatment allocation. Cerenia significantly reduced both nausea and vomiting in dogs pre-medicated with morphine. In dogs receiving morphine,

Cerenia was associated with a significantly faster return to feeding compared to placebo-treated dogs. Cerenia improved the quality of recovery (as measured by decreased aimless movements, vocalization, and panting) compared to placebo-treated dogs. However, treatment with Cerenia did not significantly change the speed with which dogs recovered from surgery or their general attitude during the recovery period, or their level of sedation during recovery compared to dogs receiving placebo treatment. Buprenorphine pre-medicated dogs failed to display signs of nausea or vomiting. In these animals Cerenia and placebo animals had similar surgical recoveries. This study demonstrates the value of pre-operative Cerenia when used in conjunction with morphine, but not buprenorphine, as a pre-medication to reduce nausea and vomiting, to hasten return to normal food consumption post-operatively, and to improve the quality of recovery from surgery.

INTRODUCTION

A large body of data indicates that brain stem substance P acting via neurokinin-1 (NK-1) receptors is a key mediator in the pathophysiology of emesis.¹⁻⁴ Cerenia™ (maropitant) is a potent and selective NK-1 receptor antagonist used to treat nausea and vomiting in dogs.⁵ In laboratory studies, Cerenia blocks emesis induced by centrally acting emetogens (eg, apomorphine) as well as peripheral emetogens (eg, syrup of ipecac).⁶ This broad spectrum of anti-emetic efficacy is also noted in clinical trials.⁵⁻⁷ In this regard, Cerenia has been shown to control canine emesis resulting from a variety of etiologies in clinical trials,⁵ to prevent and treat cisplatin-induced emesis in cancer chemotherapy⁸ and to prevent emesis associated with motion sickness.⁹ Cerenia has also been shown to be effective in preventing emesis produced by either emetogen challenge or motion sickness in cats.¹⁰

Opioids are commonly used as pre-anesthetic agents in veterinary medicine. Full mu agonists such as morphine and hydromorphone provide dose-dependent sedation and analgesia and are useful in treating moderate to severe pain. They are also used as induction agents and as post-operative analgesics. Although effective, side effects may include respiratory depression, sedation, nausea, and vomiting. The reported incidence of emesis in dogs following administration of morphine or hydromorphone given as a pre-anesthetic agent ranges from 50-100%.¹¹⁻¹³ A recent report indicates that Cerenia prevents vomiting in dogs treated with hydromorphone prior to surgery.¹⁴ The objective of the current study was to determine if Cerenia is effective in preventing nausea and vomiting in dogs pre-medicated with either the full mu agonist morphine or the partial agonist buprenorphine prior to surgery and to determine if Cerenia speeds recovery time or improves the quality of anesthetic recovery.

METHODS

This study was approved by the Zoetis Institutional Animal Care and Use Committee.

In the first arm of the study morphine was utilized as a pre-anesthetic agent. Sixteen male and 16 female Beagles (10-30 months of age, Marshall Farms) undergoing routine castration or ovariohysterectomy (OHE) surgery were evaluated.

In a second series of experiments 16 additional female dogs were given buprenorphine as a pre-anesthetic agent prior to OHE surgery. Surgeries were staged over multiple days with four surgeries conducted per day by a trained veterinarian blinded to treatment groups. Approximately 1 week prior to Study Day 0 for the first dog, an initial pre-study examination was conducted by a study veterinarian to assess suitability for inclusion in the study. As part of the physical examination, a blood sample was collected for complete blood count and serum chemistry analysis to insure the health of the animal prior to surgery. Based on the physical exam findings and results of the CBC/serum chemistry profile, a total of 48 dogs were selected for the study (16 males and 16 females for morphine study and 16 females for buprenorphine study).

Animals were randomly assigned to pen location, room, day of surgery, pre-anesthetic (morphine or buprenorphine), and treatment group (placebo or Cerenia). Dogs were transported in cages to the surgical suite where they remained for pre- and post-surgical assessments. Dogs were maintained in the surgery suite or its recovery room from the time of pre-medication until the end of the surgical recovery period (3 hours after the end of surgery). At the end of the recovery period, dogs were moved back to the room where they originated.

Cerenia Injectable Solution (1 mg/kg) or placebo (saline, 0.1 ml/kg) was administered subcutaneously, 60 minutes prior to the induction of anesthesia with propofol. Cerenia and placebo were given chilled after removal from a refrigerator in order to minimize pain upon injection produced by Cerenia.¹⁵ Dogs were pre-medicated with either morphine (0.5 mg/kg, s.c.) or buprenorphine (0.005 mg/kg, s.c.) 45 minutes

following the dose of Cerenia or placebo and 15 minutes prior to anesthesia. A trained blinded observer documented nausea and vomiting immediately prior to treatment with either Cerenia or placebo and induction of anesthesia with propofol. Each dog underwent routine surgery under general inhalant anesthesia with isoflurane. Following post-surgery extubation, dogs continued to be observed for nausea and vomiting and also observed every 15 minutes for the first 30 minutes after surgery and then every 30 minutes thereafter for a total of three hours for quality and attributes of surgical recovery as described below. Food intake was recorded for up to 26 hours post-surgery and the return to feeding time (consumption of a total of 100 grams of food) was recorded. All study participants collecting clinical assessment data (emetic events, nausea scores, clinical observations of recovery, general health observations, temperature, pulse, and respiration) were masked to treatment allocation. Only one study participant, the Treatment Administrator who prepared the syringes of the test material, knew the allocation of animal to treatment group. The Treatment Administrator did not perform any clinical assessments during the study.

Dogs were fed Lab Diet-Certified Canine Diet #5007 (dry dog food) ad libitum throughout the study except beginning at 18:00 on Study Day -1 when dogs were fasted prior to surgery. Post-operatively, dogs were initially fasted, then offered food beginning at 2 hours after the end of the surgical procedure. Water was provided ad libitum except on Study Day 0 when it was removed just prior to induction of anesthesia. Water was returned 3 hours after the end of the surgical procedure.

Primary study variables included emetic events and intensity of nausea. Quality of surgical recovery and return to feeding were secondary study variables.

Presence of Emetic Event(s). Emetic events included retching, vomiting, and presence of vomitus. Retching was defined as a strong involuntary effort to vomit when

no discharge of vomitus was observed either because the reflex mechanism was interrupted before completion or because it lacked sufficient intensity to cause ejection of gastric contents. Vomiting was defined as the forceful ejection of gastric and/or intestinal contents (vomitus) from the mouth via forceful, sustained contractions of the abdominal muscles.

Intensity of Nausea was determined using a visual analog scale (VAS) to assess and record the severity of nausea experienced by each dog during the perioperative period. For each nausea VAS assessment, a dog was observed for 15 seconds (\pm 5 seconds) and a visual analog scale measuring “no nausea” at the far left to “worst possible nausea” at the far right was marked. Signs of nausea included:

- excessive salivation
- increased or exaggerated swallowing
- licking the lips
- hunched posture
- piloerection
- restlessness and.
- vocalization.

A single observer made all of the nausea assessments for all dogs for the entire study to ensure consistency. The observer placed a single vertical line transecting a 100 mm VAS scale. The distance from the far end of the scale (0=no nausea) to the vertical mark was measured to obtain a numeric score.

Quality of Surgical Recovery was assessed using numeric 0-2. For each assessment, a dog scored 0-2. The quality of recovery for dogs graded 0 was considered smooth (dog is lying comfortably; no vocalization or panting; minimal movement even when stimulated by touch; appears sleeping; relaxed posture). Dogs graded 1 were considered to have a moderate recovery (dog changes position frequently; panting; stimulated when touched and attempts to rise or move; hunched posture). Dogs graded 2 were considered to have a rough recovery (dog is thrashing, paddling in cage; shaking, vocalizing; touch temporar-

ily calms but movement and sound resumes when stimulation is withdrawn). A single observer made all of the surgical recovery assessments for all dogs for the entire study to ensure consistency.

Attributes of Surgical Recovery included assessments of attitude, level of sedation, and speed of recovery from anesthesia. Attributes were scored on a 0-3 scale, and the percent of dogs in each attribute category was compared across treatment groups. Level of sedation was recorded according to methods published by Young¹⁶ in which a score of 0-3 was provided for each of three sedation parameters: spontaneous posture, response to noise, and relaxation of jaw and tongue. The times of key elements of recovery were recorded and compared to when the vaporizer was turned off to derive an elapsed time to extubation, time to sternal recumbency, time to standing posture, and time to return to feeding. Since dogs were not observed continuously once extubated, the recorded times were approximate and recorded when first observed. For example, if at 30 minutes into the recovery period, the dog was in lateral recumbency but at 45 minutes was sternal, the time of sternal recumbency was the time of the 45 minute observation.

Return to Feeding was assessed directly by weighing food consumed at 2, 3, 6, 20, and hours post surgery. In addition, buprenorphine dogs were assessed at 26 hours as this group had a delayed return to feeding. At each time point dogs were offered 100 grams of their normal chow and given 10 minutes to consume the food. A dog's time of return to feeding was defined as the time when a cumulative total of 100 grams of feed had been consumed.

All hypothesis tests were conducted at the 0.05 level of significance (two-tailed). The primary variables were presence of emetic events and intensity of nausea. All other variables were secondary. Presence of emetic events was summarized by treatment and time point. Whether or not an animal had an emetic event up to 150 minutes into

recovery was summarized by treatment and sex. Whether or not an animal had an emetic event was analyzed using Fisher's Exact Test as the generalized linear mixed model with a logit link function and a binomial error distribution did not converge. VAS scores were analyzed with a general linear mixed model for repeated measures. The fixed effects in the model were sex, treatment, sex by treatment interaction, time point, sex by time point interaction, treatment by time point interaction, and sex by treatment by time point interaction. The random effects in the model were room, block within room, block within room by sex interaction, block within room by sex by treatment interaction (animal term), and residual. If any interactions involving sex and treatment were significant, then treatments were compared at each time point for each sex. Otherwise, treatments were compared at each time point across sex. Treatment least squares means (LSM), standard errors, 95% confidence intervals, minimums, and maximums were calculated at the same level that the treatment comparisons were made.

RESULTS

In the first series of experiments, morphine was used as a pre-anesthetic agent in 16 male and female dogs. These animals received either Cerenia Injectable Solution (1 mg/kg, sc) or placebo (saline) 45 minutes prior to morphine administration. One Cerenia dog was removed from the statistical analysis as it was not correctly dosed. Morphine induced emesis in 15 of 16 dogs treated with placebo. Nine of these 15 dogs vomited more than one time. Emesis was noted within 5 minutes of morphine treatment and continued for 10 minutes until propofol was administered.

In contrast, none of the 15 Cerenia treated dogs vomited during the pre-anesthetic period. There were no emetic events observed during the 150 minute post-operative period in any dog in either treatment group. The ability of Cerenia to prevent emesis pre-operatively in dogs treated with morphine compared to that of the placebo

was statistically significant ($p < 0.05$). In the second series of experiments, buprenorphine was used as a pre-anesthetic agent in an additional 16 female dogs treated either with Cerenia or placebo. None of the buprenorphine dogs had an emetic event in the pre- or post-operative period.

Intensity of nausea was evaluated using a VAS scale over the 15 minutes (in 5-minute intervals) between the administration of morphine or buprenorphine until induction of anesthesia and again post-operatively for 3 hours. In animals pre-treated with morphine, the sex by treatment by time point interaction was significant so treatment comparisons were made at each time-point for each sex. For both males and females, the intensity of nausea was significantly greater in the placebo-treated dogs at 5 and 10 minutes after morphine administration pre-operatively. For females, intensity of nausea was significantly different between treatment groups post-operatively at extubation and at 30, 45, 60, 90, 120, and, 150 minutes after extubation. The least squares mean (LSM) VAS score for intensity of nausea five minutes after morphine administration was 54.7 (female) and 57.4 (male) in placebo-treated dogs and 7.5 (female) and 15.8 (male) in Cerenia-treated dogs. At 45 minutes into the post-operative recovery period, the LSM nausea VAS was 26.4 (female) and 5.2 (male) for placebo-treated dogs and 10.5 (female) and 1.9 (male) for the Cerenia-treated dogs.

Buprenorphine treated dogs displayed few signs of nausea. For example, the mean VAS nausea score 45 minutes post-operation was 8.0 for placebo dogs and 4.0 for Cerenia treated dogs. This compares to a nausea score of 26.4 in placebo dogs treated with morphine. As such, there were no significant differences in nausea intensity in Cerenia versus placebo dogs treated with buprenorphine.

Speed of surgical recovery was quantitated from the time the anesthetic vaporizer was turned off to the time of extubation, time to sternal recumbency, and time to

standing posture. No significant difference between Cerenia and placebo dogs was noted in any of these measures whether the animals were pretreated with morphine or buprenorphine. Similarly there was no difference in sedation during recovery between Cerenia and placebo dogs pre-medicated with morphine or buprenorphine.

The quality of recovery from anesthesia for each dog was graded on a 0-2 scale. In animals pre-medicated with morphine, none of the 15 Cerenia-treated dogs were considered to have a rough recovery while two placebo-treated dog were scored as having a rough recovery; one at the 15-minute and one at the 30-minute observation times. At 60 minutes into recovery, all Cerenia-treated dogs were considered to be recovering smoothly (score =0) and continued with a smooth recovery to the last observation 3 hours after surgery. In contrast, at 60 minutes into recovery, 25% of placebo-treated dogs were considered to be having a moderate recovery (changing position, panting, hunched posture) and a similar number continued through the 3-hour evaluation period. In animals pre-medicated with buprenorphine, Cerenia improved the quality of recovery at 15 minutes, but was similar to placebo throughout the remaining 3-hour observation period.

Twelve dogs pre-treated with morphine returned to feeding (100 grams of food consumed) by 6 hours post-operation (Table 1). Of the 12 dogs that returned to feeding by 6 hours into recovery, 4/12 (33.3%) had received placebo treatment and 8/12 (66.7%) had been treated with Cerenia pre-operatively. Seven of 13 placebo-treated dogs (53.8%) had not eaten at least 100 grams of food 20 hours after surgery while only one Cerenia-treated dog (6.7%) still had not eaten a total of 100 grams of food at 20 hours. The difference in the proportion of dogs that returned to feeding during the study between treatment groups was significant ($P = 0.0272$). Total food consumption during the 20 hour post operative period was measured. Table 2 shows that Cerenia dogs ate significantly

Table 1. Summary of Morphine Premedicated Dogs Returning to Feeding By Time Into Recovery

Treatment Group	Time Into Recovery (After End of Procedure)							
	3 hours		6 hours		20 hours		Did not return to feeding	
	n	%	n	%	n	%	n	%
Placebo (T01)	1	6.7	3	20.0	1	6.7	7	46.7
Cerenia (T02)	0	0	8	53.3	2	13.3	1	6.7
Total	1	6.5	11	36.7	3	10.0	8	26.7

($p = 0.0419$) more grams of food ($190 + 47.8$) than placebo dogs ($39.1 + 27.5$). No buprenorphine pre-treated dogs returned to feeding during by 6 hours following surgery. Since buprenorphine pre-medication delayed the return to feeding we evaluated these dogs 26 hours post surgery. Only 57% of placebo dogs and 37% of Cerenia dogs had returned to feeding by 26 hours. At 26 hours post recovery placebo dogs ate a LSM total of $82.6 + 36.2$ grams of food compared to $127.6 + 33.9$ grams in the Cerenia dogs (Table 3).

DISCUSSION

The purpose of the present study was to determine if Cerenia is effective in preventing nausea and vomiting in dogs pre-medicated with either the full opioid agonist morphine or the partial opioid agonist buprenorphine prior to surgery, and to determine if Cerenia speeds recovery time as well as the quality of anesthetic recovery. We found that in the 30 analyzable dogs receiving morphine as a pre-medication prior to general anesthesia for routine surgery, Cerenia, at a dosage of 1.0 mg/kg was significantly better than placebo ($p < 0.05$) in preventing vomiting

associated with the use of morphine. None of the 15 Cerenia-treated dogs vomited after receiving morphine. Fourteen of 15 placebo-treated dogs vomited post-morphine administration, and of those 14 vomiting dogs, NINE vomited more than one time. These data indicate that Cerenia blocks morphine-induced emesis and supports a recent case report in which Cerenia prevented vomiting induced by epidural administration of morphine in the dog.¹⁷ Similarly, Cerenia has been demonstrated to prevent emesis induced by hydromorphone, a potent analog of morphine.^{14, 18} In contrast to morphine, no emesis was noted in 16 dogs pre-medicated with buprenorphine prior to surgery. The decrease incidence of emesis in buprenorphine treated dogs compared to morphine treated dogs has been documented and likely results from the partial agonist activity of buprenorphine at the mu receptor.¹⁹

The dorsal motor nucleus of the vagus, the nucleus tractus solitarius (NTS) and the area postrema (AP) integrate emetic signaling and are often referred to collectively as the emetic center.²⁰ Lacking a blood brain barrier, the AP detects emetogens in

Table 2. Analysis of Food Consumption Least Squares Means (LSM) and Confidence Intervals (CI) in Morphine Pre-Medicated Dogs

Treatment	Number of Animals	LSM	Standard Error	Lower 95% CI	Upper 95% CI	Minimum	Maximum
Saline (T01)	8	39.1	27.5	-106.9	185	0	111
Cerenia (T02)	8	190.0	47.8	58.7	321.2	3.6	337.8

Table 3. Analysis of Food Consumption Least Squares Mean (LSM) and Confidence Intervals (CI) in Buprenorphine Pre-medicated Dogs

Treatment	Number of Animals	Least Squares Mean	Standard Error	Lower 95% CI	Upper 95% CI	Minimum	Maximum
T01 (SALINE)	7	82.6	36.2	4.3	160.8	0	171
T02 (CERENIA)	8	127.6	33.9	54.4	200.8	0	332

the blood and sends projections to the NTS which contains neurons controlling swallowing, respiration and stomach and lower esophageal sphincter tone. These neurons coordinate the physical and autonomic activity associated with nausea and vomiting. The emetic center receives input from four major locations: the chemoreceptor trigger zone, the GI tract, the vestibular apparatus and the cerebral cortex. Opioids exert emetogenic effects via direct stimulation of the chemoreceptor trigger zone, inhibition of gut motility, and stimulation of the vestibular apparatus by activation of mu, kappa and delta opioid receptors.²¹

In addition, acute administration of morphine causes an increase in expression of substance P in the central nervous system and up-regulates NK1 receptors.^{22,23} In this regard, a large body of evidence indicates that substance P mediates emesis via NK1 receptors in the brainstem emetic center.²⁰ Cerenia is a NK1 receptor antagonist and effectively controls emesis produced by central and peripheral acting emetogenic agents in both dogs and cats.⁶ Cerenia is thought to act at the level of the brainstem emetic center to inhibit the final site of integration of emetic stimuli. Thus, Cerenia has been shown to block emesis induced by a wide range of emetogens including as demonstrated in the present study, morphine.

The neural pathways for nausea are distinct from those associated with vomiting.²⁴ Indeed, vomiting is not always associated with nausea,²⁵ although a common pathway for nausea and vomiting may apply for stimuli acting via vagal afferents and the AP. Cerenia is registered in Europe for

the prevention of nausea as well as vomiting and several studies indicate that Cerenia prevents nausea associated with emetogens and motion sickness.⁵⁻¹⁰ In the present study we assessed nausea from the time of injection of morphine or buprenorphine to intubation and again following surgery for 3 hours. Nausea was measured by a blinded observer using VAS and nausea signs included excessive salivation, increased or exaggerated swallowing, licking the lips, hunched posture, piloerection, restlessness and vocalization. Cerenia significantly reduced nausea in both male and female dogs pre-medicated with morphine during the preoperative period compared to placebo treated animals. Following surgery, male dogs pre-medicated with morphine did not exhibit nausea whether treated with Cerenia or placebo. In contrast, female dogs given morphine and placebo were nauseous for 150 minutes following surgery. Cerenia blocked the nausea in female dogs during this time period. Female dogs likely exhibited prolonged nausea compared to males as a result of abdominal surgery in combination with the morphine pretreatment. Animals premedicated with buprenorphine did not exhibit signs of nausea.

The quality of surgical recovery from anesthesia was also evaluated in this study using a three point scale signifying smooth, moderate, and rough recovery. The surgical recovery of the 15 dogs pre-medicated with morphine and given Cerenia was judged to be smooth by a blinded observer at all time points during the recovery period. In contrast, recovery of two placebo dogs was considered rough during the first 30 minutes of anesthesia recovery and 25% of the

dogs had a moderately difficult recovery as judged by frequent position changes, panting, stimulation when touched, and hunched posture throughout the 3-hour recovery observation period. Dogs pre-medicated with buprenorphine and given placebo seemed to have a better quality of recovery than did their morphine counterparts treated with placebo. Cerenia treated dogs did recover significantly better than placebo at 15 minutes post-recovery in animals pretreated with buprenorphine. All dogs pre-medicated with buprenorphine had a smooth recovery at 30 minutes and later during the recovery period. These data indicate that Cerenia increased the quality of surgical recovery from anesthesia in animals pre-medicated with morphine. Cerenia has been shown to decrease the anesthetic requirements during visceral surgery.²⁶ This finding may be related to the increase in the quality of surgical recovery in Cerenia treated animals in the current study.

Cerenia significantly hastened the return to feeding following surgery in morphine pre-medicated dogs. At 6 hours post-surgery 66.7% of Cerenia dogs had returned to feeding (consuming a total of 100 grams of food compared to 33.3% of placebo dogs). At 20 hours post-surgery all but one Cerenia dog (93%) had returned to feeding while only 46% of placebo dogs had consumed >100 grams of food. At 20 hours Cerenia dogs had consumed a mean of 190 grams of food while placebo dogs had consumed 39 grams of chow. Thus Cerenia decreased the time to feeding return and increased the amount of food consumed in the hours following surgery compared to placebo treated dogs. Although Cerenia increased feeding post-surgery in morphine dogs this effect was not evident in animals pre-medicated with buprenorphine. Pre-medication with buprenorphine delayed the return to feeding following surgery independent of Cerenia or placebo treatment. No buprenorphine pre-treated dogs returned to feeding during by 6 hours following surgery. Only 57% of placebo dogs and 37% of Cerenia dogs had returned to feeding by 26 hours. This

was not statistically significant. At 26 hours post-recovery placebo dogs ate a LSM total of 82.6 + 36.2 grams of food compared to 127.6 + 33.9 grams in the Cerenia dogs. The difference in return to feeding in morphine versus buprenorphine medicated dogs is unknown, but may be related to either better pain control in morphine dogs or perhaps a direct hyperphagic effect produced by morphine.²⁷ In contrast buprenorphine has been shown to decrease food intake following surgery in rats.²⁸

The present study demonstrates that Cerenia provides benefit when morphine is used as a pre-anesthetic agent prior to surgery in dogs. First, Cerenia prevented emesis induced by the morphine. Cerenia has been shown to block the emesis of a second full μ agonist hydromorphone in the dog.¹ Second, Cerenia prevented nausea associated with morphine administration prior to and following surgery. Similarly, Cerenia blocks nausea produced by hydromorphone.¹⁴ Satisfaction with anesthesia is most closely tied to avoidance of vomiting and nausea in humans.²⁹ Thus avoiding nausea and vomiting by use of Cerenia when morphine or hydromorphone is given prior to surgery in dogs should be considered.

This may be especially important for abdominal surgery as the level of nausea in this study was more prolonged in female dogs undergoing ovariohysterectomy compared to male dogs undergoing routine castration. Third, Cerenia provided additional benefits in the post surgery period in animals pre-medicated with morphine. All dogs treated with Cerenia had a smooth recovery from anesthesia. In contrast, 25% of placebo dogs experienced moderate and difficult recovery from anesthesia based on behavioral observation.

In addition, dogs pre-medicated with morphine and given Cerenia returned to feeding faster and ate greater amounts than did placebo dogs. Improved feeding and smooth recovery from anesthesia may allow earlier discharge from the clinic and thus decrease related expenses and may improve

owner satisfaction of the surgical experience. Finally, it should be noted that these benefits of Cerenia apply only when full mu agonists are given as a medication during surgery.

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