Comparison of preoperative carprofen and postoperative butorphanol as postsurgical analgesics in cats undergoing ovariohysterectomy

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Abstract

Objective To compare carprofen to butorphanol, with regard to postsurgical analgesic effects, duration of analgesia, and adverse side effects.

Study design Blinded, randomized clinical study.

Animals Seventy-one cats, 0.5–5 years of age, weighing 3.24 ± 0.61 kg, undergoing ovariohysterectomy (OHE).

Methods Cats were premedicated with subcutaneous atropine (0.04 mg kg⁻¹), acepromazine (0.02 mg kg⁻¹), and ketamine (5 mg kg⁻¹). Anesthesia was induced with ketamine (5 mg kg⁻¹) and diazepam (0.25 mg kg⁻¹) given intravenously, and maintained with isoflurane. There were three treatment groups: group C (4 mg kg⁻¹ carprofen SC at induction), group B (0.4 mg kg⁻¹ butorphanol SC at end of surgery), and group S (0.08 mL kg⁻¹ of sterile saline SC at induction and end of surgery). Behavioral data were collected using a composite pain scale (CPS), prior to surgery (baseline) and 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours post-surgery. Interaction scores were analyzed separately. Cats with CPS scores >12 received rescue analgesia (meperidine, 4 mg kg⁻¹, intramuscular).

Results Sixty cats completed the study. The CPS scores did not differ significantly between groups C and B at any time period. CPS scores for groups B and C were significantly increased for 12 hours postsurgery, and in group S for 20 hours. Both group C and B CPS scores were significantly lower than group S in this 20-hour postoperative period, except at 4 hours (B and C) and at 3 and 8 hours (B alone). Interaction scores for group C returned to preoperative baseline 4 hours after surgery, while both groups B and S remained increased for at least 24 hours postsurgery. Nine cats required meperidine.

Conclusion In this study, carprofen provided better postsurgical analgesia than butorphanol.

Clinical relevance Neither drug completely abolished pain, however preoperative carprofen provided better pain control compared with postoperative butorphanol in the 24-hour period following OHE surgery in cats.

Keywords analgesia, butorphanol, carprofen, cats, postsurgical.

Introduction

Perioperative pain relief is essential in veterinary practice. It is not only aimed at reducing postsoperative suffering in animals, but also to improve recovery from anesthesia. The cat is one of the most poorly understood domestic species regarding pain recognition and control. It has been demonstrated...
that cats experience pain following ovariohysterectomy (OHE), which requires analgesic intervention (Slingsby & Waterman-Pearson 1998; Slingsby et al. 1998). Several surveys conducted in Canada, Australia, and the United Kingdom discovered that cats received less pain medication than dogs after undergoing similar soft tissue surgeries (Dohoo & Dohoo 1996, 1998; Watson et al. 1996; Lascelles et al. 1999). Less than 30% of the cats received analgesics following OHE or castration procedures. A retrospective study investigating the analgesics prescribed to small animal patients in an American veterinary teaching hospital found that of 15 cats investigated only one received analgesic treatment following major surgical procedures (Hansen & Hardie 1993).

When managing pain, it is preferable to prevent, rather than treat postsurgical pain. Analgesics given preemptively inhibit activation of the neuronal pathways involved in the perception of pain (Lamont et al. 2000). However, the limited number of approved analgesic drugs for use in cats makes it difficult to find appropriate analgesic regimes. Analgesics commonly used in cats include the opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). However, these have often been associated with potentially harmful side effects. Some opioids may produce significant respiratory depression, histamine release, and excitement in cats (Papich 1990). NSAIDs are characteristically associated with gastrointestinal and renal disturbances in dogs and cats (Kore 1990; Papich 1990).

In a nonclinical experimental study, butorphanol, a mixed action agonist-antagonist, was an effective visceral analgesic with moderate duration of action in cats (Sawyer & Rech 1987). Its safety (Sawyer & Rech 1987) and usefulness (Tranquilli et al. 1988; Carroll et al. 1998; Ansah et al. 2002) as an analgesic drug in cats have been investigated and repeatedly demonstrated. It has been well accepted as an analgesic in small animal veterinary practice. In the United States, butorphanol tartrate injection is approved for use in dogs and cats. Unlike carprofen, butorphanol is a scheduled drug (class IV) in the United States.

Carprofen, a member of the propionic acid class of NSAIDs, is considered to spare cyclooxygenase-1 (COX-1) enzyme and inhibit cyclooxygenase-2 (COX-2) enzyme (Ricketts et al. 1998) and possibly phospholipase A2 (McKellar et al. 1991). It possesses analgesic, anti-inflammatory and antipyretic properties. In the United States, carprofen is currently approved for oral and injectable use in dogs only. An injectable form of carprofen (Zenecarp, C-Vet, Suffolk, UK, or Rimadyl Injection, Pfizer Animal Health, NSW, Australia) has been approved in other countries for postoperative analgesia in both dogs and cats.

Although carprofen is an efficient analgesic in cats (Balmer et al. 1998; Slingsby & Waterman-Pearson 2002), little documentation exists on the safety of carprofen in this species. However, a single subcutaneous (SC) injection of carprofen at 4 mg kg\(^{-1}\) provides effective and long-acting analgesia in cats undergoing OHE, without producing any adverse side effects over a 20-hour period (Lascelles et al. 1995).

The objectives of this blinded, randomized clinical study were to investigate carprofen in comparison with butorphanol, with respect to postoperative analgesia, and duration of analgesic effects in cats undergoing OHE. The occurrence of any potentially harmful side effect was also investigated.

**Materials and methods**

**Animals**

A total of 71 female cats, presented to the College of Veterinary Medicine from the local Humane Society for Companion Animals (St Paul and Woodbury locations, MN) for elective OHE surgery, performed by senior students, were utilized. Informed consent was obtained from the Humane Society, and the study was approved by the Institutional Animal Care and Use Committee of the university.

All animals were clinically healthy adult female cats of various breeds, ranging in age from 6 months to 5 years. Cats undergoing combined surgical procedures (OHE and declaw) were excluded, as were aggressive animals, as both were considered significant factors affecting pain assessment. Advanced pregnancy and gastrointestinal disease were further exclusion factors. Likewise, animals on NSAID medication or animals that had received anthelmintics in the previous 7 days were rejected. Cats less than 12 weeks of age were considered to be pediatric and were not included in the study.

**Presurgical preparation**

After admission to the college, all cats were housed in individual cages in the same ward in accordance with our Guide for Care and Use of Animals (Research Animal Resources, University of Minnesota). Cats were allowed to become acclimatized for at
least 1 hour before being given a full physical examination. Following the clinical examination, each cat had one side of the neck clipped and disinfected using 70% ethyl alcohol. Approximately 2–3 mL of blood was obtained by jugular venipuncture and submitted for hematology and serum biochemistry – albumin (Alb), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, glucose (Glu), sodium (Na+), potassium (K+), and total protein (TP) concentrations were measured. Only cats with normal hematologic and biochemical values were included in the study.

Physical examinations were carried out once daily until animals were returned to the Humane Society 5–7 days later for adoption. Cats were fed and watered ad libitum up until 12 hours prior to premedication. All cats were fasted for at least 12 hours before undergoing surgery.

Pain scores
All cats were scored, at rest, preoperatively, using a composite pain score (CPS) compiled and adapted from similar scales described previously, and using behaviors suggested as indicative of pain in cats (Crane 1987; Hansen 1997; Hellyer & Gaynor 1998; Holton et al. 1998; Firth & Haldane 1999; Mathews 2000). The scale (Table 1) ranged from 0 to 21. It was divided into seven categories (temperament, appearance, body posture, unprovoked behavior, interactive behavior, movement, and vocalization), each containing three to four descriptive behaviors, where 0 was awarded to normal unaffected appearance, posture and behavior, and a maximum of 2–4 given to severe changes (Table 1). Interactive behavior scores included palpation of the surgical incision and surrounding area, as well as interaction between the animal and observer as recommended previously (Dobromylskyj 1991; Cambridge et al. 2000).

Each cat was treated in the same manner. The investigator (MG) approached the cage and at first observed the cat without opening the door or touching it. Then the cat was spoken to and any reactions recorded. Once the visual evaluation was completed, the cage door was opened and the animal handled. While talking gently to the cat, the investigator would start to touch the head and neck, slowly letting the animal get accustomed to the hand gliding over the cat’s back. Then, while keeping the thumb on the lumbar vertebrae, the other fingers were brought down the side of the abdomen toward the site of the incision. Where possible, the incision was touched, gently at first, followed by application of more pressure. Each examination lasted approximately 15 minutes.

Anesthesia and surgical procedure
Cats were admitted to the hospital at least 24 hours prior to anesthesia and surgery. All cats underwent the same anesthetic protocol. Premedication was achieved by intramuscular (IM) or SC administration of 0.04 mg kg\(^{-1}\) atropine sulfate (Phoenix Pharmaceutical Inc., St Joseph, MO, USA), acepromazine 0.02 mg kg\(^{-1}\) and ketamine 5 mg kg\(^{-1}\) (Ketaset; Fort Dodge Animal Health, Fort Dodge, IA, USA), followed 15 minutes later by anesthetic induction with ketamine 5 mg kg\(^{-1}\) and diazepam 0.25 mg kg\(^{-1}\) (Diazepam; Abbott Laboratories, North Chicago, IL, USA) given intravenously (IV) using a catheter placed in the cephalic vein. After intubation, anesthetic maintenance was accomplished using isoflurane in oxygen delivered by either a semi-closed rebreathing or pediatric circle breathing system connected to a small animal anesthetic machine (VASCO, Pro Tech Medical Inc., Franklin, WI, USA).

After a standard aseptic preparation, routine OHE surgeries were performed via a ventral midline approach by senior veterinary students. Throughout the surgeries, heart rates, respiratory rates, and vaporizer settings for isoflurane were recorded. In addition, a subjective assessment of intraoperative bleeding was made by investigators and student surgeons. Intravenous fluids (0.9% NaCl) were administered to all cats at a rate of 10 mL kg\(^{-1}\) hour\(^{-1}\). Physical monitoring, such as presence or absence of palpebral reflexes, degree of jaw tone, toe pinch, capillary refill time and color of mucous membranes, was employed. Electrocardiogram (ECG) (Vetronics, Inc., Lafayette, IN, USA), pulse oximetry (SpO\(_2\)) (Vet/Ox, BCI, Waukesha, WI, USA) and esophageal stethoscopes (Mon-a-therm, Mallincrodt Medical, Inc., St. Louis, MO, USA) were also utilized in monitoring the patient. Cats were allowed to recover from anesthesia in their carriers or cages before being returned to the wards.

Treatment groups
The investigator (MG) was ignorant of the treatment groups at all times during the study. Cats were
assigned randomly into three groups of 20 animals each. Group C (carprofen group) received carprofen (Rimadyl Injection, Pfizer Animal Health, West Ryde, NSW, Australia) at a dose of 4 mg kg\(^{-1}\), injected SC under the skin of the neck or between the scapulae immediately after induction of anesthesia. The volume of carprofen injected was 0.08 mL kg\(^{-1}\). An equal volume of sterile saline was administered SC immediately after the end of surgery. Cats in group B, the butorphanol group, were injected with 0.08 mL kg\(^{-1}\) of sterile saline SC immediately after induction. At the end of surgery, cats received butorphanol tartrate (Torbugesic; Fort Dodge Animal Health Ltd) SC at a dose of 0.4 mg kg\(^{-1}\) SC. The volume of 0.04 mg kg\(^{-1}\) of butorphanol (2 mg mL\(^{-1}\)) was diluted 1:1 with sterile water to produce a final volume of 0.08 mL kg\(^{-1}\).

<table>
<thead>
<tr>
<th>Observation</th>
<th>Score</th>
<th>Patient criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperament</td>
<td>0</td>
<td>Friendly; approaches front of cage when door is opened; may vocalize; purrs, rubs head, may lie down; easy, relaxed attitude; tail raised; may knead paws.</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Friendly; approaches front of cage when door is opened; slightly cautious in interaction with observer; may trust observer with time.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Confident, but not friendly; walks in cage; will return to back of cage if handled, but does not show any aggression; sits sternally or lies laterally; may try to escape.</td>
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<tr>
<td></td>
<td>3</td>
<td>Mildly aggressive; does not approach, but will allow observer to handle; may purr or growl; flicks tail.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Outwardly aggressive; does not approach, unless to strike; sits sternally in back of cage; may growl, hiss, or bite; pupils dilated; cannot be handled without protection/restraint.</td>
</tr>
<tr>
<td>Appearance</td>
<td>0</td>
<td>Normal (coat, eyes, etc.)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild changes; eyelids partially closed; ears carried abnormally (flattened, etc.)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate changes; eyes sunken or glazed; unthrifty appearance</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe changes; eyes pale; enlarged pupils; ‘grimacing’/abnormal facial expressions</td>
</tr>
<tr>
<td>Body posture</td>
<td>0</td>
<td>Lateral recumbency (total relaxation)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sternal recumbency; or sitting/standing with head up; moving</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Head down; abnormal position; hunched-up</td>
</tr>
<tr>
<td>Unprovoked behavior (comfort level)</td>
<td>0</td>
<td>Normal (eating, grooming, etc.), or calmly asleep</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minor changes in behavior; awake and alert</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderately abnormal; less mobile and less alert than normal; unaware of surroundings; restless and uncomfortable; depressed and uninterested in surroundings</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Markedly abnormal; very restless; vocalizing; self-mutiliating; grunting; facing back of cage; or extremely depressed</td>
</tr>
<tr>
<td>Interactive behavior</td>
<td>0</td>
<td>Normal response to handling; no reaction to touching of surgical site</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minimal response to handling and touching wound; pulls away when surgical site is touched; looks at wound; mobile</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Vocalizing when wound is touched; somewhat restless; reluctant to move, but will if coaxed</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Vocalizes (hissing and growling) and pulls away when wound is touched</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Violent reactions to stimuli; vocalizing when wound is not touched; snapping; extremely restless; or will not move when coaxed (extremely depressed)</td>
</tr>
<tr>
<td>Movement</td>
<td>0</td>
<td>Normal amount of movement</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Frequent position changes or reluctance to move</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Thrashing or motionless</td>
</tr>
<tr>
<td>Vocalization</td>
<td>0</td>
<td>Quiet</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Crying; responds to calm voice and stroking</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Intermittent crying or whimpering; no response to calm voice and stroking</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Continuous noise that is unusual for this animal</td>
</tr>
</tbody>
</table>

Table 1 Scores used to evaluate feline presurgical and postsurgical composite pain scores

Cats in group B, the butorphanol group, were injected with 0.08 mL kg\(^{-1}\) of sterile saline SC immediately after induction. At the end of surgery, cats received butorphanol tartrate (Torbugesic; Fort Dodge Animal Health Ltd) SC at a dose of 0.4 mg kg\(^{-1}\) SC. The volume of 0.04 mg kg\(^{-1}\) of butorphanol (2 mg mL\(^{-1}\)) was diluted 1:1 with sterile water to produce a final volume of 0.08 mL kg\(^{-1}\).
Cats in group S received 0.08 mL kg\(^{-1}\) sterile saline SC on induction and a second one of 0.08 mL kg\(^{-1}\) sterile saline SC at the end of surgery. This group served as the control.

**Postsurgical pain assessment**

The same blinded investigator observed all cats in the 24-hour postoperative period at intervals of 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours post-surgery. Again, total CPS were evaluated using the measurements of assessment of behavior, discomfort to palpation, mental status, and posture (Table 1).

**Rescue analgesia**

Requirement for additional analgesics or sedatives was assessed by the investigator on the basis of a high CPS (≥12), and the time of drug administration was recorded. Rescue analgesia was provided with meperidine HCl at a dose of 4 mg kg\(^{-1}\) IM. After 20 minutes (time for meperidine to take effect) cats were monitored for signs of pain or discomfort. Follow-up injections were given when signs of pain and discomfort persisted.

**Follow-up examinations**

Twenty-four and 48 hours post-surgery, venous blood samples were collected from each cat and submitted for serum biochemistry profiles as above.

**Statistical analysis**

The CPS of cats that received the rescue analgesic were included up to the point of administration of meperidine, and any pain scores following rescue analgesia were excluded from further statistical analysis. Pain scores for all other cats were included for the entire study period. Nonparametric data comprising subjective CPS and interaction scores between groups and within each group were analyzed using a two-sample Wilcoxon test. Parametric data collected from serum biochemical profiles pre-operatively and postoperatively were analyzed using single-factor ANOVA. Level of significance was set at 95% (p < 0.05). Values are expressed as mean ± SD.

**Results**

Of the 71 cats that entered the study 60 completed it. The remaining 11 had to be excluded due to high presurgical ALT values (seven), inadvertent premedication with butorphanol (one), missing preoperative laboratory data (one), and death before surgery (one). One animal was found to have been already spayed.

All cats were aged between 6 months and 5 years (mean age = 23.2 ± 14.5 months) and weighed between 1.92 and 4.9 kg (mean mass = 3.24 ± 0.61 kg). Surgery times ranged from 35 to 105 minutes (mean time = 68 ± 18 minutes) and anesthesia lasted from 40 to 135 minutes (mean = 89 ± 22 minutes). There were no significant differences between the three treatment groups for surgery time, the age of the cats or body mass.

No significant differences were noted in serum biochemistry values within and between the groups at baseline, 24 and 48 hours post-surgery. All values were within the reference range, except for one cat in the carprofen group, which exhibited increased ALT (125 and 203 U L\(^{-1}\)) and glucose (171 and 231 mg dL\(^{-1}\)) concentrations at 24 and 48 hours post-surgery, respectively. Another cat in the butorphanol group had an increased glucose concentration of 182 mg dL\(^{-1}\) at 48 hours after surgery.

With regard to pain assessment, mean CPS scores were significantly increased from presurgical baseline values in the carprofen and butorphanol groups at all times, up to and including 12 hours post-surgery (Fig. 1), while the mean CPS scores in the control group were significantly increased from baseline up to and including 20 hours post-surgery. There were no significant differences in CPS scores between the carprofen and butorphanol groups at any time period. Both carprofen and butorphanol groups had mean CPS scores that were significantly lower than the control group at 1, 2, 12, 16, and 20 hours post-surgery. The carprofen group showed significantly lower scores than the control group at 3 and 8 hours after surgery. Composite pain scores decreased over the 24-hour study in all groups. Although not statistically significant, the greatest decreases in pain scores were observed between 4 and 8 hours postoperatively.

A separate analysis of the interaction scores showed no significant differences between all groups at time 0 (preoperative baseline). Interaction scores were significantly increased from baseline scores in both the butorphanol and control groups at all time points up to and including 24 hours post-surgery (Fig. 2). Cats receiving carprofen had interaction scores that were significantly increased from baseline at 2, 3, and 4 hours post-surgery. There were no
significant differences between scores of cats receiving butorphanol or saline (as the control) at any time point postoperatively. The butorphanol group had significantly higher scores from the carprofen group at 16 hours post-surgery. Cats in the carprofen group had significantly lower scores than cats in the saline group from 1, up to and including 20 hours post-surgery.

Of the 60 cats in the study, nine required rescue analgesia (group C: one cat, group B: three cats, and group S: five cats). When tested by one-way ANOVA, differences between the groups were not statistically significant. A second injection of meperidine was administered to one cat in group C and one cat in group S.

**Discussion**

Using a CPS scoring system as a method for assessing pain, neither carprofen nor butorphanol completely abolished postoperative pain following OHE in the cats in this study. One explanation for the incomplete analgesia observed is the likelihood that anesthetic recovery produced excessive activity and therefore overly elevated CPS immediately after surgery. At some time points, auditory and visual stimulation from the other cats in the wards may have affected the behavior of the study cats. Another possibility is that composite pain scores that include postural and behavioral changes, may not accurately reflect postsurgical analgesia in cats.
The scale used in this study was compiled from similar scoring systems applied in domestic animals. The Colorado Pain Scale (Hellyer & Gaynor 1998) served as the main template for the CPS used in this study. Feline behaviors indicative of pain were added from the description of pain behaviors published by Crane (1987), Hansen (1997) and Mathews (2000). The scale was not validated prior to this study. Reports published to date regarding the reliability of both subjective and objective measures to predict pain are very controversial. Physiological variables, such as heart rate, respiratory rate, blood pressure, and rectal temperature, as well as measurement of serum cortisol or glucose concentrations, have been tested for their relationship to pain (Smith et al. 1996, 1999; Conzemius et al. 1997). However, while many of these variables directly vary with pain intensity, they have also been observed to be affected and altered by other factors, such as stress, fear, and anesthetic intervention or surgical manipulation (Smith et al. 1996, 1999; Conzemius et al. 1997).

Based on these findings, the value of objective measurements as reliable predictors of pain is in doubt. For this reason, no objective assessment of pain was conducted in this study. Interaction between the animal and observer, as well as palpation of the incision site, have been found to be reliable indicators of animal pain and are recommended to be included when assessing painful animals (Hellyer & Gaynor 1998; Cambridge et al. 2000). Therefore, we regard the category for interactive behavior, including the response of the cat during palpation of the incision, as an important component of our evaluation form.

In this study, interaction with each cat, as well as palpation of the incision and persistent wound tenderness appeared to be good indicators for judging the animal to be painful or not. These observations correlate well with those reported previously (Cambridge et al. 2000). Statistical analysis of the interaction scores of the three treatment groups in this study showed that cats in the carprofen group had significantly lower reaction scores than those in the control group for at least 20 hours post-surgery, whereas butorphanol-treated cats did not differ significantly from the control cats at any time postoperatively.

The CPS scores of the butorphanol group failed to be significantly different from the control group at 3, 4, and 8 hours post-surgery. The cats that received either carprofen or butorphanol had elevated CPS scores for at least 12 hours after surgery compared with their presurgical values. Moreover, cats in both butorphanol and control groups had significantly elevated interaction scores, compared with presurgical baseline, for at least 24 hours post-surgery. In a thermal antinociception model of somatic pain in cats, 0.4 mg kg$^{-1}$ of butorphanol produced short duration (60 minutes) analgesia, as evidenced by raised thermal thresholds (Robertson et al. 2003). When butorphanol was investigated for its analgesic properties in a colonic distension model in cats, 0.1 mg kg$^{-1}$ IV and 0.4 mg kg$^{-1}$ SC were determined to be the optimal doses in terms of duration and magnitude of action (Sawyer & Rech 1987). In this model, SC butorphanol provided comparable analgesia to the IV route, but a longer duration of action (up to 6 hours).

The CPS scores of carprofen-treated cats were significantly lower than those of the saline-treated group for at least 20 hours post-surgery, except at 4 hours, when carprofen scores did not differ significantly from the control values. Moreover, while both butorphanol and control groups had significantly increased interaction scores for at least 24 hours post-surgery, the carprofen group had scores that were significantly increased from baseline only in the early postoperative period. Interactive scores of the carprofen group were significantly elevated 2–4 hours post-surgery. Our results suggest that cats receiving carprofen returned to normal interactive behavior after the fourth postoperative hour. Therefore, carprofen was shown to be less effective in the early postoperative period. In a study investigating the pharmacodynamic and pharmacokinetic properties of carprofen in cats, peak plasma concentrations of 23.2 µg mL$^{-1}$ of total carprofen were measured 3 hours following the SC administration of a 4 mg kg$^{-1}$ dose (Taylor et al. 1996). In the same study, the same dose given IV resulted in peak plasma levels of 49.1 µg mL$^{-1}$ 1 hour after administration. This supports suggestions that carprofen may provide better analgesia in the immediate postoperative period when given prior to premedication to allow for the prolonged onset of analgesia (Lascelles et al. 1995). It may also explain why the carprofen-treated cats in our study had elevated interaction scores for up to 4 hours post-surgery.

Carprofen provides postsurgical analgesia for at least 18 hours in dogs (Lascelles et al. 1994) and cats (Lascelles et al. 1998). Another investigation proposed that analgesia associated with carprofen may last for 20–24 hours post-surgery in cats.
undergoing OHE (Slingsby & Waterman-Pearson 2002). Our results support these findings.

There is a great individual variation in pain behaviors seen in human beings and domestic animals. This may have also contributed to the variance in pain scores observed in the cat population in this study. By limiting our population to one species, one gender and one surgical procedure, as well as implementing the other exclusion factors mentioned earlier, we aimed to minimize this variance to some degree. Presurgical baseline data showed no significant differences in all baseline values between the groups of cats used, which suggests a relatively uniform population in this study. As senior students performed all OHE procedures, standardization of surgery time was not possible. However, no statistical differences were found between the groups when surgery time, cat age and mass were compared.

The need for rescue analgesic was another indicator that animals were still experiencing pain after surgery. Our threshold pain score of 12, which determined the need for rescue analgesia was based on previously published scales in dogs and cats, where threshold points were set at 55–62% of the total score (Crane 1987; Hansen 1997; Hellyer & Gaynor 1998; Holton et al. 1998; Firth & Haldane 1999; Mathews 2000). One cat in the carprofen group, three in the butorphanol group and five in the control group required meperidine. These results are consistent with previous reports. A recent investigation comparing carprofen to meloxicam in cats found that although both drugs provided adequate postsurgical analgesia following OHE, one cat in the carprofen group and two in the meloxicam group required rescue analgesia (Slingsby & Waterman-Pearson 2002). The authors do not believe the cats in the control group were pain-free following surgery. It is possible that the pain scale utilized was not sensitive enough to be used in some cats. A greater sample number may have reduced the variability between individuals. On visual assessment, cats with CPS scores of 8–10 appeared to be in moderate pain. Therefore, a lower (<12) threshold CPS score for administering the rescue analgesic may be necessary in cats. The results of this study suggest that a threshold pain score based on interaction behavior, instead of CPS scoring, may be a more sensitive indicator of the need for rescue analgesia in cats.

Another explanation for the low number of cats requiring rescue analgesic in the postoperative period may be the presence of ketamine in the anesthetic protocol. Sawyer et al. (1993) showed ketamine to have weak visceral analgesic properties in an experimental colonic distension model in cats. These analgesic effects were prolonged when combined with butorphanol (Sawyer et al. 1993). However, in human patients undergoing elective laparoscopic or proctologic surgery, a preemptive single IV bolus of 0.15 mg kg\(^{-1}\) ketamine did not provide a clinically relevant analgesic effect in the postoperative period (Lehmann & Klaschik 2001). Therefore, the contribution that ketamine may have made in providing analgesia in the cats in our three treatment groups is unknown at this time.

It would have been helpful to run assays of serum drug concentrations, as well as cortisol or catecholamines, to correlate the analgesic effects of carprofen or butorphanol with objective measures. However, as mentioned above, previous reports have been controversial, and, thus, specific tests were not performed in this study.

When the postsurgical analgesia produced by carprofen was compared with that produced by ketoprofen, meloxicam, and tolmetin acid, it was found that single injections of all the NSAIDs studied produced similarly effective analgesia (Slingsby & Waterman-Pearson 2000). However, none of the cats that had received carprofen in that study required rescue analgesia. Carprofen has also been compared with different opioids with regard to analgesic efficacy. When administered IV in dogs at 4 mg kg\(^{-1}\) body weight within 35 minutes after induction of anesthesia, carprofen provided profound analgesia as effective and long lasting as that produced by the opioid preparation papaveretum (Nolan & Reid 1993). In the same study, carprofen also produced significantly less postoperative sedation and a more rapid return to a normal conscious state than the opioid.

All doses in this study were based on previously published recommendations but it is difficult to know if the chosen doses provided equivalent analgesia because of their different modes of action. Preanesthetic IM administration of 0.4 mg kg\(^{-1}\) butorphanol in cats undergoing either castration or OHE improved visceral analgesia, lowered arterial blood pressure, and reduced heart rate (Tranquilli et al. 1988). However, significant increases in heart rate were reported in one experimental study assessing somatic and visceral analgesia by noninvasive means in cats, following the IV administration of 0.8 mg kg\(^{-1}\) butorphanol (Sawyer & Rech 1987). Intravenous injection of 0.4 mg kg\(^{-1}\) butor-
orphanol (with follow-up oral doses for 2 days) immediately following onychectomy, alone or with castration or OHE, improved analgesia, recovery, and reduced lameness (Carroll et al. 1998). But-orphanol was also given at the end of surgery in our study, as this is the usual time analgesics are administered in veterinary practice.

In a comparison of carprofen and meperidine (pethidine) in cats, administration of 4 mg kg\(^{-1}\) carprofen SC was more effective than meperidine in producing analgesia at 4 and 8 hours post-extubation. Meperidine hydrochloride provided better postsurgical analgesia for the first 2 hours post-extubation. Carprofen produced better analgesia than meperidine from 2-20 hours post-extubation (Lascelles et al. 1995). Based on investigations of the pharmacodynamics and pharmacokinetics of carprofen in cats, a dose of 4 mg kg\(^{-1}\) IV or SC was suggested to be of clinical relevance (Taylor et al. 1996).

At the time of our study, injectable carprofen was not available in the United States and, thus, the drug was imported from the United Kingdom. Carprofen appears to be a poor COX-1 inhibitor in dogs (Ricketts et al. 1998). Accordingly, its potential for producing adverse effects, such as renal toxicity, is markedly low (Jones & Budsberg 2000). Carprofen was not associated with any adverse renal effects in dogs undergoing general anesthesia (Ko et al. 2000; Bostrom et al. 2002). Our results support these findings. Postsurgically, the cats in this study did not exhibit any abnormal or significantly different creatinine and BUN values when compared with presurgical baseline biochemistry values. All cats urinated normally and did not show any clinical signs of renal disease. More detailed tests for renal function were not feasible in this study, and the investigator relied on clinical assessment of the cats.

A 5-year safety profile sponsored by Pfizer concluded that oral carprofen was associated with a low incidence of adverse effects in dogs (Fox 2002). The effects seen were limited to gastrointestinal signs and hepatopathy. The causes of hepatotoxicity were considered unpredictable and unrelated to drug dose or frequency of administration. However, one clinical report questions the safety of carprofen. It describes 21 dogs suffering from hepatocellular toxicosis associated with carprofen (MacPhail et al. 1998). Endoscopy (i.e. examination) of the gastroduodenal mucosa in dogs after the administration of carprofen, meloxicam, and ketoprofen revealed that carprofen (and the control) was associated with the fewest and least severe lesions (Forsyth et al. 1998).

Information on adverse effects of carprofen in cats is scant. To our knowledge, only one report exists, documenting a case of duodenal perforation in a cat receiving oral carprofen (Runk et al. 1999). This cat had received repeated doses of oral carprofen, at a dose rate recommended for dogs. Studies conducted in the United Kingdom reported no adverse hepatic, renal, or gastrointestinal side effects in cats following the parenteral administration of a single dose of carprofen (Lascelles et al. 1994, 1995; Balmer et al. 1998), however repeated administration after 24 hours is not recommended in cats. In a recent study in cats, IV administration of carprofen at a dose of 4 mg kg\(^{-1}\) did not cause endoscopically recognizable gastrointestinal lesions, while 20 mg kg\(^{-1}\) of IV acetyl salicylate produced minor pinpoint erosions in the gastrointestinal tract of one cat 8 hours post-injection. BUN, ALT, ALP and CBCs were not significantly altered from pretreatment values for both drugs (Parton et al. 2000).

Our results correlate well with these observations, as postsurgical biochemistry values of the majority of cats in this study were within normal limits. Only two of the 60 cats showed elevated ALT and glucose concentrations after surgery. This, however, was not considered of clinical relevance, as the cats were considered to be otherwise clinically healthy. Both cats were active, bright, alert and responsive, had a normal appetite, and urinated and defecated normally. The most common clinical symptoms associated with hepatopathy in cats are anorexia, vomiting, diarrhea, polydypisia, polyuria, icterus, hemorrhagic diathesis, and reduced performance (Kraft 1996). However, none of these signs were observed in the two cats with elevated ALT values during the 7 days following surgery.

In conclusion, single injections of either carprofen or butorphanol reduced pain scores and reduced the necessity for supplementary rescue analgesia in cats after surgical OHE procedures, without producing any clinically apparent side effects. The cats in this study which received only placebo treatment postoperatively showed increased CPS for 20 hours after surgery and increased interaction scores for at least 24 hours. Carprofen given preoperatively provided better pain control at more time periods during this 20-hour interval than butorphanol given postoperatively, as was indicated by the return to normal interactive behavior 4 hours after surgery.
References


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