Intraperitoneal administration of local anesthetics was first reported in the early 1950s in human medicine.\(^1,2\) This technique reduces early postoperative analgesic requirements, pain scores, and time to first-intervention analgesia after abdominal surgery in humans.\(^3–12\) According to meta-analyses and systematic reviews, IP administration of bupivacaine currently is recommended for laparoscopic surgery in humans as an adjuvant analgesic technique.\(^3,13–16\)

Intraperitoneal administration of bupivacaine can reduce pain scores and blunt surgery-induced stress responses in dogs undergoing ovariohysterectomy.\(^17–19\) The technique has been recommended by a panel of experts as an adjuvant technique for pain relief in dogs and cats undergoing abdominal surgery.\(^20\) However, to the authors’ knowledge, no studies have been conducted on the pharmacokinetics of bupivacaine after IP administration to cats.

The objective of the study reported here was to determine the pharmacokinetics of bupivacaine after IP administration to cats undergoing ovariohysterectomy. The authors hypothesized that there would be detectable plasma concentrations of bupivacaine after IP administration and that adverse effects would not be observed.

**Materials and Methods**

**Animals**

Eight healthy client-owned mixed-breed female cats scheduled for elective ovariohysterectomy were enrolled in the study. Cats were included if they were considered healthy on the basis of the medical history and results of a complete physical examination and hematologic evaluation (Hct and total protein values). Exclusion criteria included aggression, cardiac arrhythmias, pregnancy, lactation, obesity or thinness (body condition score > 7 or < 3, respectively, on a scale from 1 to 9), anemia, and clinical signs of disease. Abdominal ultrasonography was performed on the day before surgery to ensure that cats were not pregnant. Owner consent was obtained for cats included in the study. The study protocol was approved by the animal care committee of the Faculty of Veterinary Medicine at the University of Montreal.
Experimental procedures

Cats were admitted to the veterinary teaching hospital at the University of Montreal at least 24 hours before onset of the study. They were housed individually in adjacent cages in a cat-only room.

Food but not water was withheld for up to 12 hours before anesthesia. Approximately 20 minutes before induction, a 22-gauge catheter was inserted by use of aseptic technique into a cephalic vein. Anesthesia was induced by IV administration of propofol, to effect. Cats were intubated with an appropriately sized, cuffed endotracheal tube without instillation of lidocaine on the vocal cords. Anesthesia was maintained with isoflurane administered with oxygen (flow rate, 200 mL/kg/min) by use of a nonrebreathing circuit.

After anesthesia was induced, buprenorphine (0.02 mg/kg, IV) and meloxicam (0.2 mg/kg, SC) were administered for analgesia. Cats were positioned in dorsal recumbency on a circulating warm water blanket. Monitoring was performed constantly, and signs of bupivacaine toxicity were recorded every 5 minutes by use of a multiparametric monitor that included ECG, capnography, measurement of inspired and expired concentrations of isoflurane, pulse oximetry, and measurement of esophageal temperature. Blood pressure was measured with a Doppler ultrasonographic flow detector. The blood pressure cuff was placed around the antebrachium; width of the cuff was approximately 40% of the circumference of the limb. Lactated Ringer solution was administered IV at a rate of 10 mL/kg/h throughout surgery.

Before surgery began, a 20-gauge, 1.16-inch catheter was inserted by use of aseptic technique into a jugular vein; this catheter was used for collection of blood samples. Ovariohysterectomy was performed by only 1 surgeon (BPM). Briefly, a 3- to 4-cm-long ventral midline incision was made through the skin, subcutaneous tissues, and aponeurosis of the rectus abdominis muscle. A solution of 0.5% bupivacaine (2 mg/kg) was diluted with an equal volume of saline (0.9% NaCL) solution, which resulted in a final concentration of 0.25% bupivacaine for use in IP injection. The solution was equally divided into 3 portions and instilled into the peritoneal space, specifically over the right and left ovarian pedicles and caudal aspect of the uterus (1 portion at each of these locations). The solution was administered by use of a 3-mL syringe attached to a 22-gauge, 1.16-inch catheter. Time of bupivacaine administration was designated as time 0.

Surgery was performed approximately 2 minutes after bupivacaine administration. Surgery involved the use of a modified 3-clamp technique. The abdominal wall and subcutaneous tissues were closed with absorbable suture material in a simple continuous pattern. The skin was closed with an intradermal suture pattern. Surgery time (time elapsed from the first incision until placement of the last suture), anesthesia time (time elapsed from injection of propofol to cessation of isoflurane administration), and time to extubation (time elapsed from cessation of isoflurane administration until extubation) were recorded for each cat.

Collection and processing of blood samples

Venous blood samples (2 mL) were collected at 0, 2, 5, 10, 15, 20, 30, 60, 120, and 240 minutes after bupivacaine administration. These time points were based on results of studies on humans. All samples, except for the last 2 (120 and 240 minutes), were collected from anesthetized cats. Blood was transferred to EDTA-containing tubes. Samples were kept on ice for 15 to 30 minutes and then centrifuged (3,500 X g for 10 minutes). Plasma was separated and stored frozen (~80°C) until analysis.

Measurement of plasma bupivacaine concentrations

Plasma bupivacaine concentrations were determined by use of a liquid chromatography–tandem mass spectrometry method, as described elsewhere. Briefly, bupivacaine as a USP standard and d9-bupivacaine were used for determinations. Methanol, acetonitrile, formic acid, and water were purchased from a commercial scientific chemical company. Ten milliliters of plasma was obtained from research cats involved in another unpublished study conducted at the University of Montreal.

A protein precipitation technique was used to extract bupivacaine from feline plasma. An aliquot (500 µL) of internal standard solution (d9-bupivacaine in methanol; 5.0 ng/mL) was added to an aliquot (25 µL) of plasma sample. The sample was mixed in a vortex device for approximately 5 seconds, allowed to sit undisturbed for 10 minutes, and then centrifuged at 12,000 X g for 10 minutes. Supernatant was transferred to an injection vial for final analysis.

Plasma bupivacaine concentrations were determined by use of a triple-quadrupole instrument operated in selected reaction monitoring mode and a quadrupole-orbitrap mass spectrometer operating in full-scan high-resolution accurate-mass mode. The limit of quantification was 5 ng/mL, and the signal-to-noise ratio was > 100:1. Limit of detection was not determined because all detected plasma concentrations were substantially above the limit of detection.

Pharmacokinetic model and variables calculated for bupivacaine

Pharmacokinetic parameters of bupivacaine in feline plasma were calculated by use of noncompartmental methods in accordance with the following equation: , where Ct is the drug concentration at time point t, C0 is the drug concentration at time 0, e is the base of the natural logarithm, and k is the elimination rate constant (ie, fraction of drug eliminated per unit of time). Pharmacokinetic variables were calculated. These included area under the plasma concentration–time curve from time zero to the last measured time point, area under the plasma...
concentration–time curve from time zero extrapolated to infinity, terminal elimination rate constant, terminal elimination half-life clearance indexed by bioavailability, and volume of distribution indexed by bioavailability.

**Results**

Mean ± SD body weight of the cats was 3.2 ± 0.7 kg. Median body condition score was 5 (range, 4 to 5). Mean total dose of propofol administered was 9.8 ± 1.9 mg/kg. Mean anesthesia time was 79 ± 18 minutes, mean surgery time was 34 ± 5 minutes, and mean extubation time was 1 ± 2 minutes. All cats were discharged from the hospital within 24 hours after surgery without any postoperative complications. No signs of bupivacaine toxicosis were observed.

Plasma concentrations over time were plotted for each cat (Figure 1). The pharmacokinetic values of bupivacaine after IP administration were calculated (Table 1). Mean ± SD maximum plasma concentration of bupivacaine was 1,030 ± 497.5 ng/mL at 30 ± 24 minutes after administration. Mean elimination half-life was 4.79 ± 2.7 hours. Mean clearance indexed by bioavailability was 1,030 ± 24 minutes after administration. Mean peak plasma concentration of bupivacaine after IP administration was 1,030 ± 497.5 ng/mL in the present study. In humans, the mean maximum concentration after IP administration of bupivacaine is within the range of 0.29 to 1.14 µg/mL for doses of 1.5 to 2 mg/kg and when using bupivacaine concentrations between 0.15% and 0.75%. Peak plasma concentrations in the present study were approximately one-third the concentration that has been reported to cause a convulsive electroencephalogram pattern in cats (3.6 ± 0.7 µg/mL) and approximately one-seventh the concentration required to cause arrhythmias (7.5 to 10.9 µg/mL). A convulsive electroencephalogram pattern and hypotension have been reported for cats at higher plasma concentrations (17 and 21 to 25 µg/mL, respectively). Seizures and cardiovascular collapse have also been reported for cats at higher plasma concentrations (37 ± 11 µg/mL and 110 ± 24 µg/mL, respectively). Therefore, the doses and concentrations of bupivacaine used in the study reported here appeared to be safe for use in cats that were undergoing ovariohysterectomy.

The IP administration of bupivacaine and lidocaine has been reported in humans and rats. To the authors’ knowledge, pharmacokinetic studies after IP administration of bupivacaine to dogs have not been reported. However, the dose of bupivacaine (2 mg/kg) used in the present study resulted in serious nonfatal acute toxic effects after IV infusion to conscious sheep and corresponded with a peak arterial blood concentration of 8 µg/mL. In cats, higher doses reportedly cause arrhythmias (2.5 to 2.9 mg/kg), seizures (2.8 to 4.8 mg/kg), 5.3 mg/kg, and 6.6 to 7.0 mg/kg), and cardiovascular collapse (18.4 ± 4.9 mg/kg) after IV administration. For this reason, bupivacaine must not be administered IV. None of these aforementioned adverse effects were observed in the cats of the present study. The dose of bupivacaine used in this study was based on the veterinary literature, results of experiments on IP administration of bupivacaine to humans, and clinical experience with IP analgesia at the authors’ institutions.

It has been suggested that concentrations of bupivacaine > 0.25% should be used because lower concentrations may not be as efficacious.

Discussion

In the study reported here, IP administration of 0.25% bupivacaine (2 mg/kg) resulted in plasma concentrations that did not cause signs of bupivacaine toxicosis (eg, cardiovascular depression). Mean ± SD peak plasma concentration of bupivacaine after IP administration was 1,030 ± 497.5 ng/mL in the present study. In humans, the mean maximum concentration after IP administration of bupivacaine is within the range of 0.29 to 1.14 µg/mL for doses of 1.5 to 2 mg/kg and when using bupivacaine concentrations between 0.15% and 0.75%. Peak plasma concentrations in the present study were approximately one-third the concentration that has been reported to cause a convulsive electroencephalogram pattern in cats (3.6 ± 0.7 µg/mL) and approximately one-seventh the concentration required to cause arrhythmias (7.5 to 10.9 µg/mL). A convulsive electroencephalogram pattern and hypotension have been reported for cats at higher plasma concentrations (17 and 21 to 25 µg/mL, respectively). Seizures and cardiovascular collapse have also been reported for cats at higher plasma concentrations (37 ± 11 µg/mL and 110 ± 24 µg/mL, respectively). Therefore, the doses and concentrations of bupivacaine used in the study reported here appeared to be safe for use in cats that were undergoing ovariohysterectomy.

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It has been suggested that concentrations of bupivacaine > 0.25% should be used because lower concentrations may not be as efficacious.
present study, a final concentration of 0.25% was administered, and it is not known whether use of a higher concentration will increase the magnitude or duration of analgesia or cause adverse effects. The drug was diluted in saline solution to achieve a reasonable volume for anesthetic spread. At the dose administered, IP, bupivacaine had rapid uptake and reached peak concentrations at 30 ± 24 minutes. The mean ± SD plasma concentration of bupivacaine in the study reported here (1.03 ± 0.4 µg/mL) was similar to that of lidocaine with epinephrine (1.45 ± 0.36 µg/mL) after incisonal (2 mg/kg) or IP (8 mg/kg) administration to dogs. 37 On the other hand, bupivacaine had a longer elimination half-life (4.79 ± 2.7 hours), compared with that for lidocaine (1.17 ± 0.11 hours). The fact that those studies were performed in different species (dogs and cats) with different techniques (incisional and IP administration), doses, and drugs makes comparisons difficult. Nevertheless, on the basis of the aforementioned data, it appears that bupivacaine could result in a more rapid onset and longer duration of action than would lidocaine with epinephrine.

Findings for the present study are promising if one considers that IP analgesia has been recommended as an adjunctive analgesic method to reduce pain after ovariohysterectomy in dogs and cats. 30 Local anesthetics are low-cost drugs that are not listed as controlled substances, and they are available throughout the world. Because a large number of cats are spayed every year, the use of the local anesthetic technique described here may represent a substantial advance in pain management of cats. Future studies are warranted to investigate analgesic effects of this technique in cats and the effects of type of surgery on plasma concentrations of bupivacaine after IP administration. For example, exploratory abdominal surgery without tissue removal or greater surgical manipulation might affect plasma concentrations. In human medicine, serum concentrations of bupivacaine after IP administration were higher in individuals undergoing laparoscopic cholecystectomy, compared with concentrations in patients receiving a similar dose of bupivacaine and undergoing laparoscopic ovariolyhysterectomy. 3 This may have been attributable to the extent of dissection and tissue surface area that could have increased the absorption rate. 3

Studies are also warranted to assess the effects of epinephrine on systemic absorption of bupivacaine. Maximum concentrations of bupivacaine were decreased by 50% without adverse effects when the drug was administered with epinephrine to human patients undergoing diagnostic laparoscopy 32 and laparoscopic cholecystectomy. 38 Therefore, the addition of epinephrine to a local anesthetic solution could potentially increase the duration of action while reducing systemic absorption and providing an additional margin of safety. 3

One limitation of the present study was that active metabolites of bupivacaine were not analyzed. The clinical relevance of these metabolites in cats is not known. Another limitation of the present study was that plasma concentrations of bupivacaine were analyzed only up to 4 hours after surgery and had not returned to predadministration values by that last time point. It could be argued that this could have influenced the pharmacokinetics. However, when the concentration was converted to the natural logarithm of concentration versus time, the slope of the curve had a homogenous elimination phase without evidence of drug redistribution that could have influenced the pharmacokinetic profile.

For the doses and concentrations used in the study reported here, IP administration of bupivacaine resulted in concentrations that did not cause observable signs of toxicosis. Further studies are warranted to investigate the postoperative analgesic effects for this technique in cats.

Acknowledgments

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Footnotes

1. BDInstyke W, Becton Dickinson, Sandy, Utah.
2. Diprivan® AstraZeneca Canada Inc, Mississauga, ON, Canada.
3. Isoflurane USP Pharmaceuticals Partners of Canada Inc, Richmond, ON, Canada.
5. Boehringer Ingelheim, Burlington, ON, Canada.
6. LifeWindow 6000V Veterinary Multiparameter Monitor, DigiCare Animal Health, Boyton Beach, Fla.
7. Ultrasonic Doppler flow detector, Parks Medical Electronics Inc, Aloha, Ore.
8. Sensorcaine, Bupivacaine HCl 0.5% USP, AstraZeneca Canada Inc, Mississauga, ON, Canada.
9. Bupivacaine USP standard, Galenova, St-Hyacinthe, QC, Canada.
10. d9-Bupivacaine, Toronto Research Chemicals, Toronto, ON, Canada.

References


