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Plasma bupivacaine concentration following orbital injections in cats

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ABSTRACT

Objective: To determine the plasma bupivacaine concentration after retrobulbar or peribulbar injections in cats.

Design: Prospective, randomized, crossover, experimental trial with a two-week washout period.

Animals: Six adult healthy cats weighing 4.6 ± 0.7 kg.

Methods: Cats were sedated with 36 - 56 µg kg^{-1} dexmedetomidine and received a retrobulbar injection of 0.5 % bupivacaine (0.75 mL; 3.75 mg) and iopamidol (0.25 mL), or peribulbar injection of 0.5 % bupivacaine (1.5 mL; 7.5 mg), iopamidol (0.5 mL), and 0.9 % saline (1 mL) via a dorsomedial approach. Blood was sampled (2 mL) before, and at 5, 10, 15, 22, 30, 45, 60, 120, 240, and 480 minutes after bupivacaine injection. Atipamezole was administered approximately 40 minutes after bupivacaine injection. Plasma bupivacaine and 3-hydroxy-bupivacaine concentrations were determined using liquid chromatography/mass spectrometry. Bupivacaine maximum plasma concentration (Cmax) and time to Cmax were determined from the data.

Results: The bupivacaine median (range) Cmax, and time to Cmax were 1.4 (0.9 - 2.5), and 1.7 (1.0 - 2.4) µg mL^{-1}, and 17 (4 - 60), and 28 (8 - 49) minutes, for retrobulbar and peribulbar injections respectively. In both treatments the 3-hydroxy-bupivacaine peak concentration was 0.05 - 0.21 µg mL^{-1}.

Conclusion: In healthy cats, at a dose up to 2 mg kg^{-1}, the bupivacaine peak plasma concentration was approximately half that reported to cause arrhythmias or convulsive EEG in cats, and about one sixth of that required to produce hypotension (Chadwick 1985, de Jong et al. 1982).

Key words: Cats, bupivacaine, plasma concentration, peribulbar anesthesia, retrobulbar anesthesia.

Introduction

Local anesthetics are commonly used to block nociception before painful procedures in cats (Aprea et al. 2011). The voltage-gated sodium channel blockade responsible for the inhibition of nerve conduction and local anesthesia may also affect the central nervous system and the cardiovascular system, and may result in toxicity. Common signs of toxicity include sedation, seizures, arrhythmias, myocardial depression, hypotension, and cardiac arrest, and the systemic toxicity appears to be related to drug absorption ~~in~~ by the circulation; signs correlate with plasma drug concentrations (de Jong et al. 1982; Chadwick 1985).

The local anesthetic bupivacaine is widely used in veterinary medicine, as it has a long duration of action, market availability, low cost, and safety at recommended doses. The maximum recommended dose of bupivacaine for local and regional anesthesia in cats is 2 mg kg^{-1} (Webb & Pablo 2009). However, the authors are unaware of data regarding pharmacokinetics of bupivacaine following any perineural administration in cats. Studies assessing bupivacaine toxicity following intravenous infusion in cats revealed that arrhythmias, convulsions, hypotension, and cardiovascular collapse occurred at doses of 2.5, 3.8, 9.7, and 18.6 mg kg^{-1}, respectively (Chadwick 1985; Kasaba et al. 1998).

When performing a peribulbar anesthesia for ocular or periocular surgery, a large volume of local anesthetic is necessary in order ~~to be diffused~~for it to spread into the orbital muscle cone, where many of the nerves pass (Shilo-Benjamini et al. 2013). On a recent study in cat cadavers it was reported that administration of 4 mL of bupivacaine 0.25% (10 mg) resulted in a good distribution of the injectate into the muscle cone, and around the optic nerve (Shilo-Benjamini et al. 2013). However, this amount of bupivacaine would exceed the maximum recommended dose in all cats weighing less than 5 kg. Another solution would be to dilute the bupivacaine to a

concentration lower than 0.25%. However, this may lead to decreased efficacy as was described in humans (Krone et al. 2001).

Information regarding plasma bupivacaine concentration following peribulbar anesthesia in cats, would contribute to assessing a dose range that will achieve adequate local infiltration without causing systemic toxicity. Thus, the aim of this study was to measure the blood plasma concentrations of bupivacaine and its metabolite 3-hydoxy-bupivacaine following peribulbar and retrobulbar anesthesia techniques in cats. We hypothesized that, at the doses used in this study, the peak plasma concentration of bupivacaine would not exceed the plasma bupivacaine concentrations previously reported to cause systemic toxicity in cats.

Materials and methods

Animals

Six healthy adult female spayed cats, 1–2 year old, with a mean ± SD (range) body weight of 4.6 ± 0.7 (3.7-5.7) kg were used. A vascular access port (MINA-CBAS-C35, Solomon Scientific, Skokie, IL, USA) had been implanted in 5 of 6 cats under general anesthesia prior to the study, with the catheter in a carotid artery and the port subcutaneous between the shoulder blades. The port was used for blood sampling. Patency of the port was maintained by filling the port and catheter with heparin (100 U mL^{-1}) ~~3~~ three times per week. In 1 of 6 cats a 22-gauge, 8-inch (20.3 cm) catheter (Intracath, Argon Medical Devices, Athens, TX, USA) was placed in the medial saphenous vein before each treatment, and was used to sample blood. Cats were habituated to handling and blood sampling for at least two months prior to the beginning of the study. The study was approved by the Institutional Animal Care and Use Committee at the University of California Davis.

Drug administration

All cats received retrobulbar and peribulbar injections, using a randomized crossover design with at least a two-week washout period between injections. The treated eye was alternated, and the first treatment side (right or left orbit) was randomized using online randomizing software (www.randomizer.org). Prior to each injection, cats were fasted for 12 hours but allowed free access to water.

Approximately 45 minutes prior to injection, cats were sedated with 45 ± 7 μg kg^{-1} (mean ± SD) dexmedetomidine hydrochloride (Dexdomitor, Orion Pharma, Finland) injected intramuscularly. The hair of the upper eyelid was clipped, and the skin was aseptically prepared with povidone-iodine solution diluted 1:50 in sterile saline.

For the retrobulbar injection, a mixture containing 0.75 mL 0.5% bupivacaine (Bupivacaine HCl 0.5%; Hospira Inc., IL, USA) and 0.25 mL of radiographic contrast agent (iopamidol; Isovue 200, Bracco Dx, Princeton, NJ, USA) was used. For the peribulbar injection, a mixture containing 1.5 mL 0.5% bupivacaine, 1mL of 0.9% saline and 0.5 mL of iopamidol was used. The radiographic contrast agent was used to demonstrate distribution of the injectate using computed tomography. Injections were performed according to guidelines described by Shilo-Benjamini at al. (Shilo-Benjamini et al. 2013). Reversal of sedation was achieved with intramuscular administration of atipamezole (Antisedan, Orion Pharma, Finland) at 10 times the administered dexmedetomidine dose.

Blood sampling

Blood samples (2 mL) were collected from the vascular access port or from the intravenous catheter approximately 2 hours prior to bupivacaine administration, and 5, 10, 15, 20, 30, 45, 60, 120, 240, and 480 minutes following bupivacaine periorbital injections. Blood was transferred to tubes containing EDTA, immediately placed on ice, and then centrifuged for 10 minutes at 3901 g at 4 °C within 20 minutes of collection. The plasma was separated and frozen at -20 °C until analysis for drug concentration.

Because the vascular access port had lost patency in 1 of 5 cats at the first round of treatment, and in 2 of 5 in the second round of treatment, an intravenous catheter was placed in the medial saphenous vein as was described earlier for the cat without the vascular access port.

Drug analysis

Bupivacaine was quantitated in feline plasma by liquid chromatography-mass spectrometry analysis of protein-precipitated samples. Lidocaine was used as the internal standard. The technique was optimized to provide a limit of quantitation at 0.2 ng mL^{-1}. Accuracy (percent of nominal concentration) was 106, 96, and 103% for 3, 150, and 850 ng mL^{-1}, respectively. Precision (percent relative standard deviation) was 11, 7, and 7% for 3, 150, and 850 ng mL^{-1}, respectively.

Pharmacokinetic analysis

Non-compartmental analysis was conducted on the time-concentration data (WinNonlin 6.2, Pharsight, Cary, NC, USA). Three to five data points were used to calculate the slope of the terminal phase, and were selected by visual inspection of each individual time-concentration profile on a semi-logarithmic plot. The area under the time-concentration curve, was measured using the linear trapezoids method.

Statistical analysis

The Wilcoxon signed-rank test for paired data was used to compare the results between the two treatments. Significance was set at $p < 0.05$. Data ~~is~~ are reported as median (range).

Results

The results of the imaging and the orbital injections effects were reported elsewhere (Shilo-Benjamini et al. 2014). Reversal was performed 41 ± 4 minutes (mean ± SD) after dexmedetomidine administration in cats receiving retrobulbar injection and 42 ± 6 minutes after dexmedetomidine administration in cats receiving peribulbar injection.

Due to technical problems, blood samples from 3 cats during the initial sedation were not available. This occurred during the PBA treatment for the 5 and 10 minutes samples in one cat, and during the RBA treatment for the 5 minute~~s~~ sample in one cat, and for the 5, 10, and 22 min~~u~~te samples in another cat.

Parameters obtained from noncompartmental analysis of time–concentration data are summarized in Table 1. The median (range) 3-hydroxy-bupivacaine peak plasma concentration measured was 0.07 (0.05 - 0.18) µg mL^{-1} for RBA, and 0.14 (0.07-0.21) µg mL^{-1} for PBA. However, the concentrations were still ~~climbing~~ increasing at 8 hours (the last measurement) in 1 cat ~~at~~ in the RBA treatment, and in 4 cats ~~at~~ in the PBA treatment.

Interestingly, bupivacaine was detected in the baseline sample in 4 cats (3 after~~-~~ RBA, and 1 after PBA) at the second injection, however, the calculated concentration ranged from 0.1 ~~and~~ to 0.3 ng mL^{-1} and was considered negligible.

Discussion

This study examined the systemic exposure to bupivacaine following orbital administration in cats. A large variability in plasma bupivacaine concentrations between individuals was evident, limiting the statistical power of the drug dose comparison. The results of Cmax and time to Cmax were similar whether 1 or 2 mg kg^{-1} of bupivacaine was used, although there was a trend towards higher concentration with the higher dose. Interestingly, within individual cats, there was one cat administered ~~with~~ the lower dose that reached a higher bupivacaine plasma concentration in a faster time in comparison to when it ~~was administered with~~received the higher dose. This may be explained by the proximity of injectate deposition to blood vessels, and thus to its faster and greater absorption. The proximity to blood vessels may explain the toxicity with 1 mg~~/~~ kg^{-1} of bupivacaine reported in a 12 year old cat, as it was injected in close proximity to a mandibular neoplastic mass (Aprea et al. 2011). Other factors may also have played a role in that toxicity, such as the anesthetic depth during the bupivacaine injection (Voss et al. 2008), and the fact that the cat was simultaneously started on mechanical ventilation, which may have affected anesthetic depth further.

Studies on bupivacaine toxicity in cats have reported different plasma concentration thresholds for toxicity (Appendix) (de Jong et al. 1982; Chadwick 1985; Kasaba et al. 1998). Many factors may have contributed to these differences. For example, these studies differ in drug administration techniques (i.e., 1 mg kg^{-1} $minute^{-1}$ versus 4 mg kg^{-1} $minute^{-1}$, or, intravenous administration versus intraatrial drug administration), in measurement techniques, such as the area in the brain where the EEG activity was measured (hippocampus versus cortex), and in their end points (i.e., mean arterial pressure [MAP] of 40 mmHg versus 10 mmHg).

Depth of anesthesia may play an important role in the toxicity of local anesthetics (Kasaba et al. 1998; Voss et al. 2008). All of the above toxicity studies in cats used anesthetic drugs in

addition to muscle relaxants in order to keep the cats intubated and ventilated, as it would be unethical to use muscle relaxants in awake animals. Thus, the anesthetics used in these studies may have affected the results. On the other hand, in veterinary medicine, and especially in companion animals, regional anesthesia is often delivered during general anesthesia, or at least sedation.

We elected to measure 3-hydroxy-bupivacaine plasma concentrations, as this metabolite was reported to be one of the major metabolites in bupivacaine pharmacokinetic studies in humans, horses, and rats. The concentrations of this metabolite did not reach Cmax in 5 of the treatments at 8 hours, however, to our knowledge, the significance of this metabolite in cats or in other species is not clear.

Limitations to this study include the small sample size, with several samples missing during the initial drug absorption, the young and healthy cat population used, the use of dexmedetomidine for sedation, that could have an effect on bupivacaine absorption due to vasoconstriction (Kawaai et al. 2013), and could have an effect on bupivacaine metabolism due to decrease in cardiac output and thus decreased liver blood flow (Pypendop et al. 2013). In addition, cats were not monitored during sedation, and as we did not want to exceed the bupivacaine dose recommended in the literature, doses higher than 2 mg ~~/~~kg^{-1} were not tested.

In conclusion, in healthy cats, at a dose of 1-2 mg kg^{-1}~~mg/kg~~ bupivacaine Cmax was approximately half that reported to cause arrhythmias or convulsive EEG, and approximately one sixth of that required to produce hypotension in bupivacaine toxicity studies in cats. Further studies of plasma concentrations and adverse effects following perineural bupivacaine at 3 mg kg^{-1}~~mg/kg~~ or more in cats are indicated.

REFERENCES

Aprea F, Vettorato E, Corletto F (2011) Severe cardiovascular depression in a cat following a mandibular nerve block with bupivacaine. Vet Anaesth Analg 38**,** 614-618.

Chadwick HS (1985) Toxicity and resuscitation in lidocaine- or bupivacaine-infused cats. Anesthesiology 63**,** 385-390.

de Jong RH, Ronfeld RA, DeRosa RA (1982) Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61**,** 3-9.

Kasaba T, Shiraishi S, Taniguchi M et al. (1998) Bupivacaine-induced convulsion is suppressed by MK-801. Reg Anesth Pain Med 23**,** 71-76.

Kawaai H, Yoshida K, Tanaka E et al. (2013) Dexmedetomidine decreases the oral mucosal blood flow. Br J Oral Maxillofac Surg 51**,** 928-931.

Krone SC, Chan VW, Regan J et al. (2001) Analgesic effects of low-dose ropivacaine for interscalene brachial plexus block for outpatient shoulder surgery-a dose-finding study. Reg Anesth Pain Med 26**,** 439-443.

Pypendop BH, Escobar A, Siao KT et al. (2013) Effect of dexmedetomidine on its clearance: a pharmacokinetic model. J Vet Pharmacol Ther 36**,** 89-91.

Shilo-Benjamini Y, Pascoe PJ, Maggs DJ et al. (2013) Retrobulbar and peribulbar regional techniques in cats: a preliminary study in cadavers. Vet Anaesth Analg 40**,** 623-631.

Shilo-Benjamini Y, Pascoe PJ, Maggs DJ et al. (2014) Comparison of peribulbar and retrobulbar regional anesthesia with bupivacaine in cats. Am J Vet Res 75**,** 1029-1039.

Voss LJ, Sleigh JW, Barnard JP et al. (2008) The howling cortex: seizures and general anesthetic drugs. Anesth Analg 107**,** 1689-1703.

Webb A, Pablo L (2009) Local Anesthetics. In: Veterinary Pharmacology and Therapeutics. Riviere J & Papich M (eds). Wiley-Blackwell, Ames, Iowa. pp. 381-400.

224TABLES

225**Table 1** Median (range) pharmacokinetic data for bupivacaine following retrobulbar anesthesia 226(RBA) with 0.5 % bupivacaine (0.75 mL) and iopamidol (0.25 mL) or peribulbar anesthesia 227(PBA) with 0.5 % bupivacaine (1.5 mL), iopamidol (0.5 mL), and 0.9 % saline (1 mL), in 6 cats.

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Parameter	RBA (3.75 mg)	PBA (7.5 mg)
Cmax (µg mL^{-1})	1.4 (0.9 - 2.5)	1.7 (1.0 - 2.4)
Tmax (minutes)	17 (4 - 60)	28 (8 – 49)
AUC (minutes µg mL^{-1})	426 (184 – 818)	549 (289 – 1502)
AUC $dose^{-1}$ (minutes µg mL^{-1} mg^{-1})	113.7 (49 – 218)	73.2 (38.6 – 200.3)
Clearance (mL minute^{-1})	10.1 (4.6 – 20.4)	13.7 (5 – 25.9)

229 Cmax = peak plasma concentration, Tmax = time to Cmax, AUC = area under the curve.

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Appendix Comparison of bupivacaine toxicity studies in cats

Study	Dose administered	Other drugs administered concurrently	Arrhythmia definition	Plasma concentration for arrhythmias (dose)	EEG electrodes placement; and end point	Plasma concentration for Convulsive EEG (dose)	CVS end point	Plasma concentration for CVS end point (dose)
de Jong et al. (1982)	1 mg ~~/~~kg^{-1} ~~/~~minute^{-1} IV (1. n = 10) (2. n = 9)	70% N_2O (was discontinued right before the baseline measurements, prior to local administration); Gallamine 20 mg	Ventricular ectopic beats	Not measured; Before convulsive EEG (At ~ 2.65 mg kg^{-1} ~~mg/kg~~)	Frontal, temporal, and occipital regions of the cortex; high voltage epileptiform seizure bursts	1. 3.6 ± 0.7 µg ~~/~~mL^{-1} 2. 5.1 ± 1.6 µg mL^{-1} ~~µg/mL~~ (5.3 ± 2.1 mg kg^{-1} ~~mg/kg~~)	20-30% ↓ MAP	1. 9.9 ± 4.7 µg mL^{-1} ~~µg/mL~~ 2. 14.1 ± 2.8 µg mL^{-1} ~~µg/mL~~
Chadwick (1985)	4 mg kg^{-1} minute^{-1} ~~mg/kg/min~~ IV (n = 10) Infused into the right atrium	70% N_2O; Pancuronium 0.2 mg kg^{-1} ~~mg/kg~~ IV	Abnormal ECG trace	Not measured; Right before convulsive EEG onset * *Although abnormal ECG was evident, no change in blood	Right and left front occipital; First spike activity	37 ± 11.3 µg mL^{-1} ~~µg/mL~~ (3.8 ± 1 mg kg^{-1} ~~mg/kg~~)	MAP = 10 mm Hg	110 ± 24.6 µg mL^{-1} ~~µg/mL~~ (18.4 ± 4.9 mg kg^{-1} ~~mg/kg~~)

				pressure occurred at this point				
Kasaba et al. (1998)	**1 mg kg^{-1}~~mg/kg/~~ minute^{-1}~~min~~ IV (n = 7) Infused into the femoral vein**	**Urethane 1 g kg^{-1}~~g/kg~~ IV; Pancuronium 0.2 mg kg^{-1}~~mg/kg~~ IV**	**Ventricular ectopic beats**	**9.5 ± 2.9 µg mL^{-1}~~µg/mL~~ (2.5-2.9 mg kg^{-1}~~mg/kg~~)**	**Frontal cortex, and dorsal hippocampus; High-voltage and high-frequency convulsive spikes in the hippocampus**	**17.1 ± 2.4 µg mL^{-1}~~µg/mL~~ (6.6-7.0 mg kg^{-1}~~mg/kg~~)**	**MAP = 40 mm Hg**	**23 ± 3 µg mL^{-1}~~µg/mL~~ (9.7-12.4 mg kg^{-1}~~mg/kg~~)**

233EEG = Electroencephalogram; CVS = Cardiovascular system

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