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Plasma concentrations of buprenorphine after epidural administration in conscious cats

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ABSTRACT

Buprenorphine plasma concentrations were measured after administering buprenorphine (20 μg/kg) into the lumbosacral epidural space of conscious cats chronically instrumented with an epidural catheter. Blood was collected from a jugular vein before injection and 15, 30, 45 and 60 min and 2, 3, 4, 5, 6, 8, 12 and 24 h after administration. Plasma buprenorphine concentrations were measured using ELISA. Background concentration (before injection) was 1.27 ± 0.27 ng/mL (mean ± SD). Including background concentration, the mean peak plasma concentration was obtained 15 min after injection (5.82 ± 3.75 ng/mL), and ranged from 3.79 to 2.20 ng/mL (30 min–3 h), remaining between 1.93 and 1.77 ng/mL (4–12 h), and declined to 1.40 ± 0.62 ng/mL at 24 h. Elimination half-life was 58.8 ± 40.2 min and clearance 56.7 ± 21.5 mL/min. Results indicate early rapid systemic uptake of buprenorphine from epidural administration with plasma concentrations similar to using buccal or IM routes by 15 min postinjection.

Epidural opioid administration in cats is a useful route of administration to provide intense analgesia (Duke et al., 1994; Pypendop et al., 2008; Steagall et al., 2009). A highly lipophilic opioid, buprenorphine, has been investigated as a suitable opioid for epidural administration in cats, dogs and horses (Fischer et al., 2009; Pypendop et al., 2008; Smith and Yu, 2001). As it is a highly lipophilic drug, there is speculation as to whether it might exert its effects systemically or through migration within the spinal canal, or through both routes (Steagall et al., 2009). To the authors knowledge, no measurement of buprenorphine plasma concentrations have been made following epidural administration in domestic animals, therefore this study was designed to measure these concentrations following injection of a set dose into the lumbosacral epidural space of conscious cats.

This study was approved by the University of Saskatchewan Protocol Review Committee (protocol number 20060074). Eight adult cats were used in this study (two intact females and six neutered males) ranging in weight from 2.6 to 7.4 kg (4.77 ± 1.5 kg; mean ± SD). Their ages ranged from 2.3 to 7.7 years (4.49 ± 1.7 years; mean ± SD). Cats were group housed according to the Canadian Council for Animal Care Guidelines and were fed dry cat food ad libitum, supplemented with canned food and treats. Water was freely available. Physical and haemotological examinations were performed to ensure cats were healthy.

A long-term epidural catheter implantation model was used and several studies were performed over a five month period allowing cats to lead a normal life during this time. The results of other studies are to be presented elsewhere (Ambros et al., 2009; Steagall et al., 2009). A one week rest interval was provided between this and a previous study. Surgical epidural catheter implantation was performed using totally implantable vascular access ports (5Fr 30 cm GPV Vascular Access Port; Access Technologies, Skokie, IL, USA) and this has been previously described (Duke et al., 1994; Remedios and Duke, 1993). The distal tip of the catheter lay at the lumbosacral junction to mimic the injection position clinically used with a spinal needle. The receiving port of the catheter was passed cranially under the skin to lie between the shoulder blades. Both catheter and access port were sutured in place and the whole unit completely covered with skin. The position of the distal end of the catheter in the lumbosacral area of the cat was confirmed using fluoroscopy and injection of contrast agent. Seven days after implantation, to further test the epidural location of the catheter distal port, 0.2 mL/kg of lidocaine hydrochloride 2% (Lidocaine HCl 2%; BIMEDA-MTC Animal Health Inc., Cambridge, Ontario, Canada) was injected through the catheter to produce reversible bilateral hindlimb and tail paralysis and cats were rested for a further seven days. Flushing of the catheter occurred only when test drugs were given to limit risk of infection, and individual cats had rest periods of at least one week between all tests.

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For this study, cats were fasted for 12 h with access to water. Anaesthesia was induced and maintained with isoflurane (IsoFlo®, Isoflurane, USP, Abbott Limitée, Saint-Laurent, QC, Canada) in 100% oxygen delivered using a non-rebreathing system and endotracheal intubation. An 18G over-the-needle catheter with injection port was aseptically placed into a jugular vein, secured and bandaged. Cats were allowed to fully recover from the anaesthetic for 90 min before the epidural injection of buprenorphine (Buprenex; Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA, USA). Buprenorphine at a dose of 20 μg/kg was percutaneously injected into the receiving port of the vascular access port using a Huber needle and aseptic technique. The catheter was flushed with the appropriate amount of saline for the catheter used in the individual cat (dead space determined at surgical implantation [0.20–0.25 mL]). Blood samples (1.5 mL) were collected from the jugular vein using the preplaced catheter at the following timepoints: before injection (baseline/time 0) and 15, 30, 45 and 60 min and 2, 3, 4, 5, 6, 8, 12 and 24 h after epidural injection. Blood was placed into lithium heparin collection tubes and no later than 2 h after collection, was centrifuged at 5000 rpm for 10 min in order to remove the plasma. Plasma was stored at −80 °C until analysis. Analysis of plasma buprenorphine was through enzyme linked immunoassay (ELISA) at a wavelength of 405 nm (Single-step™ Buprenorphine ELISA test kit, Diagnostix Ltd., Missisauga, Ontario, Canada). Standard curves were used (0.5–5.0 ng/mL) and the interassay covariance was 4.2% for plasma with a concentration of 4.4 ng/mL. Sensitivity of the assay was 0.2 ng/mL.

Results (mean + SD) are presented in Fig. 1, and individual plasma concentrations for each cat are presented in Table 1. Pharmacokinetic analysis (Table 2) was performed using WinNonlin (ver 2.1) Pharsight (Cary, NC) on seven cats, and disregarding data from 6 h onwards (concentrations close to background). The model used involved extravascular administration with a lag period and a single compartment elimination phase. Standard pharmacokinetic parameters were reported including the R^2 correlation co-efficient to demonstrate the correlation between the observed data and that predicted by the final model.

Measurement of buprenorphine concentrations at time 0 (baseline) indicate the presence of a small amount of cross-reactivity with an unknown compound (background concentration), and these amounts were subtracted from the results in the graph in order to simplify the presentation, but included in Table 1 results. An assumption was made that this background concentration was similar throughout the study, but this could not be verified. The manufacturer of the ELISA kit states <1% cross-reactivity with other opioids. Buprenorphine was absorbed rapidly from injection site into plasma with a rapid elimination.

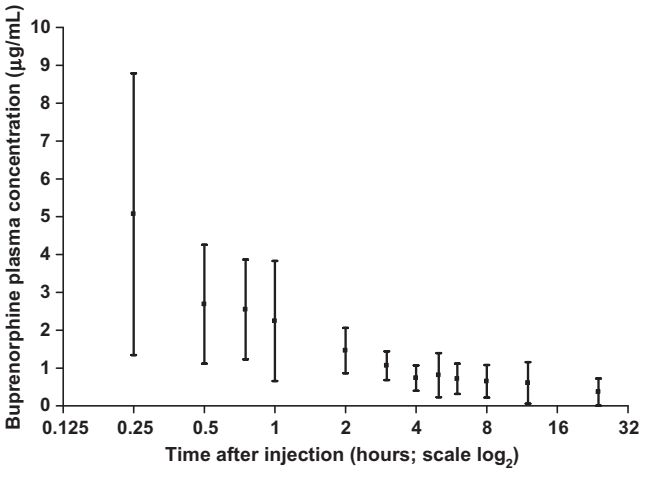

Fig. 1. Buprenorphine plasma (minus background) concentrations (mean ± SD) following injection of 20 μg/kg buprenorphine into the lumbosacral epidural space of seven conscious cats (no background concentration available for one cat).

Thermal threshold testing of nociception has been previously performed in cats and found that epidural buprenorphine produced antinociceptive actions from 1 to 10 h (Pypendop et al., 2008) and in cats used in this study, from 15 min to 24 h (Steagall et al., 2009). Nociceptive threshold testing was not performed alongside blood sampling for plasma concentrations on our group of cats to prevent the act of taking blood samples from interfering with threshold testing. Differences in statistical analyses and placement of threshold test device as well as dose-related effects may account for differences between Pypendop's study and our own. Our results reveal a rapid systemic uptake of buprenorphine from the epidural space typical of that observed with lipophilic drugs (Chauvin et al., 1985). The plasma concentrations of buprenorphine decline over the following 2 h and are near baseline concentrations by the 24 h timepoint.

Antinociception was detected at 15 min postinjection in our earlier study (Steagall et al., 2009) and this probably reflects the initial high plasma concentrations of buprenorphine and a supraspinal effect. Early supraspinal analgesia from systemically absorbed buprenorphine (30 min–2 h) has been reported in a previous study performed in humans undergoing surgery, followed by a longer period of spinal analgesia which is also dose-related (Inagaki et al., 1996).

Examination of Fig. 1 (minus background) indicates that concentrations were considered low by 24 h, but the exact time this point was reached is limited by lack of sampling between 12 and 24 h. The only other available study which investigated plasma buprenorphine concentrations after an epidural infusion found analgesia was still present despite low plasma concentrations of around 0.3 ng/mL (Shiraishi et al., 1993). This might further indicate that using the epidural route is still useful because of spinal antinociceptive effects, even though plasma levels may be low. In comparing the epidural route to other routes used in cats, intramuscular buprenorphine (20 μg/kg) provided antinociception from 35 min to 5 h (Johnson et al., 2007) but plasma concentrations were not concurrently measured.

Comparisons with other studies measuring plasma concentrations of buprenorphine in cats are difficult because we used the ELISA method and other groups used the radio-immunoassay technique (Robertson et al., 2005). With transmucosal absorption of buprenorphine, plasma concentrations were found to range from 1.26 to 8.26 ng/mL, and these concentrations are similar to those measured in our study. Relating plasma buprenorphine concentration to analgesic effect was described as difficult because of buprenorphine's slow biophase equilibration kinetics, avid binding to receptors and slow dissociation. Antinociception however, appeared to be present at plasma concentrations above 1.2 ng/mL in that study and concentrations above this level were observed for the first 12 h in our study (Robertson et al., 2005). However, as stated beforehand, examination of plasma concentrations may not accurately reflect the degree of analgesia present when epidural route is used (Shiraishi et al., 1993). Plasma concentrations in our study did not reach as high a level as found in a study examining intravenous administration at half the dose used in our study (Taylor et al., 2001). Accurate comparison is difficult as we did not have sampling points immediately postinjection and it appears from Taylor et al.'s study that plasma concentrations had decreased to those similar to the IM route and similar to concentrations in our study by 15 min postinjection.

Clearance was found to be similar to another study where buprenorphine was administered intravenously in cats, but elimination half-life was much shorter in our study compared with intrave-