PHARMACOKINETICS OF SINGLE-DOSE BUPRENORPHINE, BUTORPHANOL, AND HYDROMORPHONE IN THE DOMESTIC FERRET (*MUSTELA PUTORIUS FURO*)

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Abstract

The objective of this study was to establish the clinical pharmacokinetic profile of 4 different opioid drugs (buprenorphine, butorphanol, hydromorphone, and morphine) in the domestic ferret (*Mustela putorius furo*). Twenty-four, approximately 1-year-old, male neutered purpose-bred domestic ferrets were used for this study. The ferrets were divided into 4 groups of 6, with a different opioid drug used for each group. A preopioid venous blood sample was obtained via cranial vena cava venipuncture. Following the initial blood collection, a single injection of opioid (hydromorphone 0.1 mg/kg, buprenorphine 0.04 mg/kg, butorphanol 0.3 mg/kg, and morphine 1 mg/kg) was given to each ferret, dependent on assigned drug group, intramuscularly (buprenorphine) or subcutaneously (hydromorphone, butorphanol, and morphine). Intramuscular injections were administered in the semimembranosis and semitendinosis muscles, whereas the subcutaneous injections were delivered in the intrascapular subcutaneous space. A venous blood sample was obtained at 5, 15, 30, 60, 120, 240, 360, 480, and 720 minutes postinjection from the ferrets in the buprenorphine, butorphanol, and hydromorphone groups. Mass spectrometry and liquid chromatography was performed to obtain plasma concentrations of the administered drugs. The mean maximum concentration of buprenorphine was 6.96 ng/mL, butorphanol was 48.6 ng/mL, and hydromorphone was 17.3 ng/mL. Maximum concentrations were achieved at a mean of 9 minutes after administration for buprenorphine, 13.3 minutes for butorphanol, and 8.33 minutes for hydromorphone. The mean half-life of buprenorphine was 219.1 minutes, butorphanol was 91.1 minutes, and hydromorphone was 24.7 minutes. Owing to severe complications arising within the morphine group, including hypersalivation and vomiting, the morphine study was discontinued prior to blood sample collection. Intramuscular injections of buprenorphine and subcutaneous injections of butorphanol or hydromorphone appeared to be well tolerated by all ferrets. The pharmacokinetics of buprenorphine, butorphanol, and hydromorphone of a single equipotent dose of each drug have been established through this research investigation and may be useful for further studies.

Key words: ferret; analgesia; pharmacokinetics; butorphanol; buprenorphine; hydromorphone

The domestic ferret (*Mustela putorius furo*) is a popular pet, with an estimated 748,000 pet ferrets as of 2012, and accounts for the highest veterinary expenditures among companion exotic pets.[1] Currently, ferrets are legal in every state except California. The ferret has long been known for its tendency to develop disease conditions that require surgical intervention, from gastrointestinal obstructions to various neoplastic processes.[2-7] Despite the fact that ferrets frequently receive surgical diagnostics and treatment from veterinarians, very little is known about pain and its management in this particular species. Most of the clinical information regarding the use of

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opioids to manage pain in ferrets is extrapolated from information obtained from other mammalian species (e.g., canine and feline).[8-11] Dosages and information regarding the use of opioid drugs in ferrets extrapolated from other animal species may be problematic and potentially dangerous in the clinical setting, as ferrets are taxonomically, behaviorally, and physiologically unique among pet mammals.[8] Moreover, it has been reported that ferrets appear to become relatively more sedate than dogs and can suffer from severe respiratory suppression after administration of opioid agents.[9,12-14]

Butorphanol, buprenorphine, morphine, and hydromorphone are the most commonly recommended opioid drugs for providing analgesia in ferrets.[9,12-14] Currently, little data exist for the pharmacological or clinical profile of any of the drugs, listed earlier, for use in ferrets. Butorphanol is the best studied, with 4 publications describing anesthetic, sedative, and cardiorespiratory effects of this opioid in combination with other drugs.[15-18] In a combined (tiletamine, zolazepam, xylazine, and butorphanol) study, addition of butorphanol was shown to increase the duration of analgesia, ease endotracheal intubation, and increase time of dorsal recumbency, suggesting at least an increased analgesic and sedative effect. However, the addition of butorphanol to the combination also caused hypoxemia, prompting the author to conclude that supplemental oxygen should be provided to ferrets if butorphanol is included in the tiletamine, zolazepam, and xylazine cocktail.[15] In both a diazepam, acepromazine, xylazine, and butorphanol study, and a diazepam, ketamine, acepromazine, xylazine, and butorphanol study, statistically and clinically significant cardiorespiratory depression occurred in all ferret groups. However, owing to the presence of butorphanol in all of the cocktails and variance of other drugs, it is unclear how much effect butorphanol actually had regarding the cardiorespiratory suppression.[16,17] In a combination medetomidine, ketamine, and butorphanol study, the addition of butorphanol to the combination of drugs caused the most respiratory depression and significantly increased the duration of analgesia over the combinations that did not contain butorphanol.[18] Nevertheless, the combination of drugs used made evaluation of the effects of any single component very difficult. Therefore, clinical application to any anesthetic/sedative combination other than those described in these papers is clinically challenging.

There are no studies assessing the pharmacokinetics of morphine in ferrets; however, 1 study exists describing its epidural use in ferrets. In this double-blinded placebo controlled trial, ferrets treated with epidural morphine prior to surgical ovariohysterectomy and anal sacculectomy returned to function faster and exhibited less pain associated behaviors than placebo treated controls, suggesting that morphine administered epidurally may be an effective form of analgesia in ferrets.[19] At this time the authors of this article do not know if systemic morphine might also be an effective means of providing pain relief. In regard to hydromorphone, there are no studies of any kind relating to its use in ferrets, although it has been recommended based upon its less severe side effects in other species. An apparent benefit of using hydromorphone over other opioid drugs in ferrets would be that, anecdotally, ferrets appear to have problems with other systemically administered opioid agents.[10,13,20] There is also no published data regarding the use of buprenorphine in ferrets. However, it is used frequently in other mammalian species for pain control and sedative benefits.

In a pilot study assessing cardiorespiratory effects of butorphanol, buprenorphine, and hydromorphone in 5 ferrets, trends were found suggesting a drop in plasma pH, rise in arterial PaCO2, and concurrent drop in PaO2.[21] From this work, the need for a larger research investigation was apparent, to assess the significance of these findings, with one goal to be the establishment of pharmacokinetic parameters of opioid drugs in ferrets.

The purpose of the research investigation described in this article was to establish the single-dose pharmacokinetic profile of 4 different opioid drugs in domestic ferrets. These drugs include buprenorphine, butorphanol, hydromorphone, and morphine.

MATERIALS AND METHODS

Animals

Twenty-four, approximately 1-year-old, male neutered purpose-bred domestic ferrets weighing approximately 1 kg were housed in 4 groups of 6 and were acclimatized for a period of 5 days. When not used for the study, each ferret was given *ad libitum* water and food. The day of the study each ferret was housed separately, and held

without food or water during the duration of sample collection.

Drug Administration, Sample Collection, and Handling

A preopioid venous blood sample was obtained via cranial vena cava venipuncture, followed by a single injection of opioid. Six ferrets were used in each group. Morphine at 1 mg/kg was administered subcutaneously, and approximately equipotent doses of hydromorphone (0.1 mg/kg subcutaneously),[22] buprenorphine (0.04 mg/kg intramuscularly),[23] and butorphanol (0.3 mg/kg subcutaneously)[24] were used. Intramuscular injections were given in the semimembranosis and semitendinosis muscles. Subcutaneous injections were administered in the intrascapular subcutaneous space. A venous blood sample was obtained at 5, 15, 30, 60, 120, 240, 360, 480, and 720 minutes postinjection. Blood samples were obtained via cranial vena cava, jugular, cephalic, or dorsal pedal venipuncture. Approximately 0.5 mL to 0.8 mL of blood was collected at each time point and placed into a microtainer tube that contained sodium heparin. Within 20 minutes of collection, each tube was centrifuged for 3 minutes at 2046*g*, and the plasma was manually separated using a disposable plastic pipette. Samples were stored at −70°C until processed for determination of plasma drug concentrations.

Mass Spectrometry and Liquid Chromatography

Stock solutions for preparation of standards and quality control samples were diluted from the original clinical formulations obtained from the pharmacy at the Colorado State University Veterinary Teaching Hospital by performing a series of dilutions in a 50:50 mixture of acetonitrile (ACN) and type I ultrapure water (Milli-Q water, Millipore Corporation, Billerica, MA USA). Generation of standard curves was achieved by fortifying blank ferret plasma with hydromorphone, butorphanol, or buprenorphine with naringenin added as an internal standard.

Buprenorphine and Hydromorphone. Plasma samples (100 µL) were fortified with 10 ng (10 µL of 1 µg/mL solution) of naringenin as an internal standard. A 10 µL buprenorphine or hydromorphone standard (or blank diluent for unknowns) was then added to the samples, followed by the addition of 1 mL of methyl-tert-butyl ether (MTBE); samples were then vortex mixed for 10 minutes. Samples were then centrifuged at 17*g* for 10 minutes and 950 µL of the organic layer was transferred to fresh tubes and evaporated to dryness using a commercial vacuum system (Savant AES 1000 SpeedVac, Minneapolis, MN, USA). Samples were then resuspended in 100 µL of 50:50 ACN/H_20 and transferred to autosampler vials with glass inserts for injection onto the high-performance liquid chromatography (HPLC) system.

Butorphanol. Plasma samples (50 µL) were fortified with 5 ng (5 µL of 1 µg/mL solution) of naringenin as an internal standard. A 5 µL butorphanol standard (or blank diluents for unknowns) was then added to the samples, followed by 100 µL of ACN. Samples were then vortex mixed for 10 minutes, centrifuged at 17*g* for 10 minutes, and transferred to autosampler vials with glass inserts for injection onto the HPLC system.

Positive ion electrospray ionization mass spectra were obtained with a commercially available triple quadrupole mass spectrometer (MDS Sciex 3200 Q-TRAP, Applied Biosystems Incorporated, Foster City, CA, USA) with a turbo ionspray source interfaced to a HPLC system and an autosampler (HTC-PAL, Leap Technologies, Carrboro, NC, USA). Buprenorphine and butorphanol samples were chromatographed with a commercially available column (Waters XBridge Phenyl 2.5 µm [4.6 × 50 mm] column; Agilent Technologies, Santa Clara, CA, USA), whereas hydromorphone was chromatographed using a different commercially available column (Waters Sunfire C8 5 µm [4.6 × 50 mm] column protected by a C_{18} guard cartridge [4.0 mm by 2.0 mm]; Phenomenex, Torrance, CA, USA). For buprenorphine and hydromorphone, an LC gradient was employed with mobile phase A consisting of 10 mM ammonium acetate and mobile phase B consisting of acetonitrile. For butorphanol, an LC gradient was employed with mobile phase A consisting of 0.1% formic acid in water and mobile phase B consisting of acetonitrile. Chromatographic resolution was obtained with the following gradients:

Butorphanol: mobile phase B steady at 25% from 0 to 1.5 minutes, increasing linearly from 25% to 98% from 1.5 to 2.5 minutes, holding steady at 98% from 2.5 to 4.0 minutes, decreasing linearly from 98% to 25% from 4.0 to 4.75 minutes, followed by equilibration at 25% from 4.75 to 6.0 minutes. The LC flow rate was 0.75 mL/minute and the sample injection volume was 10 µL. The analysis run time was 6.0 minutes.

Buprenorphine: mobile phase B steady at 25% from 0 to 1.0 minutes, increasing linearly from 25% to 98% from 1.0 to 2.0 minutes, holding steady at 98% until 4.5 minutes, decreasing linearly to 25% from 4.5 to 4.75 minutes, followed by equilibration at 25% until 6.0 minutes. The LC flow rate was 1 mL/minute and the sample injection volume was 60 µL. The analysis runtime was 6.0 minutes.

Hydromorphone: mobile phase B steady at 10% until 1.0 minutes, increasing linearly to 98% at 2.0 minutes, holding steady at 98% until 4.5 minutes, decreasing linearly to 10% at 4.75 minutes, followed by equilibration at 10% until 6.0 minutes. The LC flow rate was 1 mL/minute and the injection volume was 30 µL. The analysis runtime was 6.0 minutes.

The mass spectrometer settings were optimized for buprenorphine, butorphanol, and hydromorphone (respectively) as follows: turbo ionspray temperature (T), 550, 575, and 550°C; ionspray voltage, 5500, 4500, and 5500 V; declustering potential, 80, 53, and 54 V; entrance potential, 7, 49, and 9 V; collision energy, 49, 62, and 38 V; collision cell entrance potential, 46, 6, and 35 V; collision cell exit potential, 3, 2, and 3 V; curtain gas, N_2, (CUR), 30, 10, 30 units; collision gas, N_2, (CAD), 5 units; nebulizer gas, N_2, 60 units; and auxiliary gas, N_2, 60 units. Samples were quantified by internal standard reference method in multiple reaction monitoring mode monitoring ion transitions *m/z* 468.3→396.4 for buprenophine, *m/z* 328.3→157.2 for butorphanol, *m/z* 286.4→185.1 for hydromorphone, and *m/z* 273.1→153.0 for naringenin (internal standard). The dwell times for each ion transition were 250 ms. $Quadrupole_1$ and $quadrupole_3$ were both operated in unit resolution. No interfering peaks were detected at the monitored ion transitions in extracted blank matrix.

Quantitation of analytes in plasma samples was based on linear standard curves in fortified matrix (plasma) using the ratio of analyte peak area to internal standard peak area and $1/x^2$ weighting of linear regression. Commercially available software (Analyst v1.5.1 software, Applied Biosystems Incorporated, Foster City, CA, USA) was used for peak area integration. All calculated concentrations from unknown samples fell within the linear range of the respective standard curves. Accuracy and precision of standard curves and quality control samples (low medium and high concentrations) were within 15% for all 3 analytes.

Hydromorphone, butorphanol, and buprenorphine plasma concentrations were analyzed by noncompartmental methods using a commercial software program (Phoenix WinNonlin v6.3, Pharsight Corporation, Mountain View, CA, USA) to obtain pharmacokinetic parameters.

RESULTS

After administration of morphine to 5 of the 6 ferrets within that study group, 2 of the ferrets vomited. All 5 of the ferrets became difficult to restrain for phlebotomy and all were hypersalivating. Owing to the side effects and perceived risk of aspiration of saliva during restraint for venipuncture, it was decided by the authors to discontinue the pharmacokinetic study using this opioid. One ferret in the buprenorphine group did not receive a full dose owing to

TABLE 1. Comparison of pharmacokinetic data from the current study of ferrets, and that from previously published studies in cats[25] and dogs[31] for buprenorphine. Note that equivalent doses were not used

	Ferret	Cat	Dog
Route	IM	IM	IV
Dose (mg/kg)	0.04	0.02	0.015
Cmax (ng/mL)	6.96	12.1	14
Tmax (min)	9	2.7	2.5
Vz_F (L/kg)	30.4	10.3	1.59
Cl_F (mL/min/kg)	81.9	14.2	5.4
T1/2λz (min)	219.1	460	270
AUC0-• (min*ng/mL)	519.22	2562	1804
AUMC0-• (min*min*ng/mL)	117,047.6	n/a	n/a
MRT (min)	229.6	336.2	199

AUC0-∞, area under the concentration time curve from time zero to infinity; AUMC0-∞, area under the first moment curve; Cl/F, Apparent systemic drug clearance; Cmax, maximum plasma drug concentration; IM, intramuscular; IV, intravenous; MRT, mean residence time; T1/2λz, terminal half-life; Tmax, time of maximum plasma drug concentration; Vz/F, apparent volume of distribution; λz, terminal slope plasma concentration-versus-time curve.

TABLE 2. Comparison of pharmacokinetic data from the current study of ferrets, and that from previously published studies in dogs[27,29] and cats[30] for butorphanol. Note that equivalent doses were not used

	Ferret	Cat	Dog
Route	SC	IM	SC
Dose (mg/kg)	0.3	0.4	0.25
*C*max (ng/mL)	48.6	132	33.3
*T*max (min)	13.3	21	30
Vz_F (L/kg)	10.9	7.6	8.42
Cl_F (mL/min/kg)	83.0	12.9	58.3
T1/2λz (min)	91.1	376.8	102.6
AUC0-• (min*ng/mL)	3734.7	23,520	1804
AUMC0-• (min*min*ng/mL)	334,281.6	n/a	n/a
MRT (min)	88.6	526.2	199

AUC0-∞, area under the concentration time curve from time zero to infinity; AUMC0-∞, area under the first moment curve; Cl/F, Apparent systemic drug clearance; Cmax, maximum plasma drug concentration; IM, intramuscular; MRT, mean residence time; SC, subcutaneous; T1/2λz, terminal half-life; *T*max, time of maximum plasma drug concentration; Vz/F, apparent volume of distribution; λz, terminal slope plasma concentration-versus-time curve.

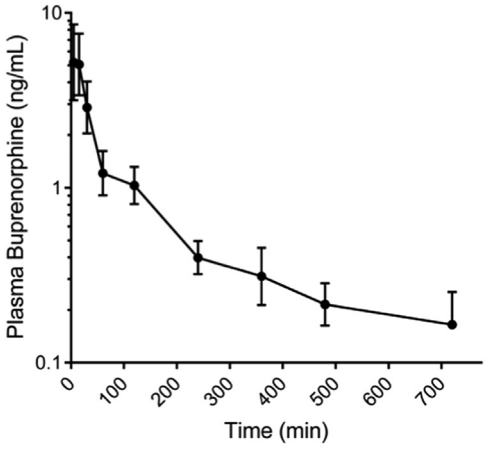

FIGURE 1. Time versus plasma concentration of buprenorphine given at 0.04 mg/kg intramuscular in 5 male castrated ferrets. The mean maximum concentration of buprenorphine was 6.96 ng/mL, and was achieved at a mean of 9 minutes after administration. The mean half-life of buprenorphine was 219.1 minutes or 3.6 hours.

difficulty with restraint, and was not included in the results. All of the other opioids agents were successfully administered and blood samples obtained without complication. There were no observable detrimental clinical side effects following the administration of butorphanol, buprenorphine, or hydromorphone, the other opioids. See (Tables 1-3 and Figs. 1-3) for results.

DISCUSSION

This study establishes pharmacokinetic data for 3 opioid medications in ferrets and will serve as a useful guide in developing further studies regarding the use of these drugs in this animal species. Although approximately equipotent doses of each drug were used, this is irrelevant to the current study, as the drugs were not compared and no pharmacodynamic effects were measured.

Intramuscular injections of buprenorphine and subcutaneous injections of butorphanol and hydromorphone appeared to be well tolerated by all ferrets to which they were administered. These routes of injection were selected over intravenous administration because intramuscular and subcutaneous routes are commonly utilized for drug application in clinical patients. Buprenorphine was given intramuscularly instead of subcutaneously owing to previous pharmacokinetic studies that report subcutaneous

TABLE 3. Comparison of pharmacokinetic data from the current study of ferrets, and that from previously published studies in dogs[27] and cats[28] for hydromorphone. Note that equivalent doses were not used

	Ferret	Cat	Dog
Route	SC	IV	SC
Dose (mg/kg)	0.1	0.1	0.1
*C*max (ng/mL)	17.3	94.25	32.77
*T*max (min)	8.33	1	11.4
Vz_F (L/kg)	5.39	51.6	3.29
Cl_F (mL/min/kg)	150.4	146.1	57.4
T1/2λz (min)	24.7	82.4	39.6
AUC0-• (min*ng/mL)	734.6	3738.23	6953.4
AUMC0-• (min*min*ng/mL)	25,702.6	433,132	8958

AUC0-∞, area under the concentration time curve from time zero to infinity; AUMC0-∞, area under the first moment curve; Cl/F, Apparent systemic drug clearance; Cmax, maximum plasma drug concentration; IV, intravenous; MRT, mean residence time; SC, subcutaneous; T1/2λz, terminal half-life; *T*max, time of maximum plasma drug concentration; Vz/F, apparent volume of distribution; λz, terminal slope plasma concentration-versus-time curve.

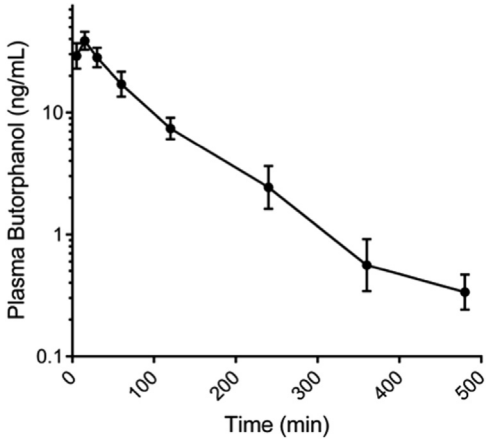

FIGURE 2. Time versus plasma concentration for butorphanol when given at 0.3 mg/kg subcutaneous in 6 male castrated ferrets. The mean maximum concentration of butorphanol was 48.6 ng/mL, and was achieved at a mean of 13.3 minutes after administration. The mean half-life of butorphanol was 91.1 minutes or 1.5 hours. Plasma concentrations of butorphanol fell below the limits of quantification at the 720 minute time point, so no data are reported.

absorption of buprenorphine was unreliable.[25] As mentioned previously, there was no evidence of overt adverse effects following the administration of buprenorphine, butorphanol, or hydromorphone to the ferrets within those study groups. However, of the 5 ferrets administered morphine subcutaneously, 2 of them vomited, and all 5 became agitated, were difficult to restrain, and had excessive ptyalism. Owing to the difficulty of restraint for phlebotomy, risk of aspiration owing to ptyalism, and apparent agitation of the animals, it was elected to not gather data on the pharmacokinetics of morphine in these ferrets. Further research is warranted to assess different dosage protocols for this medication to see if a dose can be determined that is tolerated more readily by ferrets.

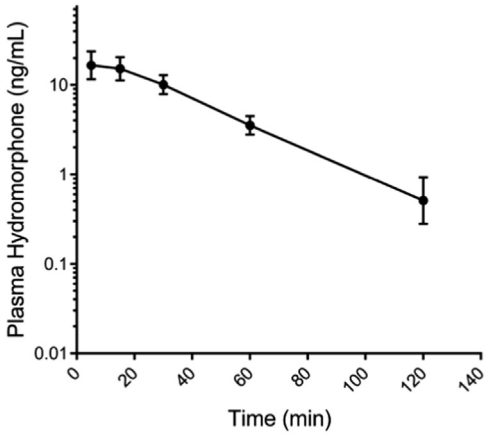

FIGURE 3. Time versus plasma hydromorphone concentration given at 0.1 mg/kg subcutaneous in 6 male castrated ferrets. The mean maximum concentration of hydromorphone was 17.3 ng/mL, and was achieved at a mean of 8.33 minutes after administration. The mean half-life of hydromorphone was 24.7 minutes or 0.41 hours. Plasma concentrations of hydromorphone fell below the limits of quantification for all time points after the 120 minute time point, so no data are reported.

It is unknown what dose of the studied opioids cause analgesia in ferrets, and more studies are required to determine the pharmacodynamics of opioid drug use in ferrets. It has been reported in cats[25] that buprenorphine given at a dose of 0.02 mg/kg will significantly increase the thermal threshold for up to 480 minutes (intravenous administration), or up to 60 minutes (intramuscular administration). At 480 minutes following intravenous administration, the concentration of buprenorphine was approximately 0.7 ng/mL, and at 60 minutes following intramuscular administration, the concentration was approximately 4 ng/mL. Following ovariohysterectomies in dogs it was determined that the patients required rescue analgesia at a mean of 5 hours after an intramuscular dose of buprenorphine at 0.02 mg/kg or 0.04 mg/kg was initially provided.[26] In dogs the concentration of buprenorphine at 5 hours is approximately 3 ng/mL.[27] In humans, analgesic properties have been shown to last over 4 hours after a single intravenous dose of buprenorphine[28], when the concentration of buprenorphine had dropped to 0.2 ng/mL. In the study reported in this article, the concentration of buprenorphine in ferrets after intramuscular administration dropped below 4 ng/mL in less than 60 minutes, dropped below 3 ng/mL in approximately 60 minutes, but dropped to 0.2 ng/mL in 720 minutes.

It has been reported that cats receiving a 0.4 mg/kg intravenous dose of butorphanol have an increased thermal threshold by 15 minutes, which is maintained until 180 minutes postinjection.[29] At 180 minutes the concentration of butorphanol in cats is approximately 40 ng/mL.[30] In dogs it has been found that a single intramuscular dose of butorphanol at 0.4 mg/kg before an elective ovariohysterectomy provided adequate postoperative pain control for 4 hours.[31] At 4 hours the concentration of butorphanol in dogs is approximately 6 ng/mL.[32] In humans it has been found that doses of butorphanol at 0.5 to 1.0 mg/kg provide analgesia for approximately 1 hour, and higher doses at 2 mg/kg provide analgesia for 3 to 4 hours.[33] At 1 hour, the approximate serum

concentration of butorphanol is 1.5 ng/mL.[34] In ferrets, the mean maximum concentration of butorphanol achieved at a mean of 9 minutes after administration was 48.6 ng/mL, and did not even achieve 40 ng/mL in 1 ferret. The concentration dropped to 6 ng/mL at approximately 200 minutes, and did not drop to 1.5 ng/mL until approximately 360 minutes after administration.

In cats after a single intravenous dose of hydromorphone at 0.1 mg/kg, the thermal threshold was increased until 450 minutes postinjection, and the majority of cats showed no aversion for 180 minutes.[35] The concentration of hydromorphone at 180 minutes was approximately 5 ng/mL, and at 450 minutes was below 1 ng/mL.[35] In dogs a single intravenous dose of hydromorphone at 0.1 mg/kg provided analgesia for over 120 minutes with the concentration of hydromorphone at 120 minutes being approximately 3 ng/mL.[36] In humans the analgesic effect of hydromorphone is variably related to the serum concentration, with effective serum concentrations at 4 ng/mL.[37] If this relationship exists in ferrets and is similar to that in other species, the duration of analgesia is likely short. Mean concentrations of hydromorphone decreased to less than 4 ng/mL in less than 1 hour, and was less than 1 ng/mL in under 2 hours. Further research investigations regarding the antinociceptive effects of opioids at different doses, given by different routes, and different lengths of times in ferrets will need to be completed before conclusions and clinical recommendations can be determined.

Based on the pharmacokinetic data obtained from this study, and understanding that pharmacodynamic data is lacking, veterinarians may need to reconsider previously recommended dosing intervals for ferrets. Previously recommended dosing intervals includes buprenorphine, every 6 to 12 hours; butorphanol, every 4 to 12 hours; and hydromorphone, every 6 to 12 hours.[38-42] From the data presented here, a dosing interval for buprenorphine every 4 to 6 hours, butorphanol every 2 to 4 hours, and hydromorphone every 1 to 2 hours may be more appropriate. In order to accurately dose these medications for their analgesic and sedative effects, a pharmacodynamics study should be performed. Given the information determined from the research study reported in this article, it is likely that dosing intervals for ferrets administered buprenorphine, butorphanol, and hydromorphone will need to be shortened. However, the authors cannot determine dosing intervals for these opioid agents for certain without pharmacodynamic data. Also, as noted previously, only young male ferrets were used in this research study. A future pharmacokinetic study using female ferrets would be warranted to see if there are any sex differences, as it has been shown that there are differences between sexes in laboratory rats with different drugs.[43-46]

In summary, we obtained relevant pharmacokinetic data on single doses of commonly used opioid drugs in domestic ferrets. It was found that each one of the opioid agents assessed had a half-life that was shorter than expected in ferrets, given previous recommended dosing intervals. Therefore, the authors conclude that buprenorphine, butorphanol, and hydromorphone may need to be dosed more frequently in ferrets than previously believed. The data obtained from this research investigation should be useful in guiding further studies regarding opioid use and analgesia in this species.

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