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PHARMACOKINETICS AND INTRAMUSCULAR BIOAVAILABILITY OF A SINGLE DOSE OF BUTORPHANOL IN ASIAN ELEPHANTS (*ELEPHAS MAXIMUS*)

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Abstract

Captive Asian elephants (*Elephas maximus*) are susceptible to lameness resulting from foot and joint pain, including chronic arthritis. In the past, opioid analgesics, such as butorphanol, have been used clinically for pain management. However, dosages used in treating elephants were often extrapolated from data in horses, with no pharmacokinetic information on the specific agents used in elephant species. In this pharmacokinetic study, six adult captive Asian elephants (5 female, 1 male castrate) were administered a 0.015 mg/kg dose of butorphanol by both i.v. and i.m. routes. A complete crossover design was used with a 3-wk washout period between treatments. Serial blood samples were collected immediately prior to butorphanol administration and at 5, 10, 20, and 40 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 h after administration. The butorphanol analysis was performed using a validated liquid chromatography–mass spectrophotometric assay with a limit of quantitation of 0.025 ng/ml. The mean C_{max} after i.m. administration was 7.9 ng/ml, with a corresponding T_{max} of 40 min and $t_{1/2}$ of 7.1 h. After i.v. administration, the mean Vd_{ss} was 1.4 L/kg and the mean Cl_p was 0.26 L/kg/h. Mean i.m. bioavailability was 37%. The results indicate that butorphanol used at 0.015 mg/kg i.m. or i.v. could be useful in elephants when given for pain control.

Keywords

Analgesia; Asian elephant; butorphanol; *Elephas maximus*; pharmacokinetics

INTRODUCTION

A retrospective study of the medical records of the North American captive elephant population established that foot problems affect more than 50% of the captive elephant population.²⁹ Pain management is a beneficial addition to the treatment of lameness and can help decrease its severity. Currently, arthritic elephants are typically treated with a wide variety of nonsteroidal anti-inflammatory drugs and opioid analgesics, which offer only palliative treatment and have limited pharmacokinetic basis for dose determination,^{2,3,19} despite the fact that these drugs can have serious side effects when used at inappropriate

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dosages. Due to the adverse effects of these agents in domestic species, accurate therapeutic regimens are critical to properly treating diseased elephants.

Lack of approved pharmaceutical agents globally for exotic species is a constant concern for zoo and wildlife veterinarians. There are currently only 8 to 10 compounds approved in the USA for mammalian zoo and wildlife species, compared with almost 300 for domestic cattle. Many veterinarians have taken approved agents for various species and extrapolated their use to exotic animals. Species differences in pharmacokinetic parameters and metabolism for numerous pharmaceutical agents have been well documented for domestic species. However, there is little information concerning the pharmacokinetics, much less the metabolism, of drugs used in nondomestic species. Pharmacokinetic information specific to elephants is extremely limited, and what is published deals mostly with antimicrobial therapies.^{2-5,12,16,19,26,34,39,40} An understanding of species-specific pharmacokinetic and drug information is needed to establish a dose for achieving therapeutic drug concentrations.^{18,21,27,28} When administration of a drug is needed in elephants, the dose is usually extrapolated from data in horses based on the assumption that pharmaceuticals administered to elephants are absorbed, distributed, metabolized, and excreted in a manner similar to horses.^{18,30,33,34} When using extrapolation, there is a risk for administering either a subefficacious dose or an overdose, both of which are serious consequences.^{21,27,28} A few anecdotal reports of the use of opioids as anesthetics in elephants have been reported.²² The available literature currently does not contain sufficient information to assist with the establishment of appropriate analgesic therapeutic butorphanol dosage regimens in elephants.

Butorphanol is an opioid agonist-antagonist and as such is a competitive antagonist at the μ receptor and an agonist at the κ receptor. This mixed agonistic-antagonist activity results in analgesia and is less likely to induce respiratory depression, compared with pure μ agonistic activity.^{14,37} This is a valuable characteristic for use in elephants because their large size, expense, and endangered status dictate the need for the safest treatment available. Butorphanol is most commonly used to control mild to moderate pain in small animals and moderate visceral pain in horses.²⁵

The purpose of this study was to determine the pharmacokinetics and bioavailability of butorphanol after a single i.v. or i.m. injection in adult, captive, Asian elephants. This study will add additional pharmacokinetic information to the literature, allow for comparison between elephant data from this study and pharmacokinetic data in the literature from other species, and provide recommendations for practical application in elephants.

MATERIALS AND METHODS

Animals

Six (five female and one castrated male) Asian elephants were used in this study. All elephants were adults between 30 and 60 yr of age with an average body weight of 3,734 kg. All animals were housed together in a single facility located in Florida, USA. The study protocol was approved by the Kansas State University Institutional Animal Care and Use Committee before the study began. Prior to the study, each elephant was assessed as healthy based on a review of health history, complete blood count, serum chemistry analysis, and serial negative mycobacterial culture of trunk wash samples.

Commercially available butorphanol, 10 mg/ml, was used in this study (Torbugesic-LA, Fort Dodge Laboratories, Fort Dodge, Iowa 50501, USA). Individual doses of butorphanol for each animal were calculated to 0.015 mg/kg based on the elephant's measured weight. The dose of 0.015 mg/kg was based on domestic animal dosages reported in pharmacology

references and considered safe for use in elephants by the attending clinician (RI).³⁶ The intent of the selected therapeutic dosage was to provide measurable serum levels that may have potentially analgesic effects but not cause marked sedation, respiratory depression, or recumbency associated with higher dosages of butorphanol in other species.²⁵

Study design

Elephants were assigned to either i.v. or i.m. administration, and the crossover design was completed after a 3-wk washout period. The elephants were given butorphanol by i.v. bolus administration into a caudal auricular vein while standing. The i.m. injections were given in the triceps brachii while standing. Intramuscular injections were administered using 12-ml syringes with 18-gauge, 1.5-inch (3.8-cm) needles. A new, sterile needle was used for each injection site. Each site was cleaned with alcohol and betadine prior to injection.

Sample collection

All blood samples were collected from the caudal auricular vein of the ear that was not used for i.v. injection of the standing elephant. Time points of sampling began immediately prior to butorphanol administration (0 hr) and at 5, 10, 20, and 40 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 hr after administration. A total of 20 ml (2×10 ml) of blood was collected in lithium heparin tubes from an ear vein at each time point. The samples were centrifuged immediately after collection, and 5 ml of plasma from each sample was placed into cryovials and frozen at -80°C until sent for analysis to Kansas State University.

Sample analysis

The concentration of butorphanol in elephant plasma was determined by the use of a liquid chromatography–mass spectrophotometric (LC–MS) assay similar to other opioid methods published.^{19,20,24,25} A 150×2 mm Synergi Hydro-RP column (Phenomenex, Torrance, California 90501, USA) was used to separate the butorphanol for detection. Each chemical used was of high-pressure liquid chromatography grade. The mobile phase consisted of 5 mM ammonium acetate with 5 mM acetic acid in a mixture of acetonitrile and H_2O (50:50) maintained at a flow rate of 0.3 ml/min. The quantification of butorphanol concentrations in elephant plasma was done between the range of 0.025 ng/ml (limit of quantitation) and 115 ng/mL. Samples that were >115 ng/ml were diluted in butorphanol naïve elephant plasma and reassayed. Mass spectrometry (LCQ_{duo}, Thermo-Finnigan, San Jose, California 95134, USA) was also used to screen for circulating metabolites. The mass-to-charge ratio (m/z) of 328.2 was selected for butorphanol screening. Then mass spectrometry was carried out with a normalized collision energy of 35%, and the product ion of 310.2 was monitored and used for quantification. Sample vaporization was achieved by electro-spray with positive ionization using a source current of 4.5 μA . Other instrument settings were as follows: axillary gas flow, 10; capillary temperature, 220°C ; capillary voltage, 40 V; intermultipole lens voltage, -16 V; ion trap DC offset voltage, -10 V; multipole 1 offset, -2 V; multipole 2 offset, -6 V; sheath gas flow, 80; tube lens offset, 0 V.

To produce quality control samples, 25 μl of 10, 100, and 1,000 ng/ml solutions of butorphanol in mobile phase was added to 975 μl of plasma, collected from elephants that had not been treated with butorphanol, to produce three different quality control solutions with concentrations within the range of the standard curve. These solutions were stored at -70°C , thawed, and extracted with the standard curve, which was prepared by adding 25, 50, or 100 μl of 1, 10, 100, or 1,000 ng/ml solutions containing butorphanol in mobile phase to 975, 950, or 900 μl of untreated elephant plasma. This yielded standard concentrations ranging from 0.025 to 100 g/ml. Accuracy and precision were within $\pm 15\%$ of actual value, and recovery of butorphanol was 40–50% across the dynamic range of the assay. Plasma

concentrations of butorphanol were obtained by the use of peak area ratios and slope-intercept from linear standard curves.

Metabolite identification

Metabolites were identified by comparing the full-scan spectra obtained for the predose samples with the spectra from postdose samples with butorphanol in them. An emphasis was placed on those metabolites reported previously in human and domestic species metabolite determination, including hydroxybutorphanol and norbutorphanol.^{6,13,14,31,45,48} The spectra were compared using the LC-MS software set to scan for metabolites while detecting butorphanol, and the metabolites were not found to cross-react with unchanged butorphanol.

Pharmacokinetic analysis

Values of pharmacokinetic parameters were determined for each elephant by use of non-compartmental analysis with a commercial software program (WinNonlin, version 4.0.1, Phar-sight, Mountain View, California 94041, USA).^{35,38} Values were calculated following the i.v. administration of butorphanol as follows: plasma area under the plasma concentration versus time curve (AUC); area under the first moment curve (AUMC); mean residence time (MRT), where $MRT = \frac{AUMC}{AUC}$; apparent volume of distribution at steady state (V_{dss}), where $V_{dss} = \frac{dose \times AUMC}{AUC^2}$; apparent volume of distribution area (V_{darea}), where $V_{darea} = \frac{dose}{AUC \times \lambda}$; plasma dose clearance (Cl_p), where $Cl_p = \frac{dose}{AUC}$; elimination rate constant (λ) calculated as the slope of the terminal phase of the plasma concentration curve (Fig. 1), that included a minimum of three time points; and terminal half-life ($t_{1/2}$), where $t_{1/2} = \frac{0.693}{\lambda}$. After i.m. administration of butorphanol, the following parameters were determined: AUC,

AUMC, MRT, and bioavailability (F), where $F = \frac{AUC_{IM}}{AUC_{IV}} \times 100$. Maximum plasma concentration (C_{max}) and the time C_{max} occurred (T_{max}) were read directly from the data. The pharmacokinetic parameters of V_{dss} and Cl_p used to compare predicted elephant values with those determined in this study were obtained from the published literature for rabbit, dog, human, cattle, goats, horses, and llamas.^{6,7,9,37,41,42,44}

RESULTS

The mean ($\pm$ SD), median, and range values for the pharmacokinetic parameters for both routes of butorphanol administration are shown in Table 1. Concentrations after either i.m. or iv. administration did not decrease below the limit of quantitation at the last sampling point 24 hr after dosing. The median V_{dss} was 0.6 L/kg, and the median V_{darea} was 1.4 L/kg. The median Cl_p was 0.21 L/hr/kg. The mean T_{max} occurred at 0.67 hr, with a corresponding mean C_{max} concentration of 7.9 ng/ml after i.m. administration. Intramuscular bioavailability (F) was highly variable in the study subjects, with a mean of F (%) 37 ± 41 with a median value of 32%. Two circulating metabolites were detected: hydroxybutorphanol and norbutorphanol.

DISCUSSION

A dose of 0.015 mg/kg was chosen for this study in order for the concentration of butorphanol to be identified in plasma at the majority of time points without marked sedation or the risk of serious adverse side effects. Subsequent to this study, this dose has shown clinical efficacy in an Asian elephant treated by one of the authors (Isaza, unpubl. data) for mild to moderate pain control. In this study, the mean C_{max} concentration was 7.9 ng/ml, compared with horses at 99.2 ± 29.5 ng/ml, and the $t_{1/2}$ of butorphanol in elephants was 7.1 hr, compared with 7.7 hr in horses.⁴¹ The lower mean C_{max} concentration compared with the therapeutic concentrations of horses (20 ng/ml), goats (9 ng/ml), llamas (>9.2 ng/

ml), dogs (9 ng/ml), and cats (45 ng/ml) with clinically subjective therapeutic effect indicates that elephants may be very sensitive to this opioid.^{6,7,41,44,47} This sensitivity could be due to the concentration at the receptor sites or differences in the distribution of these sites. Analgesia is determined by the concentration at the receptor site, which does not necessarily correlate with the plasma concentration.¹ The distribution of opioid receptors is different between dogs and cats.¹⁷ There is even a difference in the amount of receptor subtypes among different strains of rats and mice, which can lead to a difference in opioid analgesia.¹⁵

The AUC_{IV} in pharmacokinetic studies is usually lower than the $AUMC_{IV}$, but in this study, the mean AUC_{IV} of 1,233 hr*ng/ml is higher than the mean $AUMC_{IV}$ of 482 hr²*ng/ml. One of the elephants had this trend significantly enough to skew these means but not enough to significantly affect the mean MRT of 3.0 hr. For exponentially descending data, such as i.v. concentration curves, the AUC can be overestimated and the AUMC can be underestimated simultaneously. This is especially skewed when there are late time points with low sample frequency. Such a bias can be improved with an increase in the sampling frequency around the later time points,³⁸ which should be considered in future studies. There is a wide range in both the AUC_{IV} and AUC_{IM} values, which could partially be due to age, as it can be in humans.²³

The low human V_{darea} and V_{dss} of 0.7 and 0.1 L/kg, respectively, are consistent with expectations based on the high protein binding activity of butorphanol in humans of 83%.¹³ The higher elephant V_{darea} and V_{dss} of 2.7 and 1.4 L/kg, respectively, with a highly variable range reported in this study were possibly due to the varying ages of the elephants or differences in fat-to-muscle ratios. In lipophilic drugs, such as butorphanol, the V_d increases in older people.²³ When the amount of adipose tissue in the body increases or the amount of muscle tissue decreases, the V_{dss} increases in rats.³² Individual differences in protein binding can affect the V_{dss} as well as the Cl_p in humans.⁸ The large range of Cl_p could also have been influenced by age and differences in expression or activity of drug-metabolizing enzymes. The hepatic and renal Cl_p in elderly humans can be decreased by 30–50%.²³ Humans also have significant individual differences in drug-metabolizing enzymes.¹⁰ The variation in the calculated bioavailability values of 0.94 to 111% is extreme and could also be due to differences in perfusion to injection sites or extensive local tissue binding. The range is also associated with the variability of AUC values between individuals.

Perfusion variations, such as those that could cause the differences in the pharmacokinetic parameters, can be expected due to the number of blood vessels around the injection site; for example, the bioavailability value of 111% could be a result of injecting the butorphanol into muscle in proximity to blood vessels in an animal with a slightly lower perfusion to the ear vein. Rate of perfusion could also be variable due to the depth of the needle used for injection. A 1.5-inch needle was used for i.m. injections but may not have penetrated into the muscle of each elephant and thus possibly affected the bioavailability of butorphanol. The age of the animals could also contribute to the large range in values from differences in systemic blood flow from middle-aged to geriatric animals, because the elephants used were between 30 and 60 yr of age. Not all of the older animals had low bioavailability, but two of them did have the lowest bioavailability values. Systemic blood flow changes significantly in the elderly human patient.¹¹ The i.v. injections given in the superficial ear veins could be affected by lower blood flow to the periphery in older animals. In rats and rabbits, there are age-related changes to blood flow in the area of the ear.^{43,46} The animals that had very low bioavailability values of 0.94 and 1.5% had T_{max} and C_{max} values that were within the values of the other elephants. Due to the variability noted in the bioavailability and the other relatively normal values in the animals with the very low values, the bioavailability does not seem to be a reliable indicator for appropriateness of the use of i.m. injection in this case.

All of the possibilities noted that could lead to the large variability in the pharmacokinetic parameters are issues that are faced when using pharmaceuticals in elephants at any time. A previous study of i.m. ceftiofur in elephants also demonstrated large variability in the pharmacokinetic results.¹² The factors specific to an individual elephant, other than age, are not likely to be evident to the veterinarian treating the animal, so it is important to know that the wide range in values exists.

When treating an animal for which pharmacokinetic data are unavailable, dosages need to be extrapolated from other species. For elephants, these extrapolations are based on the assumption that they absorb, distribute, metabolize, and excrete pharmaceuticals similar to horses.^{30,33,34} As this study reports, the clearance of elephants cannot always be directly and effectively extrapolated from mammalian data. In this case, the dosage that would be calculated from that data would be assuming a higher clearance rate, thus risking overdosing.

When administering injectable medications to elephants, several factors must be considered. When giving i.v. medications, ear veins are the most readily accessible and therefore the most commonly used. However, this part of the body is very sensitive to irritation, and phlebitis has occurred secondary to i.v. medications in some animals. Inadvertent intra-arterial or perivascular leakage of an irritating drug from the ear vein can result in damage to surrounding tissues and, in the most extreme circumstance, sloughing of the affected section.²¹ Also, due to the risk to the care giver's safety when working at the head of an elephant, animals must be cooperative.²¹

The metabolites norbutorphanol and hydroxybutorphanol that were identified during the LC-MS scan did not interfere with the detection of butorphanol in this study. The concentrations of these metabolites were not determined at this time, because they are not likely to affect the pharmacokinetics or dynamics of butorphanol and the lack of availability of reference standards at the time of sample analysis. Neither metabolite appears to have a pharmacologic effect.¹³

This study investigated the use of butorphanol in elephants to determine recommendations on its use in this species. Increasing the dose from the 0.015 mg/kg studied here may increase the analgesic effects but may also increase sedation to unacceptable levels. This study did not quantitate the sedative effects of this drug other than to note that the animals were slightly sedated for approximately 2 hr. Based on recommendations in other species, the use of butorphanol in elephants should be reserved for mild pain. The analgesic effect of butorphanol at this dose was not evaluated in this study. The extent and duration of analgesia are important for accurate dosing and should be pursued in future studies. The results of this study add to the pharmacokinetic data already available in Asian elephants.

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Figure 1. Mean ($\pm$ SD) plasma concentrations of butorphanol from Asian elephants (*Elephas maximus*; $n = 6$) after a single 0.015 mg/kg i.v. or i.m. administration.

Table 1

Plasma pharmacokinetic values of butorphanol in Asian elephants (*Elephas maximus*; $n = 6$) after a single 0.015 mg/kg i.v. or i.m. administration.

Pharmacokinetic parameters ^a	Mean	SD	Median	Range
i.v.				
AUC _{0-∞} (hr × ng/ml)	1,233	2,180	92	22–5,482
AUMC _{0-∞} (hr ² × ng/ml)	482	657	202	122–1,808
MRT (hr)	3.0	3.0	2.4	0.1–8.5
V _{dss} (L/kg)	1.4	2.2	0.6	0.0002–5.7
V _{darea} (L/kg)	2.7	3.8	1.4	0.040–10
Cl _p (L/h/kg)	0.26	0.26	0.21	0.0027–0.67
λ (hr ⁻¹)	0.098	0.055	0.091	0.025–0.175
t _{1/2} (hr)	7.1	hm	8.1	4.0–28
i.m.				
AUC _{0-∞} (hr × ng/ml)	28	13	25	14–52
AUMC _{0-∞} (hr ² × ng/ml)	195	105	184	49–371
MRT (hr)	6.8	1.8	7.1	3.5–8.4
C _{max} (ng/ml)	7.9	5.2	5.8	4.0–18
T _{max} (hr)	0.67	0.29	0.67	0.33–1.0
F (%)	37	41	32	0.94–111

^a AUC, area under the curve; AUMC, area under the first moment curve; MRT, mean residence time; V_{dss}, volume of distribution steady-state; V_{darea}, volume of distribution area; Cl_p, plasma clearance; λ, elimination rate constant; t_{1/2}, half-life; C_{max}, maximum plasma concentration; T_{max}, time of C_{max}; F, absolute bioavailability; hm, harmonic mean.