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Journal

Journal of Veterinary Pharmacology and Therapeutics, 44(6)

ISSN

0140-7783

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Publication Date

2021-11-01

DOI

10.1111/jvp.13014

Peer reviewed

Received: 30 June 2021 | Revised: 16 August 2021 | Accepted: 12 September 2021

DOI: 10.1111/jvp.13014

PHARMACOKINETIC REPORT

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

Pharmacokinetics of butorphanol in male neutered cats anesthetized with isoflurane

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Funding information
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Abstract

This study characterized the pharmacokinetics of butorphanol in cats anesthetized with isoflurane. Six young healthy male neutered cats were used. Cats were anesthetized with isoflurane in oxygen. Catheters were placed in a jugular vein for blood sampling and in a medial saphenous vein for butorphanol and lactated Ringer's solution administration. Butorphanol tartrate (1 mg/kg over 5 min) was administered intravenously. Blood samples were collected prior to butorphanol administration and at various times up to 365 min following administration. Plasma butorphanol concentration was measured using liquid chromatography/tandem mass spectrometry. Compartment models were fitted to the time-concentration data using nonlinear mixed effect modeling. A three-compartment model best fitted the data. Typical value (% interindividual variability) for the three volumes of distribution, the metabolic clearance, and the two distribution clearances were 230 (72), 1095 (not estimated), and 2596 (not estimated) ml/kg, and 18.4 (72), 169.6 (52), and 55.0 (43), respectively. Pharmacokinetic simulation suggested that a loading dose (μg/kg) calculated as 0.287 × target plasma concentration in ng/ml (C_T) followed by intravenous infusions (μg/kg/min) of 0.098 × C_T for 20 min, 0.049 × C_T for 40 min, and 0.022 × C_T thereafter would rapidly achieve and maintain C_T ± 10% for up to 6.5 h.

KEYWORDS
butorphanol, cats, infusion, opioids, pharmacokinetics

1 | INTRODUCTION

Opioids are commonly administered during anesthesia to provide analgesia, blunt autonomic responses to nociception and reduce anesthetic requirements (KuKanich & Wiese, 2015). Few drugs in this class have received regulatory approval for use in cats. Butorphanol, an agonist of kappa opioid receptors and antagonist of mu opioid receptors, is approved for use in cats by the Federal Drug Administration of the United States for the relief of pain caused by minor or major trauma or associated with surgical procedures. In addition, because formulations for animal use are commercially available, butorphanol has been less affected than other opioids by the common drug shortages in the United States and is more likely to be available to veterinarians in countries in which the use in animals of drug formulations for humans is restricted or prohibited. To the authors' knowledge, the disposition of butorphanol in anesthetized cats has not been reported. The aim

of this study was to characterize the pharmacokinetics of butorphanol in cats during anesthesia with isoflurane.

2 | METHODS

Six 1- to 2-year-old male neutered domestic shorthair, purpose-bred research cats were used in this study. Cats were considered healthy based on lack of historical significant disease and a normal physical examination prior to commencing the study. Husbandry conditions for this facility have been previously described (Honkavaara et al., 2017). The study was approved by the Institutional Animal Care and Use Committee (protocol 21003).

2.1 | Instrumentation

Cats were anesthetized with isoflurane in oxygen delivered in an acrylic chamber via a Bain breathing system. The oxygen flow was set at 5 L/min, and the isoflurane vaporizer was set to deliver 5%. Once cats had lost their righting reflex, they were removed from the chamber and anesthetic induction was completed by administering 3%–5% isoflurane via a face mask attached to the same breathing system, with the oxygen flow reduced to 2 L/min. Once cats were deemed at an appropriate depth of anesthesia, the trachea was intubated with a 4.5 mm cuffed endotracheal tube. The tube was connected to the Bain breathing system, and the endotracheal tube cuff was inflated as to provide a seal during manual positive pressure ventilation at 20 cm H_2O. Isoflurane administration was then resumed, with the vaporizer adjusted to maintain a light surgical depth of anesthesia (as determined from lack of palpebral reflex, rotation of the eyes, and presence of a mild to moderate jaw tone) and the oxygen flow set at 2 L/min. A Doppler crystal (Parks Medical, USA) was placed over the palmar side of the metacarpus, and an occluding cuff with a width of ~40% of the circumference of the limb connected to a sphygmomanometer was placed proximal to the carpus for measurement of systolic blood pressure. A pulse oximeter probe (GE, USA) was placed on the tongue for measurement of arterial hemoglobin oxygen saturation and pulse rate. A thermistor calibrated daily against a certified thermometer was placed in the distal esophagus for measurement of body temperature. Body temperature was maintained between 38.5 and 39.5°C throughout the study by applying external heat as needed. Gas was continuously sampled from a catheter passed within the endotracheal tube so that its tip was close to the tip of the tube and inspired and end-tidal isoflurane concentration and carbon dioxide partial pressure were measured by infrared spectrophotometry (GE, USA). The spectrophotometer was calibrated daily with 4 secondary standards containing known isoflurane concentrations spanning the range of measured values. The hair over a medial saphenous and jugular vein was clipped. Following aseptic preparation of the skin with chlorhexidine and alcohol, 20 gauge, 5 cm catheters were placed in a medial saphenous vein for fluid (lactated Ringer's solution, 3 mL/kg/h) and drug administration, and in a jugular vein for blood sampling.

2.2 | Minimum alveolar concentration (MAC) determination

Following instrumentation, the end-tidal isoflurane concentration was set at approximately 2%. Pulse rate, systolic arterial pressure, hemoglobin oxygen saturation, body temperature, end-tidal carbon dioxide partial pressure, and end-tidal isoflurane concentration were recorded every 15 min throughout the study. The MAC of isoflurane was determined in duplicate, using the bracketing method and tail clamping, as previously described (Pypendop et al., 2019). Briefly, conditions were allowed to equilibrate for a minimum of 15 min. End-tidal gas was sampled by hand in triplicate, and end-tidal isoflurane concentration measured using the calibrated spectrophotometer. The mean of the three measurements was considered the end-tidal isoflurane concentration. A 20 cm Martin forceps was then applied to the cat's tail and closed to the first ratchet until movement was observed or one min had elapsed, whichever occurred first. End-tidal isoflurane concentration was then increased (if movement had been observed) or decreased (if movement had not been observed) by up to 15% of the previous concentration, a minimum of 15 min were allowed for equilibration, and measurements and stimulation were repeated until two successive concentrations, one allowing and one preventing movement, were determined. This was done twice in each cat, and the average of the four concentrations was considered the MAC of isoflurane for the individual studied.

2.3 | Treatment and blood sampling

Following the determination of the MAC of isoflurane, end-tidal isoflurane concentration was set at 0.7 times the individual's MAC and subsequently adjusted to maintain a light surgical depth of anesthesia as defined above. Butorphanol tartrate (Torbugesic, Zoetis, USA; (1*S*,9*R*,10*S*)-17-(cyclobutylmethyl)-17-azatetracyclo[7.5.3.$0^{1,10}$.$0^{2,7}$]heptadeca-2(7),3,5-triene-4,10-diol;(2*R*,3*S*)-2,3-dihydroxybutanedioic acid; CAS 58786–99–5), 1 mg/kg was administered intravenously via the medial saphenous catheter over 5 min (0.2 mg/kg/min). Blood samples (2 ml) were collected from the jugular catheter prior to butorphanol administration, and 2, 4, 6, 7, 9, 13, 20, 35, 65, 125, 245, and 365 min after starting the intravenous butorphanol infusion. Prior to each sample collection, 2 ml of blood was aspirated in a syringe containing 2 ml of heparinized isotonic saline solution (4 units of heparin per ml). This blood was returned to the cat via the jugular catheter following collection of the sample. The catheter was then flushed with 1 ml of the heparinized saline solution. Blood samples were transferred to tubes containing ethylenediaminetetraacetic acid, immediately placed on ice,

and centrifuged within 15 min of collection at 3901 g and 4°C for 10 min. The plasma was separated, placed in cryotubes, and frozen at −80°C until analyzed for butorphanol concentration. At the completion of the study, catheters were removed, and cats were allowed to recover from anesthesia.

2.4 | Plasma butorphanol concentration analysis

Butorphanol concentration was measured in protein-precipitated samples using liquid chromatography/tandem mass spectrometry, according to previously described methods (Knych et al., 2013). The assay was partly validated for cat plasma (Anonymous, 2018). The lower limit of quantitation was 0.1 ng/ml. Accuracy (% nominal concentration) and imprecision (coefficient of variation) were verified at 0.3, 80, and 1000 ng/ml and ranged from 101% to 107% and 4% to 9%, respectively.

2.5 | Pharmacokinetic analysis

Two- and three-compartment models with zero order input within and first-order elimination from the central compartment were fitted to the time-plasma butorphanol concentration data using nonlinear mixed model analysis in Phoenix NLME 8.2 (Certara, USA). The data from the 6 cats were modeled simultaneously using the first-order conditional estimation-extended least squares method. Different error and covariance structures were attempted. The models estimated typical (population) values and interindividual variability (random effects) for volumes and clearances. Interindividual variability was calculated as $\sqrt{e^{\omega^2}-1}\times 100$, where ω^2 is the variance of the random effects. Random effects for selected parameters were removed from the final model if insufficient information was contained in the data, resulting in a shrinkage >0.4. The best-fitting model was selected based on observation of the residuals plots, Akaike's information criterion and the −2 log likelihood. Pharmacokinetic parameters are presented as typical value (% interindividual variability). Other data are reported as mean ± standard deviation.

2.6 | Pharmacokinetic simulation

Pharmacokinetic simulation using the typical (population) parameter values of the final model and Phoenix NLME 8.2 was conducted to design an intravenous infusion regimen to rapidly achieve and maintain a desired plasma butorphanol concentration in cats anesthetized with isoflurane.

3 | RESULTS

The MAC of isoflurane was 1.93 ± 0.11%. Heart rate, systolic arterial pressure, hemoglobin oxygen saturation, temperature, and end-tidal partial pressure of carbon dioxide (data pooled for all cats at all time points) were 157 ± 24 beats/min, 95 ± 16 mm Hg, 98 ± 1%, 39.1 ± 0.3°C, and 38 ± 5 mm Hg, respectively. Isoflurane concentration during the blood sampling period (data pooled for all cats at all time points) was 1.66 ± 0.27%.

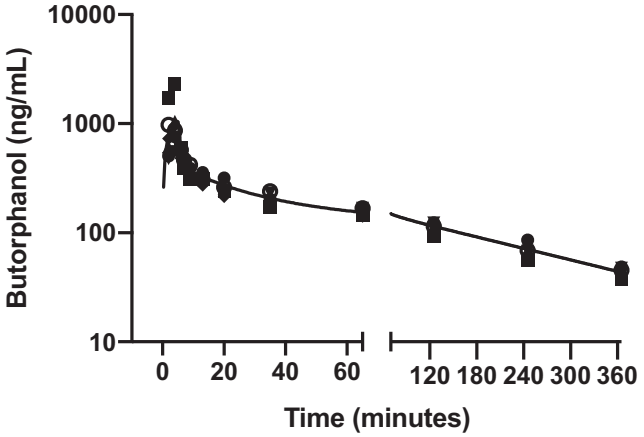

FIGURE 1 Observed (symbols) and predicted (line) plasma butorphanol concentrations over time in cats anesthetized with isoflurane ($n = 6$). Butorphanol was administered as a short intravenous infusion (1 mg/kg over 5 min; 0.2 mg/kg/min). The predicted concentrations were calculated from the typical (population) values of the parameters for a 3-compartment model

A 3-compartment model best fitted the time-plasma butorphanol concentration data (Figure 1). An additive and multiplicative error structure was used. Interindividual variability was not estimated for the volume of the two peripheral compartments (V2 and V3). Correlations between the random effects for the volume of the central compartment (V1) and the two distribution clearances (CL2 and CL3) were included in the covariance structure. Pharmacokinetic parameters are presented in Table 1.

Pharmacokinetic simulation assuming linear pharmacokinetics suggests that an intravenous loading dose (LD, μg/kg), followed by three constant rate infusions (CRI, μg/kg/min) at decreasing rates, the first two for a fixed duration, calculated as follows, would achieve the target plasma butorphanol concentration (C_T, ng/ml) within 18 min following the loading dose administration, and maintain it within 10% of the target concentration thereafter:

$$\begin{aligned}
\text{LD} &= 0.287\times C_T\\
\text{CRI}_1 &= 0.098\times C_T, \text{administered for the first 20 minutes}\\
\text{CRI}_2 &= 0.049\times C_T, \text{administered for the following 40 minutes}\\
\text{CRI}_3 &= 0.022\times C_T, \text{administered thereafter}
\end{aligned}$$

This infusion regimen is predicted to exceed 110% of the target concentration for intravenous infusions longer than 6.5 h.

For example, a 250 μg/kg LD, followed by 85 μg/kg/min for 20 min, then 43 μg/kg/min for 40 min, then 19 μg/kg/min would rapidly achieve and maintain a plasma butorphanol concentration of approximately 870 ng/ml, which is the peak plasma butorphanol

TABLE 1 Typical (population) value (% interindividual variability) of the pharmacokinetic parameters for butorphanol following intravenous administration of 1 mg/kg over 5 min (0.2 mg/kg/min) in 6 cats

Parameter	Typical value (% interindividual variability)
V1 (ml/kg)	231 (73)
V2 (ml/kg)	1094[a]
V3 (ml/kg)	2596[a]
Vss (ml/kg)	3921[b]
CL (ml/min/kg)	18.4 (5)
CL2 (ml/min/kg)	170.3 (53)
CL3 (ml/min/kg)	55.0 (43)
$T_{1/2}\alpha$ (min)	0.6[b]
$T_{1/2}\beta$ (min)	12.4[b]
$T_{1/2}\gamma$ (min)	172[b]

Abbreviations: V1: volume of the central compartment; V2: volume of the first peripheral compartment; V3: volume of the second peripheral compartment; Vss: volume of distribution at steady state; CL: metabolic clearance; CL2: first distribution clearance; CL3: second distribution clearance; $T_{1/2}\alpha$: half-life of the fast distribution phase; $T_{1/2}\beta$: half-life of the slow distribution phase; and $T_{1/2}\gamma$: elimination half-life.

[a]Interindividual variability not calculated because of excessive shrinkage (>0.4).

[b]Interindividual variability not estimated because the parameter was calculated from typical values of other parameters.

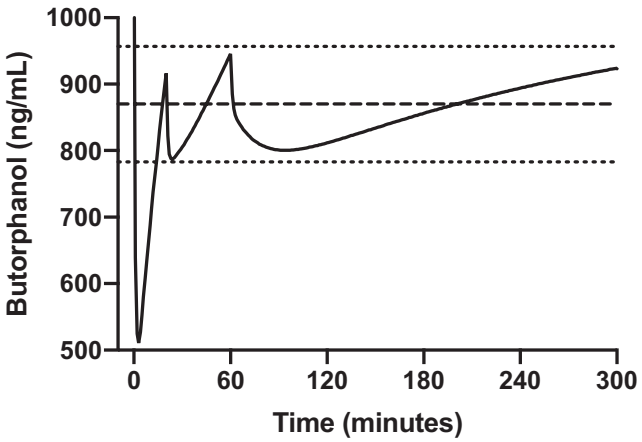

FIGURE 2 Simulated plasma butorphanol concentrations (continuous line) following administration of 250 μg/kg as an intravenous bolus and continuous rate infusions of 85 μg/kg/min for 20 min, then 43 μg/kg/min for 40 min, and then 19 μg/kg/min for the remainder of the infusion time. The plasma concentrations were calculated using the typical values of the parameters for the 3-compartment model. This infusion regimen was designed to rapidly achieve and maintain an approximate plasma concentration of 870 ng/ml (dashed line), the peak concentration predicted by the model to be produced after an intravenous bolus of 200 μg/kg of butorphanol. The dotted lines represent the target concentration (870 ng/ml) ±10%. This infusion regimen is predicted to exceed 110% of the target concentration for intravenous infusions longer than 6.5 h

concentration predicted by the model to be reached after bolus administration of 200 μg/kg (Figure 2).

4 | DISCUSSION

The disposition of butorphanol in anesthetized cats was characterized by moderate volume of distribution and clearance, resulting in a terminal half-life of approximately 3 h. The pharmacokinetics of butorphanol have been previously reported in conscious dogs and cats; however, no intravenous data were obtained in either study, making comparison to the current study difficult (Pfeffer et al., 1980; Wells et al., 2008).

In this study, butorphanol was administered as a short intravenous infusion. Short intravenous infusions have been suggested to be preferable to intravenous bolus administration when pharmacokinetic data are intended to be used for calculating a loading dose and intravenous infusion rates, as they allow better characterization of the initial disposition and avoid the physiologically erroneous assumption of instantaneous drug mixing in the central compartment (Avram & Krejcie, 2003). The dose (1 mg/kg) was selected to ensure that plasma butorphanol concentrations would remain above the lower limit of quantitation of the assay during the whole sampling period, and based on the fact that peak plasma drug concentration would be lower for an infusion than if the same dose is delivered as an IV bolus.

Pharmacokinetic simulation based on the parameters estimated in this study suggests that an intravenous loading dose followed by three constant rate infusions, each administered for a predetermined time, and with each subsequent rate lower than the previous one would allow to rapidly achieve and maintain plasma drug concentrations within 10% of a target for infusion durations relevant to anesthetic management. Based on the terminal half-life, a single constant rate infusion would take ~9 h to result in stable plasma drug concentrations approaching a target, and simulation shows that adding a loading dose only marginally shortens the time to reaching and maintaining a target plasma drug concentration (data not shown). Assuming that effects correlate with plasma drug concentration, a loading dose and single constant rate infusion would therefore fail to result in a stable effect in most clinical scenarios. Similar considerations were experimentally confirmed for alfaxalone in cats (Pypendop et al., 2018).

Several limitations should be taken into account when interpreting the results of this study. The sample size was small and may not represent the true variability of the pharmacokinetics of butorphanol in cats. This is compounded by the fact that only young, healthy male neutered cats were used. It is possible that sex, and likely that age and disease affect the disposition of butorphanol. In addition, blood was sampled during anesthesia. It has been previously shown that anesthesia with isoflurane affects drug pharmacokinetics, and the results of this study should not be extrapolated to conscious cats (Pypendop et al., 2008; Thomasy et al., 2005). A single dose of butorphanol was studied, precluding the assessment of whether the pharmacokinetics are dose-independent within the clinical dose range.

In conclusion, the pharmacokinetics of butorphanol were characterized in anesthetized cats. The parameters estimated were used to calculate an intravenous loading dose and infusion regimen. Further studies are needed to determine whether these calculated doses result in the expected plasma drug concentrations.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ANIMAL WELFARE AND ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The authors confirm that they have adhered to US standards for the protection of animals used for scientific purposes.

DATA AVAILABILITY STATEMENT

Raw data provided as supplemental file.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Pypendop, B. H., & Shilo-Benjamini, Y. (2021). Pharmacokinetics of butorphanol in male neutered cats anesthetized with isoflurane. *Journal of Veterinary Pharmacology and Therapeutics*, 44, 883–887. https://doi.org/10.1111/jvp.13014