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Comparative pharmacokinetics of intravenous fentanyl and buprenorphine in healthy Greyhound dogs

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Abstract

The purpose of this study was to compare the pharmacokinetics of two highly protein bound, lipophilic opioid drugs. Fentanyl (10 µg/kg) and buprenorphine (20 µg/kg) were administered intravenously (IV) to six healthy Greyhound dogs (3 males and 3 females). The doses were based on clinically administered doses for dogs. Plasma drug concentrations were determined using liquid chromatography with mass spectrometry and noncompartmental pharmacokinetics were estimated with computer software. The volume of distribution (area) was larger for fentanyl (7.42 L/kg) compared to buprenorphine (3.54 L/kg). The plasma clearance of fentanyl (38.6 mL/min/kg) was faster than buprenorphine (10.3 mL/min/kg). The terminal half-life of fentanyl (2.22 h) was shorter than buprenorphine (3.96 h). Despite similar physicochemical properties including: octanol:water partition coefficient and pKa the pharmacokinetics of fentanyl and buprenorphine were not similar. Both fentanyl (84%) and buprenorphine (95-98%) are considered highly protein bound, but the differences in protein binding may contribute to the lack of similarity of pharmacokinetics in healthy dogs.

Keywords

Fentanyl; buprenorphine; pharmacokinetics; IV; Greyhounds

Fentanyl is a lipophilic mu opioid agonist with an n-octanol water partition coefficient of 860:1, pKa of 8.4 and 84.4% plasma protein binding in canine plasma (Meuldermans, et al, 1982; Anonymous, 2008). Buprenorphine is a lipophilic mu opioid partial agonist with an n-octanol:water partition coefficient of 1281:1, a pKa of 8.3 and 95-98% plasma protein binding in canine plasma (Garret & Chandran, 1985; Roy, et al, 1994). The purpose of this study was to compare the intravenous pharmacokinetics of opioids with similar physicochemical properties in Greyhound dogs.

The Institutional Animal Care and Use Committee approved the study. Six healthy 1-2 year old Greyhounds (3 males and 3 females) were used weighing 26-36 kg. Treatments were administered in a non-randomized manner (Shott, 2011). Fentanyl (Hospira, Lake Forest, IL, USA), 10 µg/kg IV, was administered then buprenorphine (Reckitt Beckisser,

Pharmaceuticals, Richmond, VA, USA), 20 µg/kg IV, with at least 2 weeks between treatments. Drugs were administered through acephalic catheter which was rinsed with 10 mL sterile 0.9% saline after administration. Blood samples, 9 mL each, were collected from a jugular catheter prior to drug administration and 4, 8, 15, 30 and 45 minutes and 1, 2, 4, 6, 8, and 12 hours after drug administration. Blood was placed in lithium heparin tubes kept on ice, plasma was separated after centrifugation ($3000 \times G$ for 20 minutes) and frozen at $-70^{\circ}C$.

Plasma drug concentrations were determined with liquid chromatography (Shimadzu Prominence, Shimadzu Scientific Instruments, Columbia, MD, USA) and mass spectrometry (API 2000, Applied Biosystems, Foster City, CA, USA). Fentanyl, fentanyl d5, buprenorphine, and buprenorphine d4 reference standards were used (Cerilliant Corporation, Round Rock, TX, USA). Plasma samples were extracted using solid phase extraction cartridges (SPE) (Varian Bond Elut C18, Varian Inc, Palo Alto, CA, USA). Plasma, 1 mL was added to 0.1 mL of the internal standard solution (fentanyl d5, 10 ng/mL or buprenorphine d4, 25 ng/mL), and 1 mL 0.1 N sodium hydroxide and vortexed for 5 seconds. The SPE were conditioned with 1 mL methanol then 1 mL deionized water, the plasma samples were added, the SPE were rinsed with 1 mL 5% methanol and 1 mL methanol was used for drug elution. The eluent was evaporated to dryness under an air stream in a $40^{\circ}C$ water bath and then reconstituted with 0.2 mL 50% methanol. The injection volumes were 0.05 mL, the mobile phase consisted of 0.1% formic acid and acetonitrile with separation achieved by a C18 column (Supelco Discovery, 50 mm $\times$ 2.1 mm $\times$ 5 µm, Sigma-Aldrich, St. Louis, MO, USA) maintained at $40^{\circ}C$. The qualifying and quantifying ions for fentanyl were m/z 337 and 188, respectively and for fentanyl d5 were m/z 341.4 and 105, respectively. The fentanyl accuracy on replicates of 5 at 0.1, 1, and 10 ng/mL were 96, 99, and 102%, respectively, and the coefficients of variation were 9, 1, and 4% at the same concentrations. The qualifying and quantifying ions for buprenorphine were m/z 468 and 55, respectively and for buprenorphine d4 were m/z 472 and 55, respectively. The buprenorphine accuracy on replicates of 5 at 0.5, 5, and 10 ng/mL were 101, 103, and 99%, respectively and the coefficients of variation were 12, 4, and 5% at the same concentrations. The LLOQ of fentanyl and buprenorphine were 0.1 and 0.5 ng/mL respectively.

Noncompartmental pharmacokinetic analyses were performed (WinNonlin 5.2, Pharsight Inc, Cary, NC, USA). Reported parameters include: area under the curve from 0 to infinity (AUC), percent of the AUC extrapolated to infinity ($AUC_{\text{extrapolated}}$), plasma concentration extrapolated to time 0 by log linear regression of the first two time points (C_0), mean residence time extrapolated to infinity (MRT), terminal half-life ($T_{1/2}$), terminal rate constant (λ_z), plasma clearance (Cl), volume of distribution – area method (V_z), and volume of distribution – steady state method (V_{ss}). At least 3 time points were used for the determination of the terminal portion of the plasma profile curve. The geometric mean, minimum, median, and maximum values are reported (Table 1).

The arithmetic mean and standard deviation plasma concentrations are presented in Figure 1. The doses chosen for the study (fentanyl 10 µg/kg, buprenorphine 20 µg/kg) were based on doses used clinically in canine patients. Although the doses were not identical, the primary pharmacokinetic parameters (V_z , V_{ss} , Cl, and $T_{1/2}$) are independent of dose in drugs that

exhibit dose independent pharmacokinetics. Previous studies have confirmed that fentanyl exhibits dose independent pharmacokinetics from 6.4-640 µg/kg in dogs (Murphy et al. 1983). Therefore despite different doses of fentanyl and buprenorphine administered to dogs, it is not an unreasonable assumption that dose was not a prominent factor in the determination of the primary pharmacokinetic parameters in this study.

The volumes of distribution were much larger for fentanyl than buprenorphine. Since pKa values are similar between the drugs, it is unlikely a major factor in the differences in the volumes of distribution. The reported octanol:water partition coefficient for buprenorphine (1281:1) is larger than the reported partition coefficient for fentanyl (860:1), which would suggest buprenorphine would be more likely to distribute and accumulate in tissues than fentanyl, leading to larger volumes of distribution for buprenorphine. However since the partition coefficients are so large, the relatively small differences in the partition coefficients may not have a prominent effect on the volumes of distribution.

The plasma protein binding of buprenorphine is much larger than fentanyl, despite both drugs being highly protein bound in canine plasma (Meuldermans, et al, 1982; Garret & Chandran, 1985; Roy, et al, 1994; Anonymous, 2008;). The protein unbound fraction of buprenorphine is expected to be only 2-5% compared to 15.6% for fentanyl, at least a 3 fold difference which may have an effect of restricting distribution of buprenorphine and could result in smaller volumes of distribution for buprenorphine. This was observed with significant differences in doxycycline protein binding (98% cats vs. 91% dogs) resulting in significant differences in the volumes of distribution (V_z 0.38 L cats vs. 1.01 L dogs) (Riond et al., 1990). However the tissue binding of fentanyl and buprenorphine have not been reported in dogs and may also have an effect on the volumes of distribution.

The plasma clearance of fentanyl (38.6 mL/min/kg) was approximately 3 times greater than buprenorphine (10.3 mL/min/kg). The clearance of fentanyl was or exceeded the expected hepatic blood flow, suggesting it is a high hepatic extraction ratio drug in Greyhound dogs. A previous study in dogs suggested hepatic metabolism is the primary route of elimination of fentanyl in dogs (Murphy et al, 1979).

In contrast the plasma clearance of buprenorphine was suggestive that it has an intermediate hepatic extraction ratio. A previous study indicated 92% of buprenorphine was eliminated as glucuronide conjugates in mongrel dogs supporting it is primarily cleared by hepatic metabolism (Garret & Chandran 1990). A previous study of codeine in Greyhounds, which is also primarily eliminated as glucuronide conjugates (KuKanich, 2010), indicated codeine was a high hepatic extraction ratio drug suggesting that the slower plasma clearance buprenorphine was not likely due to a deficiency in conjugation metabolism enzymes in Greyhounds, but due to slower intrinsic clearance of buprenorphine.

It is unclear why the hepatic extraction ratios of fentanyl and buprenorphine appeared to differ in Greyhound dogs. The larger fraction of plasma protein unbound fentanyl may be a factor as unbound drug is available to interact with metabolizing enzymes. However, if the affinity of the drug is greater for the metabolizing enzyme than the plasma protein, a small fraction of unbound drug will not be a limiting factor. The affinity of fentanyl for its

metabolizing enzymes may be greater than the affinity of buprenorphine for its metabolizing enzymes which could affect clearance. The metabolism rate for the enzymes that metabolize fentanyl may also be greater than the rate of the enzymes that metabolize buprenorphine which could also result in the greater plasma clearance of fentanyl.

The AUC_{extrapolated} for fentanyl in 2 dogs was greater than 20% due to drug concentrations dropping below the LOQ of the assay. Although this extrapolation is larger than ideal, 4 of the dogs had less than 10% extrapolated and all of the dogs were similar in the AUC and T_{1/2}. Additionally the T_{1/2} for the dogs with >20% extrapolated AUC in this study were similar to a previous study of fentanyl in Greyhounds (KuKanich, 2011). Although the larger extrapolation potentially leads to less robust AUC and T_{1/2} estimates for 2 dogs administered fentanyl, the pharmacokinetic values are within previously reported ranges and within the ranges within this group of dogs.

This is the first study to compare the IV pharmacokinetics of fentanyl and buprenorphine which have similar physicochemical properties. The pharmacokinetics were not similar suggesting factors other than physicochemical properties, such as plasma protein binding, may play a role in drug distribution in dogs. Further *in vitro* studies of intrinsic metabolism and tissue binding and distribution may provide useful data in predicting the pharmacokinetics of fentanyl and buprenorphine. Additionally, enzymatic affinity for unbound fentanyl and buprenorphine *in vitro* using canine enzymes may provide insight into the differences in plasma clearance.

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Abbreviations/symbols

<i>m/z</i>	mass to charge ratio
LLOQ	lower limit of quantification

Figure 1. Plasma drug concentrations (mean and standard deviation) of fentanyl (open circles) after 10 $\mu\text{g/kg}$ IV and buprenorphine (solid circles) after 20 $\mu\text{g/kg}$ IV in 6 healthy Greyhound dogs.

Table 1

Noncompartmental pharmacokinetics of IV fentanyl and buprenorphine in 6 healthy Greyhound dogs (Geometric mean, minimum, median and maximum values reported).

		Fentanyl 10 µg/kg IV				Buprenorphine 20 µg/kg IV			
		Mean	Minimum	Median	Maximum	Mean	Minimum	Median	Maximum
AUC _{extrapolated}	%	12.1	5.5	9.3	45.6	8.0	3.7	8.9	12.2
AUC	hr*ng/mL	4.32	3.67	4.24	5.89	32.34	27.63	32.64	38.35
C ₀	ng/mL	3.43	2.36	3.28	5.56	16.05	9.64	17.27	21.93
MRT	hr	2.66	1.90	2.67	4.38	3.97	3.06	4.03	4.83
T _{1/2}	hr	2.22	1.52	2.13	4.03	3.96	2.81	3.95	4.99
λ _z	1/hr	0.312	0.172	0.327	0.457	0.175	0.139	0.176	0.247
Cl	mL/min/kg	38.6	28.3	39.3	45.4	10.3	8.7	10.2	12.1
V _z	L/kg	7.42	5.08	7.25	10.60	3.54	2.44	3.52	5.21
V _{ss}	L/kg	6.16	4.55	6.31	7.81	2.46	1.84	2.51	2.88