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Pharmacokinetics and bioavailability after intra-muscular injection of the 5-HT_{1A} serotonin agonist R-8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in domestic goats (*Capra aegagrus hircus*)

Running title: Pharmacokinetics of 8-OH-DPAT in goats

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Abstract

To determine the bioavailability and pharmacokinetic properties of the serotonin 5-HT_{1A} receptor agonist R-8-OH-DPAT in goats, 0.1mg kg⁻¹ R-8-OH-DPAT hydrobromide was administered intra-muscularly (IM) and intra-venously (IV) to six goats in a two-phase cross-over design experiment. Venous blood samples were collected from the jugular vein 2, 5, 10, 15, 20, 30, 40 and 60 minutes following treatment and analysed by liquid chromatography tandem mass spectrometry. Bioavailability and pharmacokinetic parameters were determined by a one-compartment analysis.

Mean bioavailability of R-8-OH-DPAT when injected IM was 66%. The mean volume of distribution in the central compartment was 1.47 L kg⁻¹. The mean plasma body clearance was 0.056 L kg⁻¹min⁻¹. All goats injected IV and two of six goats injected IM showed signs of serotonin toxicity.

In conclusion, R-8-OH-DPAT is well absorbed following IM injection and the observed pharmacokinetics suggest that administration via dart is feasible. Administration of R-8-OH-DPAT hydrobromide, at a dosage of 0.1mg kg⁻¹, resulted in the observation of clinical signs of serotonin toxicity in the goats. It is suggested that dose rates for the clinical use of the compound should be lower in order to achieve the desired clinical effect without causing serotonin toxicity.

Keywords: 8-OH-DPAT; Bioavailability; Pharmacokinetics; Serotonin Agonist; Wildlife Immobilisation

Introduction

Serotonergic ligands, specifically 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), through its effects on the 5-HT_{1A} receptors, alleviate opioid-induced hypoxia by reducing respiratory depression and ventilation-perfusion mismatch (Sahibzada et al. 2000; Richter et al. 2003; Meyer et al. 2006; Stettner et al. 2008; Kimura & Haji 2014). Importantly, 8-OH-DPAT does not affect analgesia, catatonia or sedation caused by opioids (Guenther et al. 2009; Meyer et al. 2006; Manzke et al. 2003; McCrimmon & Alheid 2003; Haigh 1990). It is thought that the use of the R-enantiomer of 8-OH-DPAT may produce even more pronounced results in comparison to the previously-studied racemic form because of its

high specificity at the 5-HT_{1A} receptors (Hadrava et al. 1996; Yu et al. 1996a; Lejeune et al. 1997). Two papers reported clinical respiratory changes following the intravenous (IV) use of the racemic form of 8-OH-DPAT in goats at dosages of 0.1 and 0.5 mg kg⁻¹ respectively (Herman, O'Halloran & Bisgard 2001; Meyer et al. 2006). In order to immobilise wild herbivores, R-8-OH-DPAT would have to be administered together with the opioid by means of an intra muscular (IM) injection with a dart syringe.

Some literature on the pharmacokinetic data of 8-OH-DPAT in rats and marmosets exists (Yu & Lewander 1997; Zuideveld et al. 2000; Kotani et al. 2016) but there is currently no published literature available on the pharmacokinetics of 8-OH-DPAT in ungulates. Therefore the pharmacokinetics and bioavailability after IM injection of this serotonin agonist had to be investigated in order to establish if it would be a feasible adjunct to an opioid based IM immobilisation mixture for wildlife.

The aim of this study was to characterise the pharmacokinetics and bioavailability of R-8-OH-DPAT hydrobromide in goats at a dosage of 0.1mg kg⁻¹ which equals 0.075mg kg⁻¹ of R-8-OH-DPAT.

Material and Methods

This study was approved by the Murdoch University Animal Ethics Committee (R2922/17) and the animal ethics committee of Wildlife Pharmaceuticals (WPAEC-2016-DPATGOAT-09-C). Six healthy domestic female indigenous veld goats of between four and five years of age weighing between 29 and 43kg (average 34kg) were used for this project.

A two-way cross-over experiment was undertaken with a 14 day rest period.

Each goat was injected either IV or IM with 0.1mg kg⁻¹ R-8-OH-DPAT hydrobromide (Tocris Bioscience, Bristol, UK, catalogue number 1080), equivalent to approximately 0.075mg kg⁻¹ R-8-OH-DPAT (pubchem.ncbi.nlm.nih.gov). The compound was dissolved in sterile water to a concentration of 5mg mL⁻¹. Intra-venous injection was administered with a 21G 25.4mm needle as a bolus into the jugular vein opposite to the catheterised jugular vein. After the IV injection, blood was drawn back into the syringe and reinjected to

ensure that the full dose of R-8-OH-DPAT was administered. The IM injection was given into the lateral femoral muscle group with a 21G 25.4mm needle.

Blood was collected from an intravenous catheter that was inserted into the jugular vein. Serial blood samples were collected at 2, 5, 10, 15, 20, 30, 40, 60 minutes following treatment. Within two hours post collection, the blood was centrifuged and serum decanted into cryovials and stored at -20°C until further analysis within two weeks after collection.

Laboratory analysis of the serum was performed by means of liquid chromatography tandem mass spectrometry (LC-MS/MS) by FDA Laboratories, Pretoria, South Africa similar to methods published (Yu et al. 1996b; Kotani et al. 2016). The serum (20µL) was diluted with methanol. The mixture was then centrifuged for protein precipitation. The supernatant was collected and subjected to the analysis against a reference standard made by dissolving R-8-OH-DPAT powder in methanol. Chromatographic separation was achieved using a Phenomenex Luna® 5µm C18 150 x 2mm analytical column maintained at 40°C. The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) the gradient elution program was as follows: 0-1min, 90% A; 1-2min, 90-10% A; 2-5min, 10% A; 5-6min, 10-90% A; 6-10min, 90% A.

The LC-MS/MS system consisted of an Agilent 1200 high pressure liquid chromatography system coupled to an AB Sciex triple-quadrupole 3500 mass spectrometer. Positive electrospray ionization was used, and the analysis was performed in the multiple electron monitoring mode (MRM). The turbo ion spray source was set with the following settings: capillary voltage 5500 V, nebuliser gas (N₂) 10 (arbitrary units), curtain gas (N₂) 20 (arbitrary units) and source temperature of 400°C. Two MRM transitions were selected, the most intense (248.105m/z:147.000m/z) being used for quantification and the other (248.105m/z:107.000m/z) for confirmation.

The limit of quantification (LOQ) was set according to methods described by Shabir (2003) at 20µg L⁻¹. The limit of detection (LOD) was estimated to be 5µg L⁻¹ as the lowest non-zero observation in the data-set was 5.7µg L⁻¹. The inter assay variation was 12.53% and the intra assay variation was 10.35%.

Matrix-matched calibration curve and control samples were prepared by spiking on serum, collected from goats that had not been treated with the drug, at different concentrations. Serum concentrations of R-8-OH-DPAT were obtained by the use of peak area and slope-intercept from linear matrix matched calibration curves.

Data management was conducted in Microsoft Excel 2016. Analysis and visualisation of data and definition of models was performed in MATLAB 2015 (The Mathworks, Inc.). Coding for the study was developed based on the author's previous work (Sebbag et al., 2016).

A typical data analysis scheme for the two-stage setting was used for pharmacokinetic modelling. For the compartmental analysis, after viewing the intravenous data on log₁₀ scale, a one-compartment model (Toutain & Bousquet-Mélou 2004a; Toutain & Bousquet-Mélou 2004b) was chosen. The model for IV administration was implemented as the ordinary differential equation (ODE) (**Equation 1**), where DX_1/dt is the rate of change of drug mass in the central compartment, X_1 is the drug mass (μg) in the central compartment, V_c is the central compartment volume of distribution (L kg^{-1}), and Cl_p is the plasma clearance ($\text{L kg}^{-1} \text{ min}^{-1}$).

Equation 1:
$$\frac{dX_1}{dt} = -\left(\frac{X_1}{V_c}\right) * Cl_p$$

Numeric solutions of the ODE were obtained for this model using the numeric differentiation formulas as implemented in MATLAB's 'ode15s' (Shampine & Reichelt, 1997).

For the IM model (**Equations 2 and 3**) we defined first-order absorption, where X_a is the drug mass in the absorption compartment (μg) and k_a is the first-order absorption rate constant (min^{-1}).

Equation 2:
$$\frac{dX_1}{dt} = -\left(\frac{X_1}{V_c}\right) * Cl_p + (X_a * k_a)$$

Equation 3:
$$\frac{dX_a}{dt} = -(X_a * k_a)$$

This model includes IM bioavailability F_{IM} (%), implemented in the ODE initial conditions. The model therefore includes four primary pharmacokinetic parameters to be estimated from the data; total plasma clearance (CL_P), volume of distribution of the central compartment (V_c), first-order absorption rate constant (k_a), and intramuscular bioavailability (F_{IM}). The error standard deviation (σ_ϵ^2) is also estimated in this model. Parameter estimation was governed by the following principles:

1: all BLQ data points were included as scalar observations, as for the observations above the quantification limit (LOQ) (i.e. the LOQ was ignored).

2: the BLD data points were defined as censored observations (i.e. $< 5\mu\text{g L}^{-1}$).

3: a censored non-linear regression model was defined, and instead of minimising the sum-of-squares of the weighted residuals, we implemented maximum likelihood estimation of the pharmacokinetic parameters, first for the IV phase only, then for the IV and IM phases simultaneously.

For step 3 the censored (Tobit) regression was implemented by direct definition of the log-likelihood function (Lynn, 2001), with optimization using the MATLAB functions ‘fmincon’ (constrained function minimisation), an implementation of an interior-point algorithm, and ‘patternsearch’, an adaptive mesh algorithm. For the BLD, this censored regression method is equivalent to Beal’s ‘method 3’ (Beal, 2001). For the maximum likelihood estimation, we assumed the distribution of residual errors was normal, with standard deviation as a parameter to be estimated (σ_ϵ^2). To accommodate heteroscedasticity the residuals were weighted ($1/Y$). We estimated simultaneous parameters for the IV and IM phase for each subject, to improve the robustness of the IM parameter estimates. The goodness-of-fit of the models was assessed by plots of the observed and predicted concentrations vs time for each subject, and identity (observed vs predicted concentrations) and residuals plots across subjects.

Secondary parameters were estimated from the final models.

The area-under-the-curve (AUC) was determined by numeric integration of the final models. The AUC_{inf} was obtained as the improper integral (integration from time zero to infinity).

The elimination and absorption half-lives were obtained from Equation 4.

Equation 4:
$$t \frac{1}{2} = \frac{\log_e 2}{k}$$

Where k is the rate constant. As the model was parameterised using clearance, the elimination rate constant was obtained as clearance divided by the volume of distribution.

Results

The IM data series from one subject was excluded from analysis as it contained no useful information and was probably indicative of drug administration error (numerous BLD observations). The final analysed dataset included 88 observations, from six IV subject-occasions and five IM subject-occasions.

Though the experiment was a conventional two-stage, cross-over design, the dataset was characterised by observations that were below the analytical method detection limit (BLD; $n = 6/88$), or below the quantification limit but above the detection limit (BLQ; $n = 40/88$).

The final compartmental model was an acceptable fit, to both the IM and the IV data. The goodness-of-fit visualisation indicated that the fit of the IV model across subjects was similar to that of the IM model across subjects (Figure 1 and 2). For all the modelled subject-occasions the quality of the model fit was similar; none stood out as being indicative of model failure.

Estimated primary and secondary parameters from the compartmental analysis are listed in **table 1** and **table 2** respectively.

All goats injected IV displayed clear clinical signs of serotonin toxicity (Boyer, 2005; Isbister & Buckley, 2005; Volpi-Abadie, Kaye, & Kaye, 2013), while two of five goats injected IM displayed mild signs of serotonin toxicity. The clinical behavioural effects of the R-8-OH-DPAT manifested within two minutes and five minutes after injection in goats that were injected IV and IM respectively. These clinical signs consisted of head shaking, chewing and licking, moderate to severe shivering of the entire body, vocalisation, urination and hypersensitivity to external stimulation. All goats fully recovered within twenty minutes after onset of the symptoms.

Discussion

The lower limit of quantification in this study coincided with biologically-relevant drug concentrations. Because the number of BLQ observations was large, and more prevalent in the IM phase, the reported concentrations of the BLQ observations were used directly rather than deleting these observations from the dataset. Despite widespread use in analytical method validation, quantification limits depend on arbitrary selection of an acceptable relative error limit, despite the fact that measurement error is present in all the data (Guo et al. 2010; Jelliffe et al. 2015). Simply discarding the BLQ data would result in complete failure of the IM phase, even though it contains useful information. The presence of BLQ data requires careful consideration of appropriate methodology to limit bias in parameter estimation while retaining information (Jusko, 2012). Recent observations in population analysis demonstrate that simply ignoring the LOQ is a valid approach, where numeric values for the BLQ observations are available, and superior to deletion or substitution (Keizer et al. 2015). In this study, the BLQ observations were retained, combined with the popular maximum likelihood approach (Bergstrand & Karlsson, 2009) for the BLD observations. However, the precise impact of measurement error associated with BLQ observations on the parameter estimates in this study is not known, and there is a specific risk of inaccuracy in the estimate of bioavailability due to the greater number of BLQ observations in the IM phase. The interference of the LOQ with plasma

concentrations achieved after a therapeutically-relevant dose suggests that optimisation of analytical methods is a key priority for further investigations of this drug.

Establishing bioavailability estimates for R-8-OH-DPAT administered via the IM route has significant practical value. This knowledge can be used to ascertain the practicality and a dose estimate for adding the serotonin agonist to an opioid based immobilisation dart mixture. Although, there was a large variability (range 50 to 98%), the mean bioavailability was 66% after IM injection, therefore R-8-OH-DPAT was well absorbed from the injection site. At the chosen concentration of 5mg mL^{-1} R-8-OH-DPAT hydrobromide, dissolved in sterile water, the total drug volume per animal was low. This means that a dart preparation is feasible due to the low injection volume.

With an absorption half-life of six minutes, the highest serum concentrations of R-8-OH-DPAT were reached in all goats between 11 and 17.5 minutes after IM injection (Figure 3 and 4). The mean elimination half-life of R-8-OH-DPAT in goats was 18 minutes (CV = 17%) according to the compartmental analysis in our experiment. This result is similar to that in rats reported by Yu & Lewander (1997). These researchers showed that in rats the plasma half-life of R-OH-DPAT reached 27 minutes.

The use of serotonin agonists can be associated with serotonin toxicity, also called serotonin behavioural syndrome (Boyer, 2005; Isbister et al. 2007; Volpi-Abadie et al. 2013). Serotonin toxicity has been described in humans and animals (Isbister & Buckley 2005). The choice of dosage in the current experiment (0.1mg kg^{-1} of R-8-OH DPAT) was based on previous reports in goats (Meyer et al. 2006; Herman et al. 2001) in which up to 0.5mg kg^{-1} 8-OH-DPAT was administered IV. No adverse effects were reported, suggesting that the dose (0.1mg kg^{-1}) in this experiment would be safe. It is postulated that the onset of serotonin toxicity in the experimental animals was associated with the use of the R-enantiomer of 8-OH-DPAT as opposed to the racemic mixture that was used in other studies. The R-enantiomer has been shown to have more specific action on the 5-HT_{1A}

receptors (Hadrava et al. 1996; Yu, Liu, Malmberg, et al. 1996a; Lejeune et al. 1997) and the likely reason for the toxicity symptoms described here.

Conclusions:

According to the pharmacokinetic analysis, R-8-OH-DPAT was readily absorbed with a mean bioavailability of 66% after IM injection and the observed pharmacokinetics suggest that administration via dart is feasible. Clinical relevance of the achieved concentrations is evidenced by clinical signs of serotonin toxicity observed post injection. Following the observation of clinical signs of serotonin toxicity in the goats at a dosage of R-8-OH-DPAT hydrobromide of 0.1mg kg^{-1} , it is concluded that the dosage used should be lower in order to achieve the desired clinical effect without causing serotonin toxicity.

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Conflict of Interest Statement

The research was funded by Wildlife Pharmaceuticals PTY LTD and Murdoch University.

Author Contribution Statement

SP : First author, PhD student, study design, manuscript

AW : Second author, data analysis, manuscript, data interpretation

LL : Study design, data interpretation

KW: Study designs, manuscript

R V-H: Study design, manuscript

JPR: Study design, funding

286 ML: Study design, data interpretation, funding, manuscript, main supervisor of SP

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Figure 1: Observed versus predicted concentrations of R-8-OH-DPAT in serum of goats after IV injection of 0.1mg kg⁻¹ R-8-OH-DPAT hydrobromide. The solid line is the line of identity (y = x).

Figure 2: Observed versus predicted concentrations of R-8-OH-DPAT in serum of goats after IM injection of 0.1mg kg⁻¹ R-8-OH-DPAT hydrobromide. The solid line is the line of identity ($y = x$).

Figure 3: Predicted serum concentrations in goats after IV injection of 0.1 mg kg^{-1} R-8-OH-DPAT hydrobromide. The solid lines each represent predictions for one subject while the dotted line is the analytical detection limit (LOD; $5 \mu\text{g L}^{-1}$).

Figure 4: Predicted serum concentrations in goats after IM injection of 0.1mg kg^{-1} R-8-OH-DPAT hydrobromide. The solid lines each represent predictions for one subject while the dotted line is the analytical detection limit (LOD; $5\mu\text{g L}^{-1}$).

Table 1: Estimated primary parameters from compartmental analysis for the six subjects

Subject ID	V_c	Cl_P	σ_ε^2	k_a	F_{IM}
1	1.049	0.03991	0.2331	0.1013	0.6448
2	1.962	0.06594	0.4216	0.1436	0.9769

3	0.7193	0.03987	0.4762	0.07038	0.5007
4	1.416	0.05617	0.2171	0.23015	0.5376
5	1.7486	0.07031	0.2393	0.1427	0.6393
6	1.94845	0.06496	0.2680	.*	.*
MEAN	1.474	0.0562	0.3092	0.1376	0.6599
MEDIAN	1.582	0.0606	0.2536	0.1427	0.6393
CV%	34.489	23.91	35.83	43.69	28.5

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424 **MEAN is the arithmetic mean. STD is the sample standard deviation.**425 **CV% is the coefficient of variation (STD/MEAN*100).**426 **V_C is the central compartment volume of distribution (L kg⁻¹).**427 **Cl_P is the plasma body clearance (L kg⁻¹ min⁻¹).**428 **σ_{ε}^2 Is the standard deviation of the residual error distribution.**429 **k_a is the first-order absorption rate constant after intramuscular administration (min-**
430 **1).**431 **F_{IM} is the bioavailability after intramuscular administration (as proportion).**432 *** Not estimated as the available IM data for this subject were excluded.**

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435 **Table 2: Estimated secondary parameters from the compartmental analysis for the six**
436 **subjects**

Subject ID	$T_{\max}$	$C_{\max}$	$t_{1/2} \text{ A}$	$t_{1/2} \text{ E}$	$AUC_{\text{inf IV}}$	$AUC_{\text{inf IM}}$
1	17.48	27.03	6.841	18.23	1889.2	1220.7
2	15.20	47.35	4.827	20.62	1143.4	1119.2
3	17.97	15.61	9.848	12.51	1895.7	949.0
4	11.23	28.16	3.011	17.47	1342.5	723.0
5	14.36	29.38	4.857	17.24	1072.7	686.8
6	.*	.*	.*	20.79	1160.8	.*
MEAN	15.25	29.51	5.877	17.81	1417.4	939.7
MEDIAN	15.20	28.16	4.857	17.85	1251.6	949.0
CV%	17.77	38.63	44.25	16.94	26.71	25.08

MEAN is the arithmetic mean. MEDIAN is the sample median.

CV% is the coefficient of variation (sample standard deviation /MEAN*100).

$T_{\max}$ is the predicted time of maximum plasma concentration for the IM phase (minutes).

$C_{\max}$ is the predicted maximum serum concentration during the IM phase ($\mu\text{g L}^{-1}$).

$t_{1/2} \text{ A}$ is the absorption half-life (minutes).

$t_{1/2} \text{ E}$ is the elimination half-life (minutes).

$AUC_{\text{inf IV}}$ and $AUC_{\text{inf IM}}$ are the predicted area-under-the-curve extrapolated to infinity, for the IV and IM phase respectively ($\mu\text{g hr L}^{-1}$).

* Not estimated as the available IM data for this subject were excluded.

Table 1: Estimated primary parameters from compartmental analysis for the six subjects

Subject ID	V_c	Cl_P	σ_e^2	k_a	F_{IM}
1	1.049	0.03991	0.2331	0.1013	0.6448
2	1.962	0.06594	0.4216	0.1436	0.9769
3	0.7193	0.03987	0.4762	0.07038	0.5007
4	1.416	0.05617	0.2171	0.23015	0.5376
5	1.7486	0.07031	0.2393	0.1427	0.6393
6	1.94845	0.06496	0.2680	.*	.*
MEAN	1.474	0.0562	0.3092	0.1376	0.6599
MEDIAN	1.582	0.0606	0.2536	0.1427	0.6393
CV%	34.489	23.91	35.83	43.69	28.5

MEAN is the arithmetic mean. STD is the sample standard deviation.

CV% is the coefficient of variation (STD/MEAN*100).

V_c is the central compartment volume of distribution ($L\ kg^{-1}$).

Cl_P is the plasma body clearance ($L\ kg^{-1}\ min^{-1}$).

σ_e^2 Is the standard deviation of the residual error distribution.

k_a is the first-order absorption rate constant after intramuscular administration (min^{-1}).

F_{IM} is the bioavailability after intramuscular administration (as proportion).

*** Not estimated as the available IM data for this subject were excluded.**

Table 2: Estimated secondary parameters from the compartmental analysis for the six subjects

Subject ID	$T_{\max}$	$C_{\max}$	$t_{1/2 A}$	$t_{1/2 E}$	$AUC_{\inf IV}$	$AUC_{\inf IM}$
1	17.48	27.03	6.841	18.23	1889.2	1220.7
2	15.20	47.35	4.827	20.62	1143.4	1119.2
3	17.97	15.61	9.848	12.51	1895.7	949.0
4	11.23	28.16	3.011	17.47	1342.5	723.0
5	14.36	29.38	4.857	17.24	1072.7	686.8
6	.*	.*	.*	20.79	1160.8	.*
MEAN	15.25	29.51	5.877	17.81	1417.4	939.7
MEDIAN	15.20	28.16	4.857	17.85	1251.6	949.0
CV%	17.77	38.63	44.25	16.94	26.71	25.08

MEAN is the arithmetic mean. MEDIAN is the sample median.

CV% is the coefficient of variation (sample standard deviation /MEAN*100).

$T_{\max}$ is the predicted time of maximum plasma concentration for the IM phase (minutes).

$C_{\max}$ is the predicted maximum serum concentration during the IM phase ($\mu\text{g L}^{-1}$).

$t_{1/2 A}$ is the absorption half-life (minutes).

$t_{1/2 E}$ is the elimination half-life (minutes).

$AUC_{\inf IV}$ and $AUC_{\inf IM}$ are the predicted area-under-the-curve extrapolated to infinity, for the IV and IM phase respectively ($\mu\text{g hr L}^{-1}$).

* Not estimated as the available IM data for this subject were excluded.

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Title:

Pharmacokinetics and bioavailability after intramuscular injection of the 5-HT_{1A} serotonin agonist R-8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in domestic goats (*Capra aegagrus hircus*)

Date:

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