RESEARCH PAPER

Comparison of cardiopulmonary effects of etorphine and thiafentanil administered as sole agents for immobilization of impala (*Aepyceros melampus*)

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Abstract

Objective To compare the cardiopulmonary effects of the opioids etorphine and thiafentanil for immobilization of impala.

Study design Two-way crossover, randomized study.

Animals A group of eight adult female impala.

Methods Impala were given two treatments: 0.09 mg kg^{-1} etorphine or 0.09 mg kg^{-1} thiafentanil via remote dart injection. Time to recumbency, quality of immobilization and recovery were assessed. Respiratory rate, heart rate (HR), mean arterial blood pressure (MAP) and arterial blood gases were measured. A linear mixed model was used to analyse the effects of treatments, treatments over time and interactions of treatment and time ($p < 0.05$).

Results Time to recumbency was significantly faster with thiafentanil (2.0 ± 0.8 minutes) than with etorphine (3.9 ± 1.6 minutes; $p = 0.007$). Both treatments produced bradypnoea, which was more severe at 5 minutes with thiafentanil (7 ± 4 breaths $minute^{-1}$) than with etorphine (13 ± 12 breaths $minute^{-1}$; $p = 0.004$). HR increased with both treatments but significantly decreased over time when etorphine (132 ± 17 to 82 ± 11 beats $minute^{-1}$) was compared with thiafentanil (113 ± 22 to 107 ± 36 beats $minute^{-1}$; $p < 0.001$). Both treatments caused hypertension which was more profound with thiafentanil (mean overall MAP = 140 ± 14 mmHg; $p < 0.001$). Hypoxaemia occurred with both treatments but was greater with thiafentanil [PaO_2 37 ± 13 mmHg (4.9 kPa)] than with etorphine [45 ± 16 mmHg (6.0 kPa)] 5 minutes after recumbency ($p < 0.001$). After 30 minutes, PaO_2 increased to 59 ± 10 mmHg (7.9 kPa) with both treatments ($p < 0.001$).

Conclusions and clinical relevance The shorter time to recumbency with thiafentanil may allow easier and faster retrieval in the field. However, thiafentanil caused greater hypertension, and ventilatory effects during the first 10 minutes, after administration.

Keywords etorphine, immobilization, impala, opioids, thiafentanil, wildlife.

Introduction

Impala are small to medium sized antelopes that are abundant in South Africa (Furstenburg 2016). Impala are regularly captured for trade and translocation as well as for research and clinical purposes (Zeiler & Meyer 2017b).

Drugs commonly used for the immobilization of impala in the wild include the potent opioids etorphine and thiafentanil, sometimes combined with ketamine or other sedatives and tranquillizers (Cheney & Hattingh 1987; Meyer et al. 2008; Lance & Kenny 2011; Kock & Burroughs 2012; Perrin et al. 2015; Zeiler & Meyer 2017a). When darted with potent opioids, impala may exhibit severe ventilatory depression (Meyer et al. 2008, 2010; Zeiler & Meyer 2017a,b). Veterinarians usually have the full opioid antagonist, naltrexone or an opioid agonist-antagonist such as butorphanol available to rapidly alleviate ventilatory depression if required (Meyer et al. 2010; Kock & Burroughs 2012; Zeiler & Meyer 2017b). While some individuals demonstrate moderate ventilatory depression and

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hypoxia, in others, this can be severe and life threatening (Meyer et al. 2010; Zeiler & Meyer 2017a,b).

Various immobilization protocols have been examined in an attempt to identify the drug combination with the most rapid time to recumbency (<3 minutes) and minimal cardiopulmonary side effects in this species (Janssen et al. 1993; Meyer et al. 2008; Perrin et al. 2015; Zeiler & Meyer 2017a). Many of these reports describe opioid-based immobilization protocols in which the potent opioid is mixed with a sedative or tranquillizer. However, many veterinarians use thiafentanil as the sole immobilization agent in the field (Kock & Burroughs 2012) as it can be fully reversed with naltrexone. The impala thus recover rapidly without the residual effects of co-administered sedatives or tranquilizers. Using this immobilization technique means that animals should be able to defend themselves more readily against predators or dominant herd counterparts shortly after reversal of the opioid (Rominger et al. 2004).

Thiafentanil is considered superior to etorphine for impala immobilization because it achieves a faster induction time (defined as time from dart injection to recumbency of the animal) and less respiratory depression (Meyer et al. 2008; Lance & Kenny 2011; Kock & Burroughs 2012; Zeiler & Meyer 2017a).

The two opioids have different receptor affinities. While thiafentanil is a pure μ-agonist (Vardanya & Hruby 2014; Zeiler & Meyer 2017a), etorphine is an agonist at μ-, κ- and δ-opioid receptors (Gutstein & Akil 2006). Despite this fact, field veterinarians use both opioids interchangeably for the immobilization of many antelope species (Kock & Burroughs 2012). The decision to use an opioid is a pragmatic one—often based on availability and the cost of drugs rather than on their physiological effects. Therefore, this study aimed to determine the extent to which the two opioids were equipotent with regards to time to recumbency, immobilization quality and the cardiopulmonary effects of the two drugs at these doses.

It was hypothesized that there would be clinically relevant differences in the quality of immobilization and cardiopulmonary effects produced by the two drugs.

Materials and methods

The study was approved by the Murdoch University Animal Ethics Committee (R3039/18) and Wildlife Pharmaceuticals Animal Ethics Committee (WPAEC-2017-DPATBLES-11-B).

The experiment was conducted at the Wildlife Pharmaceuticals Wildlife Research Facility, Republic of South Africa (RSA; GPS: 25°31′25.2″ S, 31°06′50.8″ E). A total of eight wild captured female impala weighing 37 ± 4 kg [mean ± standard deviation (SD)] were selected for this purpose. Research animals of the same sex and similar size were chosen; they were in good health as determined by veterinary examination. Based on a previous crossover experiment (Pfitzer et al. 2019), it was calculated that there would be an 80% chance of detecting a difference of 3 breaths minute^{-1} at a 5% significance level with a sample size of eight animals.

Experimental procedures for this study were similar to those previously described (Pfitzer et al. 2019). Briefly, housing enclosures consisted of several compartments with a compartmental floorspace of approximately 6 × 8 m and were constructed of wooden poles. The impala were held in groups of four animals. After an initial adjustment period of 2 weeks following delivery and 2 weeks before the start of the research trial, the animals were chemically immobilized, marked and subjected to a veterinary health examination. The veterinary examination consisted of faecal worm egg count, blood smear examination as well as pregnancy determination by ultrasound examination. At this time, the animals were weighed whilst immobilized (Anyload OCSL Mini Crane Scale; Anyload Transducer Co. Ltd, NJ, USA).

The immobilizing drugs etorphine [Captivon, 9.8 mg mL^{-1}; Wildlife Pharmaceuticals (Pty) Ltd, RSA] and thiafentanil [Thianil, 10 mg mL^{-1}; Wildlife Pharmaceuticals (Pty) Ltd] were administered intramuscularly (IM) via a remote dart injection. Each animal was darted into the gluteus muscle (X-Caliber dart gun with 1 mL P-type Pneudarts with 1.9 cm barbed needles; Pneu-Dart. Inc, PA, USA). Animals were darted on two separate occasions with a washout period of 2 weeks between them. Initially, treatments were randomly allocated with a coin toss and subsequently administered in a crossover design. Treatments included 0.09 mg kg^{-1} etorphine and 0.09 mg kg^{-1} thiafentanil, which are considered to be equipotent in this species (Janssen et al. 1993; Meyer et al. 2010; Pfitzer et al. 2019).

Following darting and as soon as they were recumbent and could be approached, impala were placed in sternal position. The head was elevated with the nose pointing ventrally to prevent the upper respiratory tract becoming obstructed by eructated and aspirated rumen contents. The animal was blindfolded and cotton wool was inserted into the ears to minimize external stimuli. The animal was loaded onto a stretcher in this position and carried to the monitoring table where it remained in this position throughout the monitoring period.

Physiological variables were recorded at 5 minutes after the animal became recumbent and then every 5 minutes until 40 minutes post recumbency. Barometric pressure was measured by the EPOC portable blood gas analyser (EPOC Blood Analysis System; Epocal, ON, Canada) and the environmental temperature was measured by the Weather^{+} Bluetooth Sensor (Oregon Scientific, OR, USA). Rectal body temperature was measured by means of a modified handheld digital thermometer [Hanna Checktemp 1; Hanna Instruments (Pty) Ltd, NE, USA]. Respiratory rate (f_R) in breaths minute^{-1} was measured manually by means of

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visual observation of chest expansions and auscultation with a stethoscope for 1 minute (Littman Classic II; 3M, MN, USA). The same stethoscope was also used to measure the heart rate (HR). Arterial blood pressure was measured by catheterizing the auricular (*Arteria auricularis*) or pedal arteries (*Arteria digitalis*) with a 21 gauge catheter (Jelco IV catheter radiopaque; Smith Medical International, UK) connected via a Deltran II pressure transducer (Utah Medical, UT, USA) to an IntraTorr blood pressure monitor (IntraTorr; IntraVitals, UK). Systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) in mmHg were recorded with this device. Arterial blood was drawn anaerobically into preheparinized blood gas syringes (BD A-Line; Becton Dickinson & Co, UK) at 5, 10, 15, 20 and 30 minutes after recumbency. Within 5 minutes of sampling, arterial blood was analysed by the EPOC portable blood gas analyser using EPOC BGEM test cards (BGEM smart cards; Epocal), and blood gases and acid-base status were determined. The alveolar-arterial oxygen (A-a) gradient was calculated as described by Meyer et al. (2010). Arterial blood pH, bicarbonate (HCO_3^-), base excess (BE), anion gap (Agap), lactate, arterial partial pressure of carbon dioxide at 37 °C ($PaCO_2$), arterial partial pressure of oxygen at 37 °C (PaO_2) and A-a gradient at 37 °C were statistically evaluated.

The immobilization of all animals was reversed with intravenous (IV) naltrexone [Trexonil, 50 mg mL^{-1}; Wildlife Pharmaceuticals (Pty) Ltd] injected at a ratio of 20 mg naltrexone to 1 mg etorphine and 10 mg naltrexone per 1 mg thiafentanil when the 40 minute measurement period was over. An assessor, unaware of the allocated treatment, scored immobilization, induction, and recovery according to previously described scales (Pfitzer et al. 2019). The induction score was based on the duration and quality of induction and ranged from 1 to 5, where a score of 1 indicated that the animal was recumbent in <5 minutes and a score of 5 indicated that the animal did not become recumbent. Immobilization quality was scored at each sampling interval by assessing the degree of central nervous system depression and movement on a scale of 1 to 5 (Pfitzer et al. 2019). A score of 1 indicated that the animal was conscious and mobile and needed to be re-dosed for safe handling, whereas a score of 5 indicated that the animal exhibited severe cardiopulmonary depression with no pedal, palpebral or corneal reflexes and thus was considered excessively immobilized. The subjective recovery score was based on the duration and ease of the recovery after the IV administration of naltrexone and ranged from 1 to 5, where 1 indicated that the animal stood within 3 minutes with no complications and 5 indicated that the animal failed to recover. Time to recumbency was defined as the time from dart injection to the time when the animal was recumbent and unable to rise.

Data analysis

Data analyses were performed with Genstat Version 19 (VSN International, UK). To determine whether there was a difference between the two opioids in the measured physiological variables, a linear mixed model, consisting of a fixed model and a random model, was fitted to the data. The effects of the two drugs on the monitored variables, the effects of time after recumbency on the monitored variables as well as interaction between treatment and time effect were included in the fixed model. Initially the variance/covariance structure of the data was modelled, including variances due to animal number, animal number by treatment and animal number by treatment by minutes after recumbency. It also included correlations between measurements made on the same animal in the same trial and allowed for different variances for each animal. Before assessing the significance of fixed effects, all nonsignificant random effects and nonsignificant covariances were removed from the random model. Treatment effects, treatment effects over time and the interaction of treatment effects and time were analysed for significant differences. A p value of less than 0.05 was considered significant. Standard errors of differences between means (SEDs), which can be used to compare main effect and interaction means, were estimated from the random model. If the difference between means is greater than the appropriate least significant difference (LSD: SED multiplied by a t value at the desired level of significance), the means can be regarded as significantly different. Due to the repeated measurements made on each animal, the size of the SEDs and LSDs are expected to be less when the means are being compared within a treatment than when they are made between treatments. Results are reported in tables of means ± standard deviation (SD) and average SEDs. In addition, treatment means at each time for measurements of most interest are reported with 5% LSDs in the figures.

Time from dart injection to recumbency between drug treatments was compared by means of one-way analysis of variance using SPSS Statistics for Windows Version 24 (IBM Corp, NY, USA) and are reported as mean ± SD. Induction, immobilization and recovery scores between drug treatments were analysed by means of Wilcoxon signed-rank test. The significance level was set at $p < 0.05$. Data are reported as median and interquartile range (IQR).

Results

Ambient temperatures measured during etorphine and thiafentanil treatments were 20.7 ± 4.3 °C and 21.9 ± 6.7 °C, respectively.

Mean time to recumbency was significantly faster with thiafentanil treatment (2.0 ± 0.8 minutes) than with etorphine treatment (3.9 ± 1.6 minutes; $p = 0.007$). There was a

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Table 1 Mean values ± standard deviations (SD) of physiological variables over time and significant error of differences (SED) measured in eight adult female impala immobilized with 0.09 mg kg^{-1} etorphine or 0.09 mg kg^{-1} thiafentanil. The significance is given as (*p* values) for main effects of treatment (averaged over time) and time (averaged over treatment) and the treatment × time interaction. Significant results ($p < 0.05$) are given in bold.

	Time after recumbency of impala in minutes							
	Group	**5**	**10**	**15**	**20**	**30**	**40**	**Means (treatment)**
HR (beats $minute^{-1}$)	Etorphine	132 ± 17	112 ± 18	100 ± 19	92 ± 18	82 ± 19	82 ± 11	
	Thiafentanil	113 ± 22	111 ± 35	107 ± 34	111 ± 41	110 ± 38	107 ± 36	
SED within treatment		*6*		*SED between treatments*		*14*		
Significance		Treatment		Time		Treatment × time		
p		0.392		< **0.001**		< **0.001**		
f_R (breaths $minute^{-1}$)	Etorphine	13 ± 12	13 ± 17	12 ±5	14 ± 31	13 ± 4	12 ± 6	
	Thiafentanil	7 ± 4	11 ± 4	13 ± 3	15 ± 6	15 ± 3	16 ± 5	
SED within treatment		*2*		*SED between treatments*		*2*		
Significance		Treatment		Time		Treatment × time		
p		0.844		< **0.001**		**0.004**		
RT (°C)	Etorphine	38.8 ± 0.7	38.9 ± 0.8	38.9 ± 0.6	38.9 ± 0.8	38.8 ± 0.8	38.5 ± 0.9	
	Thiafentanil	38.9 ± 0.6	39.0 ± 0.5	39.2 ± 0.6	39.2 ± 0.8	39.3 ± 0.6	39.2 ± 0.7	
	Means (time)	38.84*	38.98†‡	39.03‡	39.06‡	39.04‡	38.89*†	
SED within treatment		*0.1*		*SED between treatments*		*0.3*		
Significance		Treatment		Time		Treatment × time		
p		0.207		**0.023**		0.081		
SAP (mmHg)	Etorphine	149 ± 25	139 ± 15	135 ± 14	134 ± 36	142 ± 21	152 ± 14	141.9*
	Thiafentanil	179 ± 20	160 ± 19	158 ± 23	158 ± 18	159 ± 14	165 ± 11	162.1†
	Means (time)	163.9†	149.6*	146.7*	146.0*	150.4*	158.3†	
SED within treatment		*4*		*SED between treatments*		*6*		
Significance		Treatment		Time		Treatment × time		
p		**0.005**		< **0.001**		0.261		
DAP (mmHg)	Etorphine	103 ± 20	101 ± 9	99 ± 11	100 ± 24	109 ± 18	112 ± 15	104.9*
	Thiafentanil	134 ± 16	125 ± 18	123 ± 16	129 ± 16	125 ± 7	126 ± 14	126.2†
SED within treatment		*5*		*SED between treatments*		*5*		
Significance		Treatment		Time		Treatment × time		
p		< **0.001**		0.376		0.133		
MAP (mmHg)	Etorphine	120 ± 21	113 ± 11	110 ± 12	115 ± 27	125 ± 21	129 ± 14	120.0*
	Thiafentanil	151 ± 19	141 ± 16	133 ± 21	146 ± 17	141 ± 12	141 ± 10	141.1†
	Means (time)	135.3‡	126.5*†	121.9*	130.4†	132.7†‡	135.0‡	
SED within treatment		*6*		*SED between treatments*		*6*		
Significance		Treatment		Time		Treatment × time		
p		< **0.001**		**0.025**		0.059		
pH	Etorphine	7.30 ± 0.04	7.32 ± 0.03	7.34 ± 0.04	7.36 ± 0.04	7.39 ± 0.04		
	Thiafentanil	7.26 ± 0.05	7.31 ± 0.05	7.33 ± 0.05	7.35 ± 0.05	7.38 ± 0.03		
	Means (time)	7.280*	7.313†	7.332‡	7.354§	7.380¶		
SED within treatment		*0.01*		*SED between treatments*		*0.02*		

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Table 1 (*continued*)

	Time after recumbency of impala in minutes						
	Group	**5**	**10**	**15**	**20**	**30**	**40**	**Means (treatment)**
Significance *p*		Treatment 0.282		Time < **0.001**		Treatment × time 0.238		
HCO_3^- (mmol L^{-1})	Etorphine Thiafentanil	27.0 ± 3.2 29.2 ± 3.0	27.6 ± 3.5 28.0 ± 2.8	29.1 ± 3.4 27.9 ± 2.7	30.4 ± 3.0 28.1 ± 2.8	31.1 ± 2.6 30.1 ± 3.2		
SED within treatment		*0.4*		*SED between treatments*		*1.4*		
Significance *p*		Treatment 0.837		Time < **0.001**		Treatment × time < **0.001**		
BE	Etorphine Thiafentanil	1.1 ± 3.2 2.8 ± 3.1	2.0 ± 3.2 2.0 ± 3.1	3.7 ± 3.3 2.2 ± 3.0	5.3 ± 2.7 3.0 ± 3.0	7.0 ± 2.7 5.4 ± 3.4		
SED within treatment		*0.4*		*SED between treatments*		*1.0*		
Significance *p*		Treatment 0.571		Time < **0.001**		Treatment × time < **0.001**		
Agap (mmol L^{-1})	Etorphine Thiafentanil	12.8 ± 2.3 11.1 ± 2.1	13.1 ± 2.8 12.2 ± 1.5	10.7 ± 2.9 12.4 ± 1.3	10.8 ± 2.5 11.5 ± 1.5	10.6 ± 1.9 11.0 ± 2.0		
SED within treatment		*0.5*		*SED between treatments*		*1.0*		
Significance *p*>		Treatment 0.889		Time < **0.001**		Treatment × time **0.002**		
Lactate (mmol L^{-1})	Etorphine Thiafentanil Means (time)	5.2 ± 2.4 5.3 ± 1.7 5.24¶	4.3 ± 2.6 4.5 ± 2.0 4.43§	3.4 ± 2.4 3.7 ± 2.1 3.55‡	2.6 ± 2.1 3.0 ± 2.0 2.78†	1.5 ± 1.5 1.8 ± 1.4 1.66*		
SED within treatment		*0.2*		*SED between treatments*		*0.9*		
Significance *p*		Treatment 0.822		Time < **0.001**		Treatment × time 0.931		
$PaCO_2$ mmHg (kPa)	Etorphine Thiafentanil	52 ± 8 (6.9) 61 ± 10 (8.1)	50 ± 8 (6.7) 54 ± 8 (7.2)	51 ± 8 (6.8) 51 ± 8 (6.8)	50 ± 9 (6.7) 48 ± 8 (6.4)	49 ± 6 (6.5) 47± 5 (6.3)		
SED within treatment		*2 (0.2)*		*SED between treatments*		*2 (0.2)*		
Significance *p*		Treatment 0.402		Time < **0.001**		Treatment × time < **0.001**		
PaO_2 mmHg (kPa)	Etorphine Thiafentanil	45 ± 16 (6.0) 37 ± 13 (4.9)	50 ± 11 (6.7) 52 ± 11 (6.9)	50 ± 9 (6.7) 59 ± 8 (7.9)	53 ± 11 (7.1) 60 ± 8 (8.0)	59 ± 10 (7.9) 59 ± 4 (7.9)		
SED within treatment		*2 (0.3)*		*SED between treatments*		*4 (0.5)*		
Significance *p*		Treatment 0.635		Time < **0.001**		Treatment × time < **0.001**		
A-a gradient mmHg (kPa)	Etorphine Thiafentanil Means (time)	39 ± 11 (5.2) 40 ± 8 (5.3) 39.5‡	36 ± 5 (4.8) 33 ± 5 (4.4) 34.6†	34 ± 4 (4.5) 29 ± 3 (3.9) 31.4*†	32 ± 7 (4.3) 31 ± 6 (4.1) 31.1*†	28 ± 5 (3.7) 30 ± 4 (4.0) 29.2*		
SED within treatment		*2 (0.3)*		*SED between treatments*		*3 (0.4)*		
Significance *p*		Treatment 0.470		Time < **0.001**		Treatment × time 0.087		

Physiological values evaluated were heart rate (HR) in beats $minute^{-1}$, respiratory rate (f_R) in breaths $minute^{-1}$, rectal temperature (RT) in °C, systolic arterial pressure (SAP) in millimetres mercury (mmHg), diastolic arterial pressure (DAP) in mmHg, mean arterial pressure (MAP) in mmHg, arterial blood pH (pH), arterial bicarbonate (HCO_3^-)

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difference in induction scores using the Wilcoxon signed-rank test ($Z = -1.897$, $p = 0.05$). Median induction scores were 1 for both treatments; however, IQR of etorphine treatment was 0.5, whereas that of thiafentanil treatment was 0. Of the eight impala immobilized with etorphine, two were given an induction score of 2 because they repeatedly stood up after initial recumbency.

There was a significant difference in the median immobilization scores ($Z = -2.205$, $p = 0.027$); etorphine treatment (2.59; IQR 0.73) induced a better quality of immobilization than thiafentanil treatment (2.4; IQR = 0.75). However, after administration of the reversal agent naltrexone, the mean recovery scores did not differ between treatments and all animals achieved a recovery score of 1 (IQR = 0) irrespective of the treatment.

Significant treatment differences were detected for arterial blood pressure, whereas HR, f_R, blood gases and acid-base variables showed a significant treatment-by-time interaction. All physiological variables, except for DAP, changed significantly over the monitoring period irrespective of the treatment administered (Table 1).

The f_R increased over time with thiafentanil treatment (7 breath minute^{-1} at 5 minutes *versus* 16 breath minute^{-1} at 40 minutes) but was initially lower than values obtained following etorphine treatment (13 breaths minute^{-1} at 5 minutes; Table 1 & Fig. 1; $p = 0.004$). Panting was observed in one of the animals given etorphine, whilst initial apnoea of approximately 1 minute duration was observed in two animals given thiafentanil. The f_R varied widely between individual animals.

There was a significant effect of time ($p < 0.001$) as well as a treatment-by-time effect ($p < 0.001$) for HR, which was higher initially following etorphine administration and decreased within 10 minutes to HR values less than those following thiafentanil administration. The difference in HR between treatments was significant at the 30 minute time point only (etorphine: 82 beats minute^{-1} *versus* thiafentanil: 110 beats minute^{-1}). There was a large variation between animals, reflected in the large SDs (Table 1 & Fig. 1).

There were overall significant effects of treatment on arterial blood pressure, specifically SAP ($p = 0.005$), DAP ($p < 0.001$) and MAP ($p < 0.001$) (Table 1). All blood pressure values were higher with thiafentanil treatment than with etorphine treatment (Table 1 & Fig. 2). With both treatments, SAP decreased over time ($p < 0.001$), whereas MAP increased over time ($p = 0.025$). DAP did not change significantly over time (Table 1 & Fig. 2).

Mean arterial pH increased over time ($p < 0.001$) with both treatments (Table 1). Mean HCO_3^- increased over time with etorphine treatment, whereas it decreased initially and then increased after 15 minutes with thiafentanil treatment ($p < 0.001$; Table 1 & Fig. 3). The BE showed similar directions of changes to HCO_3^-; however, BE of thiafentanil-treated animals increased from 10 minutes after drug administration ($p < 0.001$; Table 1 & Fig. 3). Conversely, Agap increased with both treatments during the first 10 minutes after which it steadily decreased ($p = 0.002$; Table 1 & Fig. 3). Mean blood lactate significantly decreased over time with both treatments ($p < 0.001$; Table 1).

There was a significant treatment-by-time interaction for $PaCO_2$ ($p < 0.001$). The mean $PaCO_2$ decreased over time with both treatments [thiafentanil: 61 ± 10 to 47 ± 5 mmHg (from 8.1 to 6.3 kPa); etorphine: 52 ± 8 to 49 ± 6 mmHg (from 8.3 to 6.5 kPa); Table 1 & Fig. 4)]. A significant treatment-by-time interaction was also observed for PaO_2 ($p < 0.001$). Animals were severely hypoxaemic with both treatments. Hypoxaemia was more severe with thiafentanil at the beginning of the monitoring period with mean values of 37 ± 13 mmHg (4.9 kPa). The mean arterial PaO_2 increased with both treatments; however, over time and despite initial differences, both treatments were associated with a PaO_2 of 59 ± 4 and 59 ± 10 mmHg (7.9 kPa) at 30 minutes (Table 1 & Fig. 4).

The A-a gradient of both treatments decreased over time, irrespective of the treatment ($p < 0.001$; Table 1 & Fig. 4).

Discussion

This study demonstrates that opioids administered alone, at the doses used, are suitable for the effective immobilization of impala for a duration of 40 minutes. An important difference between the effects of the two drugs was the time to immobilization. Time to recumbency was faster with thiafentanil than with the etorphine treatment, as has been reported previously by Meyer et al. (2008).

The times to recumbency that we measured were similar to those previously recorded: less than 3 minutes in impala darted with 0.08 mg kg^{-1} thiafentanil (Janssen et al. 1993) and 4.0 ± 1.7 minutes in impala darted with 0.09 mg kg^{-1} etorphine (Pfitzer et al. 2019). When lower doses of potent opioids were used on their own for immobilization of impala, animals took considerably longer to become recumbent and sometimes had to be physically handled to enable the application of monitoring equipment (Cheney & Hattingh 1987; Janssen et al. 1993). The addition of sedatives or tranquilizers, such as medetomidine or azaperone, to thiafentanil is not reported to hasten the time to recumbency when compared to results of the current study (Meyer et al. 2008; Zeiler & Meyer 2017a).

concentration in mmol L^{-1}, arterial base excess (BE) in mmol L^{-1}, anion gap (Agap) in mmol L^{-1}, lactate in mmol L^{-1}, arterial partial pressure of carbon dioxide ($PaCO_2$) in mmHg and kilopascal (kPa), arterial pressure of oxygen (PaO_2) in mmHg and (kPa), alveolar-arterial oxygen gradient (A-a gradient) in mmHg, and (kPa). Within row, *Mean (time)* values denoted by different symbols differ significantly from each other. Within column, *Mean (treatment)* values denoted by different symbols differ significantly from each other. Means with superscripts in common are not significantly different from one another.

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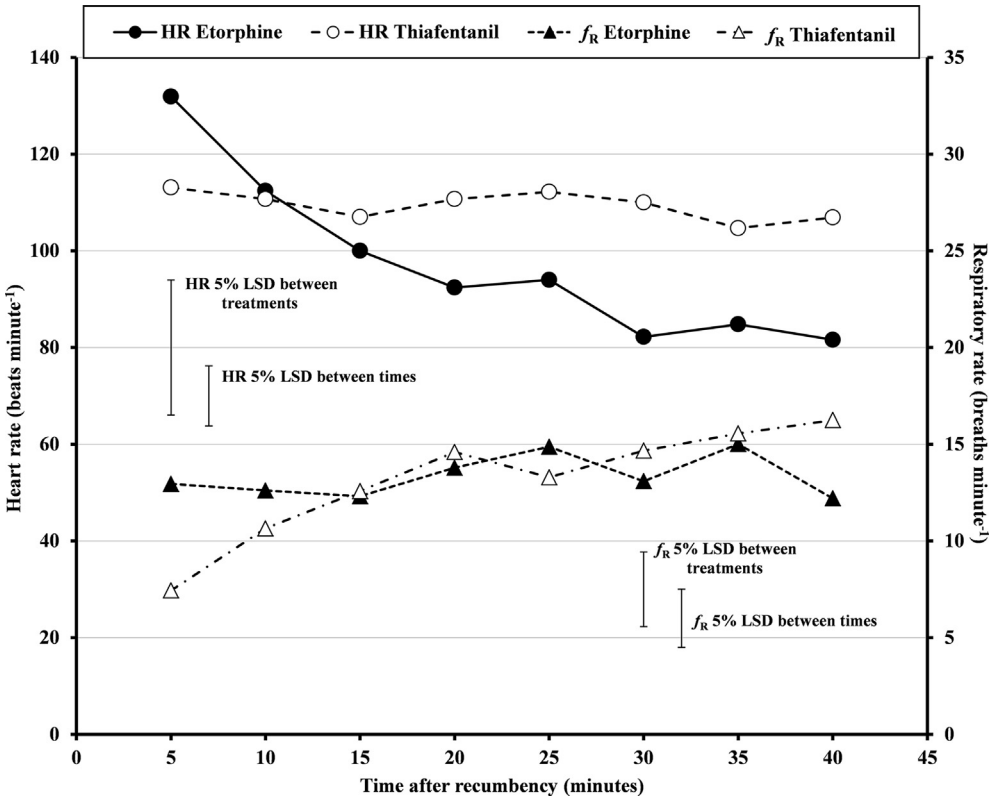

Figure 1 Effect of treatment over time on mean heart rate (HR) and mean respiratory rate (f_R) in eight female adult impala immobilized with 0.09 mg kg^{-1} etorphine and 0.09 mg kg^{-1} thiafentanil. Error bars represent the 5% least significant difference (LSD).

Rapid recumbency is desirable, especially in a field situation where impala could run long distances during the injection and effect period. This could lead to complications such as failure to capture the animal, hyperthermia, injury, predation and death (Cheney & Hattingh 1987; Janssen et al. 1993; Meyer et al. 2008; Zeiler & Meyer 2017a). At the opioid doses chosen for this study (0.09 mg kg^{-1} IM), all impala became recumbent without intervention and the time to recumbency was measured. However, distance travelled after darting was not determined as animals were inside an enclosure and in a field situation this might differ between the two opioids and depends on the degree of excitement caused. This would be an important variable to measure in future studies.

After the impala became recumbent and could be handled easily and positioned for monitoring, they showed minor infrequent movements such as chewing, tail flicking, ear twitching and sometimes limb movements. Similar movements have been observed by other authors when impala were immobilized with other drug combinations (Janssen et al. 1993; Meyer et al. 2008; Zeiler & Meyer 2017a).

The degree of apnoea caused by thiafentanil was notable; however, this initial apnoea was not reflected in the data since f_R was not recorded before the 5 minute time point. Apnoea was observed in two of the eight animals (25% prevalence) following thiafentanil administration, but it was not observed with etorphine. Thiafentanil-induced initial apnoea has also been reported by Janssen et al. (1993), Meyer et al. (2008) and Zeiler & Meyer (2017a). Rapid resolution of induction of apnoea—within 1 minute after onset and without intervention—might have resulted from the fact that no sedative or tranquillizer was added to the immobilizing mixture in this study. The administration of additional drugs potentiated ventilatory depression caused by opioids in previous studies (Meyer et al. 2008; Zeiler & Meyer 2017a).

Throughout the monitoring period, HR and arterial blood pressures varied considerably not only between the treatments but also between individual animals. Based on reference values of similar sized animals, such as sheep and goats (Prothero 2015; Izwan et al. 2018), it could be concluded that etorphine treatment produced mild hypertension (overall mean MAP = 120 ± 19 mmHg). Conversely, thiafentanil produced moderate hypertension (mean MAP = 141 ± 14 mmHg; $p < 0.001$) throughout the monitoring period, although there was a slight decrease in blood pressure over time. Similar hypertensive effects in thiafentanil-treated impala were reported by Janssen et al. (1993) and Meyer

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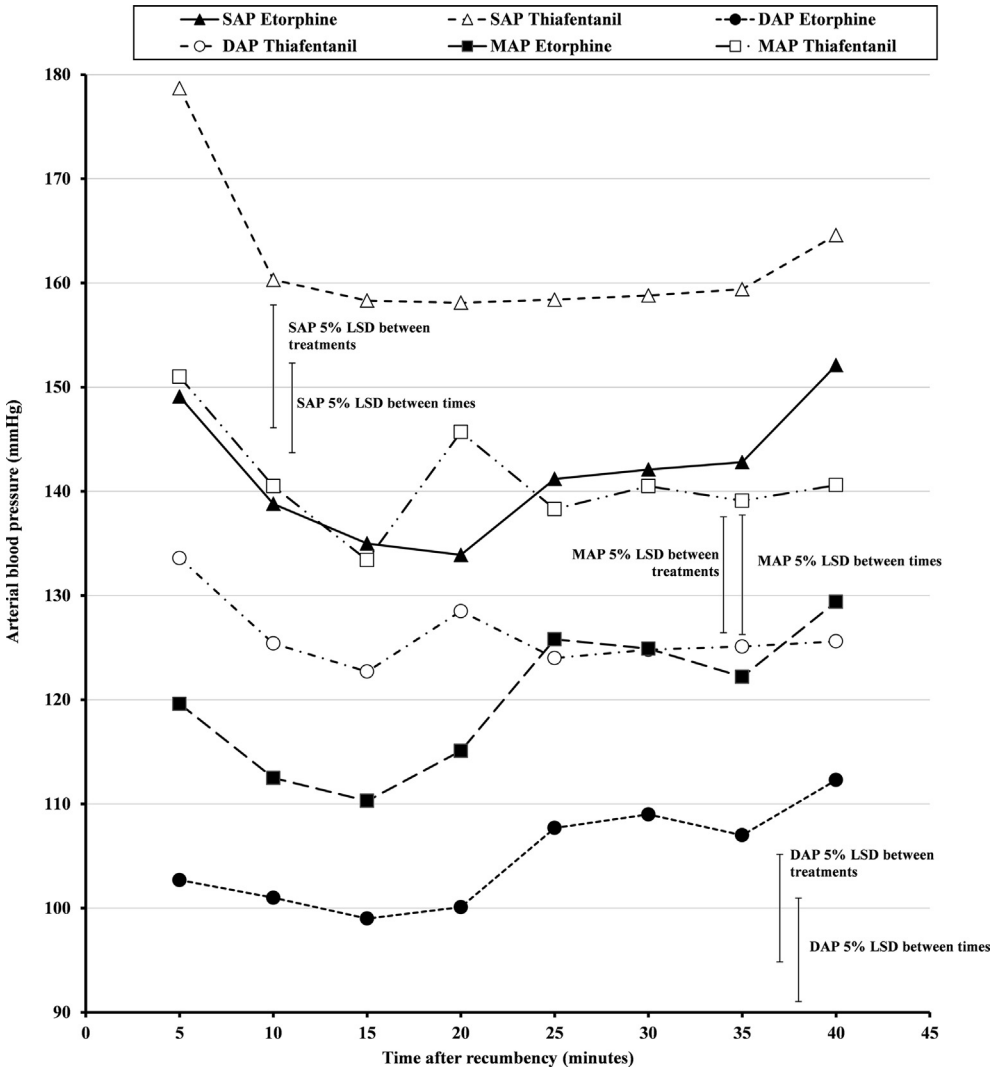

Figure 2 Effect of treatment over time on means of systolic (SAP), diastolic (DAP) and mean arterial blood pressure (MAP) in eight adult female impala after treatment with etorphine and thiafentanil. Error bars represent the 5% least significant difference (LSD). For detailed information, refer to Fig. 1 legend.

et al. (2008). Persistent tachycardia and hypertension observed in the thiafentanil-treated animals could result from sympathetic nervous system activation by various factors such as by the opioids themselves, from hypoxia or hypercapnia or it could possibly also be induced by stress from the dart impact (Heard et al. 1990; Meyer et al. 2015; Buss et al. 2016). However, the fact that there was a significant difference between thiafentanil and etorphine indicates that the hypertension in this case was most likely predominantly induced by drug rather than stress. The impala were adapted to the enclosure and human presence. The stress response to darting might be more exaggerated when non-habituated animals are darted in the field.

The normal f_R of impala at rest has been reported to be 20 ± 8 breaths minute^{-1} (Cheney & Hattingh 1987). In comparison, both drugs in the current study produced bradypnoea with mean values of f_R between 7 ± 4 and 16 ± 5 breaths minute^{-1} (Table 1 & Fig. 1). The mildly increased $PaCO_2$ values—means ranging from 49 ± 6 to 52 ± 8 mmHg (from 6.5 to 6.9 kPa) with etorphine treatment and 47 ± 5 to 61 ± 10 mmHg (from 6.3 to 8.1 kPa) with thiafentanil treatment—could indicate that the bradypnoea resulted in some alveolar hypoventilation. This condition improved within the first 15 minutes of monitoring (Fig. 4).

Animals were markedly hypoxaemic at 5 minutes after drug injection, and PaO_2 values were 37 ± 13 mmHg (4.9 kPa) and

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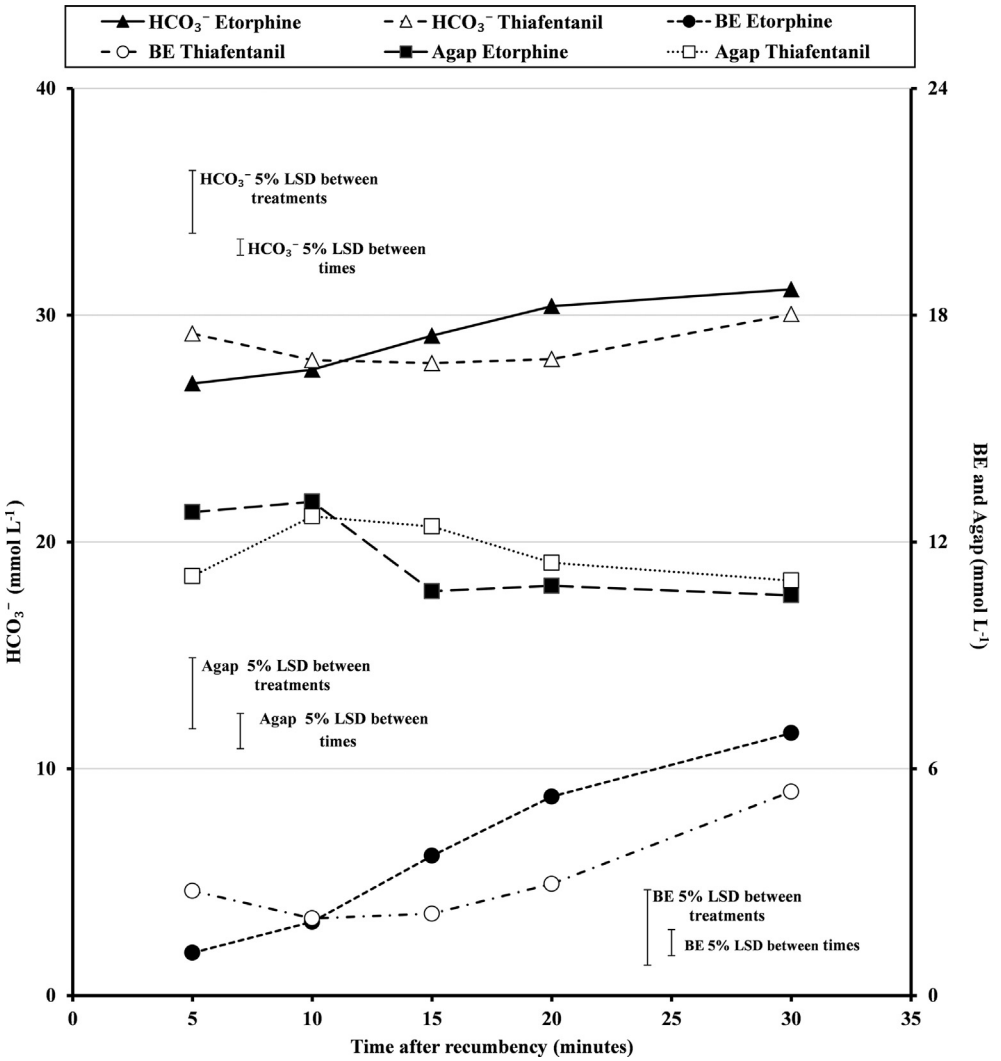

Figure 3 Effect of treatment over time on the mean values of arterial bicarbonate (HCO_3^-), base excess (BE) and anion gap (Agap) in eight adult female impala immobilized with etorphine and thiafentanil. Error bars represent the 5% least significant difference (LSD). For detailed information, refer to Fig. 1 legend.

45 ± 16 mm Hg (6.0 kPa) for thiafentanil and etorphine treatments, respectively (Table 1). This is regarded as severe hypoxaemia and may contribute to fatalities if impala cannot be given oxygen supplementation immediately or partial opioid reversal drug or both (Zeiler & Meyer 2017a,b). Although PaO_2 improved over time with both drugs, animals remained clinically hypoxic [59 ± 10 and 59 ± 4 mmHg (7.9 kPa)] at 30 minutes.

The A-a gradients of the group of impala ranged from 28 ± 5 to 40 ± 8 mmHg (3.7 to 5.3 kPa) with both treatments and were greatest at the beginning of the study. Normal A-a gradients of 21−25 mmHg (2.8−3.3 kPa) were reported in goats before opioid immobilization and increased to 33−40 mmHg (4.4−5.3 kPa) after immobilization (Meyer et al. 2006, 2015). If a normal A-a gradient is assumed, the expected PaO_2 can be calculated based on the $PaCO_2$ (Meyer et al. 2015). These large A-a gradients indicate that hypoxaemia was not caused solely by hypoventilation induced by ventilatory depression but was also the result of other disturbances that may have impeded the alveolar oxygen exchange such as a ventilation perfusion mismatch or diffusion impairment. The decrease of the A-a gradients and improvement of hypoxaemia over time suggests that ventilation as well as gas exchange improved over time.

Initially arterial pH was low (etorphine: 7.30 ± 0.04; thiafentanil: 7.26 ± 0.05), but it increased within 10 minutes to values considered normal in healthy goats [from 7.30 to 7.50; (Stevens et al. 1994)]; no data are available in impala (Table 1). $PaCO_2$ values were elevated with both drugs at 5

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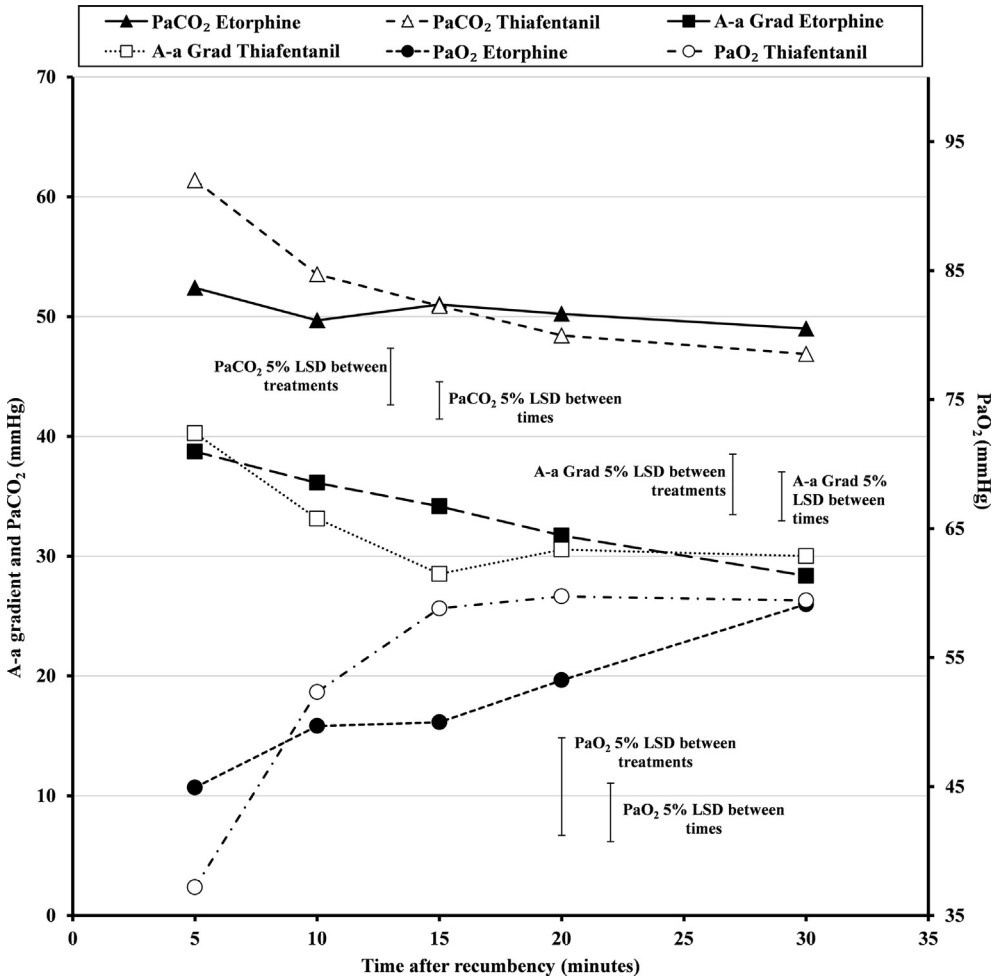

Figure 4 Effect of treatment over time on the mean values of arterial carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure (PaO_2) and alveolar-arterial oxygen gradient (A-a Grad) of eight adult female impala immobilized with etorphine and thiafentanil. Error bars represent the 5% least significant difference (LSD). For detailed information, refer to Fig. 1 legend.

minutes but decreased during the monitoring period ($p < 0.001$). Thus, the animals initially exhibited a respiratory acidosis. Normal values of HCO_3^- in ruminants range from 23 to 28 mmol L^{-1} (Muir 2015). Therefore, mean HCO_3^- levels of 29.2 ± 3.0 mmol L^{-1} for thiafentanil treatment at 5 minutes and 29.1 ± 3.4 mmol L^{-1} for etorphine treatment at 15 minutes could be considered elevated. BE appeared elevated at these times too, thus indicating possible metabolic compensation (Muir 2015). Lactate was moderately elevated (5.2 ± 2.4 and 5.3 ± 1.7 mmol L^{-1}, respectively) at the beginning of the monitoring period which might also have contributed to decreased blood pH, but lactate decreased to within normal range (<2 mmol L^{-1}) by 30 minutes (Pang & Boysen 2007).

Future studies should investigate the origin of the cardiovascular changes namely tachycardia and hypertension as a result of opioid immobilization. A better assessment of the respiratory effects of these opioid drugs should be achieved by measuring ventilation, not just f_R. Apart from depression of central respiratory centres caused by opioids, cardiovascular and metabolic changes possibly contribute significantly towards the hypoxaemia of impala during opioid immobilization (Meyer et al. 2015; Buss et al. 2018); measures of metabolism, pulmonary pressure, cardiac output and oxygen delivery should be considered. Drugs, such as sympatholytics or anxiolytics, might contribute towards improvement of blood gas values of opioid-immobilized impala and could be used in addition to potent opioids (Köhnlein &Welte 2007; Dooley 2015).

Conclusions

This study shows that etorphine and thiafentanil have different immobilization and cardiopulmonary effects. Especially in the field, where it is not always feasible to carry oxygen or give

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ventilatory support, these differences are important to consider when choosing one of these two potent opioids for the chemical immobilization of this antelope species.

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Authors' contributions

SP: study design, manuscript preparation, trial execution, data interpretation. LM and LL: study design, data interpretation, trial execution. KW: study design, manuscript preparation, funding. RV-H: study design, manuscript preparation, data interpretation, data analysis. JPR: study design, funding, data interpretation. ML: study design, data interpretation, funding, manuscript preparation, trial execution, funding, main supervisor of SP.

Conflict of interest statement

LL and JPR are affiliated with Wildlife Pharmaceuticals (Pty) Ltd. The other authors declare no conflict of interest.

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