The effects of midazolam and butorphanol, administered alone or combined, on the dose and quality of anaesthetic induction with alfaxalone in goats

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Goats are rarely anaesthetised; consequently, scant information is available on the efficacy of anaesthetic drugs in this species. Alfaxalone is a relatively new anaesthetic agent, of which the efficacy in goats has not yet been studied. In this study, the sedative and alfaxalone-sparing effects of midazolam and butorphanol, administered alone or concomitantly, in goats were assessed. Eight clinically healthy goats, four does and four wethers, were enlisted in a randomised crossover manner to receive intramuscular sedative treatments consisting of saline 0.05 mL/kg, or midazolam 0.30 mg/kg, or butorphanol 0.10 mg/kg, or a combination of midazolam 0.30 mg/kg with butorphanol 0.10 mg/kg before intravenous induction of general anaesthesia with alfaxalone. Following induction, the goats were immediately intubated and the quality of anaesthesia and basic physiological cardiorespiratory and blood-gas parameters were assessed until the goats had recovered from anaesthesia. The degree of sedation, quality of induction and recovery were scored. When compared with saline (3.00 mg/kg), midazolam, administered alone or with butorphanol, caused a statistically significant increased level of sedation and a reduction in the amount of alfaxalone required for induction (2.00 mg/kg and 1.70 mg/kg, respectively). Butorphanol alone (2.30 mg/kg) did not cause significant changes in level of sedation or alfaxalone-induction dose. During induction and recovery, the goats were calm following all treatments, including the control group. Cardiorespiratory and blood-gas parameters were maintained within clinically acceptable limits. The present study showed that midazolam, administered alone or combined with butorphanol, produces a degree of sedation that significantly reduces the dose of alfaxalone required for induction of general anaesthesia in goats, without causing any major adverse cardiorespiratory effects.

Introduction

Administration of sedatives as premedication prior to general anaesthesia is a widely accepted concept in veterinary practice (Bednarski *et al.* 2011; Dzikiti *et al.* 2009). Benefits of pre-anaesthetic sedation include reduced patient excitement during anaesthetic induction and fewer drug-related adverse effects, as lesser amounts of anaesthetic agents are required to induce and maintain general anaesthesia (Bednarski *et al.* 2011). An appropriate selection of premedication drugs can significantly improve intraoperative cardiovascular stability, perioperative analgesia and the quality of recovery from anaesthesia (Waelbers *et al.* 2009). In small ruminants, the commonly used sedatives before induction of general anaesthesia include: α_2-adrenoceptor agonists such as xylazine; phenothiazines such as acepromazine; benzodiazepines such as diazepam and midazolam; and opioids such as butorphanol (Riebold 2007). In goats, induction of general anaesthesia can be achieved by administration of ketamine, propofol or thiopentone (Dzikiti 2013; Prassinos *et al.* 2005). Recently, alfaxalone has been shown to be an alternative induction agent in: dogs (Ferré *et al.* 2006; Muir *et al.* 2008; Suarez *et al.* 2012); cats (Whittem *et al.* 2008); sheep (Andaluz *et al.* 2012); ponies (Klöppel & Leece 2011; Leece *et al.* 2009); and horses (Goodwin *et al.* 2011). However, its efficacy as an induction agent in goats has not yet been reported.

Midazolam is a water-soluble benzodiazepine that can be administered either by the intramuscular or intravenous route (Cao *et al.* 2002; Lemke 2007). It has mild cardiovascular and respiratory effects at clinical dosages and is commonly used as a mild sedative, muscle relaxant and anticonvulsant (Galatos 2011; Lemke 2007). Midazolam is reported to cause a significant reduction in the dose of propofol required for induction of anaesthesia in goats when administered intramuscularly alone and when combined with butorphanol (Dzikiti *et al.* 2009).

Butorphanol, a synthetic opioid, is an agonist at κ-opioid receptors and an antagonist at μ-opioid receptors (Carroll *et al.* 1997; Lamont & Mathews 2007; Valverde & Gunkel 2005). Opioids are

traditionally included in balanced anaesthetic protocols for their analgesic effects, but they also have species-specific sedative effects (Lemke 2007). Butorphanol has useful analgesic effects in ruminants, but it can also cause central nervous system stimulation (Carroll *et al*. 2001; Doherty, Rohrbach & Geiser 2002). Butorphanol at a dose range of 0.02 mg/kg – 0.50 mg/kg, administered intramuscularly or intravenously, increases the degree of sedation obtainable from acepromazine or benzodiazepines (Dzikiti *et al.* 2009; Riebold 2007; Valverde & Gunkel 2005). At the same time, the sedatives (benzodiazepines) help to diminish the inherent excitatory effects of butorphanol (hyperactivity, increased myoclonic activity) in goats (Carroll *et al.* 2001; Dzikiti *et al*. 2009).

Alfaxalone is a synthetic, neuroactive steroid hypnotic agent (Ferré *et al.* 2006); several research teams have recently assessed the anaesthetic and cardiorespiratory effects of it. Its pharmacokinetic and pharmacodynamic profiles make it ideal for intravenous induction and maintenance of general anaesthesia in dogs (Ambrisko *et al.* 2011; Ambros *et al.* 2008; Ferré *et al.* 2006; Jiménez *et al.* 2012; Maddern *et al.* 2010; Michou *et al.* 2012; Muir *et al.* 2008; Psatha *et al.* 2011; Rodríguez *et al.* 2012; Suarez *et al.* 2012). Alfaxalone has been reported to be a suitable anaesthetic-induction agent at a dose of 2.00 mg/kg in unsedated sheep (Andaluz *et al.* 2012, Torres *et al.* 2012), sedated dogs (Maddern *et al.* 2009; Suarez *et al.* 2012) and ponies (Klöppel & Leece 2011; Leece *et al.* 2010). Dosages of 3.47 mg/kg – 4.70 mg/kg have been reported for sedated cats (Martinez Taboada & Murison 2010; Mathis *et al.* 2012).

To the knowledge of the authors, there are currently no scientific reports on the effects of commonly used sedatives on the induction dose of alfaxalone in goats, as well as the impact of these agents on the quality of general anaesthesia arising from their use. The present study tested the null hypothesis that midazolam, alone or combined with butorphanol, does not affect the induction dose of alfaxalone *versus* the alternative hypothesis that midazolam and butorphanol affect the alfaxalone induction dose in goats.

Materials and methods

Eight clinically healthy goats, four does and four wethers, were enlisted in this prospective, blinded, randomised, crossover experimental study. The goats were exposed to four treatments, with a three-week interval between treatments. The health status of the goats was determined by a clinical examination, complete blood count and biochemical analysis (total serum protein, albumin and globulin), which were all normal. During the period of data collection, the median age of the goats was 13.5 months (12.8–15.0 months), whilst the median weight was 26.2 kg (23.4 kg – 30.2 kg).

Experimental procedure

Food and water were withheld from the goats for 16–20 h prior to anaesthesia. The goats were weighed on an electronic scale (Shekel Merav 2000 series, Shekel, Johannesburg, South Africa) just before commencement of the experimental procedure. They were placed on a custom-made sling-cum-table for easier restraint. Temperature, pulse rate and respiratory rate were determined during the clinical examination and recorded as baseline values (Table 1 and Table 2).

TABLE 1: Cardiovascular parameters and body temperature (median [interquartile range]) following pre-anaesthetic saline, midazolam butorphanol and a combination of midazolam and butorphanol before intravenous alfaxalone for induction of anaesthesia in goats.

Variable	Treatment	Baseline		30 min after sedation		Time after induction					
		Median	IQR	Median	IQR	2 min		15 min		30 min	
						Median	IQR	Median	IQR	Median	IQR
Heart rate (beats per minute)	CONTROL	79	66–82	68	63–76	108	95–116†	138	122–167†	136	108–170†
	MID	75	71–89	92	82–115	107	92–114†	129	110–140†	112	106–132†
	BUT	78	61–83	66	60–74	96	91–114†	124	111–144†	119	92–143†
	MIDBUT	71	65–81	69	58–85	92	79–107†	108	90–121†	105	93–144†
Systolic blood pressure (mmHg)	CONTROL	97	88–115	101	88–103	97	88–108	99	90–109	91	82–107
	MID	101	97–104	101	95–109	99	91–104	105	101–110	100	96–105
	BUT	104	95–121	107	101–124	98	92–102	97	89–103	99	96–106
	MIDBUT	107	100–113	89	86–94	88	73–99	95	88–104	94	86–101
Diastolic blood pressure (mmHg)	CONTROL	71	70–84	75	68–80	79	70–88	84	72–91	72	66–94
	MID	74	72–82	86	81–90	86	70–91	90	84–98	82	78–90
	BUT	72	64–93	85	76–95	75	65–84	78	67–88	74	61–87
	MIDBUT	84	78–88	71	62–76	57	53–70	78	59–88	72	69–77
Mean arterial blood pressure (mmHg)	CONTROL	85	80–92	85	80–94	88	78–97	90	79–99	78	75–99
	MID	87	85–94	92	89–98	91	79–98	96	91–102	93	86–94
	BUT	82	77–88	98	88–106	83	73–92	86	76–94	82	69–96
	MIDBUT	91	85–97	79	72–81	68	65–83	86	67–93	80	75–86
Body temperature (°C)	CONTROL	38.9	38.8–39.1	39.1	38.8–39.5	39.1	38.4–39.4	38.8	38.7–38.9	38.8	38.5–39.0
	MID	38.9	38.6–39.1	38.8	38.6–39.2	38.6	38.1–38.9	38.3	38.0–38.7	38.4	38.0–38.6
	BUT	38.9	38.8–39.0	38.9	38.7–39.2	38.9	38.4–39.2	38.6	38.1–38.8	38.6	38.0–39.1
	MIDBUT	38.9	38.6–38.9	38.7	38.5–38.9	38.6	38.2–39.0	38.1	37.6–38.3	37.9	37.7–38.2

Note: There were no statistically significant differences from control treatment value at any time point.
IQR, interquartile range; Min, minutes; CONTROL, Saline 0.05 mL/kg; MID, Midazolam 0.30 mg/kg; BUT, Butorphanol 0.10 mg/kg; MIDBUT, Midazolam 0.30 mg/kg combined with Butorphanol 0.10 mg/kg.
†, Significantly different ($p < 0.05$) from baseline reading within same treatment.

TABLE 2: Respiratory and arterial blood gas variables (median [interquartile range]) following pre-anaesthetic saline, midazolam, butorphanol and a combination of midazolam and butorphanol before intravenous alfaxalone for induction of anaesthesia in goats.

Variable	Treatment	Baseline		30 min after sedation		Time after induction					
						2 min		15 min		30 min	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Respiratory rate (breaths per min)	CONTROL	24	20–30	20	19–24	21	15–29	22	19–30	28	24–30
	MID	28	20–32	16	16–20	20	14–20	20	16–21	24	20–29
	BUT	24	20–27	22	20–24	14	12–17	20	19–20	24	19–24
	MIDBUT	26	23–30	20	18–22	13	12–20	15	12–15	22	20–26
Oxygen saturation (S_aO_2) (%)	CONTROL	96.1	95.6–96.2	95.3	94.6–96.5	91.7	89.5–93.1	-	-	94.7	94.0–95.3
	MID	96.1	95.3–96.6	95.4	94.7–96.4	90.8	89.6–91.6	-	-	95.3	93.2–96.4
	BUT	96.1	95.9–96.5	95.7	94.5–95.9	91.8	90.5–92.3	-	-	94.3	93.0–96.3
	MIDBUT	96.0	95.5–96.4	95.3	94.2–96.2	91.6	88.8–92.3	-	-	93.5	91.1–94.7
Oxygen tension (P_aO_2) (mmHg)	CONTROL	75.0	72.0–76.6	70.8	67.6–80.9	59.9	52.3–63.0	-	-	71.9	66.0–76.1
	MID	74.9	68.7–80.1	71.3	67.1–77.6	57.2	55.2–59.9	-	-	71.5	63.9–75.7
	BUT	73.6	72.9–75.7	70.5	66.6–73.8	58.0	55.5–61.2	-	-	66.9	60.5–74.3
	MIDBUT	73.8	70.6–76.3	70.7	65.9–74.4	58.1	53.3–62.2	-	-	64.0	57.8–68.6
Oxygen tension and fraction of inspired oxygen ratio (P_aO_2/F_IO_2)	CONTROL	357	343–365	336	322–385	285	249–300	-	-	342	320–363
	MID	356	327–381	340	320–369	272	263–285	-	-	340	304–361
	BUT	350	348–360	335	317–351	276	264–291	-	-	319	288–354
	MIDBUT	351	336–363	336	314–354	277	254–296	-	-	305	275–326
Carbon dioxide tension (P_aCO_2) (mmHg)	CONTROL	35.1	33.9–36.5	34.9	33.9–37.2	34.4	32.9–39.2	-	-	35.7	33.3–36.6
	MID	35.1	34.3–37.8	34.5	34.1–36.2	41.3	39.3–42.1†	-	-	37.9	34.5–42.3
	BUT	36.1	35.5–37.1	34.1	33.1–35.4	39.4†	38.8–40.7	-	-	37.0	33.1–38.2
	MIDBUT	35.4	34.5–36.6	36.8	35.4–38.4	40.7†	39.7–41.5	-	-	38.6	36.8–41.0
Hydrogen ion concentration negative logarithm (pH)	CONTROL	7.49	7.47–7.51	7.47	7.44–7.48	7.45	7.43–7.47	-	-	7.47	7.45–7.49
	MID	7.51	7.48–7.52	7.48	7.47–7.51	7.45	7.44–7.46	-	-	7.48	7.46–7.49
	BUT	7.51	7.50–7.52	7.48	7.48–7.48	7.45	7.43–7.47	-	-	7.48	7.45–7.50
	MIDBUT	7.51	7.48–7.52	7.48	7.47–7.49	7.45	7.44–7.46	-	-	7.47	7.43–7.47
Bicarbonate [HCO_3^-] (mmol/L)	CONTROL	26.1	23.9–29.1	24.6	23.3–25.7	23.9	22.1–25.1	-	-	25.1	23.8–25.8
	MID	27.7	25.4–30.1	25.4	24.2–27.7	27.3	25.8–28.1	-	-	25.8	25.0–27.9
	BUT	27.5	26.9–27.9	24.9	24.3–26.2	27.0	26.2–28.0	-	-	25.9	25.2–27.0
	MIDBUT	27.6	26.7–27.9	27.1	25.6–27.8	26.9	23.9–27.9	-	-	26.6	26.1–28.3

Note: There were no statistically significant differences from Control treatment value at any time point.
IQR, interquartile range; Min, minutes; CONTROL, Saline 0.05 mL/kg; MID, Midazolam 0.30 mg/kg; BUT, Butorphanol 0.10 mg/kg; MIDBUT, Midazolam 0.30 mg/kg combined with Butorphanol 0.10 mg/kg.
†, Significantly different ($p < 0.05$) from baseline reading within same treatment.

For measurement of arterial blood pressure and collection of arterial blood samples for analyses, a 24-gauge catheter (Jelco, Medex Medical Ltd, Rossendale, Great Britain) was percutaneously introduced into the auricular artery. The catheter was connected to a recently calibrated transducer (DTX Plus transducer, BD Medical, Johannesburg, South Africa) for measurement of systolic, diastolic and mean arterial blood pressures. For transducer calibration to atmospheric pressure, the scapulo-humeral joint or the point of the sternum were used as zero reference points in sternally-recumbent or laterally-recumbent goats, respectively. Blood pressure readings were read from an electronic strain gauge transducer connected to a multi-parameter monitor (Cardiocap/5, Datex-Ohmeda Corporation, Helsinki, Finland).

The goats were premedicated by the intramuscular route with saline (Intramed Sodium Chloride 0.9%® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) at 0.05 mL/kg (Treatment Control), or midazolam (Dormicum®, Roche Products, Isando, South Africa) at 0.30 mg/kg (Treatment MID), or butorphanol (Torbugesic®, Fort Dodge Animal Health, Fort Doge, USA) at 0.10 mg/kg (Treatment BUT), or a combination of midazolam at 0.30 mg/kg with butorphanol at 0.10 mg/kg (Treatment MIDBUT). The treatment drugs were calculated, drawn up and injected by a person other than the principal investigator, who was blinded to the treatments until the end of the data collection. This was so that the degree of sedation, the alfaxalone dose required for induction of general anaesthesia, the induction quality score and the recovery quality could be determined without bias. The degree of sedation was scored 30 min after administration of the treatments on a 0–3 scale, with 0 representing absence of apparent sedation (Table 3).

Once sedation had been assessed, an 18-gauge catheter (Jelco; Medex Medical Ltd, Rossendale, Great Britain) was introduced into the left forelimb cephalic vein for administration of alfaxalone and fluids. Thirty minutes (30 min) after administration of the treatments, alfaxalone (Alfaxalone®-CD RTU, Jurox Pty Ltd, Rutherford, Australia) was administered intravenously to induce a level of anaesthesia adequate for placement of an endotracheal tube. The main bolus dosage of alfaxalone at 1.50 mg/kg was administered using a volumetric syringe-driving pump (Perfusor® Space, B Braun Medical, Bethlehem, USA) over a 30 s period, followed by incremental boluses as required, at 0.50 mg/kg every 15 s. Depth of anaesthesia was checked by jaw tone and reflexes, immediately after administration of each intermittent bolus of alfaxalone, until the jaw was

TABLE 3: Scoring system used for sedation, induction and recovery from anaesthesia following pre-anaesthetic saline, midazolam, butorphanol and a combination of midazolam and butorphanol before intravenous alfaxalone for induction of anaesthesia in goats.

Score	Sedation	Induction	Recovery
0	No apparent sedation	Excitement, vocalizes, jumps or attempts to stand after becoming recumbent, unable to place orotracheal tube	Rough (several uncoordinated attempts to stand and ataxic)
1	Mild sedation (with head slightly lowered)	Mild signs of excitement, some struggling, may or may not be intubated within 60 s	Relatively rough (several coordinated attempts to stand and ataxic)
2	Moderate sedation (with head lowered and ataxia)	Excitement-free induction, no outward sign of excitement, tracheal intubation easy	Relatively smooth (1-2 coordinated attempts to stand with minimal short-lived ataxia)
3	Profound sedation (sternal recumbency, but may raise its head without holding it up)	Not applicable	Excitement-free (1 successful attempt to stand)

relaxed enough, and the swallowing and laryngeal reflexes, to see if they were diminished enough to allow endotracheal intubation. Placement of the endotracheal tube (silicone tube, internal diameter 7.5 mm) was performed using an illuminated laryngoscope, with the goats in sternal recumbency. Immediately after tracheal intubation, the goats were placed in right lateral recumbency and the exact total dose of alfaxalone required for induction of general anaesthesia was recorded. The quality of induction was assessed on a 0–2 score scale, with 0 representing failed intubation (Table 3).

Immediately after induction, the goats were allowed to recover from general anaesthesia, during which time they breathed room air spontaneously. Oxygen was supplemented if the goats became hypoxaemic (saturation of haemoglobin with oxygen in peripheral tissues [SpO_2] < 90%). Ringer Lactate solution (Intramed Ringer-Lactate® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) was administered intravenously using a volumetric fluid infusion pump (Infusomat® Space, B Braun Medical, Bethlehem, USA) at a rate of 4.00 mL/kg/hour, beginning from just before induction of general anaesthesia to about 30 min after induction of general anaesthesia. The endotracheal tube was removed once the goats regained a swallowing reflex. Time to extubation, sternal recumbency, standing and voluntary motion were recorded. All times were determined as the interval between the time the last amount of alfaxalone was administered and the time a particular event occurred. Quality of recovery was scored on a 0–3 score scale, with 0 representing the worst possible quality of recovery (Table 3).

Cardiopulmonary parameters including systolic, diastolic and mean arterial pressures, heart rate, respiratory rate and SpO_2, as well as body temperature, were recorded prior to and 30 min after administration of the treatments and 2 min, 15 min and 30 min after administration of alfaxalone (Tables 1 and Table 2).

Arterial blood samples for gas analyses were collected in 2 mL pre-heparinised syringes (BD A-Line, Becton™, Dickinson & Company, New Jersey, USA) prior to (baseline) and 30 min after administration of the treatments, and 2 min and 30 min after administration of alfaxalone. The syringes were sealed immediately and the samples were analysed for blood gases within 5 min. Oxygen tension (P_aO_2), carbon dioxide tension (P_aCO_2), hydrogen ion concentration negative logarithm (pH), bicarbonate ion ([HCO_3^-]) concentration and oxygen saturation (S_aO_2) were measured using a pre-calibrated blood gas analyser (Rapidlab™ 348 pH/Blood Gas and Electrolyte Analyser, Siemens Medical Solutions Diagnostics, Midrand, South Africa).

To verify respiratory status, the P_aO_2/ F_IO_2 ratio was calculated by dividing the measured arterial oxygen tension by the fraction of inspired oxygen (21% or 0.21 in the present study). During normal respiratory function this ratio is greater than 250, whilst in patients with severe respiratory failure the ratio is less than 200 (Lagutchik 2001).

Statistical analysis

Data were analysed using *Stata* statistical package (Stata® Version 12.1, StataCorp LP, Vienna, Austria). All data were assumed not to be normally distributed due to the small sample size used in the present study (eight goats per treatment) and were therefore expressed as medians and interquartile ranges. Data on alfaxalone dose for induction, scores (sedation, quality of induction and recovery from anaesthesia), and times to extubation, sternal position, standing and voluntary motion were tested for statistically significant differences amongst treatments using the Friedman rank sum test. If statistically significant differences were observed, a *post-hoc* analysis (pair-wise Wilcoxon rank sum test with a Bonferroni adjustment for multiple testing) was conducted. Repeatedly measured variables (respiratory rate, heart rate, mean arterial blood pressure, SpO_2, body temperature and blood-gas analyses data) were tested for statistically significant differences amongst and within treatments using the repeated measures analysis of variance (ANOVA) by ranks followed by *post-hoc* analysis (Tukey test). A value of $p < 0.05$ was considered to be significant.

Ethical considerations

The goats used in the present study experienced minimal discomfort. Potentially distressing or painful procedures worth noting were deprivation of food and water overnight, puncture of blood vessels for sample collection and catheterisation for administration of treatments and fluids during the experimental procedure. Puncturing of blood vessels was performed by an experienced veterinary anaesthetist so as to minimise the level of discomfort. The present study was pre-approved by both the Animal Ethics Committee and the Research Committee of the Faculty of Veterinary Science, University of Pretoria.

Results

Statistically significant differences in sedative effects were observed amongst treatments (Table 4). The level of sedation observed following the control treatment was significantly less profound than in both MID (p = 0.0002) and MIDBUT (p = 0.0002) treatments, whilst BUT treatment did not show any statistically significant difference from the control. The levels of sedation observed following MID or MIDBUT treatment were not statistically significantly different from each other.

The control dose of alfaxalone required for induction of general anaesthesia was 3.00 mg/kg (2.50 mg/kg – 3.00 mg/kg). The alfaxalone induction dose was statistically significantly higher than doses of 2.00 mg/kg (2.00 mg/kg – 2.13 mg/kg) and 1.75 mg/kg (1.5 mg/kg – 2.00 mg/kg) required following MID (p = 0.0023) and MIDBUT (p = 0.000038) treatments, respectively. An alfaxalone induction dose of 2.25 mg/kg (2.00 mg/kg – 2.52 mg/kg), which was required following BUT treatment was not significantly different from the control dose. The percentage reductions in the dose of alfaxalone required for induction of general anaesthesia following MID and MIDBUT treatments were 33.3% and 41.8%, respectively and were statistically significant, whilst BUT treatment caused a statistically insignificant reduction of 24.9% (Table 4 and Figure 1). The alfaxalone induction doses observed following MID or MIDBUT treatment were not statistically significantly different from each other.

Of the cardiovascular variables assessed, statistically significant differences were observed only in heart rate, which was higher than the baseline reading from within the same treatment group across all treatments, including the control, from 2 min of induction of general anaesthesia onwards (Table 1).

Respiratory and arterial blood gas variables showed very few statistically significant differences (Table 2). Statistically significant increases in P_aCO_2 were observed 2 min following induction of general anaesthesia within all treatment groups except Control. The P_aO_2/F_IO_2 ratio stayed above 250 with all treatments throughout the period of blood gas assessment.

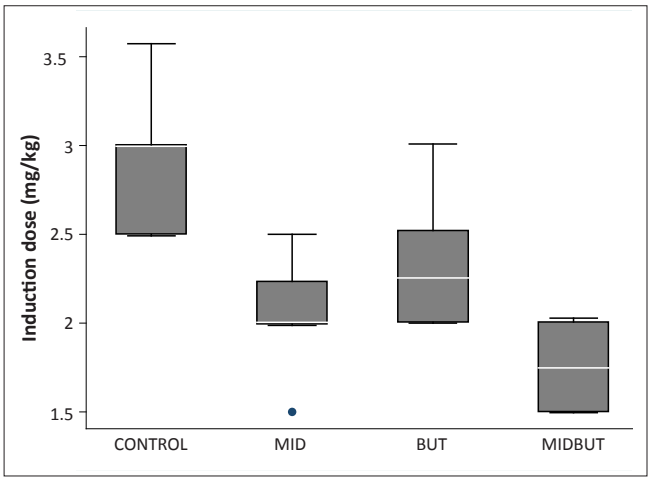
The goats recovered calmly from general anaesthesia following all treatments. Times to extubation and sternal position were statistically significantly longer than the Control equivalents (p = 0.003 and 0.002, respectively) only for MIDBUT treatment. The time taken to attain standing position did not show any statistically significant differences amongst treatments and ranged from 17.5–32.5 min following BUT treatment and both MID and MIDBUT treatments, respectively (Table 4).

Adverse effects observed following induction of anaesthesia with alfaxalone included: frequent bloat of varying degrees; some increased muscle activity in the form of brisk palpebral movements and nystagmus; and muscle twitches and

TABLE 4: Effects of pre-anaesthetic saline, midazolam, butorphanol and a combination of midazolam and butorphanol on intravenous alfaxalone induction dose, degree of sedation and quality of induction and recovery from anaesthesia in goats.

Treatment	Variable																	
	Induction dose Propofol in (mg/kg)		Reduction (%) in induction dose	Sedation score		Induction score		Extubation time (minutes)		Sternal position time (minutes)		Standing time (minutes)		Voluntary motion time (minutes)		Recovery score	
	Median	Range		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
CONTROL	3.00	2.50-3.00	0.00	0.00	0.00–0.00	2.00	2.00–2.00	6.50	4.75–8.25	10.50	10.00–11.25	27.50	22.25–30.00	30.00	27.75–30.00	3.00	2.75–3.00
MID	2.00	2.00–2.13*	33.33	2.00	2.00–3.00*	2.00	2.00–2.00	9.00	6.00–10.50	12.00	10.75–15.25	32.50	24.00–40.50	34.00	25.00–45.00	3.00	3.00–3.00
BUT	2.25	2.00–2.52	24.93	0.00	0.00–0.25	2.00	2.00–2.00	7.00	6.50–7.50	8.50	7.75–11.75	17.50	11.75–25.00	21.00	13.75–26.00	3.00	2.75–3.00
MIDBUT	1.75	1.50–2.00*	41.77	2.00	2.00–2.25*	2.00	2.00–2.00	13.00	10.00–16.00*	20.00	15.00–24.75*	32.50	28.50–39.25	32.50	28.50–40.50	2.50	2.00–3.00
Significance		†	†		†	NS		†		†		†		†		NS	

Note: Values are recorded as median (interquartile range).
IQR, interquartile range; CONTROL, Saline 0.05 mL/kg; MID, Midazolam 0.30 mg/kg; BUT, Butorphanol 0.10 mg/kg; MIDBUT, Midazolam 0.30 mg/kg combined with Butorphanol 0.10 mg/kg; NS, No significant differences amongst the four treatments.
*, Significantly different (p < 0.05) from Control treatment.
†, Significant differences (p < 0.05) amongst the 4 treatments.



Note: MID and MIDBUT are statistically significantly lower than Control.
CONTROL, Saline 0.05 mL/kg; MID, Midazolam 0.30 mg/kg; BUT, Butorphanol 0.10 mg/kg; MIDBUT, Midazolam 0.30 mg/kg combined with Butorphanol 0.10 mg/kg.

FIGURE 1: Box plot of the dose of alfaxalone (median [interquartile range]) following pre-anaesthetic saline, midazolam, butorphanol and a combination of midazolam and butorphanol before intravenous alfaxalone for induction of anaesthesia in goats.

spasms, involving mostly muscles of the face, neck and upper forelimb. The observed increased muscle activity in a select group of muscles did not seem to be associated with gross purposeful movement of any body parts or depth of anaesthesia.

Discussion

Alfaxalone produced anaesthesia of good quality, which was characterised by calm inductions and recoveries in premedicated or un-premedicated goats. Midazolam, in concurrence with earlier studies (Dzikiti *et al.* 2009; Stegmann & Bester 2001), proved to be an effective sedative in goats. Midazolam, alone or combined with butorphanol, significantly reduced the dose of alfaxalone required for induction of general anaesthesia without causing clinically significant adverse effects, whilst butorphanol premedication alone did not cause any alteration in alfaxalone dose compared with the control treatment.

Midazolam, administered alone or with butorphanol at dosages used in the present study, caused moderate to profound sedation, which was significantly different from that observed following administration of either saline or butorphanol alone. Midazolam has been previously reported to cause profound sedation in goats (Dzikiti *et al.* 2009; Stegmann & Bester 2001). Butorphanol alone, as with saline, caused no apparent sedation in goats, in agreement with observations reported in earlier studies (Dzikiti *et al.* 2009). The sedative effects of butorphanol can be unpredictable and erratic (Carroll *et al.* 2001; Dzikiti *et al.* 2009), confirming the observations of the present study. Butorphanol does not seem to improve the level of sedation obtainable from midazolam alone, as no differences were observed in the level of sedation when the two were co-administered in comparison with midazolam alone. Butorphanol has been suspected to stimulate the central nervous system in goats, with effects such as restlessness and abnormal vocalisation cited (Carroll *et al.* 2001; Galatos 2011; Doherty *et al.* 2002). These excitatory effects were not observed in the present study.

The observed alfaxalone induction doses (1.75 mg/kg – 3.00 mg/kg) are similar to those reported in earlier studies in other species such as: sheep (Andaluz *et al.* 2012; Torres *et al.* 2012); dogs (Maddern *et al.* 2010; Suarez *et al.* 2012); and ponies (Klöppel & Leece 2011; Leece *et al.* 2009), but lower than doses reported in cats (Martinez Taboada & Murison 2010; Mathis *et al.* 2012). The reason for the lack of agreement in alfaxalone dose could be the difference in the rate at which alfaxalone was administered. Administration of intravenous anaesthetic drugs for induction at slower rates significantly reduced the total dose required in humans (Berthoud *et al.* 1993; Peacock *et al.* 1990) and dogs (Dugdale *et al.* 2005). If the rate of administration is too rapid, there is a tendency to over-estimate the induction dose (Dugdale *et al.* 2005). Another factor that can influence the total dose required for induction is cardiac output (Dugdale *et al.* 2005); which was not measured in the present study.

The reductions in the dose of alfaxalone required for induction, especially following administration of midazolam alone or combined with butorphanol, demonstrate that midazolam-based premedication regimens can be used to supplement alfaxalone anaesthesia in goats, thereby reducing the dose of alfaxalone required to maintain general anaesthesia. The role of butorphanol in clinical settings would be to provide analgesia, especially for minor noxious procedures. The extent of reduction of the alfaxalone induction dose observed in the present study following MID, BUT and MIDBUT treatment of 33.3%, 24.9% and 41.8%, respectively, closely resemble those observed in an earlier study of 39.7%, 22.1% and 38.1% for propofol induction dose reduction following administration of the same premedication drugs at the same dosages in goats (Dzikiti *et al.* 2009). This observation demonstrates that midazolam and butorphanol reduce the amount of propofol or alfaxalone required for induction of general anaesthesia in a similar way in the goat. Pre-anaesthetic medication of goats with midazolam, alone or combined with butorphanol, clearly has an important role in balanced anaesthetic regimens in which alfaxalone or propofol is the induction agent.

During induction of general anaesthesia the goats were calm, irrespective of the sedation regimen used in the present study. This demonstrates that alfaxalone causes excitement-free induction in goats, even without prior calming of the goats by sedatives. This is similar to what has been reported for propofol, a closely related induction agent (Bettschart-Wolfensberger *et al.* 2000; Dzikiti *et al.* 2009; Pablo *et al.* 1997; Prassinos *et al.* 2005).

The statistically significant increase in heart rate observed following administration of alfaxalone – a common finding following all treatments in the present study – cannot be explained easily from the basic cardiovascular parameters measured, as the blood pressure did not change much

during the same period. Had the other determinants of mean arterial blood pressure, namely cardiac output and peripheral vascular resistance, been measured, it may have been possible to explain the reason for the increase in heart rate observed in the present study. The increase in heart rate, accompanied by hardly any changes in blood pressure, mirror observations previously reported in sheep following alfaxalone administration (Andaluz *et al.* 2012). Change of body position to lateral recumbency was presumed to be the reason for the increase in heart rate in sheep by Andaluz's research team. Alfaxalone appears not to cause clinically significant alterations in cardiovascular function based on observations from the present study, notwithstanding the increase in heart rate.

Respiratory and blood gas parameters were largely unaffected by the alfaxalone and midazolam or butorphanol administered for premedication. The statistically significant increase in P_aCO_2 observed in all three treatments was not clinically significant, as the values still remained below the 45 mmHg upper limit. Further confirmation of unaffected respiratory function is obtained from the P_aO_2/F_IO_2 ratio, which remained higher than 250 throughout the anaesthetic period. Patients with compromised respiratory function have P_aO_2/F_IO_2 ratios below 200 (Lagutchik 2001). In sheep, alfaxalone causes minimal respiratory changes, but induction apnoea and bradypnoea have been reported in dogs (Muir *et al.* 2008; Whittem *et al.* 2008).

Recovery from general anaesthesia was excitement-free following all treatments and the goats were able to attain standing position within 30 min of induction, as has been previously reported for propofol in goats (Dzikiti *et al.* 2009).

The adverse effects observed in the present study have been previously reported following administration of alfaxalone in other species. Bloat is known to occur in laterally recumbent goats despite prior starvation (Dzikiti 2013; Galatos 2011; Taylor 1991). Brisk palpebral movements and nystagmus have been reported in horses (Goodwin *et al.* 2011). Referred muscle movements have previously been reported in anaesthetised goats and other species, even with other induction agents such as propofol and thiopentone (Benson & Thurmon 1990; Dzikiti *et al.* 2009; Mathis *et al.* 2012).

Conclusion

The present study demonstrates that midazolam alone, or combined with butorphanol, is an effective sedative. It also demonstrates that alfaxalone, with or without midazolam and/or butorphanol, produces good-quality anaesthesia, characterised by calmness during induction and recovery, without causing major clinically significant adverse cardiorespiratory effects in goats. The dose of alfaxalone required for induction of general anaesthesia was profoundly reduced by sedation with midazolam-based regimens, but only slightly and not significantly reduced by butorphanol administered alone. This alfaxalone-sparing effect of midazolam alone or combined with butorphanol should be borne in mind when alfaxalone is used for induction of anaesthesia in goats in clinical settings.

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Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.

Authors' contributions

T.B.D. (University of Pretoria) was responsible for designing the study and writing the manuscript; G.E.Z. (University of Pretoria) assisted during data collection and in writing of the manuscript; L.N.D. (University of Pretoria) performed the statistical analysis of the data; E.R.G. (University of Pretoria) was involved in study design and writing the manuscript.

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