RESEARCH PAPER

The minimum infusion rate of alfaxalone during its co-administration with lidocaine at three different doses by constant rate infusion in goats

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Abstract

Objective: To determine the minimum infusion rate (MIR) of alfaxalone required to prevent purposeful movement in response to standardized stimulation while co-administered with lidocaine at three different doses by constant infusion rate infusion (CRI) in goats.

Study design: Prospective, blinded, randomized crossover, experimental.

Animals: Eight healthy goats; four does and four wethers.

Methods: Anaesthestic induction was with lidocaine at 1 mg kg^{-1} (L-Lid), 2 mg kg^{-1} (M-Lid) or 4 mg kg^{-1} (H-Lid) and alfaxalone at 2 mg kg^{-1}. Anaesthetic maintenance was with alfaxalone initially at 9.6 mg kg^{-1} $hour^{-1}$ combined with one of three lidocaine treatments - 3 mg kg^{-1} $hour^{-1}$ (L-Lid), 6 mg kg^{-1} $hour^{-1}$ (M-Lid) or 12 mg kg^{-1} $hour^{-1}$ (H-Lid). The MIR of alfaxalone was determined by testing for responses to a stimulation in the form of clamping on a digit with a Vulsellum forceps every 30 minutes during lidocaine CRI. Basic cardiopulmonary parameters were measured.

Results: The alfaxalone MIRs were 8.64 (6.72-10.56), 6.72 (6.72-8.64) 6.72 (6.72-6.72) mg kg^{-1} $hour^{-1}$ during L-Lid, M-Lid and H-Lid, respectively, without any significant differences among treatments. Compared to the initial rate of 9.6 mg kg^{-1} $hour^{-1}$, these reductions in MIR are equivalent to 10%, 30% and 30%, respectively. Significant increases in heart rate (HR) and arterial carbon dioxide partial pressure ($PaCO_2$) and decreases in arterial haemoglobin saturation (SaO_2), arterial oxygen partial pressure (PaO_2) and respiratory frequency (f_R) immediately after induction were observed during all lidocaine treatments.

Conclusions and clinical relevance: Lidocaine reduces the alfaxalone MIR by up to 30% with a tendency towards a plateauing in this effect at high CRIs. Immediate oxygen supplementation might be required to prevent hypoxaemia.

Keywords alfaxalone, goats, intravenous anaesthesia, minimum infusion rate, lidocaine

Introduction

Successful use of the techniques of total or partial intravenous anaesthesia (TIVA) using various alfaxalone- or propofol-based drug combinations has been reported extensively in recent times in goats (Dzikiti et al. 2010; Dzikiti et al. 2011; Ndawana et al. 2015; Dzikiti et al. 2015; Dzikiti et al. 2016; Ferreira et al. 2016). In comparison to inhalation anaesthesia, TIVA causes minimal depression of cardiopulmonary function during maintenance of general anaesthesia (Enderle et al. 2008).

Sear & Prys-Roberts (1979) defined MIR as the lowest infusion rate of an intravenous (IV) anaesthetic agent that prevents purposeful responses to a supramaximal painful stimulus in 50% of study subjects. It is comparable to minimum alveolar concentration (MAC) - defined as the minimum steady-state alveolar concentration of an inhalation anaesthetic required to prevent gross purposeful movement to a noxious stimulus in 50% of subjects (Merkel & Egger 1963).

The synthetic neuroactive steroid, alfaxalone, produces anaesthesia and muscle relaxation through modulation of gamma aminobutyric acid (GABA) type A receptors in the central nervous system (Ferré et al. 2006; Muir et al. 2008; O'Hagan et al. 2012a). Alfaxalone has been used for induction or maintenance of general anaesthesia in various species including dogs, cats, horses, rabbits and goats (Grint et al. 2008; Amengual et al. 2012; Keates et al. 2012; O'Hagan et al. 2012b; Suarez et al. 2012; Ndawana et al. 2015; Dzikiti et al. 2015; Dzikiti et al. 2016). In a previous study, the MIR of alfaxalone was determined to be 9.6 (8.4-10.8) mg kg^{-1} $hour^{-1}$ (Ndawana et al. 2015). Its TIVA-desirable characteristics include a wide safety

margin, lack of accumulation with repeated dosing, good muscle relaxation, minimal cardiorespiratory depression and a rapid recovery (Ferré et al. 2006; Muir et al. 2008). Midazolam and fentanyl significantly reduce alfaxalone requirements for maintenance of general anaesthesia without severely compromising vital cardiopulmonary function in goats (Dzikiti et al. 2015; Dzikiti et al. 2016).

Lidocaine, a local anaesthetic of the amide group, can be used systemically for treatment of ventricular tachycardia, as an analgesic, anti-inflammatory, anti-endotoxic or prokinetic agent (Feary et al. 2005; Bettschart-Wolfensberger & Larenza 2007; Enderle et al. 2008; Dzikiti 2013). Lidocaine has a short half-life and, hence, should be administered as a constant rate infusion (CRI) to achieve effective plasma concentrations for systemic analgesia. A loading bolus followed by a CRI is the recommended administration technique (Bettschart-Wolfensberger & Larenza 2007; Ringer et al. 2007). Lidocaine can be an adjuvant during maintenance of anaesthesia in various species including humans, dogs, horses and ponies (Doherty et al. 2008; Dzikiti et al. 2003; Muir et al. 2003; Steagall et al. 2006; Altermatt et al. 2012). In a study by Muir et al. (2003), lidocaine reduced halothane and enflurane MAC in dogs by 10 to 37% in a dose-dependent manner. Steagall et al. (2006), reported a reduction of expired isoflurane concentration by 34 to 44% in dogs during concurrent lidocaine administration. The mechanism by which lidocaine reduces MAC of inhalation anaesthetics agents however remains unknown, but could be due to its anti-nociceptive effects (Altermatt et al. 2012).

The present study determined the MIR of alfaxalone during its co-administration with lidocaine. If lidocaine has alfaxalone-sparing effects, it may be

used clinically to facilitate use of alfaxalone at lower dosages which tend to be associated with less adverse effects.

Materials and Methods

The study was prospectively approved by the institutional Research Committee and Animal Ethics Committee (Protocols V028/13 and V044/12). It was performed at a site 1 252 metres above sea level with a barometric pressure ranging from 651-668 mmHg (86.8-89.1 kPa). Eight adult, healthy, indigenous African goats (four does and four wethers) were used. The goats were housed in a semi-roofed enclosure at the teaching Animal Unit and were fed restricted amounts of commercial ruminant concentrate feed, while lucerne, hay and water were provided *ad libitum*. A *priori* calculation indicated that a sample size of at least 8 was required to detect a change in baseline alfaxalone MIR (9.6 mg kg^{-1} $hour^{-1}$) by at least 20% to a confidence level 95% assuming a standard deviation of 1.2 mg kg^{-1} $hour^{-1}$. Using a table of random numbers, the goats were assigned, in a cross-over pattern with a 1-month interval between treatments, to three treatments in which alfaxalone CRI was combined with a CRI of low dose lidocaine (L-Lid), moderate dose lidocaine (M-Lid) and high dose lidocaine (H-Lid) for induction and maintenance of general anaesthesia.

Preparation

Food and water were withheld from the goats for 18-24 hours before the experiment. The goats were weighed on an electronic scale (Shekel Merav 2000 series; South Africa) before commencement of the experiment. Pre-induction (baseline) rectal

temperature, respiratory rate (f_R) and heart rate (HR) were measured. A 24-gauge catheter (Jelco, Smiths Medical International, UK) was then introduced into the auricular artery percutaneously to facilitate measurement of arterial blood pressures [systolic (SAP), diastolic (DAP) and mean (MAP)] and collection of arterial blood samples for gas analyses. Into each cephalic vein, a 20-gauge catheter (Jelco, Smiths Medical International, UK) was introduced for administration of alfaxalone, lidocaine and IV fluids. Electrocardiographic (ECG) electrodes were placed on clipped areas on the middle of left shoulder, the midline (2 cm in front of the manubrium of the sternum), and the midline (2 cm cranial to the xiphoid process of the sternum) to provide an ECG tracing.

General anaesthesia and MIR determination

An initial IV loading bolus of lidocaine at a dose of 1 mg kg^{-1}, 2 mg kg^{-1} or 4 mg kg^{-1} over a 10-minute period using a volumetric syringe-driving pump (Perfusor Space; B. Braun Medical, Germany) for treatments L-Lid, M-Lid and H-Lid respectively, was administered via the right cephalic catheter. This was followed by an IV induction bolus of alfaxalone at 2 mg kg^{-1} over a 30-second period followed by incremental doses of 0.5 mg kg^{-1} over 15 seconds, if necessary, until adequate anaesthesia allowing endotracheal intubation was achieved. Calculation, drawing up and infusion of lidocaine dosages, was done by a person other than the 'blinded' principal investigator responsible for alfaxalone MIR determination later on. An endotracheal tube (silicone, internal diameter 7.5 mm) with an inflatable cuff was inserted into the trachea with the aid of an illuminated laryngoscope, while the goats were restrained into sternal recumbency. The endotracheal tube cuff was

immediately inflated to ensure an air-tight breathing circuit. The goats were placed in right lateral recumbency and allowed to breathe spontaneously. Quality of induction was assessed on a 0-2 score scale with zero representing failed intubation (Table 1).

Table 1 The scoring system used for quality of induction of and recovery from anaesthesia in goats

Score	Induction	Recovery
0	Excitement, vocalizes, jumps or attempts to stand after becoming recumbent, unable to place the orotracheal tube	Rough (several uncoordinated attempts to stand and ataxic)
1	Mild signs of excitement, some struggling, may or may not be intubated within 60 seconds	Relatively rough (several coordinated attempts to stand and ataxic)
2	Excitement-free induction, no outward sign of excitement, tracheal intubation easy	Relatively calm (1-2 coordinated attempts to stand with minimal short-lived ataxia)
3	-	Excitement-free (1 successful attempt to stand)

Immediately following administration of alfaxalone for induction, continuous IV infusions of alfaxalone and lidocaine were initiated for maintenance of anaesthesia. Alfaxalone was infused through the left forelimb catheter, using a volumetric syringe-driving pump initially at 9.6 mg kg^{-1} $hour^{-1}$ (baseline MIR determined in an earlier study by Ndawana et al. 2015). Lidocaine was administered through the right cephalic catheter at a dose of 3 mg kg^{-1} $hour^{-1}$, 6 mg kg^{-1} $hour^{-1}$, or 12 mg kg^{-1} $hour^{-1}$ using a volumetric syringe-driving pump for treatments L-Lid, M-Lid and H-Lid respectively. Lactated Ringer's solution (Intramed Ringers Lactate Solution; Kyron, South Africa) was administered at a rate of 4 mL kg^{-1} $hour^{-1}$ through the right cephalic catheter.

The goats were allowed to breathe spontaneously without any oxygen supplementation during the first 2 minutes of general anaesthesia so that the impact of the induction regimens on respiratory function could be assessed. Two minutes after induction of general anaesthesia, the goats were connected to a circle breathing circuit (Anaesthesia Systems, Clinicare; Crest Health Technology, UK) with oxygen flow set at 0.5 L $minute^{-1}$ while still breathing spontaneously.

Determination of alfaxalone MIR involved application of a standardized noxious stimulus entailing clamping a Vulsellum forceps on the soft proximal part of the hoof incorporating the distal phalanx and the bulb of the hoof for 60 seconds or until occurrence of purposeful movement of the extremities. Purposeful movement was defined as gross movement of the trunk, head or limbs. Non-purposeful movements such as twitching of the limbs, shivering, stiffening and respiratory pattern changes were ignored. Digit clamping was done in a clockwise manner around the goat's four digits on the two uppermost (left) limbs starting with the

medial digit of the left forelimb. In the absence of purposeful movement, the alfaxalone infusion rate was reduced by 1.9 mg kg^{-1} $hour^{-1}$ and held constant for another 30 minutes before application of a subsequent noxious stimulus. This was repeated until a purposeful response occurred. In the event of observation of initial purposeful movement, the alfaxalone infusion rate adjustments were performed in a reverse manner. Alfaxalone MIR during lidocaine treatments was calculated as the arithmetic mean of the alfaxalone infusion rates that allowed and abolished purposeful movement.

Following MIR determination, alfaxalone and lidocaine infusions were discontinued, and the goats disconnected from the circle breathing circuit. The monitoring instruments were detached, and the goats placed on a soft surface and assisted into sternal recumbency as they recovered from general anaesthesia. The endotracheal tube was removed after the goats regained the swallowing reflex. Times to extubation, assisted sternal recumbency, standing and voluntary motion were recorded. All times were determined as the interval between termination of alfaxalone and lidocaine administration and the time a particular event happened. Quality of recovery was assessed on a 0-3 score scale with zero representing the worst possible quality of recovery (Table 1).

Physiological parameter measurement

A multi-parameter monitor (Cardiocap/5; Datex-Ohmeda Corporation) was set up for measurement of basic physiological parameters throughout the period of general anaesthesia. Arterial blood pressures (SAP, DAP and MAP) were measured directly from the arterial catheter via a calibrated strain gauge transducer (DTX Plus

transducer; BD Medical, South Africa). The scapulo-humeral joint and the point of the sternum were used as zero reference points in sternally and laterally recumbent goats, respectively. Peripheral haemoglobin oxygen saturation (SpO_2) was measured using a pulse oximeter whose probe was placed on the tongue. Respiratory gases were sampled from a connector placed between the endotracheal tube and the Y-piece of the breathing system and inspired and expired carbon dioxide and oxygen concentrations were measured. The respiratory rate was obtained from the capnogram.

The oesophageal temperature was measured by a probe placed as close to the base of the heart as possible. Oesophageal temperature was targeted to be maintained between 37.0 and 39.5˚C using a warm air blanket (Bair Hugger Model 505; Augustine Medical Incorporated, MN, USA) and ordinary blankets.

Physiological parameters including HR, SAP, DAP, MAP, f_R and body temperature were recorded prior to induction of general anaesthesia (baseline value). These variables were also measured at 2 and 10 minutes after induction of anaesthesia and then at 10-minute intervals thereafter.

Arterial blood samples for gas analysis were collected in 2 mL heparinized syringes (BD A-Line; Becton Dickinson & Company, UK) prior to induction of general anaesthesia (baseline), and at 2, 10 and 30 minutes after induction of general anaesthesia. The samples were analysed for oxygen tension (PaO_2), carbon dioxide tension ($PaCO_2$), and hydrogen ion concentration negative logarithm (pH_a), bicarbonate ion concentration ($[HCO_3^-]$) and oxygen haemoglobin saturation (SaO_2) using a pre-calibrated blood gas analyser (Rapidlab 348 pH/Blood Gas and

Electrolyte Analyser; Siemens Medial Solutions Diagnostics, Germany) within five minutes of collection.

Statistical analyses

All statistical analyses were performed using the R statistical program (The R Foundation for Statistical Computing, Austria). All data were assumed to be non-normally distributed due to the small sample size.

Non-repeated measures (alfaxalone induction dose, alfaxalone MIR in response to lidocaine treatment, length of time to determination of MIR, induction score, recovery score as well as the times to extubation, attainment of assisted sternal recumbency, standing and voluntary motion) were compared among treatments using the Friedman rank sum test. If statistically significant differences were observed, a post-hoc analysis (pair-wise Wilcoxon signed rank test with a Bonferroni adjustment for multiple testing) was conducted. Data on repeatedly measured parameters (HR, SAP, DAP, MAP, body temperature and f_R) and arterial blood gas parameters (SaO_2, PaO_2, $PaCO_2$, $[HCO_3^-]$ and pH_a) were tested for statistically significant differences within and among treatments using repeated measures analysis of variance (ANOVA). If statistically significant differences were observed, a post-hoc analysis (pair-wise Tukey multiple comparisons test) was conducted.

A value of $p < 0.05$ was considered significant. Results are expressed as median (range).

Results

At the beginning of the study, the median (range) age of the goats was 30 (27−32) months and the weight was 32 (29−33) kg.

The alfaxalone anaesthetic induction dose was 2.5 (2.0−2.5) mg kg^{-1} for all three treatments. Additional boluses were required to achieve adequate induction above the initial bolus of 2 mg kg^{-1} in four, four and six goats during L-Lid, M-Lid and H-Lid treatments, respectively. No outward signs of excitement were observed during induction of anaesthesia for all treatments and tracheal intubation was considered easy, with scores of 2 (2−2) observed for all treatments.

The MIRs of alfaxalone were 8.64 (6.72−10.56) mg kg^{-1} $hour^{-1}$, 6.72 (6.72−8.64) mg kg^{-1} $hour^{-1}$ and 6.72 (6.72−6.72) mg kg^{-1} $hour^{-1}$ during L-Lid, M-Lid and H-Lid treatments respectively. There were no statistically significant differences in observed alfaxalone MIRs among the treatments. These reductions in MIR from the initial rate of 9.6 mg kg^{-1} $hour^{-1}$ are equivalent to 10%, 30% and 30% during L-Lid, M-Lid and H-Lid, respectively. The lengths of time required to determine MIR was 60 (60−90) minutes, 90 (60−90) and 90 (90−90) minutes for L-Lid, M-Lid and H-Lid treatments respectively, without any statistically significant differences among treatments.

Table 2 illustrates the observed physiological parameters at different time points. Statistically significant increases in HR from baseline values were observed at all time-points within the L-Lid and M-Lid treatments. A statistically significant increase in HR was observed only at 30 minutes of anaesthesia for H-Lid treatment. Arterial blood pressure observations (SAP, DAP and MAP) largely showed no statistically significant differences from baseline values within treatments or at any

Table 2 Physiological parameters [median (range)] observed in a study where anaesthesia was achieved with alfaxone (2 mg kg^{-1} induction dose followed by CRI initially at 9.6 mg kg^{-1} $hour^{-1}$, then intermittently adjusted to effect for maintenance) combined with lidocaine [1 mg kg^{-1} bolus followed by CRI at 3 mg kg^{-1} $hour^{-1}$ (L-Lid treatment), 2 mg kg^{-1} bolus followed by CRI at 6 mg kg^{-1} $hour^{-1}$ (M-Lid treatment), or 4 mg kg^{-1} bolus followed by CRI at 12 mg kg^{-1} $hour^{-1}$ (H-Lid treatment)] intravenously in goats.

Parameter	(Unit)	Treatment	Time of General Anaesthesia					
			Baseline	2 minutes	10 minutes	30 minutes	t-MIR$_{alpha}$	t-MIR$_{beta}$
			(Breathing room air)		(Breathing oxygen-supplemented air)			
Heart Rate	(beats minute^{-1})	L-Lid	67 (50-78)	108 (82-146)†	115 (82-128)†	102 (84-133)†	99 (84-133)†	109 (85-128)†
		M-Lid	69 (52-77)	99 (84-110)†	97 (84-111)†	105 (82-122)†	96 (77-122)†	119 (78-128)†
		H-Lid	67 (57-80)	88 (83-113)	97 (76-121)	107 (67-120)†	99 (64-120)	92 (74-125)†
SAP	(mmHg)	L-Lid	123 (101-157)	114 (95-138)	115 (106-125)	114 (88-129)	112 (88-129)	119 (102-129)
		M-Lid	106 (92-126)	115 (88-130)	106 (90-132)	118 (108-129)	113 (108-123)	126 (116-144)
		H-Lid	116 (96-140)	111 (92-126)	108 (100-154)	122 (104-134)	116 (100-132)	124 (110-135)
DAP	(mmHg)	L-Lid	95 (76-121)	96 (78-117)	95 (87-112)	96 (69-113)	93 (86-104)	100 (84-115)
		M-Lid	84 (70-102)	98 (69-105)	91 (76-114)	98 (90-112)	99 (84-110))	109 (94-130)†
		H-Lid	88 (74-113)	86 (71-102)	90 (75-127)	99 (71-108)	95 (79-115)	100 (91-112)
MAP	(mmHg)	L-Lid	111 (88-133)	104 (85-126)	105 (95-117)	103 (77-118)	102 (77-114)	109 (91-121)
		M-Lid	93 (86-113)	105 (78-165)	101 (83-122)	107 (98-119)	104 (97-114)	114 (105-136)
		H-Lid	103 (86-125)	97 (81-111)	99 (86-139)	109 (89-120)	105 (90-121)	112 (99-123))
Body temperature	(ºC)	L-Lid	39 (38.5-39.2)	38.8 (38.1-39.1)	38.3 (37.3-38.8)	37.9 (37-38.2)†	37.9 (37-38.2)†	37.7 (36.7-38.1)†
		M-Lid	38.9 (38.1-39.3)	39.1 (38.4-39.3)	38.5 (37.9-38.9)	38 (37.7-38.7)†	37.9 (37-38.6)†	37.7 (37.1-38.8)†

		H-Lid	38.4 (38.3-39.1)	38.7 (38.5-39.3)	38.4 (37.9-38.9)	37.8 (37.8-38.2)	37.6 (37.2-38.2)†	37.4 (36.7-38) †
f_R	(breaths minute^{-1})	L-Lid	30 (18-36)	16 (10-19)†	14 (9-26)†	20 (10-30)	22 (12-31)	21 (7-32)
		M-Lid	33 (24-40)	17 (12-24)†	18 (12-37)	22 (9-31)	26 (9-34)	23 (12-38)
		H-Lid	34 (24-48)	22 (15-31)†	18 (12-27)†	20 (9-28)†	23 (12-40)	22 (13-40)
F_IO_2	(fractional)	L-Lid	0.21 (0.21-0.21)	0.21 (0.21-0.21)	0.92 (0.68-0.96)	0.95 (0.9-0.97)		
		M-Lid	0.21 (0.21-0.21)	0.21 (0.21-0.21)	0.91 (0.78-0.96)	0.94 (0.88-0.96)		
		H-Lid	0.21 (0.21-0.21)	0.21 (0.21-0.21)	0.91 (0.74-0.97)	0.96 (0.94-0.97)		
S_aO_2	(%)	L-Lid	95.2 (94.8-97.1)	90 (66.4-93.1)†	99.6 (99.2-99.8)	99.7 (99.4-99.7)		
		M-Lid	95.6 (92.9-96.4)	89.9 (74.9-93.6)†	99.7 (99.3-99.8)	99.7 (99.4-99.8)		
		H-Lid	95.7 (95-96.4)	88.8 (70.8-93.2)†	99.6 (99.3-99.7)	99.7 (99.4-99.8)		
P_aO_2	(mmHg)	L-Lid	71 (66-81)	56 (34-63)	242 (168-372)†	307 (207-343)†		
		M-Lid	71 (59-78)	54 (40-65)	282 (200-308)†	309 (210-360)†		
		H-Lid	72 (68-79)	53 (36-65)	285 (184-304)†	322 (209-347)†		
P_aCO_2	(mmHg)	L-Lid	36 (31-37)	40 (36-44)	43 (41-45)†	44 (40-47)†		
		M-Lid	36 (34-38)	40 (38-43)	44 (41-46)†	46 (44-49)†		
		H-Lid	36 (34-38)	40 (35-43)	44 (38-48)†	45 (42-49)†		
pH_a		L-Lid	7.49 (7.45-7.54)	7.44 (7.41-7.48)	7.41 (7.38-7.42)†	7.41 (7.379-7.42)†		
		M-Lid	7.49 (7.46-7.52)	7.45 (7.42-7.50)	7.41 (7.39-7.46)†	7.41 (7.374-7.45)†		
		H-Lid	7.49 (7.46-7.54)	7.43 (7.39-7.50)	7.40 (7.36-7.47)†	7.39 (7.372-7.46)†		
$[HCO_3^-]$	(mmol litre^{-1})	L-Lid	26.2 (24.8-27.9)	27.0 (24.6-28.3)	26.3 (25-27.3)	26.9 (25.5-28.1)		
		M-Lid	26.4 (25.2-30.7)	27.0 (25.5-32.3)	27.1 (24.3-32.4)	28.2 (26.1-32.8)		
		H-Lid	25.8 (24.5-30.2)	26.1 (22.1-30.8)	26.0 (22.9-31.7)	27.8 (24.9-30.9)		

t-MIR_{alpha}: time at which alfaxalone infusion last abolished purposeful movement (lowest effective alfaxalone CRI rate); t-MIR_{beta}: time at which purposeful movement was observed and anaesthesia discontinued; HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; f_R: respiratory rate; F_IO_2: fractional inspired oxygen; S_aO_2: saturation of haemoglobin with oxygen in arterial blood; P_aO_2: partial pressure of oxygen in arterial blood; P_aCO_2: partial pressure of carbon dioxide in arterial blood; pHa: arterial hydrogen ion concentration negative logarithm; $[HCO_3^-]$: arterial bicarbonate ion concentration; †Statistically significantly different ($P < 0.05$) from the baseline observation within the treatment

time point among treatments from the control. The only exception was a statistically significant increase in DAP at time of purposeful movement in comparison to the baseline value for M-Lid treatment. Statistically significant decreases in f_R from baseline reading were observed at 2 and 10 minutes of L-Lid treatment, 2 minutes of M-Lid treatment and at 2, 10 and 30 minutes of H-Lid treatment. Statistically significant differences were observed on arterial blood gas parameters when compared to baseline values. Statistically significant and clinically relevant decreases in SaO_2 at 2 minutes of anaesthesia compared to baseline values were observed during L-Lid, M-Lid and H-Lid treatment. Across all treatments, PaO_2 was statistically significantly higher than baseline value at 10 and 30 minutes of anaesthesia. Statistically significant increases in $PaCO_2$ compared to baseline values were observed at 10 and 30 minutes of general anaesthesia during all treatments. There were no statistically significant differences in $[HCO_3^-]$ compared to the baseline values during all treatments. Statistically significant decreases in pH_a were observed, but the values remained within a clinically normal range. Statistically significant decreases in body temperature were observed compared to baseline values during all treatments. The temperature was maintained above 36.5 °C.

Adverse effects observed include occasional forelimb and facial skeletal muscle twitches. Ruminal bloat, ranging from mild to marked, was observed in all goats during anaesthesia and resolved during the recovery period as normal eructation and gas release returned.

Transitions to assisted sternal recumbency and full recovery from anaesthesia were excitement-free. Extubation could be performed within a median time of 20 minutes of terminating anaesthesia, while time to standing was within an hour across

all treatments. Times from termination of alfaxalone and lidocaine infusion to extubation, standing and walking are detailed in Table 3. There were no significant differences in induction and recovery scores; and times to standing and walking among treatments.

Table 3 Observations [median (range)] regarding recovery from anaesthesia in goats. For treatment details see Table 2.

Treatment	Time to extubation (minutes)	Time to standing (minutes)	Time to walking (minutes)	Recovery Score
L-Lid	17 (10–27)	46 (33–153)	46 (33–153)	3 (2–3)
M-Lid	14 (3–15)	41 (31–77)	41 (31–77)	3 (2–3)
H-Lid	13 (4–17)	51 (34–66)	52 (34–66)	3 (3–3)

Note: no statistically significant differences ($p < 0.05$) were observed among the treatments.

Discussion

Lidocaine reduces alfaxalone MIR in goats by up to 30% in a manner suggestive of a plateauing in effect in goats. The present study also demonstrates that hypoxaemia might occur following the initial induction boluses of alfaxalone and lidocaine.

The lower alfaxalone induction doses in comparison to a reported dose of 3 mg kg^{-1} when alfaxalone was used alone for induction (Ndawana et al. 2015) could have been the result of the anaesthetic-sparing effects of lidocaine. Premedication

with sedative and/or analgesic drugs causes a reduction in required induction dose of alfaxalone (Maddern et al 2010; Schwarz et al. 2014).

The present study demonstrated that continuous infusion of lidocaine reduces alfaxalone MIR in goats in a dose-dependent manner with some adverse effects on cardiopulmonary function. Reduction in MIR could because of the analgesic effects of lidocaine through its spinal or supraspinal mechanisms (Doherty & Frazier 1998). A quantitatively equal extent of reduction in alfaxalone MIR following either M-Lid or H-Lid treatments probably suggests a plateauing effect on alfaxalone requirements at high doses of lidocaine CRI. Mannarino et al. (2012) reported an 18% reduction in propofol MIR by a CRI of lidocaine at 15 mg kg^{-1} $hour^{-1}$ in dogs. The alfaxalone-sparing effects of lidocaine observed in the present study are quantitatively similar to the reduction of MAC of inhalant anaesthetic agents reported in previous studies (Doherty & Frazier 1998; Dzikiti et al. 2003; Wilson et al. 2008; Matsubara et al. 2009). Lidocaine, administered IV at 3 mg kg^{-1} $hour^{-1}$ and 12 mg kg^{-1} $hour^{-1}$, reduces sevoflurane MAC in dogs by 15% and 37% [1]), respectively (Matsubara et al. 2009). In dogs anaesthetized with sevoflurane in combination with lidocaine at 3 mg kg^{-1} $hour^{-1}$, 6 mg kg^{-1} $hour^{-1}$ and 12 mg kg^{-1} $hour^{-1}$, a corresponding reduction of sevoflurane MAC by 22.6%, 29.0% and 39.6% was reported (Wilson et al. 2008). Doherty and Frazier (1998) reported that lidocaine infusion led to a 15−20% decrease in halothane requirements in ponies. Lidocaine has also been reported to reduce isoflurane requirements by: 25% at doses of 3 mg kg^{-1} $hour^{-1}$ in horses (Dzikiti et al. 2003) and by 18.7% at 3 mg kg^{-1} $hour^{-1}$; 43.3% at 12 mg kg^{-1} $hour^{-1}$ (Valverde et al. 2004) and 29% at 3 mg kg^{-1} $hour^{-1}$ in dogs (Muir et al. 2003) as well as by 18.3% at 6 mg kg^{-1} $hour^{-1}$ in goats (Doherty et al. 2007). The doses of lidocaine used in these

previous studies are the similar to those used in the present study, hence results are very comparable.

It is not clear why HR increased significantly, despite minimal changes in arterial blood pressure during all treatments. Similarly, increased HRs were also observed in previous studies in which alfaxalone was administered alone (Ndawana et al. 2015) or combined with midazolam (Dzikiti et al. 2015) in goats suggesting that alfaxalone could be causing this effect. The significant decrease in SaO_2 at 2 minutes of general anaesthesia observed with all treatments was likely the result of alterations in tissue perfusion triggered by the bolus of alfaxalone during induction of general anaesthesia. A decrease in peripheral tissue perfusion commonly results from the effects of drug-induced vasodilation or reduced stroke volumes during anaesthesia, especially soon after administration of the induction bolus of most drugs used for induction of general anaesthesia (Valverde et al. 2010). The goats were breathing room air up to 2 minutes after induction of general anaesthesia, after which oxygen was provided; immediately resulting in increased SaO_2 and PaO_2 significantly from this moment onwards. An increase in $PaCO_2$ with an associated decrease of pH_a (relative respiratory acidosis) after induction of general anaesthesia with alfaxalone observed in the present study could have been a result of respiratory depression caused by alfaxalone. The greatest statistically significant increases in $PaCO_2$ were observed following oxygen supplementation. This possibly could be because of the removal of the hypoxic respiratory drive. The observed decrease in pH_a, though statistically significant from baseline values, was not clinically significant with values remaining within reference ranges. The significant decrease in respiratory rate observed during the anaesthetic period in this study remained within

clinically acceptable limits. The slight respiratory depression might have been a result of decreasing tidal volume; a parameter which was not measured in the present study. Respiratory depression has also been previously reported in dogs during induction and maintenance of general anaesthesia with alfaxalone (Muir et al. 2008; Maddern et al. 2010; Amengual et al. 2012).

Alfaxalone is associated with uneventful recovery from general anaesthesia in various species (Ferré et al. 2006; Muir et al. 2008; Muir et al. 2009) in agreement with observations of the present study.

A large single IV bolus of lidocaine may cause adverse effects such as disorientation, anxiety, vocalization, seizures, muscle twitching, respiratory depression and hypotension (Muir et al. 2003; Ferré et al. 2006). Intravenous bolus doses of lidocaine, ranging from 11 to 20 mg kg^{-1}, may result in convulsions in dogs (Steagall et al. 2006; Borer-Weir 2014). No neurological, cardiovascular, or respiratory signs of lidocaine toxicity were observed in the present study despite high infusion doses (12 mg kg^{-1} $hour^{-1}$). Alfaxalone could be the cause of the observed random skeletal muscle twitches of the face and uppermost forelimb observed in the present study as this has occurred following its administration alone (Ndawana 2015). Development of ruminal bloat was an expected observation because of the prevention of normal eructation by both anaesthesia and lateral recumbency resulting in the accumulation of ruminal gas (Taylor 1991).

The small sample size used in the present study limits the value of the observations as a true representation of the goat population. Another major limitation of the present study is failure to measure plasma concentrations of alfaxalone and

lidocaine which would have aided in exploration of the potential pharmacokinetic interactions of lidocaine and alfaxalone.

In conclusion, lidocaine reduces alfaxalone doses required for anaesthesia by up to 30% with a suggestive plateauing at high doses and causes minimal clinically significant adverse cardiorespiratory effects in goats. The hypoxaemia and respiratory depression that might arise from the induction boluses of alfaxalone following lidocaine premedication may be offset by provision of supplementary oxygen.

Significance of the work:

The study provides information on the dosages of alfaxalone when co-administered for TIVA with lidocaine in goats as well as the impact of this on the quality of general anaesthesia that can be obtained. The data arising from the present study will be a reference source for researchers and practitioners working on goats or related animals.

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Conflict of Interest Statement

The authors declare no conflict of interest regarding the funding bodies or institutions of affiliation.

Authors' contributions

BTD: conception and design of study. Involvement in all stages including manuscript preparation; **PSN**: design of study. Involvement in all stages including manuscript preparation; **LD**: Design of study and statistical analysis of data; **FGS**: data interpretation and preparation of manuscript.

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