Determination of the Minimum Infusion Rate (MIR) of alfaxalone required to prevent purposeful movement of the extremities in response to a standardised noxious stimulus in goats

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Abstract

Objective To determine the minimum infusion rate (MIR) of alfaxalone required to prevent purposeful movement of the extremities in response to noxious stimulation.

Study Design Prospective, experimental.

Animals Eight healthy goats; four does and four wethers.

Methods Anaesthesia was induced with alfaxalone 3 mg kg^{-1} intravenously (IV). A continuous IV infusion of alfaxalone, initially at 0.2 mg kg^{-1} $minute^{-1}$, was initiated. Following endotracheal intubation the goats breathed spontaneously via a circle breathing circuit delivering supplementary oxygen. The initial infusion rate was maintained for 30 minutes before testing for responses. The stimulus was clamping on the proximal (soft) part of one digit of the hoof with Vulsellum forceps for 60 seconds. In the absence or

presence of purposeful movement of the extremities, the infusion rate was reduced or increased by 0.02 mg kg^{-1} $minute^{-1}$ and held constant for 30 minutes before claw-clamping again. Alfaxalone MIR was calculated as the mean of the infusion rates that allowed and abolished movement. Cardio-respiratory parameters were measured. Recovery from general anaesthesia was timed and quality scored. Results are presented as median (range).

Results The MIR of alfaxalone was 0.16 (0.14-0.18) mg kg^{-1} $minute^{-1}$ or 9.6 (8.4-10.8) mg kg^{-1} $hour^{-1}$. Induction of and recovery from anaesthesia were excitement-free. Cardio-respiratory changes were minimal, although compared to baseline HR increased, and at 2 minutes post-induction, (prior to oxygen supplementation), P_aO_2 decreased significantly from 84 (80-88) to 70 (51-72) mmHg (11.2 (10.7-11.7) to 70 (51-72) mmHg (9.3 (6.8-9.6) kPa). Sporadic muscle twitches, unrelated to depth of anaesthesia, were observed during the period of general anaesthesia. Time (minutes) to sternal recumbency and standing were 4.0 (3.0-10.0) and 41.5 (25.0-57.0) respectively.

Conclusions and Clinical Relevance Alfaxalone can be used for total intravenous anaesthesia (TIVA) in goats and is associated with minimal adverse effects. Oxygen supplementation is recommended.

Keywords alfaxalone, anaesthesia, goat, minimum infusion rate, noxious stimulus, total intravenous anaesthesia

Introduction

Total intravenous (IV) anaesthesia (TIVA) is a technique that involves continuous IV administration of an anaesthetic agent to maintain an adequate depth of anaesthesia for a targeted level of central nervous system depression (hypnosis for diagnostic procedures or surgical anaesthesia for noxious interventions). The availability of more drugs that meet the criteria for use in TIVA, as well as recent advances in infusion pump

technology, has propelled research into TIVA (McKenzi 2008; Dzikiti 2013) and might subsequently result in its increased use in veterinary clinical practice.

Sear et al (1983) proposed the concept of the minimum infusion rate (MIR) to compare the anaesthetic requirements of IV anaesthetics during TIVA. They proposed that the 50 % effective dose (ED_{50}) in the movement response to skin incision (the stimulus used for studies in humans) during TIVA would be analogous to minimum alveolar concentration (MAC) for inhalation anaesthetic agents. Like MAC, MIR is influenced by the pharmacokinetic properties of the anaesthetic drugs, age and physical status of the patient, and concurrent administration of other drugs (opioids, sedatives) in addition to the anaesthetic requirement or responsiveness of the CNS (Kaul & Bharti 2002).

Intravenous administration of alfaxalone is characterised by: a rapid onset of action; rapid redistribution; a short terminal half-life; and dose dependent depression of cardio-respiratory function (Ferré et al. 2006; Muir et al. 2008; Suarez et al. 2012; Torres et al. 2012). These factors imply that alfaxalone is suitable for administration by a continuous rate intravenous infusion. The TIVA rates necessary to maintain general anaesthesia with alfaxalone have been determined in sedated dogs (Suarez et al. 2012) to be about 0.1 mg kg^{-1} $minute^{-1}$ (6 mg kg^{-1} $hour^{-1}$), but limited information on this subject has been reported for other species.

The aim of the present study was to determine, in goats, the MIR of alfaxalone required to prevent purposeful movement of the extremities in response to clamping on the the proximal (soft) part of one digit of the hoof with Vulsellum forceps.

Materials and methods

The study was performed at Pretoria which is at a height above sea level of 1 350 metres and has an average barometric pressure of 757 mmHg (100.1 kPa). It was approved by the Faculty's Research Committee and Animals Ethics Committee (Certificate numbers: V044/12 and V028/13). Eight indigenous African goats (four does, four wethers) were used. The goats were deemed healthy based on clinical examination, complete blood cell analysis and serum biochemical analysis (total serum protein, albumin and globulin).

The goats were 20 (20 - 23) months old, weighed 30 (24 - 34) kg and were judged to be American Society of Anesthesiologists physical status I. Food and water were withheld for 18 – 24 hours before the anaesthetic procedure.

Preparation

The goats were weighed on an electronic scale (Shekel Merav 2000 series; South Africa) 30 minutes before commencement of the experimental procedure. Baseline measurements of heart rate (HR), respiratory rate (f_R) and rectal temperature were obtained, following which the goats were placed on a custom-made sling-cum-table to ease restraint. Arterial and venous catheters were inserted before administration of any anaesthestic drugs and were tolerated well by the goats. A 24 gauge catheter was inserted percutaneously into the central auricular artery to facilitate continuous measurement of arterial blood pressures [systolic (SAP), diastolic (DAP) and mean (MAP)] and intermittent collection of arterial blood samples for gas analyses. Catheters (20 gauge) were inserted into both cephalic veins for administration of alfaxalone and intravenous fluids respectively. Ringers lactate (Intramed Ringer Lactate Solution; Kyron, South Africa) was administered at a rate of 4mL kg^{-1} $hour^{-1}$ IV using a volumetric fluid infusion pump (Infusomat Space; B. Braun Medical, Germany) through the right forelimb cephalic catheter.

General anaesthesia and MIR determination

General anaesthesia was induced with a single bolus of alfaxalone (Alfaxan CD-RTU; Kyron, South Africa) administered over a period of 30 seconds at 3 mg kg^{-1} (a rate previously determined from a pilot study) using a volumetric syringe-driving pump (Perfusor Space; B. Braun Medical, Germany), followed by incremental doses of 0.5 mg kg^{-1} administered every 15 seconds until induction of anaesthesia was sufficient, as judged by the presence of a weak medial palpebral reflex and adequate relaxation of the jaws to allow intubation of the trachea. With the aid of an illuminated laryngoscope, an endotracheal tube (silicone, internal diameter 7.5 mm) with an inflatable cuff was inserted into the trachea while the goats were restrained into sternal recumbency. Immediately after tracheal intubation, the cuff of the endotracheal tube was inflated to ensure an air-tight breathing circuit. The goats were then placed in right lateral

recumbency and allowed to breathe spontaneously. Quality of anaesthetic induction was scored on 0 - 2 score scale with 0 representing failed intubation and 2 representing an excitement-free and easy intubation (Table 1). Two minutes after induction of general anaesthesia, the goats were connected to circle breathing circuit (Anaesthesia Systems, Clinicare; Crest Health Technology, UK) with oxygen flow set at 0.5 L $minute^{-1}$ while still breathing spontaneously.

Immediately after completion of administration of the last bolus of alfaxalone for induction of general anaesthesia, a continuous IV infusion of alfaxalone was initiated for maintenance. The alfaxalone was infused through the left thoracic limb catheter, using a volumetric syringe-driving pump. The initial rate of infusion of alfaxalone was 0.2 mg kg^{-1} $minute^{-1}$ (a rate previously determined from a pilot study). The initial infusion rate was maintained for 30 minutes before testing for responses to the noxious stimulus. This procedure was always carried out by the same investigator (BD).

Determination of the MIR involved application of the noxious stimulus, which was Vulsellum forceps clamped on the proximal (soft) part of one digit of the hoof just below the coronary band (incorporating the soft proximal part of the wall of the hoof, the distal phalanx and the bulb of the hoof) for 60 seconds or until occurrence of purposeful movement of the extremities; followed by adjustment of alfaxalone infusion rate according to the response to stimulation. Purposeful movement was strictly defined as gross movement of the trunk, head or limbs. Twitching of the stimulated limb was not regarded as a positive response. Non-purposeful movements such as 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 fore limb. In the absence of purposeful movement, the alfaxalone infusion rate was reduced by 0.02 mg kg^{-1} $minute^{-1}$ and held constant for another 30 minutes before application of a subsequent noxious stimulus. This activity was repeated until a purposeful response occurred. In the event of observation of an initial positive response (purposeful movement), the alfaxalone infusion rate adjustments were performed in reverse order. The MIR of alfaxalone was calculated as the arithmetic mean of the alfaxalone infusion rates that allowed and abolished purposeful movement.

Following determination of the MIR the alfaxalone infusion was discontinued, the goats were disconnected from the circle breathing circuit and they were placed on a rubber surface and assisted into

Table 1 Physiological parameters [median (range)] observed during determination of the minimum infusion rate (MIR) of alfaxalone in goats

Parameter	Baseline (breathing air)	Period of Anaesthesia (minutes)				
		2 (breathing air)	10 (oxygen supplementation)	30	***t*-MIR$_\alpha$**	***t*-MIR$_\beta$**
Heart Rate (beats minute^{-1})	73 (56-92)	102 (88-119)*	112 (83-133)*	108 (91-120)*	111 (84-124)*	121 (89-146)*
Systolic Blood Pressure (mmHg)	104 (86-114)	102 (72-118)	99 (81-123)	103 (85-113)	107 (88-117)	108 (87-127)
Diastolic Blood Pressure (mmHg)	81 (68-88)	83 (58-99)	82 (60-104)	85 (67-98)	87 (73-98)	85 (70-107)
Mean Arterial Blood Pressure (mmHg)	92 (76-97)	91 (73-104)	89 (71-112)	93 (77-104)	98 (80-105)	95 (79-114)
Body Temperature (^oC)	38.8 (38.5-39.4)	38.7 (37.9-39.1)*	38.5 (37.1-38.5)*	37.9 (37.0-38.4)*	37.6 (36.7-38.4)*	37.5 (36.5-38.0)*
Respiratory Rate [f_R] (breath minute^{-1})	24 (18-30)	20 (13-25)	21 (6-34)	19 (10-22)	19 (10-24)	18 (10-24)
S_aO_2 (%)	95.8 (94.5-96.7)	93.4 (89.4-94.6)*	99.7 (99.0-99.7)*	99.7 (99.1-99.8)*		
F_IO_2 (fractional)	0.21 (0.21-0.21)	0.21 (0.21-0.21)	0.79 (0.73-0.89)	0.85 (0.81-0.94)		
P_aO_2 (mmHg) (kPa)	84 (80-88) 11.2 (10.7-11.7)	70 (51-72)* 9.3 (8.5-9.6)*	301 (152-331)* 40.0 (25.7-41.6)*	300 (156-342)* 39.9 (32.8-44.1)*		
P_aCO_2 (mmHg) (kPa)	37 (30-54) 5.0 (4.0-7.2)	44 (40-51)* 5.9 (5.3-6.8)*	47 (44-50)* 6.3 (5.9-6.7)*	45 (41-54)* 6.0 (5.5-7.1)*		
$[HCO_3^-]$ (mmol litre^{-1})	27.5 (25.7-30.6)	27.5 (25.9-31.6)	28.7 (27.9-32.6)*	29.3 (27.8-33.4)*		
pH_a	7.48 (7.33-7.55)	7.43 (7.36-7.47)*	7.41 (7.40-7.43)*	7.44 (7.40-7.47)*		

***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.
Note: Time it took to determine MIR was 90 (60-90) minutes.
*: Significantly different ($p<0.05$) from baseline reading

sternal recumbency (against a wall) for recovery from general anaesthesia. The endotracheal tube was removed once the swallowing reflex was regained. Times (minutes) between the termination of the alfaxalone infusion and extubation, attainment of assisted sternal recumbency, standing and voluntary motion were recorded. The quality of recovery was scored on a four-point scale from 0-3 with zero representing the worst possible quality of recovery and 3 representing an excitement-free recovery (Appendix S1).

Physiological parameters measurement

A multi-parameter monitor (Cardiocap/5; Datex-Ohmeda Corporation) was used to measure basic physiological parameters continuously throughout the period of general anaesthesia.

Three 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 a lead II ECG tracing. Arterial blood pressures were measured from the arterial catheter via a calibrated strain gauge transducer (DTX Plus transducer; BD Medical, South Africa); the scapula-humeral joint and the point of the sternum were used as zero reference points in sternally and laterally recumbent goats, respectively. Haemoglobin oxygen saturation (SpO_2) was measured using a pulse oximeter probe placed on the tongue.

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 gas analyser had recently been calibrated with calibration gas as recommended by the manufacturer and also automatically self-calibrated to atmospheric air every time the multi-parameter monitor was turned on. The respiratory rate was calculated from the capnogram.

The oesophageal temperature was measured by a probe placed as close to the base of the heart as possible. The targeted oesophageal temperature range was 37.0 - 39.5 °C which was achieved by covering the goats with ordinary blankets and supplementing body heat using a forced air warmed blanket (Bair Hugger; Augustine Medical, MN, USA).

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

Arterial blood samples for gas analysis were collected anaerobically in 2 mL pre-heparinised 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 analyzed for oxygen tension (P_aO_2), carbon dioxide tension (P_aCO_2), and pH,(pH_a) 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. Calculated values were bicarbonate ion ($[HCO_3^-]$) concentration and oxygen haemoglobin saturation (S_aO_2).

Statistical Analysis

Data were analysed using the R statistical software (The R Foundation for Statistical Computing, Austria). All data were assumed to be non-normally distributed due to the small sample size and are expressed as median (range).

The median dose of alfaxalone required for induction of anaesthesia, alfaxalone MIR, length of determination of MIR time, induction score, recovery score as well as the times to extubation, attainment of assisted sternal recumbency, standing and voluntary motion were calculated.

Data on measured physiological parameters (HR, SAP, DAP, MAP, body temperature and f_R) and arterial blood gas parameters (S_aO_2, P_aO_2, P_aCO_2, $[HCO_3^-]$ and pH_a) were tested for significant differences from the baseline value using the Wilcoxon signed rank test. A value of $p < 0.05$ was considered significant.

Results

The median alfaxalone dose required for induction of general anaesthesia was 3.0 (3.0-3.0) mg kg^{-1}, no additional boli of alfaxalone being required. Induction of anaesthesia was excitement-free and easy all the

time (scoring 2 for all goats). The MIR of alfaxalone in goats was 0.16 (0.14-0.18) mg kg^{-1} $minute^{-1}$ or 9.6 (8.4-10.8) mg kg^{-1} $hour^{-1}$. The length of time required to determine MIR was 90 (60-90) minutes.

The trends observed in physiological and arterial blood gas variables during the period of anaesthesia are reported in Table 1. Compared to baseline, HR increased statistically significantly throughout anaesthesia, while the arterial blood pressures and f_R did not show any statistically significant changes. The body temperature was successfully usually maintained within the targeted range of 37.0 and 39.5 °C, although statistically significant decreases from baseline were observed during alfaxalone anaesthesia

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Statistically significant decreases in S_aO_2 and P_aO_2 were observed 2 minutes after induction of general anaesthesia (whilst breathing air). This decrease in P_aO_2 to a median of 70 (51-72) mmHg (9.3 (8.5-9.6) kPa) was clinically significant but was immediately alleviated by inspired oxygen supplementation, which resulted in statistically (and clinically) significant increases at 10 and 30 minutes after induction of general anaesthesia. Statistically significant increases in P_aCO_2 and $[HCO_3^-]$ and decreases in pH_a were observed in comparison to baseline values but these variables remained within a clinically acceptable range.

Adverse effects observed included an increase in eye muscle activity in the form of brisk palpebral movements and nystagmus, as well as skeletal muscle twitches and spasms. These occurred sporadically throughout anaesthesia in most of the goats and involved muscles of the face, neck and upper thoracic limb. The increase in muscle activity did not appear to be associated with gross purposeful movement or the depth of anaesthesia. Ruminal tympany of varying degrees was observed in all goats by the end of the anaesthetic procedure.

Times (minutes) between the termination of the alfaxalone infusion and extubation, attainment of assisted sternal recumbency, standing and voluntary motion were 3.0 (2.0-10.0), 4.0 (3.0-10.0), 41.5 (25.0-57.0) and 43.5 (25.0-58.0); respectively. Recovery from general anaesthesia was excitement-free in all goats (scoring 3). The nociceptive stimulus did not result in any signs of pain, lameness or tissue damage after anaesthesia and when the goats were examined up to two weeks following the experiment.

Discussion

The results of this study suggest that TIVA with alfaxalone in oxygen-supplemented goats is practically feasible, and is associated with minimal cardiopulmonary effects.

There is currently no literature available on the dosages of alfaxalone required for induction and maintenance of general anaesthesia in goats. The dose of alfaxalone used for anaesthetic induction (3 mg kg^{-1}) in this study is similar to the dosages reported in other species including unsedated sheep (Andaluz et al. 2012; Torres et al. 2012), sedated dogs (Maddern et al. 2010; Suarez et al. 2012) and sedated ponies (Leece et al. 2009; Klöppel & Leece 2011). The MIR of alfaxalone in unsedated goats observed in the present study (0.16 mg kg^{-1} $minute^{-1}$) is higher than the dosages of 0.07 mg kg^{-1} $minute^{-1}$ (Ambros et al. 2008); 0.11 mg kg^{-1} $minute^{-1}$ (Suarez et al. 2012) and 0.08-0.11 mg kg^{-1} $minute^{-1}$ (Herbert et al, 2013) reported for maintenance of surgical anaesthesia in dogs sedated with a number of different agents.

The observations of a calm induction of general anaesthesia and recovery from general anaesthesia in the present study are similar to those that have been reported for propofol; a more widely available and used general anaesthetic agent. In this current study the infusion of alfaxalone had a minimal influence on mean arterial blood pressure and there was an increase in heart rate. This is similar to the effects of alfaxalone continuous rate infusions on heart rate and arterial blood pressure in dogs (Ambros et al. 2008) and sheep (Andaluz et al. 2012).

The decrease in P_aO_2 from a baseline of 84 mmHg (11.2 kPa) to 70 mmHg (9.3 kPa) two minutes after induction of general anaesthesia (before oxygen supplementation) coupled with increases in P_aCO_2 indicates that induction of general anaesthesia with alfaxalone may cause respiratory depression, which were clinically significant under conditions of low barometric pressure. In our study, during maintenance of anaesthesia alfaxalone appeared to have minimal influence on ventilation, and all goats breathed spontaneously. This contrasts with dogs, where at clinical doses apnoea or bradypnoea have been reported at induction of general anaesthesia (Muir et al. 2008; Maddern et al. 2010; Suarez et al. 2012) and positive pressure ventilation was required during anaesthetic maintenance (Herbert et al, 2013).

Ruminal tympany is a commonly observed complication in anaesthetized laterally or dorsally recumbent goats and is a positional effect rather than being caused by a pharmacological action of the anaesthetic agent. Increased muscle activity in specific muscle groups in the form of spasms, tremors and twitches, as observed in the present study, has previously been reported during alfaxalone-based TIVA in horses (Goodwin et al. 2011).

The small sample size in the present study limits the value of the observations of the present study as a true representation of the goat population. Determination of the plasma concentrations of alfaxalone could not be performed during this experiment because a validated method to do so had not been developed for goat plasma. For accurate determination of the MIR of alfaxalone the plasma concentrations should have achieved steady state before testing for nociceptive responses. The plasma half-life of alfaxalone has been reported as; 24 – 37 minutes in dogs (Ferré et al. 2006), 37 minutes in horses (Goodwin et al. 2011) and 45 - 77 minutes in cats (Whittem et al. 2008); following a single bolus injection, while its steady state attainment time during continuous IV infusion is unknown. In the present study, the waiting period before start of MIR determination and between testing for responses to noxious stimulation was 30 minutes, while the median duration of alfaxalone infusion was about 90 minutes. Determination of the end point (occurrence of movement) was not performed in duplicate in the present study. A more accurate end point could have been obtained had this been done in duplicate, but it was decided to only do it once based on observation of a pilot study that the end point was repeatable. This decision is justified by the narrow range of alfaxalone MIR reported in the present study. Only basic cardiopulmonary parameters were monitored in the study and this means that the pharmacodynamic effects reported are not exhaustive of all possible pharmacological effects of alfaxalone in goats.

In conclusion, the MIR of alfaxalone in unsedated goats is 0.16 mg kg^{-1} $minute^{-1}$. Minimal adverse effects were observed in the present study, in which alfaxalone was used for TIVA in goats. Provision of supplementary oxygen is recommended during alfaxalone-based TIVA in goats, especially at high altitude

as in this study. Further studies focusing on the pharmacokinetics of alfaxalone administered by continuous intravenous infusion in goats are recommended.

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Supporting information

Appendix S1 Scoring system used for quality of induction of and recovery from anaesthesia during determination of the minimum infusion rate (MIR) of alfaxalone that prevents purposeful movement of extremities in response to a standard noxious stimulus in goats

Score	Induction	Recovery
0	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 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)