Effects of propofol on isoflurane minimum alveolar concentration and cardiovascular function in mechanically ventilated goats

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Abstract

Objective To evaluate the effects of propofol, on isoflurane minimum alveolar concentration (MAC) and cardiovascular function in mechanically ventilated goats.

Study Design Prospective, randomized, crossover experimental study.

Animals Six goats, three does and three wethers.

Methods General anaesthesia was induced with isoflurane in oxygen. Following endotracheal intubation, anaesthesia was maintained with isoflurane in oxygen. Intermittent positive pressure ventilation was applied. Baseline isoflurane MAC was determined, the noxious stimulus used being clamping a claw. The goats then received, on separate occasions, three propofol treatments intravenously: bolus of 0.5 mg kg^{-1} followed by a constant rate infusion (CRI) of 0.05 mg kg^{-1} minute^{-1} (Treatment LPROP); bolus of 1.0 mg kg^{-1} followed by a CRI of 0.1 mg kg^{-1} minute^{-1} (Treatment MPROP), bolus of 2.0 mg kg^{-1} followed by a CRI of 0.2 mg kg^{-1} minute^{-1} (Treatment HPROP). Isoflurane MAC was re-determined following propofol treatments. Plasma propofol concentrations at the time of MAC confirmation were measured. Cardiopulmonary parameters were monitored throughout the anaesthetic period. Quality of recovery was scored. The Friedman test was used to test for differences between isoflurane MACs. Medians of repeatedly measured cardiovascular parameters were tested for differences between and within treatments using repeated ANOVA by ranks. ($P < 0.05$ for statistical significance).

Results Isoflurane MAC [median (interquartile range)] was 1.37 (1.36-1.37) vol%. Propofol CRI significantly reduced the isoflurane MAC, to 1.15 (1.08-1.15), 0.90 (0.87-0.93) and 0.55 (0.49-0.58) vol% following LPROP, MPROP and HPROP treatment, respectively. Increasing plasma propofol concentrations strongly correlated (Spearman rank correlation) with decrease in MAC (Rho = 0.91). Cardiovascular function was not affected significantly by propofol treatment. Quality of recovery was satisfactory.

Conclusions and clinical relevance In goats, propofol reduces isoflurane MAC in a dose-dependent manner with minimal cardiovascular effects.

Introduction

Major surgery and prolonged diagnostic procedures in goats usually are performed under inhalation anaesthesia, using injectable anaesthetic agents only for induction and to facilitate endotracheal intubation (Reid et al.1993).

Propofol (2,6 diisopropylphenol) conventionally is used for induction of general anaesthesia. The exact site at which propofol acts is not yet clear, although there is mounting evidence that the GABA (gamma-aminobutyric acid) receptor modulates, at least in part, propofol's effects (Hui et al. 1995, Antognini et al. 2000a). Propofol's pharmacokinetic profile makes it also useful for total intravenous anaesthesia (TIVA) in humans and other animals (Sebel & Lowdon 1989; Bettschart-Wolfensberger et al. 2000; Larenza et al. 2005; Dunn et al. 2006). In goats, propofol has a rapid and smooth onset of action, is cleared rapidly and is easy to titrate to a desired effect (Larenza et al. 2005; Prassinos et al. 2005).

Isoflurane is a commonly used inhalant anaesthetic agent, which has short induction and recovery times because of its low lipid solubility coefficient (Antognini & Eisele 1993). The most likely mechanism by which isoflurane produces anaesthetic effects is potentiation of the GABA receptor-channel complex in the brain and spinal cord (Larsen et al. 1998; Antognini & Carstens 2002). Isoflurane, like most other inhalant anaesthetic agents, causes respiratory depression, hypotension and reduced cardiac output in a dose-dependent pattern (Antognini & Eisele 1993; Hikasa et al. 2002). Isoflurane requirement for general anaesthesia in goats, as defined by MAC, has been reported to range between 1.23 and 1.5 vol% (Antognini & Eisele 1993; Hikasa et al. 1998; Antognini et al. 2000; Hikasa et al. 2002; Doherty et al. 2002; Doherty 2002a).

When propofol is given as TIVA for surgical procedures, commonly it is combined with analgesic agents such as fentanyl, ketamine and medetomidine (Correia et al. 1996; Bettschart-Wolfensberger R et al. 2003; Dzikiti et al. 2010). These analgesic agents are also often used as a CRI during isoflurane anaesthesia (often termed partial intravenous anaesthesia) with the objective of reducing the dose of isoflurane required, and possibly its cardiopulmonary side effects. To the best of the author's knowledge, there is no information on the use of propofol CRI in combination with isoflurane in goats.

In the current experimental study, the effects of propofol on isoflurane MAC were assessed. Isoflurane MAC was defined according to Merkel & Eger (1963), as the lowest isoflurane alveolar (end-tidal) concentration required by an individual goat to prevent gross purposeful movement in response to a supramaximal stimulus, which in this study was claw-clamping using a Vulsellum forceps. The null hypothesis that propofol does not affect isoflurane MAC was tested against the alternative hypothesis that propofol reduces isoflurane MAC in goats in a dose-dependent manner.

Materials and methods

Experimental Design and Instrumentation

Six clinically healthy goats (three does and three wethers) were used in the current study. The goats were assigned to three treatments, with order of treatment randomized in a cross-over pattern, and with a 4-week washout period between treatments. General anaesthesia was achieved initially with isoflurane only. Later, once a base line MAC value had been determined, anaesthesia was maintained with isoflurane combined with, following a bolus loading dose of propofol, a constant rate infusion of low dose propofol (treatment LPROP), moderate dose propofol (treatment MPROP) or high dose propofol (treatment HPROP). Median (interquartile

range) age was 19.0 (17.5-19.0) months for treatment LPROP, 18.0 (18.0-18.0) months for treatment MPROP and 18.0 (17.3-18.8) months for treatment HPROP while weight was 42.2 (36.6-45.5) kg for treatment LPROP, 41.1 (37.3-43.1) kg for treatment MPROP and 42.3 (35.2-43.6) kg for treatment HPROP. Health status was assessed by physical examination, a complete blood count and serum biochemical analysis; all findings were normal.

Food and water were withheld for 16–22 hours before anaesthesia. The goats were weighed 30 minutes before the experiment. Baseline rectal temperature measured by a digital thermometer, heart rate measured by thoracic auscultation and respiratory rate were recorded before the goats were placed on a custom-made sling-cum-table for easier restraint. The auricular artery on the right ear was catheterized using a 24 gauge catheter (Jelco; Medex Medical Ltd, UK) which was then connected to a calibrated transducer (DTX Plus transducer; BD Medical, South Africa) for measurement of systolic, diastolic and mean arterial blood pressures. The blood pressure readings were obtained from a calibrated electronic strain gauge transducer connected to multi-parameter monitor (Cardiocap/5; Datex-Ohmeda Corporation, Finland), which had been recently calibrated against a mercury column. 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. An 18 gauge catheter (Jelco; Medex Medical Ltd) was introduced into the right cephalic vein for administration of intravenous fluids and propofol. Another 18-gauge catheter was placed in the right jugular vein for collection of venous blood samples for determination of propofol plasma concentration.

Mask induction of the goats with isoflurane (Forane Liquid; Abbott Laboratories Pty Ltd, South Africa) delivered in oxygen from a circle anaesthetic breathing system with a calibrated Tec 3 out-of-circle vaporiser (Fluotec 3; BOC Health Care, UK) was achieved with the goats

restrained in sternal position. A tight-fitting facemask was used to limit dead space and gas leaks around the mask. Each goat was accustomed to the mask by initially being allowed to breathe 100 % oxygen at 6 L minute^{-1} for at least 1 minute before isoflurane administration was begun slowly with 0.5 vol% increments every 15 seconds until a 3.5 vol% vaporizer setting was reached. This vaporizer setting was then maintained until the jaw was relaxed enough to allow intubation. Placement of the endotracheal tube (silicone tube, internal diameter 7.5 mm) was performed with the goats in sternal recumbency, and using a laryngoscope to facilitate the process. If intubation was not successful, isoflurane delivery by facemask was continued before attempting again. The cuff of the endotracheal tube was inflated to a pressure of 20 cmH$_2$0 in order to prevent leakage of gases from the breathing circuit.

Immediately after endotrachaeal intubation, the goats were placed in left lateral recumbency with fresh oxygen flow set at 2 L minute^{-1} and initial end-tidal isoflurane concentration targeted to be 1.6 vol%. Intermittent positive pressure ventilation (Ohmeda 7000 Ventilator; Ohmeda, WI, USA) was used to maintain end-tidal carbon dioxide between 35 – 45 mmHg throughout the procedure. Ringer's lactate solution (Intramed Ringer-Lactate Freseniusl; Bodene Pty Ltd, South Africa) was administered by a pump (Infusomat; B.Braun, Germany) at a rate of 4 mL kg^{-1} hour^{-1} intravenously (IV).

Instrumentation for recording of physiological parameters was set up using the multi-parameter monitor. Three electrocardiography (ECG) electrodes were placed on shaven areas (on the middle of the left shoulder, on the midline 2 cm in front of the point of the sternum and on the midline 2 cm cranial to the tip of the xiphoid) to provide a lead II ECG tracing. Arterial haemoglobin oxygen saturation (SpO$_2$) was measured via a pulse oximetry infrared probe placed around the tongue, and pulse rate was taken from this measurement. Inspired

and expired concentrations of isoflurane, carbon dioxide and oxygen were measured by side-stream sampling, with the gas sampler placed between the endotracheal tube and the Y-piece of the breathing system. The flow rate through the gas sampling line was constant at 200 mL minute^{-1}. The gas module used for measuring respiratory gas concentrations had a sensor that constantly measured atmospheric pressure and adjusted reported respiratory gas readings as for one atmospheric pressure.

Respiratory rate was calculated from the capnogram. The gas analyzer had been recently calibrated with calibration gas as recommended by the manufacturer and automatically self-calibrated to atmospheric air at the beginning of the experiment. Temperature was measured by an oesophageal probe placed as close to the base of the heart as possible. We targeted to maintain oesophageal temperature between 37.5 and 39.5 ºC using a forced warmed air blanket and ordinary blankets placed around the goats. The physiological parameters were measured continuously during the anaesthetic period and recordings taken for analysis at set times, including just prior to applying stimulation for MAC testing.

Determination of the baseline isoflurane (control) MAC began 15 minutes after end-tidal isoflurane concentration had remained constant at 1.6 vol%. Isoflurane MAC determination involved application of a noxious stimulus with a Vulsellum forceps clamped to the second ratchet to the claw about 1 cm below the coronary band for 60 seconds or until occurrence of purposeful movement. The four claws on the two uppermost limbs were clamped consecutively in a clockwise fashion. Purposeful movement was strictly defined as gross movement of the head or limbs, including movement of the limb to which the Vulsellum forceps was being applied. End-tidal isoflurane concentration was then adjusted according to response to noxious stimulation. If no movement occurred, the end-tidal isoflurane

concentration was reduced by approximately 10 % of its value (or greater if anaesthesia obviously very deep as occurred following the higher doses of propofol administration), or if movement occurred increased by 10 % of its value, and the new level held constant for at least 15 minutes before further application of the noxious stimulus. Isoflurane MAC was calculated as the average of two successive concentrations; the end-tidal isoflurane concentration at which movement in response to noxious stimulation occurred and the preceeding end-tidal isoflurane concentration at which movement did not occur. The isoflurane MAC was determined in duplicate and the mean of the two MACs was taken as baseline isoflurane MAC.

Following baseline MAC determination, the goats then received a bolus dose of propofol administered manually over a 1 minute period; at 0.5, 1.0, or 2.0 mg kg^{-1} IV; followed by a maintenance CRI dose of; 0.05, 0.1, or 0.2 mg kg^{-1} $minute^{-1}$ as treatment LPROP, MPROP and HPROP, respectively. This propofol CRI was administered using a 60 mL syringe controlled by a syringe-driving pump (Perfusor Compact; B.Braun). The propofol syringe was connected to the right cephalic vein catheter, to which the Ringer's lactate administration line was also connected. The propofol loading dose was administered over a period of 1 minute and administration of the maintenance dose commenced directly afterwards. The accuracy of delivery of propofol by the pump was checked at the end of the experiment by calculating the expected infused amount based on infusion rates and comparing this to actual volume infused from the syringe.

Isoflurane MAC following propofol-treatment was then determined by applying the noxious stimulus after every 15 minutes of end-tidal isoflurane concentration equilibration, and depending on the goat's response, adjusting the end-tidal isoflurane concentration in the same

manner as described above. Response to propofol treatment for each goat was defined as the difference between baseline and propofol-treatment isoflurane MAC.

Since baseline isoflurane MAC was determined each time before a goat underwent one of the three propofol treatments, the final baseline isoflurane MAC for each goat was calculated as the average of the three baseline MAC values obtained.

Venous blood samples (4.5 mL) were collected via the right jugular vein catheter in heparinised tubes (BD Vacutainer Systems, UK) for determination of propofol plasma concentration at 0, 1, 5, 15, 30 and every 30 minutes from the time of propofol bolus administration until the propofol-treatment isoflurane MAC had been determined. The blood samples were centrifuged at 2 500 revolutions per minute for 15 minutes after which plasma was collected and stored at -20 ºC for propofol concentration analysis later.

After determination of propofol-treatment isoflurane MAC, administration of propofol and isoflurane was discontinued and the quality of recovery from anaesthesia of the goats observed. The catheters that had been inserted into the auricular artery and jugular vein were removed before the goats were moved to the recovery room. The endotracheal tube was removed once the goats regained the swallowing reflex. Time to extubation, sternal position and standing were recorded. All times were determined as the interval from the time of discontinuation of propofol and isoflurane administration. Quality of recovery from anaesthesia was scored on a $0 - 2$ scale where: $0 =$ restlessness, $1 =$ relatively smooth, with some restlessness, $2 =$ smooth. The catheter that had been inserted into the cephalic vein was removed once the goats were standing.

Propofol plasma concentration analysis

High performance liquid chromatography (HPLC) grade methanol (400 µL) containing 100 µg L^{-1} of thymol (internal standard) was added to 100 µL of thawed and centrifuged plasma. Each sample was then vortex-mixed at maximum speed for 30 seconds. The samples were then sonicated in an ultrasonic bath for 10 minutes, following which the samples were again vortexed at maximum speed for 30 seconds and then centrifuged. A volume of the supernatant was transferred to auto-sampler vials from which 15 µL was drawn for analysis. Plasma propofol concentrations were determined by a HPLC flourometric method as described by Vree et al. (1999). Separation and quantification were performed using a Shimatzu HPLC system consisting of a SIL-20AHT auto-sampler, a LC-20AB UFLC pump with a DGU-20AS de-gasser and an RF-10AXL fluorescence detector. The analytical column was an Altech Apollo C18, 150 x 4.6 mm column with a 5 µm particle size with a 4.0 x 2.0 mm Phenomenex Gemini C18 guard column run under isocratic flow of 80 % HPLC gradient grade methanol at a flow rate of 1.0 mL mimute^{-1}. Calibration was performed using a range of 0.25 − 25.00 µg mL^{-1}. Linear regression was performed using Y = aX + c, where a = 0.4429666 and c = -0.3939823. The linearity was measured using a correlation coefficient which was r^2 = 0.9914810.

The propofol plasma concentration at the time of propofol-treatment isoflurane MAC determination was calculated as an average of the propofol concentration of the sample obtained immediately prior to propofol-treatment isoflurane MAC determination and that of the sample obtained immediately after propofol-treatment isoflurane MAC determination.

Statistical analysis

Data were analysed using the R Statistical Software, Version 2.7.2 (The R Foundation for Statistical Computing, Austria). All data were assumed to be non-parametric because of the small sample size and are expressed as median and inter-quartile ranges.

Data on isoflurane MAC, isoflurane MAC reduction after propofol treatment, isoflurane MAC determination time, time to extubation, time to sternal position, time to standing, and recovery scores were tested for statistically significant differences between treatments using the Friedman test. If statistically significant differences were found between treatments, *post-hoc* analysis (pair-wise Wilcoxon test with a Bonferroni adjustment for multiple testing) was conducted. Correlation between isoflurane MAC and plasma propofol concentration at time of MAC determination was tested using the Spearman rank correlation test. The linear relationship between median isoflurane MAC and median propofol plasma concentrations at time of isoflurane MAC determination was determine using simple linear regression method.

Medians of repeatedly measured variables (heart rate, mean arterial blood pressure, SpO_2 and body temperature) were tested for statistically significant differences between and within treatments using repeated measures analysis of variance (ANOVA) by ranks. If statistically significant differences were found, a *post-hoc* analysis (pair-wise Wilcoxon test with a Bonferroni adjustment for multiple testing) was conducted. A value of $p < 0.05$ was considered significant.

Results

Mask induction of anaesthesia using isoflurane was satisfactorily achieved in about 10 minutes with minimal struggling of the goats throughout the induction period. Anaesthesia remained stable throughout the experiment and despite the movement initiated in response to the nociceptive stimulus, as soon as this was removed all movement ceased and the goat did not awake further.

Data on observed isoflurane MACs, changes in isoflurane MAC after treatment with propofol and the time it took to determine isoflurane MAC are summarized in Table 1. Times for MAC determination after propofol administration refer to the time after the first bolus of propofol was given.

The propofol-treatment isoflurane MAC values observed in this study were statistically significantly lower than the baseline isoflurane MAC of 1.37 (1.36-1.37) vol% ($P \leq 0.03$), and also isoflurane MACs of the three groups differed significantly from each other, as did the percentage reductions of isoflurane MAC ($P < 0.029$) resulting from propofol dosage. The time taken to determine baseline isoflurane MAC, 65 (65-65) minutes, was significantly shorter than that required later to determine isoflurane MAC in treatment MPROP ($P = 0.022$) and treatment HPROP ($P = 0.025$).

The trends in plasma propofol concentrations following its IV administration as a bolus followed by CRI at three different dose regimens are shown in Table 2. Median plasma propofol concentration following propofol bolus administration peaked after 1 minute following each propofol treatment. Median plasma propofol concentration at the time of propofol-treatment isoflurane MAC determination was calculated to be 1.6 (1.2-1.8) µg mL^{-1} for treatment LPROP, 2.5 (2.3-3.0) µg mL^{-1} for treatment MPROP and 7.8 (7.3-8.4) µg mL^{-1} for treatment HPROP. Peak plasma propofol concentration and plasma propofol concentration at

the time of propofol-treatment isoflurane MAC determination during treatment HPROP showed statistically significant differences from those of treatment LPROP and treatment MPROP.

Propofol concentrations at time of propofol-treatment isoflurane MAC determination (X) and the corresponding isoflurane MACs (Y) observed in this study correlated strongly (Rho = 0.91), characterized by a linear relationship whose best-fit equation was: $Y = 1.273 - 0.096X$ (Fig 1). This relationship between plasma propofol concentrations and corresponding isoflurane demonstrates that propofol reduces isoflurane MAC in a dose-dependent manner.

The data obtained for physiological variables demonstrated that these parameters did not differ significantly between groups, or from the earlier period of only isoflurane anaesthesia (Table 3).   Median mean arterial blood pressure (MAP) was above 60 mmHg at all recorded time points except at 2 minutes after administration of dose propofol when a median MAP of 56 mmHg was observed. The median SpO_2 stayed above 90 % all the time. The median end-tidal carbon dioxide concentration was maintained successfully within the range stated in the protocol of 35–45 mmHg. The median oesophageal temperature was maintained within 38.2–39.1 ºC and there were no statistically significant differences between or within groups.

All goats recovered quickly from anaesthesia (Table 4) with no significant differences in times between groups. The quality of recovery from anaesthesia was good [scored as median (IQR) of 2 (2-2) in all groups] following all propofol treatments. When inspected over the following weeks, no goat showed any signs of lameness, and when inspected in detail at the subsequent experiment, there were no signs of damage resulting from the nociceptive stimulus.

Discussion

The median isoflurane MAC in goats of 1.37 (1.36-1.37) vol% obtained in the current study closely resembles those in literature. Studies by different research teams have reported isoflurane MAC values in goats ranging from 1.23 to 1.50 vol% (Antognini & Eisele 1993; Hikasa et al. 1998; Doherty et al. 2002a,b). There are several reasons for variations in minimum alveolar concentrations among different studies, including physiological factors like breed, sex, body temperature, blood pressure and tissue oxygenation status as well as other reasons such as the method of testing (type of noxious stimuli), subjectivity in interpretation of response to method of testing, differences in anatomical site of stimulus application (Wilson et al. 2008). Various other types of noxious stimuli such as tail clamping, paw pressure or nerve stimulation have been applied to determine MAC (Levionnois et al. 2009). Of these types of noxious stimuli, electrical stimulation is often favoured as it can be applied at a consistent intensity, is totally reversible and maintains an intact neurophysiology and tissue integrity (Le Bars et al. 2001). Variation in the current study was minimized by use of a single observer to test response to stimulus, use of one anatomical structure (claw) as test site and provision of cardiopulmonary support (intravenous fluids for maintaining blood pressure, artificial ventilation with oxygen supplementation and temperature support). In addition, the baseline (control) isoflurane MAC and the propofol-treatment isoflurane MAC for each goat were determined during the same experimental setting with a short time interval, minimizing the impact of variation due to ambient conditions.

The baseline isoflurane MAC value was statistically significantly different from the propofol-treatment isoflurane MAC values at the three propofol infusion rates used in the present study indicating that propofol reduces isoflurane MAC in goats. The degree of reduction in isoflurane MAC by propofol was dose-dependent as shown by the reduction in

isoflurane MAC by 16.4 %, 34.7 % and 59.7 % following LPROP, MPROP and HPROP treatment respectively. Propofol, like isoflurane, has been reported to directly depress dorsal horn neuronal responses to noxious mechanical stimulation (Antognini et al. 2000b).

In the current study, median plasma propofol concentration following administration of the highest dose of propofol (bolus of 2.0 mg kg^{-1} followed by a maintenance dose of 0.2 mg kg^{-1} minute^{-1}) was 7.8 µg mL$^-$. This plasma propofol concentration caused a reduction in isoflurane MAC of about 60 %. There are pharmacokinetic studies on administration of a single intravenous dose of propofol in goats in literature (Pablo et al. 1997; Bettschart-Wolfensberger et al. 2000), but none following administration of propofol by CRI in goats. In sheep, plasma propofol concentrations were reported to be 2.0 − 4.7 µg mL$^-$ following administration of propofol by CRI at 0.2 mg kg^{-1} minute^{-1} together with ketamine at 0.1 mg kg^{-1} minute^{-1} (Correia et al. 1996). These values are lower than propofol plasma concentrations obtained in the current study. In ponies, following TIVA with propofol at 0.15 − 0.2 mg kg^{-1} minute^{-1} and ketamine at 50 µg kg^{-1} minute^{-1}, plasma propofol concentrations were reported to be 2.3-6.5 µg mL$^-$ (Nolan et al. 1996), which is close, but still lower than, the concentrations observed in this current study following administration of propofol 0.2 mg kg^{-1} minute^{-1}. In a pharmacokinetic study in dogs, the plasma propofol concentrations achieved when propofol was administered at 0.4 mg kg^{-1} minute^{-1} were reported to be within a range of 3.77-5.84 µg mL$^-$ (Nolan & Reid 1993). The plasma concentration of propofol that caused only 60% reduction in isoflurane MAC in the current study is higher than the range reported for full anaesthesia by Nolan and Reid (1993). The reasons why apparently higher plasma propofol concentrations were observed in the current study when compared to plasma propofol concentrations reported in previous studies in sheep, ponies and dogs that received propofol at similar CRI dosages cannot be determined from this study and requires further

investigation. Species differences in metabolism of propofol or differences in pharmacological interactions of the drugs involved may have caused the differences in propofol plasma concentrations. The lack of a specific analgesic agent among the anaesthetic agents used in the current study could have influenced the plasma propofol concentrations required to maintain general anaesthesia.

The strong correlation between the decrease in isoflurane MAC and the rise in plasma propofol concentration in this study further supports the fact that propofol reduces isoflurane MAC in a dose-dependent manner. From the linear relationship illustrated in Fig. 1, propofol and isoflurane interact additively with respect to suppression of movement in response to a supramaximal stimulus in goats. Hendrickx et al. (2008) demonstrated that interaction plots that form straight lines indicate an additivity type of drug interaction. Both propofol and isoflurane have been reported to cause anaesthetic effects due to interaction with GABA receptor sites (Hui et al. 1995; Hendrickx et al. 2008). Thus perhaps, the finding of additivity is not surprising since both drugs have effects on similar receptor sites. No previous study could be found in available literature on the interaction of propofol and isoflurane in goats, but additivity was suggested when propofol was co-administered with sevoflurane, a newer inhalation anaesthetic agent (Harris et al. 2006).

Propofol, administered by CRI at low dosages together with isoflurane to mechanically ventilated goats, had minimal impact on cardiovascular function as demonstrated by the results of the present study. The baseline (reference) values for cardiovascular parameters (pulse rate, arterial blood pressure and SpO_2) are similar to those observed in anaesthetized goats in other studies (Reid et al. 1993; Bettschart-Wolfensberger et al. 2000; Prassinos et al. 2005; Dzikiti et al. 2009, 2010; Jud et al. 2010).

The oesophageal temperature of the goats did not decrease by more that 1 ⁰C in any of the three groups indicating that heat conservation methods employed (covering with ordinary blankets and warming with a warm-air heating blanket) were successful in preventing heat loss. It was important to prevent hypothermia as this would have caused a reduction in MAC (Quasha et al. 1980).

In a number of studies in which propofol was administered alone for general anaesthesia in goats, myoclonic activity was reported as an adverse effect (Pablo et al. 1997; Bettschart-Wolfensberger et al. 2000; Prassinos et al. 2005). The tendency towards myoclonic activity was absent in the present study, probably due to the fact that propofol was co-administered with isoflurane.

Recovery from isoflurane-propofol anaesthesia was fast and excitement-free all the time as reported in previous publications on propofol anaesthesia in goats (Reid et al. 1993; Prassinos et al. 2005). The short recovery times associated with propofol are mostly due to its pharmacokinetic profile that is characterized by a high volume of distribution, rapid metabolism and a very high clearance rate even when administered as repeated doses or continuous intravenous infusion (Reid et al. 1993; Bettschart-Wolfensberger et al. 2000; Prassinos et al. 2005). Isoflurane is also known to be associated with rapid recovery from anaesthesia in goats (Antognini & Eisele 1993), more so when used in low dosages as in this study. Rapid recovery from anaesthesia is important in ruminants as they are prone to tympany and regurgitation of ruminal contents which increases the risk of hypoxaemia and aspiration of regurgitated ruminal contents (Correia et al. 1996; Prassinos et al. 2005).

It was concluded that propofol reduced isoflurane MAC in response to claw-clamping in a dose-dependent manner with minimal adverse effects on cardiovascular function in goats.

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Figure Legends

Figure 1 Plot of median isoflurane MAC against median plasma propofol concentration at time of propofol-treatment isoflurane MAC determination for individual goats. For protocol used, see Table 1.
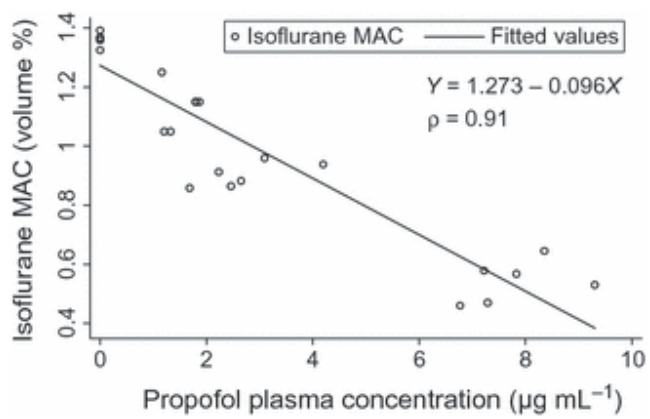
Tables

Table 1 Median (inter-quartile range) of isoflurane MAC, its reduction by propofol infusion, and the time taken to measure MACs in six goats.

Goats were anaesthetized with isoflurane and MAC measured. Goats were then given one of three treatments and MAC re-measured. Treatments were:

LPROP: propofol: 0.5 mg kg^{-1} bolus IV followed by CRI at 0.05 mg kg^{-1}minute^{-1}. MPROP: propofol 1.0 mg kg^{-1} bolus IV followed by CRI at 0.1 mg kg^{-1} minute^{-1}.

HPRP: propofol 2.0 mg kg^{-1} bolus IV followed by CRI at 0.2 mg kg^{-1}minute^{-1}

Treatment	Isoflurane MAC (vol %)	Change post-treatment (%)	Time (minutes)[a]
Control	1.37 (1.36-1.37)[*]	Not applicable	65 (65-65)
LPROP	1.15 (1.08-1.15)[*]	-16.4 (16.1-16.4)[*]	60 (60-71)
MPROP	0.90 (0.87-0.93)[*]	-34.7 (32.3-36.3)[*]	75 (75-75)[#]
HPROP	0.55 (0.49-0.58)[*]	-59.7 (57.4-64.3)[*]	113 (105-120)[*]

[*] : statistically significantly different ($P < 0.05$) from other three treatments
[#] : statistically significantly different ($P < 0.05$) from LPROP treatment
[a] : indicates time taken to determine isoflurane MAC following beginning of respective treatment (induction with isoflurane (control) or commencement of propofol administration)

Table 2 Plasma propofol concentrations (µg mL^{-1}) [expressed as median (inter-quartile range)] observed in goats anaesthetized with isoflurane and given a CRI of propofol. For treatment definition and doses of propofol see Table 1.

Treatment	Baseline	Time (minutes) from commencement of propofol infusion.						
		1	**5**	**15**	**30**	**60**	**90**	**120**
LPROP	0 (0-0)	3.1 (2.6-3.9) *	2.0 (1.8-2.1) *	1.5 (1.3-1.7) *	1.6 (1.3-1.8) *	1.7 (1.2-1.9) *	-	
MPROP	0 (0-0)	6.5 (5.0-9.9) *	3.1 (2.8-4.0) *	3.0 (2.8-3.3) *	2.5 (2.1-2.8) *	2.3 (1.6-2.8) *	3.0 (2.7-3.4) #	-
HPROP	0 (0-0)	21.1 (16.4-24.9) *	9.7 (8.6-10.9) *	8.6 (6.9-9.2) *	8.2 (7.8-8.5) *	8.4 (7.4-8.8) *	8.1 (7.8-8.5)	7.2 (6.4-8.0)

* : statistically significantly different ($P < 0.05$) from other two treatments
\# : statistically significantly different ($P < 0.05$) from HPROP treatment

Table 3 Physiological parameters [median (inter-quartile range)] in six goats anaesthetized firstly with isoflurane only, then given a CRI of propofol. For treatment definition and doses of propofol see Table 1

Variable	Unit	Treatment	Time Baseline	Period of baseline isoflurane MAC determination (minutes)				Period of propofol-treatment isoflurane MAC determination (minutes from commencement of propofol CRI)				
				2	15	30	45	2	15	30	45	60
Pulse rate	beats minute^{-1}	LPROP	86 (73-102)	88 (86-108)	86 (79-101)	88 (81-94)	87 (81-92)	100 (82-118)	95 (80-112)	92 (81-110)	95 (82-116)	103 (87-121)
		MPROP	82 (74-84)	72 (70-80)	71 (70-80)	72 (70-85)	77 (70-89)	81 (70-92)	85 (77-88)	81 (74-83)	81 (77-89)	89 (76-101)
		HPROP	80 (80-83)	74 (73-80)	75 (74-78)	74 (72-81)	76 (69-80)	67 (64-72)	74 (71-86)	72 (68-74)	74 (72-77)	76 (72-76)
SAP	mmHg	LPROP	115 (107-121)	100 (87-114)	100 (87-110)	102 (88-108)	103 (91-106)	106 (93-118)	102 (92-110)	99 (94-108)	92 (90-105)	101 (99-110)
		MPROP	109 (103-124)	86 (81-92)	87 (82-97)	89 (86-97)	94 (89-97)	87 (81-93)	96 (87-103)	86 (85-89)	97 (91-110)	95 (92-105)
		HPROP	110 (100-120)	88 (78-91)	86 (83-88)	82 (78-91)	86 (82-91)	73 (69-79)	84 (76-89)	85 (77-97)	95 (81-104)	107 (88-114)
DAP	mmHg	LPROP	77 (71-87)	62 (56-82)	70 (57-83)	71 (59-81)	71 (64-77)	75 (62-95)	76 (66-87)	76 (72-87)	74 (68-84)	85 (76-88)
		MPROP	80 (74-92)	52 (48-63)	53 (52-63)	61 (57-64)	61 (54-68)	62 (65-67)	72 (62-79)	56 (53-68)	74 (66-83)	77 (75-79)
		HPROP	75 (69-80)	60 (47-63)	59 (47-59)	59 (49-68)	59 (51-66)	44 (42-49)	56 (53-65)	62 (48-74)	72 (53-80)	82 (60-90)
MAP	mmHg	LPROP	96 (85-104)	75 (71-96)	80 (71-94)	82 (69-93)	85 (74-90)	86 (74-105)	86 (75-96)	84 (81-94)	81 (76-92)	92 (84-97)
		MPROP	92 (86-109)	63 (59-65)	67 (65-76)	74 (67-77)	78 (69-84)	71 (64-79)	82 (71-89)	67 (65-76)	83 (75-95)	85 (84-88)
		HPROP	92 (83-95)	70 (58-72)	68 (58-72)	68 (59-77)	68 (62-76)	63 (59-65)	56 (53-65)	71 (55-83)	83 (61-91)	94 (68-101)
SpO$_2$	%	LPROP	-	99 (98-99)	98 (97-99)	98 (97-99)	98 (98-99)	98 (98-98)	98 (98-98)	98 (98-98)	98 (97-99)	98 (97-98)
		MPROP	-	99 (98-99)	98 (95-99)	97 (97-98)	97 (96-99)	97 (97-99)	98 (98-98)	98 (98-98)	98 (97-99)	98 (96-99)
		HPROP	-	99 (97-99)	97 (96-99)	97 (95-99)	97 (96-99)	97 (96-97)	97 (96-98)	97 (97-98)	97 (96-98)	97 (97-98)
PE′CO$_2$	mmHg *kPa*	LPROP	-	38 (37-41) *5.2 (5.0-5.6)*	40(37-44) *5.4 (4.9-6.0)*	40 (37-43) *5.3 (4.9-5.8)*	42 (38-44) *5.6 (5.2-5.9)*	44 (40-45) *6.0 (5.3-6.1)*	44 (41-45) *6.0 (5.8-6.1)*	45 (44-47) *6.0 (5.9-6.3)*	43 (41-44) *5.8 (5.4-6.0)*	42 (41-44) *5.8 (5.5-6.0)*
	mmHg *kPa*	MPROP	-	42 (38-43) *5.6 (5.0-5.7)*	41 (41-43) *5.5 (5.4-5.7)*	43 (39-45) *5.7 (5.1-6.0)*	44 (42-45) *5.8 (5.6-6.0)*	43 (41-45) *5.7 (5.4-6.1)*	43 (42-46) *5.7 (5.6-6.1)*	42 (40-45) *5.6 (5.3-6.0)*	43 (41-45) *5.7 (5.5-6.0)*	41 (38-43) *5.4 (5.1-5.7)*
	mmHg *kPa*	HPROP	-	41 (40-43) *5.4 (5.3-5.7)*	42 40-43) *5.6 (5.3-5.8)*	41 (40-43) *5.4 (5.4-5.7)*	41 (37-41) *5.4 (5.0-5.4)*	38 (38-41) *5.1 (5.1-5.4)*	37 (36-38) *5.0 (4.8-5.0)*	37 (36-39) *5.0 (4.8-5.1)*	37 (36-38) *4.9 (4.8-5.0)*	40 (37-42) *5.3 (4.9-5.6)*
Temp	(ºC)	LPROP	39.0 (38.9-39.1)	39.0 (38.9-39.1)	38.4 (38.3-38.8)	38.4 (38.2-38.8)	38.4 (38.2-38.8)	38.4 (38.2-38.8)	38.3 (38.2-38.7)	38.4 (38.1-38.7)	38.4 (38.2-38.6)	38.5 (38.2-38.7)
		MPROP	39.0 (38.8-39.2)	38.6 (38.5-38.8)	38.6 (38.4-38.8)	38.5 (38.3-38.7)	38.5 (38.3-38.7)	38.4 (38.3-38.4)	38.2 (38.0-38.4)	38.2 (38.0-38.3)	38.1 (38.0-38.2)	38.2 (38.1-38.3)
		HPROP	38.7 (38.6-38.9)	38.6 (38.4-38.7)	38.6 (38.4-38.7)	38.6 (38.3-38.7)	38.6 (38.4-38.7)	38.5 (38.4-38.7)	38.5 (38.2-38.6)	38.4 (38.2-38.5)	38.3 (38.1-38.6)	38.3 (38.1-38.6)

Note: Recordings of physiological parameters were taken just prior to applying stimulation for MAC testing. No statistically significant differences ($P < 0.05$) between or within groups.

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; SpO$_2$, saturation of haemoglobin with oxygen in peripheral blood; PE′CO$_2$, end-tidal carbon dioxide partial pressure; Temp, body temperature.

Table 4 Time to recovery from anaesthesia [median (inter-quartile range)] in six goats following anaesthesia with isoflurane, initially alone, but then followed by a propofol CRI. For treatment definition and propofol doses, see Table 1. Times are from cessation of both isoflurane and propofol administration

Treatment	Time to extubation (minutes)	Time to sternal position (minutes)	Time to standing (minutes)
LPROP	2.5 (1.3-3.0)	4.0 (2.3-5.0)	6.0 (5.0-7.0)
MPROP	2.0 (2.0-2.8)	2.0 (2.0-2.8)	5.0 (3.5-8.0)
HPROP	2.5 (2.0-3.0)	2.5 (2.0-3.0)	5.0 (5.0-7.3)