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 A total of eight healthy goats: four does and four wethers.

Methods Anaesthetic induction was with lidocaine at 1 mg kg^{-1} [low dose of lidocaine (L-Lid)], 2 mg kg^{-1} [moderate dose (M-Lid)] or 4 mg kg^{-1} [high dose (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) and 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, lidocaine, minimum infusion rate.

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, 2011; Ndawana et al. 2015; Dzikiti et al. 2015, 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 minimum infusion rate (MIR) as the lowest infusion rate of an

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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 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, 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, 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. 2007; 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 10–37% in a dose-dependent manner. Steagall et al (2006) reported a reduction of expired isoflurane concentration by 34–44% in dogs during concurrent lidocaine administration. The mechanism by which lidocaine reduces the MAC of inhalation anaesthetics agents, however, remains unknown, but could be due to its antinociceptive 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 1252 m above sea level with a barometric pressure ranging from 651 to 668 mmHg (86.8–89.1 kPa). A total of 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. Water was provided *ad libitum*.

An *a priori* calculation indicated that a sample size of at least eight 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} $hour^{-1}$.

The goats were administered three treatments, in a crossover design, in which an alfaxalone CRI was combined with a low dose lidocaine (L-Lid), moderate dose lidocaine (M-Lid) or high dose lidocaine (H-Lid) CRI for induction and maintenance of general anaesthesia. The treatment order was assigned using a table of random numbers, in a crossover pattern, with a 1-month interval between treatments.

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

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