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RESEARCH PAPER

Determination of the minimum infusion rate of alfaxalone during its co-administration with fentanyl at three different doses by constant rate infusion intravenously 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 standardized noxious stimulation during its co-administration with fentanyl at three different doses by constant rate infusion (CRI) intravenously (IV) in goats.

Study design Prospective, blinded, randomized crossover, experimental.

Animals Eight healthy goats; four does and four wethers.

Methods For induction of anaesthesia, a bolus of fentanyl was administered at 0.005 mg kg^{-1} (LFent), 0.015 mg kg^{-1} (MFent) or 0.03 mg kg^{-1} (HFent) followed by alfaxalone at 2.0 mg kg^{-1}. For maintenance, the goats received alfaxalone at an initial infusion rate of 9.6 mg kg^{-1} $hour^{-1}$ and one of three fentanyl treatments: 0.005 mg kg^{-1} $hour^{-1}$(LFent), 0.015 mg kg^{-1} $hour^{-1}$ (MFent) or 0.03 mg kg^{-1} $hour^{-1}$ (HFent). The MIR of alfaxalone was determined during fentanyl CRI by testing for responses to stimulation (clamping on a digit with Vulsellum forceps) every 30 minutes. Some cardiopulmonary parameters were measured.

Results The alfaxalone MIR median (range) was 6.7 (6.7–8.6), 2.9 (1.0–6.7) and 1.0 (1.0–4.8) mg kg^{-1} $hour^{-1}$ during LFent, MFent and HFent, respectively. Alfaxalone MIR was significantly lower during MFENT and HFENT compared to LFENT. Significantly low oxygen haemoglobin saturation (SaO_2) and arterial oxygen partial pressure (PaO_2), observed 2 minutes into anaesthesia after all fentanyl treatments, were the most remarkable adverse cardiopulmonary effects observed. Recovery from anaesthesia was severely affected by high doses of fentanyl with excitatory behavioural signs predominant for up to 2 hours post-administration after MFent and HFent.

Conclusions and clinical relevance Fentanyl reduces alfaxalone MIR in goats in a dose-dependent manner. Immediate oxygen supplementation after induction of general anaesthesia is recommended to prevent hypoxaemia. Doses of fentanyl equal to or greater than 0.015 mg kg^{-1} $hour^{-1}$ tend to be associated with severe excitatory behaviour and should be avoided when fentanyl is administered to goats.

Keywords alfaxalone, anaesthesia, fentanyl, goat, minimum infusion rate, total intravenous anaesthesia.

Introduction

In some animal species, notably dogs and horses, total intravenous anaesthesia (TIVA) is becoming a vital technique for general anaesthesia, but information on TIVA protocols applicable to goats is still very scarce (Dzikiti 2013). Alfaxalone is one of the hypnotic drugs that possess characteristics ideal for use in TIVA and can be combined with other drugs such as fentanyl to minimize dose-dependent adverse effects of either drug as lower dosages would be required for anaesthesia.

The concept of the minimum infusion rate (MIR) can be used in research to compare the anaesthetic requirements of IV anaesthetics during TIVA. If MIR is assumed to represent the 50% effective dose (ED_{50}) in the movement response to a noxious stimulus during TIVA, it can be considered analogous to the minimum alveolar concentration (MAC) for inhalation anaesthetic agents (Sear et al. 1983).

The pharmacokinetic and pharmacodynamic profiles of alfaxalone, when used for general anaesthesia, are characterized by a rapid onset of action, rapid redistribution and a short terminal half-life (Ferré et al. 2006; Suarez et al. 2012). The general anaesthetic induction dose and MIR of alfaxalone for maintenance of general anaesthesia in unpremedicated goats have recently been reported as 3 mg kg^{-1} and 9.6 mg kg^{-1} $hour^{-1}$, respectively (Dzikiti et al. 2014; Ndawana et al. 2015). Alfaxalone has previously been associated with dose-dependent respiratory depression in dogs (Muir et al. 2008) and goats (Ndawana et al. 2015), but negligible adverse cardiovascular effects in goats (Dzikiti et al. 2014; Ndawana et al. 2015).

Pure mu-agonistic opioids, such as fentanyl, are commonly included for analgesia in balanced TIVA and have the potential to attenuate nociceptive signals from noxious stimuli at subcortical levels of the central nervous system (Bouillon et al. 2004). Fentanyl is used for the relief of moderate-to-severe pain (Carroll et al. 1999). It is one of various opioids suitable for IV infusion as it is characterized by a rapid onset time and short duration of action over a wide dose range and has a wide therapeutic margin (Carroll et al. 1999; Lamont & Mathews 2007; Meredith et al. 2008). In goats, fentanyl has been reported to be effective against thermal and mechanical stimuli in a nociceptive model study (Valverde & Gunkel 2005). Fentanyl has anaesthetic-sparing effects as evidenced by a reduction of isoflurane requirements by 28%, 41% and 57% after IV administration at 0.005, 0.015, 0.03 mg kg^{-1} $hour^{-1}$, respectively, in goats (Dzikiti et al. 2011). Fentanyl causes minimal adverse effects on the cardiopulmonary function in goats, but has previously been associated with some restlessness, increased vocalization and exaggerated tail-wagging during recovery from anaesthesia (Carroll et al. 1999; Dzikiti et al. 2011).

Co-administration of fentanyl with alfaxalone for TIVA could reduce the dose of alfaxalone and minimize adverse cardiopulmonary effects that may result from high doses of alfaxalone during anaesthesia. The present study determined the MIR of alfaxalone and accompanying anaesthestic and cardiopulmonary effects during its co-administration with fentanyl at three different constant rate infusion (CRI) doses for TIVA in goats.

Materials and methods

The study was approved by the University of Pretoria's animal ethics committee (Certificate number: V028/13). The research site is situated at a height above sea level of 1252 m; thus, atmospheric pressure ranges from 651 to 668 mmHg (86.8–89.1 kPa).

Eight healthy Boer–Indigenous African crossbreed 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 limited amounts of commercial ruminant concentrate feed, while lucerne, hay and water were provided *ad libitum*. Using the random numbers table, the goats were assigned to three treatments in a blinded, randomized cross-over pattern, with a 4-week interval between treatments, in which anaesthesia was achieved by co-administering alfaxalone with fentanyl at three doses: low dose (LFent treatment), moderate dose (MFent treatment) or high dose (HFent treatment). The fentanyl doses for induction and maintenance of general anaesthesia were calculated, drawn up and injected by a person other than the principal investigator who was unaware of treatment assignment for later determination of alfaxalone MIR. At the beginning of the study, the median (range) age was 24 months (24–27) and the weight was 31.5 kg (24.7–36.4). The goats were deemed healthy based on physical examination, blood counts and serum biochemical analyses. Food