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Cardiorespiratory and anaesthetic effects of two continuous rate infusions of dexmedetomidine in alfaxalone anaesthetized dogs

S. Quirós Carmona *, R. Navarrete-Calvo, M.M. Granados, J.M. Domínguez, J. Morgaz, J.A. Fernández-Sarmiento, P. Muñoz-Rascón, R.J. Gómez-Villamandos

Department of Animal Medicine and Surgery, University of Cordoba, Cordoba, Spain

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ABSTRACT

Six Beagles were used in this prospective randomised crossover experimental study. Dexmedetomidine was administered at 0, 1 or 2 μg/kg IV for group C, LDA and HDA, respectively. Animals were induced and maintained with alfaxalone at 0.07 mg/kg/min with a CRI dexmedetomidine dose of 0, 0.5 or 1 μg/kg/h for group C, LDA and HDA, respectively. Cardiorespiratory variables, arterial blood gases and depth of anaesthesia were recorded. The recovery times and quality of recovery were scored. Group HDA produced a greater increase in the depth of anaesthesia than LDA. However, with both protocols, CI was halved compared to normal values in dogs. The use of oxygen before and during the anaesthetic maintenance is advisable, mainly if dexmedetomidine is going to be use as a pre-medicant and maintenance agent. The quality of recovery was better in groups receiving dexmedetomidine, without causing an increase in recovery time.

1. Introduction

Total intravenous anaesthesia (TIVA) is an alternative to inhalation anaesthesia and uses drugs solely through the intravenous (IV) route. Drugs used in TIVA should have a short duration of action and rapid clearance, with no cumulative effects (Dundee and McMurray, 1984).

No anaesthetic protocol, either with intravenous or inhalation agents, uses only one drug to supply hypnosis, analgesia or muscle relaxation. Balanced anaesthesia uses a combination of different drugs to achieve synergy, so that it is possible to reduce the doses and prevent adverse effects of individual drugs (Lundy, 1926).

Dexmedetomidine is commonly used for sedation and premedication. It is a highly potent and selective alpha-2-agonist (Doze et al., 1989) which provides sedation, analgesia and reduces the requirements for anaesthetic drugs needed for induction and maintenance (Bloor et al., 1992; Gómez-Villamandos et al., 2006a; Kuusela et al., 2000, 2001a, 2001b). Doses vary between 0.5 and 10 μg/kg (Gómez-Villamandos et al., 2008). Another application for dexmedetomidine, derived from human medicine, is its use in animals for anaesthetic maintenance in continuous rate infusion (CRI) (Gómez-Villamandos et al., 2008). Dexmedetomidine infusions decrease the intra-operative requirements for isoflurane, with smooth and rapid recovery (Pascoe et al., 2006; Uilenreef et al., 2008) and an adequate tissue perfusion (Uilenreef et al., 2008) in dogs.

Alfaxalone is a steroid anaesthetic agent for intravenous use that interacts with the gamma aminobutyric acid type A ($GABA_A$) receptor (Siegwart et al., 2002) producing anaesthesia and muscle relaxation (Ferré et al., 2006; Muir et al., 2008; Pasloske et al., 2009). It has been used for the induction and maintenance of anaesthesia in dogs (Ambros et al., 2008). Alfaxalone is characterised by a high margin of safety, rapid onset of action and recovery of consciousness, good muscle relaxation and minimum cardio-respiratory side effects when an induction dose is administered slowly. Moreover, it does not accumulate after repeated doses because of its rapid metabolism and clearance, so it can be used for TIVA (Ferré et al., 2006).

Earlier studies have determined the dose of alfaxalone required to induce anaesthesia to range from 2 mg/kg (Ambros et al., 2008; Ferré et al., 2006) to 20 mg/kg in dogs (Muir et al., 2008). Ambros et al. (2008) and Suarez et al. (2012) used a CRI of alfaxalone at 0.07 and 0.11 ± 0.01 mg/kg/min in pre-medicated dogs, respectively. They reported a good anaesthetic quality and good haemodynamic stability with an evident respiratory depression.

Up to now no study has evaluated the combination of alfaxalone and dexmedetomidine for the maintenance of anaesthesia in dogs. Only Herbert et al. (2013) reported an induction and maintenance of anaesthesia with intravenous alfaxalone in dexmedetomidine premedicated dogs. Only two studies have used a CRI of dexmedetomidine during isoflurane anaesthesia (Pascoe et al., 2006; Uilenreef et al., 2008) and three have reviewed the cardiopulmo-

* Corresponding author. Tel.: +34 957212647; fax: +34 957211093.
E-mail address: v42quics@uco.es (S. Quirós Carmona).

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nary effects of a CRI of alfaxalone (Ambros et al., 2008; Herbert et al., 2013; Suarez et al., 2012). The aim of this study was to assess the cardiorespiratory, anaesthetic and recovery effects of alfaxalone TIVA anaesthesia together with two CRI of dexmedetomidine.

2. Materials and methods

This study was approved by the Institutional Animal Care and Use Committee of the University. Six purpose-bred Beagles (three males and three females), aged 2.3 ± 0.4 years and weighing 15.3 ± 2.3 kg, were used in this study. They were considered to be healthy based on the results of physical examination, plasma biochemistry and haematology. Food and water were withheld for 12 h before the study.

2.1. Experiment instrumentation

On the day of the experiment, both cephalic veins were catheterised (VasoVet 20G 1.1 × 33 mm. B. Braun Melsungen AG, Germany). Crystalloid fluid (NaCl-0.9% B. Braun Medical SA, Barcelona, Spain) was administered through the right catheter at a rate of 10 ml/kg/h.

Firstly, anaesthesia was induced and maintained with sevoflurane (SevoFlo®, Laboratories Dr. Esteve, Barcelona, Spain) in 100% oxygen. A central venous catheter (Certofix® 18G B. Braun Melsungen, Germany) was placed in the right jugular vein and was connected to a pressure transducer (B. Braun Melsungen, Germany) to record the central venous pressure (CVP, mmHg). It was also required for the calibration of the PiCCOplus® monitor (Pulsion Medical System, Germany), a minimally invasive technique of cardiac output (CO, L/min) monitoring. A 4F Pulsiocath® catheter (Pulsion Medical System, Munich, Germany) was positioned in the right femoral artery and it was connected to a PiCCO®plus monitor through a pressure transducer (Pulsion Medical System, Munich, Germany). Both pressure transducers were zeroed with a water manometer before the study, with a pressure of 0 set at the level of the thoracic inlet in laterally recumbent dogs. Calibration CO was determined via transpulmonary thermodilution, applying the modified Stewart–Hamilton equation (Shih et al., 2011), and it was necessary to perform subsequent cardiovascular measurements via PiCCO arterial pulse contour analysis as described by Gödje et al. (2002). A 10 mL bolus of cold isotonic dextrose solution at a temperature of <8 °C was rapidly injected through the central venous catheter and the change in blood temperature was detected by a femoral artery thermistor tipped catheter. This calibration was performed in triplicate and averaged. The place where the catheters were positioned was clipped and prepared, using an aseptic technique. Finally, local anaesthetic (Bupivacaine Iny. 0.5% Braun Melsungen AG, Germany) was injected in the places where the catheters were positioned to avoid discomfort when the animals awoke.

When the PiCCOplus® monitor was calibrated, sevoflurane administration ceased and the dogs were allowed to awaken.

2.2. Study design

Thirty minutes after extubation, the following data were collected (baseline period): core body temperature (CT, °C), heart rate (HR, beats/min), respiratory rate (RR, breaths/min), CO (measured by means of pulse contour analysis), mean, systolic and diastolic arterial pressures (MAP, SAP, DAP, mmHg). Systemic vascular resistance (SVR, dyn s/cm^5), stroke volume (SV, mL), cardiac index (CI, L/min/m^2), systemic vascular resistance index (SVRI, dyn s/cm^5/m^2) and stroke volume index (SI, mL/m^2) were calculated using standard formulas (Pypendop and Verstegen, 1998).

Prior to sedation, factors used in the assessment of anaesthetic depth, including jaw tone, palpebral reflex and eye position, were recorded.

As follows, the dogs randomly received 2 μg/kg dexmedetomidine (Dexdomitor® 0.5 mg/ml. Orion Pharma, Finland) (group HDA, high dose of dexmedetomidine), 1 μg/kg dexmedetomidine (group LDA, low dose of dexmedetomidine) or a bolus of saline (group C, control group) intravenously. The three doses were diluted using up to 1 ml of saline. The same parameters recorded at the baseline period were collected at 1, 5 and 10 min after drug administration, and an average of the three measurements (sedation period) was obtained. The incidence of adverse effects were recorded e.g. vomiting, salivation and bradycardia (<80 beats/min). Data were collected by a single person, always the same, who was unaware of the treatment that the dogs received.

Ten minutes after sedation, anaesthesia was induced with alfaxalone in HPBC (Alfaxan® 10 mg/ml, Vetoquinol, Spain) at 6 mg/kg IV (Rodríguez et al., 2012) administered by hand at a rate of 10% of the total volume given as a bolus every 6 s until endotracheal intubation could be achieved (Sams et al., 2008). The total dose of alfaxalone administered was recorded. Episodes of apnoea (lack of respiratory movement for >30 s) and other adverse effects were recorded. If apnoea occurred, dogs were manually ventilated at a rate of 1 breath every 30 s, until spontaneous ventilation returned (Bell et al., 2011).

After endotracheal intubation (anaesthetic period), alfaxalone CRI was commenced at 0.07 mg/kg/min in the three groups, in combination with CRI of dexmedetomidine at 1 μg/kg/h for HDA, CRI of dexmedetomidine at 0.5 μg/kg/h for LDA and CRI of saline for C, during 90 min. Volumes across doses were kept constant at 1 ml/kg/h for CRI of both drugs. The CRI of alfaxalone was administered through the catheter in the right cephalic vein and the CRI of dexmedetomidine through the catheter in the left cephalic vein. Both infusions were administered separately using two infusion pumps (Perfusor®fm Braun S.A., Spain).

Parameters of CVP, haemoglobin oxygen saturation (SpO_2, %), end-tidal carbon dioxide partial pressure ($PECO_2$, mmHg), RR and inspiratory total volume (Vti, ml) were recorded with a multiparameter monitor (Anaesthesia monitor Datex Ohmeda®, GE Healthcare®, Finland). HR, MAP, SAP, DAP, CO and CT were recorded by PiCCO®plus monitor. During the anaesthetic period, data were recorded every 10 min (M10, M20, M30, M40, M50, M60, M70, M80, and M90). Core temperature was maintained between 37 and 39 °C with a convective warming system (Equator™. Smiths Medical ASD, Inc. Weymouth, USA).

Depth of anaesthesia was assessed via evaluation of palpebral reflex, jaw tone, eye position, HR, arterial blood pressure (ABP) and response to tail clamp (60 s compression on the base of the tail with a haemostat closed to full ratchet or less if the animal reacted), once every 30 min (Gómez-Villamandos et al., 2006a, 2006b). All head or limb reactions were considered positive. If there was a strong palpebral reflex or jaw tone, the pain response was considered positive, central rotation of the eyeball occurred, or if the heart rate or blood pressure increased by 20% from baseline values, anaesthetic depth was considered inadequate and 1 mg/kg alfaxalone was injected (Herbert et al., 2013). If this was insufficient, further boluses were given until anaesthesia was adequate. The requirement for rescue anaesthesia was recorded separately.

Heparinised anaerobic blood samples were collected from the right femoral artery for blood gas analysis by a blood gas analyser (Gasometer Ciba-Corning, Model 850 Chiron Diagnostic; Madrid, Spain). Samples were immediately stored on ice until analysis within 5 min of sampling. Arterial pH (pHa), arterial oxygen partial pressure (PaO_2, mmHg), carbon dioxide partial pressure ($PaCO_2$, mmHg) and arterial oxygen saturation (SaO_2, %) were recorded at baseline, 1 min after induction (post-induction) and every 30 min during an-