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RESEARCH PAPER

Effects of different doses of dexmedetomidine on anaesthetic induction with alfaxalone – a clinical trial

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Abstract

Objective To document the effects of two doses of dexmedetomidine on the induction characteristics and dose requirements of alfaxalone.

Study design Randomized controlled clinical trial.

Animals Sixty one client owned dogs, status ASA I-II.

Methods Dogs were allocated randomly into three groups, receiving as pre-anaesthetic medication, no dexmedetomidine (D_0), 1 μg kg^{-1} dexmedetomidine (D_1) intramuscularly (IM) or 3 μg kg^{-1} dexmedetomidine IM (D_3). All dogs also received 0.2 mg kg^{-1} methadone IM. Level of sedation was assessed prior to induction of anaesthesia. Induction of general anaesthesia was performed with alfaxalone administered intravenously to effect at a rate of 1 mg kg^{-1} $minute^{-1}$; the required dose to achieve tracheal intubation was recorded. Anaesthesia was maintained with isoflurane in oxygen. Cardiopulmonary parameters were recorded throughout the anaesthetic period. Quality of intubation, induction and recovery of anaesthesia were recorded. Quantitative data were compared with one-way ANOVA or Kruskal-Wallis test. Repeated measures were log-transformed and analysed with repeated measures ANOVA ($p < 0.05$).

Results Treatment groups were similar for categorical data, with exception of sedation level ($p < 0.001$). The doses (mean ± SD) of alfaxalone required for intubation were D_0 1.68 ± 0.24, D_1 1.60 ± 0.36 and D_3 1.41 ± 0.43, the difference between D_0 and D_3 being statistically significant ($p = 0.036$). Heart and respiratory rates during the anaesthetic period were significantly different over time and between groups ($p < 0.001$); systolic arterial blood pressure was significantly different over time ($p < 0.001$) but not between groups ($p = 0.833$). Induction quality and recovery scores were similar between groups ($p = 1.000$ and $p = 0.414$, respectively).

Conclusions and clinical relevance The administration of alfaxalone resulted in a good quality anaesthetic induction which was not affected by the dose of dexmedetomidine. Dexmedetomidine at 3 μg kg^{-1} IM combined with methadone provides good sedation and enables a reduction of alfaxalone requirements.

Keywords alfaxalone, anaesthesia, dexmedetomidine, dogs, induction, methadone.

Introduction

Dexmedetomidine is an imidazole derivative with high selectivity for the alpha-2 adrenergic receptor, representing the dextro-enantiomer of the racemate medetomidine (50:50 mixture) (Kuusela et al. 2001). It is used in dogs to provide sedation and analgesia, properties that make it very useful as a premedication agent prior to induction of anaesthesia; it

also has an effect on reduction of the dose of anaesthetic induction and maintenance agents (Kuusela et al. 2000, 2001; Gomez-Villamandos et al. 2006; Bell et al. 2011).

Side effects reported for dexmedetomidine use include cardiovascular changes. Hypotension and bradycardia have been described but characteristically, an initial phase of vasoconstriction that leads to hypertension is also observed (Murrell & Hellebrekers 2005). Cardiac output decrease may occur subsequently to bradycardia, and frequently observed electrocardiographic alterations include sinus arrhythmia and first and second degree atrioventricular blocks (Kuusela et al. 2001; Murrell & Hellebrekers 2005). Dexmedetomidine is also able to combine with imidazoline receptors and their stimulation leads to a central hypotensive and anti-arrhythmogenic action which may also cause some of the effects of this drug (Murrell & Hellebrekers 2005).

Alfaxalone is a synthetic neuroactive steroid which is marketed as an anaesthetic induction agent in small animals. Its characteristics include rapid onset of action, high acute tolerance, wide margin of safety, rapid recovery of consciousness, good muscle relaxation and apparent lack of accumulation, making it a suitable agent for induction and/or maintenance of anaesthesia (Ferre et al. 2006; Ambros et al. 2008). In dogs, administration of alfaxalone produces dose dependant alterations in cardiovascular, respiratory, pH and blood gas parameters. Respiratory rate (f_R), minute volume and arterial partial pressure of oxygen are depressed in a dose dependant fashion, while tidal volume is not significantly affected (Muir et al. 2008). It produces an increase in heart rate (HR) and decreases in arterial blood pressure and mean pulmonary arterial pressure, while systemic vascular resistance is not significantly altered (Muir et al. 2008; Rodriguez et al. 2012; Amengual et al. 2013). Duration of apnoea is directly related to the alfaxalone dose, as is its frequency of occurrence (Muir et al. 2008; Keates & Whittem 2012).

The aim of this study is to document the effects of two doses of dexmedetomidine on the induction characteristics and dose requirement of alfaxalone in a clinical setting. The hypothesis of the study was that dexmedetomidine would reduce the induction dose requirements of alfaxalone and the associated side effects of the induction agent.

Materials and methods

Animals

This project received approval from the Ethics and Welfare Committee of the Royal Veterinary College. The study was designed as a randomised controlled clinical trial in which sixty-one client-owned dogs admitted for diagnostic, orthopaedic or elective soft tissue surgical procedures were incorporated. Dogs undergoing anaesthesia for the above procedures were included if they were assessed as an American Society of Anesthesiologists (ASA) score of I or II, based on the physical examination and their clinical history. Informed owner consent was obtained for all animals. Exclusion criteria included a history of cardiovascular pathology and age below twelve weeks or above eight years. Pre-study power calculations indicated that a total of sixty animals would be necessary to detect at least a 25% reduction in the anaesthetic induction dose of alfaxalone when dexmedetomidine is used as a pre-anaesthetic medication (study power 80%, confidence level 95% and assuming a standard deviation of 0.5–0.6 mg kg^{-1}, Win-Episcope version 2.0).

Study protocol

All animals were submitted to a period of fasting for a minimum of eight hours before the initiation of the protocol, while water was continuously available until time of premedication. Dogs were allocated, by means of a random number generator (Microsoft Excel; Microsoft Corp. WA, USA), to one of the following three groups: in combination with methadone hydrochloride (Physeptone; Martindale Pharma, UK) 0.2 mg kg^{-1} intramuscularly (IM): group D_0 received no dexmedetomidine (Dexdomitor; Orion Corporation, Finland), group D_1 received 1 μg kg^{-1} dexmedetomidine IM and group D_3 received 3 μg kg^{-1} dexmedetomidine IM. All administrations were performed in the quadriceps muscle group. Immediately before the drug administration, rectal temperature, f_R and HR were recorded (T_{premed}). The animals were then allowed to remain in a quiet environment for at least 15 minutes, at which point, if not yet present, an intravenous over the needle catheter (Jelco IV catheter; Smiths Medical International, UK) size 20 or 22 gauge was placed either in a cephalic or external saphenous vein. In the five minutes prior to induction of anaesthesia (T_{-5}), the level of