RESEARCH PAPER

Cardiovascular effects, induction and recovery characteristics and alfaxalone dose assessment in alfaxalone *versus* alfaxalone-fentanyl total intravenous anaesthesia in dogs

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Abstract

Objective To compare cardiovascular effects and anaesthetic quality of alfaxalone alone or in combination with a fentanyl constant rate infusion (CRI) when used for total intravenous anaesthesia (TIVA) in dogs.

Study design Prospective, blinded, randomized, experimental study.

Animals A group of 12 intact female dogs.

Methods Following intramuscular dexmedetomidine (10 μg kg^{-1}) and methadone (0.1 mg kg^{-1}) administration, anaesthesia was induced intravenously with alfaxalone (2 mg kg^{-1}) (group AP) or alfaxalone (2 mg kg^{-1}) preceded by fentanyl (2 μg kg^{-1}) (group AF). Anaesthetic maintenance was obtained with an alfaxalone variable rate infusion (VRI) started at 0.15 mg kg^{-1} $minute^{-1}$ (group AP) or an alfaxalone VRI (same starting rate) combined with a CRI of fentanyl (10 μg kg^{-1} $hour^{-1}$) (group AF). The alfaxalone VRI was adjusted every 5 minutes, based on clinical assessment. Cardiovascular parameters (recorded every 5 minutes) and recovery characteristics (using a numerical rating scale) were compared between groups. A mixed model statistical approach was used to compare the mean VRI alfaxalone dose and cardiovascular parameters between groups; recovery scores were analysed using the Wilcoxon rank-sum test ($\alpha = 0.05$).

Results The mean CRI alfaxalone dose for anaesthetic maintenance differed significantly between treatments [0.16 ± 0.01 mg kg^{-1} $minute^{-1}$ (group AP) *versus* 0.13 ± 0.01 mg kg^{-1} $minute^{-1}$ (group AF)]. Overall heart rate, systolic, mean and diastolic arterial pressures were lower in group AF than in group AP ($p < 0.0001$, $p = 0.0058$, $p < 0.0001$ and $p < 0.0001$, respectively. Recovery quality scores did not differ significantly and were poor in both groups.

Conclusions and clinical relevance In combination with a fentanyl CRI, an alfaxalone TIVA provides a cardiovascular stable anaesthesia in dogs. The addition of fentanyl results in a significant dose reduction. The quality of anaesthetic recovery remains poor.

Keywords alfaxalone, cardiorespiratory, dog, fentanyl, total intravenous anaesthesia.

Introduction

Total intravenous anaesthesia (TIVA) is a technique in which induction and maintenance of anaesthesia are obtained using intravenous (IV) drugs only (Campbell et al. 2001). It is widely used in human medicine, yet less frequently in veterinary medicine, where inhalation techniques are most commonly applied for the maintenance of anaesthesia. However, according to international treaties, the emission of volatile agents in the atmosphere will be prohibited from 2030 onwards (Joubert 2009). This forecast, together with the introduction of drugs with pharmacokinetic properties suitable for use in TIVA, might explain the growing interest in TIVA protocols in veterinary medicine. A desirable TIVA drug (or combination of drugs) is rapidly cleared from the body to avoid cumulative effects (Campbell et al. 2001) and ensures adequate anaesthetic conditions with minimal cardiovascular depression, while resulting in a smooth and rapid recovery (Kästner 2016). In humans, Hofer et al. (2003) reported that a TIVA using propofol produces an improved early postoperative patient well-being and reduces the incidence of postoperative nausea and vomiting compared with inhalation anaesthesia with sevoflurane. In veterinary medicine, TIVA with propofol or alfaxalone has been judged to be a clinically reliable technique in view of haemodynamic stability and smooth recovery (Raisis et al. 2007; Suarez et al. 2012; Herbert et al. 2013).

Alfaxalone (3-α-hydroxy−5α- pregnane-11,20-dione) is a synthetic neuroactive steroid, solubilized with 2-hydroxypropyl-beta cyclodextrin (Alfaxan; Jurox Pty Ltd, NSW, Australia), which interacts with the γ-aminobutyric acid ($GABA_A$) receptors in the central nervous system to produce anaesthesia and muscle relaxation. This veterinary formulation has been used clinically for the induction and maintenance of anaesthesia in a variety of species, including pigs (Keates 2003), dogs (Ambros et al. 2008; Maddern et al. 2010), cats (Whittem et al. 2008; Zaki et al. 2009) and ponies (Leece et al. 2009).

Alfaxalone has several appealing properties including a wide safety margin, with a therapeutic index that is three or four times greater than that of propofol or thiopental (Høgskilde et al. 1987), a fast onset and short duration of action, good muscle relaxation and rapid recovery (Herbert et al. 2013). It has a large volume of distribution, short terminal half-life and high clearance (Ferré et al. 2006). Furthermore, it does not appear to accumulate after repeated doses and has therefore been used for TIVA, resulting in excellent recovery in dogs (Ambros et al. 2008).

In general, the use of a single anaesthetic maintenance agent does not provide a balanced anaesthetic approach since most of the IV agents have poor analgesic qualities, while others only have limited anaesthetic properties. Therefore, TIVA protocols should be part of a balanced anaesthetic/analgesic plan, and the administration of additional analgesics might be considered necessary (Kästner 2016).

Fentanyl is a short-acting pure μ-opioid agonist with a potency that is 75−100 times higher than morphine (Vardanyan & Hruby 2014). The relative minimal cardiovascular effects are the result of dose-dependent bradycardia because of increased vagal tone, which is easily treatable with anticholinergics (Keating et al. 2013). In the study of Hughes & Nolan (1999), co-administration of fentanyl with propofol in dogs that did not undergo surgery resulted in a stable anaesthesia. Additionally, μ- opioid agonists decreased the minimum alveolar concentration of inhalation agents in a dose-dependent manner in dogs (Hellyer et al. 2001). To the best of the authors' knowledge, no studies have been performed regarding the combined administration of a fentanyl and alfaxalone infusion for TIVA in dogs.

The objective of the present study was to compare the cardiovascular effects during alfaxalone TIVA *versus* alfaxalone TIVA combined with a fentanyl constant rate infusion (CRI) and to additionally investigate the presumed dose reduction of alfaxalone in the latter group. Quality of induction, ease of intubation and quality of recovery were also investigated. We hypothesized that the addition of fentanyl to a VRI of alfaxalone would result in a significant dose reduction of alfaxalone combined with cardiovascular stability.

Materials and methods

Animals and randomization design

Ethical approval from the Ghent University Ethics Committee for the combined study was obtained (EC 2014/77) prior to the experiments.

A group of 12 intact female experimental Beagles were prospectively studied. The dogs were housed together conforming to Home Office Regulations. All dogs were classified as American Society of Anesthesiologists (ASA) class 1 and were deemed healthy based on physical examination performed by the

