Veterinary Anaesthesia and Analgesia 2017, **xxx**, 1–11 http://dx.doi.org/10.1016/j.vaa.2017.02.011

RESEARCH PAPER

Induction dose and recovery quality of propofol and alfaxalone with or without midazolam coinduction followed by total intravenous anesthesia in dogs

PenTing Liao[a], Melissa Sinclair[a], Alexander Valverde[a], Cornelia Mosley[b], Heather Chalmers[a], Shawn Mackenzie[c] & Brad Hanna[d]

[a]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada

[b]404 Veterinary Emergency and Referral Hospital, Newmarket, ON, Canada

[c]Toronto Veterinary Emergency Hospital, Scarborough, ON, Canada

[d]Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada

Correspondence: Melissa Sinclair, Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON N1G 2W1, Canada. E-mail: msinclai@uoguelph.ca

Abstract

Objectives To compare propofol and alfaxalone, with or without midazolam, for induction of anesthesia in fentanyl-sedated dogs, and to assess recovery from total intravenous anesthesia (TIVA).

Study design Prospective, incomplete, Latin-square study

Animals Ten dogs weighing 24.5 ± 3.1 kg (mean ± standard deviation).

Methods Dogs were randomly assigned to four treatments: treatment P-M, propofol (1 mg kg^{-1}) and midazolam (0.3 mg kg^{-1}); treatment P-S, propofol and saline; treatment A-M, alfaxalone (0.5 mg kg^{-1}) and midazolam; treatment A-S, alfaxalone and saline, administered intravenously 10 minutes after fentanyl (7 μg kg^{-1}, intravenously). Additional propofol or alfaxalone were administered as necessary for endotracheal intubation. TIVA was maintained for 35–55 minutes by infusions of propofol or alfaxalone. Scores were assigned for quality of sedation, induction, extubation and recovery. The drug doses required for intubation and TIVA, times from sedation to end of TIVA, end anesthesia to extubation and to standing were recorded. Analysis included a general linear mixed model with *post hoc* analysis ($p < 0.05$).

Results Significant differences were detected in the quality of induction, better in A-M than A-S and P-S, and in P-M than P-S; in total intubation dose, lower in P-M (1.5 mg kg^{-1}) than P-S (2.1 mg kg^{-1}), and A-M (0.62 mg kg^{-1}) than A-S (0.98 mg kg^{-1}); and lower TIVA rate in P-M (268 μg kg^{-1} $minute^{-1}$) than P-S (310 μg kg^{-1} $minute^{-1}$). TIVA rate was similar in A-M and A-S (83 and 87 μg kg^{-1} $minute^{-1}$, respectively). Time to standing was longer after alfaxalone than propofol, but was not influenced by midazolam.

Conclusions and clinical relevance Addition of midazolam reduced the induction doses of propofol and alfaxalone and improved the quality of induction in fentanyl-sedated dogs. The dose rate of propofol for TIVA was decreased.

Keywords alfaxalone, coinduction, dog, midazolam, propofol.

Introduction

Propofol and alfaxalone are commonly used induction agents in small animals; however, anesthetic induction may not always be smooth, necessitating higher induction doses and increasing the negative cardiopulmonary side effects. Coinduction agents can be used with either agent to promote a smooth

Please cite this article in press as: Liao PenTing-g, Sinclair M, Valverde A et al. Induction dose and recovery quality of propofol and alfaxalone with or without midazolam coinduction followed by total intravenous anesthesia in dogs, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2017.02.011

induction and reduction in induction dose and associated negative cardiopulmonary effects.

The main coinduction agents used in veterinary medicine are diazepam, midazolam, lidocaine and ketamine. The veterinary literature indicates variable effects of coinduction agents on the anesthesia induction dose (Lerche et al. 2000; Ko et al. 2006; Braun et al. 2007; Jolliffe et al. 2007; Covey-Crump & Murison 2008; Mair et al. 2009; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Martinez-Taboada & Leece 2014). The variability in results with benzodiazepines in dogs is associated with differences in premedication agents and the benzodiazepine that is used, the dose, and the order and speed of administration. With midazolam coinduction with propofol, the dose reduction is most consistent at midazolam doses of 0.2−0.5 mg kg^{-1} and when the midazolam is administered intravenously (IV) after an initial bolus of propofol (Robinson & Borer-Weir 2013; Sanchez et al. 2013). However, an observational study investigated the effects of administering midazolam (0.2 mg kg^{-1}) IV 5 minutes before alfaxalone (2 mg kg^{-1}) IV in butorphanol-sedated dogs, and described an excellent quality of induction (Seo et al. 2015).

The pharmacologic profiles of alfaxalone and propofol indicate that both are noncumulative, have rapid redistribution and biotransformation, and rapid clearance, all features that facilitate total IV anesthesia (TIVA). Recovery from propofol TIVA has been described as smooth and excellent (Keegan & Greene 1993; Ambros et al. 2008; Suarez et al. 2012). However, the recovery quality of alfaxalone is controversial. Most studies have identified a good to excellent overall recovery quality with alfaxalone (Ambros et al. 2008; Muir et al. 2008; Psatha et al. 2011; Suarez et al. 2012; Herbert et al. 2013). Recovery from alfaxalone TIVA has been reported comparable with propofol TIVA (Ambros et al. 2008; Suarez et al. 2012). Recovery from isoflurane anesthesia after induction with alfaxalone was better than etomidate (Rodríguez et al. 2012) or after induction with diazepam−fentanyl (Psatha et al. 2011). However, dogs with history of seizures administered a single dose of alfaxalone for induction of anesthesia followed by sevoflurane for magnetic resonance imaging (MRI) had poorer recovery scores at the time of achieving sternal recumbency, compared with dogs in which anesthesia was induced with propofol (Jimenez et al. 2012). With alfaxalone, dogs may be sensitive to external stimulation (Ferré et al. 2006), or demonstrate tremors, rigidity and myoclonus during recovery (Maney et al. 2013). Hence premedication and a quiet and undisturbed recovery are recommended (Jurox Pty Ltd, Australia). To the authors' knowledge, there has not been a direct comparison of the TIVA maintenance quality and recovery characteristics of propofol and alfaxalone, after coinduction with midazolam, in fentanyl-premedicated dogs for diagnostic computed tomography (CT) or MRI.

The goal of this study was to compare propofol and alfaxalone, with or without midazolam, in fentanyl-sedated dogs undergoing CT or MRI. The hypotheses were that the inclusion of midazolam would decrease the dose of propofol or alfaxalone required to achieve endotracheal intubation and improve the quality of induction of anesthesia, reduce the dose of propofol or alfaxalone for TIVA, and improve the overall recovery from anesthesia.

Materials and methods

Animals

All procedures were approved by the Animal Care Committee, University of Guelph, and followed the Canadian Council on Animal Care Guidelines. Ten healthy research cross-bred hound dogs, mean (range) age 3.4 (1.9−5.5) years, (mean ± standard deviation) weight 24.5 ± 3.1 kg, were used. Health status was based on general physical examination, complete blood count and biochemistry panel. Each dog was fasted for at least 12 hours but given free access to water before general anesthesia.

Study design

This study was a prospective, blinded, randomized, incomplete Latin-square experimental study with at least 7 days between anesthesia events for each dog. Four dogs were anesthetized each on five occasions, five dogs were anesthetized on three occasions and one dog was anesthetized twice. Anesthesia was maintained for a separate study that comprised three MRI (first MRI, $n = 9$, second, $n = 9$, third, $n = 5$) and two CT (first CT, $n = 9$, second, $n = 5$). The imaging was focused on the lumbosacral space and an intervertebral disc injection of gelified ethanol was performed during anesthesia for the first CT. The sample size was calculated to detect 30% difference of propofol or alfaxalone induction dose with type 1 error of 0.05 and power of 80%. A minimum of four dogs in each group was needed. A random sequence was generated using a computer algorithm (GraphPad

Please cite this article in press as: Liao PenTing-g, Sinclair M, Valverde A et al. Induction dose and recovery quality of propofol and alfaxalone with or without midazolam coinduction followed by total intravenous anesthesia in dogs, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2017.02.011