Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2013, **40**, 455–463 doi:10.1111/vaa.12052

RESEARCH PAPER

A dose titration study into the effects of diazepam or midazolam on the propofol dose requirements for induction of general anaesthesia in client owned dogs, premedicated with methadone and acepromazine

Rebecca Robinson* & Kate Borer-Weir*

*Department of Veterinary Clinical Sciences, Royal Veterinary College, University of London, Hatfield, UK

Correspondence: Rebecca Robinson, Royal Veterinary College, University of London, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire AL9 7TA, UK. E-mail: rlrobinson@rvc.ac.uk

Abstract

Objective To assess the effect of a benzodiazepine co-induction on propofol dose requirement for induction of anaesthesia in healthy dogs, to describe any differences between midazolam and diazepam and to determine an optimal benzodiazepine dose for co-induction.

Study design Prospective, randomised, blinded placebo controlled clinical trial.

Animals Ninety client owned dogs (ASA I-III, median body mass 21.5kg (IQR 10-33)) presented for anaesthesia for a variety of procedures.

Methods Dogs were randomised to receive saline 0.1 mL kg^{-1}, midazolam or diazepam at 0.2, 0.3, 0.4 or 0.5 mg kg^{-1}. All dogs received 0.01 mg kg^{-1} acepromazine and 0.2 mg kg^{-1} methadone intravenously (IV). Fifteen minutes later, sedation was assessed and scored prior to anaesthetic induction. Propofol, 1 mg kg^{-1}, was administered IV, followed by the treatment drug. Further propofol was administered until endotracheal intubation was possible. Recorded data included patient signalment, sedation score, propofol dosage and any adverse reactions.

Results Midazolam (all groups combined) significantly reduced propofol dose requirement compared to saline ($p < 0.001$) and diazepam ($p = 0.008$). Midazolam (0.4 mg kg^{-1}) significantly reduced propofol dose requirement ($p = 0.014$) compared to saline, however other doses failed to reach statistical significance. Diazepam did not significantly reduce propofol dose requirement compared to saline ($p = 0.089$). Dogs weighing <5 kg, regardless of treatment group, required a greater propofol dose than those weighing 5–40 kg ($p = 0.002$) and those >40 kg ($p = 0.008$). Dogs which were profoundly sedated required less propofol than those which were mildly sedated ($p < 0.001$) and adequately sedated ($p = 0.003$).

Conclusions and clinical relevance Midazolam (0.4 mg kg^{-1}) given IV after 1 mg kg^{-1} of propofol significantly reduced the further propofol dose required for intubation compared to saline. At the investigated doses, diazepam did not have significant propofol dose sparing effects.

Keywords anaesthesia, co-induction, diazepam, dog, midazolam, propofol.

Introduction

Propofol is a phenol compound (James & Glen 1980) which is a commonly used induction agent in small animal anaesthesia, associated with rapid, smooth induction and recovery (Watkins et al. 1987).

When administered to premedicated dogs, propofol (6 mg kg^{-1}) decreased arterial blood pressure (Smith et al. 1993); however by reducing the baroreceptor sensitivity, there was a lack of compensatory tachycardia (Ilkiw et al. 1992). Other adverse effects of propofol administration include respiratory depression, apnoea and rarely, cyanosis at higher doses (Smith et al. 1993; Muir & Gadawski 1998). Excitatory phenomena and/or muscle twitching have also been reported (Davies 1991; Muir & Gadawski 1998).

Benzodiazepines produce mild sedative effects and centrally mediated muscle relaxation (Court & Greenblatt 1992). Benzodiazepines have minimal adverse cardiopulmonary effects at clinical doses, while higher doses have been reported to cause cardiopulmonary depression (Jones et al. 1979; Heniff et al. 1997). Administration of benzodiazepines to healthy, unsedated canine patients can cause excitatory behaviour presumably due to disinhibition of suppressed behaviour or a loss of muscle tone and coordination (Court & Greenblatt 1992).

In adult humans, there is a synergistic effect between propofol and midazolam, with a reduction in propofol dose of approximately 50% when 0.13 mg kg^{-1} IV midazolam was used compared to propofol alone (Short & Chui 1991). In paediatric human patients, a similar synergistic effect was found, with improved haemodynamic stability (Goel et al. 2008). Although co-inductions with benzodiazepines and propofol have been studied in veterinary medicine, the available evidence is limited with conflicting results (Stegmann & Bester 2001; Covey-Crump & Murison 2008). Previous studies have reported a high incidence of adverse events such as excitement and increased motor activity. However, in both of these studies, the benzodiazepine was administered prior to propofol, contrary to the current clinical practice in our institution. One recent study has shown beneficial effects, both in terms of reduced propofol dose and excitement when a co-induction was performed with midazolam administered after 1 mg kg^{-1} propofol compared to its administration before propofol (Sánchez et al. 2013).

The aim of this study was to determine if there was a dose dependent sparing effect of benzodiazepines on the dose of propofol required for anaesthetic induction in premedicated dogs. A further aim was to document any differences between midazolam and diazepam. Our hypotheses were that the benzodiazepines would provide a propofol dose sparing effect with no differences between diazepam and midazolam and that this effect would be dose dependent.

Materials and methods

The study was a randomised, 'blinded', placebo controlled clinical trial which was approved by the Royal Veterinary College's ethics committee (URN 2012 1168). Owners gave consent for the anaesthetic procedure the dog was to undergo. A sample size calculation was performed based upon what was considered to be a clinically relevant difference in propofol requirement of 1 mg kg^{-1}, with an estimated standard deviation of 0.75 mg kg^{-1}. With a study power of 0.8 and an alpha of 0.05, the sample size was estimated to be nine animals per group. Therefore, we aimed to recruit 90 dogs, with 10 animals in each of nine treatment groups.

Client owned dogs, American Society of Anesthesiologists physical status (ASA) I – III, undergoing general anaesthesia for a variety of clinical reasons in a university referral hospital were enrolled on the study. All dogs underwent a pre-anaesthetic examination to ensure their suitability for the study. Patients were excluded if there were any underlying pathologies preventing the use of the planned anaesthetic protocol, or if sedative drugs had been administered in the previous 4 hours. If not already in situ, an intravenous (IV) cannula (Jelco; Medex Medical Ltd, UK) was placed in either a cephalic or lateral saphenous vein.

Dogs were assigned randomly to a treatment group by picking a card from a bag. The investigator (RR or KBW) performing the anaesthetic induction was unaware of the treatment allocation. Treatments included a control group of saline 0.1 mL kg^{-1}, midazolam (Hypnovel, 5 mg mL^{-1}; Roche Products Ltd, UK) or diazepam (Diazemuls, 5 mg mL^{-1}; Actavis, UK) treatments (Groups M and D respectively) each including doses of 0.2, 0.3, 0.4 and 0.5 mg kg^{-1}. All drugs were prepared by a suitably qualified person, who was not one of the investigators. Once prepared, syringes were covered with opaque tape to ensure the investigator could not see the colour or quantity of drug present.

All dogs were premedicated with 0.01 mg kg^{-1} acepromazine (ACP, 2 mg mL^{-1}; Novartis, UK) and 0.2 mg kg^{-1} methadone (Physeptone, 10 mg mL^{-1}; Martindale Pharmaceuticals, UK) IV. Fifteen minutes after administration, the patient's sedation