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RESEARCH PAPER

The effects of diazepam or midazolam on the dose of propofol required to induce anaesthesia in cats

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Abstract

Objectives Assess effects of benzodiazepine administration on the propofol dose required to induce anaesthesia in healthy cats, investigate differences between midazolam and diazepam, and determine an optimal benzodiazepine dose for co-induction.

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

Animals Ninety client-owned cats (ASA I and II) with a median (interquartile range) body mass of 4.0 (3.4–4.9) kg.

Methods All cats received 0.01 mg kg^{-1} acepromazine and 0.2 mg kg^{-1} methadone intravenously (IV). Fifteen minutes later, sedation was scored on a scale of 1–5, with 5 indicating greatest sedation. Propofol, 2 mg kg^{-1}, administered IV, was followed by either midazolam or diazepam at 0.2, 0.3, 0.4 or 0.5 mg kg^{-1} or saline 0.1 mL kg^{-1}. Further propofol was administered until endotracheal intubation was possible. Patient signalment, sedation score, propofol dosage and adverse reactions were recorded.

Results Midazolam and diazepam (all doses) significantly reduced the propofol dose required compared with saline ($p < 0.001$). There was no difference between midazolam and diazepam in propofol dose reduction ($p = 0.488$). All individual doses of midazolam reduced propofol requirement compared with saline (0.2 mg kg^{-1}, $p = 0.028$; 0.3 mg kg^{-1}, $p = 0.006$; 0.4 mg kg^{-1}, $p < 0.001$; 0.5 mg kg^{-1}, $p = 0.009$). Diazepam 0.2 mg kg^{-1} did not reduce the propofol dose compared with saline ($p = 0.087$), but the remaining doses did (0.3 mg kg^{-1}, $p = 0.001$; 0.4 mg kg^{-1}, $p = 0.032$; 0.5 mg kg^{-1}, $p = 0.041$). Cats with sedation scores of 3 required less propofol than cats with scores of 2 ($p = 0.008$). There was no difference between groups in adverse events.

Conclusions and clinical relevance Midazolam (0.2–0.5 mg kg^{-1}) and diazepam (0.3–0.5 mg kg^{-1}) administered IV after 2 mg kg^{-1} propofol significantly reduced the propofol dose required for tracheal intubation.

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

Introduction

Propofol is a phenolic compound licensed for use as an anaesthetic induction agent in cats in the UK. It is reported to facilitate smooth, problem-free anaesthetic induction in this species (Brearley et al. 1988). Its use in cats has been associated with adverse effects including decreases in heart rate, myocardial contractility and systolic arterial blood pressure through inhibition of the vasomotor mechanism (Yang et al. 1997; Mendes & Selmi 2003), respiratory depression and delayed recovery after prolonged anaesthesia (Pascoe et al. 2006) with some pawing of the face (Brearley et al. 1988). Excitatory phenomena have been reported in dogs

following propofol administration (Davies 1991), but such events are yet to be reported in cats.

Benzodiazepines induce centrally acting muscle relaxation with little evidence of sedation, according to studies in which midazolam was administered alone to healthy, experimental cats at supraclinical doses of up to 5 and 20 mg kg^{-1} (Leah et al. 1983; Ilkiw et al. 1996). Although at clinical doses benzodiazepines are reported to have minimal cardiovascular effects, at a dose of 0.1 mg kg^{-1} diazepam reduces myocardial contractility, systolic blood pressure and heart rate in anaesthetized cats (Chai & Wang 1966).

Benzodiazepines are used as co-induction agents with propofol in human anaesthesia; synergism between propofol and midazolam (Short & Chui 1991) and improved haemodynamic stability in paediatric medicine (Goel et al. 2008) have been demonstrated. Benzodiazepine and propofol co-inductions are becoming popular in veterinary medicine and have shown variable degrees of success in numerous studies in canine anaesthesia (Stegmann & Bester 2001; Covey-Crump & Murison 2008; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Hopkins et al. 2014). However, minimal evidence exists for co-inductions in feline anaesthesia and, to the authors' knowledge, is based on a single report (Bley et al. 2007). There are no reports on the systematic assessment of the effects of benzodiazepine dose or the effects of the administration of propofol prior to benzodiazepine, although this sequence of administration has been shown to incur fewer adverse effects in dogs compared with the prior administration of benzodiazepine (Sanchez et al. 2013).

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

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). Each cat owner consented to the anaesthetic procedure the cat 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}. To achieve a study power of 0.8 with an α of 0.05, the sample size was estimated to be nine animals per group. Therefore, we aimed to recruit 90 cats and to place 10 animals in each of nine treatment groups.

Client-owned cats, with American Society of Anesthesiologists (ASA) status of I or II, undergoing general anaesthesia for a variety of clinical reasons in a university referral hospital, were enrolled in the study. All cats underwent a preanaesthetic examination to ensure their suitability for the study. Cats were excluded if any underlying pathologies preventing the use of the planned anaesthetic protocol emerged, 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, lateral or medial saphenous vein.

Cats were randomly assigned to treatment groups by cards picked from a bag. The investigator (RR or KBW) performing the anaesthetic induction was unaware of the treatment allocation. Treatments included a control treatment of saline 0.1 mL kg^{-1}, and midazolam (Hypnovel, 5 mg mL^{-1}; Roche Products Ltd, UK) or diazepam (Diazemuls, 5 mg mL^{-1}; Actavis UK Ltd, UK) treatments, each of which were administered at 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 prevent the investigator from seeing the colour or quantity of drug present.

All cats were premedicated with 0.01 mg kg^{-1} acepromazine (ACP, 2 mg mL^{-1}; Novartis Animal Health UK Ltd, UK) and 0.2 mg kg^{-1} methadone (Physeptone, 10 mg mL^{-1}; Martindale Pharmaceuticals Ltd, UK) IV. Fifteen minutes after administration, the patient's sedation was assessed by one of the two investigators (RR or KBW) and graded on a scale of 1–5, as shown in Table 1 (Maddern et al. 2010).

Immediately after the assessment of sedation, induction of anaesthesia was commenced. One of the primary investigators (RR or KBW) administered 2 mg kg^{-1} propofol IV (Propoflo, 10 mg mL^{-1}; Abbott Laboratories Ltd, UK) over 15–45 seconds to sedate the patient. After flushing the IV cannula

