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RESEARCH PAPER

Comparison of two intravenous anesthetic infusion regimens for alfaxalone in cats

Bruno H Pypendop[a], MG Ranasinghe[b] & Kirby Pasloske[b]

[a]Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, CA, USA

[b]Jurox Pty Ltd, Rutherford, NSW, Australia

Correspondence: Bruno Pypendop, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA 95616, USA. E-mail: bhpypendop@ucdavis.edu

Abstract

Objective To compare the performance of an alfaxalone constant rate intravenous (IV) infusion *versus* a 3-step IV infusion, both following a loading dose, for the maintenance of a target plasma alfaxalone concentration of 7.6 mg L^{-1} (effective plasma alfaxalone concentration for immobility in 99% of the population) in cats.

Study design Prospective randomized crossover study.

Animals A group of six healthy, adult male neutered cats.

Methods Catheters were placed in a jugular vein for blood sampling and in a medial saphenous vein for drug administration. An IV bolus of alfaxalone (2 mg kg^{-1}) was administered, followed by either 0.2 mg kg^{-1} $minute^{-1}$ for 240 minutes (single infusion; SI) or 0.4 mg kg^{-1} $minute^{-1}$ for 10 minutes, then 0.3 mg kg^{-1} $minute^{-1}$ for 30 minutes, and then 0.2 mg kg^{-1} $minute^{-1}$ for 200 minutes (3-step infusion; 3-step). Plasma alfaxalone concentration was measured at six time points during the infusions. Measures of performance were calculated for each infusion regimen and compared using the paired Wilcoxon signed-rank test.

Results Median (range) absolute performance error, divergence, median prediction error and wobble were 15 (8–19)%, −8 (−12 to −6)% $hour^{-1}$, −12 (−19 to −7)% and 10 (8–19)%, respectively, in the SI treatment, and 6 (2–16)%, 0 (−13 to 2)% $hour^{-1}$, 1 (−16 to 4)% and 4 (3–6)% respectively, in the 3-step treatment and were significantly smaller in the 3-step treatment than in the SI treatment.

Conclusion and clinical relevance After IV administration of a bolus dose, a 3-step infusion regimen can better maintain stable plasma alfaxalone concentrations close to the target concentration than a single constant rate infusion.

Keywords alfaxalone, cats, constant rate infusion.

Introduction

Alfaxalone is a short-acting neurosteroid anesthetic that is commonly used for induction of anesthesia in dogs and cats. In addition, it can be used for maintenance of anesthesia via intermittent intravenous (IV) boluses or IV infusion. Although a number of studies have reported the use of IV alfaxalone infusions in dogs (Ambros et al. 2008; Suarez et al. 2012; Quiros Carmona et al. 2014; Warne et al. 2014; Raisis et al. 2015; Conde Ruiz et al. 2016; Hunt et al. 2016; Navarrete et al. 2016; Bennett et al. 2017; Dehuisser et al. 2017; Liao et al. 2017; Quiros-Carmona et al. 2017), the information available in cats in scarce (Vettorato 2013; Beths et al. 2014; Schwarz et al. 2014).

The effective plasma alfaxalone concentration for the production of immobility during noxious stimulation in 99% of cats (EC_{99}) was recently estimated to be 7.6 mg L^{-1} (Pypendop et al. 2018). In a subsequent study, the pharmacokinetics of alfaxalone in six cats following administration by target-controlled infusion was characterized (Pypendop et al. unpublished data). The combined knowledge of effective plasma concentration and pharmacokinetics allows the design of pharmacokinetic-based infusion regimens (Glass et al. 2005).

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The aim of this study was to compare the performance of an alfaxalone constant rate IV infusion and a 3-step IV infusion, both following a loading dose, for the maintenance of the EC_{99} of alfaxalone in cats. We hypothesized that the 3-step infusion would maintain plasma concentrations closer to the targeted EC_{99} over the duration of infusion.

Materials and methods

This study was approved by the Institutional Animal Care and Use Committee at the University of California, Davis, CA, USA. A group of six male neutered cats aged 1 year and weighing 5.8 ± 0.5 kg (mean ± standard deviation) were studied. Cats were considered healthy based on history and physical examination 2 days prior to, and on the day of an experiment, and daily observations compatible with the absence of illness for 7 days prior to each experiment. Husbandry conditions for this facility have been previously described (Honkavaara et al. 2017). Cats were fed a commercial diet (Laboratory Feline Diet 5003; LabDiet, MO, USA) once daily. Food, but not water, was withheld for at least 8 hours prior to each experiment.

The day before each experiment, each cat was anesthetized with isoflurane in oxygen delivered in an acrylic chamber. Once the righting reflex was lost, the cat was taken out of the chamber. The trachea was intubated and anesthesia was maintained with isoflurane in oxygen delivered via a coaxial Mapleson F system, with a fresh gas flow of 2 L minute^{-1}. The hair over a jugular vein and a medial saphenous vein was clipped and the skin was aseptically prepared using chlorhexidine and alcohol. A 19 gauge, 15 cm catheter and a 20 gauge, 5 cm catheter were placed in the jugular and medial saphenous vein, respectively. Catheters were sutured (jugular) or taped (medial saphenous) to the skin and a light bandage was placed over them. The cat was allowed to recover from anesthesia with an Elizabethan collar.

The next day, the cat was administered alfaxalone, 2 mg kg^{-1} over 5 seconds, followed by either a constant rate infusion at 0.2 mg kg^{-1} minute^{-1} (treatment single infusion; SI) or three successive constant rate infusions: 0.4 mg kg^{-1} minute^{-1} for 10 minutes, then 0.3 mg kg^{-1} minute^{-1} for 30 minutes, and then 0.2 mg kg^{-1} minute^{-1} for the remainder of the infusion (3-step treatment). The infusions were administered for a total of 240 minutes. The order of treatments was randomly selected using an online randomizer (www.random.org). Infusions were administered via the medial saphenous vein catheter using a syringe pump (Medfusion 2010i; Medex, Inc., GA, USA). A formulation of alfaxalone (10 mg mL^{-1}) in hydroxypropyl-β-cyclodextrin containing the preservatives ethanol (150 mg mL^{-1}), chlorocresol (1 mg mL^{-1}) and benzethonium chloride (0.2 mg mL^{-1}) was used.

The cat was positioned in lateral recumbency on a heating pad. An attempt was made at intubating the trachea if the cat was deemed at an appropriate depth of anesthesia based on jaw muscle relaxation, lack of palpebral reflex and eccentric position of the eye. Oxygen (2 L minute^{-1}) was administered via a coaxial Mapleson F system connected to the endotracheal tube (if placed) or to a face mask. Pulse rate (PR) and hemoglobin oxygen saturation (SpO_2; OxiMax N-65; Nellcor, MA, USA), respiratory rate (f_R; observation of chest excursions) and rectal temperature (RT; VETone thermometer; MWI, ID, USA) were recorded every 5 minutes starting 5 minutes after administration of the alfaxalone bolus until the end of infusion. A noxious stimulus was applied 5 and 20 minutes after administration of the alfaxalone bolus and every 20 minutes thereafter until the end of infusion. The stimulus consisted of clamping the tail with a 20 cm Martin forceps closed to the first ratchet for 60 seconds or until movement was observed, whichever occurred first. Movement related to coughing or gagging was ignored. Times from discontinuation of the infusion to the first head lift, return to sternal recumbency and ability to stand without assistance were recorded. Quality of induction of anesthesia, anesthesia and recovery were scored on 100 mm visual analog scales (VAS), with 0 corresponding to the worst possible quality and 100 to the best possible quality, as previously described (Pypendop et al. 2018). The same investigator (BHP) always made the assessments and was not blinded to the treatment.

Blood samples (2 mL) were collected from the jugular catheter prior to drug administration and 15, 30, 60, 120, 180 and 240 minutes after the alfaxalone bolus had been administered. Prior to collection of the sample, 2 mL of blood was aspirated in a syringe containing a small amount of heparinized saline solution; this blood was returned to the cat via the jugular catheter after the sample had been collected. The catheter was flushed with approximately 1 mL of heparinized saline solution (heparin 4 U mL^{-1}) following collection of each sample. Blood samples were immediately transferred to tubes containing lithium heparin and placed on ice. They were

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