Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2013, **40,** e76–e82 doi:10.1111/vaa.12057

RESEARCH PAPER

Effect of low dose rate ketamine infusions on thermal and mechanical thresholds in conscious cats

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Abstract

Objective To determine the thermal and mechanical antinociceptive effects of two different subanesthetic constant rate infusions of racemic ketamine in cats.

Study design Prospective, randomized, blinded, experimental study.

Animals Eight healthy adult domestic shorthair cats (two intact females and six neutered males).

Methods The thorax and the lower thoracic limbs of each cat were shaved for thermal (TT) and mechanical threshold (MT) testing and a cephalic catheter was placed. Three intravenous treatments of equivalent volume were given as loading dose (LD) followed by an infusion for 2 hours: (K5) 0.5 mg kg^{-1} ketamine followed by 5 μg kg^{-1} $minute^{-1}$ ketamine infusion, (K23) 0.5 mg kg^{-1} ketamine followed by 23 μg kg^{-1} $minute^{-1}$ ketamine infusion or (S) 0.9% saline solution. Effects on behavior, sedation scores, MT and TT were obtained prior to drug treatment and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.25, 2.5 2.75, 3 hours then every 0.5 hours for 7 hours and 10, 12, 14 and 26 hours after loading dose administration.

Results Ketamine induced mild sedation for the period of the infusion, no adverse behavioral effects were observed. Thermal threshold was significantly higher than baseline (K5: 44.5 ± 0.7 °C; K23: 44.5 ± 0.5 °C) at 15 minutes in the K5 group (46.8 ± 3.5 °C) and at 45 minutes in the K23 group (47.1 ± 4.1 °C). In the K23 group TT was significantly increased compared to S and K5 at 45 minutes. In K5 at 15 minutes MT (9.6 ± 4.0 N) was different to baseline (6.1 ± 0.8 N) and to the S group (5.9 ± 2.3 N).

Conclusion and clinical relevance Low dose rate ketamine infusions minimally affect thermal and mechanical antinociception in cats. Further studies with different nociceptive testing methods are necessary to assess whether ketamine could be a useful analgesic in cats.

Keywords analgesia, antinociception, cats, infusion, ketamine.

Introduction

Ketamine is widely used for induction and maintenance of anesthesia in veterinary medicine (Wright 1982) and has been recently re-evaluated as an analgesic drug (Muir 2010). Subanesthetic concentrations of ketamine have gained acceptance for acute and chronic pain management in dogs, horses and humans and are recommended for balanced anesthesia and peri-operative analgesia in clinical veterinary patients (Hansen 2008; Lamont 2008; Suzuki 2009; Muir 2010). The exact mechanism of ketamine-produced analgesia is not clearly understood. The antinociceptive activity of ketamine is mainly related to the noncompetitive inhibition of N-methyl-D-aspartate (NMDA) receptors in the

spinal cord. Ketamine is also known to interact with opioid, monoaminergic, and muscarinic receptors, as well as voltage-sensitive ion-channels, such as Na^{2+} and Ca^{2+} channels (Hirota & Lambert 2011). In experimental studies ketamine however has been shown to produce variable antinociceptive effects in humans, dogs and ponies (Arendt-Nielsen et al. 1995; Bergadano et al. 2009; Levionnois et al. 2010). In cats there is limited published evidence of the antinociceptive efficacy of ketamine when given alone (Robertson et al. 2002, 2003).

Low and high dose infusions of ketamine have been investigated in cats as part of total intravenous anesthesia in combination with propofol (Ilkiw et al. 2003; Boudreau et al. 2012; Zonca et al. 2012) or for anesthetic sparing effects during isoflurane anesthesia (Pascoe et al. 2007). The use of ketamine infusions with increasing dose rates over an extended time period resulted in prolonged recoveries from general anesthesia in cats (Pascoe et al. 2007). Thus, it is important to find an adequate dose rate for ketamine infusion therapy that can effectively relieve pain without significant side effects. Currently there are no published investigations on the use of low dose rate ketamine infusions in conscious cats. Several studies have revealed that ketamine suppresses the temporal summation of repetitive stimuli, rather than a single painful stimulus (Arendt-Nielsen et al. 1995; Bergadano et al. 2009; Levionnois et al. 2010; Lee et al. 2011). Results of previous studies in cats (Robertson et al. 2002, 2003), however, indicate that thermal threshold testing might be a suitable model to test for ketamine-induced antinociception. The objective of this preliminary study was to evaluate the antinociceptive activity of two different low dose rate ketamine infusions in conscious cats using a mechanical and thermal threshold device.

Ketamine infusions have a place as a supplement to veterinary anesthesia, the usefulness in conscious cats, however, might be limited by the undesirable side effects ranging from sedation to emergence phenomena, complicating handling of the animals. An additional objective of this study was to record and describe the behavioral side effects associated with drug administration.

Materials and methods

Animals

Eight healthy purpose-bred adult domestic shorthair cats (two intact females and six neutered males) were used in the study. Ages ranged from 2 to 6 years with a mean ± SD age of 3.2 ± 1.3 years. Bodyweight ranged from 3.7 to 6.7 kg with a mean bodyweight of 4.5 ± 1 kg. Cats were determined to be healthy based on physical examination. Results of a complete blood count and serum chemistry analysis were within accepted normal limits for our laboratory. Four weeks before the study began, the cats were tested for FIV and FeLV infections, and results were negative for all cats.

All cats were housed in a group in a climate-controlled room. Water was provided *ad libitum*, dry and canned food was provided twice daily. All cats were socialized and familiar with the study procedure and the testing environment.

The study (AUP 2009139) was approved by the Institutional Animal Care and Use Committee at the University of Saskatchewan. All cats were cared for in accordance with the Canadian Council for Animal Care guidelines.

Instrumentation and drug administration

In the morning of testing, cats were weighed, shaved over their lateral thorax and circumferentially around their lower thoracic limbs for thermal and mechanical threshold testing. A 22-gauge catheter (BD Insyte-W; Becton Dickinson Infusion Therapy Systems Inc., UT, USA) was placed in a cephalic vein. All cats were allowed to move freely in a cage (115 × 75 × 85 cm) with unlimited access to food and water, a litter tray and toys during the experiments, except that food was removed during infusion.

A masked, randomized cross over study design with a minimum rest period of 8 days between treatments was used. Eight cats were randomly allocated to treatment order and all cats received three treatments. For each cat randomization was accomplished by use of three envelopes containing the assignment to a treatment. The investigator was unaware of treatment or treatment order.

A loading dose (LD) of ketamine (0.5 mg kg^{-1}, 10 mg mL^{-1}, Ketamine HCl Inj.; Sandoz Canada Inc., QC, Canada) diluted with 0.1 mL kg^{-1} of 0.9% saline solution (0.9% Sodium Chloride; Hospira, QC, Canada) was manually administered intravenously (IV) over 15 seconds and immediately followed by a constant rate infusion (CRI) of either 5 μg kg^{-1} $minute^{-1}$ ketamine (treatment group K5) or 23 μg kg^{-1} $minute^{-1}$ ketamine (treatment group K23). The control group (S) received an