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SHORT COMMUNICATION

Naltrexone does not affect isoflurane minimum alveolar concentration in cats

Robert J Brosnan, Bruno H Pypendop, Chalon R Majewski-Tiedeken, Yael Shilo-Benjamini & Jan E Ilkiw
Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, CA, USA

Correspondence: Robert Brosnan, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA 95616, USA. Email: rjbrosnan@ucdavis.edu

Abstract

Objective To test whether naltrexone, an opioid receptor antagonist, affects the minimum alveolar concentration (MAC) of isoflurane in cats, a species that is relatively resistant to the general anesthetic sparing effects of most opioids.

Study design Randomized, crossover, placebo-controlled, blinded experimental design.

Animals Six healthy adult cats weighing 4.9 ± 0.7 kg.

Methods The cats were studied twice. In the first study, baseline isoflurane MAC was measured in duplicate. The drug (saline control or 0.6 mg kg^{-1} naltrexone) was administered IV every 40–60 minutes, and isoflurane MAC was re-measured. In the second study, cats received the second drug treatment using identical methods 2 weeks later.

Results Isoflurane MAC was 2.03 ± 0.12% and was unchanged from baseline following saline or naltrexone administration.

Conclusion and clinical relevance Minimum alveolar concentration was unaffected by naltrexone. Because MAC in cats is unaffected by at least some mu-opioid agonists and antagonists, spinal neurons that are directly modulated by mu-opioid receptors in this species cannot be the neuroanatomic sites responsible for immobility from inhaled anesthetics.

Keywords cats, isoflurane, minimum alveolar concentration, naltrexone.

Introduction

Inhaled anesthetics act within the spinal cord to prevent movement during surgery, although the specific neurons and receptors responsible for this effect are unknown at present (Sonner et al. 2003). The immobilizing potency for inhaled anesthetics is commonly described in terms of the minimum alveolar concentration or MAC (Eger et al. 1965), which is equivalent to the mean effective concentration (EC_{50}) required to prevent movement in response to a noxious stimulus.

Opioids dose-dependently decrease MAC in many species. For example, remifentanil, a mu-opioid receptor agonist, decreases halothane MAC by up to 65% in rats (Criado & Gomez De Segura 2003) and enflurane MAC by up to 71% in dogs (Michelsen et al. 1996). Nevertheless, opioid receptors are not regarded as relevant to the mechanism of inhaled anesthetic immobility since opioid receptor antagonists do not increase MAC in either rats (Harper et al. 1978) or dogs (Pace & Wong 1979).

Anesthetic effects of opioids are very different in cats than in rats or dogs. Some mu- and kappa-opioid receptor agonists cause modest or minimal reductions in isoflurane requirement in cats (Ilkiw et al. 2002). Furthermore, remifentanil in cats does not affect isoflurane MAC at all (Brosnan et al. 2009), despite an ability for selective mu-receptor agonists to modulate motor function within the cat spinal cord (Steffens & Schomburg 2011).

Since MAC-sparing effects of opioid agonists are different in cats compared to rats or dogs, the effects of opioid antagonists might likewise differ. The purpose of this study was to test whether high doses of the opioid receptor antagonist naltrexone could increase isoflurane MAC in cats.

Materials and methods

Six healthy adult cats weighing 4.9 ± 0.7 kg (mean ± SD) were studied using a blinded, randomized, placebo-controlled, crossover design that was approved by the Animal Use and Care Committee at the University of California, Davis. Each cat was anesthetized twice, 2 weeks apart. Food, but not water, was withheld overnight prior to study.

Anesthesia was induced in unsedated cats using isoflurane in oxygen administered in an acrylic chamber. Cats were tracheally intubated with a cuffed 4.5 mm endotracheal tube and anesthesia was maintained using isoflurane in oxygen delivered via a coaxial Mapleson F circuit. Breathing was controlled using a pressure-cycled, flow-controlled ventilator (Mark 7; Bird Corporation, CA USA) to achieve a 10 cm H_2O peak inspiratory pressure and a rate sufficient to maintain normocapnia, as measured using a Raman scatter analyzer (Rascal II, Ohmeda, UT, USA). Percent hemoglobin saturation with oxygen (SpO_2) was estimated using a pulse oximeter placed on the tongue (Rascal II). End-tidal isoflurane was hand-sampled in glass syringes and measured using an infrared analyzer (Beckman LB2, Sensormedics, CA, USA) that was calibrated against multiple standard gases that spanned the range of study concentrations. Systolic arterial pressure was measured indirectly by use of a Doppler probe (Model 811-BTS; Parks Medical Electronics, OR, USA) placed over the radial artery plus a sphygmomanometer with a cuff width equal to 40% of the antebrachial circumference. Body temperature was measured using an esophageal thermistor probe (400 series, YSI, OH, USA) that was calibrated against a certified standard mercury thermometer (SRM934-FC; ERTCO, IA, USA). Heating pads and forced air warmers were used to maintain body temperature between 38 and 39 °C. Lactated Ringer's solution was administered through a 22-gauge medial saphenous catheter at 10 mL kg^{-1} $hour^{-1}$.

Baseline isoflurane MAC was determined using a standard bracketing design and previously described methods (Brosnan et al. 2009). Briefly, cats were equilibrated at a constant isoflurane concentration for 20 minutes. After anesthetic and physiologic measurements were collected, a Martin forceps was clamped to the first ratchet on the distal tail for 1 minute or until the cat exhibited nonreflex movement. The end-tidal isoflurane concentration then was increased by 10–15% if the cat moved or was decreased by 10–15% if the cat did not move. After 20 minutes equilibration at the new isoflurane concentration, movement in response to forceps clamping was assessed at a site immediately proximal to the previous tail test. A single MAC value equaled the mean of the highest and lowest isoflurane concentrations that respectively allowed and prevented movement in response to noxious stimulation. For each cat, MAC was measured in duplicate and averaged.

Cats were assigned *a priori* to receive either 0.6 mg kg^{-1} of naltrexone HCl (ZooPharm, CO, USA) diluted to 10 mg mL^{-1} or an equivalent volume of 0.9% NaCl intravenously after every other movement test (every 40–60 minutes). This dose and frequency of naltrexone administration was selected because it completely reverses analgesia from very high dose remifentanil infusions in cats (Pypendop et al. 2011). The study drug—naltrexone or saline—for each cat was prepared in individual unmarked vials by an investigator who did not participate in MAC measurements. The order of drug or saline administration among study animals was determined using a random number table. Each cat received the other study treatment during a subsequent experiment 2 weeks later in which identical methods were used to measure MAC before (baseline) and after drug administration. The investigators who measured isoflurane MAC were always unaware of which treatment was administered. Isoflurane MAC during naltrexone or control treatment was re-determined in duplicate using methods identical to those described for baseline measurements. After each experiment, cats were recovered from anesthesia and were returned to the vivarium once awake and ambulatory.

Data were summarized as mean ± SD and checked for normality using Shapiro-Wilk tests. Treatment effects were evaluated using repeated-measures ANOVA with Dunn-Sidak corrections for pairwise comparisons. Differences were statistically significant when $p < 0.05$.

Results

Baseline minimum alveolar concentration for isoflurane was 2.03 ± 0.12%. Neither naltrexone nor

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