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RESEARCH PAPER

Effect of morphine, methadone, hydromorphone or oxymorphone on the thermal threshold, following intravenous or buccal administration to cats

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Abstract

Objective To determine the effects of morphine, methadone, hydromorphone or oxymorphone on the thermal threshold in cats, following buccal and intravenous (IV) administration.

Study design Randomized crossover study.

Animals Six healthy adult female ovariohysterectomized cats weighing 4.5 ± 0.4 kg.

Methods Morphine sulfate (0.2 mg kg^{-1} IV or 0.5 mg kg^{-1} buccal), methadone hydrochloride (0.3 mg kg^{-1} IV or 0.75 mg kg^{-1} buccal), hydromorphone hydrochloride (0.1 mg kg^{-1} IV or 0.25 mg kg^{-1} buccal) or oxymorphone hydrochloride (0.1 mg kg^{-1} IV or 0.25 mg kg^{-1} buccal) were administered. All cats were administered all treatments. Skin temperature and thermal threshold were measured in duplicate prior to drug administration, and at various times up to 8 hours after drug administration. The difference between thermal threshold and skin temperature (ΔT) was analyzed.

Results Administration of methadone and hydromorphone IV resulted in significant increases in ΔT at 40 minutes after drug administration. Buccal administration of methadone resulted in significant increases in thermal threshold, although no significant difference from baseline measurement was detected at any time point. IV administration of morphine and oxymorphone, and buccal administration of morphine, hydromorphone and oxymorphone did not cause significant thermal antinociception.

Conclusion and clinical relevance At the doses used in this study, IV administration of methadone and hydromorphone, and buccal administration of methadone resulted in transient thermal antinociception. The results of this study do not allow us to predict the usefulness of these drugs for providing analgesia in clinical patients.

Keywords buccal, cats, intravenous, opioids, thermal threshold.

Introduction

Opioids are commonly considered the most effective class of drugs for the management of acute pain, including in cats (Epstein et al. 2015). Traditional routes of administration include intravenous (IV), intramuscular (IM), subcutaneous (SC) and oral. Parenteral routes are typically reserved for hospitalized patients, making alternatives routes of interest for patients after they leave the hospital. Additionally, nonparenteral administration may be preferred

in some situations even in hospitalized patients (e.g. repeated administration during prolonged hospitalization, patients with coagulopathies in which injections are preferably avoided). Oral bioavailability of opioids has been poorly studied in cats, but based on studies in dogs, it is probably low (Aungst et al. 1985; Ritschel et al. 1987; Dohoo et al. 1994; Dohoo & Tasker 1997; KuKanich et al. 2005 a, b). Buccal (oral transmucosal) administration has been proposed as an alternative to oral administration, in an attempt to avoid the acidic gastric environment, the intestinal enzymes and the first-pass effect, and to promote faster onset of effect (Sattar et al. 2014). Buccal administration of buprenorphine in cats has been reported to produce good thermal antinociception (Robertson et al. 2005), although more recent studies have found inconsistent effects and lower bioavailability than previously reported (Hedges et al. 2014 a, b; Steagall et al. 2014, 2015). Buccal administration of methadone was reported to produce mechanical antinociception in cats (Ferreira et al. 2011). We have previously reported the bioavailability of morphine, methadone, hydromorphone and oxymorphone following buccal administration in cats (Pypendop et al. 2014). The purpose of this study was to characterize the effects of these opioids on the thermal threshold in cats, following IV or buccal administration. We hypothesized that all four opioids would result in an increase in thermal threshold, and that following buccal administration, the magnitude and duration of the effect would be correlated with the previously reported bioavailability of the drug.

Materials and methods

Animals

Six healthy Domestic Short Hair female ovariohysterectomized cats, aged 1–2 years and weighing 4.5 ± 0.4 kg [mean ± standard deviation (SD)] were used. A vascular access port had been implanted under general anesthesia, approximately 2 weeks prior to starting the study, with the catheter in a carotid artery and the port subcutaneously between the shoulder blades. The port was used for blood sampling in order to determine plasma drug concentrations. Blood sampling was performed on the same days as thermal threshold determinations; methods and results related to plasma drug concentrations are presented in detail elsewhere (Pypendop et al. 2014). Cats were acclimatized to the laboratory and to thermal threshold testing for 4 weeks prior to the study. Hair over the lateral aspect of the chest was clipped on the day before each experiment. Alternating sides of the chest were used for thermal threshold testing for each study treatment, but the same side was used for the 8 hours of measurements within a study treatment. The study was approved by the Institutional Animal Care and Use Committee at the University of California, Davis.

Drug administration

A 22 gauge, 2.5 cm catheter was placed in a cephalic vein and used for IV drug administration. For buccal administration, the drug was deposited in a cheek pouch, and the cat's mouth was held closed for 30 seconds to 1 minute. Treatments were as follows: morphine (0.2 mg kg^{-1}; Morphine Sulfate, 15 mg mL^{-1}; Baxter Healthcare Corp., IL, USA), IV; morphine (0.5 mg kg^{-1}) buccal; methadone (0.3 mg kg^{-1}; Dolophine Hydrochloride, 10 mg mL^{-1}; aaiPharma, NC, USA) IV; methadone (0.75 mg kg^{-1}) buccal; hydromorphone (0.1 mg kg^{-1}; Hydromorphone Hydrochloride, 2 mg mL^{-1}; Hospira Inc., IL, USA) IV; hydromorphone (0.25 mg kg^{-1}) buccal; oxymorphone (0.1 mg kg^{-1}; Opana, 1 mg mL^{-1}; Endo Pharmaceuticals, PA, USA) IV; oxymorphone (0.25 mg kg^{-1}) buccal. The commercial injectable drug solutions were used and were not altered prior to administration. The order of the route of administration was randomized according to a computer-generated list, while the order of drug was always as above. This order had been randomly selected for the entire group of cats, but the drug order was not selected randomly within cats for logistical reasons (i.e. the laboratory analyzing the drug concentrations required that all samples for a single drug be obtained within a short time). All cats were administered all treatments, with at least 2 weeks between treatments.

Thermal threshold testing

Cats were placed in individual 80 × 80 × 65 cm cages with a transparent acrylic door for thermal threshold testing. Thermal threshold testing was conducted using a commercially available system (WTT1; Topcat Metrology, UK) and was always determined by the same investigator (YS-B), who was unaware of the treatment. A probe containing a heater element and an adjacent temperature sensor,

