

RESEARCH PAPER

Methadone in combination with acepromazine as premedication prior to neutering in the cat

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Abstract

Objective To investigate the safety, sedative and analgesic properties of methadone in combination with acepromazine prior to neutering in cats.

Study design Controlled clinical, block randomized, prospective, blinded study designed for regulatory purposes.

Animals 24 female and 21 male healthy cats.

Methods Cats received one of three opioids combined with acepromazine (0.05 mg kg^{-1}) intramuscularly (IM) for premedication: Group 1: buprenorphine (0.02 mg kg^{-1}), group 2: methadone (0.5 mg kg^{-1}), group 3 butorphanol (0.4 mg kg^{-1}). Sedation was assessed 30 minutes after premedication using a visual analogue scale (VAS) and simple descriptive scale. Anaesthesia was induced with alfaxalone and maintained with isoflurane in oxygen. Surgical ovariohysterectomy or castration was performed. Pain was assessed using an interactive VAS (IVAS) and mechanical nociceptive threshold (MNT) with a pressure rate onset device. Methadone (0.5 mg kg^{-1} IM) and meloxicam (0.2 mg kg^{-1} subcutaneously) were provided 6 and 8 hours after premedication respectively, or together as rescue analgesia (IVAS above 50).

Results Sedation scores, induction agent dose, pain scores at all time points and rescue analgesia were not statistically different between groups. In methadone treated cats there was no significant variation

in MNT over time, suggesting a possible anti-hyperalgesic action, whereas in the other two groups lower thresholds were recorded at various time points after surgery compared to baseline. No cats required rescue analgesia after the second dose of methadone. No perioperative adverse effects occurred.

Conclusion and clinical relevance Methadone provided comparable sedation and analgesia to both buprenorphine and butorphanol when combined with acepromazine. Differences in analgesic efficacy between opioids might have been undetectable because of the surgical model and surgeon competency. Nevertheless, methadone is an effective analgesic in cats and its administration prior to feline neutering may be advantageous.

Keywords acepromazine, analgesia, cat, methadone, sedation.

Introduction

The need to improve pain assessment and management in cats has been recently recognised and has led to publication of many clinical and research studies. Opioids are currently considered the most effective analgesic drugs to treat acute and perioperative pain in most species due to their efficacy, good safety margin and versatility (Robertson 2008). Several studies have investigated the use of morphine, buprenorphine, butorphanol, hydromorphone and oxymorphone in cats (Briggs et al. 1998; Robertson et al. 2003; Wegner & Robertson 2007; Taylor et al. 2010), but in comparison to

other opioids, relatively few studies have evaluated methadone in this species.

Methadone is a synthetic opioid that is used to provide analgesia in humans, cats, dogs and horses. It is a racemic mixture, with an asymmetric carbon atom resulting in two enantiomeric forms, the D and L isomers. The analgesic action of the chiral mixture is primarily attributed to levo-methadone, which is thought to bind principally to the μ opioid receptor, while the D isomer exerts an antagonist action at the N-methyl-D-aspartate (NMDA) receptor (Inturrisi 2005). Additionally methadone exerts biogenic amine reuptake inhibitory effects and promotes the blockade of nicotinic cholinergic receptors (Codd et al. 1995; Xiao et al. 2001). In people methadone is used as an alternative to morphine for patients with severe pain (Inturrisi 2005) and methadone appears to give promising results in treating neuropathic type pain (Morley et al. 2003).

A limited number of studies have evaluated methadone in cats. Clinical and experimental studies have shown that methadone is an efficacious analgesic drug that provides a dose dependent period of analgesia without significant adverse effects (Dobromylskyj 1993; Bley et al. 2004; Mollenhoff et al. 2005; Steagall et al. 2006). Generally clinical studies of methadone in cats have used a dose of 0.5–0.6 mg kg⁻¹ and have demonstrated duration of analgesia of 1–6 hours after surgery (Dobromylskyj 1993; Bley et al. 2004; Mollenhoff et al. 2005). Acepromazine is one of the most commonly used sedatives for premedication prior to anaesthesia in cats in the United Kingdom (Murrell 2007). It is a phenothiazine derivative with sedative and muscle relaxation effects, but it is generally considered not to provide clinically significant analgesia (Lemke 2007). The onset of sedation after parenteral administration of acepromazine in cats is relatively slow and sedation lasts for several hours (Lemke 2007). In veterinary practice acepromazine is commonly combined with an opioid for premedication prior to induction of anaesthesia, termed neuroleptanalgesia (Murrell 2007). Many veterinary surgeons consider that the combination provides increased sedation compared to administration of either drug alone, reduces the amount of induction and inhalant agents required and contributes to the intra/post operative analgesia regimen as part of a multimodal protocol.

In this study, pain was assessed using an interactive visual analogue scale (IVAS) for cats, together with a mechanical nociceptive threshold

(MNT) test performed using a ProD (pressure rate onset device) (Topcat Metrology Ltd, UK), a device whose use has been described previously (Hunt et al. 2010).

The aim of this study was to evaluate the safety, sedative and analgesic effects of methadone in combination with acepromazine as part of a premedication regimen prior to neutering in healthy cats, compared to butorphanol as a positive control for sedation, and buprenorphine as a positive control for analgesia. We wanted to investigate if the use of a full μ opioid receptor agonist, like methadone, provided better analgesia than the other two opioids, as full μ agonist opioids are generally accepted to provide the best analgesia for moderate to severe pain in mammals (Kerr 2007).

Material and methods

Animals and housing

A total of 45 healthy cats admitted to our institution for elective neutering were enrolled in this study, performed in accordance with Good Clinical Practice (VICH 2000); owner's written consent and local ethical approval from the University of Bristol were obtained. Inclusion criteria were: age older than 5 months, ASA classification 1 or 2 following clinical examination, temperament suitable for the study, and no administration of an analgesic or sedative in the previous 7 days. Cats were admitted to the clinic the night before the surgical procedure in order to acclimatize to the new environment and to the investigators. The cats were housed individually in cages in a quiet environment. The animals were fasted overnight prior to the study and water was available until the time of premedication.

Treatments and study protocol

Cats undergoing neutering, castration or flank ovariohysterectomy were randomly allocated to three treatment groups. Allocation to treatment groups was randomized using a random number generator. All cats were administered acepromazine (ACP 2 mg/mL; Novartis Animal Health, UK) at a dose of 0.05 mg kg⁻¹ combined with one of the three opioids: 0.02 mg kg⁻¹ of buprenorphine (Vetergesic; Alstoe, UK) (group 1), 0.5 mg kg⁻¹ methadone (Comfortan, Eurovet Animal Health, UK) (group 2) or 0.4 mg kg⁻¹ butorphanol (Dolorex, MSD Animal Health, UK) (group 3). The premedicant agents were

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