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RESEARCH PAPER

Investigation of the interaction between buprenorphine and sufentanil during anaesthesia for ovariectomy in dogs

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Abstract

Objective To investigate the effect of buprenorphine pre-treatment on sufentanil requirements in female dogs undergoing ovariectomy.

Study design Randomized, 'blinded', prospective clinical study.

Animals Thirty healthy female dogs referred for ovariectomy.

Materials and methods Dogs were randomly assigned to one of two pre-anaesthetic treatment groups. Those in the buprenorphine group (B) received buprenorphine 20 μg kg^{-1} and acepromazine 0.03 mg kg^{-1} IM. Control group (C) animals received an equal volume of NaCl 0.9% and acepromazine 0.03 mg kg^{-1} IM. The anaesthetic technique was identical in both groups. Pre-anaesthetic medication consisted of intravenous (IV) sufentanil (1.0 μg kg^{-1}) and midazolam (0.05 mg kg^{-1}) and intramuscular atropine (0.03 mg kg^{-1}). Anaesthesia was induced with propofol and maintained with a constant rate infusion of sufentanil (1.0 μg kg^{-1} $hour^{-1}$) and with oxygen-isoflurane. Ventilation was controlled mechanically. Ovariectomy was performed using a standard technique. Baseline heart rate (HR) and direct mean arterial blood pressure (MAP) were recorded before the first incision. Increases in HR and MAP of ≥20% over baseline and, or spontaneous ventilation were controlled using IV sufentanil (1.0 μg kg^{-1}) repeated after 5 minutes if haemodynamic variables remained elevated or attempts at spontaneous ventilation persisted. Analysis of variance was used to determine group differences in mean and median HR and MAP and to compare the maximum HR and MAP attained during surgery. Poisson regression was used to compare the number of sufentanil injections required in both groups.

Results Group B required 2.46 times more sufentanil injections ($p = 0.00487$) than dogs in group C to maintain haemodynamic stability and prevent spontaneous ventilation during surgery. Group B dogs also had a significantly higher ($p = 0.034$) marginal mean of the log maximum MAP (4.756 ± 0.036) compared with group C (4.642 ± 0.036).

Conclusions Pre-treatment with buprenorphine appears to negatively influence the antinociceptive efficacy of intra-operative sufentanil.

Clinical relevance Withholding buprenorphine therapy 6–8 hours before anaesthesia incorporating pure μ receptor agonists is probably advisable. Alternative methods of analgesia should be provided in this period.

Keywords anaesthesia, antinociception, buprenorphine, dogs, opioid, sufentanil.

Introduction

Buprenorphine is a synthetic opioid analgesic derived from thebaine. It has high lipid solubility, a relatively slow onset and long duration of action (Cowan et al. 1977b; Roughan & Flecknell 2002; Cowan 2003). Clinical and experimental studies have shown that it is an effective analgesic in both small and large animal species (Green et al. 1985; Brodbelt et al. 1997; Dobbins et al. 2002; Roughan & Flecknell 2002, 2004; St A Stewart & Martin 2003). Buprenorphine is widely used clinically to provide peri-operative analgesia in dogs (Joubert 2001; Roughan & Flecknell 2002).

Three classical types of opioid receptors have been identified. Opioids can be classified as pure (full) agonists, partial agonists and antagonists, according to their effect on the different types of receptors. The term partial agonist describes those opioids that possess agonist activity at the receptor, but their maximal effect is less when compared with pure agonists (Stephenson 1956; Morgan et al. 1999; Roughan & Flecknell 2002).

Studies in several species have demonstrated the complex pharmacological profile and opioid receptor binding properties of buprenorphine. It has been described as a partial μ receptor agonist (Martin et al. 1976), a partial μ receptor agonist/antagonist (Cowan et al. 1977a; Walker et al. 1995), a partial μ receptor agonist and κ receptor agonist (Tyers 1980; Rovati et al. 1987; Pick et al. 1997) and a partial μ receptor agonist and κ receptor antagonist (Leander 1987, 1988). However, the experimental models and species studied were diverse, which may account for these different descriptions. A bell-shaped dose–response curve for buprenorphine has been reported in rats and rhesus monkeys with agonistic activity at low doses and antagonistic activity at high doses (Cowan et al. 1977a; Tyers 1980; Sadée et al. 1982; Lizasoain et al. 1991; Walker et al. 1995).

An additive or synergistic interaction is usually expected between two opioids that both have agonist effects on a certain receptor type. However, this may not always be the case when opioids with different intrinsic efficacies at specific opioid receptors are combined. Additive interactions may occur if both opioids produce an effective antinociceptive effect, although antagonistic interactions may occur when one exerts an ineffective antinociceptive response or an unusual pharmacological profile (Morgan et al. 1999). This may be relevant to the interaction between buprenorphine and other full opioid agonists, such as sufentanil.

Several studies in different species have reported contradictory results about the interaction between buprenorphine and pure μ receptor agonists. In some, buprenorphine did not antagonize the effects of pure μ receptor agonists (Cowan et al. 1977a) while in others, antagonistic effects were found (Cowan et al. 1977a; Flecknell et al. 1989; Walker et al. 1995; Morgan et al. 1999); dose-dependency in the antagonism has also been reported (Lizasoain et al. 1991; Pick et al. 1997). Despite these experimental studies, the clinical relevance of the interaction between buprenorphine and other pure μ receptor agonists has not been fully evaluated in any species. This is an important deficiency given the widespread use of buprenorphine in dogs and the desirability of improving current peri-operative analgesic techniques in this species.

Taylor & Walsh (2003) investigated the effect of pre-anaesthetic medication with buprenorphine on the intra-operative antinociceptive effect of fentanyl in dogs undergoing sternal thoracotomy. The ability of fentanyl to obtund intra-operative changes in haemodynamic variables was compared in dogs given buprenorphine preoperatively and a control group. Pre-anaesthetic medication with buprenorphine did not modify the intra-operative effect of fentanyl. However, conditions were imperfectly standardized in this clinical study: animals were either ASA status II or III, the reason for performing sternal thoracotomy differed, while animals in the control group received morphine (not buprenorphine) for pre-anaesthetic medication while animals in both groups received carprofen preoperatively. The total number of animals studied was relatively small (23 dogs).

The aim of the present study was to investigate the effect of pre-treatment with buprenorphine on the dose of sufentanil, a pure μ receptor agonist (Moeniralam et al. 1998; Latasch & Freye 2002) required intra-operatively in bitches undergoing ovariectomy. Sufentanil was administered as a constant rate infusion (CRI) in conjunction with a fixed end-tidal concentration of isoflurane. The hypothesis that buprenorphine would exert an antagonistic effect on sufentanil-induced antinociception was tested by attempting to demonstrate

