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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

that dogs pre-treated with buprenorphine would require higher doses of sufentanil during anaesthesia compared with a control group.

Materials and methods

The present study was approved by the Research Committee of the Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, University of Utrecht.

Thirty female dogs presenting to the Department of Clinical Sciences of Companion Animals, University of Utrecht, for elective ovariectomy were studied. Mean (±SD) age and body mass were 25.4 ±20.2 months and 20.2 ±14.3 kg respectively. All animals were judged to be healthy based on preoperative physical examination. A single anaesthetist, unaware of the treatment group, anaesthetized all the dogs studied.

The dogs were randomly assigned to one of two pre-anaesthetic treatment groups. One group (group B) received a combination of buprenorphine (Temgesic; Schering-Plough BV, Amstelveen, The Netherlands) 20 μg kg^{-1} and acepromazine (Acepromazine racemic mixture; Pharmacy Preparation, University of Utrecht, Utrecht, The Netherlands) 0.03 mg kg^{-1} intramuscularly (IM). The other group (group C) received 0.066 mL kg^{-1} of NaCl 0.9% (sodium chloride 0.9%; B. Braun Melsungen AG, Melsungen, Germany) (equivalent to the buprenorphine volume used in group B) and acepromazine 0.03 mg kg^{-1} IM. The effects of pre-anaesthetic medication were recorded by subjectively scoring the level of sedation as mild, moderate or marked. The anaesthetic technique was otherwise identical in both groups: 30 minutes after pre-anaesthetic medication, an 18 or 20 SWG catheter was placed in the cephalic vein and an infusion of Ringer's lactate solution (Ringer Lactaat; B. Braun Melsungen AG) begun at 10 ml kg^{-1} $hour^{-1}$. A mixture of sufentanil (Sufentanil-hameln 5 μg ml^{-1}; Hameln Pharmaceuticals Gmbh, Hameln, Germany) 1.0 μg kg^{-1} and midazolam (midazolam; racemic mixture; Pharmacy Preparation, University of Utrecht) 0.5 mg kg^{-1} was then administered by slow intravenous (IV) injection after which atropine (Atropine sulphate; Eurovet Animal Health BV, Bladel, The Netherlands) 0.03 mg kg^{-1} was injected IM. The effect of this combination was recorded as either poor (vocalization or excitation encountered) or good (sedation achieved).

Anaesthesia was induced with propofol (Propofol 1%; Fresenius TM; Fresenius, 's-Hertogenbosch, The Netherlands) administered slowly IV to effect. Immediately after this, a CRI of sufentanil (1.0 μg kg^{-1} $hour^{-1}$) was begun using an infusion pump (Graseby 3500; Sims Graseby Limited, Watford, Hertfordshire, UK). The rate of sufentanil administration was maintained throughout anaesthesia. Orotracheal intubation was carried out with a suitably sized cuffed endotracheal tube. Following connection to a circle breathing system, manual intermittent positive pressure ventilation (IPPV) with 100% oxygen (2 L $minute^{-1}$) was initiated immediately. Animals were prepared for surgery and transferred to the operation room. Isoflurane (IsoFlo; Abbott Laboratories Ltd, Queenborough, Kent, UK) vaporized (Isotec 5; Datex-Ohmeda Division Instrumentarium Corporation, Helsinki, Finland) in a 1:1 mixture of air and oxygen (1–2 L $minute^{-1}$) was administered and IPPV imposed mechanically (SmartVent Ventilator; Datex-Ohmeda Division Instrumentarium Corporation).

An 18 or 20 SWG cannula was placed in the right femoral or dorsal pedal artery and connected to a pressure transducer (Gabarith PMSET 1 DT-XX 1 ROSE; Becton Dickinson Critical Care Systems Pte Ltd, Singapore) for arterial blood pressure (BP) monitoring. Monitoring consisted of arterial BP measurement and electrocardiography (lead II) (S/5 ECG Module; Datex-Ohmeda Division Instrumentarium Corporation). Pulse oximetry (Oxy Tip; Datex-Ohmeda Division Instrumentarium Corporation) and oesophageal temperature measurement (Datex central temperature probe; Datex-Ohmeda Division Instrumentarium Corporation) were conducted continuously. The body temperature was supported using a circulating warm waterbed and a heat and moisture exchanger.

Airway gases were sampled continuously from the circuit end of the endotracheal tube. Both isoflurane and carbon dioxide were measured using an infrared monitor (S/5 Compact Airways Modules; Datex-Ohmeda Division Instrumentarium Corporation). End-tidal [isoflurane] was maintained at 0.75% (±0.05%). Mechanical IPPV was adjusted to maintain end-tidal carbon dioxide concentrations ($F_E'CO_2$) between 5.0 and 5.5 kPa (37 and 41 mmHg).

After arrival in the operating theatre, heart rate (HR) and mean arterial blood pressure (MAP) were recorded every 5 minutes for the 15 minutes before surgery began. The average of these measurements

was used as baseline values for these variables. Ovariectomy was performed by different surgeons using a standard midline approach. The time at first incision was taken as $t = 0$ and the values of HR and MAP were recorded at 5-minute intervals thereafter. A 20% increase in either HR and/or MAP compared with baseline values and/or the onset of spontaneous ventilation were taken to indicate inadequate anaesthesia, and were controlled with IV sufentanil at 1.0 μg kg^{-1}. A second sufentanil injection was given if either HR and/or MAP continued to rise after the first dose, or if spontaneous ventilation persisted. Sufentanil was then administered at 5-minute intervals until the haemodynamic variables returned to baseline values or until spontaneous ventilation ceased.

Sufentanil infusion was maintained until the onset of closure of the abdominal incision. At this time, both carprofen (Rimadyl; Pfizer Animal Health, Vericore Limited, Dundee, UK) 4 mg kg^{-1} IV and methadone (Methadon racemic mixture; Pharmacy Preparation, University of Utrecht) 0.3 mg kg^{-1} IM were administered. On completion of surgery, mechanical IPPV was discontinued and ventilation supported manually until spontaneous breathing resumed. Administration of isoflurane was continued until the animal breathed spontaneously. The time of tracheal extubation was recorded and the quality of the recovery evaluated subjectively by the presence of crying, excitation or calmness.

Postoperative analgesia consisted of buprenorphine 20 μg kg^{-1} IM given at 6-hour intervals for the first 24 hours after surgery. The first dose was given 4 hours after with the injection of methadone. Carprofen (4 mg kg^{-1}) was given orally for 3 days after surgery.

Analyses of all data were performed using statistical software packages (SPSS 12.0.1 for Windows; SPSS Incorporated, Chicago, IL, USA and R version 2.0.1; R Foundation for Statistical Computing, Vienna, Austria). Data were tested for equality of variances (Levene's test for equality of variances) when necessary. Data were log-transformed to achieve approximate normality when necessary. Normality was checked with Normal Q-Q plots of the residuals. Student's *t*-test was used to determine differences between the groups in age and body mass and the time to tracheal extubation after the discontinuation of isoflurane. Scores for the effects of pre-anaesthetic drugs and pre-anaesthetic medication, the quality of induction and of recovery were compared using Fisher's exact test. Analysis of variance was used to identify differences between the groups in values for mean and median HR and MAP. Analysis of variance was also used to determine differences between groups in the maximum intra-operative HR and MAP, and whether or not the baseline HR and baseline MAP affected these values. A Poisson regression was used to compare the number of sufentanil injections given during surgery in the groups. Differences were considered to be statistically significant when $p < 0.05$.

Results

The age and body mass of the dogs were not significantly different between the two groups. There was a significant difference between the groups ($p < 0.01$) in the number of intra-operative sufentanil injections required: dogs in group B required 2.46 times as many as dogs in group C (Tables 1 & 2). Dogs in group B required a median of three sufentanil injections (mean 4.13 ± 3.13) while dogs in group C required a median of two sufentanil injections (mean 2.27 ± 1.03). Two dogs in group B required 9 and 13 injections respectively. In the dog requiring 13 injections, $F_{E'ISO}$ was increased to effect (maximum $F_{E'ISO}$ was 1.6%) because surgery was impossible at the lower concentration. It is possible that the data from these two animals may have skewed the results and so

Table 1 Number of sufentanil injections administered to each dog ($n = 15$) during anaesthesia for ovariectomy in the control group

Dog no.	No. injections
1	2
2	4
3	2
4	3
5	3
6	2
7	1
8	2
9	4
10	1
11	3
12	1
13	2
14	1
15	3

Table 2 Number of sufentanil injections administered to each dog ($n = 15$) during anaesthesia for ovariectomy in the buprenorphine group

Dog no.	No. injections
1	2
2	2
3	2
4	3
5	2
6	2
7	4
8	3
9	5
10	2
11	6
12	4
13	13
14	9
15	3

data were re-analysed using a negative binomial distribution. This revealed that the difference in sufentanil requirement in groups B and C was still significantly ($p < 0.01$) different. Moreover, the residuals showed that there were no outliers in either group, indicating the appropriateness of retaining the data from these two dogs within the buprenorphine group.

Differences in mean and median HR and MAP were not significant between groups (Figs 1 & 2). There were also no significant differences between groups in the log-maximum HR recorded in the dogs during surgery. Group B had a higher marginal mean of the log maximum MAP (4.756 ± 0.036) when compared with the marginal mean of the log-maximum MAP of group C (4.642 ± 0.036) ($p = 0.034$). These marginal means were log transformed back to obtain geometric means and 95% confidence intervals (95% CI) based on the model for each group. Group B had a higher geometric maximum MAP mean [116 mmHg (95% CI 108–125 mmHg)] compared with group C [103.75 mmHg (95% CI 96–111 mmHg)]. The baseline HR and MAP had a positive effect on the mean, median and maximum HR ($p = 0.00$) and MAP ($p = 0.00$), respectively, such that animals with a low baseline value for these variables also tended to have a low mean, median and maximum values during surgery.

There were no significant differences between groups in the effects of the pre-anaesthetic drugs,

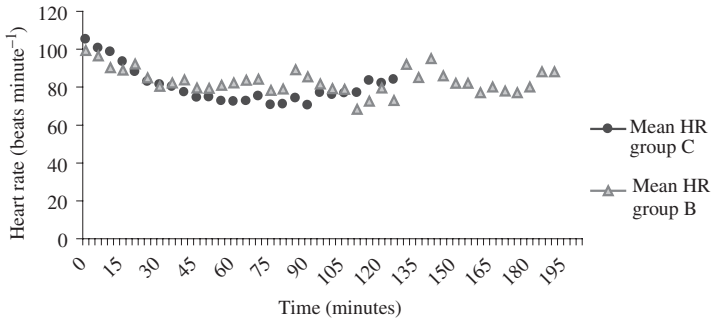

Figure 1 Change in heart rate (HR) over time during anaesthesia for ovariectomy in the control (group C) and buprenorphine (group B) dogs. Each data point represents the mean of all animals in each group. Time 0 is the time at first incision.

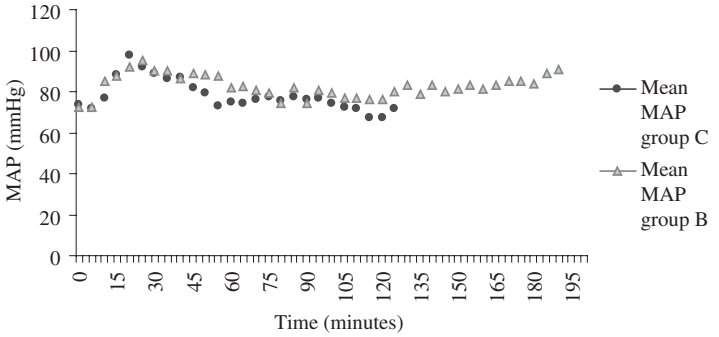

Figure 2 Change in mean arterial blood pressure (MAP) over time during anaesthesia for ovariectomy in the control (group C) and buprenorphine (group B) dogs. Each data point represents the mean of all animals in each group. Time 0 is the time at first incision.

the effect of the pre-anaesthetic medication and the recovery quality. Most dogs demonstrated a satisfactory response to pre-anaesthetic drugs and pre-anaesthetic medication. Induction of anaesthesia was smooth in all of the dogs. The recovery from anaesthesia was described as 'calm' in most dogs in both groups. There were no significant differences between the groups in the time at endotracheal extubation.

Five dogs (one in group B and four in group C) developed second-degree heart block after pre-anaesthetic medication which disappeared in all animals before surgery began.

Discussion

Dogs pre-treated with buprenorphine required more sufentanil injections to maintain intra-operative haemodynamic stability and/or to avoid spontaneous ventilation when compared with the control group. Dogs in group B also demonstrated a greater increase in MAP during surgical stimulation when compared with those in group C. These results suggest that preoperative buprenorphine impairs the ability of sufentanil to provide haemodynamic stability and/or prevent spontaneous ventilation, i.e. that the antinociceptive efficacy of sufentanil is reduced.

Similar findings have been reported in experimental studies in other animal species. In an *in vitro* model using rat cells, buprenorphine administration suppressed fentanyl binding to μ opioid receptors suggesting that the antinociceptive efficacy of fentanyl would also be reduced (Boas & Villiger 1985). Using the warm water tail withdrawal test in rats, buprenorphine blocked the activity of morphine, suggesting that buprenorphine acted as a partial agonist/antagonist (Cowan et al. 1977a; Morgan et al. 1999) while in rhesus monkeys, using the same test, buprenorphine was able to block the antinociceptive effect of μ receptor agonists (alfentanil and etonitazene) (Walker et al. 1995).

However, the results of other studies indicate that the antagonistic effects of buprenorphine on pure μ receptor agonists appears to be dose-dependent, suggesting a variable and complex interaction. In a mouse model using the warm water tail withdrawal test, low doses of buprenorphine antagonized morphine analgesia in a dose-dependent manner (reaching maximum effect at 15 mg kg^{-1}) while higher doses of buprenorphine co-administered with morphine enhanced morphine-induced analgesia (Pick et al. 1997). In contrast, there are experimental studies in which buprenorphine failed to antagonize the effects of pure μ receptor agonists. In an analgesiometric model using the rat-tail pressure test, buprenorphine did not antagonize the antinociceptive effects of morphine, suggesting that in this model it acts as a full agonist (Cowan et al. 1977a). In a clinical study of dogs undergoing thoracotomy (Taylor & Walsh 2003), preoperative buprenorphine did not affect the requirement for fentanyl suggesting that the interaction between buprenorphine and μ receptor agonists was insignificant.

Discrepancies between the findings of these studies may have resulted from the different analgesiometry models used to evaluate antinociception. Studies suggest that buprenorphine is more effective against noxious pressure than against heat-induced nociception or electrical stimulation in rats (Tyers 1980; Sadée et al. 1982). Furthermore, several findings (Cowan et al. 1977a; Walker et al. 1995; Morgan et al. 1999) are based on acute nociceptive assays, e.g. thermal-based tests, the analgesic requirements for which may differ from surgical pain where tissue damage and inflammation are present (Roughan & Flecknell 2002; St A Steward & Martin 2003). Phasic analgesiometry tests (thermal-based techniques) are related to high-intensity stimulation that activate Aδ mechano-thermal nociceptors while tonic analgesiometry tests (mechanical and chemical tests) are related to low or intermediate stimulation that activates C-polymodal nociceptors (Yeomans & Proudfit 1994, 1996; Roughan & Flecknell 2002). The interaction between buprenorphine and pure μ receptor agonists may therefore be dependent on the model studied.

The bell-shaped dose–response curve of buprenorphine demonstrated in rats and rhesus monkeys (Cowan et al. 1977a; Tyers 1980; Dum & Herz 1981; Sadée et al. 1982; Lizasoain et al. 1991; Walker et al. 1995) is not considered to be of clinical relevance because antagonism occurs at buprenorphine doses much higher than those used clinically. Therefore, it is unlikely to account for the antagonist effect of buprenorphine shown in this study (Roughan & Flecknell 2002).

Although this study demonstrated a significant interaction between buprenorphine and sufentanil, some confounding factors require consideration. More than one surgeon was involved, and although all were experienced, it is probable that surgical

nocistimulation varied between animals. It is also probable that individual variation in pharmacodynamics played a role, as plasma concentrations of buprenorphine and sufentanil were not measured. However, buprenorphine plasma concentration correlates poorly with its analgesic effect (Nolan et al. 1987; Lascelles et al. 2003).

Haemodynamic changes to surgical stimulation were the clinical variables used to assess depth of anaesthesia and nociception in the present study. Dogs pre-medicated with buprenorphine presented more pronounced increases in MAP during surgery. Some authors have argued that autonomic nervous changes in response to surgery are poor indicators of anaesthetic depth (Evans & Davies 1984; Hug 1990; Domino et al. 1999), although significant increases in haemodynamic variables related to noxious surgical stimulation have also been reported (White & Boyle 1989; Zbinden et al. 1994; Kazama et al. 1998; Otto & Gerich 2001; Otto & Mally 2003). The stability in HR, compared with MAP, found in the present study may be the result of increased vagal activity caused by sufentanil CRI (Freye et al. 2000; Prakanrattana & Suksompong 2002; Cardinal et al. 2004). A similar mechanism probably caused the second-degree heart block observed in five dogs (one in group B and four in group C) after pre-anaesthetic medication. Although this was not evaluated, it is possible that buprenorphine mediated antagonism of the vagal effects of sufentanil, causing a lower incidence of heart block in group B.

Two animals in group B required markedly more sufentanil (9 and 13 injections respectively) compared with all other animals. In the former case, all nine injections were required to suppress both spontaneous ventilation and increases in HR and/or MAP, whereas in the latter, sufentanil was primarily required to abolish spontaneous ventilation. Eventually, end-tidal isoflurane concentration had to be increased in this animal, because surgical conditions were unacceptably poor. A reason for the higher numbers of injections in these animals could not be identified, and there was no reason to regard the animals as extraordinary. Statistical analysis confirmed that the difference detected between the two groups was not dependent on the results from these two animals.

Morgan et al. (1999) suggested that the antagonistic effect of buprenorphine on sufentanil occurs when opioids with unusual pharmacological profiles, e.g. buprenorphine, are given with opioids that have effective antinociceptive effects when used alone. Buprenorphine has a slow receptor association, but a high affinity, and both slow and incomplete dissociation (Boas & Villiger 1985) which may prevent sufentanil from binding to the μ receptor. Moreover, studies reveal that buprenorphine has both partial μ receptor agonist and κ receptor agonist effects (Tyers 1980; Rovati et al. 1987; Pick et al. 1997). It has been suggested that κ receptor agonism may be antagonistic to μ receptor effects (Sadée et al. 1982; Boas & Villiger 1985; Rovati et al. 1987). During the current study, the antinociceptive efficacy of sufentanil may have been antagonized by the action of buprenorphine on κ opioid receptors.

There are few reports on the pharmacokinetic properties of buprenorphine in animals (Garrett & Chandran 1990; Taylor et al. 2001). Its duration of action after IM administration in the dog is considered to be 6–8 hours (Lascelles 2000; Pascoe 2000). However, it has a long onset of action, with peak effects occurring 45–60 minutes after IV administration (Pascoe 2000). This slow latency is probably the result of slow receptor-binding kinetics (Boas & Villiger 1985). In the light of the present study, it seems advisable to avoid the preoperative administration of buprenorphine to animals already experiencing pain, when μ receptor agonists are intended to be used during surgery. In these animals, full μ receptor agonists or adjuvant analgesics such as NSAIDs, ketamine or local anaesthetics are required.

Conclusion

The results of the current study indicate that pre-treatment with buprenorphine decreases the antinociceptive efficacy of sufentanil given during surgery. Consequently, it is advisable to withhold buprenorphine for 6–8 hours before surgery when the use of pure μ agonist drugs is intended.

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