The Veterinary Journal 200 (2014) 157–161

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Randomized clinical trial of the effects of a combination of acepromazine with morphine and midazolam on sedation, cardiovascular variables and the propofol dose requirements for induction of anesthesia in dogs

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ARTICLE INFO

Article history:
Accepted 28 January 2014

Keywords:
Benzodiazepine
Neuroleptanalgesia
Opioid
Phenothiazine
Tranquilizer
Dog

ABSTRACT

The present study evaluated the effects of acepromazine combined with midazolam and morphine on sedation and cardiovascular variables as well as the propofol dose required for induction of anesthesia in dogs compared with acepromazine–morphine or midazolam–morphine. Dogs were randomly assigned to receive an intramuscular administration of (1) acepromazine (0.05 mg/kg) with 0.5 mg/kg of morphine (group AM, $n = 10$), (2) midazolam (0.5 mg/kg) with 0.5 mg/kg of morphine (group MM, $n = 9$), or (3) acepromazine with midazolam and morphine at the same doses (group AMM, $n = 10$). After 30 min, sedation was assessed by a numeric descriptive scale (NDS, range 0–3) and a simple numerical scale (SNS, range 0–10). Dogs were then administered IV propofol to allow endotracheal intubation.

NDS and SNS scores were significantly higher in the AMM than in the MM group ($P < 0.05$). There was a trend towards more dogs presenting with intense sedation (NDS = 3) in AMM (6/10 dogs) compared with AM (1/10 dogs) and MM (1/9 dogs) ($P = 0.057$). The propofol dose required for induction of anesthesia was significantly lower in AMM (4.0 mg/kg) compared with MM (6.0 mg/kg, $P < 0.01$) but not AM (4.6 mg/kg). Heart rate decreased in AM after treatment and after intubation. Blood pressure decreased in groups AM and AMM following treatment and in all groups after intubation. The combination AMM resulted in intense sedation more frequently than AM and MM, and provided the greatest sparing effect in the propofol dose. Administration of AM and AMM but not MM decreased blood pressure although hypotension was not recorded in healthy dogs.

Introduction

Phenothiazine derivatives, benzodiazepines, alpha-2 adrenoceptor agonists and opioid analgesics are often used to facilitate the handling of dogs for diagnostic procedures and in preparation for surgery (Lemke, 2007). Of these, the alpha-2 agonists are the only class of drugs that provides deep sedation associated with analgesia. When administered alone, phenothiazines, benzodiazepines and opioids cause only mild to moderate sedation in dogs (Lemke, 2007) and this is often insufficient for procedures that require chemical restraint.

Acepromazine is the phenothiazine derivative most frequently used for sedation in dogs. The major concern when using acepromazine is the reduction in arterial blood pressure that results from a decrease in systemic vascular resistance (Monteiro et al., 2007). A reduction of approximately 25% in cardiac output has also been reported after administration of acepromazine in dogs (Stepien et al., 1995). Several studies in dogs have reported the use of acepromazine in combination with opioids such as morphine, methadone, oxymorphone, hydromorphone, meperidine, fentanyl, tramadol, buprenorphine and butorphanol (Cornick and Hartsfield, 1992; Stepien et al., 1995; Smith et al., 2001; Monteiro et al., 2008, 2009; Gomes et al., 2011). With all combinations, sedation appears to be improved by the addition of the opioid. A decrease in heart rate (HR) and mild hypotension were reported after the administration of such combinations but these effects did not seem to be greater than with each drug alone.

The use of benzodiazepines as part of neuroleptanalgesic combinations has also been reported in dogs (Hayashi et al., 1994; Kojima et al., 2002; Sano et al., 2003). The combination of midazolam with medetomidine resulted in better quality of sedation in dogs than four times the dose of medetomidine alone, suggesting synergism between midazolam and medetomidine (Hayashi et al., 1994). In another study, sedation was considered adequate after administration of midazolam with butorphanol in dogs, but

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http://dx.doi.org/10.1016/j.tvjl.2014.01.018
1090-0233/

the authors reported a wide variation in the individual response of animals after administration of this combination (Kojima et al., 2002). In our clinical experience, administration of midazolam in combination with morphine often results in excitement in healthy young dogs (E.R. Monteiro, personal communication).

Although the combination of phenothiazines or benzodiazepines with opioids may be used for chemical restraint in dogs, intense sedation occurs more frequently after administration of alpha-2 agonists (Kojima et al., 2002). However, this class of drugs induces severe adverse effects within the cardiovascular system such as marked bradycardia and reduction of cardiac output, arterial vasoconstriction (Kojima et al., 2002) and atrioventricular block (Lemke, 2007). When administered intravenously (IV), initial hypertension followed by subsequent reduction in blood pressure is also expected (Kojima et al., 2002). Therefore, a drug or drug combination capable of inducing deep sedation in dogs with fewer cardiovascular adverse effects would be of value for the veterinary practitioner.

Although the use of combinations of phenothiazines or benzodiazepines with opioids have been widely reported in the literature, to our knowledge, there are no studies on the sedative effects in dogs of a three-drug combination. The present study evaluated the effects of a combination of acepromazine with midazolam and morphine on the degree of sedation, and cardiovascular variables, as well as the propofol dose required for induction of anesthesia in dogs in comparison with combinations of acepromazine with morphine or midazolam with morphine. It was hypothesized that a three-drug combination would result in greater sedation and greater sparing effect on the propofol dose than the two-drug combinations.

Materials and methods

Animals

This study was approved by the Institutional Animal Care Committee (protocol 225/2012). Twenty-nine client-owned healthy dogs scheduled to undergo anesthesia for routine surgical or diagnostic procedures were enrolled in the study. Health status was assessed by means of physical examination, an electrocardiogram (ECG), a complete blood count (CBC) and serum chemistry. Dogs were included only if they were classified as American Society of Anesthesiologists (ASA) status 1 or 2.[1]

Study design and treatments

The dogs were randomly assigned to receive one of three treatments as premedication. Randomization was performed by drawing pieces of paper from a bag. Dogs in group AM ($n = 10$) received acepromazine (0.05 mg/kg; Acepran 0.2%, Vetnil) and morphine (0.5 mg/kg; Dimorf, Cristália). Dogs in group MM ($n = 9$) received midazolam (0.5 mg/kg; Dormire, Cristália) and morphine (0.5 mg/kg). Dogs in group AMM ($n = 10$) received acepromazine, midazolam and morphine at the same doses. In all occasions, the drugs were mixed in a single syringe and injected into the semitendinosus muscle (IM) by a veterinarian.

Experimental procedure

Food but not water was withheld for 12 h prior to anesthesia. The animals were acclimatized to a quiet room for approximately 20 min prior to administration of any treatment. Subsequently, baseline cardiovascular variables were recorded. An oscillometric device (petMAP Classic, Ramsey Medical) was used to measure indirect systolic (SAP), mean (MAP) and diastolic (DAP) arterial blood pressures and HR. The blood pressure cuff was positioned around the antebrachium, proximal to the carpus. The cuff used was selected from one provided with the device according to the manufacturer's instructions. During measurements, the dog was gently restrained in sternal or lateral recumbency. Four consecutive readings were obtained on each occasion and the average was used for analysis.

After data collection at baseline, the animals received any one of the treatments and cardiovascular variables and sedation scores were measured 30 min later (Time 30). The degree of sedation was evaluated using a numeric descriptive scale (NDS), with a range from 0 to 3 (Valverde et al., 2004; Monteiro et al., 2009) (Table 1), and a simple numerical scale (SNS). The SNS consisted of a scale ranging from 0 to 10 where 0 represents no sedation and 10 represents the most sedation possible (Gomes et al., 2011).

After measurements at Time 30, a 20 or 22 G catheter was placed in a cephalic vein and the resistance to venous catheterization was scored using a scale ranging from 0 (strong resistance) to 3 (no resistance, Table 1). The animals received IV propofol (Propovan, Cristália) for induction of anesthesia at 0.5 mg/kg every 10 s until endotracheal intubation could be performed, as assessed by rotation of the eyeball, loss of interdigital and palpebral reflexes. Resistance to tracheal intubation was scored using a scale ranging from 0 (strong resistance) to 3 (no resistance, Table 1). Immediately after intubation and before inflation of the tube cuff, cardiovascular variables were measured again. All assessments were made by a single observer who was experienced in evaluating scores and was familiar with the oscillometric device used in this study. This person was unaware of the treatment administered to each dog. The time from premedication to induction of anesthesia and the occurrence of excitement were recorded.

Statistical analysis

Normality was tested by the Shapiro–Wilk test. Differences among groups in HR, SAP, MAP and DAP were analyzed with two-way ANOVA followed by the Bonferroni correction. A one-way repeated measures ANOVA and Dunnett test were used to detect differences from baseline within each group. The Kruskal–Wallis and Dunn's tests were used to assess differences among groups and differences from baseline within each group in the dose of propofol and in scores. Values for weight, age and time from premedication to induction of anesthesia were compared among groups by ANOVA and a Tukey test. The incidence of intense sedation (NDS score = 3) in each group was compared by the Fisher's exact test. Differences were considered significant when $P < 0.05$.

Results

Demographic data for the three groups are shown in Table 2. The times elapsed from premedication to the induction of anesthesia were (mean ± standard deviation SD): AM, 42 ± 8 min; MM, 46 ± 11 min; and AMM, 45 ± 8 min. There was no significant difference among the groups in age, weight and the time from premedication to the induction of anesthesia.

Post hoc analyses revealed a power of 66% for the means of NDS scores in groups AM, MM and AMM and a SD of 0.9 for all three groups. For the means of SNS scores, the power was 58% for a SD of 2.6. Two animals in MM group showed excitement which began within 5 min after premedication and lasted until the induction of anesthesia. One dog in the AMM group presented transitory excitement which began a few minutes after premedication and lasted for approximately 5 min. At Time 30, NDS and SNS scores were significantly higher in AMM than in MM group ($P < 0.05$). No statistically significant difference was found in sedation scores between AM vs. MM or AMM (Table 3). There was a trend towards more dogs presenting with intense sedation (NDS score = 3) in group AMM compared with groups AM and MM ($P = 0.057$; Fig. 1).

Strong or moderate resistance to venous catheterization was observed in 3/10 (30%), 4/9 (44%) and 0/10 (0%) dogs in groups AM, MM and AMM, respectively. Resistance to tracheal intubation was mild in one dog each in groups AM and AMM, and moderate in one dog in the MM group. In all other dogs, there was no resistance to intubation. The scores of resistance to venous catheterization and tracheal intubation did not differ among groups (Table 3). The dose of propofol required for induction of anesthesia was significantly lower in group AMM compared with MM ($P < 0.01$; Table 3).

Cardiovascular variables were not measured in one dog (group MM) because of failure of oscillometric device. Therefore, cardiovascular data reported for group MM were obtained from eight dogs. In the AM group, HR decreased from baseline at Time 30 and remained lower than baseline after intubation. At Time 30, HR was lower in the AM group than in MM and AMM groups (Fig. 2).

In the AM and AMM groups, SAP, MAP and DAP were significantly lower at Time 30 and after intubation compared to baseline whereas in the MM group, SAP, MAP and DAP were lower than

[1] See: http://www.avta-vts.org/site/view/93251_asaratings.pml.