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Comparison of sedation scores and propofol induction doses in dogs after intramuscular administration of dexmedetomidine alone or in combination with methadone, midazolam, or methadone plus midazolam

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ABSTRACT

The objectives of this study were to determine: (1) the sedative effects of dexmedetomidine in combination with methadone, midazolam, or both, and (2) the propofol dose required to achieve endotracheal intubation in healthy dogs. Seven healthy Beagle dogs were included in a prospective experimental, crossover, randomised and masked design. All dogs received four treatments IM, with at least 1 week between sessions, as follows: dexmedetomidine 5 μg/kg (D) alone, or combined with methadone 0.3 mg/kg (DMe), midazolam 0.3 mg/kg (DMi), or both (DMeMi). The degree of sedation was evaluated using a numerical scale (maximum 15 points). The dose of propofol required for intubation was also calculated for each group. Recovery time and quality were determined. Statistical analysis was performed using parametric (ANOVA) and nonparametric tests (Friedman, Cochran Q), as appropriate.

The degree of sedation obtained with DMe and DMeMi (13, [7–14]; 13, [6–14], respectively) was significantly higher than in the control group (2, [1–4]; $P = 0.023$, $P = 0.006$, respectively). The required dose of propofol was lower in all groups (DMi, 1.5 ± 0.5 mg/kg, $P = 0.002$; DMe, 1.2 ± 0.5 mg/kg, $P < 0.001$; DMeMi, 0.9 ± 0.3 mg/kg) than in the control group (2.9 ± 0.9 mg/kg; $P < 0.001$). Recovery quality was not different between groups ($P = 0.137$). In healthy dogs, the addition of midazolam did not enhance the sedative effects of dexmedetomidine or a dexmedetomidine–methadone combination at the doses studied, and propofol requirements were reduced. The sedative effect of dexmedetomidine was enhanced with methadone, and the required dose of propofol was reduced.

Introduction

Alpha-2 adrenoceptor agonists such as medetomidine and dexmedetomidine are among the most commonly used sedatives in small animals. These drugs produce deep sedation, muscle relaxation and analgesia, and allow a reduction in the dose of anaesthetics, thereby reducing their dose-dependent undesirable effects (Dart, 1999; Murrell and Hellebrekers, 2005). Additionally, alpha-2 adrenoceptor agonists can be reversed effectively with antagonists such as atipamezole (Granholm et al., 2007). Alpha-2 adrenoceptor agonists are usually combined with opioids, such as methadone, which potentiate their analgesic and sedative effects (Monteiro et al., 2008). A common side effect of both alpha-2 adrenoceptor agonists and opioids is bradycardia (Monteiro et al., 2009). While alpha-2 adrenoceptor agonists do not produce respiratory depression on their own, they can when combined with opioids (Sinclair, 2003). Alternatives to opioids may include benzodiazepines such as midazolam, which have minimal effects on the cardiovascular system (Rankin, 2015). However, while this drug does not induce reliable sedation when used as a sole agent in dogs, it may increase the effects of other anaesthetics and analgesics (Tranquilli et al., 1991). Potentiation by drugs with analgesic and/or sedative actions may improve quality of sedation and reduce unwanted dose-dependent side effects of alpha-2 adrenoceptor agonists (Dart, 1999).

Alpha-2 adrenoceptor agonists are widely used in veterinary practice for sedative purposes, and the effects of combining methadone and/or midazolam with them have been studied using high doses of medetomidine (Hayashi et al., 1994). However, more recent papers recommend lower doses of medetomidine (Pinelas et al., 2014).

We hypothesised that a relatively low dexmedetomidine dose would be potentiated by both midazolam and methadone and that the sedative effect of low dose dexmedetomidine would correlate inversely with the required dose of the anaesthetic induction agent.

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Therefore, we aimed to determine: (1) the sedative effects of lower doses of dexmedetomidine alone or in combination with either midazolam, methadone or both; and (2) how these sedative combinations might modify the necessary dose of propofol required to perform endotracheal intubation in dogs.

Materials and methods

Animals

Seven adult healthy Beagle dogs (six males and one female) were used. Food but not water was withheld 12 h before the experiment began. The study was approved by the ethics committee of the Complutense University of Madrid and by the competent authority (PROEX 89/14).

Experimental design

In a blinded crossover design, dogs were administered four different sedative combinations in a random order at least 1 week apart. Randomisation was performed using a computerised program that generated random permutations of treatments for situations where group members received all of the treatments in random order.[1] The treatments were as follows: either dexmedetomidine 5 μg/kg alone (D, control group), or combined with either methadone 0.3 mg/kg (DMe), midazolam 0.3 mg/kg (DMi), or both (DMeMi). The drugs were mixed in the same syringe, adjusted to equal volumes with normal saline, and administered by IM injection into the lumbar musculature in all groups. Data were recorded at baseline (T0; before drug administration); 20 min following drug administration (T1); after dogs were pre-oxygenated and an IV catheter was placed (T2); and after intubation (T3).

Assessment of sedation

Sedation was assessed in a quiet room maintained at 22–26 °C. A single observer masked to treatment allocation (SC) performed all the assessments. A previously described sedation score (Gurney et al., 2009) was used (Appendix: Supplementary Table S1), which ranged from 0 (no sedation) to 15 (deep sedation), at T0 and T1. In addition, response to the introduction of the catheter into the cephalic vein was assessed using a score ranging from 0 to 2 as follows: 0: no resistance; 1 (mild): slight vocalisation or withdrawal of the limb; and 2 (moderate): evident vocalisation or withdrawal of the limb (Valverde et al., 2004).

Propofol requirements

After evaluating sedation at T1, a catheter was placed in the cephalic vein and dogs were pre-oxygenated with 100% O_2 for 5 min via a facemask. Propofol was then administered in 0.5 mg/kg increments administered over 15 s and at 30 s intervals until endotracheal intubation was performed (T2); the palpebral reflex, jaw tone, gag reflex and ease of intubation were also assessed (Raszplewicz et al., 2013). A laryngoscope was used to depress the tongue and visualise the larynx with the dog in sternal recumbency, using an appropriately sized endotracheal tube. Presence or absence of coughing at intubation was recorded. Presence and duration (min) of post-intubation apnoea were assessed. Apnoea was defined as the absence of spontaneous breaths within 30 s after intubation (Pinelas et al., 2014). The person assessing the propofol dose was also masked to the sedative combination used. Time to induction was defined as the time from drug administration (T0) to anaesthetic induction (T1).

Recovery

After anaesthetic induction, dogs were connected to a Mapleson A Magill's non-rebreathing system with an O_2 flow rate of 4–5 L/min and the time required from intubation to extubation was recorded. Then dogs were left undisturbed and the recovery quality and the times from extubation until sternal and standing positions were regained were recorded. Quality of anaesthetic recovery was scored using a standardised scale (Sams et al., 2008), ranging from 0 to 3 (Table 1). However, to simplify statistical analysis, quality of recovery was classified as acceptable (score 0 or 1) or unacceptable (score 2 or 3). Evidence of any clinical abnormalities during induction and recovery times was recorded, including adverse effects and ECG alterations.

Monitoring

During the procedure, the following variables were evaluated: heart (HR) and respiratory (RR) rates and non-invasive arterial blood pressure, body temperature and end-tidal CO_2 ($EtCO_2$). The HR, RR and non-invasive arterial blood pressure were recorded at all study times. Body temperature was recorded at T0 and after recovery, when dogs were able to stand. The HR was determined by pulse palpation at the femoral artery and ECG lead II. The RR was determined by observation of chest movements. Mean blood pressure (MAP) was measured by means of an oscillometric device with the cuff placed at the pedal metatarsal artery (PM8050, Drager). The cuff width was 40–60% of the limb circumference. Rectal temperature was measured with a digital thermometer, and $EtCO_2$ measurements were taken using a sidestream capnograph placed at the end of the endotracheal tube (PM8050, Drager).

Table 1
Quality of anaesthetic recovery scale (adapted from Sams et al., 2008).

Criteria	Score
Perfect, walking without ataxia, smooth uncomplicated recovery	0
Good, walking with minimal ataxia, uncomplicated recovery	1
Adequate, walking with moderate ataxia, difficult recovery	2
Rough, walking with significant ataxia or crawling	3

Statistical analysis

Data were tested for normality using the Shapiro–Wilk test. Mean and standard deviation are reported for the normally distributed variables, and median and range for variables that were not normally distributed. To compare the drug combinations, data were tested using an analysis of variance with repeated measures followed by post-hoc test with Bonferroni adjustment for parametric data (propofol induction dose, time to extubation, sternal and standing positions, physiological variables). The Friedman test followed by the Dunn post-hoc test with Bonferroni adjustment was used for non-parametric data (sedation scores, resistance to IV catheterisation, quality of recovery). The Cochran test was used to analyse data on the occurrence of apnoea and/or coughing. $P < 0.05$ was set to indicate statistical significance. All statistical analyses were performed using SPSS for Windows (IBM SPSS Statistics release 22).

Results

Animals

Dogs weighed 14.1 ± 1.5 kg and were aged 53 ± 3 months.

Sedation

The sedation scores (Table 2) in groups DMe and DMeMi were significantly higher than in group D ($P = 0.023$ and $P = 0.006$, respectively). Sedation was not different between groups DMi and D ($P = 0.586$). There were no differences between groups with respect to response to catheter introduction into the cephalic vein ($P = 0.106$).

Propofol requirements

The propofol dose required for intubation was significantly higher in group D than in groups DMi, DMe and DMeMi (Table 2; $P = 0.002$,

Table 2
Sedation scores 20 min after pre-medication (T1), propofol requirements to perform endotracheal intubation, incidence of cough and apnoea, and recovery characteristics for dogs treated with dexmedetomidine 5 μg/kg alone (D), or combined with either methadone 0.3 mg/kg (DMe), midazolam 0.3 mg/kg (DMi), or both (DMeMi). Data are expressed as mean ± standard deviation or median (range), as appropriate.

	D	DMi	DMe	DMeMi
Sedation scores at T1	2 (1–4)	8 (2–14)	13 (7–14)[a]	13 (6–14)[a]
Induction characteristics				
Propofol dose (mg/kg)	2.9 ± 0.9	1.5 ± 0.5[a]	1.15 ± 0.5[a]	0.9 ± 0.3[a]
Cough (*n* from *n* = 7)	5	6	2[a]	1[a]
Apnoea (*n* from *n* = 7)	4	2	4	2
Recovery characteristics				
Extubation time (min)	9.4 ± 1.25	13.3 ± 1.3	14.1 ± 1.8	18.1 ± 1.6[a]
Sternal time (min)	17.7 ± 1.9	21.7 ± 5.9	22.4 ± 6.6	19.6 ± 3.7
Standing time (min)	24.8 ± 3.5	24.9 ± 6.2	25.9 ± 6.5	21.1 ± 3.4
Recovery quality	1 (1–2)	1 (1–2)	1 (0–1)	1 (1–2)

[a] Statistically significant differences from group D ($P < 0.05$).

[1] See: www.randomization.com (Accessed 23 January 2016).