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RESEARCH PAPER

The sedative effects of intramuscular low-dose medetomidine in combination with butorphanol or methadone in dogs

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Abstract

Objective To compare the sedative effects of an intramuscular (IM) low dose of medetomidine in combination with butorphanol or methadone in dogs.

Study design Prospective, blinded, randomized clinical trial.

Animals Forty-eight healthy adult dogs that required sedation for diagnostic or surgical elective procedures.

Methods Dogs were sedated IM with medetomidine (2.5 μg kg^{-1}) and either butorphanol (0.4 mg kg^{-1}) or methadone (0.4 mg kg^{-1}). The degree of sedation was assessed every 10 minutes, for 30 minutes, using a numeric descriptive scale. Data on heart rate (HR), respiratory rate, capillary refill time, temperature and response to a toe pinch were recorded. The response to venous catheterization at minute 30 was also evaluated.

Results Both combinations produced moderate to deep sedation with a maximal effect at 20–30 minutes without significant differences in the degree of sedation between the treatments at any studied time-point. HR decreased from minute 10 to minute 30 with both opioid combinations ($p < 0.05$); this reduction did not differ between groups ($p > 0.05$). No differences between groups were detected in any of the other variables.

Conclusions and clinical relevance Combinations of a low dose of medetomidine with butorphanol or methadone, respectively, provide similar degrees of sedation.

Keywords butorphanol, dogs, medetomidine, methadone, sedation.

Introduction

Medetomidine is a highly selective α_2-adrenoceptor agonist commonly used before general anaesthesia to provide sedation and analgesia. Medetomidine induces cardiovascular effects such as bradycardia and a decrease in cardiac output (Kuo & Keegan 2004). These effects are produced in a dose-dependent fashion at doses of <5 μg kg^{-1} administered intravenously (IV) in dogs (Pypendop & Verstegen 1998). The sedative effect is also dose-dependent (Vainio et al. 1989; Pypendop & Verstegen 1998) and low doses (i.e. <5 μg kg^{-1}) may not provide adequate levels of sedation (Muir et al. 1999).

The combination of medetomidine with opioids produces a synergistic sedative effect (Kuo & Keegan

2004), although the potential of some opioids to induce additive depressive effects on the respiratory and cardiovascular systems must also be considered (Muir et al. 1999). Several studies have reported the use of butorphanol to potentiate the sedative effects of medetomidine in dogs (Muir et al. 1999; Kuo & Keegan 2004). Butorphanol is a synthetic opioid with κ-agonist and μ-antagonist properties. Its analgesic efficacy in domestic species is considered to be lower than that produced by pure μ-agonist opioids, drugs that can elicit a maximal activation of the receptor and a maximal analgesic effect (Lamont & Mathews 2007). When administered alone, butorphanol causes dose-dependent sedation with minimal cardiopulmonary depression (Trim 1983).

Methadone and L-methadone have been reported to potentiate the sedative effects of xylazine and medetomidine, respectively (Monteiro et al. 2008; Raekallio et al. 2009). Methadone is a synthetic opioid with high affinity for μ-receptors and analgesic potency similar to that of morphine (Hall et al. 2001). In addition, methadone has affinity for *N*-methyl-D-aspartate (NMDA) receptors, which may contribute to its analgesic effect (Gorman et al. 1997). When administered alone, methadone causes dose-dependent sedation and a decrease in heart rate (HR) (Menegheti et al. 2014), an effect attributed to a centrally mediated increase in vagal tone (Stanley et al. 1980).

In combination with acepromazine, pure opioid agonists provide better sedation than butorphanol (Cornick & Hartsfield 1992) and compared with other opioids, the use of methadone has been found to induce the highest level of sedation (Monteiro et al. 2009). To the present authors' knowledge, the degrees of sedation provided by combinations of medetomidine with butorphanol or methadone, respectively, have not been compared. The addition of butorphanol to low doses of medetomidine (1 μg kg^{-1} IV) has been investigated and although it improved the level of sedation (with no further decrease in HR), this was considered to be mild (Girard et al. 2010). Raekallio et al. (2009) studied the combination of methadone and medetomidine, but used a high dose of medetomidine (20 μg kg^{-1}) and therefore the effects on sedation and HR of a low dose of medetomidine combined with methadone have not been reported.

The aim of this study was to assess and compare the sedative effects of a low dose of medetomidine in combination with either butorphanol or methadone, and to evaluate the effects on HR of both combinations.

We hypothesized that the combination of a low dose of medetomidine with methadone would provide a higher degree of sedation than that provided by a low dose of medetomidine with butorphanol, but that the inclusion of methadone might promote a higher degree of bradycardia.

Materials and methods

Dogs that required sedation for diagnostic or surgical elective procedures were initially enrolled in the study with the informed consent of their owners in accordance with the regulations of and approval obtained from the Ethics Committee of the Universitat Autònoma de Barcelona (CEEAH 2220). Based on the results of previous reports (Girard et al. 2010), we estimated that a minimum of 20 dogs per group would be necessary to attain a 95% confidence level of achieving a clinically significant difference (at least 25%) in sedation scores between groups with 80% power.

A prospective, blinded, randomized clinical trial was designed. Dogs were randomly assigned to either of two groups using a computer-generated randomized sequence. Sixty dogs were assessed for eligibility and 48 were finally included in the analysis (Fig. 1). The study inclusion criteria required the dogs to be aged 1–10 years and to weigh 10–40 kg. Very fractious dogs were not included.

All dogs were judged to be healthy based on physical examination and blood work (haematological and biochemical analyses). Food but not water was withheld for 12 hours prior to anaesthesia. Group MBUT received medetomidine 2.5 μg kg^{-1} (Domtor; Pfizer SA, Spain) and butorphanol 0.4 mg kg^{-1} (Torbugesic; Fort Dodge Veterinaria SA, Spain). Group MMET received medetomidine 2.5 μg kg^{-1} and methadone 0.4 mg kg^{-1} (Metasedin; Laboratorios Dr Esteve SA, Spain). Each drug combination was mixed in the same syringe and injected intramuscularly (IM) into the semimembranosus muscle.

Dogs were allowed to acclimatize to a quiet environment at an average room temperature of 20 °C and to the personnel for at least 10 minutes before the administration of drugs. Each animal was assessed before and during the 30 minutes after the administration of drugs at 10 minute intervals (at baseline, 10, 20 and 30 minutes). The degree of sedation was assessed by a single blinded assessor unaware of the treatment administered, using a