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RESEARCH PAPER

Effects of three methadone doses combined with acepromazine on sedation and some cardiopulmonary variables in dogs

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Abstract

Objective To evaluate the sedative and cardiopulmonary effects of three methadone doses, combined with acepromazine, in dogs.

Study design Prospective, randomized, complete block study.

Animals Six healthy, adult, cross-bred dogs weighing 17.2 ± 4.4 kg (mean ± standard deviation).

Methods Each dog was administered four treatments: acepromazine (0.05 mg kg^{-1}) alone or acepromazine (same dose) in combination with methadone (0.25, 0.50 or 0.75 mg kg^{-1}). All drugs were administered intramuscularly. Sedation was scored by a numeric descriptive scale (NDS, range 0–3) and a simple numerical scale (SNS, range 0–10). Heart rate, invasive blood pressure, arterial blood gases and rectal temperature were measured at 15 to 30 minute intervals for 120 minutes.

Results According to NDS scores, mild to moderate sedation (NDS = 1–2) was observed in most dogs in the acepromazine treatment, with only one out of six dogs scored as exhibiting intense sedation (NDS = 3). All treatments with methadone resulted in significantly higher SNS scores compared with acepromazine alone. In these treatments, most dogs exhibited intense sedation (NDS = 3). Increasing the dose of methadone from 0.25 to 0.50 or 0.75 mg kg^{-1} prolonged sedation in a dose-related manner, but did not influence the degree of sedation. The main adverse effects following administration of acepromazine–methadone treatments were decreased blood pressure, mild respiratory acidosis and decreased rectal temperature. These effects were well tolerated and resolved without treatment.

Conclusions and clinical relevance In this study in six dogs, acepromazine–methadone administration resulted in intense sedation in most dogs. The results are interpreted to indicate that a low dose of methadone (0.25 mg kg^{-1}) administered in combination with acepromazine (0.05 mg kg^{-1}) will induce short-term sedation in dogs, whereas higher doses of methadone should be administered when prolonged sedation is desired.

Keywords canine, neuroleptanalgesia, opioid, phenothiazine, sedation.

Introduction

Acepromazine is the most commonly used phenothiazine agent in dogs. The exact mechanism by which phenothiazine derivatives induce sedation is not entirely understood, but these drugs were found to interact with dopaminergic, serotonergic, α-adrenergic and histamine receptors within the central nervous system of rats (Peroutka & Synder 1980). In dogs, acepromazine alone provides mild to moderate sedation (Monteiro et al. 2008, 2009; Gomes et al. 2011).

Methadone is an opioid analgesic classified as a full agonist at μ-receptors (Volpe et al. 2011). Although the relative potency of methadone has not been fully elucidated in dogs, it was considered more potent than morphine in rats and mice on the basis of antinociceptive studies (Peckham & Traynor 2006; Miranda et al. 2014). Mild to moderate sedation was observed after administration of methadone or morphine alone in dogs. However, no significant difference was observed in the degree of sedation between the two drugs (Maiante et al. 2009). One advantage of methadone over morphine in dogs is that it does not induce vomiting (Monteiro et al. 2008,

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2009). In addition, it has been proposed that methadone possesses antagonistic activity at *N*-methyl-D-aspartate receptors, which may confer an antihyperalgesic effect to this opioid analgesic (Gorman et al. 1997).

Combinations of acepromazine with an opioid have been extensively studied in dogs, and previous reported data suggest that sedation is greater following administration of a combination than after the administration of acepromazine alone (Monteiro et al. 2008, 2009; Gomes et al. 2011). However, the degree of sedation may differ depending upon the opioid in the combination, and methadone was found to induce intense sedation in more dogs (six out of six dogs) than morphine (one out of six dogs), butorphanol or tramadol (none of the six dogs for both) (Monteiro et al. 2009).

The influence of the dose of methadone combined with acepromazine has not been investigated in dogs. The present study aimed to evaluate the sedative and cardiopulmonary effects of three doses of methadone combined with acepromazine in dogs. The hypothesis was that increasing the dose of methadone would enhance the degree of sedation and the frequency of adverse effects.

Materials and methods

Animals

The study was approved by the Institutional Animal Care Committee of the University of Vila Velha, Brazil (no. 23-2014). Six adult cross-bred dogs of unknown ages (three males and three females) weighing 17.2 ± 4.4 kg [mean ± standard deviation (SD)] were used. Dogs were considered healthy based on physical examination, electrocardiography and echocardiography examinations and clinical laboratory parameters: complete blood count, serum total protein, blood urea nitrogen, creatinine, alkaline phosphatase and alanine aminotransferase. All findings were within reference limits for dogs.

Study design and experimental protocol

Dogs were administered four treatments at intervals of 1 week in a randomized complete block design. The randomization plan was generated from a website (http://www.randomization.com). In the acepromazine treatment (ACP), the dogs were administered acepromazine maleate (0.05 mg kg^{-1}; Acepran 0.2%; Vetnil Indústria e Comércio de Produtos Veterinários Ltda, SP, Brazil) alone. In the other three treatments, acepromazine (0.05 mg kg^{-1}) was administered in combination with methadone hydrochloride (Mytedom; Cristália Produtos Químicos Farmacêuticos Ltda, SP, Brazil) as treatment $AM_{0.25}$ (0.25 mg kg^{-1}), treatment $AM_{0.50}$ (0.50 mg kg^{-1}) and treatment $AM_{0.75}$ (0.75 mg kg^{-1}). All drugs were administered intramuscularly (IM) in the pelvic limb. In treatments $AM_{0.25}$, $AM_{0.50}$ and $AM_{0.75}$, acepromazine and methadone were mixed in a single syringe.

Food was withheld for 12 hours and water was freely available. A 20 gauge catheter was percutaneously introduced into a dorsal pedal artery after subcutaneous infiltration of lidocaine. Thereafter, dogs were acclimated to the laboratory environment for 30 minutes. During this period, dogs were maintained on the floor and allowed to interact with the personal involved in the study. Baseline values were then recorded with dogs gently restrained in lateral recumbency. Heart rate (HR) was measured by auscultation with a stethoscope, respiratory frequency (f_R) was counted by observation of chest wall movements, and rectal temperature was measured with a digital thermometer. The arterial catheter was connected by noncompliant tubing to a pressure transducer (TruWave; Edwards Lifesciences, UT, USA) filled with heparinized saline to display systolic (SAP), mean (MAP) and diastolic (DAP) pressures (Lifewindow 6000Vet; Digicare Animal Health, FL, USA). The pressure transducer was leveled at the manubrium and its calibration was checked on a range of values (from 0 to 200 mmHg) before each experiment by use of a mercury manometer (Oxigel Materiais Hospitalares Indústria e Comércio Ltda, SP, Brazil).

Blood samples (1 mL) were anaerobically collected from the arterial catheter into sodium heparin-coated syringes. Samples were immediately analyzed (i-STAT 1; Abbott Point of Care, NJ, USA) for measurement of pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), bicarbonate (HCO_3^-), oxygen saturation (SaO_2) and lactate concentration.

Sedation was scored using a numeric descriptive scale (NDS) and a simple numerical scale (SNS). The NDS ranged from 0 to 3 as follows: 0, no sedation; 1, mild sedation, less alert but still active; 2, moderate sedation, drowsy, recumbent but can walk; 3, intense sedation, very drowsy, unable to walk (Valverde et al. 2004; Monteiro et al. 2014). The SNS scores ranged from 0 (no sedation) to 10 (most sedation possible) (Monteiro et al. 2014). The degree of sedation was evaluated by a single observer who was familiar with

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