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RESEARCH PAPER

The cardiopulmonary effects of a peripheral alpha-2-adrenoceptor antagonist, MK-467, in dogs sedated with a combination of medetomidine and butorphanol

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Abstract

Objective To compare the cardiopulmonary effects of intravenous (IV) and intramuscular (IM) medetomidine and butorphanol with or without MK-467.

Study design Prospective, randomized experimental cross-over.

Animals Eight purpose–bred beagles (two females, six males), 3–4 years old and weighing 14.5 ± 1.6 kg (mean ± SD).

Methods All dogs received four different treatments as follows: medetomidine 20 μg kg^{-1} and butorphanol tartrate 0.1 mg kg^{-1} IV and IM (MB), and MB combined with MK-467,500 μg kg^{-1} (MBMK) IV and IM. Heart rate (HR), arterial blood pressures (SAP, MAP, DAP), central venous pressure (CVP), cardiac output, respiratory rate (f_R), rectal temperature (RT) were measured and arterial blood samples were obtained for gas analysis at baseline and at 3, 10, 20, 30, 45 and 60 minutes after drug administration. The cardiac index (CI), systemic vascular resistance index (SVRI) and oxygen delivery index (DO_2I) were calculated. After the follow-up period atipamezole 50 μg kg^{-1} IM was given to reverse sedation.

Results HR, CI and DO_2I were significantly higher with MBMK after both IV and IM administration. Similarly, SAP, MAP, DAP, CVP, SVRI and RT were significantly lower after MBMK than with MB. There were no differences in f_R between treatments, but arterial partial pressure of oxygen decreased transiently after all treatments. Recoveries were uneventful following atipamezole administration after all treatments.

Conclusions and clinical relevance MK-467 attenuated the cardiovascular effects of a medetomidine-butorphanol combination after IV and IM administration.

Keywords butorphanol, dog, haemodynamics, medetomidine, MK-467.

Introduction

Intravenous administration of sedative drugs to a fractious or uncooperative animal can be a challenge. Consequently, it is often more convenient to induce sedation and restraint via the intramuscular (IM) route. Medetomidine, a potent α_2-adrenoceptor agonist, is used commonly as a sedative or premedicant in small animal medicine, and it can be administered both intravenously (IV) and IM. The disadvantages in using medetomidine include the marked cardiovascular changes, such as hypertension, bradycardia with associated brady-arrhythmias, increased systemic vascular resistance, and reduced cardiac

output and oxygen delivery (Pypendop & Verstegen 1998; Murrell & Hellebrekers 2005). MK-467, also know as L-659,066, is a α_2-adrenoceptor antagonist, which in rats or marmosets has been shown not to cross a blood brain barrier (Clineschmidt et al. 1988). Intravenous administration of MK-467 has been documented to prevent the peripheral cardiovascular effects of α_2-agonists in many animal species (Pagel et al. 1998; Enouri et al. 2008; Honkavaara et al. 2008, 2011; Raekallio et al. 2010; Rolfe et al. 2012; Vainionpää et al. 2013; Salla et al. 2014).

Butorphanol, a synthetic opioid with κ-agonist activity with partial μ-agonist and δ-antagonist properties (Lamount & Mathews 2007), is combined frequently with medetomidine to enhance the level and quality of sedation and analgesia in dogs (Pypendop & Verstegen 1998; Ko et al. 2000; Kuo & Keegan 2004). Bartram et al. (1994) suggested that butorphanol might accentuate the cardiovascular effects of medetomidine. When administered alone, butorphanol has been shown to cause a small but significant decrease in the heart rate, mean arterial pressure, cardiac index and arterial partial pressure of oxygen (Sederberg et al. 1981; Trim 1983). Moreover, a minor increase in the systemic vascular resistance index after administration has also been detected (Sederberg et al. 1981). Butorphanol induces mild hypoventilation in dogs, although the effects are considered to be less than after pure μ-agonist administration (Dodam et al. 2004).

The primary aim of our study was to examine the cardiopulmonary effects of MK-467 in dogs sedated with medetomidine and butorphanol via two administration routes: IV and IM. Our secondary aim was to compare the effects between the routes of administration.

Material and methods

This study was approved by the National Animal Experiment Board of Finland. Eight healthy purpose-bred beagles, age 3–4 years and weighing 14.5 ± 1.6 kg (mean ± SD) were used in the study. Prior to the experiments, food was withheld for 12 hours but water was provided *ad libitum*. The dogs were considered healthy based on thorough clinical examination, a complete blood count and routine serum chemistry.

Instrumentation and measurement

The cephalic vein was cannulated with a 20 gauge catheter (Terumo Europe N.V., Belgium). Each dog was preoxygenated using a mask (100% oxygen at 5 L minute^{-1}) before induction of anaesthesia with propofol (Propovet 10 mg mL^{-1}; Abbott Laboratories Ltd, UK) maximum 6 mg kg^{-1}. Anaesthesia was maintained with isoflurane in oxygen (Isoflo; Orion Pharma Ltd, Finland). Acetated Ringer's solution was infused at approximately 10 mL kg^{-1} hour^{-1}. A 7 Fr double-lumen central venous catheter (CV-12702; Arrow International, PA, USA) was premeasured from the cranial border of the second rib at the costo-chondrial junction, and it was aseptically inserted under local anaesthesia (0.5 mL Lidocain 20 mg mL^{-1}; Orion Pharma Ltd) through the jugular vein and secured in place. The dorsal pedal artery was aseptically cannulated with a 22 gauge catheter (Terumo; Europe N.V.). After instrumentation, dogs were allowed to recover for a minimum of 60 minutes prior to baseline measurements.

A continuous lead II electrocardiogram and direct arterial and central venous pressures were monitored throughout the study (S/5 Compact Critical Care Monitor; Datex-Ohmeda, UK). The blood pressure transducers (Gabarith PMSET; Becton Dickinson, UT, USA) were zeroed to the atmosphere and calibrated with a transducer simulator tester (Delta-Cal Utah Medical Products Inc., UT, USA) prior to each experiment. Transducers were placed at the level of the manubrium sternum as the animals were positioned in lateral recumbence on a standard isolating mattress. Cardiac output was measured by the lithium indicator dilution method (LidCO Plus Hemodynamic Monitor; LidCO Ltd, UK) as previously described by Mason et al. (2001) using a standard dose 0.075 mmol of lithium chloride injected via central venous catheter. Standard values of 10 g L^{-1} haemoglobin and 140 mmol L^{-1} sodium were used initially and later corrected with measured values obtained from simultaneously taken arterial blood gas samples. Arterial samples for blood gas analysis were obtained anaerobically into pre-heparinised syringes (Pico50; Radiometer, Denmark) and analyzed (ABL 855; Radiometer). The following parameters were obtained: oxygen and carbon dioxide partial pressures (PaO_2 and $PaCO_2$, respectively) pH and bicarbonate (HCO_3^-), lactate, haemoglobin and sodium concentrations. The samples were stored in iced water and analyzed within 15 minutes.