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Effects of a constant rate infusion of medetomidine–propofol on isoflurane minimum alveolar concentrations in horses

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A B S T R A C T

The aim of this investigation was to determine the isoflurane-sparing effect and impact on arterial blood pressure and anaesthetic recovery of a constant rate infusion of medetomidine–propofol in horses. In a prospective, crossover, randomised study, six healthy horses (mean ± SD age, 13.7 ± 7.7 years; weight, 433 ± 51 kg) were anaesthetised twice with isoflurane and were randomly assigned to receive one of two treatments on each occasion, at least 2 weeks apart. The first treatment was saline (CTL group) and the second a medetomidine–propofol infusion (MP group; 1.25 µg/kg/h medetomidine and 3 mg/kg/h propofol). The isoflurane minimum alveolar concentration (MAC) was determined and the reduction in anaesthetic requirements was calculated. Cardiopulmonary data were recorded at different intervals during the procedure and anaesthetic recovery was blindly assessed using three independent scales.

The MAC in the MP group (0.43 ± 0.08%) was 65% lower than in the CTL group (1.23 ± 0.10%). The MP group had a higher mean arterial blood pressure and required less dobutamine than the CTL group. The recovery quality in both groups was considered fair or good and an improvement was observed using the Donaldson scale in the MP group. The administration of a medetomidine–propofol constant rate infusion reduced anaesthetic isoflurane requirements to a clinically significant extent and improved stability of arterial blood pressure together with a good quality recovery. This regime could be useful for providing balanced anaesthesia in horses.

Introduction

Inhalational anaesthesia is commonly used in equine surgery, although inhaled agents are potent dose-dependent cardiopulmonary depressants (Steffey et al., 1977; Steffey and Howland, 1978). Prevention of a nociceptive response to surgery requires higher concentrations of agents than are needed to produce unconsciousness. Total intravenous anaesthesia (TIVA) is usually characterised by a lower degree of cardiovascular depression than inhalational anaesthesia, maintaining clinically acceptable cardiopulmonary function.

Ketamine and guaifenesin, with or without alpha-2 adrenoceptor agonists, are commonly used in TIVA. Nevertheless, prolonged periods (>1–2 h) of anaesthesia with these drugs should be avoided to prevent drug accumulation that can result in poor recovery (Greene et al., 1986; Young et al., 1993; Taylor et al., 1995). Propofol has been described as the only IV anaesthetic suitable for TIVA in procedures lasting >2 h because of its short half-life and resultant rapid recovery (Nolan et al., 1996; Bettschart-Wolfensberger et al., 2001a). However, propofol provides poor suppression of the nociceptive response to surgery and, when used as the sole anaesthetic drug, failed to induce satisfactory anaesthesia, produced side effects such as hypoxemia and hypercapnia, and added a significant increase in cost (Mama et al., 1995; Bettschart-Wolfensberger et al., 2003).

Earlier work showed that the combination of propofol with medetomidine resulted in a considerable reduction in the infusion rate of propofol compared with previously reported drug combinations (Bettschart-Wolfensberger et al., 2001a, 2001b). Medetomidine–propofol TIVA has been successfully employed in a wide range of surgical procedures in horses with good cardiovascular function and anaesthetic recovery reported although artificial ventilation was required to prevent severe hypercapnia, and the quality of anaesthetic induction was variable and unsatisfactory in some individual animals (Bettschart-Wolfensberger et al., 2002). In ponies, induction of anaesthesia with medetomidine–ketamine followed by a medetomidine–propofol infusion provided a good quality of induction and controllable anaesthesia with acceptable levels of cardiovascular depression, although the minimum arterial oxygen levels were low despite oxygen supplementation (Bettschart-Wolfensberger et al., 2003). The combination of ketamine–medetomidine constant rate infusion (CRI) with propofol produced a sparing effect on propofol requirements but did not improve hypoventilation (Umar et al., 2006).

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The combined use of inhalational and IV analgesic and anaesthetic drugs may provide better analgesia and cardiopulmonary stability, improving overall anaesthetic quality. Several drugs have been used for this purpose, and a CRI of lidocaine, ketamine, and lidocaine–ketamine reduced inhalational anaesthetic requirements by 15–25%, 15–31% and 50%, respectively (Muir and Sams, 1992; Doherty and Frazier, 1998; Dzikiti et al., 2003; Villalba et al., 2011). The alpha-2 adrenoceptor agonists are potent analgesics and sedatives that reduce the minimum alveolar concentration (MAC) of inhaled anaesthetic agents and improve recovery (Steffey et al., 2000; Santos et al., 2003; Bennett et al., 2004).

Medetomidine is a highly specific and potent alpha-2 adrenoceptor agonist that has been demonstrated to reduce isoflurane and desflurane requirements by 20% and 28%, respectively (Bettschart-Wolfensberger et al., 2001c; Neges et al., 2003) and contributed to a good quality of recovery in horses anaesthetised with isoflurane (Ringer et al., 2007; Valverde et al., 2010). The combination of medetomidine–propofol CRI with inhalational anaesthesia has not been described. We hypothesised that this CRI might produce a relevant decrease in isoflurane MAC, associated with acceptable cardiovascular function and a good quality recovery. The purpose of the present study was to determine the isoflurane-sparing action, assess the main cardiovascular effects and examine the recovery characteristics of a medetomidine–propofol CRI in horses following premedication with medetomidine and induction with ketamine.

Materials and methods

Animals

Six healthy mature mares, aged 13 ± 7 years (mean ± SD; range 4–19 years) and weighing 433 ± 51 kg (range 394–480 kg), were studied. Animals were kept on a pasture and housed overnight before each procedure. The Institutional Animal Care Committee approved the study protocol (CEA-UCM, Madrid; 16 June 2011).

Experimental design

Using a randomised, crossover study design, horses were anaesthetised twice, once with isoflurane and saline CRI (CTL) and once with isoflurane and medetomidine–propofol CRI (MP), at least 2 weeks apart. Horses in the CTL group received saline (0.9% NaCl, Braun) at 0.3 mL/kg/h IV, and those in the MP group received medetomidine (Dorbene Vet, Fort Dodge) at 1.25 µg/kg/h IV diluted in saline and propofol (Propofol-lipuro 1%, Braun) at 3 mg/kg/h IV using a programmable infusion pump (Infusomat fm, Braun). The medetomidine CRI was prepared by adding 0.625 mL of medetomidine (0.1%) to 94 mL of saline, resulting in a 6.6 µg/mL solution that was infused at 0.2 mL/kg/h IV. The MAC was determined in both groups, and the cardiopulmonary function and quality of recovery were assessed.

Procedure

Food but not water was withheld from the horses for approximately 12 h before the procedure. After aseptic catheterisation (16 G; Terumo, Braun) of the right jugular vein, horses were transported to an induction stall and were premedicated with medetomidine at 7 µg/kg IV. Five minutes later, anaesthesia was induced with ketamine at 3 mg/kg IV, and orotracheal intubation (cuffed endotracheal tube; internal diameter, 26 mm) was performed. Following intubation, the horses were positioned in left lateral recumbency on a padded bed and connected to a large animal breathing circuit (2800, Mallard Medical).

Anaesthesia was maintained with isoflurane (Isoflo, Abbott Laboratories) in oxygen (5 L/min), and the end-tidal isoflurane concentration (Et-ISO) was adjusted to 1.3% in the CTL or 1.0% in the MP group. Mechanical ventilation was set at a rate of 8 breaths/min and a tidal volume between 10 and 15 mL/kg to maintain an end tidal partial pressure of carbon dioxide between 35 and 45 mmHg. Respiratory rate, tidal volume, peak inspiratory pressure, Et-ISO and carbon dioxide concentrations, determined from a sample obtained from the distal end of the endotracheal tube, were monitored (PM8050, Draeger).

To avoid discrepancies between animals with regard to medetomidine administration, horses received the indicated doses of medetomidine and propofol CRI in the MP group (or saline in the CTL group) 10 min after the loading dose. Lactated Ringer's solution (Ringer Lactate, Braun) was infused for the duration of the anaesthesia at a rate of 5 mL/kg/h in both groups.

The following parameters were continuously monitored: heart rate (HR), by placing base to apex electrocardiograph leads; arterial haemoglobin oxygen saturation, by attaching a pulse oximetry transducer to the tongue; arterial blood pressure via a catheter placed in the facial artery connected to a pressure transducer (Vet Care, Braun). The arterial pressure transducer was calibrated against a mercury manometer before each procedure, and the zero reference point was determined at the level of the manubrium of the sternum. If the mean arterial blood pressure (MAP) decreased below 55 mmHg, inotropic support was provided with dobutamine (Dobutamina, Mayne Pharma) starting at 1 µg/kg/h IV, and horses requiring this treatment in each group were recorded.

Monitored data were recorded every 5 min, and arterial blood samples were collected before premedication (baseline) and at 30, 60, 120 and 180 min after induction and analysed immediately for pH and blood gas tension (PaO_2 and $PaCO_2$; ABL80 Flex, Radiometer Medical). The urinary bladder was catheterised for passive urine collection until the horse was disconnected from the breathing system.

MAC determination

Two non-blinded anaesthetists determined the MAC, in duplicate, as described by Steffey et al. (1977). An electrical noxious stimulation was applied (50 V, 5 Hz, 10 ms) by placing crocodile electrodes on the lip for 60 s or until a positive response was elicited. A response was judged to be positive when a purposeful movement was detected during the application of the noxious stimulus.

The Et-ISO was maintained at 1.3% (CTL) or 1.0% (MP) during the first 60 min. Subsequently, the stimulus was applied; if no response to the stimulation occurred, the Et-ISO concentration was lowered by 10–20% (Et-ISO decrements at a maximum of 0.2%) and the stimulus was repeated after 20 min had elapsed for equilibration. If a positive response was then obtained, the Et-ISO was increased by between 10% and 20% (Et-ISO increments at a maximum of 0.2%), again allowing 20 min additional equilibration before the stimulus was repeated.

The MAC was defined as the isoflurane concentration midway between the highest concentration allowing, and the lowest concentration preventing, movement. As the MAC determination was performed at an altitude of 650 m, values were corrected to the barometric pressure at sea level by using the following formula (Mama et al., 1999):

MAC at sea level barometric pressure (760 mmHg; altitude adjusted MAC) = measured MAC × measured ambient barometric pressure (700 mmHg in Madrid)/sea level barometric pressure (760 mmHg).

Recovery

Once the MAC had been determined, treatments were discontinued and horses were disconnected from the breathing system. They were then hoisted to a padded recovery stall and positioned in right lateral recumbency. The trachea was extubated once the swallowing reflex returned.

Horses were allowed to recover without assistance and recovery events were timed and blindly assessed using three scoring systems. A qualitative overall recovery score based on a five point scale (1, dangerous; 2, poor; 3, fair; 4, good; 5, excellent) was employed (Wagner et al., 2008). A quantitative 10 category scoring system was used to assess each horse's overall attitude, activity in recumbency, movement to sternal recumbency, number of attempts to achieve sternal recumbency, duration in sternal recumbency, move to stand, number of attempts to stand, strength and balance after standing and knuckling at this position (Donaldson et al., 2000). Ataxia during recovery was evaluated using a descriptive six point scale that ranged from 0 (worst) to 5 (best) (Young and Taylor, 1993).

The total anaesthesia time from the time of intubation until disconnection from the anaesthesia machine was recorded. Time from disconnection to extubation, first movement, sternal recumbency and standing were also recorded.

Statistical analysis

Data were grouped and reported as means ± SD, and normal distribution of the data was ascertained with the Kolmogorov–Smirnov test. Differences between CTL and MP groups with regards to the MAC of isoflurane, HR, MAP, blood gases, total anaesthesia time and quality, and times of recovery were analysed with the paired *t* test. A one-sided *t* test was used for the MAC and MAP. The HR and MAP values employed were those recorded at MAC level (5 min before the first positive response to the stimuli). The Pearson chi-squared test was used to determine differences in dobutamine requirements between both groups. Differences were considered to be significant at a *P* value <0.05. Statistical analysis was performed using the SPSS statistical package (15 for Windows).

Results

MAC of isoflurane

The MAC of isoflurane determined in the CTL and MP groups for the six horses was 1.23 ± 0.10% and 0.43 ± 0.08%, respectively. This outcome represented a 65% reduction in the MAC in the MP group ($P < 0.01$) (Fig. 1).