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Comparison of the influence of two different constant-rate infusions (dexmedetomidine *versus* morphine) on anaesthetic requirements, cardiopulmonary function and recovery quality in isoflurane anaesthetized horses

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ABSTRACT

Twenty adult healthy horses undergoing elective surgery were involved in this prospective, blinded, clinical study. Horses were randomly allocated to receive a constant rate infusion (CRI) of morphine or dexmedetomidine. After induction, anaesthesia was maintained with isoflurane in oxygen/air and mechanical ventilation applied. The end-tidal isoflurane concentration ($F_E'ISO$) was initially set at 0.9% and adjusted by the anaesthetist, to maintain a light surgical plane of anaesthesia, according to an objective flow-chart. The cardiopulmonary function was only minimally different between groups and maintained within clinically normal ranges. Less ketamine was required, $F_E'ISO$ was lower after 1 h and fewer alterations in the anaesthetic depth were needed in horses receiving dexmedetomidine, with better recoveries. One horse receiving morphine developed post-operative colic and pulmonary oedema and two showed box-walking behaviour. This study showed that a dexmedetomidine CRI produced a more stable anaesthetic depth, reduced isoflurane requirements and better recoveries, without post-operative complications compared with a morphine CRI.

1. Introduction

The use of intravenous (IV) constant-rate infusions (CRIs) of alpha-2-agonists has been widely studied in horses (Bettschart-Wolfensberger et al., 2001; Devisscher et al., 2010; Schauvliege et al., 2011; Pöppel et al., 2012). Dexmedetomidine, the dextro-rotary and active enantiomer of the racemic mixture medetomidine, is currently the most potent and selective alpha-2-agonist which is commercially available for use in humans and small animals. Experimental studies in isoflurane anaesthetized ponies showed that dexmedetomidine at two different rates produces limited cardiopulmonary effects, typical of alpha-2-agonists, despite isoflurane administration being at >1 MAC, while the arterial partial pressure of oxygen (PaO_2) tended to be low (Marcilla et al., 2010). In a blinded clinical study involving forty healthy isoflurane anaesthetized horses comparing the effects of dexmedetomidine (3.5 μg/kg followed by a CRI 1.75 μg/kg/h) with a saline group, the PaO_2 values were significantly lower in horses receiving dexmedetomidine, whereas oxygen delivery indexed to body weight (DO_2I) was comparable between groups (Marcilla et al., 2012). Moreover, a dexmedetomidine infusion improved the quality of the recovery. A minimal alveolar concentration (MAC) study performed in six ponies showed that the same protocol reduced the MAC of sevoflurane by 53 ± 15% (mean ± SD) (Gozalo-Marcilla et al., 2013a). As a dexmedetomidine CRI causes minor cardiopulmonary effects, improves recovery quality and reduces the MAC of sevoflurane, the proposed protocol is probably useful for clinical equine balanced anaesthesia.

The use of systemically administered opioids in horses to provide analgesia remains controversial (Bennett and Steffey, 2002; Clutton, 2010). Some authors reported that IV morphine can increase locomotion in conscious pain-free horses (0.91 mg/kg being the median effective value) (Combie et al., 1979) and induce dangerous behaviour in individuals recovering from general anaesthesia at 2.0 mg/kg (Steffey et al., 2003), doses considerably greater than those used to produce analgesia. Decreased intestinal motility (Kohn and Muir, 1988; Boscan et al., 2006), increasing the risk of colic (Senior et al., 2004), and respiratory depression (Steffey et al., 2003) have also been reported. In contrast, other investigators reported minimal haemodynamic and ventilatory changes (Mircica et al., 2003; Clark et al., 2005) without an increased

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incidence of post-operative colic (Mircica et al., 2003). Even more, improved recovery qualities were observed, after boluses (Love et al., 2006) and CRIs (Clark et al., 2008) of morphine in horses undergoing elective surgical procedures. With regard to anaesthetic sparing effects, the IV administration of boluses of morphine at two different doses (0.25 and 2.0 mg/kg) (Steffey et al., 2003) failed to reduce the MAC of isoflurane. Moreover, the minimum end-tidal concentration to prevent movement (MAC_{NM}) value of sevoflurane obtained in experimental ponies receiving a morphine CRI (0.15 mg/kg/h after loading dose 0.1 mg/kg) was higher than the one obtained under the same conditions when receiving saline (Gozalo-Marcilla et al., 2013b). Both studies were performed in healthy, pain-free horses under experimental conditions, where the applied electrical stimulation was qualitatively different from classic surgical nociception (Clutton, 2010). In contrast, clinical equine patients under a morphine CRI tended to receive fewer and lower doses of additional anaesthetic drugs, although this was not of statistical significance (Clark et al., 2005).

The aim of the present study was to evaluate and compare the cardiopulmonary function and recovery quality of clinically healthy horses undergoing elective surgery either receiving a morphine or a dexmedetomidine CRI at the doses reported by Clark et al. (2005) and Marcilla et al. (2012) respectively. A second aim was to determine which treatment produced a more stable anaesthesia, with lower requirements for isoflurane and ketamine.

2. Materials and methods

The study was approved by the Ethical Committee of the aculty of Veterinary Medicine of Ghent University (2010/177).

2.1. Animals and instrumentation

After obtaining written owner consent, twenty adult healthy horses [American Society of Anesthesiologists (ASA) category I or II] undergoing elective surgery (soft tissue and orthopaedic procedures) lasting more than 1 h were included in this clinical study. Head or neck surgeries were excluded due to the difficulty of assessment of the clinical parameters related to anaesthetic depth. Respecting the current EU laws of medication in animals, horses classified as 'food producing animals' were excluded as dexmedetomidine is not licensed for use in the horse.

The horses were randomly allocated (by picking a prescribed treatment from a box) to receive treatment M (morphine) or treatment D (dexmedetomidine). Food, but not water, was withheld for 12 h before anaesthesia and pre-anaesthetic examinations were performed the evening before the surgical procedure. All the anaesthetic procedures were performed by the same evaluating anaesthetist (MGM), who was unaware of the treatment. All medication syringes were prepared by one of the co-authors. Sedation scores, depth of anaesthesia and recovery scores were evaluated by the main anaesthetist.

The horses in treatment M received for sedation dexmedetomidine (3.5 μg/kg, IV) (Dexdomitor; Orion Corporation, Finland) plus morphine (0.15 mg/kg, IV) (Morphine.HCl; Sterop, Belgium) and those in treatment D received dexmedetomidine (3.5 μg/kg, IV) plus a bolus of saline of equivalent volume as morphine in treatment M. Depth of sedation was scored as 0 (no sedation), 1 (slight sedation), 2 (good sedation) or 3 (deep sedation). After sedation, a 12-gauge × 80 mm catheter (Intraflon 2; Ecouen, France) was placed in the jugular vein. If required, additional doses of dexmedetomidine (1/4–1/2 of the initial dose) were given to achieve an adequate level of sedation prior to anaesthetic induction. Anaesthesia was induced 7–10 min after sedation, with midazolam (0.06 mg/kg) (Dormicum; Roche, Belgium) and ketamine (2.2 mg/kg) (Anesketin; Eurovet, Belgium) IV mixed in the same syringe.

After orotracheal intubation (24–30 mm OD tracheal tube; Willy Rusch AG, Germany) the horses were hoisted on a surgical table covered with soft foam rubber pillows (20 cms) and positioned according to the planned surgical procedure. The endotracheal tube was connected to a large animal anaesthetic unit (Matrx Medical Inc., NY, USA mounted on a Sulla 909 V; Dräger, Germany) with an out-of-circuit vaporizer (Drägerwerk AG, Germany) and a large animal ventilator (Smith respirator LA 2100; model 2002, Veterinary Technics/BDO-Medipass, The Netherlands). Connection to the anaesthetic circuit was considered as the beginning of anaesthesia (T0). Anaesthesia was maintained with isoflurane (Isoflo; Abbott Laboratories Ltd., UK) in a mixture of oxygen (O_2) and air to maintain the inspired O_2 fraction (FiO_2) between 55% and 60%. The lungs of all the horses were mechanically ventilated immediately after positioning on the table. Intermittent positive pressure ventilation (IPPV) was applied, using an assisted-controlled respiration mode, with a tidal volume (V_T) of 10 mL/kg, peak inspiratory pressure close to 20 cm H_2O, inspiratory time of around 2.2 s and f_R near to 8 breaths/min. All parameters were adapted to maintain arterial partial pressure of CO_2 ($PaCO_2$) between 4.66 and 6.00 kPa (35–45 mmHg).

Inspiratory and expiratory CO_2, O_2 and isoflurane concentrations were measured using a calibrated, methane-insensitive, multiparameter monitoring device (S/5, D-LCC15-03; Datex Ohmeda, OR, USA). This monitor was also used to record the electrocardiogram (base-apex lead), systolic (SAP), diastolic (DAP) and mean arterial pressures (MAP), peripheral arterial saturation by pulse oximetry (probe on the tongue) and body temperature by a nasal probe.

Catheterization of the facial artery was performed in all horses (22-gauge Vasocan Braunüle Luer Lock; B. Braun Melsungen AG, Germany) to obtain arterial blood for analysis, for withdrawal of blood for lithium dilution cardiac output measurements and for continuous invasive measurement of arterial blood pressures. The pressure monitoring system was zeroed at the level of the right atrium.

Cardiac output $\dot{Q}t$ was determined using the lithium dilution technique (LiDCOplus Haemodynamic Monitor, LiDCO Ltd., UK). A bolus of lithium chloride (4.5 μmol/kg) was injected through the jugular catheter, while arterial blood for detection of lithium chloride by the LiDCO sensor (CM10 LiDCO sensor, LiDCO Ltd., UK) was withdrawn from the facial artery by the LiDCO Flow Regulator (CM 33 LiDCO flow regulator, LiDCO Ltd., UK). Plasma sodium values were determined (AVL 9180 Electrolyte Analyzer, AVL Scientific Corporation, GA, USA) on a blood sample withdrawn from the right jugular vein before sedation and were entered into the LiDCOplus monitor to allow correct LiDCO measurements. Haemoglobin (Hb) concentration was estimated for each measurement from the packed cell volume (PCV) [Hb (g/dL) = 34 × PCV (L/L) (Linton et al., 2000)].

Intraoperatively, all the horses received flunixin meglumine (1.1 mg/kg, IV) (Endofluxin 50; Ecuphar, Belgium) and intramuscular procaine benzylpenicillin (15,000 IU/kg) (Pen-30; V.M.D., Belgium).

2.2. Experimental design

The vaporizer was adjusted to obtain an $F\acute{}_E$ISO of 0.9% during the first 10 min of general anaesthesia. Horses allocated to treatments M and D received at T0 a CRI of morphine (0.1 mg/kg/h) and dexmedetomidine (1.75 μg/kg/h) respectively. Constant rate infusions were administered by a syringe driver (Ohmeda 9000; BOC Health Care, UK) until the end of anaesthesia. Lactated Ringer's solution