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RESEARCH PAPER

Effects of dexmedetomidine and xylazine on cardiovascular function during total intravenous anaesthesia with midazolam and ketamine and recovery quality and duration in horses

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Abstract

Objectives To compare cardiovascular effects and recovery quality and duration of total intravenous anaesthesia (TIVA) with xylazine-ketamine-midazolam or dexmedetomidine-ketamine-midazolam.

Study design Prospective, randomized experimental cross-over trial.

Animals Eight adult warmblood horses.

Methods After sedation with acepromazine and either xylazine [0.5 mg kg^{-1}, intravenously (IV)] or dexmedetomidine (3.5 μg kg^{-1} IV) anaesthesia was induced with ketamine and midazolam and maintained with a constant rate infusion (CRI) of xylazine (1 mg kg^{-1} $hour^{-1}$) [XKM] or dexmedetomidine (7 μg kg^{-1} $hour^{-1}$) [DKM] in combination with midazolam (0.1 mg kg^{-1} $hour^{-1}$), and ketamine infusion (initially 3 mg kg^{-1} $hour^{-1}$) for 120 minutes. Ketamine infusion rate was increased in response to positive reactions to electrical nociceptive stimulation performed every 30 minutes. Heart rate (HR), mean arterial blood pressure (MAP) and cardiac output ($\dot{Q}t$) were measured before treatment (baseline), after sedation (not $\dot{Q}t$), and during anaesthesia. Xylazine, dexmedetomidine, midazolam and ketamine kinetics were calculated, from plasma drug concentrations. Twenty minutes after end of TIVA, flumazenil (0.01 mg kg^{-1} IV) was administered. Recovery quality and duration were assessed. Two-way analysis of variance with repeated measurements or Wilcoxon signed rank test as relevant were used to analyse data with an alpha of 5%.

Results Compared to baseline, MAP did not change, while similar, but limited, decreases in HR and $\dot{Q}t$ were observed in both TIVA's. Mean ketamine doses of 3.7 mg kg^{-1} $hour^{-1}$ were required with both treatments. Plasma concentrations of dexmedetomidine and xylazine showed high intra- and inter-individual changes with elimination half-lifes of 46 ± 7 minutes and 64 ± 13 minutes, respectively. Recovery quality was good to excellent with mean duration of 37 ± 16 and 46 ± 21 minutes after stopping TIVA with XKM and DKM, respectively.

Conclusions and clinical relevance Both drug combinations are suitable to maintain anaesthesia for

two hours, with good cardiovascular and good to excellent recovery conditions.

Keywords dexmedetomidine, flumazenil, ketamine, midazolam, total intravenous anaesthesia, xylazine.

Introduction

Total intravenous anaesthesia (TIVA) for short procedures seems to carry a lower risk of intra-anaesthetic death than with volatile agents (Johnston et al. 2002; Bidwell et al. 2007). Volatile anaesthetics cause dose-dependent cardiopulmonary depression and hypoventilation (Steffey 2002). Blood pressure is preserved better during infusion of injectable drugs but this does not always reflect overall cardiopulmonary function.

A variety of ketamine based TIVA techniques have been investigated (Muir & Hubbell 2009a). Of these, the most common for TIVA in the horse has been the combination of guaifenesin, ketamine and a α2-adrenoceptor agonist (most usually xylazine, detomidine, or romifidine), the combination being known as "triple drip" (McCarty et al. 1990; Taylor et al. 1995; McMurphy et al. 2002). However, α2-adrenoceptor agonists cause bradycardia and a resultant significant decrease in cardiac output ($\dot{Q}t$). The duration and intensity of this effect depends on the type of α2-adrenoceptor agonist, its dose and route of administration (England & Clarke 1996). Xylazine has a European marketing authorization for use in horses and its pharmacokinetic profile is such that it is very suitable for infusion. After a single bolus injection xylazine has a short duration of action and elimination half-life (Kerr et al. 1972; Garcia-Villar et al. 1981). A bolus of 1 mg kg^{-1} xylazine followed by a CRI of 0.69 mg kg^{-1} $hour^{-1}$ for two hours provided constant sedation and constant plasma concentrations (Ringer et al. 2012).

Dexmedetomidine, the active D-enantiomere of medetomidine, is a highly selective α2-adrenoceptor agonist (Virtanen et al. 1988). Dexmedetomidine causes similar cardiopulmonary changes to other α2-adrenoceptor agonists, but of very short duration and the pharmacokinetic profile also makes it suitable for prolonged infusion (Bettschart-Wolfensberger et al. 2005).

The use of the guaifenesin and ketamine based triple drips for prolonged periods of anaesthesia is hampered by cumulation of ketamine and its metabolites and also by guaifenesin induced muscle relaxation and ataxia, which leads to prolonged recoveries with poor quality (Young et al. 1993). Guaifenesin is long acting and cumulative and its action cannot be antagonized. In contrast, benzodiazepines drugs such as climazolam and midazolam have a specific antagonist, and therefore are an attractive alternative for guaifenesin as part of TIVA protocols (Bettschart-Wolfensberger et al. 1996; Yamashita et al. 2007; Hubbell et al. 2012).

The objective of this study was to compare two different TIVA protocols based on midazolam and ketamine combined with the $alpha_2$ adrenoceptor agonists xylazine (XKM) or dexmedetomidine (DKM) and subsequent reversal of midazolam with flumazenil. Cardiovascular effects, anaesthetic quality and recovery quality and time were evaluated.

Materials and methods

Animals

The subjects of the study were eight adult warmblood horses, two geldings and six mares, weighing 525 ± 54.4 kg (mean ± SD) and aged 13.5 ± 6.8 years. All horses were considered to be healthy by clinical and laboratory examination and echocardiography. Food, but not water, was withheld six hours before anaesthesia. The Ethical Committee of Lower Saxony approved the experimental protocol.

Study design

The study was carried out as a prospective, randomized experimental cross-over trial. Each horse was anaesthetized twice with at least four weeks 'washout' between anaesthetic episodes.

Instrumentation

Before anaesthesia, each horse was weighed and rectal temperature, heart (HR), and respiratory rate (f_R) were obtained. Packed cell volume (PCV), white blood cell count (WBC) and total protein (TP) were determined from venous blood. The skin areas over the right and left jugular veins were clipped and surgically prepared. After infiltration of the skin with mepivacaine hydrochloride (Scandicain 2%, AstraZeneca GmbH, Germany), a 12 gauge catheter (EquiCathTM Fastflow, Germany) was placed into each jugular vein, one close to the superior thoracic aperture for drug administration and one for blood collection. The skin over the right transverse facial artery was shaved, cleaned and desensitized with a

