Research in Veterinary Science 107 (2016) 202–206

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Blood concentrations of remifentanil during and after infusion in horses anesthetized with isoflurane and dexmedetomidine

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ARTICLE INFO

Article history:
Received 23 February 2016
Received in revised form 6 June 2016
Accepted 12 June 2016

Keywords:
Dexmedetomidine
Horse
Isoflurane
Remifentanil concentration
Infusion

ABSTRACT

Objective: To determine blood remifentanil concentration in isoflurane-anesthetized horses during and after a 1 h remifentanil and dexmedetomidine infusion.
Study design: Prospective study.
Animals: Six adult mixed breed horses with (mean ± SD) bodyweight of 507 ± 61 kg and 14 ± 4 years of age.
Methods: Following sedation with xylazine IV, anesthesia was induced with ketamine IV mixed with diazepam IV. Anesthesia was maintained with isoflurane in oxygen. After 52 ± 7 min for instrumentation, dexmedetomidine (0.25 μg kg^{-1} followed by 1.0 $μg^{-1}$ kg^{-1} h^{-1}) and remifentanil infusions (6 μg kg^{-1} h^{-1}) were administered for a minimum of 60 min and horses recovered from anesthesia. Drug infusions were administered into the left jugular vein. Blood was sampled (4 mL) from the right jugular vein at predefined intervals before and during administration of remifentanil infusion. Following catheter flush, blood was sampled from the left jugular vein after the infusion was terminated while the horse was recovering from anesthesia. Blood was placed into tubes containing sodium heparin with citric acid, flash frozen in liquid nitrogen, and stored at −80 °C until analysis. Blood remifentanil concentration was measured using high performance liquid chromatography and tandem mass spectrometry.
Results: Mean peak remifentanil concentration was 7.14 ηg mL^{-1} at 50 min after start of infusion. Mean volume of distribution was 268 ± 40 mL kg^{-1} and mean half-life was 12.8 min. Blood concentration decreased to 1 ηg mL^{-1} 27 min after termination of infusion.
Limit of quantification was 0.2 ηg mL^{-1}.

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1. Introduction

Remifentanil is a synthetic opioid structurally related to phenylpiperidine derivatives such as fentanyl, and has similar effects on the μ-opioid receptor. The methyl-ester linkage of remifentanil is susceptible to rapid breakdown by nonspecific esterases in blood and tissues, and produces an ultrashort duration of action with lack of accumulation in the body following repeated administration (Glass et al., 1999). In conscious horses, an intravenous bolus of approximately 10 μg kg^{-1} bwt remifentanil has been reported to cause an increase in locomotor activity, but the focus of that study was to investigate which urinary metabolites are present (Lehner et al., 2000).

Remifentanil has been successfully used in dogs and cats for intraoperative analgesia (Correa et al., 2007; Kulka et al., 2012), but its use in horses during anesthesia is still under investigation (Benmansour et al., 2014). Remifentanil infusions have been successfully used in anesthetized horses undergoing clinical procedures by the senior author at this institution, but these details have not been published except for one case report (Benmansour and Duke-Novakovski, 2013).

Currently, there are no published pharmacokinetic studies or reports of remifentanil blood concentrations during its use in horses. This study was performed alongside the investigation into the cardiopulmonary effects of remifentanil infusion administered to isoflurane-dexmedetomidine anesthetized horses (Benmansour et al., 2014), and reports the concentrations of remifentanil achieved in the blood during and following the infusion.

2. Materials and methods

This work was approved by the University of Saskatchewan's Animal Research Ethics Board, and adhered to the Canadian Council on Animal Care guidelines for humane animal use (#20090056).

Six mixed breed horses (five mares and one gelding) with body weight between 443 kg and 580 kg (507 ± 61 kg; mean ± SD), and age between 8 and 20 years (14 ± 4 years) were used for this study.

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http://dx.doi.org/10.1016/j.rvsc.2016.06.008
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The horses were deemed healthy based on physical and hematological examinations. Horses were kept outdoors, were fed hay, and had free access to water. Horses were brought indoors the day before the study and fasted, but allowed access to water, for 12–16 h prior to induction of anesthesia.

On the day of the study, a 14-gauge × 133 mm catheter (BD Angiocath; Becton Dickinson, UT, USA) was aseptically placed in the left jugular vein, with the distal end towards the heart, to allow administration of drugs and lactated Ringer's solution at a rate of approximately 10 mL kg^{-1} h^{-1} using gravity. Final rate of fluid administration was calculated at the end of anesthetic period. Horses were sedated with xylazine hydrochloride (1 mg kg^{-1}; Rompun, Bayer Healthcare, ON, Canada) intravenously (IV). Anesthesia was induced with ketamine hydrochloride (2 mg kg^{-1}; Vetalar, Bioniche Animal Health, ON, Canada) and diazepam (0.1 mg kg^{-1}; Diazepam Injection USP; Sandoz, QC, Canada) IV. The trachea was intubated with a 24-mm-ID cuffed endotracheal tube. Horses were hoisted onto a padded mattress and positioned in left lateral recumbency. The endotracheal tube was attached to a large animal circle breathing system and anesthesia was maintained with isoflurane in oxygen (Isoflo; Abbott Laboratories, QC, Canada). Intermittent positive pressure ventilation (Dräger AV; Anesthesia Ventilator, N. American Dräger, PA, USA) was adjusted to achieve an end-tidal CO_2 of 5.3 ± 0.7 kPa (40 ± 5 mmHg). The vaporizer isoflurane concentration was adjusted to maintain the presence of a sluggish palpebral reflex throughout the study period. Two 8 Fr introducer sheath catheters (Fast-Cath Hemostasis Introducer; St. Jude Medical, CA, USA) were placed in the cranial and caudal portions of the right jugular vein to allow placement of a thermistor-tipped, triple lumen pulmonary artery balloon catheter and a pigtail catheter for a concurrent study (Benmansour et al., 2014). Following instrumentation, dexmedetomidine hydrochloride (Dexdomitor; Pfizer Animal Health Canada Inc., QC, Canada) was administered at a rate of 1.0 μg kg^{-1} h^{-1} after a loading dose of 0.25 μg kg^{-1}. Remifentanil hydrochloride (Ultiva; Abbott Laboratories, QC, Canada) was administered at a rate of 6.0 μg kg^{-1} h^{-1} with no bolus injection dose given beforehand, and started at the same time as the dexmedetomidine infusion. The IV infusions were given separately using calibrated syringe pumps (Medfusion 2010, Medex Inc., GA, USA) through the left jugular vein. The remifentanil infusion was discontinued after a 60 min infusion period. Dexmedetomidine infusion and isoflurane was continued to allow removal of both right jugular vein introducer sheath catheters and the arterial catheter before entry into the recovery box. This period also enabled the first blood samples to be safely removed after terminating the remifentanil infusion. Horses were placed in left lateral recumbency for recovery and administered oxygen by nasal insufflation at 15 L min^{-1} until the nasal catheter was dislodged by the horse's movements.

2.1. Blood collection

Before the remifentanil infusion was started, a baseline blood sample (4 mL) was obtained from the right jugular vein using the cranial introducer sheath extension tubing (baseline sample) and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min from start of infusion.

Following discontinuation of the remifentanil infusion and appropriate catheter void volume removed to avoid blood sample contamination with the infusion dose, blood samples were taken from the left jugular vein (right jugular vein catheter not available) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 35, 40, 45, 50, 60, 75, 90, 105 and 120 min after finish of infusion, during recovery from anesthesia (if deemed to be safe).

Before each collection of the blood sample, 5 mL of fluid/blood from the catheter was withdrawn to avoid sample contamination. After each blood sample was obtained the catheter was flushed with 0.9% saline. Blood samples were collected into sodium heparin tubes (BD Vacutainer; Sodium Heparin (68 USP units) tubes; NJ, USA) containing 20 μL of 50% citric acid (w/v) per mL of blood to avoid remifentanil hydrolysis by controlling the pH (Bender et al., 1999), and flash frozen in liquid nitrogen before storage at −80 °C until analysis.

2.2. Preparation of remifentanil stock and working internal standard solutions

Stock solutions (1 mg mL^{-1}) of remifentanil hydrochloride and remifentanil ^{13}C-6, as internal standard, (Toronto Research Chemicals, ON, Canada) were prepared in 1 mM HCl and stored at −20 °C. Working solutions were prepared by serial dilution of the remifentanil stock solution using 1 mM HCl to produce concentrations for the calibration curve (0.2–50 ηg mL^{-1}) while the internal standard was diluted in 1 mM HCl to a concentration of 25 ηg mL^{-1}. Quality control (QC) standards were prepared similarly to achieve working stock solutions (as per USFDA guidelines) at the low quality control (LQC), middle quality control (MQC) and high quality control (HQC). Calibration and QC samples were prepared on ice on each day of sample analysis by adding 25 μL of remifentanil standard to 15 mL polypropylene tubes (SuperClear Ultra-High Performance Centrifuge Tube, VWR, AB, Canada). To 500 μL thawed whole blood sample, 25 μL of internal standard was added along with 500 μL 0.1 M Na_2HPO_4 pH 7.4. After a brief vortex mix, 4 mL of diethyl ether was added, the tubes were shaken for 10 min, and subsequently centrifuged for 5 min at 4 °C at 1000*g* and placed at −80 °C for 5–10 min to freeze the lower layer. Ether was decanted into a disposable glass tube and subsequently dried to evaporation using a vacuum concentrator. To the glass tube, 100 μL of mobile phase was added and vortexed to mix and then transferred to high performance liquid chromatography (HPLC) vials for analysis. For HPLC, 10 μL was injected onto a 4.6 × 12.5 mm, 5 μm, Zorbax Eclipse XDB-C18 guard column (Agilent Technologies, ON, Canada) with the column temperature set at 20 °C. Samples were separated using an Agilent series 1200 binary pump with an online degasser and auto sampler set at 4 °C (Agilent Technologies, ON, Canada). Analytes were detected with an AB Sciex API 4000 Q-Trap mass spectrometer (AB Sciex, ON, Canada). The mobile phase consisted of 60:40 (30 mM NaH_2PO_4 pH 3.0:acetonitrile) set at an isocratic flow of 250 μL min^{-1} with an analysis time of 1 min. The ABSciex QTRAP 4000 mass spectrometer utilized a curtain gas pressure of 10 lb per square inch (psi) and GS1 and GS2 parameters were set at 50 psi. The ionspray voltage was set at 4500 V and the temperature of the ESI source interface was maintained at 650 °C. The mass spectrometer utilized multiple reaction monitoring (MRM) to quantify the analyte, remifentanil, by using the transition of [M] + (m/z 378.303 > 318.200) (declustering potential of 76, collision energy of 23, collision cell exit potential of 8); peak areas were summed through use of Analyst Software. The internal standard, remifentanil ^{13}C-6, utilized a transition of [M] + (m/z 384.196 > 113.000) (declustering potential of 61, collision energy of 47, collision cell exit potential of 20). The ratio of peak areas of remifentanil and the internal standard were plotted against the nominal concentrations to construct the calibration curve.

Analytical method validation for remifentanil was performed in accordance with USDFA guidelines. Appropriate validation procedures are well established in our laboratory (Elbarbry et al., 2006; Mukker et al., 2010; Singh et al., 2010; Buse et al., 2013). The assay was specific, linear from 0.2–50 ηg mL^{-1}, extraction efficiency ranged from 50 to 72%, and intra- and inter-day precision and accuracy of the method was within ±15%.

3. Pharmacokinetic parameter estimation

Pharmacokinetic (PK) parameters were estimated from concentration versus time data for each individual horse using GraphPad Prism 5.0 (GraphPad Prism Inc., La Jolla, CA). All PK parameter estimates were reported as mean ± SD. Systemic clearance (Cl_S) was estimated from the ratio of infusion dose and steady state concentration, where steady state was considered as the average of the last two or three

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