Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2015, **42**, 17–29 doi:10.1111/vaa.12165

RESEARCH PAPER

Pharmacokinetic-pharmacodynamic modelling of intravenous buprenorphine in conscious horses

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Abstract

Objective Describe the pharmacokinetics of buprenorphine and norbuprenorphine in horses and to relate the plasma buprenorphine concentration to the pharmacodynamic effects.

Study design Single phase non-blinded study.

Animals Six dedicated research horses, aged 3–10 years and weighing 480–515 kg.

Methods Thermal and mechanical nociceptive thresholds, heart and respiratory rates and locomotor activity were measured before and 15, 30, 45 & 60 minutes and 2, 4, 6, 8, 12 & 24 hours post-administration of 10 μg kg^{-1} buprenorphine IV. Intestinal motility was measured 1, 6, 12 & 24 hours after buprenorphine administration. Venous blood samples were obtained before administration of buprenorphine 10 μg kg^{-1} IV and 1, 2, 4, 6, 10, 15, 30, 45 & 60 minutes, and 2, 4, 6, 8, 12 & 24 hours afterwards. Plasma buprenorphine and norbuprenorphine concentrations were measured using a liquid chromatography-tandem mass spectroscopy (LC-MS/MS) assay with solid-phase extraction. A non-compartmental method was used for analysis of the plasma concentration–time data and plasma buprenorphine concentrations were modelled against two dynamic effects (change in thermal threshold and mechanical threshold) using a simple Emax model.

Results Plasma buprenorphine concentrations were detectable to 480 minutes in all horses and to 720 minutes in two out of six horses. Norbuprenorphine was not detected. Thermal thresholds increased from 15 minutes post-buprenorphine administration until the 8–12 hour time points. The increase in mechanical threshold ranged from 3.5 to 6.0 Newtons (median: 4.4 N); and was associated with plasma buprenorphine concentrations in the range 0.34–2.45 ng mL^{-1}.

Conclusions and clinical relevance The suitability of the use of buprenorphine for peri-operative analgesia in the horse is supported by the present study.

Keywords equine, mechanical nociceptive threshold, opioid, pain, thermal nociceptive threshold.

Introduction

Buprenorphine is a partial μ opioid agonist that has been used extensively to provide both intra- and post-operative analgesia in man and a number of animal species (Conzemius et al. 1994; Roughan & Flecknell 2002; Dahan et al. 2006; Steagall et al. 2009a). It has recently gained a UK Marketing Authorisation for administration to horses for analgesia at a dose of up to 10 μg kg^{-1} intravenously (IV). Previous studies have indicated that buprenorphine (at this dose) administered in combination with acepromazine produces antinociception to a

thermal stimulus for approximately 9 hours (Love et al. 2012). In a very recent study, buprenorphine 10 μg kg^{-1} provided near comprehensive analgesia for 24 hours in ponies undergoing castration (Love et al. 2013).

A few published papers describe the pharmacokinetics of buprenorphine in horses (Seino et al. 2003; Messenger et al. 2011; Davis et al. 2012), but none have evaluated concentration-effect data. The aim of this study was therefore to describe the pharmacokinetics of buprenorphine and its metabolite norbuprenorphine in horses, and to relate the plasma buprenorphine concentration to the pharmacodynamic effects, particularly antinociception.

Materials and methods

Animals

Six Thoroughbred horses, aged 3–10 years and weighing 480–515 kg, were used in this 'non-blinded' single phase study. Horses were kept at grass and were brought into individual pens, comprising both an indoor and outdoor area, at least 24 hours prior to experimental procedures. Hay was removed the night prior to treatment but water was freely available at all times. Horses were assessed as healthy based on physical examination, a complete blood count and serum biochemistry. No sedatives or analgesics were administered to the animals within three weeks of the start of this study. All assessments and blood sampling were performed by the same investigator. The study was conducted under UK Home Office Project Licence Number 30/2420.

Drug dosage and administration

The horses were weighed using an electronic weighbridge on the day of the experiment and fly repellent was applied to the body of the horse. Local anaesthetic cream (EMLA Cream 5%; Astra Zeneca UK Ltd, UK) was applied to the skin over both jugular veins following clipping of hair. Two IV catheters were placed and secured with tissue adhesive; an 18 gauge catheter was inserted into the right jugular vein and a 14 gauge catheter was inserted into the left jugular vein. Following collection of baseline blood samples and measurements each horse received 10 μg kg^{-1} buprenorphine over 30 seconds (Vetergesic Multidose, Alstoe Animal Health, Sherriff Hutton, UK) through the 18 gauge catheter.

Measurements

Thermal and mechanical thresholds were measured using apparatus described previously (Chambers et al. 1993 (mechanical), Love et al. 2012 (thermal)). In brief the thermal testing equipment consisted of a 1 cm^2 probe comprising a small heating element and a thermistor (Topcat Metrology Ltd, UK). This was applied to a clipped area of skin over the horses' withers. The starting skin temperature was recorded and the probe activated via a remote controlled handset so that heating started at 0.5 °C $second^{-1}$. A skin twitch signified the end-point, heating was stopped and the threshold temperature recorded. If no response occurred heating stopped at a 'cut-out' of 53 °C to prevent skin damage. Mechanical thresholds were measured using an actuator cuff attached to a control box via 3 mm internal diameter PVC tubing (Custom built for the School of Veterinary Sciences). The cuff was positioned with the upper edge 4 cm distal to the carpus so that a 1.5 mm blunt ended pin was in contact with the dorsal aspect of the third metacarpal bone. The force used to drive the pin against the leg was increased at a constant rate until the horse lifted his leg, signifying the end-point. A 'cut-out' of 15 N was included in the equipment design. On a separate occasion control data were collected from the same horses with respect to mechanical (n = 6 horses) and thermal (n = 5 horses) thresholds after IV injection of 5% glucose. The collection and analysis of these data are reported elsewhere (Love et al. 2012).

Locomotor activity was measured using a pedometer that was attached to a bandage on the forelimb to record the total number of steps throughout the investigation. On a separate occasion control data with respect to locomotor activity was collected from the same horses after IV injection of 5% glucose; the collection and analysis of these data are reported elsewhere (Love et al. 2012). In addition, prior to measurement of nociceptive thresholds, heart rate (HR) was determined by auscultation; respiratory rate (f_R) was measured by counting the number of thoracic excursions in 1 minute. Gastrointestinal motility was assessed by abdominal auscultation and the number of piles of faeces produced were counted at intervals after drug administration.