Research in Veterinary Science 112 (2017) 46–51

Contents lists available at ScienceDirect

Research in Veterinary Science

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

Sedative and mechanical antinociceptive effects of four dosages of romifidine administered intravenously to donkeys

Ignacio Lizarraga *[,1], Fernanda Castillo-Alcala [1], Lauren S. Robinson

Department of Biomedical Sciences, Ross University School of Veterinary Medicine, P.O. Box 334, Basseterre, Saint Kitts and Nevis

ARTICLE INFO

Article history:
Received 12 July 2016
Received in revised form 6 December 2016
Accepted 13 January 2017

Keywords:
α_2 agonist
Analgesia
Donkey
Mechanical nociceptive threshold testing
Pain assessment
Sedation

ABSTRACT

Although romifidine is commonly used to provide sedation and analgesia for the facilitation of clinical procedures in donkeys, limited scientific information is available for this drug in this species. This randomized, controlled, crossover, Latin-square, blinded study compared the sedative and antinociceptive effects of four dosages of romifidine (40, 60, 80, and 100 μg/kg IV; R40, R60, R80, and R100, respectively), acepromazine (0.1 mg/kg IV; ACE) and saline (0.9%, 5 mL IV) by assigning sedation scores (SS) and measuring head heights above ground (HHAG) and mechanical nociceptive thresholds (MNT) in donkeys. Areas under the curve (AUC) from 0 to 30, 30–60, 60–120, and 120–180 min after administration were computed for SS, HHAG, and MNT and compared among treatments. Romifidine and ACE, but not saline, induced clinical signs of sedation. SS-$AUC_{0–30}$ for R60, R80 and R100, and SS-$AUC_{30–60}$ for R100 were higher than corresponding values for saline. HHAG-$AUC_{30–60}$ for R40 and R80, and HHAG-$AUC_{60–120}$ for R40, R60, R80 and R100 were smaller than for saline. HHAG-$AUC_{60–120}$ for R100 were also smaller than those for ACE. Romifidine, but not saline or ACE, increased MNT. MNT-$AUC_{0–30}$ and MNT-$AUC_{30–60}$ for R40, R60, R80 and R100, and MNT-$AUC_{60–120}$ for R80 and R100 were higher than corresponding values for saline and ACE. MNT-$AUC_{60–120}$ for R100 were higher than for all other romifidine treatments. In donkeys, the degree of sedation was similar for the four dosages of romifidine, but antinociception was dose-dependent.

1. Introduction

Romifidine is an α_2-adrenoceptor agonist approved for intravenous (IV) administration in horses as sedative and analgesic for the facilitation of handling, diagnostic and therapeutic procedures, and as preanaesthetic. It is also used in donkeys, off-label, for the same indications as in horses (Spanton et al., 2009; Amin et al., 2012; The Brooke, 2013).

Although the sedative and analgesic effects of romifidine have been extensively documented in horses (England et al., 1992; Hamm et al., 1995; Freeman and England, 2000; Moens et al., 2003; Figueiredo et al., 2005; Spadavecchia et al., 2005; Christovão et al., 2006; DeRossi et al., 2009; Wojtasiak-Wypart et al., 2012; Costa et al., 2015), there are pharmacological differences between horses and donkeys and donkeys may require larger dose rates of α_2-adrenoceptor agonists, such as detomidine (Lizarraga et al., 2004). Few studies have investigated the sedative and analgesic actions of romifidine in donkeys, but the administration of one dose rate only, the use of methodologies not capable of quantifying the analgesic response or the lack of negative controls limits the usefulness of their results (El-Maghraby et al., 2005; Lizarraga and Janovyak, 2013; El-Kammar and Gad, 2014).

This study investigated the sedative and analgesic effects of four dose rates of romifidine in donkeys along with saline as negative control and acepromazine as positive control for sedation and negative control for analgesia (Lizarraga et al., 2017). Using methodologies validated for the assessment of sedation and antinociception induced by α_2-adrenoceptor agonists in donkeys (Lizarraga and Castillo-Alcala, 2015; Lizarraga et al., 2015, 2016, 2017), it was hypothesised that romifidine would induce both sedation and mechanical antinociception in a dose-dependent fashion.

2. Material and methods

2.1. Animals

The study protocol and the procedures described here were reviewed and approved by the Institutional Animal Care and Use

Abbreviations: ACE, acepromazine; AUC, area under the curve; HHAG, head height above ground; IV, intravenous; MNT, mechanical nociceptive threshold; N, Newton; R40, romifidine 40 μg/kg; R60, romifidine 60 μg/kg; R80, romifidine 80 μg/kg; R100, romifidine 100 μg/kg; SS, sedation score.

* Corresponding author at: Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11 222, Palmerston North 4442, New Zealand.
E-mail address: madrigal@unam.mx (I. Lizarraga).
[1] Current address: Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North, 4442, New Zealand.

http://dx.doi.org/10.1016/j.rvsc.2017.01.010
0034-5288/

Committee at Ross University School of Veterinary Medicine. Six 5- to 7-year-old, gelded, standard, healthy donkeys, based on physical examination, complete blood cell counts and serum biochemical analysis, owned by Ross University School of Veterinary Medicine were used in the study. The donkeys were weighed weekly (mean ± SD: 160.0 ± 10.4 kg) during the study. They were group housed in a single open paddock and offered local Guinea grass twice daily and water ad libitum.

2.2. Treatments

The donkeys were assigned to each of the following six treatments: saline (0.9%, 5 mL), romifidine hydrochloride (Sedivet 1% Injection; Boehringer Ingelheim Vetmedica, St. Joseph, MO, USA) at 40, 60, 80 and 100 μg/kg (R40, R60, R80 and R100, respectively), and acepromazine maleate (Acepromazine Maleate Injection; Vedco, St. Joseph, MO, USA) at 0.1 mg/kg (ACE). Treatments were randomized (http://www.random.org/lists) in a crossover, Latin square design with a 7-day washout period between treatments. To ensure that investigators were blinded, one individual (FC-A) prepared all treatments by drawing them into 1 mL syringes to ensure accuracy of the dose, then transferring them into 10 mL syringes and creating the final volume of 5 mL by adding 0.9% saline solution as needed. The 10 mL syringe barrels and their needle hubs were covered with white medical tape. Treatments were administered by the same person (IL) by direct needle stick into the left external jugular vein and injecting them as a bolus over 10 s.

Two donkeys were brought into a stall, loosely tied (approximately 1.5 m from one another), sprayed with fly repellent (Equine Fly & Mosquito Spray; Manna Pro Corp., St. Louis, MO, USA), and allowed 15 min to acclimate to the environment in the stall. Sedation scores (SS), head heights above ground (HHAG) and mechanical nociceptive thresholds (MNT) were assessed in this order by investigators who stayed inside the stall for the duration of the trials ((LSR) assessed SS and HHAG, and (IL) measured MNT). Assessments were performed at 15, 12, 9, 6 and 3 min before the administration of treatments and at 5 min intervals for the first 60 min after treatment, then at 10 min intervals until 120 min and then at 30 min intervals until 180 min.

2.3. Assessment of sedation

Sedation was assessed by assigning SS and measuring HHAG (Lizarraga and Castillo-Alcala, 2015; Lizarraga et al., 2015, 2016, 2017). For SS, a 4-point simple descriptive scale was used: 0 – no sedation, donkey is alert with normal posture; 1 – mild sedation, low head carriage, ears pointing out and pendulous upper lip; 2 – moderate sedation, head lowered towards ground and wide stance of fore legs; 3 – marked sedation, swaying of hind legs with or without attempts to become recumbent. HHAG was acquired by measurement between the ground and the ventral aspect of the donkeys' nostrils. To account for variations in donkeys' heights, mean baseline values were considered as 100% HHAG for each trial and actual HHAG values after treatment administration were converted to percentages of the 100% HHAG.

2.4. Assessment of antinociception

Quantification of MNTs was performed as previously described (Lizarraga and Beths, 2012; Lizarraga and Janovyak, 2013; Lizarraga and Castillo-Alcala, 2015; Lizarraga et al., 2015, 2016, 2017). Mechanical nociceptive devices were fastened with a hook-and-loop strap to the proximodorsal aspect of the left metacarpal bone. The devices contained a 2 mm blunt-ended pin housed in the plunger of a 5 mL syringe for loss of resistance technique. The loss of resistance syringe was connected, via plastic tubing and a three-way tap, to a 50 mL air-filled syringe and a pressure gauge. By manually pressurizing the 50 mL syringe, the pin was displaced against the limb until the donkey lifted it (i.e., nociceptive threshold). The pressure (in kPa) required to produce this behaviour was recorded and the applied pressure discontinued.

Prior to testing, the devices were calibrated by clamping the actuator over an electronic scale (3000 g maximum capacity, 1 g resolution) and recording the pressure required to produce 100 g increments up to 2 kg; 100 g was equated to 1 Newton (N). Ten measurements at each N interval for up to 20 N were used for linear regression analysis of pressure vs. force ($Y = 2.027 + (0.1545 * X)$, $R = 0.9989$). Hence, recorded pressure was converted into and reported as force (in N). To avoid tissue damage, the force applied to the limb was constantly increased (approximately 0.5 N/s) up to a cut-off force of 20 N and this value recorded if there was no reaction. Fly spray was re-applied as needed to prevent flies from triggering leg withdrawal.

2.5. Statistical analysis

Data are presented as mean ± SD and median (range) as appropriate. Data distribution was analysed by use of the D'Agostino and Pearson test. Areas under the curve (with the baseline subtracted) for 0–30, 30–60, 60–120 and 120–180 min were computed for SS ($SS\text{-}AUC_{0-30}$, $SS\text{-}AUC_{30-60}$, $SS\text{-}AUC_{60-120}$ and $SS\text{-}AUC_{120-180}$), HHAG ($HHAG\text{-}AUC_{0-30}$, $HHAG\text{-}AUC_{30-60}$, $HHAG\text{-}AUC_{60-120}$ and $HHAG\text{-}AUC_{120-180}$) and MNT ($MNT\text{-}AUC_{0-30}$, $MNT\text{-}AUC_{30-60}$, $MNT\text{-}AUC_{60-120}$ and $MNT\text{-}AUC_{120-180}$) using the trapezoidal rule. Differences between treatments for SS-AUC were analysed using the Friedman test followed by the Dunn multiple comparison test, and for HHAG-AUC and MNT-AUC by means of repeated measures one-way analysis of variance followed by the Tukey test. The lowest HHAG value and its time of occurrence were determined for each trial and differences between treatments were analysed by use of one-way analysis of variance followed by the Bonferroni test and Kruskal-Wallis test, respectively. All analyses were performed with the aid of commercially available statistical software (Prism, v4.0b for Macintosh; GraphPad Software, La Jolla, CA, USA). Values of $P < 0.05$ were considered significant.

3. Results

Clinical signs of sedation (i.e., SS ≥ 1) were observed 1 to 4 min after the administration of all romifidine treatments with SS reaching its peak between 5 and 10 min and gradually decreasing over time. Sedation was also observed following ACE administration, but onset occurred 5 to 20 min after injection. Saline induced no sedation throughout the study (Fig. 1, Table 1). Compared to saline (0 (0–0)), significantly higher $SS\text{-}AUC_{0-30}$ values were obtained following R60 (11.5 (8–15)), R80 (10.5 (7–12)) and R100 (12.5 (11 − 13)) administration ($P < 0.05$), and $SS\text{-}AUC_{30-60}$ values following R100 administration (8 (7–13))

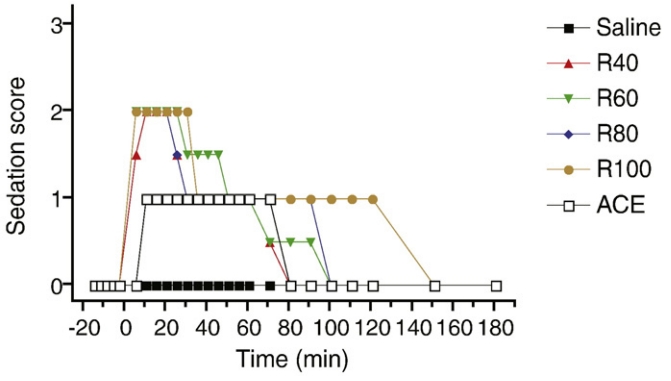

Fig. 1. Effect of intravenous administration of 5 mL, 0.9% saline; 40 μg/kg romifidine (R40); 60 μg/kg romifidine (R60); 80 μg/kg romifidine (R80); 100 μg/kg romifidine (R100); and 0.1 mg/kg acepromazine (ACE) on sedation scores (median) in donkeys ($n = 6$). Treatments were administered at time 0 min.