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RESEARCH PAPER

Pharmacokinetics and pharmacodynamics of intravenous romifidine and propranolol administered alone or in combination for equine sedation

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Abstract

Objective Propranolol has been suggested for anxiolysis in horses, but its sedation efficacy and side effects, both when administered alone and in combination with α_2-adrenoceptor agonists, remain undetermined. This study aimed to document the pharmacokinetics and pharmacodynamics of propranolol, romifidine and their combination.

Study design Randomized, crossover study.

Animals Six adult horses weighing 561 ± 48 kg.

Methods Propranolol (1 mg kg^{-1}; treatment P), romifidine (0.1 mg kg^{-1}; treatment R) or their combination (treatment PR) were administered intravenously with a minimum of 1 week between treatments. Alertness, behavioral responsiveness (visual and tactile) and physiologic variables were measured before and up to 960 minutes after drug administration. Blood was collected for blood gas and acid-base analyses and measurement of plasma drug concentrations. Data were analyzed using repeated-measures analysis of variance or Friedman with Holm–Sidak and Wilcoxon rank-sum tests ($p < 0.05$).

Results Systemic clearance significantly decreased and the area under the concentration-time curve significantly increased for both drugs in PR compared with P and R. Both PR and R decreased behavioral responsiveness and resulted in sedation for up to 240 and 480 minutes, respectively. Sedation was deeper in PR for the first 16 minutes. Heart rate significantly decreased in all treatments for at least 60 minutes, and PR significantly increased the incidence of severe bradycardia (<20 beats minute^{-1}).

Conclusions and clinical relevance Although not associated with reduced behavioral responsiveness or sedation alone, propranolol augmented romifidine sedation, probably through alterations in romifidine pharmacokinetics, in horses administered PR. The occurrence of severe bradycardia warrants caution in the co-administration of these drugs at the doses studied.

Keywords bradycardia, equine, propranolol. romifidine, sedation.

Introduction

Alpha$_2$-adrenergic receptor agonists (α_2-agonists), such as romifidine, are the most widely used

perioperative class of sedatives in equine practice and are used either alone or in combination with other drugs. Romifidine in horses produces sedation, analgesia and muscle relaxation with less ataxia than other α_2-agonists (England et al. 1992; Moens et al. 2003), and dose-dependently improves the quality of recovery from isoflurane anesthesia compared with xylazine (Woodhouse et al. 2013). Sedation is mediated by downregulation of central norepinephrine following activation of α_2-adrenergic receptors in the locus coeruleus (Doze et al. 1989). However, α_2-adrenoceptor-mediated sympatholysis (Wang et al. 1994), increased systemic vascular resistance with reflex increased vagal tone (Gasthuys et al. 1990), and direct inhibition of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Knaus et al. 2007) within the sinoatrial node together can produce profound and persistent bradycardia, hypertension and reduced cardiac output (CO) in horses (Wojtasiak-Wypart et al. 2012). Ataxia and gastrointestinal stasis are also common side effects of α_2-agonists (Freeman & England 2001).

The co-administration of two or more sedative and/or anxiolytic drugs at lower doses often reduces the dose-dependent side effects of each drug. Propranolol is a β_1- and β_2-adrenoceptor blocker that attenuates adrenergic activity throughout the body. In humans, propranolol reduces amygdala hyperactivation to stressful stimuli (Hurlemann et al. 2010) in patients with anxiety disorders (Etkin & Wager 2007); anxiolysis is likely to be attributable to the blockade of locus coeruleus norepinephrine input to the amygdala (Hurlemann et al. 2010). Propranolol also modulates the amygdala–hippocampus interactions during declarative memory encoding and consolidation of stimuli (Strange & Dolan 2004). In horses, propranolol has been used to control supraventricular tachyarrhythmia (Muir & McGuirk 1985). Bradycardia and decreased cardiac contractility are known adverse effects of this drug (Muir & McGuirk 1985). Propranolol has been proposed anecdotally as a potentially useful equine anxiolytic, tranquilizer or sedative; however, the utility of propranolol for these purposes, either alone or in combination with other α_2-adrenoceptor agonists, has not been studied experimentally.

The aim of this study was to describe the pharmacokinetic and pharmacodynamic profile of romifidine, propranolol and their co-administration following a single intravenous (IV) bolus injection in awake horses. We hypothesized that propranolol would both cause sedation and enhance romifidine sedation. Because each drug can cause bradyarrhythmias, we also hypothesized that co-administration of propranolol and romifidine would exacerbate this adverse effect compared with the administration of either drug alone.

Materials and methods

Animals

Six horses consisting of four mares and two geldings (three Thoroughbreds, two Quarter Horses, one Dutch Warmblood) with a mean ± standard deviation (SD) age of 10 ± 5 years and weight of 561 ± 48 kg were studied in a randomized crossover trial approved by the Institutional Animal Care and Use Committee at the University of California Davis, CA, USA. All horses were deemed healthy based on history and physical examination.

Horses were randomly assigned to the administration of propranolol IV (1 mg kg^{-1}; treatment P), romifidine IV (0.1 mg kg^{-1}; Sedivet 1%; Boehringer Ingelheim VetMedica, Inc., MO, USA) (treatment R), or IV propranolol (1 mg kg^{-1}) and romifidine (0.1 mg kg^{-1}) (treatment PR), with an interval of at least 1 week between treatments. Propranolol is commercially available only as a 1 mg mL^{-1} injectable solution and therefore non-pharmaceutical grade propranolol was prepared as a 25 mg mL^{-1} solution as follows: to a quantity of (±) propranolol hydrochloride powder of ≥99% purity (Sigma-Aldrich Corp., MO, USA) was added 19.75 times the mass of sterile, distilled and deionized water plus 0.25 times the mass of a sterile 50% solution of citric acid (Sigma-Aldrich Corp.). These were mixed in a sterile beaker until the initial white slurry became clear. Finally, additional sterile water equal to 20 times the mass of the initial propranolol was added and mixed, yielding a final solution of 25 mg mL^{-1} propranolol, which was passed through a 0.2 μm filter (Millex-GS; Millipore Corp., MA, USA) and stored in a sterile multi-dose vial (Allergy Laboratories, Inc., OK, USA) for up to 24 hours before use. Romifidine was diluted from its original packaged 10 mg mL^{-1} solution to 2.5 mg mL^{-1} using sterile 0.9% preservative-free saline (Baxter Healthcare Corp., IL, USA). All drugs were prepared by one of the authors (RJB), who was not involved in evaluating responses.

Two days before the study, each horse was stabled individually in a stall to acclimatize. Access to grass hay and water was provided at all times. On the day

