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RESEARCH PAPER

The pharmacokinetics and pharmacodynamics of the injectable anaesthetic alfaxalone in the horse

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Abstract

Objective To determine the pharmacokinetics and pharmacodynamics of the neurosteroidal anaesthetic, alfaxalone, in horses after a single intravenous (IV) injection of alfaxalone, following premedication with acepromazine, xylazine and guaiphenesin.

Study design Prospective experimental study.

Animals Ten (five male and five female), adult, healthy, Standardbred horses.

Methods Horses were premedicated with acepromazine (0.03 mg kg^{-1} IV). Twenty minutes later they received xylazine (1 mg kg^{-1} IV), then after 5 minutes, guaiphenesin (35 mg kg^{-1} IV) followed immediately by IV induction of anaesthesia with alfaxalone (1 mg kg^{-1}). Cardiorespiratory variables (pulse rate, respiratory rate, pulse oximetry) and clinical signs of anaesthetic depth were evaluated throughout anaesthesia. Venous blood samples were collected at strategic time points and plasma concentrations of alfaxalone were assayed using liquid chromatography-mass spectrometry (LC/MS) and analysed by noncompartmental pharmacokinetic analysis. The quality of anaesthetic induction and recovery was scored on a scale of 1–5 (1 very poor, 5 excellent).

Results The median (range) induction and recovery scores were 4 (3–5) (good: horse slowly and moderately gently attained recumbency with minimal or no rigidity or paddling) and 4 (1–5) (good: horse stood on first attempt with some knuckling and ataxia) respectively. The monitored cardiopulmonary variables were within the range expected for clinical equine anaesthesia. The mean ± SD durations of anaesthesia from induction to sternal recumbency and from induction to standing were 42.7 ± 8.4 and 47 ± 9.6 minutes, respectively. The mean ± SD plasma elimination half life ($t_{1/2}$), plasma clearance (Clp) and volume of distribution (V_d) for alfaxalone were 33.4 minutes, 37.1 ± 11.1 mL $minute^{-1}$ kg^{-1} and 1.6 ± 0.4 L kg^{-1}, respectively.

Conclusions and clinical relevance Alfaxalone, in a 2-hydroxypropyl-beta-cyclodextrin formulation, provides anaesthesia with a short duration of recumbency that is characterised by a smooth induction and satisfactory recovery in the horse. As in other species, alfaxalone is rapidly cleared from the plasma in the horse.

Keywords alfaxalone, alfaxan, anaesthetic, horse, neurosteroid, pharmacokinetic.

Introduction

Alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione), a progesterone analogue, is a neurosteroid which interacts with the gamma aminobutyric acid $(GABA)_A$ receptor and produces anaesthesia and

muscle relaxation. Alfaxan, alfaxalone in 2-hydroxypropyl-beta-cyclodextrin, is registered in several countries for intravenous (IV) induction and maintenance of anaesthesia in dogs and cats.

Alfaxalone was introduced into human and veterinary anaesthesia as Althesin and Saffan respectively in 1971. Each millilitre of the formulation contained 9 mg mL^{-1} alfaxalone and 3 mg mL^{-1} alfadolone acetate (21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione) solubilised in saline with 20% Cremophor-EL, a polyoxyethylated caster-oil based surfactant (Child et al. 1971; Davis & Pearce 1972). Major side effects reported with this formulation have been ascribed to histamine release associated with the Cremophor-EL and these eventually led to the voluntary withdrawal of Althesin from the human medical market in the mid 1980s, although Saffan remained available for use in cats in the UK for considerably longer.

Despite the availability of Althesin and Saffan since 1971, little work has been conducted with this formulation in the horse. Hall (1972) noted marked excitement and hyperaesthesia during recovery in four un-premedicated horses after induction of anaesthesia with Althesin but found these effects were almost completely suppressed by prior administration of xylazine dosed at 1 mg kg^{-1}. A similar study found that pre-medication with acepromazine maleate administered IV or intramuscularly failed to suppress these unwanted effects after Saffan administration (Eales 1976).

A new formulation of alfaxalone 10 mg mL^{-1} (without alfadolone acetate or Cremophor-EL) has been developed for use in dogs and cats by solubilising alfaxalone in 2-hydroxypropyl-beta-cyclodextrin (HPCD). Recently, Leece et al. (2009) used this formulation for induction and maintenance of anaesthesia in ponies undergoing field castration. Ponies were premedicated with romifidine, butorphanol and diazepam and the authors reported no adverse effects as seen with earlier formulations. In a subsequent study (Kloppel & Leece 2011) anaesthesia was extended by further boluses of alfaxalone as required to enable castration to be completed.

The aim of this current work was to study the pharmacokinetic parameters of the HPCD-based formulation of alfaxalone in the horse at a dose similar to the clinical dose used in the dog and cat and to determine its pharmacodynamic suitability as an anaesthetic induction agent for clinical use in this species in combination with suitable premedicant agents.

Materials and method

Animals

This study was performed with the approval of the University of Queensland Production and Companion Animals Ethics Committee (SVS/366/05/UQ). Ten Standardbred horses (five mares and five geldings), mean ± SD age 8.9 ± 2.8 years and weight 434 ± 38.1 kg, from the University of Queensland Equine Research Herd were included in the study. Horses were considered healthy on the morning of the study based on the results of a physical examination. Horses were housed in a free-range grass paddock and yarded the day prior to the study. Animals were fed lucerne hay and fasted for 12 hours prior to commencement of the study although fresh water was available *ad libitum*. Horses were stabled for up to 48 hours after completion of the study and returned to the herd after a final physical examination.

Study protocol

The skin overlying both jugular veins was clipped and disinfected. Following deposition of 20 mg lignocaine (Lignomav; Mavlab Pty Ltd, Qld, Australia) at the site of catheter placement, 9 cm 14 G catheters (Surflo; Terumo Corporation, Philippines) were placed towards the heart in both the right and left jugular veins. The right jugular catheter was used for drug administration and the left for venous blood collection. Horses were premedicated with 0.03 mg kg^{-1} acepromazine (A.C.P. 10; Delvet Pty Ltd, Australia) IV. Twenty minutes after premedication 1 mg kg^{-1} xylazine (Xylazil 100; Troy Laboratories Pty Ltd, Australia) was administered IV, then, 5 minutes later, guaiphenesin 35 mg kg^{-1} (Giafen; Parnell Pty Ltd, Australia) was infused IV. Immediately after the guaiphenesin, an IV dose of alfaxalone (1 mg kg^{-1}) (Alfaxan; Jurox Pty Ltd, Australia) was given over a period of approximately 10 seconds. The quality of induction was assessed by a veterinarian experienced in equine anaesthesia using a descriptive scale of 1–5 (5 being optimal induction; Table 1).

Once recumbent, horses were placed in right lateral recumbency and oxygen was supplied via an intranasal catheter at 15 L $minute^{-1}$. Cardiorespi-