The Veterinary Journal 196 (2013) 209–212

Contents lists available at SciVerse ScienceDirect

The Veterinary Journal

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

The effects on cardio-respiratory and acid–base variables of a constant rate infusion of alfaxalone–HPCD in sheep

Xavier Moll *[,1], Laura Santos [1], Felix García, Anna Andaluz

Departament de Medicina i Cirurgia Animals, Facultat de Veterinària, Universitat Autònoma de Barcelona (UAB), 08193 Bellaterra, Barcelona, Spain

ARTICLE INFO

Article history:
Accepted 17 September 2012

Keywords:
Sheep
Alfaxalone
Steroid anaesthesia
Constant rate infusion
Cardio-respiratory effects

ABSTRACT

Alfaxalone in a 2-hydroxypropyl-β-cyclodextrin (HPCD) formulation is an intravenous (IV) hypnotic agent characterised by the stability of cardiorespiratory effects after a single-bolus administration. The objective of this study was to investigate the cardiovascular, respiratory, and acid–base effects of alfaxalone–HPCD administered during a continuous rate infusion in six Ripollesa sheep. After instrumentation, a 2 mg/kg IV bolus of alfaxalone followed by a continuous infusion of 10 mg/kg/h was administered to the sheep. Heart rate, arterial blood pressure, respiratory rate and arterial blood gases were recorded. Occasional side effects and time to standing were also noted.

No significant changes were observed in arterial blood pressure, but during the infusion and the initial stages of recovery, a significant increase in heart rate occurred during the last 120 min of the study. Significant respiratory depression was detected during the infusion period and the first 15 min of recovery. This study showed that a constant rate infusion alfaxalone in un-premedicated sheep produced clinically acceptable haemodynamic results and a mild respiratory depression that may require intermittent positive pressure ventilation.

Introduction

General anaesthesia is a drug-induced state of unconsciousness characterised by a controlled and reversible depression of the central nervous system (CNS) and analgesia, in which the patient is not arousable by noxious stimulation (Thurmon and Short, 2007). In veterinary medicine, anaesthesia is commonly maintained using volatile anaesthetics, although total intravenous anaesthesia (TIVA) can provide reliable and useful anaesthesia, providing haemodynamic stability, good intraoperative analgesia, and smooth recovery. Furthermore, TIVA avoids the risk of fumes in the theatre and the requirement for specialised anaesthetic equipment (Nolan and Reid, 1993; Beths et al., 2001; Raisis et al., 2007; Andreoni and Hughes, 2008).

Alfaxalone is a synthetic neuroactive lipophilic steroid, which interacts with the gamma-aminobutyric acid (GABA) receptor, inducing anaesthesia and muscle relaxation. Alfaxalone and alfadolone have previously been formulated in combination with a Cremophor solvent, but this may induce histamine release and has been associated with adverse side effects, such as hypotension, oedema of the pinna and paws in cats and anaphylactic reactions in dogs and mini-pigs (Glen et al., 1979; Middleton et al., 1982). Interestingly, Cremophor may not be the only causative factor since the combination of alfaxalone and alfadolone in mini-pigs also contributes to the adverse reactions observed (Glen et al., 1979).

A new formulation containing alfaxalone in 2-hydroxypropyl-β-cyclodextrin (HPCD), without alfadolone and Cremophor, is now available (Alfaxan, Jurox). Following IV injection, it facilitates rapid onset of action, rapid redistribution, and a short terminal half-life (Ferre et al., 2006). It has several advantages over other injectable anaesthetic drugs, including its safety margin, with a therapeutic index that is three- or four-times greater than that of propofol or thiopentone (Høskilde et al., 1987).

Experimental studies investigating the cardiorespiratory and anaesthetic effects of a single bolus of alfaxalone without alfadolone in dogs (Ambros et al., 2008; Muir et al., 2008; Psatha et al., 2011), cats (Muir et al., 2009; Zaki et al., 2009), rabbits (Grint et al., 2008) and sheep (Andaluz et al., 2012) have shown minimal cardiorespiratory depression, making alfaxalone an acceptable induction agent in many species.

To our knowledge, no published studies have evaluated the cardiorespiratory effects of continuous rate infusion of alfaxalone in sheep without other anaesthetic drugs. The aim of the current study was therefore to determine the effects of alfaxalone–HPCD on the cardiovascular system and the acid–base status in sheep following the administration of a continuous IV infusion over 1 h preceded by a single IV induction bolus.

* Corresponding author. Tel.: +34 9 358 11387.
E-mail address: xavier.moll@uab.cat (X. Moll).
[1] These authors contributed equally to the manuscript.

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http://dx.doi.org/10.1016/j.tvjl.2012.09.010

Materials and methods

The study protocol was approved by the Ethical Commission of Animal and Human Experimentation (Spanish Government, Authorisation Number DARP4544) under the auspices of the Ethical Commission of the Autonomous University of Barcelona (Authorisation Number 791).

Animals

Six 2- to 4-year-old female Ripollesa sheep with a mean bodyweight (BW) of 45.7 ± 5.3 kg (mean ± SD) were used in the study. All sheep were judged as healthy based on their physical examination, complete blood count test results and biochemical profiles.

Experimental preparation

Prior to the study, the auricular artery was cannulated. The hair on the external pinnae of the ears was prepared aseptically and a topic local anaesthetic was applied (Crema EMLA 5%, AstraZeneca Farmacéutica). The auricular artery was located by palpation for a pulse along the cranial margin of the ear, and was catheterised percutaneously with a 22 G polyurethane catheter (Vasocan, Braun). The auricular artery catheter was used for blood gas determination, and for heart rate and arterial blood pressure measurement.

Animal treatment

The heart rate, arterial blood pressure and respiratory rate (RR) were recorded from 30 min before alfaxalone injection at 5 min intervals and was defined as the control time. Arterial blood gases were determined 15 min before administration using an i-STAT Portable Clinical Analyser. Arterial samples for acid–base determination (PaO_2 [arterial partial pressure of oxygen], $PaCO_2$ [arterial partial pressure of carbon dioxide], SO_2 [calculated haemoglobin saturation], HCO_3, base excess [BE], and pH) were collected in a 1 mL heparinized insulin syringe and processed within 5 min.

After baseline data had been collected, an initial IV bolus of 2 mg/kg of alfaxalone was administered for 120 s through an 18 G polyurethane catheter (Vasocan, Braun) placed in the cephalic vein. This was followed immediately by a continuous IV infusion of 10 mg/kg/h alfaxalone for 1 h. The trachea was intubated with a 9–10 mm endotracheal tube and 100% oxygen (25 mL/kg/min) was administered through a circular rebreathing system during the anaesthetic period.

The heart rate, arterial blood pressure (systolic arterial pressure [SAP], mean arterial pressure [MAP], and diastolic arterial pressure [DAP]), and RR were recorded at 2, 5, 10, 15, 20, 30, 45, and 60 min during alfaxalone infusion, and then at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min once the infusion was completed. Variables were recorded using a multi-parametric monitor (VetCare Multiparamétrico). Samples for acid–base evaluation were obtained at 5, 15, and 45 min during alfaxalone infusion, and then at 5, 15, 30, 60, 120, and 240 min during the recovery period.

Throughout the study period, Ringer's lactate solution was infused through the cephalic vein at 2.5 mL/kg/h. Oxygen therapy was stopped when the swallowing reflex returned, and the animal was extubated. All sheep remained in sternal recumbency while unconscious.

Occasional side effects (salivation, regurgitation, myoclonus, and apnoea [absence of spontaneous breathing for >30 s]), time of anaesthesia (defined as the time between the induction and the first head lift), and time to standing (time between the induction and when the animal stands) were also recorded.

Statistics

Data were analysed using SPSS version 19.0 (SPSS). Normality was tested using the Shapiro–Wilk statistic. The results were analysed by analysis of variance using a mixed-model procedure, with time as the fixed effect and sheep as the random effect. A Toeplitz type of variance was considered. A value of $P < 0.01$ was considered to indicate significance. When significant differences were found, a Bonferroni post hoc analysis for pairwise comparisons was performed.

Results

Time to anaesthesia and standing were 72.5 ± 2.2 and 94.8 ± 6.7 min (mean ± SD), respectively. Mild generalised myoclonus was observed during administration of the bolus in all animals. Excessive salivation was also present during the infusion period in all animals.

Cardiovascular, respiratory, and acid–base variables are shown in Tables 1 and 2. Significantly lower HR was observed from 120 min of the recovery with respect to the infusion time and the first 20 min of the recovery. No significant differences were observed in SAP, MAP, and DAP (Table 1).

The RR was lower during the infusion period and the first 10 min of the recovery period, and was significantly different from control time ($P < 0.01$; Table 1). During the infusion period, the lowest RR was at 2 min (7.2 ± 3.9 rpm), and was significantly different from the RRs at other recovery times ($P < 0.01$). Likewise, there were differences in RR between the fifth minute of the infusion (10.8 ± 3.4 rpm) and those at 15, 20, 30, 45, 60, 90, 120, and 150 min of the recovery period ($P < 0.01$; Table 1).

The pH decreased significantly throughout the infusion period and remained lower during the first 15 min of recovery. This fall in pH was accompanied by a significant increase in $PaCO_2$ ($P < 0.01$) and an increase in HCO_3 (Table 2). PaO_2 was significant higher ($P < 0.01$) during the infusion period. Oxygen saturation and blood sodium and potassium concentrations remained stable throughout the study.

Discussion

This is the first published study to investigate the cardiovascular and respiratory effects of alfaxalone–HPCD administered by IV constant rate infusion without other anaesthetic drugs in sheep. The selection of the infusion dose of alfaxalone–HPCD was based on results obtained in a preliminary trial (unpublished data), in which the authors observed that an infusion rate of 10 mg/kg/h, after a single IV dose of 2 mg/kg, provided an acceptable light-to-medium anaesthetic state.

The time to standing after constant rate infusion of alfaxalone–HPCD observed in this study (22.8 ± 6.7 min) was similar to that described in dogs (Ambros et al., 2008) and after IV single-bolus administration in sheep (Andaluz et al., 2012), rabbits (Grint et al., 2008) and cats (Zaki et al., 2009). Excessive salivation observed during the infusion period has also been described after a single bolus in sheep (Torres et al., 2012), although the current study noted, for the first time, the presence of mild generalised myoclonus. Most importantly, a constant rate infusion of alfaxalone–HPCD to maintain anaesthesia in sheep produced no clinically significant alterations in cardiovascular function, although a mild respiratory depression was observed.

In the current study, arterial blood pressure remained within the normal range described for sheep (Lin et al., 2012) during the entire study period. Although heart rate also remained within a normal range, a significant increase was observed during the entire infusion period and the first 20 min of recovery (Table 1). Increased heart rate has been described previously during constant rate infusion of alfaxalone in dogs (Ambros et al., 2008), and after a single bolus in sheep (Andaluz et al., 2012) and dogs (Muir et al., 2008; Psatha et al., 2011; Rodríguez et al., 2012). These studies postulated that the increased heart rate could represent compensation due to the decreased systemic vascular resistance or reduced cardiac contractility observed after alfaxalone administration. Alternatively, the increase could be attributed to the positioning of the sheep during anaesthesia and the first few minutes of recovery, since the animals remained in sternal recumbency during this period. Sternal recumbency could be associated with decreased venous return of blood induced by rumen compression on the abdominal great vessels. This effect has been previously described in sheep positioned in sternal and lateral recumbency (Hikasa et al., 2000; Fresno et al., 2008; Andaluz et al., 2012) and in cows positioned in lateral and dorsal recumbency (Klein and Fisher, 1988; Wagner et al., 1990; Dunlop et al., 1994). In the present study, heart rate decreased after the sheep returned to the standing position (Table 1).