Veterinary Anaesthesia and Analgesia 2017, **xxx**, 1–9 http://dx.doi.org/10.1016/j.vaa.2016.11.005

RESEARCH PAPER

Cardiovascular effects and intraoperative pharmacokinetics of tramadol in sheep undergoing spinal surgery

Giulia Maria De Benedictis*, Mario Giorgi†, Alice Depase*, Virginia De Vito‡, Giorgia della Rocca§ & Luca Bellini*

*Department of Animal Medicine, Production and Health, University of Padua, Legnaro, Italy
†Department of Veterinary Sciences, University of Pisa, Pisa, Italy
‡Department of Veterinary Medicine, University of Sassari, Sassari, Italy
§Department of Veterinary Medicine, University of Perugia, Perugia, Italy

Correspondence: Luca Bellini, Department of Animal Medicine, Production and Health, University of Padua, Agripolis, Viale dell'Università 16, Legnaro, Padua 35020, Italy. Tel.: +39 (0)49 8272679; fax: +39 (0)49 8272954. Email: luca.bellini@unipd.it

Abstract

Objective To evaluate the pharmacokinetics of two doses of tramadol during isoflurane anaesthesia in sheep and their ability to prevent the cardiovascular response induced by surgical stimulation.

Study design Prospective randomized controlled study.

Animals Twelve healthy sheep (mean weight 47.5 ± 7.9 kg) undergoing lumbar transpedicular intervertebral disk nucleotomy.

Methods Sheep were sedated with medetomidine, anaesthesia was induced with propofol and maintained with isoflurane at 1.5 vol%. Baseline heart rate and blood pressure were measured and were randomly assigned an intravenous injection of tramadol 4 mg kg^{-1} or 6 mg kg^{-1}. Fentanyl was injected as rescue analgesic if cardiovascular parameters were increased more than 20% compared to baseline. If those variables were below 20% of baseline, the concentration of isoflurane was gradually decreased until parameters returned to the original value. Blood collections were performed at pre-assigned times and concentrations of tramadol and O-desmethyltramadol (M1) assessed by High-Performance Liquid Chromatography.

Results Time from premedication to anaesthesia induction, anaesthesia time, propofol dose and intraoperative body temperature were similar between doses. Cardiovascular variables remained between ±20% of baseline value and no statistical difference was observed between treatments. Regardless the dose of tramadol administered, arterial blood pressure was statistically higher than baseline 10 minutes after tramadol administration but it gradually returned to previous values. A 2-compartment model and a non-compartment model described pharmacokinetic of tramadol and M1 respectively. Plasma concentrations of tramadol rapidly decreased in the first two hours for both doses with an elimination half-life of more than 40 minutes. The M1 maximum concentration was similar for both doses and it was detected in plasma after 35 minutes.

Conclusions and clinical relevance Both doses of tramadol provided adequate cardiovascular stability during spinal surgery in sheep. The pharmacokinetics variables may be used to plan the dosage regime during general anaesthesia.

Keywords cardiovascular, isoflurane, pharmacokinetics, sheep, tramadol.

Introduction

Tramadol is a synthetic drug structurally related to codeine with a central analgesic activity (Vazzana et al. 2015). Binding to μ-opioid receptors is considered one of the mechanisms of action of tramadol, although it is a weak agonist and the affinity for this receptor is 300-fold lower than that of its main metabolite O-desmethyltramadol (M1). Moreover a non-opioid mechanism of inhibition of noradrenaline and serotonine reuptake contributes to its

Please cite this article in press as: De Benedictis GM, Giorgi M, Depase A et al. Cardiovascular effects and intraoperative pharmacokinetics of tramadol in sheep undergoing spinal surgery, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2016.11.005

antinociceptive activity (Lehmann et al. 1990; Itami et al. 2011; Vazzana et al. 2015).

In veterinary medicine, the use of tramadol in farm animals has been poorly investigated. Although in small ruminants this drug is sometimes used intraoperatively (Coulter et al. 2009, Plummer & Schleining 2013), its efficacy in controlling nociceptive-induced cardiovascular responses during surgery has not been reported yet. The pharmacokinetics of tramadol in small ruminants has been formerly tested in awake non-painful goats and sheep (de Sousa et al. 2008; Bortolami et al. 2015). Nevertheless in anaesthetised animals, volatile or injectable agents used to maintain anaesthesia may alter cardiac output and vascular tone thus interfer with the perfusion of different pharmacologic compartments (Avram et al. 2000; Funes et al. 2015). Therefore, the pharmacokinetics of tramadol might vary during anaesthesia: plasma concentration, tissue disposition, metabolism and elimination may be altered and consequently its clinical efficacy.

The aim of this study was to evaluate the intraoperative efficacy of two doses of tramadol in attenuating the cardiovascular response to surgical stimulation in isoflurane-anaesthetized sheep undergoing spinal surgery. No differences in cardiovascular parameters between doses were considered as null hypothesis. Another aim of this study was to describe for each dose the pharmacokinetics of tramadol and its metabolite M1.

Material and methods

Animals

The study was performed with the ethical approval of the University of Padua committee for animal experimentation and authorized by the Italian Ministry of Health (CEASA 80/2012).

Twelve healthy Brogna non-pregnant female sheep undergoing spinal surgery consisting of a transpedicular intervertebral disk nucleotomy from L1 to L4-5 as part of another experimental study (Vadalà et al. 2015) were used.

Sheep were housed in pens with six animals each and fed with a commercial pellet and hay diet. Prior to the experiment, food was withheld for 12 hours but water was provided ad libitum. Sheep were considered healthy on thorough clinical examination, complete blood count and routine serum chemistry.

Sheep were randomized evenly into two groups using an online randomiser program (Research Randomizer Version 4.0; www.randomizer.org). Group T4 was administered 4 mg kg^{-1} and group T6, 6 mg kg^{-1} tramadol intravenously (IV) prior to surgical incision.

Anaesthesia

On the day of the surgery, each sheep was administered 8 μg kg^{-1} medetomidine (Sedator; Dechra, Italy) into the jugular vein. Fifteen minutes later, they were moved into the research facility. Two 20 gauge catheters (Delta Ven, Delta Med Spa, Italy) were inserted into the medial ear vein and auricular artery for drug and fluid administration and invasive blood pressure measurement, respectively. The area from T8 to S1 was clipped and laterolateral lumbosacral radiographs were taken. The right side of the neck was clipped and aseptically prepared and a 14 gauge over the needle catheter (Delta Ven, DeltaMed Spa, Italy) was placed into the jugular vein for blood sampling.

The sheep were then moved to theatre and propofol was administered to effect for induction of anaesthesia. Orotracheal intubation was performed and each animal was connected to the anaesthetic machine via a circle breathing system and mechanically ventilated with a volume-controlled mode (Datex-Ohmeda 7900 SmartVent, GE Healthcare, Finland). An equal volume of oxygen and medical air was delivered; fresh gas flow was initially 4 L $minute^{-1}$ and ten minutes later the flow was decreased to 1 L $minute^{-1}$. Respiratory rate and tidal volume were adjusted to maintain haemoglobin oxygen saturation (SpO_2) greater than 95% and end-tidal carbon dioxide concentrations ($P_{E'}CO_2$) between 37 and 45 mmHg (4.9 − 6.0 kPa). Sheep were positioned in sternal recumbency and a gastric tube was passed through the mouth to avoid rumen distension and bloating. Isoflurane was used to maintain anaesthesia and the vaporizer was set to deliver a target end-tidal concentration of isoflurane ($F_{E'}ISO$) of 1.5% (Minimum Alveolar Concentration in sheep = 1.53 ± 0.12%; Funes 2015). Heart rate (HR), direct systolic (SBP), diastolic (DBP) and mean blood pressure (MBP), SpO_2, $F_{E'}ISO$, $P_{E'}CO_2$, oesophageal temperature and the electrocardiogram were monitored continuously by a multiparametric monitor (Datex-Ohmeda S/5 Compact Anesthesia Monitor; GE Healthcare, Finland). Lactated Ringer's solution (5 mL kg^{-1} $hour^{-1}$) was infused IV into the auricular catheter throughout anaesthesia.

Physiological parameters, drug and fluid administration, surgical and anaesthetic events were

Please cite this article in press as: De Benedictis GM, Giorgi M, Depase A et al. Cardiovascular effects and intraoperative pharmacokinetics of tramadol in sheep undergoing spinal surgery, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2016.11.005