RESEARCH PAPER

The uptake of transdermal fentanyl in a pregnant sheep model

Gabrielle C Musk[a], **CS Melanie Catanchin**[b], **Haruo Usuda**[c], **Eleanor Woodward**[c] & **Matthew W Kemp**[c]

[a]Animal Care Services, University of Western Australia, Crawley, WA, Australia

[b]School of Animal and Veterinary Sciences, Charles Sturt University, Wagga Wagga, NSW, Australia

[c]School of Women's and Infants' Health, University of Western Australia, Crawley, WA, Australia

Correspondence: Gabrielle Musk, Animal Care Services, M720, University of Western Australia, 35 Stirling Highway, Crawley 6009, WA, Australia. E-mail: gabrielle.musk@uwa.edu.au

Abstract

Objective To evaluate the maternal and foetal uptake of transdermal fentanyl patch applied to the groin of pregnant sheep following surgery.

Study design Prospective series.

Animals A group of 16 singleton pregnant sheep underwent anaesthesia for laparotomy, hysterotomy and instrumentation of the foetus. Of these ewes 10 (101 ± 12 days of gestation) were used to evaluate the maternal uptake of transdermal fentanyl, and the efficacy of the drug in the postoperative period ($n = 10$). To determine the extent of transplacental transfer of fentanyl, six ewes from the group of 10, and six other ewes (92 ± 1 days' gestation) were studied.

Methods A 75 μg hour^{-1} fentanyl patch was placed onto the woolless skin of the medial thigh close to the groin at the end of surgery. Maternal blood samples were collected from the cephalic or jugular vein, and pain and sedation scores were determined, prior to application of the patch (time 0) and at 3, 6, 12, 24, 36 and 48 hours after. A commercial Fentanyl ELISA kit was used to determine the concentration of fentanyl. Paired maternal and foetal blood samples were collected 48 hours after surgery. Animals were euthanized at the end of the study. Data were tested for normality and compared with Student *t* test or one-way ANOVA and are expressed as mean ± standard deviation or median (range).

Results Recovery from anaesthesia and surgery was uneventful in all ewes. The dose of fentanyl was 1.4 ± 0.2 μg kg^{-1} hour^{-1}. The maximum maternal plasma concentration of fentanyl was 0.547 ng mL^{-1} (range, 0.349–0.738 ng mL^{-1}) at 12 hours. After 48 hours, the concentration of fentanyl was 0.381 ng mL^{-1} (range, 0.211–0.487 ng mL^{-1}; maternal) and 0.295 ng mL^{-1} (range, 0.185–0.377 ng mL^{-1}; foetal; $p = 0.175$). The placental transfer rate of fentanyl was 77%.

Conclusions and clinical relevance The uptake of fentanyl varied between animals. The placental transfer rate of fentanyl was 77%.

Keywords analgesia, fentanyl, Merino ewes, postoperative analgesia, pregnant sheep.

Introduction

Pregnant sheep are used commonly as a model for biomedical research and may undergo invasive surgical procedures requiring perioperative analgesia (Maneenil et al. 2015; Kemp et al. 2016). The provision of adequate postoperative analgesia is, however, problematic as pain assessment is difficult in this species and pregnancy presents some specific considerations for the safety of common analgesic drugs, such as nonsteroidal anti-inflammatories (Lizarraga & Chambers 2012). Despite these issues, postoperative pain management is essential for good animal welfare. Furthermore, it is important to draw upon a solid evidence base when designing anaesthetic and analgesic regimes for animals used in research and teaching. Unfortunately, this approach is difficult with pregnant sheep models, as there are significant gaps in the literature regarding pain assessment and pain management in this cohort of animals.

A recent review focused on the role of nonsteroidal anti-inflammatories for analgesia in sheep (Lizarraga & Chambers 2012). Although this class of drugs is commonly used in sheep, their administration to pregnant animals may be associated with premature closure of the foetal 'ductus arteriosus', and based on evidence from other species (mice and humans; Baragatti et al. 2003; Van Overmeire & Chemtob 2005), nonsteroidal anti-inflammatories are not routinely administered to pregnant sheep. This review also suggests that opioid analgesic drugs are of dubious efficacy in sheep and that the benefits of their use may be outweighed by the potential side effects (Lizarraga & Chambers 2012).

Fentanyl is a pure μ opioid receptor agonist that is used extensively for perioperative pain management in many species. The pharmacokinetics of this drug when administered by the transdermal route have been described in pregnant sheep (Heikkinen et al. 2015), but there is only one study evaluating the efficacy of transdermal fentanyl in pregnant sheep (Musk et al. 2014). In non-pregnant sheep, transdermal fentanyl has been evaluated from both a pharmacokinetic and a pharmacodynamic perspective (Ahern et al. 2009, 2010; Christou et al. 2015). In all but one of these studies the patch was applied to the antebrachium of the sheep and secured with a circumferential bandage. The site was clipped of wool and cleaned before application of the patch and bandage (Ahern et al. 2009, 2010; Christou et al. 2015; Heikkinen et al. 2015). Musk et al. (2014) applied the fentanyl patch to the skin in the medial thigh close to the inguinal region of pregnant sheep. This site is woolless so does not require clipping of the wool.

The factors that affect the ability of a drug to cross the placenta include lipid solubility, plasma protein binding, molecular weight and the degree of ionization along with uterine and umbilical blood flow (Musk et al. 2012). Fentanyl is highly lipid soluble and is reported to cross the human placenta at a rate of 86% (de Barros Duarte et al. 2009) and 90% (Moisés et al. 2005). In sheep, fentanyl is reported to cross the placenta at a rate of 69% in one study (Heikkinen et al. 2016), and to a lesser extent in another study, where the maternal concentration of fentanyl was a mean of 2.5 times the foetal concentration after bolus injections (Craft et al. 1983).

The aim of this study was to evaluate the uptake and efficacy of transdermal fentanyl patch applied to the medial thigh close to the inguinal region (the groin) of pregnant sheep for postoperative analgesia. Furthermore, the study aimed to determine the extent of transplacental transfer of fentanyl from the maternal to the foetal circulation.

Materials and methods

This study was approved by the Animal Ethics Committee at the University of Western Australia in accordance with the Australian code for the care and use of animals for scientific purposes (National Health and Medical Research Council 2013).

A total of 16 singleton pregnant Merino ewes underwent anaesthesia and surgery for maternal and foetal catheterization as part of another study. In brief, a catheter was placed in the jugular vein of the ewe, and following laparotomy and hysterotomy for exposure of the foetus, a catheter was placed in the foetal jugular vein and foetal carotid artery. The sheep were acclimatized to the research facility for 1 week prior to surgery in shared raised pens. Then, 2 days prior to surgery they were moved to individual raised pens. Rooms were controlled for temperature (20.5−21.5 °C) and relative humidity (40−60%). Ewes were weighed on the morning of surgery and were not fasted beforehand.

The ewes were premedicated with a combination of acepromazine (0.03 mg kg^{-1}, ACP 2 injection, 2 mg mL^{-1}; Ceva Delvet Pty Ltd, Australia) and buprenorphine (0.01 mg kg^{-1}, Temgesic, 0.3 mg mL^{-1}; Reckitt Benckiser, Australia) by intramuscular injection 30−40 minutes prior to induction of anaesthesia. Anaesthesia was induced with a combination of midazolam (0.25 mg kg^{-1}, midazolam injection, 5 mg mL^{-1}; Pfizer Australia Pty Ltd, Australia) and ketamine (5 mg kg^{-1}, Ketamil, 100 mg mL^{-1}; Troy Laboratories, Australia) by intravenous (IV) injection and the trachea was intubated (Portex cuffed tracheal tube, 8.5 mm internal diameter; Portex Ltd, UK). The sheep were positioned in dorsal recumbency and anaesthesia was maintained with isoflurane (1−2%, Attane isoflurane, 1 mg mL^{-1}; Bayer, Australia Ltd, Australia) in 100% oxygen through a circle breathing system. The isoflurane vaporizer was adjusted, as judged by an experienced veterinary anaesthetist, to maintain an adequate depth of anaesthesia. A line block of ropivacaine (100 mg, Naropin 1%; AstraZeneca, Australia) was performed along the laparotomy incision site prior to surgery. Intermittent mechanical ventilation was commenced immediately after tracheal intubation to target permissive hypercapnia [end-tidal carbon dioxide ($P_E'CO_2$), 45−55 mmHg or

