July, 2018

Adverse reactions to fentanyl transdermal patches in calves: a preliminary clinical and pharmacokinetic study

Jonathan P. Mochel, *Iowa State University*

SHORT COMMUNICATION

Adverse reactions to fentanyl transdermal patches in calves: a preliminary clinical and pharmacokinetic study

Joe S Smith[a], Jonathan P Mochel[a], David J Borts[a], Kerrie A Lewis[b] & Johann F Coetzee[c]

[a]Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, USA

[b]Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada

[c]Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

Correspondence: Joe S Smith, 2462 Lloyd Vet Med, Ames, IA 50011, USA. E-mail: jss303@iastate.edu

Abstract

Objective To describe adverse reactions and measure plasma fentanyl concentrations in calves following administration of a fentanyl transdermal patch (FTP).

Study design Prospective, experimental clinical study.

Animals Six female Holstein calves and one male Angus calf. Four calves were healthy experimental animals and three calves were clinical patients.

Methods Plasma fentanyl concentrations were measured in blood collected from a jugular vein. FTP 2 μg kg^{-1} $hour^{-1}$ and 1 μg kg^{-1} $hour^{-1}$ was applied to four and three calves, respectively. Heart rate, respiratory rate, temperature and ataxia were recorded at the same times as blood collection (0, 2, 4, 6, 12, 24, 36, 48, 60, 72, 84 and 96 hours). Substance P concentrations were determined via radioimmunoassay for two calves.

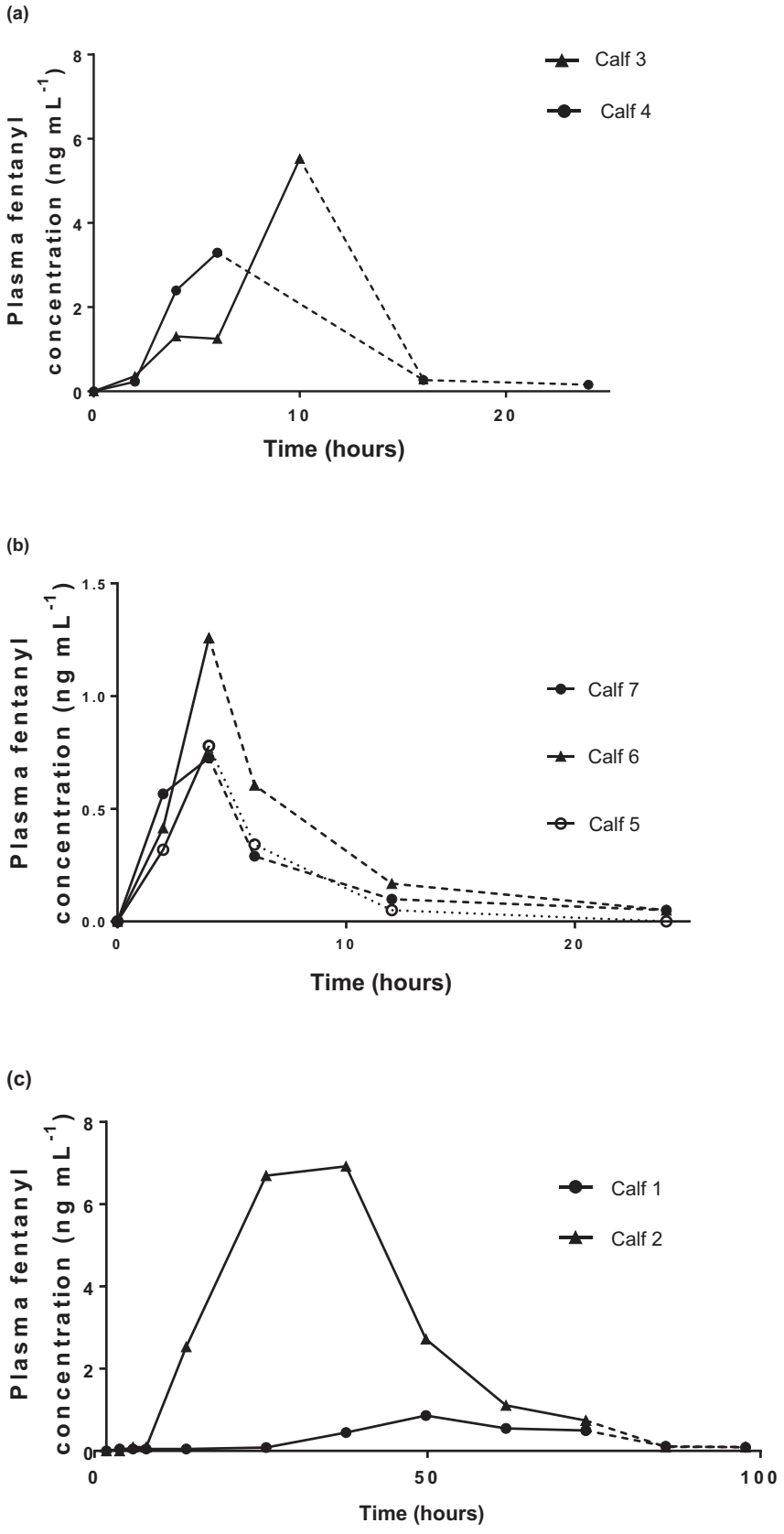
Results After the FTP (2 μg kg^{-1} $hour^{-1}$) application, two calves developed tachycardia, hyperthermia, excitement and ataxia within 6 hours; no adverse effect was observed in the other two calves. The three calves administered FTP (1 μg kg^{-1} $hour^{-1}$) exhibited tachycardia and excitement, and the FTP were removed at 4 hours. Naloxone was administered to two calves before the adverse clinical signs ceased, while adverse events in the other three calves resolved within 2 hours of FTP removal. Variables returned to previous baseline values by 2–4 hours after FTP removal. Maximum plasma fentanyl concentrations were variable among calves (0.726–6.923 ng mL^{-1}). Substance P concentrations measured in two calves were not consistently depressed during FTP application. Fentanyl concentrations at 4 and 6 hours were significantly associated with the appearance of adverse effects.

Conclusions and clinical relevance FTP (1–2 μg kg^{-1} $hour^{-1}$) administered to calves may result in adverse behavioral and cardiovascular effects. Patch removal and treatment with an opioid antagonist may resolve these adverse effects. Additional research is needed to determine optimal FTP dosing for cattle.

Keywords adverse event, calf, fentanyl, fentanyl transdermal patch.

Introduction

Analgesia for cattle during surgical procedures is important for promoting animal welfare. While cattle are commonly subjected to potentially painful production procedures and nonroutine surgeries, practitioners have limited options for pain management since there are currently no drugs labeled for surgical pain in cattle in the US (Smith 2013). Additionally, there are very few reports of adverse effects of long-acting analgesics, such as fentanyl transdermal patches (FTP), in cattle.



Fentanyl is a μ-opioid agonist having a short duration of action when administered as a single intravenous bolus. For long-term analgesia, FTP have been developed for humans and have been used in many veterinary species. Adverse effects described in large animal species include sedation in sheep (Christou et al. 2015), vocalization (bleating) and excitement in goats (Carroll et al. 1999) and increased locomotor responses in horses (Wetmore et al. 2016). The only reported adverse effects of FTP in cattle are mydriasis, nystagmus, increased locomotor activity, vocalization, myoclonus of the tail, hyperesponsiveness and hyperthermia which are described in one case describing administration of a FTP and concurrent morphine epidural in a calf (Marchionatti et al. 2015). The effects of FTP as a sole opioid in cattle have not been investigated at this time.

The purpose of this study was to describe the effects of FTP placement on calves and to generate concentration *versus* time data for FTP use in this species. The hypothesis of this study was that the observed effects would be mild and consistent with those reported in other large animal species and to record any differences in adverse effects between healthy animals and animals with clinical disease.

Materials and methods

This study was approved by the Animal Care and Use Committee of Iowa State University (protocols 6-16-8301, 7-16-8318). Two studies were initiated, one utilizing healthy calves from the university dairy and a second enrolling client-owned animals presented to the Iowa State University Food Animal and Camelid Hospital under informed consent.

Six female Holstein calves aged 3–4 weeks and weighing 52.9 ± 5.2 kg (mean ± standard deviation) and one male Angus calf, aged 16 weeks and weighing 171.0 kg, were studied. All calves were individually housed in a climate-controlled facility. A catheter (MILACATH-EU; MILA International Inc., KY, USA) was placed in a jugular vein for blood collection. FTP (Fentanyl Transdermal System; Mylan Pharmaceuticals Inc., WV, USA) dosing was initially 2 μg kg^{-1} $hour^{-1}$. After adverse reactions were observed in two calves, the dose was reduced to 1 μg kg^{-1} $hour^{-1}$ and rounded to the nearest whole patch (Fig. S1, online). The hair was clipped and skin prepped with chlorhexidine and alcohol and allowed to dry prior to patch placement. Patches were lightly wrapped as described for sheep (Christou et al. 2015).

Heart (HR) and respiratory rates (f_R) were measured by thoracic auscultation and rectal temperature (RT) using a lubricated digital thermometer (VetOne, ID, USA). These variables and ambulatory status were monitored at a minimum of every other hour for the 96 hour duration of the study. Adverse effects were defined as any deviations from accepted HR and f_R ranges and behavior. Blood samples were collected before (0) and 2, 4, 6, 12, 24, 36, 48, 60, 72, 84 and 96 hours after application. The FTP was to be removed at 72 hours after application. In the event that an adverse effect was noted and deemed deleterious to animal health by the attending veterinarian, the FTP was removed.

Blood (10 mL) was collected from the catheter, after a scavenged sample was discarded, using a syringe and placed into sodium heparin tubes (Vacutainer; Becton Dickinson & Co., NJ, USA). The catheters were flushed with 5 mL of heparinized saline (1000 U L^{-1}; Heparin Sodium in 0.9% Sodium Chloride Injection; Baxter Healthcare Corp., IL, USA) after each use. Analysis of fentanyl concentrations was performed as described (Smith et al. 2018). The samples were centrifuged at 300 ***g*** for 10 minutes. Plasma was stored at −80 °C until analysis of plasma concentrations of fentanyl and two metabolites, norfentanyl and despropionyl fentanyl. Samples were thawed and vortexed and 200 μL aliquots were transferred into a vial with 800 μL of internal standard, fentanyl-D5, in acetonitrile with 0.1% formic acid added. Samples were vortexed and then centrifuged at 4402 ***g*** for 20 minutes. The supernatant was transferred and the samples were dried, then reconstituted in 125 μL of 25% acetonitrile in water, vortexed and transferred into an autosampler vial (with glass insert), centrifuged for 20 minutes at 768 ***g*** and analyzed using high performance liquid chromatography (Agilent 1100; Agilent Technologies, CA, USA) coupled to a Thermo LTQ ion trap mass spectrometer (Thermo Scientific, CA, USA). The lower limit of quantification for fentanyl and the metabolites was

Figure 1 Plasma fentanyl concentrations in seven calves, six Holstein heifers weighing 52.9 ± 5.2 kg and one male Angus weighing 171.0 kg, after application of a fentanyl transdermal patch (FTP). (a) Calves 3 and 4 (FTP 2 μg kg^{-1} $hour^{-1}$) with severe adverse reactions; (b) calves 5–7 (FTP 1 μg kg^{-1} $hour^{-1}$) with mild adverse reactions; and (c) calves 1 and 2 (FTP 2 μg kg^{-1} $hour^{-1}$) with no adverse reactions.

0.03 ng mL^{-1} for this assay. Substance P was measured using radioimmunoassay.

Statistical analysis

Based on the occurrence and severity of adverse events observed in calves, three study groups were retrospectively defined: 1) severe adverse reactions with increases in physiologic variables and recumbency (group SA); 2) mild adverse reactions with increases in physiologic variables (group MA); and 3) no adverse reactions (group NA). Plasma fentanyl concentrations at the time of adverse reactions among SA, MA and NA were compared using a Wilcoxon rank-sum test in R Version 3.3.2 (R Foundation, Austria). A p value < 0.05 was considered statistically significant.

Results

The first two calves were clinical patients. An FTP (2.0 μg kg^{-1} $hour^{-1}$) was placed 12 hours before an arthrotomy. Additional drugs administered were meloxicam (1 mg kg^{-1}; ZyGenerics, India) orally and daily and florfenicol (20 mg kg^{-1}; Nuflor; Merck Animal Health, NJ, USA) intramuscularly (IM) every 48 hours. No adverse events were noted (Table S1, online). The maximum plasma fentanyl concentration at 36 hours was 0.859 ng mL^{-1} in calf 1 and 6.92 ng mL^{-1} in calf 2 (Fig. 1). A noncompartmental pharmacokinetic analysis of fentanyl and plasma substance P concentrations for calves 1 and 2 are reported (Table S2 & Fig. S2, online). Substance P values were variable amongst these calves. An initial depression was noted, but values for both calves increased while FTPs were applied.

FTP (2 μg kg^{-1} $hour^{-1}$) was administered to calves 3 and 4. Severe adverse events were noted (Table S1, online). Calf 3 was a healthy calf aged 27 days. At 5 hours after FTP application, the calf developed ataxia progressing to recumbency and excessive vocalization (Video S1, online). At 6 hours, HR was 210 beats $minute^{-1}$, f_R was 72 breaths $minute^{-1}$ and RT was 40.5 °C. The patch was removed at this time, and naloxone (total 0.12 mg; Naloxone HCl; Hospira Inc., IL, USA) was administered intravenously (IV). Clinical signs were normal by 2 hours after patch removal. Plasma fentanyl concentration was 3.29 ng mL^{-1} at the time of patch removal.

Calf 4 was a male calf aged 120 days-old and presented for a nonresolving septic radiocarpal joint of 2 months duration. The calf underwent a radiocarpal joint curettage procedure for ankylosis. The FTP was applied before surgery and was removed 10 hours later when the calf exhibited tachycardia (180 beats $minute^{-1}$), hyperthermia (40 °C), pacing and excessive vocalization. Plasma fentanyl concentration at this time was 5.52 ng mL^{-1}. Naloxone was administered IV, and physiologic variables and behavior returned to normal within 2 hours.

The FTP dose for calves 5–7 was decreased to 1 μg kg^{-1} $hour^{-1}$. Mild adverse reactions (MA) were observed but did not include recumbency (Table S1, online). The calves were all healthy calves, aged 3–4 weeks. Tachycardia (174, 180 and 196 beats $minute^{-1}$ for calves 5, 6, and 7, respectively) were recorded at 4 hours after patch application, with excitement and increased vocalization; therefore, FTP were removed. At this time, plasma fentanyl concentrations for these calves were 0.73, 1.26 and 0.78 μg kg^{-1} $hour^{-1}$, respectively. No concentrations of fentanyl metabolites were detected in any blood sample.

After adverse effects were noted in the calves 5–7, the study was terminated for animal safety concerns. No long-term effects were observed in the calves that were not attributable to the underlying presentation, and all were healthy ≥ 6 months after the study. At the time of onset of adverse reactions (4–6 hours for all calves), the group plasma fentanyl concentrations were 1.85 ± 0.77, 0.92 ± 0.29 and 0.073 ± 0.038 ng mL^{-1} at 4 hours and 2.27 ± 1.44, 0.41 ± 0.17 and 0.072 ± 0.031 ng mL^{-1} at 6 hours for SA, MA and NA, respectively (Fig. S3, online). Pooled 4 and 6 hour fentanyl concentrations were significantly different for SA *versus* NA ($p = 0.03$), MA *versus* NA ($p < 0.01$) and SA *versus* MA ($p = 0.02$).

Discussion

Most publications regarding peculiar behaviors associated with fentanyl have been in goats. Dzikiti et al. (2011) found that goats display tail wagging in response to high- and low-dose fentanyl infusions. Activity increases have been noted in horses and goats (Dzikiti et al. 2011; Wetmore et al. 2016). Increased excitatory behaviors post-IV infusion, including star-gazing, itchiness, restlessness, paddling and bruxism, have been noted in goats (Dzikiti et al. 2016). By contrast, sheep were moderately sedated after FTP application (Christou et al. 2015).

Wide variations were noted in plasma fentanyl concentrations between calves. Factors that could have contributed to this include presence of disease and/or pain. It is not entirely clear as to why some calves had adverse effects and some calves did not. Interestingly, calves exhibiting adverse reactions also had high fentanyl plasma concentrations shortly after patch application, with a pattern resembling a 'burst' absorption into the systemic circulation. Conversely, calves with no adverse reactions had a more prolonged absorption of fentanyl in plasma, typical of extended release formulations. As both calves that exhibited no reactions had concurrent disease, and were administered other medications, it is possible that disease altered fentanyl metabolism, or a potential drug–drug interaction occurred. Disease and disease severity have been shown to alter drug pharmacokinetics in Holstein cattle, an example being the elimination of oxytetracycline based on metritis severity (Gorden et al. 2016). It has also been suggested that the risk of adverse effects to opioids is inversely related to the clinical disease or pain that the patient is experiencing (Muir 1981; Clutton 2010). This could be partially supported by this project, as two of the three calves with no observed adverse effects had pain from surgery as well as clinical disease, while all of the calves that were healthy experienced adverse effects. However, calf 4 would not support this, as this was a clinical case. A polymorphism of the G57C fentanyl opioid receptor has been identified in horses that leads to increased locomotor activity when administered fentanyl (Wetmore et al. 2016). It is currently unknown if cattle possess a similar polymorphism.

Limitations of this study include a small sample size and limited breed representation. The adverse effects noted were not anticipated; therefore, the authors deemed it prudent to decrease the patch dose from 2 μg kg^{-1} $hour^{-1}$ to 1 μg kg^{-1} $hour^{-1}$. After additional effects were observed, the decision was made to pause the study until more information could be assessed. Recording of physiological variables was limited and established at sample collection time points; therefore, it is possible that adverse effects could have been present for up to 90 minutes before being recorded and that other cardiopulmonary effects could have gone unnoticed. Additionally, more research is needed on the analgesic effects of fentanyl in calves including behavior, appetite, as well as pain biomarkers such as substance P.

In conclusion, fentanyl administered via FTP resulted in adverse effects in calves manifested by hyperthermia, tachycardia, tachypnea, recumbency, vocalization and increased locomotor response. These reactions were reversed by naloxone and/or FTP removal. Healthy calves may be more likely to display adverse effects of opioids as opposed to calves with clinical disease, although more research is necessary to investigate this further. Clinicians should exercise prudent judgment when utilizing FTP for calves, considering dosages below 1 μg kg^{-1} $hour^{-1}$ while realizing that the analgesic effects of fentanyl in cattle is currently unknown and should monitor these calves closely for adverse reactions.

Authors' contributions

JSS: study design, data acquisition, sample preparation, manuscript preparation. JPM: sample preparation, manuscript preparation. DJB: study design, sample preparation, manuscript preparation. KAL and JFC: study design, manuscript preparation.

Conflict of interest statement

Authors declare no conflict of interest.

References

Carroll GL, Hooper RN, Boothe DM et al. (1999) Pharmacokinetics of fentanyl after intravenous and transdermal administration in goats. Am J Vet Res 60, 986–991.

Christou C, Oliver RA, Rawlinson J, Walsh WR (2015) Transdermal fentanyl and its use in ovine surgery. Res Vet Sci 100, 252–256.

Clutton RE (2010) Opioid analgesia in horses. Vet Clin North Am Equine Pract 26, 493–514.

Dzikiti TB, Stegmann GF, Dzikiti LN, Hellebrekers LJ (2011) Effects of fentanyl on isoflurane minimum alveolar concentration and cardiovascular function in mechanically ventilated goats. Vet Rec 168, 429.

Dzikiti BT, Ndawana PS, Zeiler G et al. (2016) Determination of the minimum infusion rate of alfaxalone during its co-administration with fentanyl at three different doses by constant rate infusion intravenously in goats. Vet Anaesth Analg 43, 316–325.

Gorden PJ, Ydstie JA, Kleinhenz MD et al. (2016) A study to examine the relationship between metritis severity and depletion of oxytetracycline in plasma and milk after intrauterine infusion. J Dairy Sci 99, 8314–8322.

Marchionatti E, Lardé H, Steagall PVM (2015) Opioid-induced adverse effects in a Holstein calf. Vet Anaesth Analg 42, 229–230.

Muir WW (1981) Drugs used to produce standing chemical restraint in horses. Vet Clin North Am Large Anim Pract 3, 17–44.

Smith G (2013) Extralabel use of anesthetic and analgesic compounds in cattle. Vet Clin North Am Food Anim Pract 29, 29–45.

Smith JS, Coetzee JF, Fisher IWG et al. (2018) Pharmacokinetics of fentanyl citrate and norfentanyl in Holstein calves and effect of analytical performances on fentanyl parameter estimation. J Vet Pharmacol Ther. https://doi.org/10.1111/jvp.12501 [Epub ahead of print].

Wetmore LA, Pascoe PJ, Shilo-Benjamini Y, Lindsey JC (2016) Effects of fentanyl administration on locomotor response in horses with the G57C μ-opioid receptor polymorphism. Am J Vet Res 77, 828–832.

Received 23 October 2017; accepted 21 February 2018.

Available online 11 April 2018

Supporting Information

Supporting information related to this article can be found at https://doi.org/10.1016/j.vaa.2018.02.009.

Figure S1. Timeline.

Tables S1–S3 & Figures S2, S3. Additional data from individual calves and pooled 4 and 6 hour fentanyl concentrations by group.

Video Clip S1. Abnormal behavior in one calf.

