Evaluation of the analgesic and pharmacokinetic properties of transdermally-administered fentanyl in goats.

Megan J. Burke DVM; Lawrence R. Soma VMD; Raymond C. Boston PhD; Jeffery A. Rudy MS; Thomas P. Schaer VMD

From the Department of Clinical Studies, New Bolton Center Campus, 382 West Street Road, Kennett Square, PA (Burke, Soma, Boston), Pennsylvania Equine Toxicology & Research Center, West Chester University, West Chester PA (Rudy), and the University of Pennsylvania School of Veterinary Medicine, Center for Medical Translation, Comparative Orthopaedic Research Laboratory, 382 West Street Road, Kennett Square, PA (Schaer)

Address correspondence and reprint requests to: Thomas P. Schaer, VMD, University of Pennsylvania School of Veterinary Medicine, Center for Medical Translation, Comparative Orthopaedic Research Laboratory, 382 West Street Road, Kennett Square, PA 19348. Email: tpschaer@vet.upenn.edu

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ABSTRACT

Objective – Evaluate the analgesic properties and pharmacokinetics of transdermal fentanyl patches (TFPs) in goats

Design – Prospective, randomized study

Setting – Preclinical Testing Facility at a University Teaching Hospital

Animals – Thirty-four adult female Boer-cross goats

Interventions – Goats underwent surgery as part of a concurrent orthopedic research study. Twelve hours prior to surgery, each goat received a TFP (target dosage of 2.5 µg/kg/h), or a placebo patch with analgesia provided by buprenorphine (0.01 mg/kg, IM, q 6h). Patches were removed after 72 h. Blood was sampled at specified intervals, up to 84 hours following TFP placement. Plasma concentrations of fentanyl (FEN) were determined using liquid chromatography-mass spectrometry. Postoperative pain assessments were performed by two independent blinded observers.

Measurements and Main Results – TFPs were applied at a mean ($\pm$ standard deviation, SD) dose of 2.54 ± 0.36 µg/kg/h. No adverse events occurred. Pain scores between TFP and BUP groups were not significantly different at any time point. Mean plasma FEN concentration ($\pm$ SD) 2 hours following patch application was 1.06 ± 0.85 ng/mL, and remained above 0.5 ng/mL for 40h. Maximum mean plasma FEN concentration ($C_{\max}$) was 1.84 (ranging from 0.81-3.35) ng/mL with average time to maximum concentration ($T_{\max}$) of 12h after patch application.

Conclusions – TFP resulted in consistent FEN absorption and plasma concentrations within the human and ovine therapeutic ranges. Pain scores for goats administered TFP were not different

than those administered buprenorphine. Ease of administration, duration of analgesia, and decreased dosing frequency make TFPs an attractive option for pain management in goats.

ABBREVIATIONS

AUC_0^{∞} - Total predicted area under the plasma concentration curve from 0 to infinite time

BUP – Buprenorphine

C_{max} - Maximum plasma fentanyl concentration

$C_p(t)$ - Plasma fentanyl concentration at time t (pharmacokinetic variable)

D - dose (pharmacokinetic variable)

FEN – Fentanyl

k_e - Elimination rate constant (pharmacokinetic variable)

k_t - Transfer rate constant (pharmacokinetic variable)

LC-MS – Liquid chromatography – mass spectrometry

t – Time (pharmacokinetic variable)

TFP – Transdermal fentanyl patch

t_{lag} - lag time (pharmacokinetic variable)

T_{max} - Time to reach the maximum plasma fentanyl concentration

TPP – total plasma protein

V - Estimated volume (pharmacokinetic variable)

Introduction

Goats are a popular large animal model for preclinical surgical studies.¹⁻⁵ Additionally, they are used to produce meat and milk, and are kept as companion animals. When working with goats in either a research or clinical setting, it is the responsibility of veterinarians to select an effective and rational analgesic protocol. Transdermal fentanyl patches (TFPs) contain fentanyl citrate, a μ -agonist opioid approximately 100 times more potent than morphine.⁶ Fentanyl (FEN) patches are commonly used to provide analgesia in humans and have been used in an extra-label manner for veterinary species.⁷⁻¹⁵ Recently, a non-patch transdermal fentanyl product was approved for use in dogs.¹⁶ Transdermal fentanyl patches have potential applications in small ruminant medicine and surgery because they may provide a long duration of analgesia, mitigating the need for multiple daily administrations of analgesic drugs.

The pharmacokinetics of transdermally-administered FEN in goats was previously reported using a radioimmunoassay for FEN validated in goat plasma.⁷ Results indicated that administration of FEN via a transdermal patch resulted in variable plasma concentrations that occasionally exceeded anticipated plasma concentrations based on the theoretical delivery rate of the drug from the patch. To our knowledge, evaluation of the postoperative analgesic efficacy of TFPs in goats undergoing orthopedic surgery has never been investigated. Liquid chromatography-mass spectrometry (LC-MS) has also been used to quantify FEN concentrations in plasma and other fluids.¹⁵⁻²⁰

The goals of this study were to compare the clinical analgesic efficacy of TFPs to intramuscular buprenorphine (BUP) in goats following an orthopedic surgical procedure, and to evaluate the

pharmacokinetics of FEN from TFPs using LC-MS. We hypothesized that TFPs placed on the antebrachium of goats would result in consistent plasma FEN concentrations and provide analgesia that was equivalent to that provided by intermittent intramuscular administration of BUP.

Materials and methods

This study was approved by the University Institutional Animal Care and Use Committee. Thirty-four adult female Boer-cross goats concurrently enrolled in a preclinical trial investigating the efficacy of articular cartilage resurfacing of the medial femoral condyle were enrolled in this study. Goats were between 3-5 years of age, with a mean ($\pm$ standard deviation, SD) weight of 36.6 ± 5.6 kg. Goats were maintained in 12 x12 foot stalls in groups of 4-6 animals per stall for the duration of the study, and were fed a maintenance diet of timothy hay and formulated goat feed. Water was available *ad libitum*.

Twelve hours prior to surgery, an intravenous catheter^h was placed in either the right or left jugular vein using aseptic technique. The catheter was retained for the duration of the study and used to obtain all blood samples. Blood for a preoperative CBC, serum biochemistry panel, and plasma fibrinogen concentration was obtained from each goat, in addition to measurement of PCV, total plasma protein (TPP), and body temperature. The catheter was flushed with heparinized saline every 12 hours to maintain patency throughout the trial.

Drug administration and sample collection

Goats used in this study were concurrently enrolled in a joint resurfacing trial, which dictated the size of each experimental group.²¹ Goats were randomly allocated into 2 analgesic treatment groups using a random number generator. Twenty-four goats were administered TFPs^a and 10 goats received a placebo patch, with analgesia provided with BUP^b (0.01 mg/kg, IM, q. 6h, for

60 h after surgery and 72 hours after placebo patch placement). The first dose of BUP was provided at the induction of anesthesia. For animal welfare reasons, there was no negative control group for this study. Goats in both groups received phenylbutazone^c (2.2 mg/kg, IV, q. 24 h), with the first dose given at the induction of general anesthesia. The target dose of FEN (2.5 µg/kg/h) was extrapolated from a recommended dosage of 2-4 µg/kg/h for dogs.²⁰ Twelve h prior to surgery, the goats in the TFP group received one or a combination of 2.5, 5, 7.5 or 10-µg/h TFPs to achieve the targeted dosage. The hair on the antebrachium ipsilateral to the hind limb selected for surgery was clipped with a No. 40 clipper blade circumferentially from the cubital joint to the carpus. The skin on the lateral aspect of the antebrachium was then shaved, taking care not to traumatize the skin. The site was cleaned with gauze sponges soaked in dilute chlorhexidine^d for 30 sec. The site was then wiped using gauze sponges soaked in isopropyl alcohol for 30 sec to remove the chlorhexidine. The skin was then allowed to air-dry for 2 minutes. The required combination of patches was applied to the skin and held in place for 30 seconds. Patches were then covered with 2 circumferential layers of adhesive bandage^e, and the proximal and distal borders secured with white tape^f. Care was taken to ensure that patches did not fold or crease during bandage application.¹⁴ Patches were removed 72 h after application and examined for folds or creases prior to disposal. Goats in the group designated to receive BUP had their antebrachium prepared in the same manner 12 h prior to surgery and a placebo patch^g applied as for the FEN group. Seventy two hours after placement, the placebo patches were removed.

Blood samples were collected from all goats prior to patch placement (time 0), and at 2, 4, 6, 8, 12 (time of surgery), 24, 36, 48, 60, 72, and 84 h following patch application. Blood samples were collected into lithium heparinized tubes and gently mixed for 30 seconds. Within 1 hour of

blood collection, plasma was obtained via centrifugation (2,500 X g for 15 minutes) and stored at -80°C until analyzed.

Surgical procedure

Twelve hours following TFP or placebo patch application, goats underwent a unilateral stifle arthrotomy under general anesthesia. The surgical procedure involved the creation of an osteochondral defect 7 mm in diameter and 8 mm deep in the central portion of the medial femoral condyle. Prior to anesthesia, all goats were sedated using diazepamⁱ (0.3 mg/kg, IV, with additional doses of 0.1 mg/kg, IV as required) until sternal recumbency was attained. Anesthesia was induced using 2% lidocaine^l (2.2 mg/kg, IV) and 5% thiopental^k (2.2 mg/kg, IV, to effect) and maintained with isoflurane^l in 100% oxygen delivered at 2-3 L/min using a semi-closed circle anesthetic system. Mechanical ventilation was used when determined necessary by the anesthetist. Criteria for instituting mechanical ventilation included but were not limited to decreased respiratory rate, hypercapnea, and hypoxemia. The patch application site was elevated above the level of the surgery table to ensure air circulation and to prevent the application of excessive heat from patient warming devices. Following anesthetic induction and immediately after creation of the osteochondral defect in the medial femoral condyle, the isoflurane vaporizer setting, respiratory rate, tidal volume, airway pressure, and estimated hemoglobin oxygen saturation were recorded for all goats. The time to endotracheal extubation after conclusion of surgery was also recorded for each goat (Table 1). After surgery, goats were hand-recovered on a mat. All goats received procaine penicillin G^m (22,000 IU/kg, IM, q12 h), and gentamicinⁿ (6.6 mg/kg, IV, q 24 h) for 3 days, starting at the induction of anesthesia.

Postoperative monitoring

Goats were returned to their stalls following recovery from general anesthesia. For the first 3 days postoperatively, goats were monitored hourly by registered or licensed veterinary technicians employed by the university, but not affiliated with the research. In addition, goats were assessed every 12 h by a non-blinded veterinarian involved with the study, with the first assessment occurring immediately after anesthetic recovery.

Pain assessments were performed by 2 independent veterinarians unaffiliated with the surgical research, and unaware of the details of the surgical procedure or treatment groups. To remove the confounding effects of general anesthesia, the first assessment by these veterinarians was performed 24 h after surgery (36 h after application of the placebo or TFP). For the goats in the BUP group, this first timepoint corresponded to 2 h after the administration of the fourth dose of BUP. Assessments were performed at 12 h intervals, for a total of 5 assessments. At all timepoints, a rescue analgesic protocol was in place in the event of inadequate analgesia (see below).

The pain assessment scoring rubric used in this study has been used extensively by our group to assess pain in small ruminants and pigs following surgery (Table 2).¹⁴ Goats were scored as being either mentally alert or having signs of mental dullness, with no gradations. Respiratory rate was scored as normal or abnormal in relation to clinically normal goats at a given ambient temperature. Willingness of the goats to rise from recumbency was evaluated and scored. Once standing, goats were evaluated for comfort on the operative limb by assessing and recording the presence or absence of weight shifting and willingness to ambulate. Comfort during ambulation was evaluated by watching goats move around the 12 x 12 foot stall, noting their gait and ability to stay with the group. The surgical site was palpated, and the degree of painful reaction was scored. Appetite was evaluated by response to offering fresh hay, as well as evaluation of rumen motility in each goat.

The final pain assessment was performed at 84 h, 12 h after TFP removal or the last dose of BUP. At any point during the postoperative period, rescue analgesia was available in goats with a pain score > 15, or if a goat was determined to have inadequate analgesia following evaluation by veterinary nurses or non-blinded study veterinarians. Available rescue analgesics included BUP (0.01-0.03 mg/kg, IM or IV), or butorphanol tartrate^o (0.01 mg/kg, IV or IM).

Plasma fentanyl analysis

All plasma samples were analyzed on the same day, using previously described LC-MS methodology.^{12,15,19} Fentanyl citrate standard^p (0.05 mg/mL) was used, and the internal standard was d-₉ clenbuterol^q (200 µg/mL in methanol stock solution). Water, acetonitrile-methyl tert-butyl ether, ammonium hydroxide and formic acid were of analytical quality^r.

Working solutions were prepared from reference materials in 50:50:1 acetonitrile:water:formic acid at 0.1, 2.5, 5.0, 7.5, 10, 50, 1, and 100 ng/mL. Calibration curves were prepared in drug-free goat plasma containing 1% NaF to inhibit plasma cholinesterase activity. A calibration curve was prepared in 0.9 mL of negative control plasma using 0.1 mL of the working solutions. Positive controls were similarly prepared in duplicate at 0.5 and 5 ng/mL. Calibrators and controls were analyzed in duplicate. Negative control plasma samples (with and without internal standard) were analyzed with each analytical batch. Working solutions were stable throughout the duration of the analysis.

For sample preparation and extraction, 1 mL of ammonium hydroxide solution (1:1 ammonium hydroxide:water) was added to 1 mL of calibrators, controls, and test samples. The internal standard (0.1 mL of 100ng/mL d₉ clenbuterol working solution) was added to all calibrators, control samples (except 1 of 2 negative controls), and test samples, and mixed by vortex for 15 seconds. Methyl tert-

butyl ether (5 mL) was added to all tubes, which were then capped and mixed by roto-rack for 10 minutes prior to centrifugation at 377 x g for 10 minutes. The organic layer was transferred to clean borosilicate tubes and evaporated to dryness at 65°C under a steady stream of nitrogen. The residues were reconstituted in 100 µL of 0.1% formic acid in water and transferred to 2 mL auto-sampler vials fitted with 0.2 mL limited-volume inserts. Analyte recovery from the matrix was 94.5%.

Analysis of the sample extracts was performed using a linear ion trap interfaced to a liquid chromatograph and auto-sampler⁵. Analysis was performed in positive ion electrospray mode. The mobile phase comprised 2.33 mM aqueous formic acid (A; pH 6) and 0.1 % formic acid/acetonitrile (B). The pump was operated in a linear gradient from 15% A to 100 % B at 0.2 mL/min at ambient temperature for 4 minutes with 1 minute hold time at 100 % B. The system was re-equilibrated to initial conditions for 1 min. Total cycle time per sample was 7.5 min. Chromatographic separation of analytes was achieved using a fused core HALO C₁₈ column^t (2.7 µm particle size, 2.1 x 50 mm). The electrospray ionization source was operated with a positive spray voltage of 5.5 kV and sheath gas (high purity nitrogen) of 18 arbitrary units. The capillary temperature was 350°C. Ion trap settings for tandem mass spectrometry analyses were as follows: FEN protonated molecular ion [M+H]⁺ at m/z 337.3, collision energy of 20 eV; norfentanyl protonated molecular ion [M+H]⁺ at m/z 233.1, collision energy of 20 eV; hydroxyfentanyl protonated molecular ion [M+H]⁺ at m/z 353.3; collision energy of 26 eV wideband, and d₉ clenbuterol protonated molecular ion [M+H]⁺ of m/z 286.2, collision energy of 23 eV wideband. Product ions monitored for quantitative analysis were FEN (m/z 188, 216), norfentanyl (m/z 84), hydroxyfentanyl (m/z 188, 204), and clenbuterol (m/z 204, 268).

Quantitative analysis

Analytes were quantified by use of liquid chromatography acquisition software^u. Calibrations and determinations of unknown samples were the summed ion currents of the product ions. A linear un-weighted calibration curve with forced zero intercept was used for FEN quantification. Limit of quantification was 10 pg/mL. The standard operating procedures for the quantification of analytes by this laboratory meet requirements for accreditation by the American Association for Laboratory Accreditation and ISO 17025 International Guidelines.

Pharmacokinetic analysis

A one-compartment first-order absorption model was fitted to the plasma FEN concentration-versus-time curves from each goat using conventional nonlinear least-squares regression analysis^v. The Gauss-Newton (Levenberg & Hartley) algorithm²² was used for the fitting process. A number of weighting schemes were applied to the data with and without a lag time, and the $1/(Y*Y)$ weighting scheme with a lag time provided the best fit based on the appearance of predicted and observed concentrations and the Akaike's information criterion.^{23,24} Macro constants for FEN were estimated from the following equation:

$$C_p(t) = D * k_t / V / (k_e - k_t) * (\exp(-k_e * t - t_{lag}) - \exp(-k_t * t - t_{lag}))$$

Where $C_p(t)$ was plasma concentration at time t , k_t and k_e were transfer and elimination rate constants, respectively, D = dose, t = time, t_{lag} = lag time, and V = estimated volume.²⁵ The total area under the plasma concentration curve from 0 to infinite time (AUC_0^∞) was calculated using linear trapezoid-linear interpolation plus end area correction which was the last plasma concentration ($C_{p(t^*)}$) to ∞ and estimated by $C_{p(t^*)}/k_e$, where k_e was the relevant terminal

elimination rate constants.²⁶ Half-lives were calculated as $\ln 2$ divided by the exponents. Maximum plasma concentration ($C_{\max}$), and the time to reach the maximum plasma concentration ($T_{\max}$) were derived from the plasma concentration time-curve.

Statistical analysis

Intraoperative variables between FEN and BUP groups were compared using Kruskal-Wallis rank tests, and paired t-tests.^w Initial analysis of postoperative pain scores and intra-observer differences in pain scoring using a Wald test indicated a non-normal distribution. Prior to analyzing the intra-observer variability and pain score data using linear regression, bootstrapping was performed to ensure that parametric tests could be used to analyze data despite a non-normal distribution. Pharmacokinetic parameter estimates of FEN were expressed as median and range, and plasma concentrations of FEN were expressed as mean and standard deviation. Significance was set at $P < 0.05$ for all analyzed variables.

Results

There were no complications associated with intravenous catheter insertion sites, application or removal of placebo patches or TFPs, or administration of intramuscular BUP. The mean body weight of the animals was 36.6 ± 5.6 kg with no significant difference between TFP and BUP groups. Preoperative PCV, TPP, and WBC count were within established reference intervals for all animals. Surgeries were performed without complications, and all goats recovered from anesthesia uneventfully. Wound healing was appropriate in all animals, and no postoperative adverse effects associated with the surgical procedure occurred. All animals reached their designated survival time without incident. There was no significant difference between the TFP and BUP groups in the amount of diazepam needed to produce sternal recumbency, or the in amount of

thiopental needed to induce general anesthesia. There were no significant differences between the TFP and BUP groups for any measured intraoperative variable. Additionally, there were no significant changes in the measured variables at induction compared to time of osteochondral defect creation in either group (Table 1).

No goat required rescue analgesia at any timepoint, and pain scores did not approach the rescue threshold in any animal. No significant intra-observer difference in pain scores was noted over the course of the study. A kappa score of 0.50 indicated fair to moderate agreement between observers. Regardless of treatment group, pain scores for all goats decreased with time. Between 36 and 72 hrs, pain scores for goats in the TFP group were lower than those for the BUP group, however the differences were not statistically significant at any time point ($P = 0.215$, Figure 1).

Pharmacokinetic analysis

The mean rate of FEN administered in this study was $2.54 \pm 0.36 \mu\text{g/kg/h}$, or a mean of 9.25 ± 1.63 mg administered per goat. The pharmacokinetics of the plasma concentrations of FEN following transdermal patch administration was described by a transfer and elimination model with first-order transfer into, and elimination from, the central compartment (Figure 2). Estimated pharmacokinetic behavior is described in Table 3. The median transfer and elimination half-lives were 3.05 (0.22 - 14.02) and 11.3 (0.8 - 17.9) h respectively. Fentanyl was quantifiable in all goats at 84h, with a mean plasma concentration of $0.030 \pm 0.024 \text{ ng/ml}$.

Discussion

There was no statistically significant difference in pain scores between the experimental cohorts in this study. This is in contrast to previous work by our group comparing TFP and BUP in sheep using an identical analgesic protocol.¹⁴ Regardless of treatment group, pain scores ranged

from 8 – 10 out of a possible score of 20 at the first evaluation time point (24 h postoperatively, Figure 1). This corresponds to a moderate degree of pain. Pain scores recorded for goats during the postoperative period were substantially higher than those seen by our group in sheep (where a maximum score of 5.5 out of 20 was observed 24 hours following a procedure for placement of a bone plate).¹⁵ Based on our experience, the parapatellar arthrotomies of the femoro-tibial joint performed in small ruminants cause a greater degree of soft tissue pain when compared to the incisions for long bone plating used in the sheep trial reported by Ahern et al, which may account for the differences.¹⁴ Additionally, behavioral differences between sheep and goats may have contributed to the divergence in pain scores between these two species, as sheep are particularly stoic when compared to other species used in laboratory research.²⁷

Goats administered FEN via TFP had lower mean pain scores than those that received BUP at all timepoints; however, the difference was not significant at any point. It is possible that FEN does provide superior analgesia to BUP, and due to the relatively small sample sizes in our study it was subject to Type II error. Therefore, it may be valuable to investigate larger cohorts to achieve sufficient analytical power to determine if differences in pain scores can be identified. Conversely, it may be that FEN and BUP both provide equivalent and adequate analgesia after orthopedic surgery in goats. The analgesic equivalence between FEN and BUP shown in this model affords flexibility to the clinician in the choice of analgesic regimen. Moreover, use of the transdermal patch application system available with FEN significantly mitigates the logistical needs of q6 hours BUP administration for already strained hospital systems.

The plasma FEN concentration required to achieve analgesia in goats has not been established. Concentrations of 0.5 – 2.0 ng/mL are associated with analgesia in humans, and this number has been extrapolated to animal species.^{8,21,28} In people, plasma FEN concentrations greater

than 2.0 ng/ml can cause clinically significant respiratory depression.²⁹ A review of the veterinary literature revealed isolated cases of respiratory depression in animals receiving TFPs. However, clinically relevant respiratory depression did not appear to correlate with increasing plasma FEN concentrations in the species evaluated.²⁰ In our study, clinical signs of respiratory depression were not observed at any time while the TFPs were in place. The only complication attributable to the TFP observed in previous work from our group on sheep^{14, 15} is an occasional prolonged anesthetic recovery. Opioid reversal using naloxone combined with TFP removal effectively addressed this complication in all instances.

In the present study, TFP application resulted in plasma concentrations > 0.5 ng/ml as early as 2 h after patch placement. Mean plasma FEN concentration decreased below this threshold to 0.35 ± 0.16 ng/ml at 40 h after patch application. The median time to peak plasma FEN concentration was 12 h (range 2-36 h). These results are similar to those reported in sheep.¹⁵ When these values are compared to cats and dogs, the time taken to reach plasma FEN concentrations of 0.5 ng/ml in goats was substantially shorter than for cats (5-8 hours), or dogs (6 hours), while the T_{max} was similar for goats and cats (8-12 hours), but much longer for dogs (24-36 hours).^{9,21}

For maximal analgesic efficacy, patches should be applied to goats approximately 12 h before the start of surgery, which will account for variability of absorption among animals. If patches are applied less than 12 hours before surgery, or are used for pain management in non-surgical cases, supplementary analgesics may be necessary until analgesia plasma FEN concentrations have been reached. Plasma concentrations of FEN were quantified for 84 h in this study using a single patch application, while they were undetectable at the 84 h timepoint in 5/6 goats in the prior report.⁷ No adverse effects associated with patch application were noted. No animals in our study interfered with their patches. However, careful monitoring should be

emphasized when patches are used in goats, as they are more inquisitive than sheep, and accidental ingestion could result in serious adverse effects.

The TFP studied herein resulted in consistent FEN absorption, with less variability in plasma concentrations compared to a previous study in 8 goats.⁷ The previous report used a radioimmunoassay to determine plasma FEN concentrations, and reported C_{max} that varied between 1.12 - 16.69 ng/mL (with an average TFP dosage of 1.25 µg/kg/h), while the present study had less variability, with C_{max} ranging between 0.62 - 2.73 ng/mL.

Several factors may have contributed to the variation seen in the previous report. Differences in the patch location and application protocol may have decreased uptake variability in the present study. In the work by Carroll et al., patches were placed on the neck. Skin was clipped but not cleaned prior to application, and a gauze pad was placed between the patch and the elastic tape used to anchor the patch. In that report, 2 of 8 patches were folded or inadequately adhered at the time of removal. In the present study, patches were applied to the lateral aspect of the antebrachium after careful clipping and cleaning of the site, and nothing was placed between the patch and the elastic tape anchoring it in place. The antebrachium was chosen as the patch application site after extensive pilot trials in our laboratory aimed at optimizing drug delivery (unpublished data). No folding or inadequate adherence was noted in the present study. The presence of the gauze pad in the previous study may have promoted patch movement, increasing the risk of folding or poor adherence. Additionally, dirt or secretory material present on the skin surface because of the lack of skin preparation in the previous study may have resulted in non-uniform absorption of FEN from the site of patch application. In addition, studies of human plasma FEN concentrations have shown that radioimmunoassay analysis can overestimate plasma FEN concentrations by 30-100% compared with <7% with LC-MS.²⁹

Although effects on the goat epidermis have not been specifically studied, it is accepted that use of chlorhexidine which is cytotoxic, or polar solvents like alcohol can cause changes to the stratum corneum, and potentially alter transdermal drug uptake.³⁰⁻³⁴ Chlorhexidine removes layers of stratum corneum, reducing barrier function, while alcohol decreases the lipid content of skin. Given these effects, uptake of FEN after application of polar solvents may be increased. However, work by Harada et al. showed that the absorption of highly lipophilic substances like FEN are almost unchanged after application of polar solvents.³⁰ This suggests that the skin preparation protocol used in this study should not alter FEN absorption from the patch.

When pharmacokinetic parameters for FEN administered via a TFP in goats were compared to previous reports in sheep, values were equivalent for C_{max} , T_{max} , elimination half-life ($t_{1/2el}$) and elimination rate constant (k_{el}). However, the transfer rate constant from patch to animal (k_t) was two times greater in goats than in sheep.¹⁵ The increased transfer time from patch to plasma in goats relative to sheep may be related to differences in dermal characteristics between species. Additionally, fentanyl is a highly lipophilic drug. Therefore, differences in amount and distribution of adipose tissue may also explain the difference in transfer rate constant for these two species. There were no significant differences in pre- or intraoperative data between the TFP and BUP groups. This is in contrast to reports in sheep, where the TFP group required significantly less preoperative diazepam to achieve sternal recumbency than the BUP group.¹⁴ Differences in the amount of diazepam required to achieve sternal recumbency in sheep versus goats is likely explained by differences in temperament between the two species. Fentanyl, like other opioids, can augment sedation created by benzodiazepines.³⁵ In general, sheep display less stress during routine handling than do goats.^{3,27} Therefore, it is not unreasonable to assume that a TFP would provide more effective augmentation to diazepam sedation in sheep compared to goats.

Buprenorphine was selected as a comparison to TFPs because of its long duration of action and because it is frequently used for analgesia in goats in clinical and research settings.³⁶ Buprenorphine doses above 0.01 mg/kg were not used because a prior report of doses higher than 0.02 mg/kg, IM, resulted in agitation and decreased rumen motility in healthy, lactating goats, for at least 7 hours after a single administration.³⁶ These adverse effects were not seen in our study, but it is important to monitor animals receiving opioids for signs of decreased gastrointestinal motility and agitation.

One limitation of this study was the concomitant administration of phenylbutazone with either FEN or BUP in all study animals. It is incumbent on researchers to provide adequate postoperative analgesia for animals enrolled in surgical studies, and this potential confounder was unavoidable. However, because both the TFP and BUP groups received the same anti-inflammatory regime, the contribution of phenylbutazone to pain relief should be consistent between treatment groups, with any difference in pain scores between groups due to the opioid. Although not commonly administered to ruminants, phenylbutazone was chosen for use in this study because it is permitted for extra-label use in goats, our laboratory has had excellent clinical experience with its use in orthopedic models, and it has shown efficacy for controlling pain in goats.³⁷

The use of TFPs in goats showed robust equivalence in treating postoperative pain in goats when compared to every 6 h IM injection of BUP. This finding, along with the ease of patch application, prolonged duration of analgesia, and a reduced dosing frequency support the use of TFPs as an alternative to BUP for the management of postoperative pain in goats. Appropriate skin preparation and patch application may have been important for achieving uniform patch contact with underlying skin, and may have resulted in sustained absorption of FEN from the patch. Although the goats in this study were used in surgical research, the information provided by this study used in

compliance with guidelines set out in the Animal Medicinal Drug Use Clarification Act can serve as a guide to utilizing TFPs in clinical practice for the provision of analgesia to goats.^{37,38}

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- a. Duragesic, Janssen Pharmaceutica, Titusville, NJ
- b. Buprenex, Hospira Inc, Lake Forest, IL
- c. Phenylbutazone, Baxter, Deerfield, IL
- d. Novalsan, Pfizer, Collegeville PA
- e. Elastikon, Johnson & Johnson, New Brunswick, NJ
- f. Zonas Porous Tape, Johnson & Johnson, New Brunswick, NJ
- g. Duragesic Placebo, Janssen Pharmaceutica, Titusville, NJ
- h. BD Angiocath, Becton Dickinson, Franklin Lakes, NJ
- i. Diazepam, Hospira Inc, Lake Forest, IL
- j. Lidocaine, Pheonix Pharmaceutical Inc, St Joseph MO
- k. Thiopental, Abbott Laboratories, North Chicago, IL
- l. Isoflurane, Abbott Laboratories, North Chicago, IL
- m. Penicillin, MWI Veterinary Supply, Boise, ID

- n. Gentamicin, Pheonix Pharmaceutical Inc, St Joseph MO
- o. Butorphanol tartrate, Fort Dodge Animal Health, Overland Park, KS
- p. Sublimaze Janssen Pharmaceutica, Titusville, NJ
- q. Neogen Corporation, Lexington, KY
- r. ThermoFisher Scientific Pittsburgh, PA
- s. LC-MS (LXQ) and Surveyor auto-sampler, ThermoFisher Scientific, San Jose, CA
- t. Mac-Mod Analytical, Chadds Ford, PA
- u. Excalibur software v. 2.0 Quan Browser, ThermoFisher Scientific, San Jose, CA
- v. Phoenix WinNonLin 6.3, Pharsight, Cary NC
- w. Stata, version 10.0, StatCorp, College Station, TX

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Table 1 * . Mean $\pm$ standard deviation of intraoperative data obtained from goats in 2 study groups (buprenorphine n = 10, fentanyl n = 24) that underwent unilateral stifle arthrotomy and creation of an osteochondral defect on the medial femoral condyle.

Intra-op Data	Buprenorphine	Fentanyl
Iso % (Ind)	2.8 ($\pm$ 0.9)	2.7 ($\pm$ 0.5)
Iso % (OD)	2.0 ($\pm$ 0.6)	2.0 ($\pm$ 0.9)
RR/min (Ind)	14.1 ($\pm$ 5.7)	13.8 ($\pm$ 7.7)
RR/min (OD)	14.1 ($\pm$ 9.5)	15.2 (6.9)
Vt ml (Ind)	325 ($\pm$ 106)	265 ($\pm$ 125)
Vt ml (OD)	330 ($\pm$ 99)	283 ($\pm$ 136)
Paw cmH ₂ O (Ind)	15.0 ($\pm$ 7.1)	16.0 ($\pm$ 3.6)
Paw cmH ₂ O (OD)	15.0 ($\pm$ 7.1)	16.8 ($\pm$ 5.1)
SpO ₂ % (Ind)	96.4 ($\pm$ 1.6)	96.9 ($\pm$ 1.7)
SpO ₂ % (OD)	96.1 ($\pm$ 1.9)	97.0 ($\pm$ 1.7)
Extub.(mins)	18.3 ($\pm$ 8.2)	19.8 ($\pm$ 7.9)

Iso = Isoflurane vaporizer percentage setting; RR = respiratory rate; Vt = tidal volume; Paw = airway pressure; SpO₂ = oxygen saturation; Extub = time to extubation; Ind = time of induction; OD = time osteochondral defect was completed. * No statistically significant differences.

Table 2. Pain Assessment Scoring System (0 to 3); Zero is the score for completely normal goats and 20 is the highest possible cumulative abnormal score.

Parameters	0	1	2	3
Mental assessment	Normal and alert			Depressed
Respiratory rate	Normal		Abnormal (slow or panting)	
Recumbency	Normal	Slightly delayed rising	Requires encouragement to stand	Unwilling or unable to stand
Shifting weight	Normal	Mild / occasional	Moderate	Constant shifting
Herd movement	Normal	Occasionally trails herd	Regularly trails herd	Consistently apart from herd
Appetite	Normal	Mildly reduced interest	Moderately reduced interest	Anorectic
Palpation of surgical site	Pain free	Mild pain	Moderate pain	Severe pain

Table 3. Pharmacokinetic parameter estimates of fentanyl (median and range) obtained by use of transdermal fentanyl patches at 2.54 $\mu\text{g kg h}^{-1}$

Parameter	Median (Range)
k_t (/h)	0.23 (0.05 – 3.05)
$t_{1/2t}$ (h)	3.05 (0.22 – 14.02)
k_{el} (/h)	0.06 (0.04 – 0.86)
$t_{1/2el}$ (h)	11.3 (0.8 – 17.9)
AUC_0^∞ (ng•h/mL)	49.8 (26.5 – 80.8)
AUC_0^{last} (ng•h/mL)	48.9 (25.7 – 79.4)
T_{max} (h)	12.0 (2.0 – 36.0)

¹ ± 0.36 applied to 27 goats.

k_t = transfer rate constant; k_{el} = elimination rate constant; $t_{1/2t}$ = transfer half-life; $t_{1/2el}$ = elimination half-life; AUC_0^∞ = Area under the curve to infinity; AUC_0^{last} = Area under the curve-last value - 84 hr; T_{max} = time to maximum concentration; C_{max} = maximum concentration.

Figure 1 **. Box plot of mean ($\pm$ standard deviation) combined observer pain scores at each time point. Buprenorphine (cross hatches), fentanyl (black). **No statistically significant differences.

Figure 2. Plasma concentration (Mean $\pm$ standard deviation) of fentanyl in 27 goats following transdermal administration at a rate of $2.54 \pm 0.36 \mu\text{g kg h}^{-1}$. Solid line is the line of best fit of the predicted data.

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Author/s:

Burke, MJ;Soma, LR;Boston, RC;Rudy, JA;Schaer, TP

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