Comparison of the analgesic properties of transdermally administered fentanyl and intramuscularly administered buprenorphine during and following experimental orthopedic surgery in sheep

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Objective—To evaluate the analgesic properties of transdermally administered fentanyl and IM administered buprenorphine in sheep undergoing unilateral tibial osteotomy.

Animals—20 mature sheep.

Procedures—Fentanyl patches (n = 15 sheep) or placebo patches (5 sheep) were applied 12 hours before sheep underwent general anesthesia and a unilateral tibial osteotomy. Buprenorphine was administered to the placebo group every 6 hours commencing at time of induction. Signs of pain were assessed every 12 hours after surgery by 2 independent observers unaware of treatment groups.

Results—There were no differences in preoperative and intraoperative physiologic data between the 2 groups. Sheep treated with fentanyl required less preoperative administration of diazepam for sedation and had significantly lower postoperative pain scores, compared with those treated with buprenorphine. No complications associated with the antebrachium at the site of patch application were detected.

Conclusions and Clinical Relevance—Under the conditions of this study, transdermally administered fentanyl was a superior option to IM administered buprenorphine for alleviation of postoperative orthopedic pain in sheep. This information can be used to assist clinicians in the development of a rational analgesic regimen for research and clinical patients. (*Am J Vet Res* 2009;70:418–422)

The use of animals is an essential component in the development of medical instrumentation, pharmaceuticals, biomaterials, and many other devices used in human and veterinary medicine. Sheep have been used in preclinical animal trials for decades.[1–3] The care and welfare of sheep enrolled in such trials is of utmost importance, and efficacious pain management plays a central role. The selection of appropriate analgesics is a consideration researchers must be aware of during study planning. Presently, various protocols are used and include NSAIDs, opioids, local anesthetics, and glucocorticoids. Most of these medications are administered via IV or IM injection and often require multiple daily administrations for maintenance of adequate analgesia. Transdermally applied fentanyl patches are another modality that has become available to researchers; however, there is a paucity of data available regarding their use in large animals. The analgesic in transdermal patches is fentanyl citrate, a μ-agonist opioid, which is approximately 80 to 100 times as potent as morphine.[4,5] Fentanyl patches are commonly used for human analgesia and have increasingly been used off-label for veterinary applications.[6–11] The fentanyl patch has many potential applications in ovine surgical research to provide reliable, minimally invasive, extended analgesia. The analgesic effect of transdermally administered fentanyl in sheep, interanimal variability, and assessment of the antebrachium for ease and efficacy of patch application have not been published. As such, the study reported here was designed to evaluate the analgesic properties of transdermally administered fentanyl, compared with IM administered buprenorphine, in sheep undergoing unilateral tibial osteotomy.[12] Our hypothesis was that fentanyl patches, placed on the antebrachium of sheep, would provide consistent analgesia that was superior to that provided by intermittent IM administration of buprenorphine.

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Materials and Methods

Animals—Twenty adult Polypay-cross ewes were used in this study. All sheep were 3 to 5 years of age and weighed a mean ± SD of 63.0 ± 8.2 kg. All sheep were

concurrently enrolled in a tibial osteotomy research trial. Sheep were housed in 4 × 4-m hospital stalls, in groups of 4 to 6, for this component of the study. All sheep were fed a maintenance diet of timothy hay and a daily ration of formulated sheep feed.

Study protocol—The study was conducted according to the guidelines set forth by the University of Pennsylvania Institutional Animal Care and Use Committee. All sheep were screened to ensure good physical condition and were acclimatized to their new environment for 14 days prior to surgery. Twenty sheep were randomly allocated into 2 groups. One group consisted of 15 sheep that received transdermally administered fentanyl[a] dosage of 2 µg/kg/h. The remaining 5 sheep received buprenorphine,[b] IM, at a dosage of 0.01 mg/kg every 6 hours for 60 hours following surgery. All sheep were weighed 12 hours prior to surgery and allocated into a study group. The required dose of fentanyl was calculated, and the appropriate number and combination of patches were prepared either individually or in a combination of 2.5-, 5-, 7.5-, or 10-mg fentanyl patches to obtain a total dose as close to 2 µg/kg/h as possible. The left antebrachium was clipped with a No. 40 clipper blade circumferentially from the elbow joint to the carpus. The skin of the lateral aspect of the antebrachium was shaved, taking care not to traumatize the skin. The site was cleansed with chlorhexadine[c] scrub for 30 seconds and defatted with isopropyl alcohol wipes for a further 30 seconds. The skin was subsequently allowed to air dry thoroughly for 2 minutes. The required combination of patches (maximum of 2 patches) was applied to the skin and held in place for 30 seconds. The patches were then covered with 2 circumferential layers of adhesive bandage,[d] and the proximal and distal borders were secured with white tape.[e] Care was taken to ensure that the adhesive bandage was fitted but not tight and that no folds or creases were created. Patches were removed 72 hours after application and examined for any evidence of folds or creases prior to disposal.

The 5 control sheep designated to receive buprenorphine as analgesia had their antebrachium prepared 12 hours prior to surgery and placebo fentanyl patches[f] applied as for the fentanyl group. Buprenorphine was administered at a dosage of 0.01 mg/kg, IM, every 6 hours, starting at the anesthetic induction time for surgery. Sixty hours after surgery, concurrently with removal of the placebo patches, buprenorphine administration was discontinued. At the time of patch application, preoperative blood samples from all sheep were obtained and CBCs, serum biochemical panels, and fibrinogen concentrations were recorded.

Surgical procedure—Twelve hours after patch application, all sheep underwent a unilateral left tibial osteotomy that was repaired with a locking compression plate. All sheep were sedated with diazepam[g] at 0.3 mg/kg, IV, initially, with additional doses of 0.1 mg/kg, IV, as required until sternal recumbency was obtained. Anesthesia was induced with 2% lidocaine[h] (2.2 mg/kg, IV) and 5% thiopental[i] (2.2 mg/kg, IV). Anesthesia was maintained with isoflurane[j] in oxygen at a flow rate of 10 mL/min, and mechanical ventilation was used as determined necessary by anesthetists. Isoflurane vaporizer settings were recorded at induction and at completion of the osteotomy. During surgery, the left forelimb patch site was elevated away from the surgery table to ensure air circulation around the region of application to prevent increased drug delivery caused by increasing temperature. Sheep were assisted during recovery from general anesthesia and subsequently returned to the stall. All sheep received perioperative administration of penicillin[k] (22,000 U/kg, IM, q 12 h) and gentamicin[l] (6.6 mg/kg, IV, q 24 h) for 3 days and phenylbutazone[m] (2.2 mg/kg, IV, q 24 h) for 3 days starting at time of induction of anesthesia.

Pain assessment scoring—Two veterinarians masked to the method of analgesia and not associated with the surgical research independently assessed the sheep for signs of pain (**Appendix**). The first pain assessment was performed the morning after the day of surgery, which was approximately 36 hours after patch application and approximately 4 hours following the second dose of buprenorphine. Pain evaluation was conducted every 12 hours until 12 hours after patch removal and administration of the last dose of buprenorphine, for a total of 5 examination points. Both observers evaluated each sheep for 2 to 3 minutes from outside the stall and subsequently by physical examination. The pain assessment scoring was adapted from reported sheep pain studies.[n] For the scoring of pain in this study, sheep were scored as either alert or having signs of depression with no gradations between. Their respiratory rate was scored as either normal or abnormal with relation to clinically normal sheep at a given ambient temperature. Sheep were scored with regards to their willingness to rise from a recumbent position. Once standing, they were evaluated for their apparent level of comfort standing on the limb, as evidenced by shifting of weight and the willingness to ambulate. Sheep were evaluated on their ability to move around the stall (with gentle encouragement) and stay with the group. Degree of signs of pain was evaluated by palpation of the surgical site and evaluation of the response. The maximal pain score possible was 20. Appetite was evaluated by response to offering fresh hay and grain and evaluation of gastrointestinal activity via twice-daily abdominal auscultation. Rescue treatment criteria were a pain score > 15 or fracture instability.

Statistical analysis—The Shapiro-Francia W test was used to test for normality. Initial statistical analysis revealed the data to be non-normally distributed. Score data were subsequently normalized by use of $\log_{10}$ of the square root of score and analyzed by use of 2-way ANOVA.[o] Random regression models in which sheep and slope of the score within sheep were treated as random effects were used. All data are expressed as mean ± SD. Differences were considered significant at $P \leq 0.05$.

Results

Mean administration dose rate of fentanyl was 2.08 ± 0.13 µg/kg/h (128 ± 8.1 µg/h). There was a significant ($P = 0.02$) difference between the 2 treatment groups with respect to preoperative diazepam administration, with diazepam doses of 38.0 ± 7.6 mg and 27.0 ± 9.9 mg

Table 1—Mean ± SD intraoperative physiologic data obtained from sheep that underwent unilateral osteotomy and were treated for pain by use of buprenorphine administered IM (n = 5) or fentanyl administered transdermally by use of a patch (15).

Variable	Buprenorphine	Fentanyl
Iso (Ind [%])	2.8 ± 0.8	2.9 ± 0.5
Iso (EO [%])	2.5 ± 0.5	2.2 ± 0.4
RR (Ind)	17.8 ± 5.5	13.9 ± 6.6
RR (EO)	18.2 ± 4.9	14.0 ± 7.6
Vt (Ind [L])	0.6 ± 0	0.7 ± 0.1
Vt (EO [L])	0.6 ± 0	0.7 ± 0.1
Paw (Ind [cm H_2O])	19.0 ± 1.4	20.9 ± 2.9
Paw (EO [cm H_2O])	19 ± 1.4	20.5 ± 2.7
SpO_2 (Ind [%])	97.2 ± 2.2	96.5 ± 2.0
SpO_2 (EO [%])	98.6 ± 0.9	96.7 ± 1.7
Extub (min)	7.5 ± 2.9	7.9 ± 3.5

Iso = Isoflurane vaporizer percentage setting. Ind = Time of induction. EO = Time the osteotomy was completed. RR = Respiratory rate (per minute). Vt = Tidal volume. Paw = Airway pressure. SpO_2 = Oxygen saturation. Extub = Time to extubation.

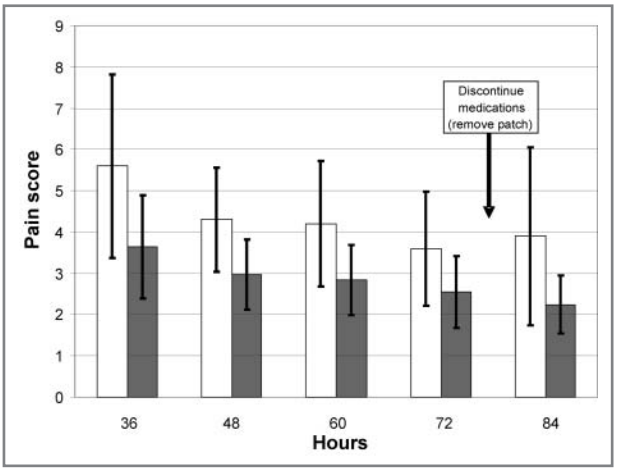

Figure 1—Mean ± SD pain scores at various time points after surgery in sheep that underwent unilateral osteotomy and were treated for pain by use of buprenorphine administered IM (white bars; n = 5) or fentanyl administered transdermally by use of a patch (shaded bars; 15).

for buprenorphine and fentanyl, respectively. There was no significant difference between the anesthesia induction dose of lidocaine (7.8 ± 1.2 mL and 6.9 ± 0.8 mL) or thiopental (3.1 ± 0.5 mL and 2.8 ± 0.3 mL) for the buprenorphine- or fentanyl-treated groups, respectively. No significant differences were detected for all other pre-, intra-, and postoperative values (**Table 1**).

There was no significant interobserver difference regarding the pain score evaluations over the course of the study. Fentanyl-treated sheep had significantly lower pain assessment scores than sheep treated with intermittent IM administration of buprenorphine. Pain assessment score for both groups declined at the same rate over time at approximately 0.85 times the pain assessment score/12-hour observation period. Fentanyl pain scores continued to decrease in a linear manner for the duration of the study (r^2 = 0.958; **Figure 1**). In comparison, the buprenorphine pain scores increased (84 hours after patch application), compared with previous observation point 4. This was the only assessment point to not decrease, compared with previous observation times. All sheep completed the study with no adverse effects. All patches were in complete contact with the antebrachial skin with no tenting or folding detected at time of removal.

Discussion

Results of this study indicated that transdermally administered fentanyl provided superior analgesia in sheep undergoing unilateral tibial osteotomy, compared with intermittent IM administration of buprenorphine. Pain assessment scores for fentanyl- and burprenorphine-treated sheep decreased in a roughly linear fashion. However, fentanyl-treated sheep had consistently reduced pain scores for the duration of the study, compared with buprenorphine-treated sheep.

An uneven number of sheep were included in each group because of the requirements of a parallel study examining the pharmacokinetics of transdermally administered fentanyl. More sheep were allocated to the fentanyl group to ensure that reliable serum fentanyl concentrations were obtained by use of this method of drug delivery. Such a lower number of buprenorphine-treated sheep reduced the likelihood of detecting a significant difference between the 2 groups. The number of sheep in each group was determined during the design and planning of the experiment to be sufficient for analysis.

Buprenorphine is 20 to 50 times as potent as morphine and is a partial μ-receptor agonist with a long duration of action.[5,13] Extrapolation from humans and other species along with recommended clinical and research administration regimens led to a buprenorphine dosage of 0.01 mg/kg, IM, every 6 hours.[13–15] Fentanyl is 80 to 100 times as potent as morphine and is a μ-receptor agonist used commonly in human and veterinary medicine. In humans and other species, it is recommended to apply transdermal patches 12 hours prior to surgery, which is reported to have a duration of action of 72 hours.[13] The administration rate used of 2 μg/kg/h was an extension of the administration regimens used in another sheep study and also in other species.[6,8,16,a] Both administration regimens were at the high end of the recommended or extrapolated therapeutic ranges and, as such, were expected to provide equipotent opioid analgesic effects. Sheep in the present study treated with buprenorphine may have had a ceiling analgesic effect related to the partial agonist activity of the drug. In comparison, the fentanyl-treated sheep received a pure agonist drug that does not induce a ceiling effect and, as such, fentanyl may have induced a more profound analgesic effect. This may be a reason why the fentanyl-treated sheep had reduced pain scores, compared with buprenorphine-treated sheep.

The placement of the transdermal fentanyl and placebo patches was on the left forelimb ipsilateral to the operated tibia. The left antebrachium had been used as a location for transdermal patch application previously in sheep without a description of the actual process of application.[17] In the present study, the method of application was closely evaluated and described. During surgery, sheep were positioned in left lateral recumbency with the operated limb and the patch on the down side. The patch was slightly elevated from the surgi-

cal table during surgery. The left lateral antebrachium was selected for these sheep because of the tendency of sheep with unilateral orthopedic surgery and pain to lie after surgery in sternal or lateral recumbency with the operated limb uppermost. Consequently, during recovery and in the postoperative period, the sheep did not lie for prolonged periods on the patch, which could substantially increase the temperature of the skin and patch. This is important because the rate of fentanyl delivery is affected by body temperature.[18] The rate of delivery could increase by up to one third if the body temperature of the site of application increased to 40°C. Sheep lying on the patch in the postoperative period for extended periods may receive abnormally high doses of fentanyl, which could cause adverse effects. For this reason, when transdermal fentanyl patches are applied to sheep, care must be taken that the site of application is not in a position exposing the patch to abnormally high temperatures. The lateral portion of the antebrachium was readily accessible and could be prepared with the sheep under gentle restraint by a handler. All patches at time of removal were examined and noted to be in close contact with the skin and without folds or creases. No patches moved or required any additional care to maintain position for the duration of the study. The lateral portion of the antebrachium provides an excellent location for patch application, but care should be taken to consider the probable postoperative behavior and resultant recumbent positioning and its effect on patch placement.

Results of preoperative blood analyses were within reference ranges for all sheep and not significantly different between the 2 treatment groups. The only significant difference between the intraoperative drug requirements for the 2 groups was the diazepam sedation dose. Fentanyl-treated sheep required less diazepam, compared with the buprenorphine-treated group. The dose of diazepam for each sheep was initially calculated on a per kilogram basis. However, if insufficient sedation was achieved with that dose, additional sedative was administered. Results suggested that sheep treated with transdermally administered fentanyl were more likely to be calm and obtain sternal recumbency prior to anesthetic induction, compared with buprenorphine-treated sheep. The lower drug dosage required for preanesthesia sedation was a benefit of transdermally administered fentanyl patches. It should be noted that this difference could additionally be influenced by the fact that the sheep that received fentanyl most likely had higher serum concentrations of opioid, compared with the sheep that received buprenorphine IM minutes before anesthetic induction.

After anesthetic induction and for the duration of the surgical procedure, both groups had intraoperative monitoring values and anesthetic requirements that were not significantly different. This suggested that both groups had similar analgesia levels after induction and during the orthopedic procedure.

For the pain assessment scores, there was no difference between the observers. The scoring began the morning after surgery (36 hours after patch application), which corresponded to 16 to 20 hours after surgery. This time was chosen because the evening following surgery, most sheep were still recovering from the effects of the general anesthesia and could not be assessed adequately. Pain assessment scores were significantly lower for sheep that received fentanyl than those that received buprenorphine. Some portion of the analgesia that occurred in the postoperative period was attributed to the daily administration of the anti-inflammatory drug phenylbutazone, but differences in analgesia between the groups were attributed to a difference in the analgesic properties of the 2 opioid medications. Both pain assessment scores decreased at a similar rate over time, which suggested that the degree of analgesia attributable to fentanyl was consistently greater, compared with buprenorphine, for the entire 72 hours of application. Interestingly, the pain assessment score for buprenorphine 12 hours after the last dose was the only assessment point to increase relative to the previous point in either group. This suggested that 12 hours after the discontinuation of buprenorphine administration, the sheep had more pain than 12 hours after removal of the fentanyl patch. This was most likely a reflection of continued analgesic effects.

Animal welfare is of supreme importance when undertaking preclinical trials. It is believed that for orthopedic pain, administration limited to NSAIDs is not adequate. Therefore, the study design required that the control group receive an opioid. Buprenorphine was considered the best opioid for comparison with fentanyl because of its common use. We believe that the increase in pain assessment scores at 12 hours after administration of the last buprenorphine dose adds weight to the common understanding that NSAIDs alone are not as effective at managing postoperative orthopedic pain as are NSAIDs combined with opioids.

Results of the present study indicated that fentanyl patches can be applied to the antebrachium of sheep 12 hours prior to surgery as an easy, effective procedure. Furthermore, by use of the dosage regimens reported here, transdermally administered fentanyl provided a degree of analgesia that was superior to that of buprenorphine for control of postoperative pain associated with orthopedic surgery.

a. Duragesic, Janssen Pharmaceutica, Titusville, NJ.
b. Buprenex, Hospira Inc, Lake Forest, Ill.
c. Betasept, Purdue Products LP, Stamford, Conn.
d. Elastikon, Johnson and Johnson, Arlington, Tex.
e. Zonas porous tape, Johnson and Johnson, Skillman, NJ.
f. Duragesic placebo, Janssen Pharmaceutica, Titusville, NJ.
g. Diazepam, Hospira Inc, Lake Forest, Ill.
h. Lidocaine, Phoenix Pharmaceutical Inc, St Joseph, Mo.
i. Thiopental, Hospira Inc, Lake Forest, Ill.
j. Isoflurane, Abbott Laboratories, North Chicago, Ill.
k. Penicillin, MWI, Meridian, Idaho.
l. Gentocin, Phoenix Pharmaceutical Inc, St Joseph, Mo.
m. Phenylbutazone, Phoenix Pharmaceutical Inc, St Joseph, Mo.
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o. Stata, version 10.0, StataCorp, College Station, Tex.

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Appendix

Pain assessment scoring system (0 to 3) used in a study of sheep that underwent unilateral osteotomy and were treated for pain by use of buprenorphine administered IM or fentanyl administered transdermally by use of a patch.

Variable	0	1	2	3
Mental assessment	Normal and alert	NC	NC	Signs of depression
Respiratory rate	Normal	NC	Abnormal (slow or panting)	NC
Recumbency	Normal	Slightly delayed rising	Requires encouragement to stand	Unwilling or unable to stand
Shifting weight	Normal	Mild or occasional	Moderate	Constant
Flock movement	Normal	Occasionally trails flock	Regularly trails flock	Apart from flock consistently
Appetite	Normal	Mildly reduced interest	Moderately reduced interest	Inappetent
Palpation of surgical site	No signs of pain	Mild signs of pain	Moderate signs of pain	Severe signs of pain

NC = No criteria applicable for this category.