

RESEARCH PAPER

Efficacy and cost-effectiveness of transdermal fentanyl patches for the relief of post-operative pain in dogs after anterior cruciate ligament and pelvic limb repair

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Abstract

Objectives To determine whether transdermal fentanyl patches provided cost-effective post-operative analgesia in dogs with pelvic limb injuries.

Study design Prospective, randomized, blinded clinical trial.

Animals Twenty-four dogs undergoing repair of ruptured cranial cruciate ligaments or pelvic limb fractures.

Methods Dogs were randomly assigned to one of two groups: those receiving transdermal fentanyl patches (group F) and those receiving injectable morphine for control of post-operative pain (group M). Patients in both treatment groups were monitored for adequacy of analgesia and alterations in physiological variables. Plasma fentanyl concentrations were measured in Group F. Rescue morphine was given if a dog was deemed uncomfortable. The time of first rescue morphine, the total amount, and number of doses of morphine administered over 72 hours was quantified and compared for each group.

Results There was no significant treatment effect on any of the parameters, except for serum cortisol concentration, which was significantly lower overall in group F ($p = 0.01$). Pain scores peaked at

6 hours post-extubation and were higher than baseline from 2 to 20 hours post-extubation. Cortisol concentrations were the highest at time 0 (extubation) and were significantly higher than baseline until 2 hours post-extubation. Pain scores correlated with fentanyl plasma concentrations ($p = 0.0001$ and $p = 0.01$, respectively), but the correlation was low ($r = 0.26$ and $r = 0.16$, respectively). No correlation was found between serum cortisol concentrations and pain scores in either group. Fentanyl cost and total cost for pain management were considerably higher for group F.

Conclusions Fentanyl patches did not provide better analgesia or a reduced requirement for rescue opioid compared with intramuscular morphine.

Clinical relevance When considering overall costs to the client for comparable analgesic intervention, fentanyl patches increased rather than decreased cost during the first 24 hours post-operatively.

Keywords analgesia, dog, economics, efficacy, orthopedic, transdermal fentanyl.

Introduction

Transdermal fentanyl (TDF) patches are used in veterinary medicine for the control of post-operative pain in dogs and are frequently used after orthopedic procedures to theoretically provide post-operative

analgesia for a period of approximately 3 days (Schultheiss et al. 1995; Kyles et al. 1996, 1998; Egger et al. 1998; Robinson et al. 1999). While the cost of the patches is relatively high compared with injectable morphine, the use of the patches offers many advantages. Transdermal delivery of opioid analgesics offers a convenient means of maintaining analgesia for an extended period of time and provides relatively steady-state plasma concentrations. This method of administration allows patients to remain ambulatory, reduces monitoring costs, avoids frequent injections, avoids hepatic first-pass metabolism that occurs with oral administration, and may minimize some of the side effects seen with intermittent delivery, such as bradycardia, respiratory depression, sedation, and reduced body temperature (Hug & Murphy 1979; Cartwright et al. 1983; Arndt et al. 1984; Schultheiss et al. 1995; Kyles et al. 1998; Riviere & Papich 2001). In addition, the use of the patches may reduce the overall consumption of analgesics (Hofmeister & Egger 2004). Avoiding intermittent injections reduces personnel and material costs, thereby reducing the cost of pain management.

Transdermal fentanyl patches are commonly used in veterinary patients for the alleviation of acute post-operative pain following surgery for pelvic limb injuries. One proposed reason for their use is that they may reduce the requirement for supplemental analgesia, and thus be more economical than intermittent (every 4–6 hours) injection of opioids. A number of studies have described the use of the patches in canine, nonsurgical, research populations (Schultheiss et al. 1995; Kyles et al. 1996; Egger et al. 1998), and a few studies show the clinical efficacy of transdermal patches in dogs (Kyles et al. 1998; Robinson et al. 1999). There have been no studies showing a decrease in requirements for additional injectable opioid and any reduction in cost of pain management. Because of the variability in plasma fentanyl concentrations in canine patients, and the prolonged period of time required to attain steady-state plasma concentrations (Schultheiss et al. 1995; Kyles et al. 1996; Egger et al. 1998), additional analgesics are often required in the post-operative period. If canine orthopedic patients with transdermal fentanyl patches applied are receiving comparable amounts of rescue morphine and requiring comparable nursing care when compared with dogs receiving morphine only, then any cost savings may not be a viable indication for their use.

The purpose of this study was to determine whether TDF patches provided effective post-operative analgesia in dogs with pelvic limb injuries, as well as a reduction in the requirement for additional post-operative analgesic intervention. The purpose was also to determine whether the use of TDF patches provides a cost-effective method of post-operative analgesia in this patient group.

Materials and methods

Animals

Approval for this study was obtained from the University of Georgia Teaching Hospital Board of Directors and the Institutional Animal Care and Use Committee. The study group consisted of 24 dogs presented to the University of Georgia Veterinary Teaching Hospital for repair of ruptured cranial cruciate ligaments (21 dogs) or simple pelvic limb fractures (3 dogs). Dogs were randomly assigned to one of two groups: those receiving transdermal fentanyl patches (group F) and those receiving injectable morphine (group M) for control of post-operative pain. Owner approval was obtained for entry into the study. All dogs were given a complete physical examination and blood was analyzed for Packed cell volume (PCV), total solids, blood glucose, and serum chemistry determination. Accurate body weights were obtained. Dogs with significant orthopedic trauma (multiple fractures) or nonorthopedic disease (i.e., extensive soft tissue trauma, pneumothorax, ruptured bladder, hepatic disease, or renal disease) were excluded from the study. In addition, those dogs on concurrent medication were excluded from the study, with the exception of dogs with fractures, which were given one to three doses of morphine sulfate (0.5 mg kg^{-1}) up until 12 hours prior to pre-medication. The dogs were housed and treated as clinical patients during the study.

Study groups

Dogs in group F had transdermal fentanyl patches (Duragesic; ALZA Corporation, Palo Alto, CA, USA) applied to the lateral thorax 12 hours prior to pre-medication, based on body weight: <10 kg ($25 \mu\text{g hour}^{-1}$), 10–20 kg ($50 \mu\text{g hour}^{-1}$), 20–30 kg ($75 \mu\text{g hour}^{-1}$), and 30–40 kg ($100 \mu\text{g hour}^{-1}$). The skin was prepared by clipping the hair, gentle washing with warm water, and then air-drying. At the time of patch placement, blood was sampled for

the determination of serum cortisol and plasma fentanyl concentrations. Dogs in group M had blood drawn for the determination of serum cortisol 12 hours prior to pre-medication. Dogs in both groups had light bandages applied to cover the thorax and to blind the observers to treatment. Dogs in both groups were pre-medicated 12 hours later with intramuscular (IM) injection of 0.05 mg kg⁻¹ acepromazine maleate (Fermenta Animal Health Co., Kansas City, MO, USA), 0.04 mg kg⁻¹ atropine sulfate (Phoenix Scientific, Saint Joseph, MO, USA), and morphine sulfate, 0.5 mg kg⁻¹ (Baxter Healthcare Corporation, Cherry Hill, NJ, USA). Anesthetic was induced with propofol intravenous (IV) to effect and maintained with isoflurane in oxygen. Jugular catheters (18 SWG, 8 in., I-Cath; Charteredmed, Inc., Lakewood, NJ, USA) were placed at the time of anesthetic induction to facilitate blood sampling. A venous catheter (22 SWG, 2 in., Sovereign Indwelling Catheter; Sherwood Medical Industries, Tullamore, Ireland) was placed in a cephalic vein for administration of anesthetic induction drugs and IV fluids. Lactated Ringer's solution (McGaw, Inc., Irvine, CA, USA) was administered IV throughout the anesthetic period at 10 mL kg⁻¹ hour⁻¹.

Following completion of surgery, dogs in group M were given a second dose of morphine (0.5 mg kg⁻¹) IM at extubation and as required, as assessed by a blinded observer, during the 72-hour monitoring period. The dogs in group F did not automatically receive a post-operative morphine dose at extubation, unless they were deemed painful

following assessment by the blinded observer. The fentanyl patches were left in place for 72 hours, and patients in both treatment groups were monitored throughout that time period for adequacy of analgesia by a blinded observer. Measurement and blood sampling times (fentanyl and cortisol) were at -4, -3, 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 56, 64, and 72 hours from the time of extubation. Time -4 was just prior to pre-medication (12 hours after fentanyl patch placement) and was considered the baseline measurement, time -3 was just prior to induction and approximately 1 hour after pre-medication, and time 0 was the time of extubation.

Two blinded observers (MH and Lynette Williams), with comparable experience and training, assessed the dogs throughout the study. Both observers were veterinary technicians, trained to assess pain in dogs using physiological and behavioral observations. Dogs were assessed for sedation, excitement, and adequacy of analgesia using descriptive behavior rating scales to derive a cumulative pain score (Table 1), and a visual analog scale (VAS) pain score (100 mm scale, with 0 indicating no pain and 100 indicating the maximum possible pain) at each assessment time (Morton & Griffiths 1985; Sanford et al. 1986; Conzemius et al. 1997; Holton et al. 1998; Firth & Haldane 1999). In addition, oscillometric indirect arterial blood pressure (Dinamap model 1846; Criticon Inc., Tampa, FL, USA), heart rate (auscultation and pulse palpation), respiratory rate (observation), and rectal body temperature were measured in all patients and used

Behavior	
Descriptive score for excitement/sedation	
-3	Unrousable
-2	Moderately sedated, but rousable
-1	Mildly sedated
0	No sedation or excitement
+1	Restless, calms with petting or holding
+2	Agitated, vocalizing, moving about in the cage; no response to petting or holding
+3	Thrashing, rolling in cage, clawing at bedding
Simple descriptive score for pain	
1	No pain, allows palpation of surgical site, normal posture
2	Faint pain, attention to, but allows palpation of abdomen and/or surgical site, tucked up when standing
3	Mild pain, withdraws from or vocalizes in response to palpation, hunched body position in sternal recumbency, paws tucked beneath body
4	Moderate pain, tries to escape in response to palpation, frequent body position changes, restless
5	Extreme pain, intensely still to writhing

Table 1 Descriptive cumulative excitement/sedation and pain scoring system. Excitement/sedation score was added to the pain score for the cumulative score; animals with a cumulative pain score ≥ 4 or the attainment of the highest value for pain or excitement were given rescue morphine

in the assessment of adequacy of the analgesia, and blood was collected at specific times (see above) for the determination of blood glucose, serum cortisol, and plasma fentanyl concentrations. Dogs demonstrating moderate-to-severe pain behavior (VAS pain score >50 mm and cumulative pain score ≥ 4 , or the attainment of the highest value for the pain or excitement descriptive rating scales) were given additional morphine IM (0.5 mg kg^{-1}) and reassessed in 30 minutes. Morphine was then administered (IM) every 30 minutes until they were considered to be comfortable. The time of administration of first rescue morphine, the total amount of morphine administered, and the frequency of administration of rescue morphine over 72 hours was quantified for each group. Body weight, age, sex, time to first rescue morphine, total morphine administered, frequency of rescue morphine administration, serum cortisol concentration, cumulative pain score, and VAS pain scores were compared between groups. In addition, the cost of analgesia was determined and compared between groups. Drug administration charges included ICU charges that were required for the first post-operative night if additional analgesic administration was required.

Fentanyl and cortisol assays

Serum cortisol concentrations were measured via radioimmunoassay (Coat-a-Count Cortisol Kit; Diagnostic Products Corporation, Los Angeles, CA, USA). Samples were analyzed in duplicate and the values obtained were averaged to obtain the final serum cortisol concentrations. Plasma fentanyl concentrations were measured via radioimmunoassay (Janssen Biotech N.V., Olen, Belgium). Samples were analyzed in duplicate and the values obtained were averaged to obtain the final plasma fentanyl concentrations. The interassay and intra-assay coefficients of variation were estimated to be 6.8% and 6.4%. The limit of detection of the assay was 0.08 ng mL^{-1} (Michiels et al. 1977).

Statistical analysis

Comparisons of age and weight among treatment groups were evaluated using unpaired *t*-tests. The mean plasma fentanyl concentrations from 0 to 12, 16 to 40, and 48 to 72 hours after extubation (corresponding to 16–28, 32–56, and 64–88 hours after patch placement) were calculated by averaging the plasma fentanyl concentrations for each dog

during that time period. Maximum plasma fentanyl concentration achieved (C_{max}) and the time at which it was achieved after placement of the patch (T_{max}) were also determined. Unpaired *t*-tests were used to compare C_{max} , T_{max} , and the average fentanyl concentration during each time period between the dogs in group F.

The effects of treatment, time, and treatment by time interaction on VAS pain scores, cumulative pain scores, serum cortisol concentrations, time to first rescue morphine, frequency of rescue morphine, and total rescue morphine were evaluated using a mixed model analysis of variance procedure (Proc Mixed, SAS version 9.1; SAS Institute Inc., Cary, NC, USA). Dog was included in the model as a random factor. Significant differences in least square means among the various levels of treatment, time, and treatment by time interaction were adjusted using the method of Bonferroni. The Pearson correlation coefficient technique was used to evaluate the relationship of fentanyl concentration with VAS and cumulative pain scores, and serum cortisol concentration. A *p*-value ≤ 0.05 was considered significant for all statistical analyses.

Results

There were no significant differences in age, body weight, or surgical procedures performed between groups (Table 2). There were six spayed females, one castrated male, and five uncastrated males in

Table 2 Comparison of demographic characteristics, amount of drug administered, pain scores and serum cortisol among dogs in group F and group M. Data are reported as mean \pm SEM or median (range)

Parameter	Group F	Group M
Weight (kg)	31.4 \pm 3.2	30.6 \pm 2.8
Age (years)	3.4 \pm 0.7	4.6 \pm 0.8
Cruciate ligament repair	10	11
Pelvic limb fracture repair	2	1
Time to first rescue morphine (hours)	7.0 \pm 1.3	7.5 \pm 1.1
Number of doses of rescue morphine	1 (0–3)	1 (0–3)
Total morphine (mg kg^{-1})	0.49 (0–1.69)	0.49 (0–1.46)
Cumulative pain scores	5 \pm 0.3	5 \pm 0.3
VAS pain scores	11 \pm 2	13 \pm 2
Serum cortisol (mg dL^{-1})	0.44 \pm 0.04*	0.62 \pm 0.04*

*Differences were statistically significant, *p* = 0.01.

each group. Anterior cruciate ligament rupture repair was performed in 10 dogs in group F and 11 dogs in group M. One dog in group F underwent femoral fracture repair and one dog underwent tibial fracture repair. One dog in group M underwent femoral fracture repair. None of the dogs with cruciate ligament injury were on analgesic drugs of any type at the time of surgery, but all three of the dogs with pelvic limb fractures (two in group F and one in group M) had received one to three doses of morphine (0.5 mg kg^{-1}) at least 12 hours prior to pre-medication. Eight dogs in group F and eight dogs in group M required post-operative morphine administration. There was no significant effect of treatment or treatment by time interaction on frequency of rescue morphine, time to first rescue dose of morphine, or total morphine administration (Table 2), but serum cortisol concentration was significantly lower overall in group F ($p = 0.01$) (Table 2 & Fig. 3).

There was a significant overall effect of time on cumulative pain scores ($p < 0.0001$) (Fig. 1), VAS pain scores ($p < 0.0001$) (Fig. 2), and serum cortisol concentrations ($p < 0.001$) (Fig. 3) in dogs in both treatment groups. Pain scores peaked at 6 hours post-extubation, then gradually decreased, and were the lowest by 72 hours and not significantly different from baseline. Cortisol concentrations from the time of induction to 2 hours post-extubation were significantly higher than baseline cortisol concentrations taken just prior to

pre-medication. Cortisol concentrations were the highest at the time of endotracheal extubation, but by 4 hours post-extubation serum cortisol concentrations were not significantly different from baseline or at 72 hours. An attempt was made to correlate plasma fentanyl concentrations with cumulative and VAS pain scores, and serum cortisol concentrations in the dogs in group F. Correlations of VAS and cumulative pain scores with fentanyl were significant ($p = 0.0001$ and $p = 0.01$, respectively), but correlation was low ($r = 0.26$ and $r = 0.16$, respectively) for both. There was a very slight negative correlation of serum cortisol concentration and plasma fentanyl concentration, but this was not significant ($p = 0.08$ and $r = -0.11$). No correlation was found between serum cortisol concentrations and pain scores in either group.

Fentanyl data

The mean plasma fentanyl concentration for the period from 0 to 12, 16 to 40, and 48 to 72 hours after endotracheal extubation, the maximum plasma fentanyl concentration (C_{max}), and time to maximum plasma fentanyl concentration after patch placement (T_{max}) are shown in Table 3. Of the dogs in group F receiving morphine post-operatively, six dogs received rescue morphine when their plasma fentanyl concentrations were greater than 0.5 ng mL^{-1} (range $0.9\text{--}2.2 \text{ ng mL}^{-1}$) and two dogs received morphine when their fentanyl

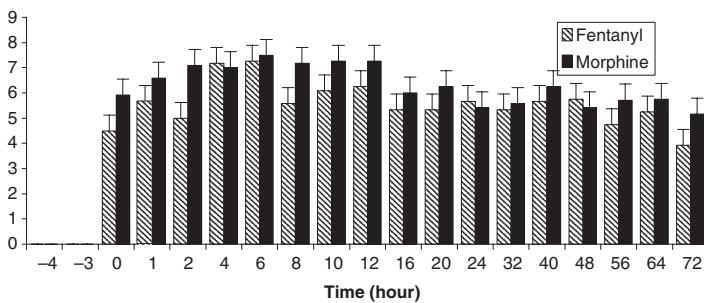


Figure 1 Cumulative pain/sedation/excitement scores (see Table 1 for scoring system) assessed for 12 dogs receiving fentanyl patches and 12 dogs receiving morphine following pelvic limb orthopedic surgery. (-4 = pre-medication time, -3 = induction time, 0 = extubation time).

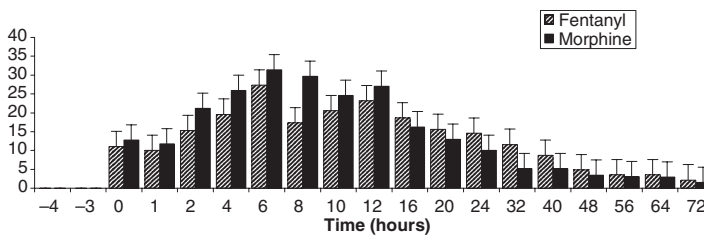


Figure 2 Visual analog pain scores (x of 100 mm) assessed for 12 dogs receiving fentanyl patches and 12 dogs receiving morphine following pelvic limb orthopedic surgery.

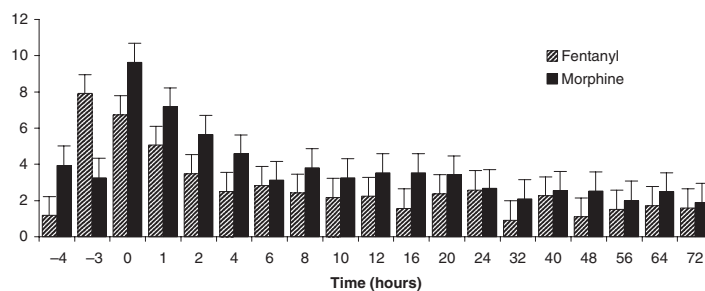


Figure 3 Serum cortisol concentrations over 76 hours in dogs undergoing pelvic limb orthopedic surgery.

Table 3 Mean plasma fentanyl concentrations and C_{\max} and T_{\max} in dogs in group F

Plasma fentanyl concentration (ng mL ⁻¹)	Mean \pm SD	Range
0–12 hours after extubation (16–28 hours after patch placement)	1.1 \pm 0.7	0.4–2.88
16–40 hours after extubation (32–56 hours after placement)	1.1 \pm 0.4	0.5–1.9
48–72 hours after extubation (64–88 hours after placement)	0.8 \pm 0.4	0.37–1.72
C_{\max} (ng mL ⁻¹)	2.1 \pm 1.4	0.7–5.83
T_{\max} (hours from patch placement)	22 \pm 13	12–52

concentrations were less than 0.5 ng mL⁻¹ (0.16 and 0.39 ng mL⁻¹). Of the dogs in group F, that did not receive morphine post-operatively, two had plasma fentanyl concentrations less than 0.5 ng mL⁻¹ and two had plasma concentrations greater than 1 ng mL⁻¹ throughout the post-operative assessment period.

Cost of analgesia

The cost of analgesia was estimated from the cost of fentanyl patches, the cost of additional injections, and the cost of ICU monitoring, a requirement at many veterinary teaching hospitals for animals requiring injectable analgesia. The patch cost was averaged at \$20 per 25 $\mu\text{g hour}^{-1}$ (so a 25 $\mu\text{g hour}^{-1}$ patch would cost \$20, a 50 $\mu\text{g hour}^{-1}$ patch would cost \$40, etc.); injections were charged at \$10 per injection, which included the cost of morphine, a syringe, a needle, and a \$75 ICU monitoring charge to cover the first 24 hours of post-operative analgesia. Total cost for pain management was considerably higher for group F.

Discussion

The use of the transdermal fentanyl patch did not result in a significant difference in VAS or cumulative pain scores, frequency of rescue morphine, time to first rescue morphine, or total morphine administered between the two treatment groups in this study. The

highest pain scores in both groups occurred in the first 24 hours post-operatively, as would be expected with acute post-operative orthopedic pain (Figs 2 & 3). The dogs with transdermal fentanyl patches appeared to be as painful as those without the patch, requiring analgesic intervention even when plasma fentanyl concentrations were above what are considered analgesic concentrations of 0.5–1 ng mL⁻¹ (Kyles et al. 1996; Egger et al. 1998; Kyles et al. 1998; Robinson et al. 1999). Other dogs did not require analgesic intervention, although the plasma fentanyl concentrations were well below accepted analgesic levels.

There are several possible factors contributing to the lack of significant differences in pain scores and morphine administration between the two groups. One of the major deficiencies of this study is that it lacks statistical power, and it is possible that significantly larger treatment groups would have shown significant differences in analgesia and morphine requirements in the two groups. As with most clinical studies, it is difficult to control factors such as degree of bone or soft tissue trauma, surgical technique used, chronicity of the problem, or administration of pre-emptive analgesics. It is often presumed that dogs presenting for fracture repair have more significant soft tissue and bone trauma than dogs that present for anterior cruciate ligament repair. However, dogs requiring either of these procedures were evenly distributed between the two groups, and the fracture repair group made up

a very small proportion of the total number of dogs (3 of the 24). In addition, animals with extensive traumatic injuries to bone (multiple fractures, rib, pelvic, or forelimb fractures), extensive soft tissue injury, or significant nonorthopedic disease were excluded from the study in an attempt to minimize these variables. Only dogs with relatively simple pelvic limb fractures (two femoral fractures and one tibial fracture) and minimal soft tissue trauma were included. Exclusion of the dogs with simple fractures from the study did not alter the results, so it was decided to retain them in the data set.

Differences in chronicity of the injury, degree of tissue trauma, and administration of analgesics prior to presentation could result in varying degrees of analgesia and central sensitization among the dogs. All of the dogs undergoing cruciate ligament repair had been injured relatively acutely, within 2 weeks of surgery, and all of the dogs undergoing fracture repair were injured and admitted to hospital the day prior to surgery. Dogs on any type of analgesic therapy prior to the day of surgery were excluded from the study, with the exception of the dogs with pelvic limb fractures, which received one to three doses of morphine on the day prior to surgery. Although it was quite likely that there was variability in both the degree and chronicity of pain, as well as the level of analgesia and central sensitization, the dogs were evenly distributed to both treatment groups in an attempt to account for these differences.

Another possible reason for the lack of significant difference between the two groups is that the scoring systems used were not sensitive enough to pick up the more subtle pain behaviors in the post-operative period. There is a high degree of individual variability in pain tolerance, display of overt pain behaviors, and stress response in clinical canine populations, as well as differences in interpretation of behavior by different observers. In addition, the effects of drugs such as opioids, sedatives, or inhalational agents on behavior can provide a confounding factor in the assessment of pain in the early post-operative period. Some of the dogs in this early post-operative period may have been painful, but were still somewhat obtunded for the first 1–2 hours post-endotracheal extubation, a factor that has a strong effect on pain behavior (Sanford et al. 1986, Holton et al. 1998; Firth & Haldane 1999). Alternatively, some of the dogs may have been dysphoric and exhibiting behavior that was interpreted as signs of pain. Recognizing the subjectivity of the pain scoring systems, and to minimize these variables, we used the same two

blinded observers throughout the study, both with similar levels of experience and training in differentiating the sedative, analgesic, and dysphoric effects of the drugs used. Careful assessment of behavior, along with cardiopulmonary parameters, was used in the decision as to whether or not a patient was painful. In addition, because one of our goals was to determine whether the patches resulted in reduced requirement for rescue morphine, we did not withdraw rescued animals from further assessment. This is likely a confounding factor in assessing differences in pain scores. The addition of a control group, receiving no analgesics and scored and 'rescued' similarly to the other groups, would have provided a better measure of the effectiveness of the assessment tool used in the study.

It is also possible that morphine administration at a dose of 0.5 mg kg^{-1} did not provide adequate levels of analgesia and was not an appropriate positive control. Morphine plasma concentrations were not measured, so the actual plasma levels achieved at this dose were not known. In addition, while the published dose for morphine in dogs is $0.05\text{--}1 \text{ mg kg}^{-1}$ (Thurmon et al. 1996), there are few studies that have reported on the pharmacokinetics and pharmacodynamics of morphine in dogs, particularly in dogs undergoing orthopedic surgery. One recent study in dogs indicated that a dose as low as 0.2 mg kg^{-1} was equianalgesic to 2 mg kg^{-1} of tramadol in patients undergoing ovariohysterectomy (Mastrocinque & Fantoni 2003). Another study indicated that doses of 0.5 mg kg^{-1} or lower may not be any more efficacious than a saline control (Barnhart et al. 2000) in an experimentally induced thermal and mechanical pain model. However, dogs in group F were no more pain free than those in group M, indicating that TDF provided analgesia comparable to a low dose of morphine that may be no more effective than a saline control.

There were significant differences in serum cortisol concentrations between the two groups, with group F maintaining lower cortisol concentrations over all. Serum cortisol concentrations in both groups, however, were still within the acceptable normal range for dogs (Frank & Oliver 1998). Cortisol, while a good indicator of stress, may not be a reliable indicator of pain (Sanford et al. 1986; Holton et al. 1998; Firth & Haldane 1999). Cortisol concentrations peaked at endotracheal extubation but were not significantly different from baseline by 2 hours post-extubation. Pain scores

were significantly higher than baseline from 2 to 20 hours after extubation. Cortisol release was the highest in the immediate perioperative period when pain scores were not significantly different from baseline and decreased during the period when pain scores were the highest. There was very poor correlation of pain scores and cortisol concentrations, indicating that the two techniques are not measuring the same parameter. It is also possible that transdermal fentanyl may have a stress reducing (cortisol lowering) effect, separate from any analgesic effect, which has been demonstrated in other species (Broadbear et al. 2004). It is likely, however, that the differences in cortisol concentrations are of little clinical significance.

Fentanyl plasma concentrations ranging from 0.5 to 1 ng mL⁻¹ are considered analgesic in dogs (Kyles et al. 1998; Robinson et al. 1999). At 12 hours post-extubation, the patches had been in place for 24 hours and it was assumed, based on previous reported studies, that analgesic plasma fentanyl concentrations had been attained by this time, and in most of the dogs in our study that was true. Plasma fentanyl concentrations of dogs in group F showed a high degree of variability, consistent with published findings in this species (Schultheiss et al. 1995; Kyles et al. 1996, 1998; Egger et al. 1998; Robinson et al. 1999). This variability may be greater in the perioperative period because of alterations in cardiac output, tissue perfusion, volume of distribution, clearance, and body temperature (Egger et al. 1998; Barnhart et al. 2000; Mastrocinque & Fantoni 2003; Pettifer & Hosgood 2003, 2004), and may have influenced the attainment of significance. Fentanyl-induced dysphoria may also have confounded the pain scoring of these dogs, although both observers were trained to differentiate dysphoria from pain behavior in dogs.

One reason cited for retraction of FDA approval for acute post-operative use of transdermal fentanyl patches in humans is the unpredictability of analgesic efficacy and fentanyl concentrations attained (Holley & Van Steennis 1988; Gourlay et al. 1989). This is also a concern in veterinary medicine, given the variability of individuals and situations in clinical practice. The use of the patches in this group of dogs did not result in a better quality of analgesia or in a reduced requirement for rescue opiate. There was a great deal of individual variability in scores and responses to both the analgesic drugs, but this is typical of a normal clinical

situation. The surgery was performed by both ACVS-board-certified surgeons and surgery residents, possibly resulting in differences in tissue handling, tissue trauma, and duration of procedure, and contributing to the variability. It is possible that with a much larger group of clinical patients and standardization of the surgical procedure, some of the variability would have been removed and more significant differences between the two treatment groups may have been obtained.

When considering the overall costs for comparable analgesic intervention, fentanyl is not necessarily an economical solution. Costs were calculated based on the average costs in a veterinary teaching hospital, using nongeneric fentanyl patches, and would likely be somewhat different in a private clinical setting, or with the recent introduction of generic fentanyl patches. Generic fentanyl patches cost 40–45% less than the proprietary patches in our veterinary hospital, but the efficacy of the generic patches in canine patients has not been determined. Given that there was no reduced requirement for morphine rescue therapy or for nursing intervention between the two groups, the additional cost burden of the fentanyl patches may not be justifiable from a purely economic standpoint, as they did not improve the quality of the analgesia in this study.

Given the high degree of individual variability seen in pain scores and requirements for morphine post-operatively, it is obvious that close observation of canine patients for adequacy of analgesia is critical when using transdermal fentanyl patches. Close monitoring and provision of supplemental analgesia, if required, in the post-operative period is recommended. Continuous rate infusions of opioids, ketamine, or local anesthetics, and/or administration of epidural opioids and local anesthetics may be more economical and efficacious techniques for pain management in the pre-operative period and in the first 24 hours after orthopedic surgery whenever frequent monitoring is possible. Finally, although there is limited experience with their use in veterinary patients, the introduction of generic fentanyl patches reduces the cost by up to 45%, making the use of the patches more appealing.

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