Comparison of transdermal administration of fentanyl versus intramuscular administration of butorphanol for analgesia after onychectomy in cats

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Objective—To compare postoperative discomfort assessed by subjective pain score and plasma cortisol concentrations in cats undergoing onychectomy that received analgesia by use of transdermal fentanyl (TDF) patches or an IM injection of butorphanol.

Design—Randomized prospective clinical trial.

Animals—22 client-owned cats weighing 2.2 to 5 kg (4.84 to 11 lb) undergoing onychectomy.

Procedure—Researchers were blinded to which cats received a TDF patch (25 µg/h) 18 to 24 hours prior to surgery or an IM injection of butorphanol (0.2 mg/kg [0.09 mg/lb]) at the time of sedation, immediately following extubation, and at 4-hour intervals thereafter for 12 hours. Clinical variables, plasma cortisol concentration, and pain scores were evaluated and recorded 24 hours prior to surgery, at extubation, and 2, 4, 6, 12, 24, 36, and 48 hours after surgery.

Results—The TDF group had a lower pain score than the butorphanol group only at 8 hours after surgery. Both groups had significantly lower mean plasma cortisol concentrations at 0, 24, 36, and 48 hours after surgery, compared with mean plasma cortisol concentrations prior to surgery. No significant differences in appetite or response to handling feet were observed between the 2 groups.

Conclusions and Clinical Relevance—Our data did not reveal a difference in pain relief between administration of TDF and butorphanol. Plasma cortisol concentrations were not different between groups. Fentanyl appeared to provide equivalent analgesia to butorphanol in cats undergoing onychectomy. The primary advantage of using a TDF patch is that repeated injections are not required. (J Am Vet Med Assoc 2002;220:1020–1024)

In the past, analgesics have been withheld or given in a limited manner to cats undergoing onychectomy because of concerns regarding the adverse effects of opioids in this species. However, many studies have revealed that opioids can be given safely and provide adequate analgesia in cats. There are known adverse physiologic consequences of restricting analgesia after surgery. Pain activates the stress response and may have a negative impact on immune function. Thus, adequate analgesia is essential from both a humane standpoint and for maintenance of homeostasis.

Owners often notice that cats have signs of pain following onychectomy after discharge from the hospital. Additionally, 1 report indicates that cats have signs of pain at least 24 hours after onychectomy.

Transdermal delivery of fentanyl (TDF) has been used to achieve pain relief in cats. Studies investigating TDF in cats found that it was a safe, satisfactory method of pain management. Advantages of using TDF include noninvasive, continuous delivery of an analgesic, long duration of analgesia, relative ease of application and maintenance, and tolerance by the animals. Other analgesics, such as butorphanol, require repeated injections or oral administration. Although subjective pain scoring has been used to evaluate the analgesic effects of TDF in cats and compare it to other analgesics, previous studies have not directly compared the effectiveness of TDF to other analgesic techniques after surgery, by use of an objective index of pain such as plasma cortisol concentrations. Plasma cortisol concentrations have been shown to correspond to pain in cats following ovariohysterectomy, and it has been suggested that plasma cortisol concentrations may provide an objective index of pain in this species.

The purpose of the study reported here was to compare postoperative discomfort (by subjective pain score) in cats undergoing onychectomy that received either TDF or butorphanol IM and to determine the effects of these analgesics on plasma cortisol concentrations (as an objective index of pain) following onychectomy. We hypothesized that TDF would provide more effective and longer lasting analgesia in cats following onychectomy, compared with intermittent IM administration of butorphanol. Additionally, we hypothesized that postoperative plasma cortisol concentrations would be lower in cats receiving TDF than in those given butorphanol. Subjective pain scoring, plasma cortisol concentrations, appetite, and response to handling feet were determined prior to drug administration and surgery and up to 48 hours after surgery.

Materials and Methods

Cats—Twenty-two client-owned cats weighing 2.2 to 5 kg (4.84 to 11 lb) admitted to the Veterinary Medical Teaching Hospital at the University of Wisconsin for elective onychectomy were enrolled in the study. Owners of all cats signed an informed consent form prior to participation in the study. Cats were considered in good health on the basis of history, physical examination, Hct, and plasma total solids concentration. The study was approved by the University of Wisconsin School of Veterinary Medicine Animal Care and Use Committee.
Study design—Cats were randomly assigned to receive either application of a TDF patch (25 µg/h) or butorphanol (0.2 mg/kg [0.09 mg/lb], IM). For cats in the TDF group (n = 11), the patch was applied 18 to 24 hours prior to induction of anesthesia and surgery. Mean weight of the TDF group cats was 3.74 kg (7.13 ± 1.63 lb; range, 2.2 to 4.3 kg [4.84 to 9.46 lb]). Each cat received a 25-µg TDF patch (dosage range based on body weight range, 5.81 to 11.36 µg/kg; mean ± SD, 8.09 ± 1.86 µg/kg). For the butorphanol group (n = 11), butorphanol was administered at the time of sedation, immediately following extubation, and at 4-hour intervals thereafter for 12 hours. Cats in the butorphanol group received a placebo patch 18 to 24 hours prior to induction of anesthesia, and cats in the TDF group received injections of similar volume of saline (0.9% NaCl) solution at the times scheduled for butorphanol injections.

Clinical variables including heart rate, respiratory rate, temperature, appetite, and subjective evaluation of response to handling feet were evaluated and recorded 24 hours prior to surgery. Scoring of pain in individual cats was performed by 1 of 2 individuals who were blinded to which cats had TDF patches or which cats received butorphanol. A comparison of simultaneous evaluations was performed periodically to determine observer consistency. Baseline plasma cortisol concentrations were also obtained 24 hours before surgery. Following completion of baseline evaluations, a blood sample (1.5 ml) was obtained from the medial saphenous vein for determination of Hct, plasma total solid concentration, and plasma cortisol concentration. Hair over a 7 X 5-cm area on the thorax just caudal to the left or right forelimb was shaved. For cats in the TDF group, a TDF patch was applied to the shaved area over the thorax. Bandage material was placed over the patch and encircled the thorax. For the butorphanol group, a placebo patch was applied to the shaved area over the thorax, and a similar bandage was placed. At least 18 hours after application of the patches, cats were sedated with acepromazine (0.05 mg/kg [0.02 mg/lb], IM) and ketamine hydrochloride (7 mg/kg [3.2 mg/lb], IM). Cats in the butorphanol group were given butorphanol (0.2 mg/kg, IM) rather than acepromazine and ketamine. Cats in the TDF group were given saline solution (volume was equivalent to the volume of a 0.2 mg/kg dose of butorphanol, IM). The individuals administering drugs to the cats and evaluating pain scores were blinded to the treatment.

Twenty minutes after sedation, anesthesia was induced in all cats with thiopental sodium (10 mg/kg [4.5 mg/lb] to effect). The cats were anesthetized and maintained with halothane in oxygen via an endotracheal tube. Throughout surgery, cats were monitored by use of pulse oximetry and Doppler ultrasound blood pressure measurements. Jugular catheters were placed at the time of surgery to facilitate collection of blood samples after surgery. Onychectomies were performed by 1 individual (KLG) using the guillotine technique,11 and only those cats undergoing forefoot onychectomies were included in the study. The toe incisions were closed, using 1 drop of tissue glue,10 and no bandages were applied. Bandages were not used after onychectomies in this study, because placement of bandages alone without surgery has been shown to increase plasma cortisol concentrations and agitation in cats.11 These findings could be mistaken for signs of pain and falsely increase pain scores. Closing the wound with tissue glue allowed cats to function more normally following surgery. If bleeding occurred following surgery, a temporary bandage was placed for 30 minutes to control bleeding.

At the time of extubation, blood samples were collected for determination of plasma cortisol and fentanyl concentrations. At that time, the butorphanol group received butorphanol (0.2 mg/kg, IM), and the TDF group received an equivalent volume of saline solution. Heart rate, temperature, respiratory rate, response to handling feet, and pain scores were determined as previously described (Appendix) at the time of extubation and 2, 4, 8, 12, 24, 36, and 48 hours after surgery. If a cat had a total pain score > 8 at any time during the procedure or a score of 3 in any of the first 3 categories, it was given oxymorphone hydrochloride (0.05 mg/kg, IM). Appetite was also recorded 8, 12, 24, 36, and 48 hours after surgery. Blood samples were taken 12 and 48 hours after surgery to determine plasma fentanyl concentration and 2, 4, 8, 12, 24, 36, and 48 hours after surgery to determine plasma cortisol concentration. Four, 8, and 12 hours after extubation, cats in the butorphanol group were given additional doses of butorphanol (0.2 mg/kg, IM), and cats in the TDF group received an equal volume of saline solution IM.

Measurement of plasma fentanyl concentrations—Blood was collected in sodium fluoride tubes for measurement of plasma fentanyl concentration and refrigerated at 4 C until analyzed. Plasma fentanyl concentration was measured, using gas chromatography-mass spectrometry.13 The lowest limit of detection for this assay is 0.1 ng/ml.

Measurement of plasma cortisol concentrations—Plasma was collected and frozen at −70 C until analysis. Cortisol was assayed by use of radioimmunoassay.14 The detection range of this assay is 2 to 500 ng/ml.

Statistical analyses—An unpaired Student t-test was used to compare data between treatment groups at each time point. A 1-way ANOVA was performed, and when F was significant (P < 0.05), a least significant difference test was performed to evaluate changes over time. A Wilcoxon rank sum test was used to compare pain scores. A Pearson χ² test was used to evaluate appetite and response to handling feet. Differences were considered significant when P < 0.05.

Results—There was 1 sexually intact male, 9 castrated males, and 12 spayed females. There was no difference between groups in regard to gender. Mean ± SD age of cats was 13.45 ± 12.69 months (range, 5 months to 4 years); mean ± SD weight was 3.34 kg ± 0.81 kg (7.35 ± 1.78 lb; range, 2.2 to 5 kg [4.84 to 13.2 lb]). Age and weight of the TDF group were not significantly different from age and weight of the butorphanol group.

Twenty-two cats completed the study. Two cats in the TDF group removed their jugular catheter before blood samples for the 12-hour plasma cortisol concentrations were obtained. One cat in the butorphanol group removed its jugular catheter after the 24-hour plasma cortisol concentration was obtained. Plasma cortisol concentrations were not measured in these 3 cats once their jugular catheters were removed. No cat had a pain score > 3 in the first 3 categories or a total pain score > 8; therefore, supplemental oxymorphone was not administered (Appendix).

Significant differences in mean rectal temperature between the TDF group and butorphanol group were observed 2 and 4 hours after surgery (P = 0.021 and 0.023, respectively), with the TDF group having a higher temperature (Fig 1). The TDF group also had a significantly higher mean heart rate 2 hours after surgery, compared with the butorphanol group (Fig 2). There were no significant differences in mean respiratory rates between the 2 groups at any time during the study.
Eight hours after surgery, the TDF group had a significantly lower pain score than the butorphanol group ($P = 0.045$). Both groups had significantly lower mean plasma cortisol concentrations 0, 24, 36, and 48 hours after surgery, compared with mean plasma cortisol concentrations 18 to 24 hours prior to surgery. Cats in the TDF group were subjectively euphoric, as noted in their hospital records.

Mean $\pm$ SD plasma fentanyl concentrations at 0, 12, and 48 hours after surgery were 1.73 $\pm$ 1.25, 2.88 $\pm$ 1.79, and 1.94 $\pm$ 0.96 ng/ml, respectively. Twelve hours after surgery, 1 cat had a plasma fentanyl concentration of 7 ng/ml, and this was accompanied by a rectal temperature of 105.4 F (40.8 C). No other cat had a plasma fentanyl concentration or a temperature increase of this magnitude.

Discussion

Other than a difference in pain score 8 hours after surgery, results of the present study did not reveal a difference in pain relief between TDF and IM butorphanol administration. Significantly lower plasma cortisol concentrations after surgery in both groups could be attributable to the fact that the preoperative blood samples were obtained by venipuncture, and subsequent blood samples were drawn from the jugular catheter.
without physical restraint. We also compared postoperative plasma cortisol concentrations to those obtained immediately after extubation and found no significant differences. Plasma cortisol concentrations in the cats of this study did not indicate a difference in analgesic effect between the TDF group and butorphanol group. Plasma cortisol concentrations have been observed to decrease after the administration of butorphanol, however, decreased plasma cortisol concentrations subsequent to administration of analgesics were not observed in another study. Similarity of plasma cortisol concentrations in the TDF and butorphanol groups indicates that both analgesics provided adequate pain relief. It is important to state that, for humane reasons, we did not have a control (ie, no analgesics) group.

Subjective pain scoring has been reported to be an accurate method of assessing pain in cats, as long as the observer is experienced and trained. In fact, observer knowledge and consistency appeared to be the most valuable factors in determining pain in 1 study; compared with measurement of plasma cortisol and β-endorphin concentrations. As with any subjective scoring system, there is always observer bias, results may depend on the evaluators’ experience, and results may not always be consistent. In our study, the observers were consistent with pain score assessment relative to each other and within their own observations. Unfortunately, objective measures such as plasma cortisol, endorphin, and catecholamine concentrations have not always been consistent measures of postoperative pain, and our current results demonstrate that plasma cortisol may also not be a consistent measure of analgesic efficacy in the absence of an untreated control group. Most recently, a pressure mat has been evaluated as an objective measure of pain following onychectomy in cats. Although use of the mat demonstrated that cats place less pressure on their feet following an onychectomy, no difference could be determined between groups that were given different analgesics. In contrast, dogs undergoing an orthopedic procedure given TDF were more likely to be sufficiently weight bearing 48 hours after surgery to obtain force plate data than dogs given morphine epidurally. Results of our study as well as previous studies emphasize the difficulty in finding a reliable, objective measure of pain in cats.

Results of a previous study revealed that TDF patches were associated with decreased appetite in cats. This was not observed in any of the cats in our study or the preliminary pharmacodynamic study with fentanyl patches in cats. Although cats in the current study that had fentanyl patches were thought to be euphoric and friendlier than cats in the butorphanol group, similar behavior changes were not reported in earlier studies. Plasma fentanyl concentrations in the present study were consistent with previous findings by others and similarly demonstrated a wide variation among cats (range, 0.3 to 7.0 ng/ml). Plasma fentanyl concentrations were highest 36 hours after application, although there was no sample taken between 36 and 72 hours after patch application to determine whether the concentration increased or remained the same. Lee et al. found that peak plasma fentanyl concentrations were obtained 48 hours after TDF patch application. No cats weighing less than 2.2 kg (4.84 lb) were used in this study; therefore, it is difficult to predict the effects of a 25-µg fentanyl patch on a smaller patient. None of the cats in the present study had clinical signs of overdosage from the TDF; however, this may be a problem in cats weighing less than 2.2 kg (4.84 lb). Also, it is important to state that the plasma fentanyl concentration associated with pain relief in cats is still undetermined. It has been speculated that a concentration of 0.95 ng/ml is effective for analgesia in dogs. In humans, a plasma fentanyl concentration between 0.23 to 1.90 ng/ml has been associated with analgesia. Given the results of our study, it appears that cats also have a range of plasma fentanyl concentrations that are associated with an analgesic effect.

In conclusion, TDF provides similar analgesia to butorphanol given for 12 hours after surgery. The primary advantage of TDF is that it provides continuous, noninvasive delivery of an analgesic, whereas butorphanol has to be repeatedly administered by IM injection to provide a similar analgesic effect to TDF. We found the patch was easy to apply and well tolerated by cats. These advantages may be enough to compensate for ready availability of butorphanol in most veterinary practices and a cost of TDF patches that is approximately 2 times that of butorphanol as used in this study.

References


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**Appendix**

**Pain score assessment in cats following onychectomy**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying/growling</td>
<td>Not crying or growling</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Responds to calm voice</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Does not respond to calm voice</td>
<td>2</td>
</tr>
<tr>
<td>Movement/Agitation</td>
<td>None/calm asleep</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Occasional position changes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Frequent position changes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Thrashing/hysterical</td>
<td>3</td>
</tr>
<tr>
<td>Feet</td>
<td>Not bothering feet</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Shaking feet</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Occasionally chewing at feet</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Frequently chewing at feet</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate</td>
<td>&lt; 10% increase above preoperative value</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11–20% increase above preoperative value</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21–30% increase above preoperative value</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 30% increase above preoperative value</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt; 10% increase above preoperative value</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11–20% increase above preoperative value</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21–30% increase above preoperative value</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 30% increase above preoperative value</td>
<td>3</td>
</tr>
<tr>
<td>Total possible points</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

Supplemental analgesics are administered to cats with a pain score > 8 or if they obtain the highest score in any of the first 3 categories.