Evaluation of an osmotic pump for fentanyl administration in cats as a model for nondomestic felids

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Objective—To evaluate the reliability of an SC implanted osmotic pump (OP) for fentanyl administration in cats and to compare serum concentrations of fentanyl delivered via an OP and a transdermal patch (TP).

Animals—8 spayed female cats.

Procedures—in a crossover design, cats received fentanyl at 25 µg/h via a TP or an OP. All cats were anesthetized for the pump or patch placement (0 hours) and again when it was removed (96 hours). Venous blood samples were collected for measurement of serum fentanyl concentrations at 0, 6, 12, 24, 36, 48, 72, and 96 hours and at 24 and 48 hours after device removal. After a 3-week washout period, the experiment was repeated with each cat receiving the other treatment.

Results—Mean serum fentanyl concentrations at 24, 36, 72, and 96 hours were greater when the OP was used than when the TP was used. Mean residence time and half-life were greater when the TP was used. Fentanyl concentration changed significantly faster in initial and elimination phases when the OP was used. Marked interindividual variation in serum fentanyl concentrations was evident with both administration methods. No adverse effects were evident with either method.

Conclusions and Clinical Relevance—Use of the OP to administer fentanyl to cats resulted in a shorter initial lag phase to a therapeutic serum concentration, higher bioavailability, and faster elimination after removal, compared with use of a TP. These advantages, in addition to the inability of cats to remove the OP, may make OPs useful for fentanyl administration in nondomestic felids. (Am J Vet Res 2009;70:950–955)
sustained blood concentration of the drug, and tolerance by cats and their owners. However, transdermal patches are easily removed by cats, there is an initial lag phase before therapeutic blood concentrations of fentanyl are reached, and the half-life of fentanyl is typically long after patches are removed. In addition, some studies have revealed that plasma or serum concentrations of fentanyl administered via transdermal patches can be highly variable. In the authors' experience, use of transdermal fentanyl patches to manage postoperative pain in nondomestic felids yields poor results because the felids remove the patches within minutes after recovery from anesthesia.

Osmotic pumps have been designed for continuous dosing of medications in laboratory animals. These miniature cylindric implants range in length from 1.5 to 3.1 cm. The pumps operate on the basis of an osmotic pressure difference between the extracellular fluid and the osmotic agent in the pump; no battery or external power source is required. As water diffuses across the outer semipermeable membrane, the so-called salt-sleeve compartment expands and presses on the flexible drug reservoir, thereby releasing the drug at a controlled, continuous rate. Because the pump rate is determined by properties of the semipermeable membrane and osmotic agent, it is independent of the properties of the drug dispensed. Although used in domestic cats for research purposes, osmotic pumps have not been evaluated for clinical use in felids. Similar to transdermal patches, implanted osmotic pumps eliminate the need for oral administration or repeated injections of analgesics. Additional advantages include the facts that an osmotic pump cannot be removed by the recipient, it does not require any protective bandaging, and it may eliminate the lag phase, prolonged half life, and variable blood concentrations characteristic of fentanyl patches because it does not rely on skin contact for absorption.

The purpose of the study reported here was to evaluate the reliability of an SC implanted osmotic pump for fentanyl administration in cats and to compare serum concentrations of fentanyl administered via an osmotic pump with those achieved via a transdermal patch. Fentanyl was chosen as the analgesic because of its wide experience, use of transdermal fentanyl patches to manage postoperative pain in nondomestic felids yields poor results because the felids remove the patches within minutes after recovery from anesthesia. A 2-cm skin incision was made, and the subcutaneous tissue was bluntly dissected 8 to 10 cm caudal from the incision. An osmotic pump loaded with fentanyl was placed into a subcutaneous pocket, and the skin was closed with 3-0 polydioxanone in a subcuticular pattern. Site preparation, patch placement, bandaging, and surgeries were all performed by the same individual (JMS) to ensure consistency.

At 96 hours after patch or pump placement, all cats were again sedated with acepromazine and ketamine to equalize the potential effects of sedation on fentanyl metabolism between fentanyl delivery methods; no isoflurane was administered. For the cats with pumps, the incision site was infiltrated with lidocaine and reopened and the pump was removed. The skin incision was subsequently closed with 3-0 polydioxanone in a subcuticular pattern. After a 3-week washout period, the experiment was repeated with each cat receiving the other treatment. Throughout the study, cats were subjectively evaluated for adverse reactions including dysphoria, inappetence, and local skin irritation or infection at the device placement site.

Sample collection—Blood samples (1.5 mL) were obtained just prior to (0 hour) and at 6, 12, 24, 36, 48, 72, and 96 hours after pump or patch placement and at 24 and 48 hours after pump or patch removal. The samples were obtained from the IV catheter until it failed or was removed at 72 hours, after which they were obtained via direct venipuncture. Serum was separated and stored at −70°C until analyzed. To maintain patency of blood vessels, the catheters were flushed with 0.5 to 1 mL of heparinized saline solution (2 U of heparin/mL) every hours until removed. To maintain blood volume and prevent dilution of the sample from the heparinized saline solution in the catheter, an initial 0.5 to 1.0 mL of blood was withdrawn into 0.25 mL of heparinized saline solution and injected back through the catheter after the blood sample was obtained.

Materials and Methods

Animals—Eight spayed female cats were acquired on loan from a research colony maintained for use in minimally or noninvasive nutritional or pharmacokinetic studies. Mean ± SD age of the cats was 56 ± 4 months, and mean body weight was 4.5 ± 0.9 kg. The study protocol was approved by the University of Tennessee Institutional Animal Care and Use Committee.

Fentanyl and pump preparation—A particular model of osmotic pump was selected to deliver fluid at a rate of 10 µL/h. The target dosage of fentanyl was 25 µg/kg, which was equivalent to the theoretic dosage of fentanyl in the transdermal patch also used in the study. The concentration of fentanyl required was calculated as the target dosage divided by the pump rate. Powdered fentanyl was dissolved in sterile saline (0.9% NaCl) solution to a concentration of 2.5 mg/mL, and each pump was filled with 2 mL of this solution. Pumps were weighed before and after loading to verify the exact fluid volume. The volume of fentanyl solution remaining in the pumps after removal was also measured.

Experimental protocol—A crossover study design was used, with 4 cats assigned to first receive a transdermal patch and the other 4 assigned to first receive an osmotic pump. All cats were sedated with acepromazine maleate (0.05 mg/kg, IM) and ketamine (10 mg/kg, IM), and anesthesia was induced with isoflurane in 100% oxygen delivered via a face mask. A 19- or 22-gauge central-line catheter was placed in a medial saphenous or jugular vein and secured in place with protective bandaging. In the cats assigned to receive a transdermal patch, hair on the lateral thorax was shaved with care taken not to abrade the skin. No other preparation of the skin was performed. One transdermal fentanyl patch was placed on the shaved site and secured in place with an adhesive bandage placed around the thorax. In the other 4 cats, the dorsal midline between the scapulae was clipped and aseptically prepared with chlorhexidine scrub. A 2-cm skin incision was made, and the subcutaneous tissue was bluntly dissected 8 to 10 cm caudal from the incision. An osmotic pump loaded with fentanyl was placed into a subcutaneous pocket, and the skin was closed with 3-0 polydioxanone in a subcuticular pattern. Site preparation, patch placement, bandaging, and surgeries were all performed by the same individual (JMS) to ensure consistency.

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Fentanyl assay and pharmacokinetic analysis— Serum fentanyl concentrations were measured with a radioimmunoassay kit. The limit of detection of the assay was 0.25 ng/mL. For the purpose of statistical analysis, measurements < 0.25 ng/mL were assigned a value of 0.0 ng/mL. The calibration curve was obtained by use of fentanyl standards supplied with the kit (0, 0.25, 0.5, 1.0, 2.5, and 7.5 ng/mL). The assay was validated by use of pooled serum from blood samples obtained before treatment of cats; samples were fortified with fentanyl at 5 concentrations (0, 1.5, 3, 4.5, and 6.0 ng/mL). Samples were analyzed in duplicate, and the values were reported as the mean of the 2 results. Mean ± SD intra-assay variation was 2.7 ± 1.8%, and interassay variation was 2.7 ± 1.3%.

Pharmacokinetic analysis—The following pharmacokinetic parameters for fentanyl in each cat were calculated individually by use of noncompartmental analysis and a statistical software program: maximum serum concentration, AUC<sub>0-144</sub>, AUC from 0 hours to infinity, AUMC from 0 to 144 hours, AUMC from 0 to infinity, AUC from 0 to 144 hours, MRT<sub>0-144</sub>, MRT from 0 to 144 hours, and T<sub>1/2</sub> eff. Maximum serum concentrations of fentanyl, T<sub>max</sub>, T<sub>det</sub>, and T<sub>eff</sub> were also calculated. Because a true steady state was not achieved, a C<sub>mean</sub> was calculated from measurements obtained from 24 through 96 hours after device placement.

Statistical analysis—Data were evaluated by use of statistical software and a crossover repeated-measures ANOVA model, with cat, treatment order (whether cats were first treated with a patch or a pump), delivery type, and measurement time as factors. Cat age and body weight were included as covariates. The variability of data obtained when the osmotic pump was used was compared with that obtained when the transdermal patch was used by means of fit statistics from a model that allowed unequal variances. The pharmacokinetic parameters were compared with an ANOVA for a crossover design, with cat, treatment order, and delivery type as variables. Post hoc comparison of means was performed with the least significant difference method. In addition, statistical contrasts were used to compare the rate of change in the initial phase (measurements made at 0 and 6 hours vs 12 and 24 hours after device placement) and recovery phase (measurements made at 96 vs 120 hours and 96 vs 144 hours after device placement) between the pump and patch devices. Significance was set at P < 0.05. Results are reported as mean ± SD.

Results
All 8 cats completed the study, and no adverse reactions were detected in any cat during the study period. Although behavior was not objectively scored, the cats appeared to be calmer and more social when either device was applied, compared with their behavior after the osmotic pump or transdermal patch was removed. There were no anesthetic complications during sedation for pump or patch removal in any cat.

Data from 1 cat were removed from pharmacokinetic and statistical analyses because of high pretreatment serum fentanyl concentrations measured prior to patch or pump placement (0.9 and 1.26 ng/mL, respectively) and serum fentanyl concentrations that were consistently higher than those of the other cats throughout the study. Two other cats had low but measurable serum fentanyl concentrations at 0 hours (0.38 and 0.26 ng/mL) at 1 sampling time and were included in all analyses.

Because no difference in fit was detected when variances were allowed to differ during statistical modeling, additional analyses were performed with the assumption of equal variances between data from the pump and patch treatments. Visual examination of SDs across times and treatments also revealed no apparent changes in variability attributable to the pump or patch device.
Post hoc analysis of the data revealed an overall difference between delivery devices (pump vs patch), with specific significant differences in serum fentanyl concentrations at 24 (3.7 vs 1.5 ng/mL), 36 (3.6 vs 2.1 ng/mL), 72 (3.7 vs 2.0 ng/mL), and 96 (3.7 vs 3.0 ng/mL) hours after device placement (Figure 1). The AUC_{0–144}, T_{max}, and T_{1/2} were detected between treatment devices. This lag phase was consistent with findings of other studies of fentanyl transdermal patches in cats but was unexpected for the osmotic pump. One explanation is that the osmotic pumps did not start delivering the drug immediately after implantation because it took time for the salt-suckle compartment to expand enough to compress the flexible drug reservoir. In a laboratory setting, this delay may be eliminated by soaking the pump for 4 to 6 hours in sterile saline solution prior to implantation. Priming was not performed in the present study because it was deemed impractical for a clinical setting. However, although the aforementioned pharmacokinetic parameters were not significantly different between analgesic delivery methods, serum fentanyl concentrations associated with the transdermal patch did not differ from 0 to 24 hours after patch placement, whereas the serum fentanyl concentrations achieved by use of the osmotic pump did differ from 0 to 12 hours. In addition, the initial-phase statistical contrasts revealed that serum fentanyl concentrations increased at a faster rate when fentanyl was delivered via a pump instead of a patch. Therefore, whereas use of an osmotic pump did not eliminate the lag phase that was evident when a transdermal patch was used, it did decrease the lag phase and therefore may have yielded an analgesic effect sooner than the patch. We were unable to explain why this difference in lag phase duration was not reflected in the pharmacokinetic calculations, but the small sample size and large degree of variation in fentanyl concentration between cats may have contributed to the lack of significant findings.

Fentanyl was more quickly eliminated from serum when an osmotic pump rather than a transdermal patch was used, as indicated by the significantly shorter T_{1/2}, MRT, and T_{1/2}, when the pump was used. In addition, results of the statistical contrasts indicated a faster return to lower concentrations when the pump rather than the patch was used. The long T_{1/2} achieved when the patch was used was consistent with findings of studies involving cats. The long elimination period associated with the transdermal patch is hypothesized to be attributable to a cutaneous depot of fentanyl that is created in the skin beneath the patch and that continues to release fentanyl into circulation after the patch is removed.22,23 This so-called depot effect reportedly develops in cats,1,5,6,13,22 and, to a lesser degree, goats,10 but does not develop in dogs.6,13 Because osmotic pumps do not rely on the skin for absorption of analgesic and there is no opportunity for creation of a cutaneous depot of drug, the faster elimination period associated with the osmotic pump in the study reported here supported the depot-effect hypothesis.

The serum concentrations of fentanyl achieved by use of the 2 delivery devices decreased to less than the therapeutic concentration of 1 ng/mL at similar time points, suggesting that, despite the faster drug elimination rate when the osmotic pump rather than the transdermal patch was used, the timing of the therapeutic effect would be similar with either device. However, use of the pump resulted in a higher C_{10}, than did use of the patch. If the dose of fentanyl in the pump was adjusted such that the C_{10} for both delivery devices was the same, it would be expected that the serum concentration of fentanyl achieved by use of the pump would decrease to lower than the therapeutic concentration before it would if a patch was used. The concentration at which adverse effects of fentanyl develop in domestic cats is unknown. Such adverse effects can include respiratory depression, dysphoria, and inappetence.7 The sensitivity of nondomestic cats to these adverse effects is also largely unknown. Although specific opiate-receptor antagonists (eg, naltrexone) are available in the event of adverse reactions, faster fentanyl elimination may require less frequent antagonist administration and result in a safer situation should an adverse event occur. Therefore, if fentanyl is to be used for nondomestic cats, then the faster elimination of fentanyl after removal of a delivery device is an important advantage of the osmotic pump versus the transdermal patch.

The variability of serum fentanyl concentrations when the transdermal patch was used in the present study was consistent with findings in other studies involving humans and other animals. Explanations for the variability among results of various studies, taxa, and study subjects have included differences in patch adherence, skin anatomy (ie, thickness and composition of the stratum corneum), skin temperature, and local cutaneous blood flow.4,13,22 This variability, however, was still evident in the present study when the osmotic pump was used to administer fentanyl, even though this method theoretically should not be affected by many of the aforementioned sources of variation. Some of the variability evident when the pump was used may be explained by our attempt to maintain the same dose of fentanyl per cat despite the variation in the body weight among cats. However, when age and body weight were included in the ANOVA model, there was no difference in variation between results for the pump and patch methods. This finding suggested that individual variation in metabo-
lisim of fentanyl may be a more important source of variability in serum fentanyl concentrations than factors related to patch placement or cutaneous anatomy. Results of other studies that support this supposition include pharmacokinetic studies of IV fentanyl administration in humans, 22–25 dogs, 13 and cats, 11 in which large degrees of interindividual variation were also detected. To further elucidate the most important sources of variation in serum fentanyl concentrations, additional studies are needed in which IV, SC (via an osmotic pump), and transcutaneous administration of fentanyl are evaluated in larger numbers of cats.

Another source of variability in the present study may have been the assay with which serum fentanyl concentrations were measured. Radioimmunoassays, particularly the type we used, have been used to measure serum or plasma fentanyl concentrations in domestic cats in other studies. 1,5–11,12,13 However, most radioimmunoassays for fentanyl detection were developed for use with horse urine. Therefore, whereas validation procedures were used in the present and previous studies, the assay is not optimized for cat serum; consequently, results may be more variable than those of other types of assays such as high-performance liquid chromatography. The cause for the consistently high concentrations measured in the cat that was excluded from statistical and pharmacokinetic analyses in the present study was unknown, although it should be considered that this was the heaviest cat. The radioimmunoassay involves competitive binding to precoated vials between a known quantity of radiolabeled fentanyl and an unknown quantity of fentanyl in the test sample. A higher measured radioactivity in the vial indicates a lower fentanyl concentration in the test sample. Thus, it is possible that some factor in that cat’s serum displaced the radiolabeled fentanyl from the vial, resulting in inaccuracy in high serum fentanyl concentrations.

The reason for detection of fentanyl in serum from blood samples obtained from 2 cats before fentanyl administration is also unclear. An inadequate washout period between trials is unlikely because only one of these samples (0.38 ng/mL) was obtained after the washout period. Cross-contamination of samples may have occurred, although this is unlikely because pipette tips were changed between serum samples throughout sample handling. Hemolysis can also affect the results of radioimmunoassays of fentanyl in cats such that serum fentanyl concentrations appear falsely high. 3 Whereas the serum samples used in the present study did not have gross evidence of hemolysis, it is possible that inapparent hemolysis interfered with analysis of the samples from the 2 cats, resulting in falsely high values. Because these anomalies were more likely attributable to the sample as opposed to the cat and the values were near the limit of assay detection (0.25 ng/mL), the data were still included in the analyses.

The higher values for \( \text{AUC}_{0–48} \), \( \text{AUC}_{0–144} \) and \( \text{C}_{\text{mean}} \) associated with osmotic pump versus transdermal patch administration of fentanyl were likely attributable to higher bioavailability of fentanyl delivered via pumps. Bioavailability of fentanyl administered via transdermal patches is reportedly 18% to 62% of the theoretic dose in cats 4 and 27% to 99% in dogs. 13 This decrease in bioavailability is believed to be primarily attributable to incomplete patch adherence, although the aforementioned sources of variation and first-pass cutaneous metabolism may also play a role. 1,3 Unlike transdermal patches, osmotic pumps do not rely on the properties of skin for absorption of drugs that they are intended to administer; therefore, cutaneous factors are not involved, resulting in more fentanyl available for absorption and a higher overall serum drug concentration. Whereas more studies are needed to test this hypothesis, a lower dosage of fentanyl administered via the pump may yield therapeutic drug concentrations that are similar to those of transdermal patches.

Compared with a transdermal patch, an osmotic pump provides several pharmacokinetic advantages for fentanyl administration in cats. The initial lag phase to achieve a therapeutic serum fentanyl concentration is shorter, the bioavailability of fentanyl is higher, and fentanyl is eliminated from the circulation faster after device removal. In addition, an osmotic pump does not require protective bandaging and cannot be removed by cats. The major disadvantages of using a pump for administration of fentanyl are that a second minor surgery for pump removal is required and there is the potential for infection at the surgical site. These disadvantages may limit the usefulness of osmotic pumps in domestic cats. However, in nondomestic cats that have undergone surgery, a second anesthetic session or immobilization is commonly required for follow-up diagnostics such as radiographic evaluation or blood tests, at which time a pump could be removed. On the basis of the findings of the present study, additional studies are warranted in which the usefulness of osmotic pumps for fentanyl administration in nondomestic felids is evaluated.

References