

Transdermal Fentanyl Patches in Small Animals

Fentanyl citrate is a potent opioid that can be delivered by the transdermal route in cats and dogs. Publications regarding transdermal fentanyl patches were obtained and systematically reviewed. Seven studies in cats and seven studies in dogs met the criteria for inclusion in this review. Dogs achieved effective plasma concentrations approximately 24 hours after patch application. Cats achieved effective plasma concentrations 7 hours after patch application. In dogs, transdermal fentanyl produced analgesia for up to 72 hours, except for the immediate 0- to 6-hour postoperative period. In cats, transdermal fentanyl produced analgesia equivalent to intermittent butorphanol administration for up to 72 hours following patch application. *J Am Anim Hosp Assoc* 2004;40:468-478.

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Introduction

Fentanyl citrate, an opioid from the 4-anilinopiperidine class, has been used for decades in both human and veterinary medicine.^{1,2} In 1991, the Alza Corporation designed a patch system^a to continuously release fentanyl through the skin and into the systemic circulation.³ The patch delivery would theoretically achieve and maintain steady-state therapeutic plasma levels more readily than bolus administration. The first appearance of transdermal fentanyl patches in the clinical veterinary literature was in 1996.⁴ Including that study, eight research studies in cats and seven in dogs have been published over the past 8 years.⁴⁻¹⁸

Despite these reports, there is still confusion and disagreement regarding some aspects of fentanyl patch placement, use, and disposal. Systematic reviews have been used in human medicine to collate a variety of disparate publications and have several advantages over narrative reviews.¹⁹ These advantages include the use of explicit methods to limit bias in identifying and rejecting studies, the development of more reliable and accurate conclusions because of the methods used in the review, identification of inconsistencies across studies, the generation of new hypotheses about particular subgroups, and the ability to formally compare different studies to establish universality of findings and consistency of results.²⁰ The purpose of this paper was to develop clinical recommendations for the use of transdermal fentanyl patches in dogs and cats on the basis of a narrative review, a systematic review, and a simple cost analysis.

Fentanyl Characteristics

Fentanyl is a potent mu opioid-receptor agonist.²¹ The reported potency of fentanyl has varied widely but is generally accepted to be approximately 100 times that of morphine.^{21,22} The absolute receptor-binding affinity, however, is only 1.7 times that of morphine.²³ The higher potency

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of fentanyl has been attributed to its lipophilic nature, which enhances its ability to cross the blood-brain barrier.²³ Fentanyl has an oral bioavailability of 30% in people and a transdermal bioavailability of 63.8% in the dog and 35.9% in the cat.^{6,10,24}

Characteristics of mu-agonists include analgesia, sedation, increased segmental contractions in the gastrointestinal tract, decreased propulsive contractions in the gastrointestinal tract, increased tone of certain sphincters (i.e., bile duct, urethra), respiratory depression, emesis, physical dependence, bradycardia, and miosis.²⁴ The pharmacokinetics of injectable fentanyl in the dog have been described.⁶ Although the mean distribution half-life in the dog is substantially longer than in people, the clinical effects of injectable fentanyl are too short-acting in the dog for it to be used effectively for long-term analgesia by bolus administration.^{6,25-28} Fentanyl has been used as a component of balanced anesthesia in dogs and can be used for analgesia via intravenous constant-rate infusion.^{29,30}

In people, transdermal fentanyl is contraindicated in postoperative situations but is indicated in patients with cancer pain. These indications are based on premarketing clinical evaluations that documented an incidence of respiratory depression in 4% of postoperative patients and in 2% of cancer patients who received fentanyl.^b In normal dogs, clinically insignificant respiratory depression occurs at the plasma concentrations of fentanyl obtained by transdermal patches.³¹ Following surgery in dogs, transdermal fentanyl does not cause respiratory depression, despite reaching relatively high plasma fentanyl concentrations.¹⁴ Therefore, transdermal fentanyl is not contraindicated in dogs in the postoperative period. Careful monitoring of effectiveness and potential adverse effects is warranted, however, in all animals after application of a transdermal fentanyl patch.

In the United States, fentanyl is a Schedule II drug according to the Controlled Substances Act of 1970. A Schedule II drug has a high potential for abuse and a currently accepted human medical use with severe restrictions, and abuse of the drug may lead to severe psychological or physical dependency.^c It has been documented that significant reserves of fentanyl may remain in transdermal patches even after several days of use, and these reserves can be abused.^{32,33} Fentanyl patches may be prescribed and applied to an animal that is to leave the veterinary hospital.^d

As with all off-label drug applications, a consent form signed by the owner is required by some states for use of these patches. Owners should be informed of the potential risks of fentanyl exposure to people within the household, particularly children. Disposal of the patch is done by folding the patch upon itself and flushing it down a toilet, as recommended by the manufacturer.^b Some sources recommend wearing gloves and cutting the patch before flushing it down the toilet, so that any fentanyl remaining in the patch diffuses out and an individual finding a patch fragment will be unable to abuse it.³⁴ Any other disposal method may not fully prevent access to unused drug in the patch.

Transdermal Delivery

Transdermal delivery systems have been used to administer a variety of medications in people, including clonidine, estradiol, fentanyl, nicotine, nitroglycerin, scopolamine, and testosterone.³⁵ Although historically the transdermal route has been limited to pesticides in small animals, it is becoming a more popular method of administering pharmaceutical agents.³⁵ Advantages of transdermal delivery include continuous delivery that minimizes plasma concentration peaks and troughs, bypass of hepatic first-pass metabolism associated with oral and rectal administration, noninvasiveness, and reduced frequency of dosing. Disadvantages of transdermal delivery include the potential for cutaneous irritation, unpredictable and variable uptake, and the need to shave a patch of hair for placement of the delivery system in some instances.³⁵

The skin's natural structures serve to prevent transmission of substances to the systemic circulation. The stratum corneum, the outermost layer of the epidermis, is the location of most of the skin's chemical barriers.³⁵ The keratinized cells of the stratum corneum are surrounded by an intercellular lipid matrix that maintains the structure of the stratum corneum.³⁵ This lipid matrix is the primary route of transit for transdermal drugs and is the source of the requirement that the drug be lipophilic.³⁵ Hydrophilic drugs are unable to pass through the lipid matrix. Deep to the epidermis lies the dermis, which is largely aqueous. A highly hydrophobic (lipophilic) compound cannot pass through this barrier and into the underlying circulation. Hence, transdermal drugs must be mildly to moderately lipophilic.³⁵ Fentanyl and related drugs fulfill this criterion, whereas morphine is significantly less lipid-soluble, making it unsuitable for transdermal delivery.³⁶

Disruption of the stratum corneum (e.g., wounds, scratches) can significantly alter absorption of transdermal medications.³⁵ Caution must be taken in clipping animals in preparation for patch placement, because of the potential for abrading the skin. Hydration of the stratum corneum also affects absorption.³⁷ Dermal perfusion can change by a factor of 100, thereby altering the amount of drug taken up by the local circulation and distributed to the body.³⁸ Factors affecting dermal perfusion (e.g., body temperature, cardiac output, oxygenation, etc.) may theoretically influence transdermal fentanyl absorption. However, it has been demonstrated in people that cutaneous blood flow is not a significant factor in the rate of absorption of transdermal fentanyl.³⁹

Even though transdermal delivery bypasses hepatic first-pass metabolism, cutaneous metabolism may occur.³⁵ Although it has been documented that cutaneous metabolism of fentanyl does not occur in people, similar studies in animals have not been performed.⁴⁰ Skin thickness in people may affect the rate of uptake of the fentanyl.³⁹ A small study in four dogs documented a positive correlation between increased epidermal thickness and the time needed to attain 0.5 ng/mL plasma fentanyl concentrations ($r^2=0.94$, $P<0.05$).⁵ Epidermal thickness, however, did not affect peak plasma concentrations or area under the (fentanyl

absorption) curve between 24 and 72 hours. Therefore, thick skin may delay the onset of effective plasma levels, but it probably does not affect peak plasma levels or the amount of fentanyl delivered.

A change in body temperature of 3°C has been shown to alter plasma levels of fentanyl from transdermal absorption in people.³⁹ This effect has not yet been investigated in animals but should be considered in hyperthermic patients. Overdosage has occurred in people when the patched area was exposed to a heating pad.³⁹

The effects of mild hypothermia (95°F) concurrent with general anesthesia on transdermal fentanyl absorption have been investigated in dogs and cats.^{17,18} In both animals, plasma fentanyl concentration decreased compared to baseline in the hypothermic but not the normothermic groups.^{17,18} Anesthesia resulted in a significant decrease in plasma concentration in the normothermic animals.^{17,18} There was no difference between hypothermic and normothermic groups in regard to the area under the curve for the plasma concentrations, and there was no difference between groups in the amount of decrease in plasma concentration resulting from general anesthesia.^{17,18} These results suggested that hypothermia has an impact on plasma fentanyl concentrations, but the impact seemed to be mild.

The transdermal fentanyl patch system presently in use is composed of five layers [Figure 1]. The drug reservoir contains 10 mg, 7.5 mg, 5 mg, or 2.5 mg fentanyl mixed with alcohol and hydroxyethylcellulose. Alcohol enhances fentanyl uptake through the epidermis by approximately 500 times.⁴⁰ The rate of drug release from the patch is related to the surface area of the patch exposed to skin (25 µg/hour per 10 cm²). A rate-limiting membrane is responsible for reducing interindividual variations in skin permeation by up to 50%.^{37,40} The patch adhesive also contains fentanyl so that an initial bolus of drug is delivered after placement of the patch. It is unknown if this initial bolus has any significant impact on plasma levels in animals. The system must remain intact. Cutting the patch allows the contents of the drug reservoir to come into direct contact with the skin, possibly resulting in a profound overdose.⁴²

Literature Review

A Pubmed[®] search was performed using the search terms “dog” or “cat” and “transdermal fentanyl.” Other published journal articles (not cited by PubMed) relating to pharmacokinetics, pain management, and anesthesia were also searched. Studies that compared pain scores between proto-

cols had to satisfy the following criteria for inclusion in this review: randomization of cases, blinding of observers, and specification of which pain scoring system was used. Studies that documented plasma levels had to include the following data for inclusion in the review: description of times of sampling, accurate accounting of all samples taken, description of sample analysis, and use of radioimmunoassay methodology.⁴³ Abstracts were not included.

When necessary, data included in this review were derived from graphs provided in the publication or from direct contact with publications' authors. Mean dosages for each patch size and species were derived from the literature by multiplying the number of animals with the mean weight of the animals to achieve an overall weight for each study. These overall weights were then totaled together and divided by the total number of animals for all studies. This provided the total mean weight. The patch size was then divided by this total mean weight. This calculation was performed because individual weights were not available for all animals in all the studies.

Results of Literature Review

Fourteen publications satisfied the selection criteria for this review. Seven publications dealt with the use of transdermal fentanyl patches in cats.^{10-13,15,16,18} Seven publications evaluated patch use in dogs.^{5-9,14,17} Six studies evaluated the analgesic efficacy of transdermal fentanyl.^{8,9,11-13,15} The results of these studies are summarized in Table 1.

The location of patch application in dogs varied between studies and included the lateral thorax (n=3), dorsal thorax (n=2), dorsal cervical region (n=1), and caudal abdomen (n=1). In dogs, the application area was cleaned with water (n=3), with soap (n=2), or not cleaned (n=2). All patches were covered with a bandage wrapped around the dog and over the patch, except for one study where the patches were left uncovered.¹⁴

Patches were applied either to the dorsal cervical region (n=1) or lateral thorax (n=6) of cats. The patch application area was cleaned with water (n=1) or not cleaned (n=3). There was no mention of how the patch site was prepared in three of the feline studies. All patches were covered with a wrap that encircled the cat.

All cats received 25 µg/hour patches except for one group of eight animals, which received 25 µg/hour patches that were only half uncovered.¹⁶ The mean dose of fentanyl received by the cats was 7.29 (range 4.2 to 11.4) µg/kg per hour for the 25 µg/hour patches. The mean dose could not

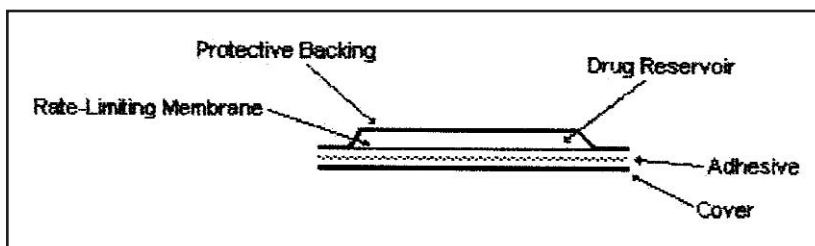


Figure 1—Fentanyl transdermal patch structure.

Table 1
Summary of Publications Evaluating Transdermal Fentanyl Patches in Dogs and Cats

No. Animals Per Group; Patch Size ($\mu\text{g}/\text{h}$)	Pain Assessment Method*	Method of Skin Preparation and Placement Site	Mean Dose of Fentanyl ($\mu\text{g}/\text{kg}/\text{h}$)	Time (in h) to Effective Plasma Concentration†	Duration (in h) of Effective Plasma Concentration†	Adverse Reactions‡	Reference No.
Dogs							
8; 100	NA: Pharmacokinetic study	Lateral thorax, rinsed with water	3.4	18	≥ 54	Bradycardia (n=1), anorexia (n=7), mild sedation (n=7)	5
6; 50	NA: Pharmacokinetic study	Dorsal thorax, cleaned with soap	3.7	10	≥ 62	None reported	6
6; 50 and 75; 100	NA: Pharmacokinetic study	Lateral thorax, rinsed with water	2.5, 3.77, 5.0	24, 10, 14	$\geq 48, \geq 62, \geq 58$	Moderate to severe skin reaction (n=2), mild sedation (n=3)	7
10; 50	Noninteractive behaviors, interactive behaviors, visual analogue scale, cortisol assays, physiological variables	Dorsal neck, no preparation	2.36	NA	NA	None reported	8
8; 100	Numeric rating scale, physiological variables	Dorsal thorax, cleaned with soap	4.3	19	≥ 53	None reported	9
3; 75 or 5; 100	NA: Respiratory depression study	Caudolateral abdomen, cleaned with water	4.14 or 5.12	$<30, <30$	$\geq 18, \geq 18$	None reported	14
6; 50	NA: Temperature effect study	Lateral thorax, brushed clean	4.72	15 (average)	47 (average)	Hypotension concurrent with inhalant anesthetic (n=not reported)	17

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Table 1 (cont'd)
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Cats							
6; 25	NA: Pharmacokinetic study	Dorsal neck, cleaned with water	7.19	7	≥ 65	Affectionate (n=3)	10
23; 25	Numeric rating scale, force applied by feet to pressure mat	Lateral thorax, no preparation	6.4	Not reported	Not reported	Mild anorexia (n=not reported)	11
8 or 12; 25	Numeric rating scale, physiological variables, cortisol, visual analogue scale	Lateral thorax, preparation not described	8.33	Not reported	Not reported	Hyperthermia (n=6)	12
8 or 12; 25	NA: Pharmacokinetic study	Lateral thorax, preparation not described	8.33	7, 7, 7	47, 47, ≥ 65	None reported	15
11; 25	Numeric rating scale, physiological variables, cortisol assays	Lateral thorax, preparation not described	7.49	Not reported	Not reported	Hyperthermia (n=1), euphoria (n=not reported)	13
8; ~12.5 or 25	Physiological variables, simple categorical 5-point scale	Lateral thorax, brushed clean	~4.17 or 8.33	Never or 26	Never or 42	Dysphoria (n=3)	16
7; 25	NA: Temperature effect study	Lateral thorax, brushed clean	4.46	24 (hypothermic) or 28 (normothermic)	8 (hypothermic) or 20 (normothermic)	One death likely from hypercarbia	18

* NA=not applicable

† Effective Plasma Concentration= 0.6 ng/mL (dogs) or 1.56 ng/mL (cats)

‡ n=number of animals with each adverse reaction

be accurately calculated for cats exposed to half of a 25 $\mu\text{g}/\text{hour}$ patch, as it could not be assumed that uncovering half of the patch resulted in a dose of 12.5 $\mu\text{g}/\text{hour}$.

Dogs received 50, 75, or 100 $\mu\text{g}/\text{hour}$ patches. The mean dosages of fentanyl received by the dogs were 2.77 (range 2.29 to 4.72) $\mu\text{g}/\text{kg}$ per hour for 50 $\mu\text{g}/\text{hour}$ patches, 3.89 (range 3.77 to 4.14) $\mu\text{g}/\text{kg}$ per hour for 75 $\mu\text{g}/\text{hour}$ patches, and 4.55 (range 3.4 to 5.13) $\mu\text{g}/\text{kg}$ per hour for 100 $\mu\text{g}/\text{hour}$ patches.

Pharmacokinetic Results in Dogs

The frequently recommended dose for transdermal fentanyl in the dog is 2 to 4 $\mu\text{g}/\text{kg}$ per hour, although the validity of this recommendation has never been established.⁴⁴ By graphing dose versus peak plasma concentration for five dog studies, it was shown that the highest peak plasma levels were obtained by applying a 100 $\mu\text{g}/\text{hour}$ patch to the caudal abdomen [Figure 2]. The second highest peak plasma concentrations occurred at a dose of approximately 4 $\mu\text{g}/\text{kg}$ per hour. The three studies delivering a dosage of 4 $\mu\text{g}/\text{kg}$ per hour used different-sized patches, different methods of skin preparation, and a variety of application sites. Until future studies investigate the relationship of dose to peak plasma levels in more depth, a dosage of 4 $\mu\text{g}/\text{kg}$ per hour is recommended for patches applied to the lateral thorax, dorsal cervical region, or caudal abdomen in dogs. Data from one study were not included because of variables introduced to the plasma concentrations as a result of the study design.¹⁷

In dogs, plasma fentanyl concentrations as low as 0.6 ng/mL have been correlated with analgesia.⁹ Dogs with a mean plasma fentanyl concentration of 1.18 ng/mL also had clinically appreciable analgesia.⁸ In the studies reviewed, six groups of dogs evaluated at 24 hours after patch application achieved plasma fentanyl concentrations ≥ 0.6 ng/mL [Figure 3]. Only two groups achieved plasma concentrations >1.18 ng/mL at 24 hours following patch application. In all the dogs, patches were removed at 62 to 72 hours. At patch removal, plasma concentrations were ≥ 0.6 ng/mL in all groups examined and were ≥ 1.18 ng/mL in one group.¹⁷ Based on these results, it appeared that the transdermal fentanyl system accomplished the goal of inducing near steady-state plasma concentrations in dogs.

In one study in which patches were placed on the caudal abdomen, dogs achieved markedly higher plasma concentrations [Figure 3].¹² These results suggested that plasma levels may vary depending on the site of application. In all studies reviewed, there were often marked intra- and interindividual variations in plasma fentanyl concentrations. This variability may have arisen because of differences in cutaneous and core body temperatures, vascular perfusion of the skin, states of hydration, skin integrity at the application site, and environmental temperatures.⁷

Elimination half-life following patch removal has been reported as 2.5, 3.6, and 1.39 hours in dogs.^{6,7} In people, elimination half-life following patch removal has been reported as between 13 and 25 hours.^{45,46} The longer elimination half-life following patch removal in people has been

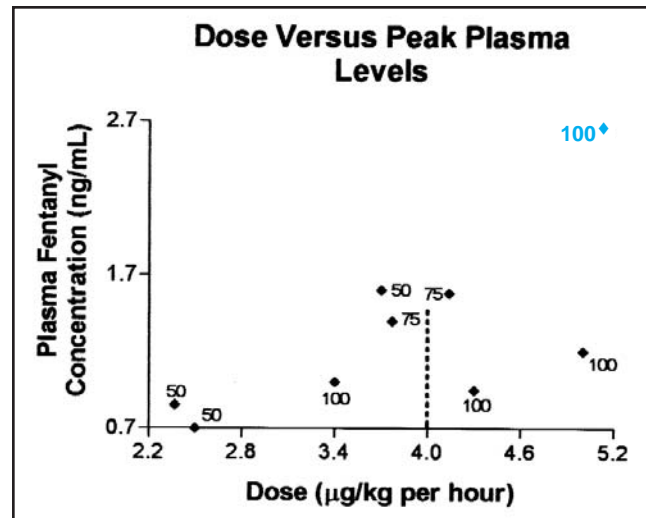


Figure 2—Dog dose versus peak fentanyl plasma concentration. Note that peak plasma concentration does not rise in a linear fashion as the dosage increases. The grouping of high peak plasma concentrations around a dose of 4 $\mu\text{g}/\text{kg}$ per hour suggested this may be the optimum dose for transdermal fentanyl patches in the dog. The plasma concentration marked in blue was obtained in one dog with the patch placed on the caudal abdomen. (50=50 $\mu\text{g}/\text{hour}$ patch; 75=75 $\mu\text{g}/\text{hour}$ patch; 100=100 $\mu\text{g}/\text{hour}$ patch.) Information is derived from previously published data.^{3-5,7,12}

attributed to the presence of a drug depot in the skin.⁴⁶ Because dogs have a much shorter elimination half-life, a drug depot may not develop or dogs may metabolize the drug differently. Plasma levels decreased to <0.6 ng/mL by a mean of 5.2 hours after patch removal in those canine study groups that had sufficient data for analysis.

Pharmacokinetic Results in Cats

In cats, plasma fentanyl concentrations as low as 1.56 to 1.73 ng/mL have correlated well with analgesia.^{11-13,16} In a study with a positive correlation between analgesia and plasma concentrations as low as 0.9 ng/mL, the least detailed pain-scoring system was used, the transdermal fentanyl protocol was not compared with any other analgesic protocol, and a Type II (power) statistical error may have occurred, making interpretation of the results difficult.¹⁶ For these reasons, a minimum plasma fentanyl concentration of 1.56 ng/mL was considered more valid. In the studies reviewed for this report, cats in four of the six groups for which complete data were available had plasma fentanyl concentrations >1.56 ng/mL at 7 hours after patch application, and one group attained plasma fentanyl concentrations >1.56 ng/mL at 22 hours after patch application. Three groups remained above that threshold until the end of 72 hours, and two groups fell below that threshold at 54 hours postapplication. The group of cats that received one-half of a 25 $\mu\text{g}/\text{hour}$ patch never reached the threshold of 1.56 ng/mL [Figure 4].

Patches were removed from the cats at 72, 73, or 100 hours. Plasma levels decreased to <1.56 ng/mL in a mean of 4 hours after patch removal in two groups. In one paper by Egger, *et al.* that evaluated three groups of cats, elimination

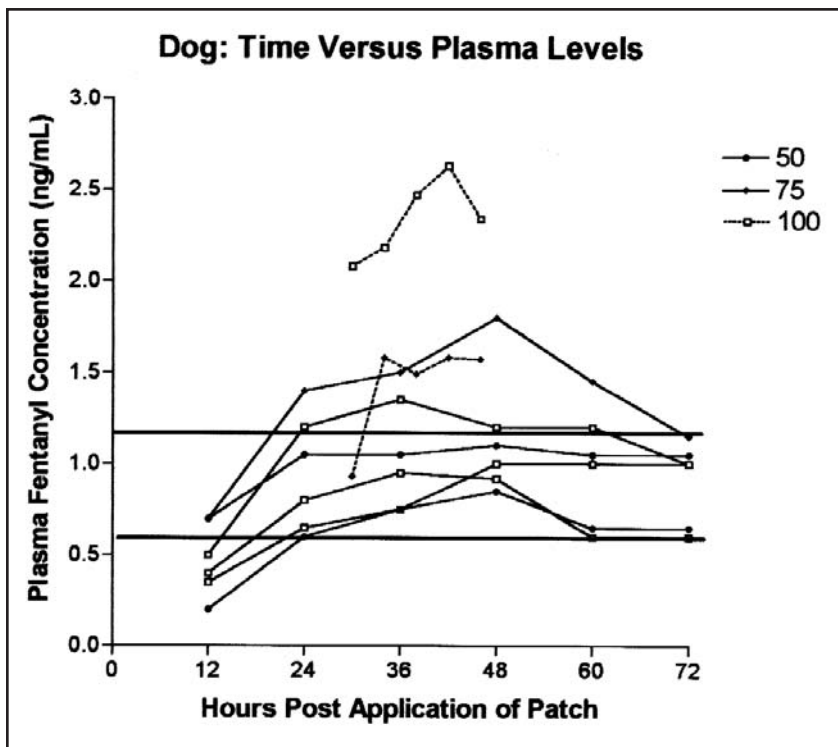


Figure 3—Time versus fentanyl plasma concentrations in six groups of dogs. Three transdermal fentanyl patch sizes were used in the studies (100=100 µg/hour patch; 75=75 µg/hour patch; 50=50 µg/hour patch). The solid horizontal lines on the graph represent the minimum (0.6 ng/mL) and mean (1.18 ng/mL) plasma fentanyl concentrations that have been shown to be consistent with analgesia. The two dotted lines represent plasma concentrations from dogs where the fentanyl patch was placed on the caudal abdomen.¹² Information is derived from previously published data.^{3-5,7,12}

half-lives were 4.5, 6.1, and 5.1 hours.¹⁵ In another paper that examined plasma levels following patch removal, half-life could not be calculated because the plasma levels did not decline appreciably by 20 hours after removal.¹⁰ This latter paper proposed that the cats may have a developed dermal depot, similar to humans.¹⁰ Further investigation is required before a definitive statement can be made regarding the presence of a dermal depot in cats.

In only one prior report did the transdermal fentanyl system accomplish steady-state plasma concentrations in the cat.¹⁶ In all other papers, the plasma concentration curve was similar to an injectable drug, with an initial rapid decline in plasma concentrations and then a slow elimination.²¹ The discrepancy between these two sets of results was difficult to explain, since the first paper had a methodology similar to the other publications.

Analgesic Effects

Two studies evaluated the analgesic effects of transdermal fentanyl in the dog.^{8,9} One study compared transdermal fentanyl with epidural morphine in dogs undergoing major orthopedic procedures, and one study compared transdermal fentanyl with oxymorphone in dogs undergoing ovariohysterectomy.^{8,9} Both studies documented higher pain scores in dogs receiving transdermal fentanyl in the immediate postoperative period (0 to 6 hours) but lower pain scores at 12 to 18 hours.^{8,9} Analgesia persisted for the duration of the studies (72 hours).^{8,9}

Four studies evaluated the analgesic effects of transdermal fentanyl in the cat.^{11-13,16} Two studies compared transdermal fentanyl with butorphanol in cats undergoing elective onychectomy.^{11,13} One study compared transdermal fentanyl with ketamine in cats undergoing ovariohysterectomy.¹²

Another study compared the effects of a 25 µg/hour transdermal fentanyl to those of one-half of a 25 µg/hour transdermal fentanyl patch exposed in cats undergoing ovariohysterectomy.¹⁶ In one onychectomy paper, no significant difference was found for pain scores between transdermal fentanyl and butorphanol.¹³ In the other report, transdermal fentanyl produced significantly greater analgesia, although an objective measurement of lameness did not detect differences between the two groups.¹¹ In the paper comparing transdermal fentanyl and ketamine, no significant differences were identified between the study groups.¹² The authors attributed their results to the nature of pain caused by ovariohysterectomy (i.e., relatively mild, localized, sharp visceral pain).¹² In the paper comparing two transdermal fentanyl systems, there was no significant difference between the groups for pain scores. Analgesia persisted for the duration of the studies (40 to 72 hours).¹⁶

Adverse Reactions

Bradycardia was reported in five dogs of one study.⁵ Two studies reported no significant impact of transdermal fentanyl on temperature, respiratory rate, or heart rate.^{8,9} One dog in one study developed bradypnea.⁵ Other adverse effects reported in dogs included sedation, anorexia, and mild to severe skin reactions at the site of application.⁵⁻⁹

Six studies reported no change in respiratory rate following patch placement in cats.^{10-13,15,16} One study reported hypoventilation concurrent with general anesthesia.¹⁸ In that study, one cat died, presumably from severe respiratory depression.¹⁸ Two studies reported hyperthermia in cats following patch placement.^{12,13} Five feline studies reported no unfavorable behavioral effects even in cats weighing as little as 2.0 kg.^{10-13,15,18} Several subjective comments were

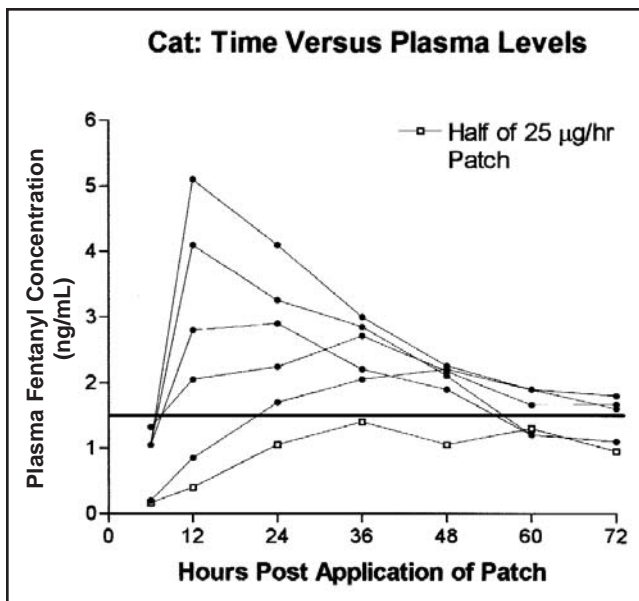


Figure 4—Time versus fentanyl plasma concentration in six groups of cats. All cats receiving a 25 µg/hour transdermal fentanyl patch are denoted by solid circles. One group was exposed to half of a 25 µg/hour patch. The solid horizontal line on the graph represents a plasma fentanyl level of 1.56 ng/mL, which has been correlated to analgesia. Note that the cats given half of a 25 µg/hour patch did not achieve plasma levels shown to be consistent with analgesia. Information is derived from previously published data.^{8,13,14}

made about euphoria and increased purring in cats that received transdermal fentanyl patches.^{10,13} One study reported dysphoria in cats given 25 µg/hour patches but not in cats exposed to half of a 25 µg/hour patch.¹⁶

Clinical Recommendations

Based on the veterinary literature, the human literature, and the authors' experience, several recommendations are offered for the use of transdermal fentanyl patches. Many aspects of transdermal fentanyl application have yet to be explored in small animals, so these recommendations must be considered as preliminary.

Transdermal fentanyl patches are indicated for use in dogs and cats believed to be in pain that cannot receive a constant-rate infusion, but can be monitored and treated for breakthrough pain postoperatively. Transdermal fentanyl patches may also be indicated for animals suffering from chronic pain, for which a constant-rate infusion is impractical.⁵⁻¹⁸ A constant-rate infusion of an opioid is preferable to transdermal fentanyl in many cases because of the potential variability in uptake of fentanyl from a transdermal patch.⁵⁻¹⁸

The recommended dosage in dogs is 4 µg/kg per hour. Because the patch sizes are static, patches can be combined to approximate 4 µg/kg per hour as closely as possible. Cats weighing as little as 2.0 kg may have a 25 µg/hour patch applied.^{10-13,15,18} Uncovering only half of a 25 µg/hour patch for small cats is unnecessary, as adverse effects with

small cats have not been well documented, and the plasma concentrations attained in cats exposed to only half the patch were subtherapeutic.¹⁶ Patches should be applied 24 hours prior to the need for analgesia in dogs and 7 hours prior in cats.⁵⁻¹⁸

Patches may be applied to the dorsal or lateral thorax in both dogs and cats. The pharmacokinetics and pharmacodynamics of placement of the patch on the distal limb have not been evaluated, so that location is not recommended. The area of application is gently clipped without abrading the skin.^b The skin may then be gently washed with water and allowed to dry.^b The patch is applied by holding it against the skin for 60 seconds, and a light wrap is placed over it. If the bandage begins to loosen, it should be reinforced. It is best not to expose patches to sources of external heat.³⁹ Any animal that becomes hyperthermic should be monitored closely for opioid overdose.³⁹

Mu-receptor antagonists and partial agonists, such as butorphanol and buprenorphine, may antagonize the actions of the fentanyl and should not be administered concurrently with transdermal fentanyl.^{47,48} Breakthrough pain may occur and require treatment with a full mu-agonist such as injectable fentanyl, morphine, oxymorphone, or hydromorphone.⁹ Patches may be left in place for at least 72 hours in dogs and cats.⁵⁻¹⁸ In some cats, plasma levels at 72 hours may be below analgesic levels.^{10,15} Whether there is any benefit to leaving patches on animals >72 hours is unknown.

Once a patch is removed, it may be folded upon itself, cut while wearing gloves, and flushed down a toilet.³⁴ If a patch lifts off or appears tattered, it should be replaced. New patches are placed on a newly prepared area of skin to avoid irritation at one application site.^b No studies have evaluated chronic, long-term transdermal fentanyl administration or the pharmacokinetics of repeat patch placement. Hence, these forms of treatment are left to the discretion of the individual veterinarian.

If an animal ingests a patch, it should be monitored for signs of opioid overdose. If clinical signs of opioid overdose occur, a long-acting mu-receptor antagonist, such as naltrexone, is indicated.²⁵ In comparison to naltrexone, naloxone has a short half-life and may allow renarcotization if any fentanyl is present at the end of naloxone's clinical duration.⁴⁹ Repeat naloxone administration may be necessary in this instance.

Animals that already have a patch in place and are placed under general anesthesia require monitoring of their ventilatory status through the use of end-tidal carbon dioxide (CO₂) or arterial CO₂ sampling in order to detect respiratory depression. Opioids combined with general anesthesia can produce significant respiratory depression, and one cat in the reviewed studies purportedly died as a result of this combination.⁵⁰

Costs of Treatment

Approximate costs associated with various opioid analgesics used at the University of Georgia are supplied in Tables 2 and 3 for dogs and cats, respectively. These costs

Table 2

Costs Associated With Various Opioid Analgesics Used in Dogs for 3 Days*

Drug†	10 kg Body Weight	30 kg Body Weight
Morphine 0.5 mg/kg IM q 4 h	\$1	\$3
Hydromorphone 0.1 mg/kg IM q 4 h or hydromorphone 0.025 mg/kg per h IV	\$12	\$35
Buprenorphine 0.01 mg/kg IM q 6 h	\$12	\$37
Fentanyl patch 4 µg/kg per h	\$21	\$55
Butorphanol 0.4 mg/kg IM q 2 h	\$74	\$220
Fentanyl injectable 3 µg/kg per h IV	\$101	\$304

* Costs are in US dollars, as purchased at the University of Georgia

† IM=intramuscularly; IV=intravenously

Table 3

Costs Associated With Various Opioid Analgesics Used in Cats for 3 Days*

Drug†	2 kg Body Weight	5 kg Body Weight
Hydromorphone 0.1 mg/kg IM q 4 h or hydromorphone 0.025 mg/kg per h IV	\$3	\$7
Buprenorphine 0.01 mg/kg IM q 6 h	\$3	\$6
Fentanyl patch 25 µg/h per cat	\$13	\$13
Butorphanol 0.4 mg/kg IM q 2 h	\$20	\$40
Fentanyl injectable 3 µg/kg per h IV	\$21	\$52

* Costs are in US dollars, as purchased at the University of Georgia

† IM=intramuscularly; IV=intravenously

represent the fees paid by the University to acquire the drugs; they do not represent the cost to the client. The costs listed for transdermal fentanyl do not include supplemental analgesics that may be needed in the postoperative period. Note that the agents listed are also not necessarily equipotent with respect to their induction of analgesia. Because of the relatively high cost of transdermal fentanyl in comparison with other agents, it is recommended that transdermal

fentanyl patches be reserved for selected cases, as noted above. It may be helpful to perform a similar cost assessment in every hospital, as prices may vary and may affect recommendations for drug usage.

Conclusion

Transdermal fentanyl patches provide a good option for treating pain in small animals. There are still many gaps in

the clinical knowledge regarding this therapeutic modality, however. Future investigations may include documentation of the specific plasma level required to obtain appropriate analgesia in dogs and cats, identification of variables that alter the pharmacokinetics of transdermal fentanyl, investigation of the pharmacokinetics of chronic treatment and repeated placement of patches, determination of the duration of effective plasma levels following patch placement, and the development of strategies to maintain plasma levels at effective concentrations. Expanding the body of information available about transdermal fentanyl allows the practicing veterinarian to make more informed clinical decisions based on the principles of evidence-based medicine.

^a Duragesic; Alza Corporation, Janssen Mountain View, CA 94043

^b Package Insert; Janssen Pharmaceutica Products LP, Titusville, NJ 08560

^c 21 United States Code, Section 801, 01/22/02

^d Georgia General Assembly, Unannotated Code 26-4-80.

^e Pubmed; U.S. National Library of Medicine, Bethesda, MD 20894

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References

- Krahwinkel DJ Jr, Sawyer DC, Eyster GE, *et al.* Cardiopulmonary effects of fentanyl-droperidol, nitrous oxide, and atropine sulfate in dogs. *Am J Vet Res* 1975;36:1211-1219.
- Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983;8:422-446.
- Southam MA. Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. *Anti-Cancer Drugs* 1995;6(Suppl 3):29-34.
- Scherk-Nixon MA. A study of the use of a transdermal fentanyl patch in cats. *J Am Anim Hosp Assoc* 1996;32:19-24.
- Schultheiss PJ, Morse BC, Baker WH. Evaluation of a transdermal fentanyl system in the dog. *Contemp Top Lab Anim Sci* 1995;54:75-81.
- Kyles AE, Papich M, Hardie EM. Disposition of transdermally administered fentanyl in dogs. *Am J Vet Res* 1996;57:715-719.
- Egger CM, Duke T, Archer J, *et al.* Comparison of plasma fentanyl concentrations by using three transdermal fentanyl patch sizes in dogs. *Vet Surg* 1998;27:156-166.
- Kyles AE, Hardie EM, Hansen BD, *et al.* Comparison of transdermal fentanyl and intramuscular oxymorphone on post-operative behaviour after ovariohysterectomy in dogs. *Res Vet Sci* 1998;65:245-251.
- Robinson TM, Kruse-Elliott KT, Markel MD, *et al.* A comparison of transdermal fentanyl versus epidural morphine for analgesia in dogs undergoing major orthopedic surgery. *J Am Anim Hosp Assoc* 1999;35:95-100.
- Lee DD, Papich MG, Hardie EM. Comparison of pharmacokinetics of fentanyl after intravenous and transdermal administration in cats. *Am J Vet Res* 2000;61:672-677.
- Franks JN, Boothe HW, Taylor L, *et al.* Evaluation of transdermal fentanyl patches for analgesia in cats undergoing onychectomy. *J Am Vet Med Assoc* 2000;217:1013-1020.
- Glerum LE, Egger CM, Allen SW, *et al.* Analgesic effect of the transdermal fentanyl patch during and after feline ovariohysterectomy. *Vet Surg* 2001;30:351-358.
- Gellasch KL, Kruse-Elliott KT, Osmond CS, *et al.* Comparison of transdermal administration of fentanyl versus intramuscular administration of butorphanol for analgesia after onychectomy in cats. *J Am Vet Med Assoc* 2002;220:1020-1024.
- Welch JA, Wohl JS, Wright JC. Evaluation of postoperative respiratory function by serial blood gas analysis in dogs treated with transdermal fentanyl. *J Vet Emerg Crit Care* 2002;12:81-87.
- Egger CM, Glerum LE, Allen SW, *et al.* Plasma fentanyl concentrations in awake cats and cats undergoing anesthesia and ovariohysterectomy using transdermal administration. *Vet Anaesth Analg* 2003;30:229-236.
- Davidson CD, Pettifer GR, Henry JD. Plasma fentanyl concentrations and analgesic effects during full or partial exposure to transdermal fentanyl patches in cats. *J Am Vet Med Assoc* 2004;224:700-704.
- Pettifer GR, Hosgood G. The effect of inhalant anesthetic and body temperature on peri-anesthetic serum concentrations of transdermally administered fentanyl in dogs. *Vet Anaesth Analg* 2004;31:109-120.
- Pettifer GR, Hosgood G. The effect of rectal temperature on peri-anesthetic serum concentrations of transdermally administered fentanyl in cats anesthetized with isoflurane. *Am J Vet Res* 2003;64:1557-1561.
- Greenhalgh T. How to read a paper: papers that summarise other papers (systematic reviews and meta-analyses). *Br Med J* 1997;315:672-675.
- Chalmers I, Altman DG, eds. *Systematic Reviews*. London: BMJ Publishing Group, 1995.
- Stoelting RK. *Pharmacology and Physiology in Anesthetic Practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.
- Pascoe PJ. Opioid analgesics. *Vet Clin North Am Small Anim Pract* 2000;30:757-772.
- Terenius L. Contribution of 'receptor' affinity to analgesic potency. *J Pharm Pharmacol* 1974;26:146-148.
- Streisand JB, Varvel JR, Stanski DR, *et al.* Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* 1991;75:223-229.
- Plumb DC. *Veterinary Drug Handbook*. 3rd ed. Ames: Iowa State Univ Press, 1999.
- Fung DL, Eisele JH. Fentanyl pharmacokinetics in awake volunteers. *J Clin Pharmacol* 1980;20:652-658.
- Hengstman JH, Stoekel H, Schuttler J. Infusion model for fentanyl based on pharmacokinetic analysis. *Br J Anaesth* 1980;52:1021-1025.
- Hess R, Stibler G, Herz A. Pharmacokinetics of fentanyl in man and the rabbit. *Europ J Clin Pharmacol* 1972;4:137-141.
- Bailey PL, Port JD, McJames S, *et al.* Is fentanyl an anesthetic in the dog? *Anesth Analg* 1987;66:542-548.
- Hellyer PW, Mama KR, Shafford HL, *et al.* Effects of diazepam and flumazenil on minimum alveolar concentrations for dogs anesthetized with isoflurane or a combination of isoflurane and fentanyl. *Am J Vet Res* 2001;62:555-560.
- Hug CC, Murphy MR. Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. *Anesthesiology* 1979;50:342-349.
- Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. *Ann Pharmacother* 1995;29:969-971.
- Flannagan LM, Butts JD, Anderson WH. Fentanyl patches left on dead bodies: potential source of drug for abusers. *J Forensic Sci* 1996;41:320-321.
- Yerasi AB, Butts JD, Butts JD. Disposal of used fentanyl patches. *Am J Health-Syst Pharm* 1997;54:85-86.
- Riviere JE, Papich MG. Potential and problems of developing transdermal patches for veterinary applications. *Adv Drug Dev Res* 2001;50:175-203.
- Roy SD, Flynn GL. Solubility and related physicochemical properties of narcotic analgesics. *Pharm Res* 1988;5:580-586.
- Chang SK, Riviere JE. Effect of humidity and occlusion on the percutaneous absorption of parathion in vitro. *Pharm Res* 1993;10:152-155.
- Riviere JE, Sage BS, Williams PL. The effects of vasoactive drugs on transdermal lidocaine iontophoresis. *J Pharm Sci* 1991;80:615-620.
- Gupta SK, Southam M, Gale R, *et al.* System functionality and physicochemical model of fentanyl transdermal system. *J Pain Symptom Manage* 1992;7 (Suppl):S17-26.

-
40. Hwang SS, Nichols KC, Southam M. Transdermal permeation: physiological and physicochemical aspects. In: Lehmann KA, Zech D, eds. *Transdermal Fentanyl: A New Approach to Prolonged Pain Control*. 1st ed. Berlin: Springer-Verlag, 1991:1-17.
 41. Rose PG, Macfee MS, Boswell MV. Fentanyl transdermal system overdose secondary to cutaneous hyperthermia. *Anesth Analg* 1993;77:390-391.
 42. Klockgether-Radke A, Hildebrandt J. Opioid intoxication. Inappropriate administration of transdermal fentanyl. *Anaesthesist* 1997;46:428-429.
 43. Michiels M, Hendriks R, Heykants J. A sensitive radioimmunoassay for fentanyl. Plasma level in dogs and man. *Eur J Clin Pharmacol* 1977;12:153-158.
 44. Hardie EM, Hyles AE. Pain management in the small animal patient. In: Bojrab MJ, ed. *Current Techniques in Small Animal Surgery*. 4th ed. Baltimore: Williams & Williams, 1998:3-17.
 45. Broome IJ, Wright BM, Bower S, *et al.* Postoperative analgesia with transdermal fentanyl following lower abdominal surgery. *Anaesthesia* 1995;50:300-303.
 46. Plezia PM, Kramer TH, Linford J, *et al.* Transdermal fentanyl: pharmacokinetics and preliminary clinical evaluation. *Pharmacotherapy* 1989;9:2-9.
 47. Lemke KA, Tranquilli WJ, Thurmon JC, *et al.* Ability of flumazenil, butorphanol, and naloxone to reverse the anesthetic effects of oxymorphone-diazepam in dogs. *J Am Vet Med Assoc* 1996;209:776-779.
 48. Schuh KJ, Walsh SL, Stitzer ML. Onset, magnitude and duration of opioid blockade produced by buprenorphine and naltrexone in humans. *Psychopharmacology (Berl)* 1999;145:162-174.
 49. Dyson DH, Doherty T, Anderson GI, *et al.* Reversal of oxymorphone sedation by naloxone, nalmefene, and butorphanol. *Vet Surg* 1990;19:398-403.
 50. Thurman JC, Tranquilli WJ, Benson GJ. *Lumb & Jones' Veterinary Anesthesia*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1996.
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