

Comparison of Plasma Fentanyl Concentrations by Using Three Transdermal Fentanyl Patch Sizes in Dogs

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Objective—To compare plasma fentanyl concentrations attained after the application of three transdermal fentanyl patch sizes (50, 75, and 100 $\mu\text{g}/\text{hour}$) in dogs.

Design—Repeated Latin square controlled study.

Animals—Six intact, mixed-breed adult dogs (2 males, 4 females) weighing 19.9 ± 3.4 kg.

Methods—Each dog was randomly assigned to receive each of three treatments: 50 (P50), 75 (P75), or 100 (P100) $\mu\text{g}/\text{hour}$ transdermal patches. Patches were left in place for 72 hours. Jugular venous blood was collected at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after patch application and for 1, 2, 4, 8, and 12 hours after patch removal. Plasma fentanyl concentrations were measured using a radioimmunoassay technique. After a 96-hour washout period, each dog was moved to another treatment group and received a different patch size.

Results—The following results were obtained (mean \pm SD): average plasma fentanyl concentration from 24 to 72 hours, 0.7 ± 0.2 ng/mL (P50), 1.4 ± 0.5 ng/mL (P75), 1.2 ± 0.5 ng/mL (P100); the total area under the concentration versus time curve (0 hours to infinity), 46 ± 12.2 ng/h/mL (P50), 101.2 ± 41.4 ng/h/mL (P75), 80.4 ± 38.3 ng/h/mL (P100); and the apparent elimination half-life, 3.6 ± 1.2 hours (P50), 3.4 ± 2.7 hours (P75), and 2.5 ± 2.0 hours (P100). There was a high degree of variability in plasma fentanyl concentrations achieved. Plasma fentanyl concentrations declined rapidly after patch removal.

Conclusions—The attainment of steady-state plasma concentrations takes up to 24 hours, and there is a great deal of variability in the final concentrations reached in different individuals. In this study, the 100 $\mu\text{g}/\text{hour}$ patches did not provide statistically increased plasma concentrations when compared with the 50 $\mu\text{g}/\text{hour}$ patches.

Clinical Relevance—Because of the interindividual and intraindividual variation in plasma fentanyl concentrations, patches should be applied 24 hours before the anticipated time that analgesia will be required. Adequacy of analgesia and potentially deleterious side effects, such as sedation and respiratory depression, should be monitored while the patches are in place. Skin reactions may occur, and the patches should be removed if such skin irritation is seen. After the patch is removed, it is expected that analgesia will wane rapidly because of the brief elimination half-life.

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TRANSDERMAL FENTANYL patch systems are used in human medicine to provide analgesia for chronic cancer pain.¹ Transdermal delivery of opioid analgesics offers an attractive means of maintaining analgesia for extended periods of time in

veterinary patients and avoids many of the disadvantages of parenteral or oral periodic administration. Periodic administration often requires frequent dosing, resulting in peak and trough plasma concentrations. To attain analgesia, large priming doses are

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initially administered, risking toxicosis and undesirable side effects, such as excessive sedation and respiratory depression.²⁻⁵ These disadvantages may be alleviated by a continuous administration system that provides steady-state plasma concentrations. Steady-state plasma concentrations can be achieved by continuous intravenous infusion or transdermal administration of opioids.⁶⁻⁸ If effective, transdermal administration of analgesics should be ideal for veterinary patients because it allows the patient to be ambulatory, avoids frequent dosing, and minimizes some of the side effects seen with periodic delivery.

Fentanyl is a synthetic opioid of the 4-anilinopiperidine class of drugs. Fentanyl is estimated to be 50 to 100 times more potent than morphine, has a low molecular weight, is both lipid and water soluble, is rapidly eliminated from the plasma, and is rapidly metabolized.² The terminal elimination half-life is 3 to 6 hours in dogs after intravenous administration.^{3,9-11} The mean elimination half-life after transdermal administration in dogs was found to be 1.39 hours.¹⁰ Fentanyl has minimal affinity for cutaneous tissue and does not undergo significant cutaneous metabolism in humans, however, this has not been investigated in dogs.^{8,12} These properties of fentanyl make it an ideal opioid for transdermal administration.¹

Transdermal fentanyl delivery systems are designed to provide a continuous release of drug to the systemic circulation for up to 72 hours. Release rate is dependent on patch area. Transdermal patch systems are available in four nominal dosage rates: 25, 50, 75, and 100 $\mu\text{g}/\text{hour}$, corresponding to 10, 20, 30, and 40 cm^2 patch areas. The dose/hour indicated on the patch represents the average amount of drug delivered to the systemic circulation per hour across average human skin.¹³

Transdermal fentanyl patch systems are used clinically in veterinary medicine to provide postoperative analgesia, despite few published scientific studies indicating their efficacy. Some reports of their clinical use have been published.^{10,14-16} The purpose of this study was to compare plasma fentanyl concentrations after application of three transdermal fentanyl patch sizes (50, 75, and 100 $\mu\text{g}/\text{hour}$) in dogs.

MATERIALS AND METHODS

This study was approved by the University of Saskatchewan Animal Care Committee. Animals were kept and

treated in accordance with the Canadian Council for Animal Care and Use Guidelines and housed individually in runs with environmental temperature maintained at 20°C. The dogs were fed canine maintenance dry food (Hills Science Diet; Hills Pet Products, Division of Colgate Palmolive, Mississauga, Ontario, Canada). Six intact, mixed-breed adult dogs (two males and four females) weighing 19.9 ± 3.4 kg (mean \pm standard deviation [SD]) were used in the study. All dogs were considered healthy based on physical and hematologic examinations (CBC).

Three patch sizes were used: 50, 75, and 100 $\mu\text{g}/\text{hour}$ (Duragesic; Janssen Pharmaceutica Inc, Mississauga, Ontario, Canada). Each dog was randomly assigned to receive each of three treatments using a repeated Latin square design. The treatments received were one of three fentanyl patches: P50 (50 $\mu\text{g}/\text{hour}$), P75 (75 $\mu\text{g}/\text{hour}$), and P100 (100 $\mu\text{g}/\text{hour}$). After a washout period of 96 hours, each dog was moved to another treatment group and received a different patch size. This washout period was considered to be adequate based on the terminal elimination half-life for fentanyl in dogs. On the morning of patch application, a 0.95×305 mm catheter (Intracath; Becton Dickinson, Sandy, UT) was percutaneously placed in one jugular vein of the dog, and a blood sample was withdrawn through the jugular catheter before patch application (0 hour sample). The patches were applied to the lateral thorax of the dog, alternating sides for each subsequent patch application. The area for patch application was prepared by clipping, gently washing with warm water, and air drying. After patch application, a light wrap of conformable bandage (Kling Plus Conform Bandage; Johnson and Johnson Inc, Montreal, Quebec, Canada), orthopedic padding (Protouch Synthetic Orthopedic Padding; Smith and Nephew, Ltd, Hull, England), and Vetrap (Vetrap 3M Animal Care Products, St. Paul, MN) was applied over the site and around the thorax of the dog. Patches remained attached for a period of 72 hours. Three milliliters of blood was withdrawn through the jugular catheter for plasma fentanyl concentration analysis at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after patch application and for 1, 2, 4, 8, and 12 hours after patch removal. Catheters were flushed with 6 mL of heparinized saline after blood sampling. All blood samples were placed in vacutainer tubes containing ethylenediaminetetra-acetic acid (EDTA) (Venoject; Terumo Medical, Elkton, MD) and centrifuged immediately or stored at 4°C and centrifuged for plasma extraction within 2 hours of collection. Plasma was frozen at -30°C pending fentanyl assay. The same procedure was followed until each dog had received each patch size.

After patch removal, the skin underlying the patch was examined for signs of irritation by a single observer who was not blinded to the patch dosage at the time of observation. Skin appearance was classified using a subjective

skin reaction classification system as follows: I, no reaction visible; II, slight erythema of a portion of the patch application site (mild reaction); III, slight erythema of the entire patch application site (moderate reaction); IV, severe erythema of application site, with skin plaques (severe reaction). If a severe reaction was noted, a full-thickness skin punch biopsy was taken from the application site for histological examination.

Plasma fentanyl concentrations were measured using a radioimmunoassay (RIA) kit (Janssen Biotech NV Research Products; Research Diagnostics, Inc, Flanders, NJ). The RIA is highly specific for fentanyl, has no cross-reaction with metabolites of fentanyl, and has a limit of detection for fentanyl of 0.1 ng/mL. The intra-assay and interassay coefficients of variation for the RIA kit are estimated to be 6.0 and 6.9%.^{17,18} Samples were analyzed as duplicates, and the values obtained were averaged to obtain the final plasma concentrations.

The mean plasma fentanyl concentrations (\pm SD) for each patch size were plotted over time. Mean plasma fentanyl concentrations at steady-state were calculated by averaging the mean plasma fentanyl concentration for each dog during the 24- to 72-hour period. It was determined that the decline in plasma fentanyl concentrations after patch removal was best described using a one-compartment model after plotting the natural logarithm of the concentration over time and obtaining a straight line. The apparent elimination rate constant (K_{el}) was then determined by performing linear regression on the terminal portion of the natural log (ln) concentration versus time curve after patch removal for each dog, and these values were averaged to obtain the mean (\pm SD) apparent elimination rate constant (K_{el}) for each patch size.¹⁹ The apparent elimination half-life ($t_{1/2} K_{el}$) was calculated using the following formula¹⁹:

$$t_{1/2} K_{el} = 0.693/K_{el}$$

The partial area under the concentration versus time curve (AUC) (0 to 84 hours after patch application) was

determined for each patch dosage using the trapezoidal rule. The residual AUC (84 hours to infinity) was estimated by dividing the last concentration measured by the apparent elimination rate constant. The total AUC (0 hours to infinity) was obtained by adding the residual AUC to the partial AUC.¹⁹

A two-way analysis of variance (ANOVA) for repeated measures was used to compare the effects of patch size and time after patch application on plasma fentanyl concentration. A one-way ANOVA with protected least significant difference pairwise comparisons was used to compare the descriptive information (data in Table 1) from the three treatments, when the variances were found to be equal. When unequal variances were found, a Kruskal-Wallis one-way ANOVA was performed to compare the patch sizes.

It was assumed that, given the rapid elimination of fentanyl from the plasma of dogs after patch removal and the relatively rapid metabolism and excretion from the body, there was adequate washout between patch applications and the crossover could be disregarded for the analysis.^{3,9,10} A *P* value $< .05$ was considered significant in all statistical analyses.

RESULTS

Mean plasma fentanyl concentration over time for P50, P75, and P100 are presented in Fig 1. Two-way repeated measures ANOVA indicated a significant effect on plasma fentanyl concentration for all three patch sizes. Means comparison for the three treatments indicated that P50 and P75 were significantly different from each other for plasma fentanyl concentrations attained. The P50 and the P100 treatment and the P75 and the P100 treatment were not significantly different for plasma fentanyl concentrations attained.

Two-way repeated measures ANOVA indicated

Table 1. Plasma Concentration Values and Times, AUC, and K_{el} for Each Patch Size

Parameter Measured	P50 (mean \pm SD)	P75 (mean \pm SD)	P100 (mean \pm SD)
Time to first detectable plasma fentanyl concentrations	16.7 \pm 8.5 h	13.5 \pm 13.8 h	14.0 \pm 7.9 h
Steady-state plasma fentanyl concentrations	0.7 \pm 0.2 ng/mL	1.4 \pm 0.5 ng/mL*	1.2 \pm 0.5 ng/mL
Total AUC (0 h to infinity)	46.1 \pm 12.2 ng/h/mL	101.2 \pm 41.4 ng/h/mL*	80.4 \pm 38.3 ng/h/mL
Elimination rate constant	-0.19 \pm 0.06	-0.20 \pm 0.13	-0.28 \pm 0.17
Elimination half-life ($t_{1/2} K_{el}$) [†]	3.6 \pm 1.2 h	3.4 \pm 2.7 h	2.5 \pm 2.0 h

* Indicates a significant difference from P50 (*P* \leq .05).

[†] Harmonic mean and pseudostandard deviation.

Abbreviations: AUC, area under the concentration versus time curve; SD, standard deviation.

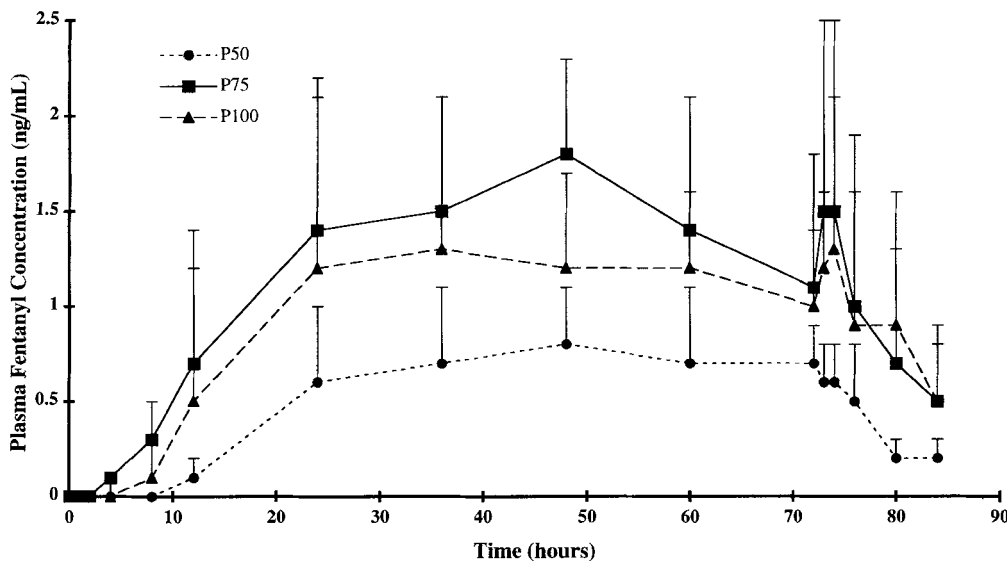


Fig 1. Plasma fentanyl concentration for P50, P75, P100 (mean + SD). The steady-state period was considered to be from 24 to 72 hours, and the patches were removed at 72 hours. P50 is statistically different from P75 at 24 and 48 hours; P75 is statistically different from P100 at 48 hours.

time after patch application had a significant effect on plasma fentanyl concentration for all three treatments. The plasma fentanyl concentration for P50 was significantly different from baseline from 24 hours after patch application until 4 hours after patch removal. The plasma fentanyl concentration for P75 was significantly different from baseline from 12 hours after patch application until 12 hours after patch removal. The plasma fentanyl concentration for P100 was significantly different from baseline from 24 hours after patch application until 8 hours after patch removal.

Mean data from each treatment revealed a steady-state period from approximately 24 to 72 hours after patch application (Fig 1). Stable plasma fentanyl concentrations during the steady-state period were not achieved in individual dogs, however, and in one dog with P50, six dogs with P75, and four dogs with P100, plasma fentanyl concentrations appeared to increase at 1 or 2 hours after patch removal. Comparison of plasma fentanyl concentrations at 1 hour and 2 hours after patch removal with plasma fentanyl concentrations at the time of patch removal (72 hours) revealed that this increase was not statistically significant for any of the three treatments.

Table 1 shows data for each of the three treatments (mean \pm SD) for time to first detectable plasma fentanyl concentration, plasma fentanyl concentration at steady-state, total AUC, elimination rate constant, and elimination half-life. The P75 treatment was statistically different from the P50 treatment for plasma fentanyl concentrations at steady-state and the total

AUC only. The P100 treatment was not statistically different from the P50 treatment for any parameter. Comparisons of plasma fentanyl concentrations at 24, 48, and 72 hours (beginning, midpoint, and end of the steady-state period) indicated that P50 was statistically different from the P75 at 24 and 48 hours, P50 was not statistically different from P100 at any of the chosen times, and P75 was significantly different from P100 at 48 hours (Fig 1).

Skin reactions were observed as a result of patch application. Table 2 shows the observed skin reactions for each patch size, and Table 3 shows the observed skin reactions by week of patch application. Dogs that had moderate or severe reactions during one patch application period did not necessarily have moderate or severe reactions on either prior or subsequent patch application periods. There did not appear to be an association between week of patch application, patch size, previous or subsequent

Table 2. Skin Reactions According to Size of Patch Applied*

	Skin-Reaction Classification [†]			
	I	II	III	IV
P50	0	5	0	1
P75	2	2	1	1
P100	1	3	2	0
Totals	3	10	3	2

* Numbers indicate the number of dogs.

[†] I, no reaction; II, mild reaction; III, moderate reaction; IV, severe reaction.

Table 3. Skin Reactions According to Week of Patch Application*

	Skin-Reaction Classification†			
	I	II	III	IV
Week 1	1	2	2	1
Week 2	1	4	1	0
Week 3	1	4	0	1
Totals	3	10	3	2

* Numbers indicate the number of dogs.

† I, no reaction; II, mild reaction; III, moderate reaction; IV, severe reaction.

reactions to the patch, and severity of reaction. The histological examination of the skin biopsies (score IV) revealed a superficial eosinophilic/neutrophilic reaction consistent with allergic or irritant contact dermatitis. Two dogs with P100 and one dog with P75 were noted to become mildly sedated.

DISCUSSION

The time to first detectable plasma fentanyl concentrations was similar for all three patch sizes (16.7 hours for P50, 13.5 hours for P75, and 14.0 hours for P100), but there was considerable individual variation (Table 1). This has not been investigated in previous studies in dogs, but the time to first detectable plasma fentanyl concentration in humans was found to be 2.0 ± 0.67 hours.²⁰ The average time to reach steady-state plasma fentanyl concentrations in this study was approximately 24 hours for all three patch sizes (Fig 1). A similar time to steady-state plasma fentanyl concentration was found in a previous study in dogs.¹⁰

The plasma fentanyl concentrations attained during the steady-state period with the 50 $\mu\text{g}/\text{hour}$ patch was 0.7 ± 0.2 ng/mL. This is less than the plasma fentanyl concentrations attained during steady-state in a previous study in dogs using 50 $\mu\text{g}/\text{hour}$ patches (1.5 ng/mL); however, the average weight of those dogs was 13.5 ± 1.9 kg, whereas the average weight of the dogs used in the present study was 19.0 ± 3.4 kg, which may account for the difference.¹⁰ Plasma fentanyl concentrations during the steady-state period appeared higher for both P75 and P100, but only P75 was statistically different than P50. No studies determining plasma fentanyl concentration at steady-state with 75 or 100 $\mu\text{g}/\text{hour}$ patches in dogs have been reported.

The AUC can be a measure of the extent of bioavailability of a drug and is usually directly proportional to the dose (as dose increases, so should AUC).¹⁹ The total AUC obtained for P50 in this study was 46.1 ± 12.1 ng/h/mL. A previous study found the total AUC for P50 to be 102.0 ± 25.0 ng/h/mL in smaller dogs.¹⁰ Total AUC for P100 in this study was 80.4 ± 38.2 ng/h/mL. The study by Schultheiss et al¹⁶ using 100 $\mu\text{g}/\text{hour}$ patches determined AUC from 24 to 72 hours only, so a similar comparison cannot be made.

Although one of the proposed advantages of transdermal drug delivery systems is that they provide fairly constant plasma concentrations of the drug, the results from this study revealed considerable intraindividual and interindividual variability in plasma fentanyl concentrations achieved. In individual dogs, plasma fentanyl concentrations increased and decreased throughout the period of patch application, and steady-state fentanyl concentrations were not attained. When the data for all the dogs in one group were averaged, a steady-state period of relatively stable plasma fentanyl concentrations does occur from 24 to 72 hours (Fig 1). This observed steady-state period with averaged data, but not with individual subjects, has been noted in previous studies in dogs and is also typical of human studies.^{8,10,16}

Variability in plasma fentanyl concentrations attained could arise from variations in drug release from the patch, absorption across the epidermis and dermis, uptake by the cutaneous vasculature, and patient volume of distribution and metabolic clearance. The predicted or nominal delivery rate from transdermal fentanyl patches is subject to variation, with reported actual delivery rates in dogs in the range of 27% to 100% of the theoretical rate of delivery.¹⁰ Large variations in actual delivery rates also occur in humans.^{7,8,21}

Transdermal fentanyl delivery systems consist of four layers: a protective polyester film backing, a drug reservoir of fentanyl in alcohol, a rate-controlling semipermeable membrane that limits the release rate of the drug, and a fentanyl-saturated silicone adhesive layer that allows attachment to the skin. The rate-controlling membrane in the transdermal fentanyl system is designed to release drug more slowly than the rate of absorption through the most impermeable stratum corneum and, ideally, allows the control of the rate of drug absorption to reside in the design of the transdermal system and not be

dependent on the variable permeability of the underlying skin.^{1,8} *In vivo* percutaneous absorption, however, is a complex biological process. The skin is a multilayered biomembrane with particular absorption characteristics. Because skin is a dynamic, living tissue, the absorption parameters are susceptible to constant change, and many factors and skin conditions can rapidly alter these parameters. Factors such as individual and species variation, blood flow, cutaneous vasoactivity, exposure to the environment, skin damage, body and skin temperature, and skin hydration all have an influence on transdermal absorption.^{1,8,12,22} Individual variation with absorption of fentanyl in humans is thought to be due to differences in cutaneous and body temperature, vascular perfusion of the skin, state of hydration, skin integrity at the application site, and environmental temperature.^{1,8,12,23,24} In fact, drug permeation through human skin at a selected application site can vary from 46% to 66% among individuals, and variations between skin regions within one individual can vary by 20% to 40%.¹

By applying the patches to the same area of the body on each dog, preparing the patch application site in a similar manner, and housing the dogs in the same facility with the same environmental conditions, it was thought that some of these variables might be reduced. Activity of the dogs was limited to movement within runs, however, some dogs were definitely more active than others. Body temperature was not routinely measured, and it is not known if body temperature remained normal in these dogs. We also did not prevent the dogs from lying on the side with the patch applied, and this could have resulted in a local change in skin temperature. State of hydration and vascular perfusion at the patch application site were also not monitored or controlled.

Variation in patient metabolic clearance and volume of distribution affects the time to reach steady-state plasma concentrations, the plasma fentanyl concentration at steady-state, peak plasma fentanyl concentration, and time to reach peak plasma fentanyl concentration in each individual.^{19,22,25} The volume of distribution for intravenously administered fentanyl in dogs has been reported to be 9.5 L/kg and 10.65 L/kg.^{10,26} Clearance of intravenous fentanyl is 27 to 37 mL/kg/min in dogs.^{10,26} The elimination half-life for intravenous fentanyl is 211 to 360 minutes in dogs.^{10,26} There is a high degree of individual variability in volume of distribution, clearance, and

elimination half-life in dogs.^{10,26} In addition, although cutaneous metabolism of fentanyl has been investigated and found not to occur in humans,^{8,12} to our knowledge this has not been investigated in dogs. Metabolism of fentanyl by enzymes in the skin or degradation by the skin's bacterial flora may alter the amount of fentanyl reaching the systemic circulation.^{12,27} These factors may account for the variability in time to first detectable fentanyl concentrations, time to reach steady-state plasma fentanyl concentrations, maximal plasma fentanyl concentrations obtained, and plasma fentanyl concentrations obtained during the steady-state period noted in this study. Some of the species and individual variation in absorption could also relate to differences in epidermal thickness and structure. One study in dogs found that both the thickness of the cellular layer of the epidermis and the thickness of the full epidermis were correlated with the time to reach plasma fentanyl concentrations of 0.5 ng/mL, but not with AUC or maximal plasma fentanyl concentration achieved.¹⁶ Thus, variations in time to first detectable plasma fentanyl concentration may be partially due to variation in epidermal thickness among the dogs. Assay variability may also cause error at low plasma concentrations and may account for some of the variation in time to first detectable plasma fentanyl concentrations, plasma fentanyl concentrations measured after patch removal, and the apparent half-life of elimination observed in this study.²⁸

Although there was a significant change in plasma fentanyl concentration over time for all three patch sizes, only P50 and P75 were statistically different and P100 did not result in greater mean plasma fentanyl concentrations than P50 or P75. Comparison of the patches at 24, 48, and 72 hours (chosen as the beginning, midpoint, and end of the steady-state period) revealed that P100 did not differ from P50 at any of these times but did differ from P75 at 48 hours. This lack of a statistically significant difference between P100 and P50 or P75 is difficult to explain in terms of variations among individual dogs, given the crossover design of the study. One possibility is that there is greater variability in drug release from the 100 μ g/hour patches, although this has not been documented. Further studies with a greater number of dogs may demonstrate clearer between-patch differences in release rates and drug absorption.

In humans, there is a significant depot effect with

transdermal fentanyl patch systems, and plasma fentanyl concentrations remain elevated for several hours after patch removal. Apparent terminal elimination half-life values in humans have ranged from 14 to 25 hours.^{7,8,20,29} In our study, plasma fentanyl concentrations declined fairly rapidly after patch removal (Fig 1). In one dog with P50 and many of the dogs with P75 and P100, there was a transient increase in plasma fentanyl concentrations noted at 1 and 2 hours after patch removal. This increase was not statistically significant, and by 4 hours after patch removal the plasma fentanyl concentrations had decreased again. The harmonic mean of the apparent elimination half-life after patch removal in our study ranged from 2.5 to 3.6 hours. An even shorter elimination half-life (1.39 hours) was found in a previous canine study.¹⁰ These values are shorter than the values found in humans. The shorter elimination half-life values obtained in this study indicate that the prolonged depot effect found in humans may not occur to the same extent in dogs. A depot effect should normally give a continual release of fentanyl to the systemic circulation.^{19,27} One possible explanation for the spikes in plasma fentanyl concentration that we observed may be that there was a slight depot of drug in the dermis of these dogs, and removal of the patch with subsequent licking of the area by the dog may have resulted in increased perfusion and increased absorption of the drug remaining in the dermis or oral mucosal absorption of the drug. In general, however, it can be said from this study that plasma fentanyl concentrations decline quickly after patch removal.

Although there are many advantages to the use of transdermal fentanyl systems, they are not without their disadvantages. Adverse effects reported in humans include respiratory depression, dermatologic reactions, sedation, constipation, urinary retention, headaches, anxiety, depression, delirium, euphoria, and death.²⁷ The study by Schultheiss et al¹⁶ in dogs reported observing varying degrees of sedation, depression of heart rate and respiratory rate, appetite suppression, and hypothermia. In the present study, ventilation was not assessed, so it is not known if respiratory depression occurred in the dogs. Mild sedation was observed in three dogs, two with P100 and one with P75 applied. Dermatologic reactions were commonly observed. In humans, pruritic, erythematous reactions occur in up to 60% of patients and are transient.¹ Although both irritant and allergic

contact dermatitis have been reported, as a result of the active ingredient (fentanyl), the vehicle (alcohol), or the adhesive, systemic allergic reactions have not been reported.³⁰

Because of the high degree of interindividual and intraindividual variation in absorption and plasma fentanyl concentrations achieved, supplemental analgesia is often required in human patients using the patch systems, until an appropriate patch size is determined. This is also likely to be true in dogs, given the results of this study. No reliable studies have been performed to determine the analgesic plasma fentanyl concentrations for dogs. Plasma fentanyl concentrations considered to be analgesic in humans range from 0.63 to 3.0 ng/mL, but this is subject to a great deal of intersubject and intrasubject variability.⁶⁻⁸ A study examining the reduction of enflurane minimal alveolar concentration (MAC) by fentanyl in dogs demonstrated a significant MAC reduction at plasma fentanyl concentrations in the range of approximately 3.0 to 30.0 ng/mL. It was not determined in this study if MAC reduction occurred at plasma fentanyl concentrations less than 3.0 ng/mL.³¹ Another study in conscious dogs demonstrated a decrease in heart rate and blood pressure responses and somatic pain reactions (withdrawal of the tail, head raising, opening of the eyes) to tail clamping with plasma fentanyl concentrations of 5 to 30 ng/mL.³² Further clinical studies are required to determine a range of analgesic plasma fentanyl concentrations in the dog, which may provide guidelines for the most appropriate patch size to use in clinical patients.

There was a high degree of interindividual and intraindividual variation in plasma fentanyl concentrations achieved in this study. The 75 or 100 $\mu\text{g}/\text{hour}$ patches may be adequate for 20-kg dogs, but adequacy of analgesia as well as deleterious side effects such as respiratory depression should be monitored continuously. Patch application should occur at least 24 hours before the time analgesia is required, or supplemental analgesics should be provided in the interim.

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