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Effect of transdermally administered fentanyl on the minimum alveolar concentration of isoflurane in cats

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Abstract

Objective To determine the effect of two doses of fentanyl, administered transdermally, on the minimum alveolar concentration (MAC) of isoflurane in cats.

Study design Prospective, randomized study.

Animals Five healthy, spayed, female cats.

Methods Each cat was studied thrice with at least 2 weeks between each study. In study 1, the baseline isoflurane MAC was determined in triplicate for each cat. In studies 2 and 3, isoflurane MAC was determined 24 hours after placement of either a 25- or 50-μg $hour^{-1}$ fentanyl patch. In each MAC study, cats were instrumented to allow collection of arterial blood and measurement of arterial blood pressure. Twenty-four hours prior to studies 2 and 3, a catheter was placed and secured in the jugular vein and either a 25 or 50-μg $hour^{-1}$ fentanyl patch was placed in random order on the left thorax. Blood samples for plasma fentanyl determination were collected prior to patch placement and at regular intervals up to 144 hours. After determination of MAC in studies 2 and 3, naloxone was administered as a bolus dose (0.1 mg kg^{-1}) followed by an infusion (1 mg kg^{-1} $hour^{-1}$) and MAC redetermined.

Results The baseline isoflurane MAC was 1.51 ± 0.21% (mean ± SD). Fentanyl (25 and 50 μg $hour^{-1}$) administered transdermally significantly reduced MAC to 1.25 ± 0.26 and 1.22 ± 0.16%, respectively. These MAC reductions were not significantly different from each other. Isoflurane MAC determined during administration of fentanyl 25 μg $hour^{-1}$ and naloxone (1.44 ± 0.16%) and fentanyl 50 μg $hour^{-1}$ and naloxone (1.51 ± 0.19%) was not significantly different from baseline MAC (1.51 ± 0.21%).

Conclusions and clinical relevance Fentanyl patches are placed to provide long-lasting analgesia. In order to be effective postoperatively, fentanyl patches must be placed prior to surgery. Plasma fentanyl concentrations achieved intraoperatively decrease the need for potent inhalant anesthetics in cats.

Keywords MAC reduction (minimum alveolar concentration), cats, isoflurane, transdermal fentanyl.

Introduction

In human beings and animals, opioids are often administered with potent inhalant anesthetic agents because they induce minimal cardiovascular depression and promote stable hemodynamics both in the presence and absence of noxious stimuli (Bailey et al. 1994; Ilkiw et al. 1994). When administered with [Q1] potent inhalant anesthetics, opioids generally reduce the inhalant concentration required for a given depth of anesthesia. This reduction in anesthetic requirement is dependent on the specific opioid, the dose of the opioid and the species to which the opioid is administered. It is quantified by determining the

reduction in minimum alveolar concentration (MAC) before and after opioid administration and these studies are commonly referred to as MAC reduction studies. For each opioid, MAC reduction generally increases as the dose is increased until a maximal or ceiling effect is obtained. Generally, opioids, such as morphine, fentanyl, alfentanil and sufentanil, which possess agonist properties at the OP3 receptor, induce greater maximal MAC reduction than opioids that have agonist properties at other receptors (Murphy & Hug 1982a, b; Hall et al. 1987). Species differences also exist and for alfentanil maximal MAC reduction has been reported as no change in horses (Pascoe et al. 1993), 35% in cats (Ilkiw et al. 1997) and 69% in dogs (Hall et al. 1987). Similar species differences have been reported for morphine (Steffey et al. 1994).

In order to achieve maximal MAC reduction, opioids are usually administered by continuous rate infusion resulting in constant plasma concentrations and, at these levels, there is minimal cardiovascular depression and stable hemodynamics. In cats, alfentanil administered to achieve maximal MAC reduction, was reported to improve cardiovascular variables and blunt respiratory, hormonal and most hemodynamic responses to a noxious stimulus, compared with isoflurane alone (Pascoe et al. 1997). However, continuous rate infusion in small animals requires an accurate method of delivery such as syringe pumps and these are not always available in veterinary practices.

Recently, new methods of opioid administration have been advocated to achieve long-lasting postoperative analgesia in veterinary practice (Bruecker 1998). Two methods, epidural and transdermal opioid administration, are easily adaptable to veterinary practice. With both methods, in order to be effective immediately postoperatively, opioids must be administered prior to surgery and thus effective concentrations are available during the intraoperative period. While the plasma opioid concentrations achieved by these routes of administration do not approach those reported to induce maximal MAC reduction (Valverde et al. 1992; Egger et al. 1998), it is likely that they will alter the anesthetic requirement and thus may improve hemodynamics. In dogs, epidural administration of morphine was found to induce 42% halothane MAC reduction (Valverde et al. 1989) and improved hemodynamics were reported when this MAC multiple was compared with halothane alone (Valverde et al. 1991). In cats, epidural administration of morphine 0.1 mg kg^{-1} was reported to induce 31% isoflurane MAC reduction (Golder et al. 1998). While plasma fentanyl concentrations following transdermal administration have been reported in dogs and cats (Kyles et al. 1996; Scherk-Nixon 1996; Egger et al. 1998; Lee et al. 2000), the effect of these concentrations on anesthetic requirement has not been studied previously. The study reported here was undertaken to determine MAC reduction induced by transdermal administration of fentanyl in isoflurane-anesthetized cats.

Materials and methods

Animals

Five conditioned spayed female domestic cats were assigned to this study after approval by the Animal Care and Use Committee of the University of California, Davis. The cats weighed 4.3 $\pm$ 0.7 kg (mean $\pm$ SD) and were 2.94 $\pm$ 0.26 years old. They were housed with other cats in two large rooms, in compliance with established standards, and were fed a commercial dry cat food *ad libitum*.

Design

Each cat was studied thrice with at least 2 weeks between each study. In the first study, isoflurane MAC was determined. In the second and third studies, cats were randomly allocated to receive each of two treatments (fentanyl patch 25 or 50 μg $hour^{-1}$) during which isoflurane MAC was again determined.

Instrumentation

Twenty-four hours prior to each study to determine MAC reduction induced by the fentanyl patch, anesthesia was induced and maintained with isoflurane and oxygen. A catheter (Central Venous Catheter Set, 20 g, 8 cm, Cook Inc., IN, USA) was placed and secured in the jugular vein for collection of blood to determine plasma fentanyl concentration. An area on the left thorax was clipped, washed with water and thoroughly dried prior to placement of either a 25- or 50-μg $hour^{-1}$ fentanyl patch (Duragesic, Janssen Pharmaceutica, Titusville, NJ, USA) in random order.

Prior to each MAC determination study, food was withheld for 12 hours, each cat was weighed, and anesthesia was induced by placing the cat in an acrylic chamber into which 5% isoflurane (Aerrane, Anaquest, Madison, WI, USA) in oxygen was deliv-

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ered. Once anesthesia was induced, the trachea was intubated, and anesthesia was maintained with isoflurane in oxygen (2 L minute^{-1}), delivered via a circle re-breathing system. Ventilation was controlled, using a respirator (Bird Mark 4, Bird Corp., Palm Springs, CA, USA), in an attempt to maintain arterial carbon dioxide tension ($PaCO_2$) at 35 ± 5 mm Hg [4.66 ± 0.6 kPa] and for ease of obtaining end-tidal gas samples. A catheter was passed down the lumen of the orotracheal tube so that its distal tip was level with the end of the orotracheal tube. End-tidal gas samples (total sample volume of 5 mL from at least five breaths) were collected manually from this catheter for measurement of isoflurane concentration by use of an infrared absorption technique (Beckman LB-2, Beckman Instruments Inc., Fullerton, CA, USA). Prior to, midway through, and at completion of each study, the analyzer was calibrated with gases containing known concentrations of isoflurane [0.5, 1.5, and 2.5% (Isoflurane balance in nitrogen, Matherson Gas Products, CA, USA)]. A catheter (Insyte, 22 g, Deseret Medical Inc., Becton Dickinson and Company, UT, USA) was placed percutaneously in a cephalic vein for administration of a balanced electrolyte solution (Lactated Ringer's Injection, USP, Baxter Healthcare Corporation, IL, USA). Total fluid administration throughout the experimental period was 3 mL kg^{-1} hour^{-1}. An incision was made over the femoral artery, and the subcutaneous tissue was dissected to expose the artery. Using the Seldinger technique, a catheter (Central Venous Catheter Kit, 24G, 9 cm, Arrow International Inc., PA, USA) was passed into the aorta dorsalis and the incision was sutured. This catheter was used for continuous measurement of arterial blood pressure and repeated anaerobic collection of arterial blood samples for measurement of pH, gas tensions, PCV (%), total protein [TP (mg dL^{-1})] and fentanyl concentrations. Packed cell volume was determined in duplicate by use of a microhematocrit technique (International Microcapillary, model MB, International Equipment Company, Needham Hts, MA, USA) and total protein concentration was estimated by use of a refractometer (10346 Veterinary refractometer, Cambridge Instruments, Buffalo, NY, USA). Limb leads were attached to record the ECG (lead II). All measurements were recorded using a physiograph (Interface 4600, Gould Inc., OH, USA). Mean arterial pressure [MAP (mm Hg)] was measured, using a pressure transducer (Transpac II Disposable Transducer, Abbott Laboratories, IL, USA). Prior to each study, the pressure transducer was calibrated against a mercury manometer, with zero level set at the thoracic inlet in laterally recumbent cats. Arterial oxygen tension (PaO_2), and $PaCO_2$, and pH were measured, using a blood gas analyzer (ABL 505, Blood Gas and Electrolyte System, Radiometer Medical A/S, West Lake, OH, USA). Rectal temperature (°C) was measured using a thermister (YSI 400 probe thermometer, Scientific Division, Yellow Springs, OH, USA) with the aim to maintain it at 38 ± 1 °C using circulating water blankets (K Module, Model K-20, American Pharmaseal Company, American Hospital Supply Company, CA, USA). Blood gas and pH values were corrected for rectal temperature (Severinghaus 1966). Bicarbonate (HCO_3) concentration (mEq L^{-1}) and base deficit (BD [mEq L^{-1}]) were calculated, using standard formulae (Siggaard-Anderson et al. 1988; Christiansen 1981). Plasma fentanyl concentration (ng L^{-1}) was measured by use of a radioimmunoassay (Michiels et al. 1977), with sensitivity between 0.15 and 3.85 ng mL^{-1}. At completion of the study, the femoral arterial catheter was removed and the incisions in the femoral artery, subcutaneous tissue, and skin were sutured. Isoflurane delivery was discontinued, and cats were watched closely in the immediate postanesthesia period.

Experimental protocol

First, the baseline isoflurane MAC was determined in triplicate using the tail-clamp method and standard technique (Quasha et al. 1980; Webb & McMurphy 1987). Cats were then randomly allocated to receive each of two treatments during which isoflurane MAC was again determined in triplicate. The two treatments consisted of placement of a 25- or 50-μg hour^{-1} fentanyl patch and, in these studies, after determination of isoflurane MAC, naloxone was administered as a bolus dose (0.1 mg kg^{-1}) followed by an infusion (1 mg kg^{-1} hour^{-1}) and isoflurane MAC redetermined.

Prior to each MAC determination, arterial blood pressure and heart rate were measured and blood was obtained for measurement of plasma fentanyl concentration, gas tensions, pH, PCV, and TP concentration. In addition, blood samples for determination of plasma fentanyl concentration were collected at the following times; prior to patch placement, every 2 hours from 0 to 12 hours, every 4 hours from 12 to 24 hours and every 12 hours from 24 to 144 hours after patch placement. Patches and central venous catheters were not removed until after collection of the last sample.

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Statistical analysis

All results are expressed as mean ± SD, and differences were considered significant when $p < 0.05$. The control MAC value and cardiovascular and respiratory variables were compared with those at each drug treatment using a repeated measures ANOVA, in which the different treatments were the within-subject factor. Using the same test, the MAC value and cardiovascular and respiratory variables for the two fentanyl treatments were compared with one another. Logarithmic transformations were used on these variables whenever necessary to satisfy the model assumptions of normality and constant residual variance. When significant effects were detected, pair-wise posthoc comparisons were made, using Tukey's honestly significant difference method. Plasma fentanyl concentrations were also compared between treatment groups and with the control period using a repeated measures ANOVA. When significant effects were detected, multiple comparisons were made using Dunnett's method.

Table 1 Isoflurane minimum alveolar concentration (MAC), MAC multiple, and MAC reduction after placement of 25 or 50 μg hour^{-1} fentanyl patch alone and together with administration of naloxone (bolus and infusion) ($n = 5$)

		Fentanyl patch (μg hour^{-1})		Fentanyl patch + naloxone administration (μg hour^{-1})	
Drug treatment (%)	**Control**	**25**	**50**	**25**	**50**
Isoflurane MAC	1.51 ± 0.21[a]	1.25 ± 0.26[b,c]	1.22 ± 0.16[b,c]	1.44 ± 0.16[a]	1.51 ± 0.19[a]
Isoflurane MAC reduction	NA	17.8 ± 7.4	18.1 ± 10.3	3.7 ± 8.6	−0.8 ± 5.3

[a,b]For control *versus* each drug treatment, mean values with common superscripts are not significantly different from one another.
[c]For 25 μg hour^{-1} *versus* 50 μg hour^{-1} drug treatments, mean values with common superscripts are not significantly different from one another.

Table 2 Cardiovascular, blood gas and acid–base effects of isoflurane during determination of MAC, using controlled ventilation, and after placement of 25 or 50 μg hour^{-1} fentanyl patch alone and together with administration of naloxone (bolus and infusion) in cats ($n = 5$)

		Fentanyl patch (μg hour^{-1})		Fentanyl patch + naloxone administration (μg hour^{-1})	
Variable	**Control**	**25**	**50**	**25**	**50**
Rectal temperature (°C)	38.9 ± 0.4[a]	38.7 ± 0.3[a,c]	38.2 ± 0.4[a,c]	39.1 ± 1.0[a]	38.7 ± 0.3[a]
Packed cell volume (%)	23 ± 2[a]	24 ± 3[a,c]	27 ± 4[a,c]	25 ± 3[a]	25 ± 3[a]
Total protein (mg dL^{-1})	6.1 ± 0.3[a]	6.0 ± 0.6[a,c]	6.3 ± 0.3[a,c]	5.7 ± 0.5[a]	5.7 ± 0.4[a]
PaO_2 (mm Hg)	505.6 ± 13.0[a]	475.4 ± 35.6[a,c]	477.7 ± 23.4[a,c]	495.6 ± 41.6[a]	482.2 ± 15.6[a]
(kPa)	(67.4 ± 1.7)	(63.4 ± 4.8)	(63.7 ± 3.1)	(66.1 ± 5.6)	(64.3 ± 2.1)
$PaCO_2$ (mm Hg)	34.2 ± 3.2[a]	35.8 ± 4.2[a,c]	34.9 ± 3.3[a,c]	31.1 ± 2.1[a]	32.7 ± 3.5[a]
(kPa)	(4.6 ± 0.4)	(4.8 ± 0.6)	(4.7 ± 0.4)	(4.2 ± 0.3)	(4.4 ± 0.5)
pH*a* (units)	7.394 ± 0.037[a]	7.368 ± 0.040[a,c]	7.394 ± 0.052[a,c]	7.402 ± 0.030[a]	7.399 ± 0.037[a]
Bicarbonate concentration (mEq L^{-1})	20.4 ± 1.3[a]	19.7 ± 0.4[a,c]	20.4 ± 1.0[a,c]	18.7 ± 1.0[b]	19.5 ± 0.7[a]
Actual base deficit (mEq L^{-1})	2.9 ± 1.6[a]	3.9 ± 0.7[a,c]	2.6 ± 1.7[a,c]	3.9 ± 1.3[a]	3.4 ± 0.8[a]
Mean arterial blood pressure (mm Hg)	86 ± 17[a]	102 ± 22[a,c]	113 ± 19[a,c]	113 ± 32[a]	89 ± 15[a]
Heart rate (beats minute^{-1})	169 ± 32[a]	199 ± 44[a,c]	225 ± 15[b,c]	183 ± 19[a]	169 ± 30[a]

[a,b]For control *versus* each drug treatment mean values with common superscripts are not significantly different from one another.
[c]For 25 μg hour^{-1} *versus* 50 μg hour^{-1} drug treatments, mean values with common superscripts are not significantly different from one another.

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Results

Transdermally administered fentanyl was found to significantly ($p < 0.05$) reduce isoflurane MAC. The isoflurane MAC reduction induced by a 25-μg hour^{-1} patch (17.8 ± 7.4%) was not significantly different from that induced by a 50-μg hour^{-1} patch (18.1 ± 10.3%) (Table 1). Administration of naloxone to cats with either a 25- or a 50-μg hour^{-1} patch returned the isoflurane MAC to one that was not significantly different from control (Table 1).

Fentanyl administration (25 and 50 μg hour^{-1}) and reduction of isoflurane concentration did not change rectal temperature, PCV, TP, MAP, blood gas tensions or acid-base variables (Table 2). Heart rate was significantly increased in the cats with a 50- but not 25-μg hour^{-1} patch, compared with control. Administration of naloxone to the cats with a 25- but not 50-μg hour^{-1} patch, and return of isoflurane to control resulted in a significant decrease in bicarbonate concentration compared with control (Table 2).

Following application of transdermal patches, there was no significant difference in plasma fentanyl concentrations between the different treatment groups. In both treatment groups, the plasma fentanyl concentrations were significantly greater than control levels from 12 to 36 hours after application. Plasma fentanyl concentrations were highest during the MAC reduction studies, with a mean plasma fentanyl concentrations of 0.92 ± 0.32 ng mL^{-1} for a 25-μg hour^{-1} patch, and 1.01 ± 0.39 ng mL^{-1} for a 50-μg hour^{-1} patch.

Discussion

Since previous studies have documented that intravenous administration of opioids decreases the need for inhalant anesthetics in cats, we were interested in determining the magnitude of the effect following transdermal fentanyl administration. The reason for studying this effect is that transdermal administration is easy and its use in veterinary practice, as a method of providing postoperative analgesia, is increasing. Because of the delay in drug absorption, fentanyl patches must be placed preoperatively and thus plasma fentanyl concentrations are often steady-state during surgery.

In this study, we tested the effect of two doses of fentanyl (25 and 50 μg hour^{-1}) in cats. The lower dose is that commonly recommended for small dogs and cats (<10 kg body weight) while the higher dose is usually recommended for medium dogs (10–29 kg

[Q2] **Table 3** Plasma fentanyl concentrations (mean ± SD) in cats after placement of 25 and 50 μg hour^{-1} fentanyl patches ($n = 5$)

Plasma fentanyl concentration (ng mL^{-1})	Time (in hours) after placement of patch																					
	0	2	4	6	8	10	12	16	24	36	48	60	72	84	96	108	120	132	144
25-μg hour^{-1} patch	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.06 ± 0.13	0.19 ± 0.21	0.33 ± 0.25	0.52 ± 0.20	0.53 ± 0.32	0.54 ± 0.41	0.82 ± 0.49	0.25 ± 0.21	0.13 ± 0.13	0.13 ± 0.20	0.03 ± 0.06	0.12 ± 0.16	0.08 ± 0.10	0.04 ± 0.09	0.01 ± 0.02	0.05 ± 0.11
50-μg hour^{-1} patch	0.00 ± 0.00	0.00 ± 0.00	0.07 ± 0.16	0.12 ± 0.15	0.25 ± 0.21	0.47 ± 0.20	0.56 ± 0.37	0.72 ± 0.21	0.83 ± 0.21	0.86 ± 0.49	0.36 ± 0.22	0.39 ± 0.42	0.30 ± 0.19	0.28 ± 0.20	0.24 ± 0.14	0.32 ± 0.41	0.33 ± 0.47	0.18 ± 0.22	0.15 ± 0.18

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body weight) (Hellyer 1997). Possible delivery doses, calculated using the expected patch delivery rate and the body weight of the cats, were 5.8 μg kg^{-1} $hour^{-1}$ for the 25 μg $hour^{-1}$ patch and 11.6 μg kg^{-1} $hour^{-1}$ for the 50 μg $hour^{-1}$ patch. For the 25 μg $hour^{-1}$ patch, this dose is between that of 4 and 6.6 μg kg^{-1} $hour^{-1}$, doses determined in published studies (Scherk-Nixon 1996; Lee et al. 2000). For the 50 μg $hour^{-1}$ patch, the dose is higher, however, the reason for including the higher dose was to determine whether it offered advantages over the lower dose by inducing a greater MAC reduction.

In our study, control isoflurane MAC was found to be 1.51 ±0.21%, which is similar to other published values (1.63 ± 0.02, 1.61 ±0.04%) (Steffey & Howland 1977; Drummond et al. 1983). Administration of 25 μg $hour^{-1}$ of fentanyl transdermally significantly reduced isoflurane MAC by 17.8%. However, increasing the administered dose (50 μg $hour^{-1}$) did not result in a significantly greater isoflurane MAC reduction (18.1%). While a greater MAC reduction might have been expected from the higher dose, the result is not surprising since no difference was found in plasma fentanyl concentrations between the two doses. The MAC reduction reported in this study of approximately 18%, is lower than the maximal MAC reduction of 35% reported for alfentanil in cats (Pascoe et al. 1997). In the latter study, a plasma alfentanil concentration of 50 ng mL^{-1} induced an isoflurane MAC reduction of 20%, whereas a plasma alfentanil concentration of 500 ng mL^{-1} was required to induce maximal MAC reduction (Ilkiw et al. 1997). The MAC reduction induced by fentanyl has not been reported in cats, but in dogs maximal MAC reduction (65%) resulted from a plasma fentanyl concentration of approximately 30 ng mL^{-1} (Murphy & Hug 1982b). Administration of naloxone, an opioid antagonist, returned the isoflurane MAC value to one not significantly different from control indicating that the MAC reduction was due to an interaction of fentanyl at the opioid receptor level.

The cardiovascular, blood gas, acid-base, and temperature variables measured at isoflurane MAC are similar to those reported previously (Steffey & Howland 1977), although the heart rate of 169 ± 32 beats $minute^{-1}$ is higher, but closer to that reported by us previously (Ilkiw et al. 1997). In the study reported here, packed cell volumes are lower than those reported in other studies (Steffey & Howland 1977; Ilkiw et al. 1997) possibly due to blood sampling. In the previously mentioned studies, blood was only sampled during the study time whereas in this study blood sampling for plasma fentanyl determinations was carried out before, as well as, during the study. During the MAC reduction studies, sampled blood amounted to <5% of blood volume and was replaced with 0.9% saline, at a greater amount (approximately twice). Transdermal administration of fentanyl and reduction of the isoflurane concentration did not result in any significant changes in rectal temperature, MAP, blood gas tensions and acid–base variables. Heart rate was significantly increased in cats with a 50-μg $hour^{-1}$ patch compared with control. In a previous study, intravenous administration of alfentanil and reduction of isoflurane concentration, also resulted in a significant increase in heart rate, but mean arterial blood pressure was also increased (Pascoe et al. 1997). It is difficult from this study to determine whether fentanyl administration together with a 17–18% reduction in isoflurane concentration is likely to provide better hemodynamics than isoflurane alone. In order to demonstrate beneficial hemodynamic effects, a further study would be required which focused on the measurement of cardiovascular variables such as cardiac output. A previous in-depth cardiovascular study has documented that doses of opioids that induce maximal MAC reduction do result in significant MAC reduction with beneficial hemodynamic effects (Pascoe et al. 1997). Administration of naloxone did not induce any changes except a significant decrease in bicarbonate concentration in the cats with a 25-μg $hour^{-1}$ patch. The reason for this is unknown and the change is not considered clinically important.

In our study, plasma fentanyl concentrations after application of both 25 and 50 μg $hour^{-1}$ fentanyl patches showed marked inter- and intra-individual variation. This has been previously documented in all reported studies in dogs and cats (Scherk-Nixon 1996; Lee et al. 2000; Kyles et al. 1996; Egger et al. 1998). In a previous study in cats (Scherk-Nixon 1996), sustained plasma fentanyl concentrations of 0.23–0.52 ng mL^{-1} were found within 2–6 hours of patch application (25 μg $hour^{-1}$) and these concentrations lasted the entire 104 hours (last sampling time). In a more recent study, the duration of steady-state was 18–100 hours (patch removed at 100 hours) and the mean concentration at steady-state from the 25 μg $hour^{-1}$ patch was 1.88 ± 0.14 ng mL^{-1} (Lee et al. 2000). However, in the latter study, two cats had undetectable plasma fentanyl concentrations for the entire 100 hours. In our study, plasma fentanyl concentrations were not significantly different from control until 12 hours after application of the

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patch and had decreased to a level that was not significantly different from control by 48 hours. Plasma fentanyl concentrations were highest for both patch sizes during the MAC determination studies. The reason for this is unknown but perhaps anesthetic induced changes in peripheral circulation, as well as external warming devices, increased drug uptake. The variability of our results over the entire sampling period is similar to other studies and is due to the great variability in drug absorption by this method.

In summary, transdermal administration of fentanyl in cats did result in a significant decrease in the need for the potent inhalant anesthetic agent, isoflurane. However, isoflurane MAC reduction with this method was less than has been reported in cats following administration of opioids by other methods such as constant rate infusion and epidural injection.

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1	**Bailey & Stanley 1994** has been changed to **Bailey et al. 1994** so that this citation matches the list	
2	**Table 3** has not been found in the text.	

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