

## The history and pharmacology of fentanyl: relevance to a novel, long-acting transdermal fentanyl solution newly approved for use in dogs

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KuKanich, B., Clark, T. P. The history and pharmacology of fentanyl: relevance to a novel, long-acting transdermal fentanyl solution newly approved for use in dogs. *J. vet. Pharmacol. Therap.* 35 (Suppl. 2), 3–19.

Fentanyl is a potent mu opioid receptor agonist that was discovered to identify an improved human health analgesic over morphine, an opioid frequently associated with histamine-release, bradycardia, hyper- or hypotension, and prolonged postoperative respiratory depression. Historically, the pharmacological features of fentanyl have been described primarily through the study of the human approved fentanyl citrate formulation. In conscious dogs, fentanyl has a wide margin of safety, possesses minimum effects on the cardiovascular and respiratory systems, and is readily reversible. Other pharmacological features include sedation, mild reductions in body temperature, and dose-dependent reduction in food intake. The short duration of effect of available fentanyl citrate solutions has limited its clinical use to perioperative injections or constant rate infusions (CRIs). To extend the analgesic effect, additional fentanyl delivery technologies have been developed for human health including the fentanyl patch that has been used in an extra-label manner in dogs. Beyond the slow onset and variability in fentanyl delivery, several additional disadvantages have precluded common use of patches in dogs. The recent approval of long-acting transdermal fentanyl solution for dogs provides a new approach for sustained delivery of fentanyl for the control of postoperative pain in dogs. It has a rapid onset of action, prolonged duration, and mitigates the disadvantages of oral, parenteral, and patch-delivered opioids. The availability of a safe and effective approved opioid in dogs may allow further optimization of postoperative analgesia in this species. The objective of this review is to summarize the history and pharmacology of fentanyl and to integrate information about the newly approved long-acting transdermal fentanyl solution.

(Paper received 31 January 2012; accepted for publication 18 April 2012)

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### INTRODUCTION

Fentanyl is a synthetic opioid that has been used clinically in several pharmaceutical formulations as an analgesic and tranquilizer in dogs. The impetus for its discovery was to identify an improved human health analgesic over morphine, an opioid frequently associated with nausea, histamine-release, bradycardia, hyper- or hypotension, and prolonged postoperative respiratory depression (Lowenstein, 1971). Early toxicology studies in dogs showed that even large intravenous doses of fentanyl of up to 3 mg/kg (approximately 600× the recommended dose 0.005 mg/kg) resulted in only small reductions in cardiac output, peripheral resistance, and arterial pressure, supporting the idea that fentanyl would be a useful human anesthetic agent

(Freye, 1974; Liu *et al.*, 1976). As a result, fentanyl citrate was initially introduced for use in humans as an injectable general anesthetic in combination with droperidol and later as a sole injectable agent.

Historically, there has only been one fentanyl-containing product that has achieved regulatory approval for use in dogs: a parenteral solution containing droperidol that was indicated for use as an analgesic and tranquilizer (FDA-CVM, 2011). This product ceased to be commercially available several years ago and, lacking regulatory approval for use in dogs, the predominant use of fentanyl has been through extra-label use of pharmaceutical formulations that were approved for use in humans. Following the experience in human health, fentanyl has been widely adapted to anesthetic case management in dogs,

and because of rapid clearance and short duration of effect, has been primarily limited to perioperative single or repeat injections or constant rate infusion (CRI) (Pascoe, 2000). To extend the duration of action, alternate pharmaceutical forms of fentanyl have been developed for use in humans that include transdermal patches and these too have been used in an extra-label manner in dogs (Hofmeister & Egger, 2004). More recently, in October 2011, the European Medicines Agency approved a novel, long-acting transdermal fentanyl solution (TFS).<sup>a</sup> Developed specifically for use in dogs, it is indicated for the control of pain associated with orthopedic and soft tissue surgery. With the use of novel delivery technology, a single, rapid drying, small-volume (~50 µL/kg) dose applied to the skin 2–4 h prior to surgery delivers fentanyl into the stratum corneum and provides sustained therapeutic plasma fentanyl concentrations over a period of at least 4 days (Freise *et al.*, 2012c, 2012d). With this newly approved formulation available for use in dogs, the objective of this review is to summarize the pharmacology of fentanyl and to integrate information about the newly approved TFS.

#### OPIOID TERMINOLOGY AND FENTANYL CLASSIFICATION

Opioids are classified by the receptor they interact with and the type of drug–receptor interaction once bound. Three major opiate receptor types are well recognized and were named based on the compound that originally resulted in specific receptor binding. These are the mu (µ), delta (δ), and kappa (κ) opiate receptors that specifically bind to morphine, dynorphin, and ketocyclazocine, respectively (Fine & Portenoy, 2004) (Table 1). Each of these is further characterized into additional subtypes based on the selectivity of ligand binding. A secondary level of opioid classification is based on the effect mediated when bound to opioid receptors; agonists result in increased receptor-mediated activity to a maximum effect, partial agonists result in increased receptor-mediated activity that plateaus at a submaximum effect and antagonists which bind to the receptor, but lack of receptor-mediated activity. Therefore, opioids can be classified as mu, delta, and/or kappa receptor agonists, partial agonists and/or antagonists. Whereas some opioids may be limited to interaction with a single receptor type, other opioids such as butorphanol bind to multiple opioid receptors resulting in mixed activation (Pallasch & Gill, 1985).

The classification of opioids most commonly used in clinical medicine for dogs with respect to their receptor binding and activity is given in Table 2 (KuKanich & Papich, 2009). Mu opiate receptor agonists are considered to possess the greatest analgesic effect and produce a dose-dependent increase in analgesia until unconsciousness occurs. Fentanyl is a mu opioid receptor agonist along with morphine, hydromorphone and oxymorphone. In contrast, kappa receptor agonists, such

<sup>a</sup>Recuvyra™ 50 mg/mL transdermal solution for dogs, Nexcyon Pharmaceuticals Ltd, London, UK.

**Table 1.** Opioid receptor classification, anatomic location, and function

Receptor	Subtypes	Location	Function
Delta (δ)	δ <sub>1</sub> , δ <sub>2</sub>	Brain <ul style="list-style-type: none"> <li>• Pontine nuclei</li> <li>• Amygdala</li> <li>• Olfactory bulbs</li> <li>• Deep cortex</li> </ul>	Analgesia Antidepressant effects Physical dependence
Kappa (κ)	κ <sub>1</sub> , κ <sub>2</sub> , κ <sub>3</sub>	Brain <ul style="list-style-type: none"> <li>• Hypothalamus</li> <li>• Periaqueductal gray matter</li> <li>• Claustrum</li> </ul> Spinal Cord <ul style="list-style-type: none"> <li>• Substantia gelatinosa</li> </ul>	Spinal analgesia Sedation Miosis Inhibition of ADH release
mu (µ)	µ <sub>1</sub> , µ <sub>2</sub> , µ <sub>3</sub>	Brain <ul style="list-style-type: none"> <li>• Cortex (laminae III and IV)</li> <li>• Thalamus</li> <li>• Periaqueductal gray matter</li> </ul> Spinal Cord <ul style="list-style-type: none"> <li>• Substantia gelatinosa</li> </ul>	µ <sub>1</sub> : <ul style="list-style-type: none"> <li>• Supraspinal analgesia</li> <li>• Physical dependence</li> </ul> µ <sub>2</sub> : <ul style="list-style-type: none"> <li>• Respiratory depression</li> <li>• Miosis</li> <li>• Euphoria</li> <li>• Reduced GI motility</li> <li>• Physical dependence</li> </ul>

**Table 2.** Opioid receptor activity for opioids more commonly used in clinical medicine in dogs

Drug	µ	κ	δ
Fentanyl	++		
Morphine	++		
Oxymorphone	++		
Buprenorphine	+		
Butorphanol	+	++	
Tramadol*	+		
Naloxone	–	–	–
Naltrexone	–	–	–

++ agonist, + partial agonist, - antagonist, – partial antagonist.

\*Binding and activity is through metabolism to o-desmethyltramadol.

as nalbuphine and butorphanol, result in a plateau of analgesic effects where further increases in dose do not result in increased analgesia. Therefore, a mu agonist such as fentanyl has greater analgesic effects compared to nalbuphine, a kappa agonist, despite both being opioid agonists (Morgan *et al.*, 1999).

Potency is a pharmacological characteristic that describes the relative dose needed to achieve an effect. For example, the effective doses of fentanyl and morphine are 0.01 and 1 mg/kg, respectively (Wegner *et al.*, 2008). Therefore, fentanyl is 100 times more potent than morphine. The potencies of opioids commonly used in clinical medicine for dogs are given in Table 3. In contrast to the term potency, efficacy is related to the maximum effect elicited by a drug independent of dose. Fentanyl is more potent than morphine but the two opioids are considered to have similar analgesic efficacy in dogs (Wegner *et al.*, 2008).

**Table 3.** Comparative potency of opioids relative to morphine for those more commonly used in clinical medicine in dogs (Adapted from Wegner *et al.*, 2008)

Drug	Potency
Morphine	1
Fentanyl	100
Hydromorphone	5
Buprenorphine	33
Butorphanol	2.5

#### AVAILABLE PHARMACEUTICAL FORMS OF FENTANYL

There are several formulations containing fentanyl as the active pharmaceutical ingredient approved for use in humans. These include a solution for injection, transmucosal formulations, and a fentanyl transdermal patch. Intended for parenteral injection, fentanyl citrate (Sublimaze<sup>®</sup>, Taylor Pharmaceuticals, Decatur, IL, USA) has never been approved for use in dogs. A product containing fentanyl citrate in combination with droperidol is approved, but not currently available. However, fentanyl citrate has been assessed in laboratory and clinical studies in dogs and utilized for extra-label clinical use. There are several transmucosal fentanyl formulations approved for use in humans to treat breakthrough pain in cancer: oral transmucosal fentanyl citrate (Actiq<sup>®</sup>, Cephalon, Inc., Frazer PA, USA), fentanyl buccal tablet (Fentora<sup>®</sup>, Cephalon, Inc., Frazer PA, USA), fentanyl buccal soluble film (Onsolis<sup>®</sup>, Meda Pharmaceuticals, Inc., Somerset, NJ, USA), and fentanyl citrate sublingual tablets (Abstral<sup>®</sup>, ProStakan, Galashiels, UK). There are no reports of these products being used extra-label in dogs.

To overcome the short duration of action of fentanyl injections, variations in pharmaceutical delivery have been advanced in human health to prolong therapeutic duration. For prolonged use to treat moderate to severe chronic pain in humans, patches intended as devices to deliver fentanyl transdermally have been developed (Janssen Pharmaceutica Products, 2005). Because of abuse problems with the patch, it has been reformulated from a liquid gel to a patch in which the drug is included in an adhesive layer which is bioequivalent in humans. However, no studies have assessed both formulations simultaneously in the dog; therefore, it is unknown whether they are bioequivalent in dogs.

Transdermal drug delivery has several advantages. It bypasses first-pass intestinal and hepatic metabolism, may provide prolonged drug concentrations, avoids multiple injections, and avoids the need for a constant rate IV infusion. Transdermal drug flux can be predicted by Fick's law of diffusion. Drug flux is directly proportional to the diffusion coefficient (ability of the drug to diffuse through the stratum corneum), the partition coefficient (ability of the drug to partition from the drug formula into the stratum corneum because of the drug's lipophilicity), the concentration gradient of the drug from the drug formula to the stratum corneum, and surface area the drug is applied and inversely proportional to the thickness of the stratum corneum. Therefore, some drugs are poor candidates for transdermal

absorption because of insufficient lipophilicity (inability to partition from the drug formula to the stratum corneum, such as morphine). Drug flux is also directly proportional to surface area; therefore, highly potent drugs require a relative small surface area to administer effective doses whereas less potent drugs may require such large surface areas that transdermal dosing is impractical.

Therefore, potency is an important factor in transdermal drug delivery as maximum drug flux of an ideal drug is 1 mg/cm<sup>2</sup> per 24-h period for human skin (Riviere & Papich, 2001). Highly potent drugs are feasible candidates for transdermal delivery because of the relatively small surface area needed to administer an effective dose. For example, the effective doses of fentanyl and morphine in dogs are 0.01 q 2 h and 1 mg/kg q 4 h, respectively (Wegner *et al.*, 2008). Therefore, the effective daily doses of fentanyl and morphine are 0.12 and 6 mg/kg per 24 h, respectively. If both drugs are well absorbed transdermally (which morphine is not due to poor lipophilicity) than the relative surface area to effectively dose both drugs would be at least 0.12 and 6 cm<sup>2</sup>/kg, respectively for fentanyl and morphine, which would be equivalent to 1.2 and 60 cm<sup>2</sup> for a 10 kg dog. Therefore, the high potency of fentanyl lends itself to transdermal delivery in that only small quantities of drug are necessary to penetrate the dermal barrier to achieve an analgesic effect. Opioids of lesser potency would require doses too large to feasibly or practically penetrate the dermal barrier because of the large surface area required.

Fentanyl transdermal patches have been examined for extra-label use in dogs to treat postoperative pain. However, shortcomings associated with their use include the lack of regulatory approval in dogs (Janssen Pharmaceutica Products, 2005), slow onset of action (Hofmeister & Egger, 2004), problems associated with maintaining patch contact on skin (Riviere & Papich, 2001), variable fentanyl delivery rate and extent (Kyles *et al.*, 1996; Mills *et al.*, 2004), potential inadvertent fentanyl exposure to the pet or pet owner (Schmiedt & Bjorling, 2007), severe adverse events in children that inadvertently ingest patches (Teske *et al.*, 2007), concern for proper control and disposal of used patches, the possibility of diversion and illicit patch use when the pet is discharged from the hospital, and lack of regulatory oversight and pharmacovigilance to track adverse events in dogs.

A newly approved long-acting TFS formulation specifically developed for use in dogs is now available for the control of pain associated with orthopedic and soft tissue surgery in dogs. As a delivery method, direct drug absorption via transdermal approaches encounters the barrier nature of skin making it difficult for most drugs to be delivered via this route (Barry, 1983). As a result, some pharmaceutical attempts to extend the delivery of fentanyl without a patch have not been successful; topical fentanyl in a pluronic lecithin organogel did not result in measurable plasma concentration in dogs (Krotscheck *et al.*, 2004). However, the use of novel penetration enhancers coupled with highly lipophilic and potent drugs such as fentanyl is a strategy to improve percutaneous absorption (Roy & Flynn, 1988). Penetration enhancers may exert their effect by

disrupting the packing of skin lipids and thus altering the barrier nature of the stratum corneum, by changing the partitioning behavior of the drug at the stratum corneum–epidermis interface or by affecting the thermodynamic activity of the drug (Barry, 1987; Beastall *et al.*, 1988). TFS is a volatile liquid-based drug delivery technology that contains octyl salicylate (OS) as a penetration enhancer (Morgan *et al.*, 1998a,b,c).

There are several advantages to TFS for use in dogs. It is approved for use in dogs and thus there have been extensive studies to demonstrate safety and effectiveness; it is readily available commercially; there is no concern for the legal implications of extra-label drug use as with nonapproved drugs; there is regulatory oversight in its manufacturing process unlike compounded drugs, and up-to-date adverse events information is mandated through pharmacovigilance. TFS is not delivered via a device and therefore there is no need for hair clipping, concern for adhesion of a device to the skin, or adverse clinical consequences because of temperature-induced altered fentanyl flux. As a concentrated liquid, only a small volume (50  $\mu\text{L}/\text{kg}$ ) of TFS applied to the skin of the dorsal scapular area is necessary and is readily applied with the aid of an applicator designed for dogs. Once applied, the dose is dried within 2–5 min where fentanyl is deposited into the stratum corneum for prolonged systemic absorption. As a professional, in-hospital only product, there is no need for owner handling or re-administration; thus, compliance issues are eliminated. A single dose applied prior to surgery delivers fentanyl at therapeutic concentrations with an onset of action of 2–4 h and duration of at least 96 h (4 days). These characteristics allow for both preemptive analgesia and sustained opioid-level analgesia for 4 days postoperatively delivered to conscious ambulatory dogs.

## FENTANYL PHARMACOKINETICS AND METABOLISM IN DOGS

### *Intravenous fentanyl*

The pharmacokinetics (PK) of parentally administered fentanyl has been well described in dogs (Table 4). The plasma profile of IV fentanyl has been described as either bi- or triphasic with

substantial decreases in plasma fentanyl concentrations during the redistribution phase(s) of the plasma profile. Following intravenous (IV) administration, the elimination half-life, clearance, and volume of distribution have been reported to range from 0.75 to 6.0 h, 20–77.9 mL/min/kg and 4.68–10.7 L/kg, respectively (Murphy *et al.*, 1979, 1983; Lin *et al.*, 1981; Kyles *et al.*, 1996; Hughes & Nolan, 1999; Sano *et al.*, 2006; Little *et al.*, 2008; KuKanich & Hubin, 2010). Although the elimination half-life has been reported as short as 0.75 h (Sano *et al.*, 2006), most studies report the elimination half-life in the range of 2–6 h. The shortest reported half-life, 0.75 h, is most likely due to sampling during the distribution phase of the plasma profile as opposed to the true elimination phase. The effect of fentanyl is rapidly lost after IV injection, typically within 2 h of clinical recommended dosing (Hug & Murphy, 1979; Wegner *et al.*, 2008). The rapid loss of opioid effects primarily occurs during the extensive redistribution phase(s) of the plasma profile, and therefore the terminal half-life is not a good predictor of duration of effect for fentanyl. This rapid loss of effect relative to plasma half-life is similar to the situation observed with thiopental anesthesia in which a rapid anesthetic recovery occurs in dogs, 1.3 h to standing, despite a prolonged half-life, 8.3 h (Sams, *et al.*, 1985). It is because of this short duration of effect in combination with poor oral bioavailability that fentanyl citrate use has been limited to perioperative injections, CRI, or transdermal patch with limited use in conscious ambulatory dogs beyond the perioperative period. Half-life is independent of dose, up to at least the highest reported dose of 100  $\mu\text{g}/\text{kg}$  IV in dogs, and no breed-specific effects have been reported. Therefore, throughout the clinically used dose range, the plasma concentrations of fentanyl are relatively well predicted independent of the dog breed and this is supported by numerous studies. Anesthetic agents have minimal effects on the primary pharmacokinetic parameters of clearance, volume of distribution, and half-life (Table 4), although randomized crossover studies directly examining the effect of anesthesia has not been performed.

Fentanyl has a large volume of distribution, which is independent of dose and remains constant up to at least 100  $\mu\text{g}/\text{kg}$  IV in dogs (Table 4). Following an IV injection, fentanyl rapidly

**Table 4.** Pharmacokinetics of IV fentanyl in dogs

Study	Dog breed	Method of analysis	Study conditions	Dose ( $\mu\text{g}/\text{kg}$ )	Terminal half-life (h)	Clearance (mL/min/kg)	Vdss (L/kg)
Murphy <i>et al.</i> (1979)	Mongrels	Radiolabeled chromatography	Enflurane anesthesia	10	3.3	38.4	10.2
Murphy <i>et al.</i> (1979)	Mongrels	Radiolabeled chromatography	Enflurane anesthesia	100	3.4	32.6	9.42
Lin <i>et al.</i> , 1981	NR	GC/MS	Pentobarbital anesthesia	50	2.4	58.9	7.7
Kyles <i>et al.</i> (1996)	Beagles	RIA	No concurrent drugs	50	6.0	27.9	10.7
Little <i>et al.</i> (2008)	Various	RIA	No concurrent drugs	10	2.7	NR	NR
Sano <i>et al.</i> (2006)	Beagle	LC/MS	No concurrent drugs	10	0.75	77.9	NR
KuKanich and Hubin (2010)	Greyhounds	LC/MS	Midazolam	15.7	3.3	20.0	4.68

NR: Not reported.

penetrates into the cerebrospinal fluid (CSF) with a  $T_{\max}$  between 2.5 and 10 min (Hug & Murphy, 1979) and the  $T_{\max}$  in brain tissue is also rapid between 10 and 20 min (Ainslie *et al.*, 1979). The CSF fentanyl concentrations declined in parallel to plasma concentrations, with CSF concentrations consistently being lower than plasma concentrations (Hug & Murphy, 1979). In contrast, fentanyl brain concentrations decline at a slower rate than plasma concentrations and from 30 min to 2 h (the last sampling point in the study) brain concentrations exceeded plasma concentrations by 7- to 18-fold (Ainslie *et al.*, 1979). This is expected as fentanyl is a lipophilic drug, and large amounts of lipids are present in the brain. In contrast, the  $T_{\max}$  of morphine, an opioid about 800× less lipophilic than fentanyl, in the CSF is about twice as long after IV administration (Hug *et al.*, 1981).

### Metabolism

Fentanyl undergoes extensive metabolism in dogs. The clearance of fentanyl in dogs is rapid, approximating hepatic blood flow, suggesting it is a high hepatic extraction ratio drug (Table 4). High extraction ratio drugs are less prone to drug–drug interactions and mild-to-moderate liver dysfunction, as their clearance is primarily related to hepatic blood flow (Riviere & Qiao, 1999). However, the clearance of fentanyl is expected to be decreased in conditions in which blood flow to the liver is limited, such as advanced cardiac disease or other causes of decreased cardiac output. Following IV and subcutaneous administration,  $^3\text{H}$ -fentanyl was extensively metabolized and excreted in both urine and feces (Ohtsuka *et al.*, 2001). In a second study, a single IV  $^3\text{H}$ -fentanyl administration resulted in 4% of parent drug and 36% of the total dose recovered in a 6-h urine collection (Murphy *et al.*, 1979). While the specific enzymes involved with fentanyl metabolism in dogs have not been identified, metabolism of fentanyl is well characterized in other species. In both humans and rats, fentanyl is primarily metabolized by the liver cytochrome P450 3A subfamily of enzymes by dealkylation to norfentanyl (Feierman, 1996; Feierman & Lasker, 1996; Labroo *et al.*, 1997). Minor metabolites identified in humans include despropionylfentanyl and hydroxyfentanyl.

Pharmacological inhibition of CYP3A4 in humans decreases fentanyl clearance following IV administration that is reflected by a mild increase in the area under the curve plasma concentration–time curve (AUC). For example, co-administration IV fentanyl and voriconazole, an inhibitor of CYP3A4, CYP2C9, and CYP2C19, significantly decreased fentanyl clearance by 23% and increased fentanyl AUC by 39%, which is considered a weak drug interaction according to the FDA because the AUC increase was <50% and dosage adjustments are not typically needed (Saari *et al.*, 2008). In the same study, a lesser effect was observed following the co-administration of IV fentanyl and fluconazole, a CYP2C9 and CYP2C19 inhibitor, where fentanyl clearance diminished by 16% and fentanyl AUC increased by 28%. Although significant changes in the PK of fentanyl were observed following CYP inhibition in humans, the magnitudes of the changes were relatively weak with limited clinical impact. The low magnitude of the inhibition is likely due

to fentanyl being a high extraction ratio drug in which moderate changes in CYP activity have minor effects on the clearance and the subsequent plasma profile of fentanyl.

In dogs, CYP3A12 is the analogous CYP isoform for human CYP3A4, and ketoconazole is an inhibitor of CYP3A12 (Lu *et al.*, 2005). Administration of ketoconazole for 3 days prior to IV fentanyl resulted in no significant changes in fentanyl half-life, clearance, or dose-normalized AUC (KuKanich & Hubin, 2010). As observed in humans, these data suggest a low likelihood of drug–drug interaction when CYP3A4/CYP3A12 inhibitors and IV fentanyl are co-administered to dogs consistent with a high hepatic extraction ratio drug. This study may also indicate CYP3A12 is not a major metabolizing enzyme of fentanyl in dogs. The results of co-administration of IV fentanyl and other CYP inhibitor drugs, such as voriconazole, fluconazole, and chloramphenicol, have not been reported in dogs and may provide valuable information.

Fentanyl delivered by constant rate IV infusion (CRI) produces relatively consistent plasma concentrations. A fentanyl CRI of 10  $\mu\text{g}/\text{kg}/\text{h}$  from 1 to 4 h in healthy Beagle dogs produced stable plasma fentanyl concentrations although pharmacokinetic variables were influenced by the duration of administration (Sano *et al.*, 2006). Total intravenous anesthesia has been achieved in normal Greyhounds by combining a fentanyl CRI (0.1–0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) for 70 min with a propofol infusion (0.2–0.4  $\text{mg}/\text{kg}/\text{min}$ ) (Hughes & Nolan, 1999). In this study, fentanyl concentrations ranged from 1.22 to 4.54  $\text{ng}/\text{mL}$ . Whereas these studies demonstrated the PK features of CRI in dogs, a fentanyl plasma concentration–effect relationship was not established.

### Subcutaneous fentanyl

The PK of subcutaneous fentanyl (15  $\mu\text{g}/\text{kg}$ ) have been reported in Greyhound dogs (KuKanich, 2011). The mean  $T_{\max}$  was rapid at 0.24 h, the mean  $C_{\max}$  was 3.5  $\text{ng}/\text{mL}$ , and the mean terminal half-life was 2.97 h. The mean  $\text{Cl}/F$  and  $V_z/F$  were similar to previous reports of the IV  $\text{Cl}$  and  $V_z$  in Greyhounds, and the dose-normalized AUCs were also similar for subcutaneous (SC) and IV fentanyl, which is suggestive the drug was well absorbed. However, a randomized crossover study was not performed to confirm the extent of absorption. Plasma concentrations exceeded 1  $\text{ng}/\text{mL}$  in 6/6 dogs at 2 h, but only 3/6 dogs 3 h post administration and 0/6 dogs at 4 h. The rapid decrease in fentanyl plasma concentrations after SC administration suggests SC administration of fentanyl citrate does not result in a sustained drug release. Pain was noted on injection, which was ameliorated by adding sodium bicarbonate solution suggesting the low pH of the fentanyl citrate solution was the cause of the pain.

### Transmucosal fentanyl

There are no reports of extra-label use of human approved transmucosal fentanyl used in dogs. However, delivery of fentanyl by a transmucosal route has been demonstrated by

use of experimental formulations. The PK of a carboxymethyl-cellulose gel fentanyl formulation (0.05 mg/kg) administered by application to the buccal mucosa of six healthy adult dogs was evaluated in comparison with IV fentanyl (0.01 mg/kg). Five minutes following transmucosal administration, serum fentanyl concentrations exceeded 0.95 ng/mL in all dogs. Except for a greater time above 0.95 ng/mL, no significant pharmacokinetic differences were found between IV and transmucosal fentanyl. Transmucosal fentanyl absorption is pH dependent; as pH increases, a greater proportion of fentanyl molecules became nonionized resulting in greater absorption. In one study, the variables peak plasma concentration, bioavailability, and permeability coefficient increased three- to fivefold as the pH of an experimental fentanyl buccal solution increased (Streisand *et al.*, 1995).

#### Fentanyl patch

Transdermal delivery of fentanyl is based on the physical and chemical characteristics of the molecule. To deliver a drug transdermally, the stratum corneum provides the primary barrier function to the skin, which is composed of keratinized cells embedded in a lipid matrix (Riviere & Papich, 2001). Drug absorption occurs primarily through the lipid matrix; therefore, drugs must have a high lipophilicity, in order to be effectively absorbed through the skin. Fentanyl is a highly lipophilic drug with an octanol/water partition coefficient of 717:1 (Roy & Flynn, 1988). In contrast, morphine does not lend itself to transdermal delivery because of poor lipophilicity with an octanol/water partition coefficient of 0.7:1.

Several studies have evaluated the PK and plasma concentration of fentanyl when administered by a transdermal patch to dogs (Table 5). However, it is important to note that the formulation of the fentanyl patch has changed and therefore the patches used in these studies may be different. Fentanyl is absorbed from the transdermal patch to reach plasma concentrations of 1–2 ng/mL within 24 h of patch application (Kyles *et al.*, 1996; Egger *et al.*, 1998). As a result of this lag time, it is necessary to administer other analgesics to achieve immediate

analgesia. Plasma fentanyl concentrations begin to decline at 72 h after patch application to concentrations that may not be effective; therefore, the effective duration action of the fentanyl patch in dogs is about 48 h (from 24 h after patch application to 72 h after patch application). The PK of fentanyl patches applied consecutively to achieve analgesia beyond 48 h has not been described in dogs. Fentanyl delivered by transdermal patch does not depot in the skin as removal of the patch results in a rapid decline in fentanyl plasma concentrations. The sustained delivery is attributed to the patch device providing a high fentanyl concentration gradient. Once the fentanyl patch is removed, plasma concentrations decrease rapidly with a terminal half-life 2–3.6 h (Kyles *et al.*, 1996; Egger *et al.*, 1998).

Plasma fentanyl concentrations are variable in response to patch-delivered fentanyl in the dog. The dog to dog variation in plasma fentanyl concentrations across several studies is about 30% (70–130%) (Kyles *et al.*, 1996; Egger *et al.*, 1998; Welch *et al.*, 2002). The almost twofold difference in plasma concentrations, even within a small homogenous group of dogs (3–6 dogs), suggests a large variability in clinical effects. The variability in a large population of diverse dogs is expected to be greater. Additionally, it appears that patches do not produce a dose-dependent increase in plasma concentrations where the average plasma concentration for the 75 and 100 µg/h patches were nearly identical at 1.4 and 1.2 ng/mL, respectively (Egger *et al.*, 1998).

As a device, fentanyl patch PK is affected by blood flow and body temperature. Anesthesia with isoflurane, as well as hypothermia during isoflurane or halothane anesthesia, results in an approximate 50% reduction in plasma fentanyl concentrations delivered by fentanyl patches (Pettifer & Hosgood, 2004). Possible reasons for this effect include decreased fentanyl absorption from skin because of hypothermia-induced reduced cutaneous blood flow, anesthesia-induced decreased cardiac output (and secondary reduced cutaneous blood flow), or reduced fentanyl flux from the patch device secondary to reduced skin temperature. Although anesthesia-induced decreased cardiac output could theoretically increase systemic fentanyl concentrations following IV administration as it is a

**Table 5.** Pharmacokinetics of transdermal fentanyl in dogs

Study	Dog breed	Weight* (kg)	Mean dose	Patch location	Method of analysis	Study conditions	Plasma concentration at steady-state* (ng/mL)
Kyles <i>et al.</i> (1996)	Beagles	13.5 ± 1.9	50 µg/h	Dorsal thorax	RIA	Awake	1.60 ± 0.38
Egger <i>et al.</i> (1998)	Mixed-breed	19.9 ± 3.4	50 µg/h	Lateral thorax	RIA	Awake	0.7 ± 0.2
Egger <i>et al.</i> (1998)	Mixed-breed	19.9 ± 3.4	75 µg/h	Lateral thorax	RIA	Awake	1.4 ± 0.5
Egger <i>et al.</i> (1998)	Mixed-breed	19.9 ± 3.4	100 µg/h	Lateral thorax	RIA	Awake	1.2 ± 0.5
Welch <i>et al.</i> (2002)	English pointer, Basset Hound	13.9–24.9 (range)	4.8 µg/kg/h	Caudal lateral abdomen	RIA	Postoperative	2.01 ± 0.68
Pettifer and Hosgood (2004)	Beagles	10.6 ± 0.43	50 µg/h	Lateral thorax	RIA	Awake	1.72 ± 0.26–2.19 ± 0.31
Chang, <i>et al.</i> (2007)	Beagles	10–12 kg (range)	25 µg/h	Unstated	LC/MS	Awake	2.06 ± 0.66 and 4.00 ± 3.44 [C <sub>max</sub> ]

\*Mean ± SD

high extraction ratio drug, patch-delivered fentanyl undergoes absorption-dependent (flip-flop) PK where the terminal portion of the plasma fentanyl concentration–time curve is determined by the absorption rate and not the elimination rate; therefore, changes in clearance in a flip-flop PK are expected to have minor effects. For short half-life drugs such as fentanyl that are delivered by a patch device, this process results in an elongated apparent half-life that is attributed to prolonged absorption and variations in PK are more likely the result of perturbations in absorption. Fentanyl flux from patches has been demonstrated to be temperature dependent and human safety warnings specifically caution against encountering high temperatures while wearing a patch to avoid potentially fatal increased fentanyl concentrations (Janssen Pharmaceutica Products, 2005). It follows that reduced skin temperature from hypothermia could result in reduced fentanyl flux in anesthetized dogs.

#### Transdermal fentanyl solution

The PK of TFS has been extensively studied during its development. In a dose titration study, the PK of 1.3 (25), 2.6 (50), and 5.2 mg/kg (100  $\mu$ L/kg) of TFS was examined in healthy laboratory Beagles (Freise *et al.*, 2012d). The PKs were characterized by a rapid initial absorption of fentanyl, within hours of application, followed by a slow terminal decline in the plasma fentanyl over a period of days controlled by flip-flop kinetics (Fig. 1). Maximum plasma concentrations from lowest to highest dose were 2.28, 2.67 and 4.71 ng/mL. The AUC and  $C_{\max}$  were dose proportional, the  $T_{\max}$  was consistent between the doses, and half-lives were also consistent between the doses and ranged from approximately 50–100 h. A dose of 2.6 mg/kg was proposed for further study based on the lack of adverse events that were observed in the 5.2 mg/kg group and a more rapid onset of action and longer duration of action compared to the 1.3 mg/kg group.

Diverse anatomic transdermal application sites are known to result in dissimilar drug delivery characteristics. For example, in humans, sites with the greatest to least potential for drug absorption are scrotal > forehead > axilla/scalp > back/abdomen > palmar and plantar (Feldmann & Maibach, 1967). The abdomen versus back skin in dogs has been shown to differ with regard to blood flow, and therefore different absorption characteristics may be apparent when drugs are applied to these sites (Monteiro-Riviere *et al.*, 1990). To examine the effect of application site, the PKs and bioequivalence of a single 2.6 mg/kg (50  $\mu$ L/kg) dose of TFS were determined when applied to the skin of the ventral abdominal or dorsal interscapular skin in 40 healthy laboratory Beagles (Freise *et al.*, 2012c). The PKs were differentiated by a more rapid initial absorption of fentanyl following dorsal application. Bioequivalence analysis demonstrated that the sites were not equivalent; the 90% CI for both the  $C_{\max}$  and AUC<sub>0-LLOQ</sub> were not contained within the 80–125% interval. Both application sites were characterized by slow terminal decline in the plasma fentanyl concentrations over time with concentrations dropping below 0.6 ng/mL by 96 and 144 h for dorsal and ventral sites,

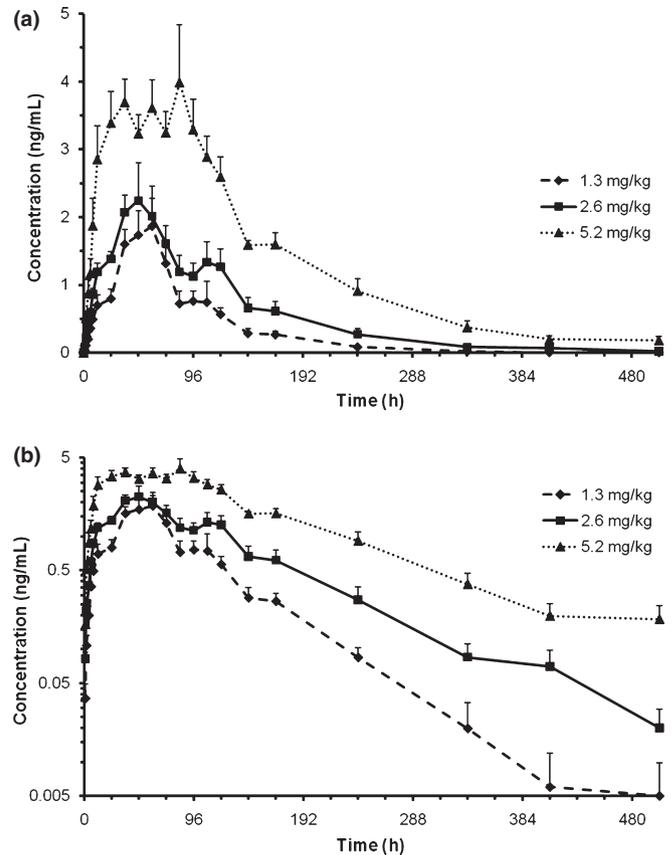


Fig. 1. Mean plasma fentanyl concentrations versus time after transdermal fentanyl solution administration by dose group on a linear (Panel a) and logarithmic (Panel b) scale from Freise *et al.*, 2012d. Bars represent the standard error.

respectively (Fig. 2). An absorption rate of  $\geq 2$   $\mu$ g/kg/h was from 2 to 144 h following dorsal application and 2–264 h following ventral application. These results demonstrated the selection of the dorsal inter-scapular skin for further examination in a field study where TFS could be applied as a single dose 2–4 h prior to surgery with analgesia lasting a minimum of 4 days.

The PKs were evaluated in a target animal safety study where the objective was to describe the margin of safety of TFS following application of multiples of the proposed dose. Twenty-four laboratory dogs were administered placebo or 1 $\times$ , 3 $\times$ , or 5 $\times$  multiple of the use dose of 2.6 mg/kg (50  $\mu$ L/kg) to the ventral abdominal skin and observed for 14 days (Savides *et al.*, 2012). Plasma fentanyl concentrations increased in proportion to dose (Fig. 3).

The PK results in healthy, conscious laboratory dogs were confirmed in the target population of client-owned dogs undergoing anesthesia and surgery. In a randomized field study of 249 dogs undergoing orthopedic or soft tissue surgery, TFS was administered 2–4 h prior to surgery and random blood samples were collected for fentanyl analysis in 215 dogs for inclusion in a population PK analysis (Freise *et al.*, 2012a). The estimated fentanyl concentration from days 0 to 4 (96 h) for a typical (median) subject was 1.32 ng/mL (Fig. 4). The time to reach 0.5 and 1 ng/mL was 1.6 and

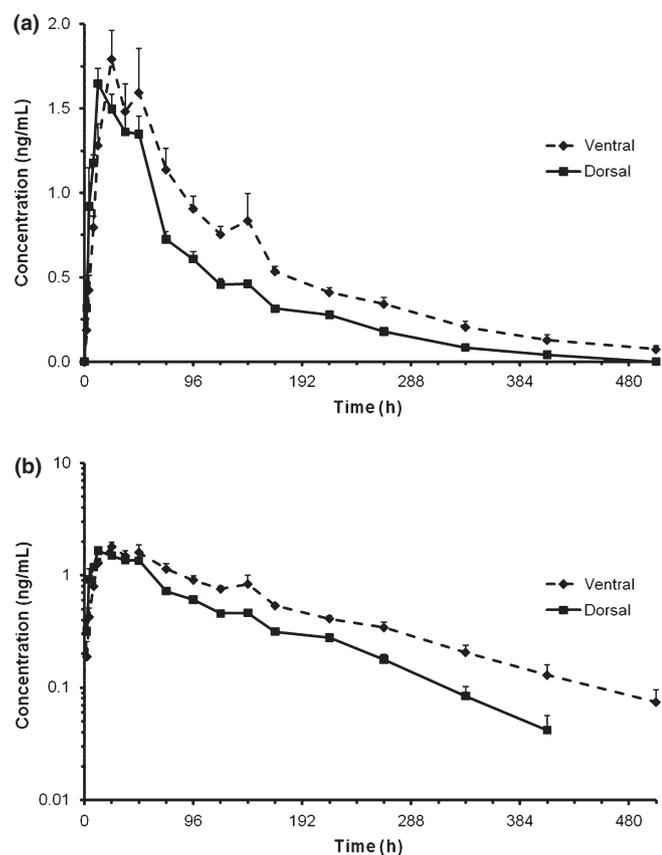


Fig. 2. Mean plasma fentanyl concentrations following 2.6 mg/kg transdermal fentanyl solution administration applied to anatomical locations represented on a linear (Panel a) and logarithmic (Panel b) scale from Freise *et al.*, 2012c. Bars represent the standard error.

3.08 h, respectively. The  $C_{max}$  and  $T_{max}$  was 1.83 ng/mL and 13.6 h, respectively and the  $t_{1/2}$  was 74.0 h.

#### FENTANYL PHARMACOKINETIC–PHARMACODYNAMIC RELATIONSHIP

With respect to analgesia, a PK–PD relationship for fentanyl has not been clinically established in dogs. However, in human health, the concentration–response relationship for fentanyl has been examined in a clinical study that established the minimum effective plasma concentration (MEC) of fentanyl. The MEC is defined as the minimum plasma concentration of an analgesic that is sufficient to prevent a patient from requesting a supplementary analgesic. The MEC of fentanyl has been established in a population of adult, human beings undergoing abdominal surgery (Gourlay *et al.*, 1988). Following surgery, fentanyl was delivered at a basal IV infusion rate of 20  $\mu$ g/h with 20  $\mu$ g on demand boluses self-administered by the patient when pain became unacceptable. A blood sample collected just prior to the patient administering additional analgesia was considered the MEC. Over 48 h, the MEC ranged from 0.23 to 1.18 ng/mL (mean 0.63 ng/mL) and remained relatively constant within individual patients over the 48-h study period.

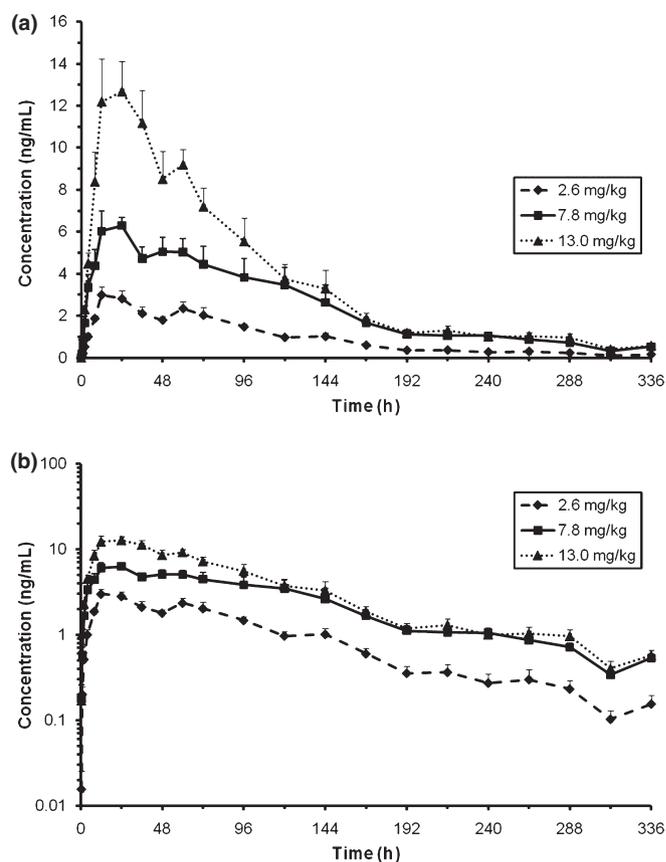


Fig. 3. Mean plasma fentanyl concentrations versus time after transdermal fentanyl solution administration by dose group on a linear (Panel a) and logarithmic (Panel b) scale from Savides *et al.*, 2012. Bars represent the standard error.

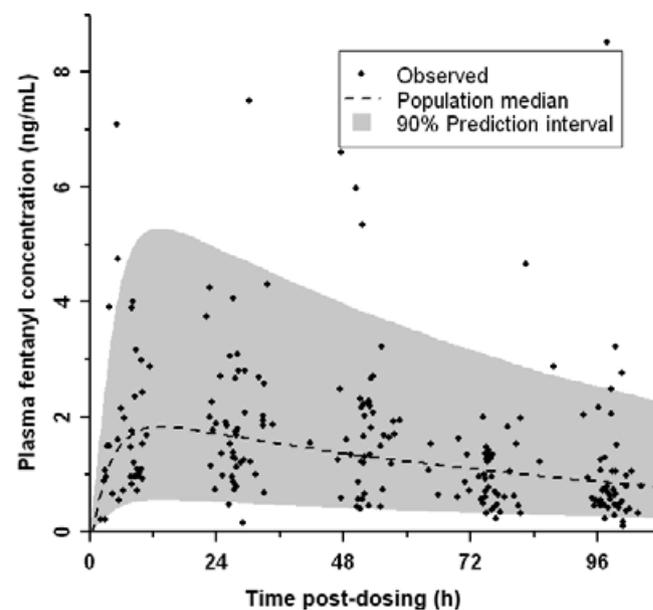


Fig. 4. Population plasma fentanyl pharmacokinetics of 215 dogs administered 2.6 mg/kg transdermal fentanyl solution in a randomized field study (Freise *et al.*, 2012a).

Thus, in patients where pain was alleviated at 0.2 ng/mL, this remained constant over time as well as for those where pain was alleviated with 1.18 ng/mL. This suggests a sixfold range of minimally effective fentanyl concentrations dependent on individual responsiveness for postoperative pain.

Establishing the MEC for fentanyl in dogs lacks the sensitivity of the techniques used in human beings. As stated previously, the MEC is defined as the minimum plasma concentration of an analgesic that is sufficient to prevent the patient from *requesting* a supplementary analgesia. Dogs cannot request their own supplementary analgesia, thus quantifying the true MEC remains elusive and rather, depends on an observer making inferences from presumed pain related behaviors displayed by dogs. Despite these limitations, behavior-based studies have evaluated analgesia and plasma fentanyl concentration in dogs to approximate analgesia and drug concentrations. The results support the notion that the MEC in dogs likely overlaps with that observed in human beings. Studies in dogs undergoing various surgeries have shown that fentanyl concentrations ranging from 0.4 to 1.28 ng/mL were effective in controlling pain (Kyles *et al.*, 1998; Robinson *et al.*, 1999; Gilbert *et al.*, 2003; Egger *et al.*, 2007). A review and analysis of all studies conducted with fentanyl patches in dogs suggests that a mean plasma fentanyl concentration of 0.6 ng/mL is suggestive of analgesia (Hofmeister & Egger, 2004), which is within the range of previously published studies. It is important to realize that a specific individual's response to an opioid analgesic will be dependent on the severity of pain, duration of pain, preemptive use of opioid analgesics, and individual sensitivity to the opioid. Therefore, a single dose or concentration will not provide the same degree of analgesia in all patients and is the reason most opioid dosage regimens have ranges of doses and dose intervals to account for the large variability in an individual animal's response to the opioid. For TFS, using a presumed (from human data) MEC of 0.2–1.2 ng/mL and dog effective concentrations of 0.4–1.28 ng/mL, the use dose of 2.6 mg/kg predicts an onset time could range from 2 to 12 h with a duration action ranging from 3.5 to 10 days (Freise *et al.*, 2012d). However, as with any analgesic the individual animal should be monitored for effective pain control and therapy adjusted to the individual animal's response.

## FENTANYL SAFETY IN DOGS

Several studies have evaluated the effects of fentanyl in dogs demonstrating a wide therapeutic index; that is, the toxic dose relative to the therapeutic dose is wide (Freye *et al.*, 1983; Arndt *et al.*, 1984; Bailey *et al.*, 1987; Hirsch *et al.*, 1993; Salmenpera *et al.*, 1994; Grimm *et al.*, 2005). Therefore, fentanyl is considered a safe and well-tolerated drug in dogs. Fentanyl administered IV to 13 dogs at a dose of 1.273 mg/kg fentanyl base and to 13 different dogs at a dose 1.91 mg/kg fentanyl base, resulted in no deaths despite the lack of intubation or other supportive measures (Bailey *et al.*, 1987). The higher dose, 1.91 mg/kg fentanyl base, is equivalent to 38.2 mL/kg of the commercially

available fentanyl citrate solution for injection (50 µg/mL). This dose is approximately 100–200 times higher than the recommended IV dose of 5–10 µg/kg (Papich, 2007) confirming the large therapeutic index of fentanyl in dogs.

Several physiological functions are influenced by activation of mu opioid receptors (Table 1), and thus fentanyl, like other opioids, can have effects beyond analgesia. The specific effects of fentanyl on various systems are discussed below along with recent data about TFS providing a large amount of data.

### Cardiovascular effects

At therapeutic doses, fentanyl has minimal effects on the cardiovascular system. When a 15 µg/kg IV bolus was administered to mixed-breed awake dogs, there were no significant changes in the cardiac index (cardiac output) or mean arterial pressures, but heart rate did significantly decrease from 103 ± 19 to 72 ± 13 bpm at 15 min post administration (Grimm *et al.*, 2005). The lack of change in cardiac output, despite the decrease in heart rate, likely means that stroke volume increased proportionally to the decrease in heart rate. Similarly, mongrel dogs anesthetized with enflurane administered a 15 µg/kg IV bolus of fentanyl had no significant effects on cardiac output or mean arterial pressures, but was accompanied by a decreased heart rate (Salmenpera *et al.*, 1994).

Even at high doses, fentanyl has minimal detrimental effects on the cardiovascular system. Supra-therapeutic doses, 2.5–5 times clinically recommended doses, typically result in bradycardia, but cardiac output and blood pressure are minimally affected. Massive doses of fentanyl, 5–200 times the clinically recommended dose, result in slight to moderate decreases in cardiac output, heart rate, and blood pressure. Mongrel dogs administered a 50 µg/kg IV bolus of fentanyl (five times the recommended IV bolus dose for analgesia) while under enflurane anesthesia had no significant effects on cardiac output, but the mean arterial pressure decreased from 98 ± 3 to 76 ± 5 mmHg and the heart rate decreased from 148 ± 4 to 109 ± 9 bpm (Hirsch *et al.*, 1993). Awake dogs (unstated breed) administered increasing doses of fentanyl had significant increases in mean arterial pressure (MAP) after a cumulative dose of 67.5 µg/kg IV bolus, but not after 27.5 µg/kg IV; the heart rate was significantly decreased after 67.5 µg/kg IV bolus, but not after 27.5 µg/kg IV; the cardiac output was also decreased after a cumulative dose of 27.5 µg/kg IV, but remained at a similarly decreased cardiac output from cumulative doses of 67.5–167.5 µg/kg IV (Arndt *et al.*, 1984). Mixed-breed spontaneously breathing dogs administered fentanyl (base) at doses from 80 to 1910 µg/kg (0.08–1.19 mg/kg) had significant decreases in heart rate to a low of 48 ± 2 bpm, but other cardiovascular parameters were not reported (Bailey *et al.*, 1987).

Transdermal fentanyl solution has minimal effect on heart rate or rhythm when evaluated in laboratory dogs or in a randomized clinical field study. In a laboratory safety study, 24 laboratory dogs were administered placebo or 1×, 3×, or 5× multiple of the approved dose of 2.6 mg/kg (50 µL/kg) to the ventral abdominal skin and observed for 14 days (Savides *et al.*,

2012). Mean heart rates decreased in a dose-dependent manner for 2 days following dose administration and returned to rates similar to that in the placebo group from Day 3 through 14. The maximal decrease in heart rate was observed in the 5 $\times$  dose group and was an approximately 50% decrease relative to the placebo controls. There were no changes to cardiac indices nor were arrhythmias observed in the present study consistent with previous reports (Gardocki and Yelnosky, 1964).

Assessing a drug in a large population of clinical patients may be more predictive of the expected clinical results compared to assessing the drug in a small number of homogenous laboratory dogs. The effects of TFS have been compared to buprenorphine injection in a randomized field study in Europe. Buprenorphine is a partial mu opioid agonist, compared to fentanyl which is a full mu agonist, so some pharmacology differences are expected between the two opioids. However, buprenorphine is an opioid approved for use in dogs for postoperative analgesia at 10–20  $\mu\text{g}/\text{kg}$  q 6 h in Europe; therefore, it was chosen as the positive control. In the randomized field study, 445 client-owned dogs undergoing surgery that were administered either TFS, 2.6 mg/kg, ( $n = 223$ ) or buprenorphine, 20  $\mu\text{g}/\text{kg}$  q 6 h, ( $n = 222$ ), the heart rates were observed for 96 h (Linton *et al.*, 2012). Mean heart rates ranged from 94.2–100.6 and 91.5–103.1 bpm over the 4-day study for TFS- and buprenorphine-treated dogs, respectively, suggesting similar effects on heart rate for both drugs.

#### Respiratory effects

Hypoventilation and respiratory depression are dose-limiting adverse reactions in human health, and this adverse event has been associated with patch-delivered fentanyl that has resulted in acute death (Janssen Pharmaceutica Products, 2005). This is not the case with dogs where fentanyl produces a dose-dependent respiratory depression that is minimal, plateaus at mild-to-moderate depression, and is not considered a severe adverse effect even with massive overdoses. However, studies are lacking on the effects of fentanyl in dogs with preexisting pathology of the respiratory system such as lung trauma, cor pulmonale, or in dogs with head trauma that are at risk for increased arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ).

Measurement of  $\text{PaCO}_2$  is considered an accurate means to monitor for respiratory function with normal  $\text{PaCO}_2$  around 35 mmHg in the dog and  $\text{PaCO}_2$  exceeding 60 mmHg being considered substantial respiratory depression (Hall *et al.*, 2001). A 15  $\mu\text{g}/\text{kg}$  IV dose of fentanyl resulted in no significant changes in the  $\text{PaCO}_2$  in awake healthy mixed-breed dogs, increasing from  $33.2 \pm 3.6$  to  $38.3 \pm 1.8$  mmHg at 15 min post drug administration (Grimm *et al.*, 2005). Awake dogs (unstated breed) administered increasing doses of fentanyl had significant increases in  $\text{PaCO}_2$  after a cumulative dose of 67.5  $\mu\text{g}/\text{kg}$  IV bolus, but not after 27.5  $\mu\text{g}/\text{kg}$  IV (Arndt *et al.*, 1984). Healthy, mixed-breed, spontaneously breathing dogs administered fentanyl at doses from 80 to 1910  $\mu\text{g}/\text{kg}$  (0.08–1.19 mg/kg) had significant increases in  $\text{PaCO}_2$  to a high of  $53 \pm 4$  mmHg at the 1910  $\mu\text{g}/\text{kg}$  15 min after injection (Bailey *et al.*, 1987). Fentanyl, 50  $\mu\text{g}/\text{kg}$ , to awake dogs (unstated breed), resulted in a 30% increase in  $\text{PaCO}_2$  to

49.6 mmHg, which was rapidly reversed with the administration of naloxone, 1  $\mu\text{g}/\text{kg}$  IV (Freye *et al.*, 1983).

Transdermal fentanyl solution has minimal effect on respiratory rate when evaluated in laboratory dogs or in a randomized clinical field study. In a laboratory safety study, 24 laboratory dogs were administered placebo or 1 $\times$ , 3 $\times$ , or 5 $\times$  multiple of the use dose of 2.6 mg/kg (50  $\mu\text{L}/\text{kg}$ ) to the ventral abdominal skin and observed for 14 days (Savides *et al.*, 2012). Reductions in respiratory rates were transient and marginally dose-dependent with a maximum reduction in rate of approximately 30% in the 3 $\times$  and 5 $\times$  groups over the first 48 h. In a randomized field study of 445 client-owned dogs undergoing surgery that were administered either TFS ( $n = 223$ ) or buprenorphine ( $n = 222$ ), respiratory rates were observed for 96 h (Linton *et al.*, 2012). Mean respiratory rates ranged from 36.6–46.6 and 33.9–44.2 rpm over the 4 day study for TFS- and buprenorphine-treated dogs, respectively, and the 95% CI of the mean difference of TFS-buprenorphine respiratory rates contained 0 at all time points. When taken together, there is no data to support the necessity of prior opioid tolerance or contraindication with anesthesia for TFS in dogs.

#### The effects on inhalant anesthesia

Fentanyl is an anesthetic sparing drug whereby its administration reduces the minimal alveolar concentration (MAC) of the inhalant anesthetics enflurane, isoflurane, and sevoflurane. As a clinical practice, the administration of fentanyl prior to use of an inhalant anesthetic is expected to decrease the MAC. Therefore, appropriate monitoring and reductions in gas anesthetic concentrations should be practiced to avoid adverse events and anesthetic overdoses.

Fentanyl administered as a 5  $\mu\text{g}/\text{kg}$  IV bolus followed by 0.5  $\mu\text{g}/\text{kg}/\text{h}$  infusion decreased the MAC of isoflurane by 54–66% compared to saline infusion (Steagall *et al.*, 2006). The effects were similar when a 75  $\mu\text{g}/\text{h}$  fentanyl patch was applied to  $26 \pm 3.5$  kg dogs where MAC was reduced by 37% compared to normothermic animals administered a placebo patch (Wilson *et al.*, 2006).

The effects of fentanyl on enflurane produced a dose-dependent decrease in the MAC following a fentanyl loading dose and infusion which plateaued at about 65% MAC reduction (Murphy & Hug, 1982). Plasma fentanyl concentrations of  $3.0 \pm 0.4$ ,  $6.5 \pm 0.9$ ,  $10.5 \pm 1.2$ ,  $28.2 \pm 5.9$ , and  $97.0 \pm 31.8$  ng/mL resulted in a  $33 \pm 5\%$ ,  $53 \pm 6\%$ ,  $57 \pm 8\%$ ,  $64 \pm 6\%$ , and  $66 \pm 2\%$  reduction in the enflurane MAC, respectively. Male mongrel dogs administered fentanyl and anesthetized with enflurane exhibited a dose-dependent decrease in enflurane MAC which plateaued at about 70% reduction, similar to the previous study (Schwieger *et al.*, 1991). The fentanyl concentration that reduced the enflurane MAC by 50% was 5.5 ng/mL with a maximum MAC reduction of 70% when fentanyl concentrations were  $>100$  ng/mL.

The isolated effects of fentanyl when administered as a sole agent in combination with sevoflurane or halothane have not been reported. Although studies assessing the effects of fentanyl

on the MAC of halothane in dogs are unavailable, it is reasonable to assume that fentanyl will decrease the MAC of halothane. Administration of the combination of fentanyl (10 µg/kg) and midazolam (0.2 mg/kg) reduced the MAC of sevoflurane by 38% compared to saline (Mutoh, 2007). Midazolam has been shown to have subadditive effects on the reduction of the enflurane MAC in dogs (Schwieger *et al.*, 1991); therefore, fentanyl and midazolam combination would be expected to have a greater effect on the sevoflurane MAC that if fentanyl was administered as a sole agent.

In a randomized field study of 445 client-owned dogs undergoing surgery that were administered either TFS ( $n = 223$ ) or buprenorphine ( $n = 222$ ), a variety of injectable and gas anesthetics were used (Linton *et al.*, 2012). Although the objective of the study was not to quantify anesthetic agent reductions, all drugs were administered to effect based on careful patient monitoring. All mean dosages of injectable and gas anesthetics were within the recommended range and there were no dogs withdrawn because of anesthetic-related adverse events.

### Thermoregulation

Opioids appear to alter the equilibrium point of the hypothalamic heat-regulatory mechanism resulting in reduced body temperature (Gutstein & Akil, 2006). In dogs, opioids may decrease the body temperature set point, thereby decreasing heat production and increasing heat loss through panting (Hammel *et al.*, 1963). Although fentanyl-induced reduced body temperature is discussed in general terms for dogs, there are minimal reports on body temperature in anesthetized or conscious dogs following fentanyl administration. However, rectal temperatures were evaluated in conscious laboratory dogs administered multiples of the dose of TFS as well as in client-owned dogs undergoing anesthesia and various orthopedic and soft tissue surgeries.

In a laboratory safety study, 24 laboratory dogs were administered placebo or 1×, 3×, or 5× multiple of the use dose of 2.6 mg/kg (50 µL/kg) TFS to the ventral abdominal skin and observed for 14 days (Savides *et al.*, 2012). Mean rectal body temperatures decreased in a dose-dependent manner and remained below the placebo control in all treated dose groups from 1 h postdose administration through Day 3 or 4 (Fig. 5). The maximum drop in body temperature was approximately 2, 3, and 4 °C on Day 1 in the 1×, 3×, and 5× groups, respectively. There was no adverse outcome associated with transient reduction in body temperature.

In a randomized field study of 445 client-owned dogs undergoing surgery that were administered either TFS ( $n = 223$ ) or buprenorphine ( $n = 222$ ), rectal temperatures were monitored for 96 h (Linton *et al.*, 2012). Rectal temperatures were lowest at the first pain assessment time, 1 h post extubation where the temperatures were  $36.8 \text{ °C} \pm 1.2$  (mean  $\pm$  SD) in both TFS- and buprenorphine-treated dogs. Mean temperatures returned above  $37.7 \text{ °C}$  in TFS- and buprenorphine-treated dogs at 24 and 6 h post extubation, respectively. At the study conclusion on Day 4, temperatures

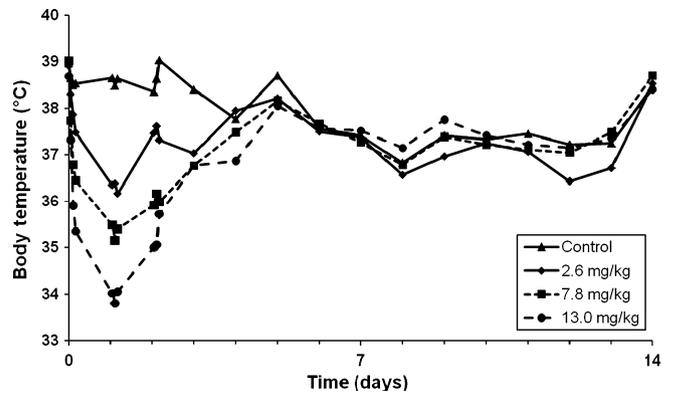


Fig. 5. Mean rectal body temperature following a single topical dose of placebo control, 2.6, 7.8, or 13.0 mg/kg transdermal fentanyl solution ( $n = 6$  per group) in healthy, nonpainful dogs from Savides *et al.*, 2012.

were  $38.4 \pm 0.5$  and  $38.2 \pm 0.5 \text{ °C}$  in TFS- and buprenorphine-treated dogs, respectively. These differences did not have any reported clinical significance. Postoperative hypothermia was recorded in <2% of dogs as an adverse event in both groups following treatment. There have been no placebo-controlled data published on postoperative body temperatures in dogs for 96 h following surgery; thus, it cannot be concluded with certainty that the observed body temperatures in this study was attributed to opioid, anesthesia, or other surgical related postoperative co-morbidity. However, these data support the notion that postoperative hypothermia following TFS can occur, but is not a primary concern requiring additional case management intervention if large reductions in body temperature do not occur. In addition, population PK analysis from a randomized clinical trial in dogs treated with TFS prior to orthopedic or soft tissue surgery suggest that fentanyl flux and analgesia is maintained in the presence of decreased body temperature during the postoperative period (Freise *et al.*, 2012a). This is not the case regarding patch-delivered fentanyl. In the instance of hypothermia, significant reductions in plasma fentanyl concentrations have been demonstrated in dogs following fentanyl patch application (Pettifer & Hosgood, 2004). Moreover, when external heat is applied directly against a dermal patch, such as with a recirculating water heater, this may result exaggerated fentanyl flux from the patch and subsequent severe adverse reactions and death in humans (Janssen Pharmaceutica Products, 2005). TFS is not a device like a dermal patch where flux of fentanyl is influenced by outside factors such as external heat. When intra-operative external heat was applied to approximately 85% of 249 dogs in a randomized clinical trial, postoperative analgesic fentanyl concentrations were maintained without enhanced transdermal flux (Freise *et al.*, 2012a).

### Food intake and body weight

There are no controlled studies that have examined the effect of fentanyl on appetite and body weight in dogs. However,

inappetence has been occasionally described with transdermal patch fentanyl administration (Hofmeister & Egger, 2004), and the reduction in food intake may be a direct result of the drug, independent of sedation. However, other variables may have contributed to the inappetence including anesthesia and surgery in the previous report. To examine the safety of TFS during development, body weight and food intake were measured variables in two studies. In a laboratory safety study, 24 laboratory dogs were administered placebo or 1 $\times$ , 3 $\times$ , or 5 $\times$  multiple of the use dose of 2.6 mg/kg (50  $\mu$ L/kg) TFS to the ventral abdominal skin and observed for 14 days (Savides *et al.*, 2012). Mean food consumption decreased in all TFS-treated groups with the greatest decrease in food consumption in the 5 $\times$  group where no food was consumed on Days 0 through 2 (Fig. 6). Food consumption was reduced to a lesser magnitude in the 1 $\times$  group and returned to pretreatment amounts by Day 4 in the 1 $\times$  group and Day 6 in the 3 $\times$  and 5 $\times$  groups. Mean body weights decreased slightly in the 1 $\times$  group over 7 days and to a slightly greater extent in the 3 $\times$  and 5 $\times$  groups. Reduced food intake may have been the result of sedation as mild sedation was observed sporadically in some dogs in the 1 $\times$  dose group over 48 h and with a greater magnitude and duration in the 3 $\times$  and 5 $\times$  groups. These observations are consistent with previous reports where sedation increased with plasma fentanyl concentrations when parenterally administered (Bailey *et al.*, 1987; Hendrix & Hansen, 2000). Sedation has been reported in dogs following fentanyl transdermal patch application as well when used at the recommended dose (Hofmeister & Egger, 2004). Although the study did not discern an underlying mechanism, reduced food intake was unlikely the result of nausea as the emesis rate was not different in placebo- and fentanyl-treated dogs.

A standard preoperative practice is to limit food intake prior to anesthesia to eliminate the likelihood of intra- or postoperative regurgitation and aspiration. Postoperative food is gradually reintroduced at an amount and frequency appropriate for the condition that required surgery. Despite these common practices of nutritional management during the perioperative period,

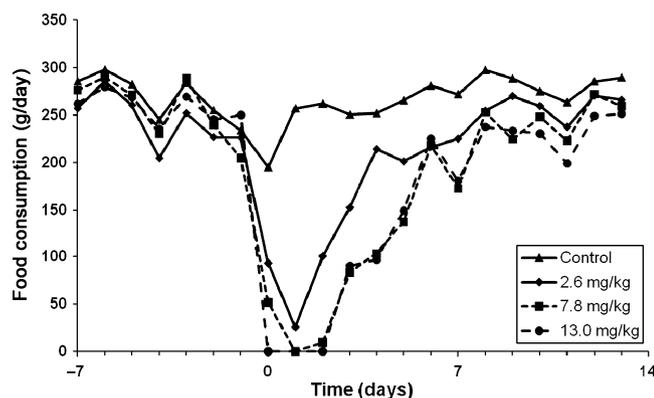


Fig. 6. Mean daily food consumption following a single topical dose of placebo control, 2.6, 7.8, or 13.0 mg/kg transdermal fentanyl solution ( $n = 6$  per group) in healthy, nonpainful dogs from Savides *et al.*, 2012.

there are no data available regarding expected body weight changes in response to surgery in the veterinary literature. In a randomized field study of 445 client-owned dogs undergoing surgery that were administered either TFS ( $n = 223$ ) or buprenorphine ( $n = 222$ ), body weight was measured prior to surgery and 96 h later (Linton *et al.*, 2012). In this study, 76% and 88% of TFS- and buprenorphine-treated dogs lost weight compared to baseline. Most body weight loss in both groups was between 0% and 5% but a small percentage of dogs lost >10% of body weight. There was no obvious morbidity problems associated with dogs that lost body weight over 4 days. The body weight change over a period of days following surgery in a placebo-controlled study has not been reported in veterinary medicine. Therefore, it cannot be concluded with certainty that the observed change in body weight was attributed to opioid, anesthesia, or other surgically related postoperative co-morbidity. However, in the absence of adverse events associated with the observed body weight loss, it is concluded that a small degree of weight loss may be a typical outcome of surgery but that a placebo-controlled study would be necessary to confirm this observation. However, disadvantages of a placebo-controlled study would include the ethical dilemmas of uncontrolled pain as well as unmitigated pain, which in itself produces immunosuppressive effects (Ahlers *et al.* 2008), enhanced metastatic potential of neoplasia surgeries (Page *et al.*, 2001), and delays wound healing (McGuire *et al.*, 2006).

#### Opioids in normal versus painful dogs

Most controlled studies with fentanyl are carried out in healthy laboratory dogs not in pain. The absence of pain as stimulus in laboratory studies is important in the consideration of opioid safety evaluations in that the clinical safety of opioids appears to be greater in the presence of pain. In human health, the idea that patients with more severe pain may tolerate 3–4 times greater doses of opioids is based in part on the observation of greater adverse events (e.g., respiratory depression) in nonpainful humans (Gutstein & Akil, 2006). It has been proposed that opioid adverse events in humans can be antagonized by pain, particularly decreased respirations (Eckenhoff & Oech, 1960). Similarly, in veterinary medicine, it has been suggested that clinical doses of opioids can be used safely in some species, particularly when pain is present (Hall *et al.*, 2001). Adverse effects of morphine, such as vomiting and dysphoria, were subjectively observed less frequently in traumatized dogs in pain compared to healthy nonpainful dogs (KuKanich, personal observations); however, controlled clinical trials are not available. Taken together, this suggests that proper, safe use of opioids is predicated on administration to patients with sufficiently painful stimuli. Therefore, the full evaluation of the safety of fentanyl will depend on the outcome of well-controlled clinical studies in dogs experiencing pain. The safety of TFS has been evaluated and confirmed in nonpainful laboratory dogs (Savides *et al.*, 2012) as well as in client-owned dogs undergoing anesthesia and surgery in multicentered studies (Linton *et al.*, 2012; Freise *et al.*, 2012c).

### Pharmacological reversal

The characteristics of an ideal analgesic may include, in part, that the agent is a full agonist providing maximal analgesia for a wide range of pain states and it is reversible (Smith, 2008; Moore, 2009). Reversibility allows clinicians to terminate the clinical effects of a drug when they are no longer deemed necessary to case management and permits intervention in the event of an overdose. Naloxone is an approved opioid antagonist that is considered the fentanyl reversal agent of choice in dogs because, as a pure opioid receptor competitive antagonist, it does not have the respiratory side effects of other opioid antagonists (Adams, 2001; Plumb, 2002). It has the highest affinity at the micro-opioid receptor, and successfully reverses the effects of fentanyl citrate injections in the dog (Paddleford & Short, 1973; Veng-Pedersen *et al.*, 1995; Adams, 2001).

For the development of TFS, two different intramuscular (IM) doses of naloxone were examined for their suitability to reverse the opioid-induced effects of an overdose of TFS (Freise *et al.*, 2012b). Twenty-four healthy Beagles were administered a single 13 mg/kg dose (fivefold overdose) of TFS and randomized to two naloxone treatment groups, hourly administration of 40 ( $n = 8$ ) or 160  $\mu\text{g}/\text{kg}$  IM ( $n = 16$ ). In response to the TFS overdose, all dogs were sedated and had reduced body temperatures and heart rates prior to naloxone administration. Both dosage regimens significantly reduced sedation, and the 160  $\mu\text{g}/\text{kg}$  naloxone regimen resulted in a nearly threefold lower odds of sedation than that of the 40  $\mu\text{g}/\text{kg}$  IM naloxone regimen. Additionally, naloxone significantly increased the mean body temperatures and heart rate; though, the 160  $\mu\text{g}/\text{kg}$  regimen increased body temperature and heart rate to a greater degree.

These results demonstrate that naloxone can effectively reverse TFS in the event of an overdose. Naloxone reversal allows veterinarians to effectively manage cases where an inadvertent overdose is applied or to terminate the clinical effects of a fentanyl when they are no longer deemed necessary to case management. The shorter duration of action of naloxone relative to TFS may necessitate repeat injections until an overdose is satisfactorily treated. It should be noted that a single three- and fivefold overdose without naloxone reversal did not result in fatality (Savides *et al.*, 2012) and therefore accidental overdose has not posed an immediate medical concern. Although not studied, an alternate route to sustained, long-term reversal is naloxone CRI. The naloxone  $k_{el}$  and  $V_d$  calculated from a pilot IV study in dogs were 2.44 1/h and  $V = 2.55$  L/kg, respectively, using a 1-compartment model (Freise *et al.*, 2012b). These data would predict that a naloxone CRI of approximately 1–4  $\mu\text{g}/\text{kg}/\text{min}$  would maintain steady-state plasma naloxone concentrations similar to the 10 min post naloxone injection concentrations achieved with 40 and 160  $\mu\text{g}/\text{kg}$ .

### FENTANYL ANALGESIA IN DOGS

The analgesic effects of fentanyl in dogs have been examined when delivered by parenteral, patch, and TFS routes. Two

laboratory studies examined the analgesic effects of fentanyl in a thermal threshold model. A single 10  $\mu\text{g}/\text{kg}$  IV dose of fentanyl produced significant increase in withdrawal time from a thermal stimulus in dogs within 5 min of drug administration (Wegner *et al.*, 2008). The onset of action was rapid. However, the response returned to baseline within 2 h of administration consistent with the rapid redistribution and short duration of effect of IV fentanyl. In neonatal dogs (ages 1–34 days), fentanyl was infused at a rate of 2  $\mu\text{g}/\text{kg}/\text{min}$  until a heat stimulus reached its maximum predetermined cutoff for two consecutive 1-min interval measurements (Luks *et al.*, 1998). The dose range of fentanyl was 7–16  $\mu\text{g}/\text{kg}$  to reach the maximum predetermined cutoff.

Several small clinical studies have examined the analgesic effects of extra-label fentanyl patch administration. In a clinical study of 24 dogs undergoing cranial cruciate ligament surgery or pelvic limb fracture repair, fentanyl patches were compared to morphine sulfate (0.5 mg/kg IM) (Egger *et al.*, 2007). Patches were applied 12 h prior to premedication and patch size was based on body weight: <10 kg (25  $\mu\text{g}/\text{h}$ ), 10–20 kg (50  $\mu\text{g}/\text{h}$ ), 20–30 kg (75  $\mu\text{g}/\text{h}$ ) and 30–40 kg (100  $\mu\text{g}/\text{h}$ ). There were no statistical differences, which is not surprising given that both treatments were mu receptor agonists. In a clinical study of 18 dogs undergoing orthopedic surgery, fentanyl patches (100  $\mu\text{g}/\text{h}$ ) were compared to epidural morphine (0.1 mg/kg) when premedicated with oxymorphone 0.1 mg/kg (Robinson *et al.*, 1999). Mean pain scores were higher for fentanyl patches at 6 h, but less from 12 to 48 h after surgery; however, there were no significant differences in the pain scores at any individual time point. In a clinical study of 16 dogs (9–12 kg) undergoing orthopedic surgery, fentanyl patches (50  $\mu\text{g}/\text{h}$ ) were compared to oral meloxicam using a subjective pain scale (Lafuente *et al.*, 2005). The authors subjectively assessed pain control as good in both groups. Plasma concentrations of fentanyl were not determined. In a clinical study of 20 dogs ( $21.1 \pm 5.2$  kg) undergoing ovariohysterectomy, fentanyl patches (50  $\mu\text{g}/\text{h}$ ) applied 20 h prior to surgery were compared to intramuscular oxymorphone (0.05 mg/kg) (Kyles *et al.*, 1998). The dogs that had fentanyl patches applied had significantly higher pain scores from 0 to 6 h, compared to oxymorphone, but pain scores were significantly decreased from 12 to 18 h postoperatively. The rectal temperature of the oxymorphone treated dogs was significantly lower at 6 and 12 h compared to the fentanyl patch group. The mean concentration of fentanyl was 1.18 ng/mL from 19 to 46 h after patch application.

As a part of drug development, a prospective, double-blinded, positive-controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of TFS for the control of postoperative pain (Linton *et al.*, 2012). Four hundred and forty-five client-owned dogs of various breeds were assigned to TFS ( $n = 223$ ) or buprenorphine ( $n = 222$ ). There were 159 (35.7%) males and 286 (64.3%) females ranging from 0.5 and 16 years of age and 3–98.5 kg. Dogs were randomly allotted to a single dose of TFS (2.6 mg/kg [ $\sim 50$   $\mu\text{L}/\text{kg}$ ]) applied 2–4 h prior to surgery or buprenorphine (20  $\mu\text{g}/\text{kg}$ ) administered

intramuscularly 2–4 h prior to surgery and q 6 h through 90 h. Pain was evaluated by blinded observers using the Glasgow modified pain scale, and the *a priori* criteria for treatment failure was a pain score  $\geq 8$  (20 maximum score) or the occurrence of an adverse event necessitating withdrawal. Dogs were divided between soft tissue ( $n = 235$ ) and orthopedic surgical procedures ( $n = 210$ ). Seven fentanyl-treated dogs were withdrawn because of lack of pain control and eight because of adverse events. Six buprenorphine-treated dogs were withdrawn because of lack of pain control and two because of adverse events. The one-sided upper 95% confidence interval of the mean difference between fentanyl and buprenorphine treatment failures was 5.6%, which was not greater than the *a priori* selected margin difference of 15%, demonstrating that TFS is noninferior to repeated injections of buprenorphine, an approved opioid for postoperative pain control in dogs. Adverse events attributed to either treatment were minimal in magnitude, and frequency and were approximately equal between groups. This study demonstrated that sustained, steady-state fentanyl delivery provided by a single preoperative dose of TFS was safe and effective in controlling postoperative pain for a period of at least 4 days.

## CONCLUSIONS

Fentanyl is a potent mu opioid receptor agonist that was discovered to identify an improved human health analgesic over morphine, an opioid frequently associated with nausea, histamine-release, bradycardia, hyper- or hypotension, and prolonged postoperative respiratory depression. In dogs, both laboratory and clinical studies have demonstrated the pharmacological and clinical features of various pharmaceutical formulations of fentanyl. With the lack of an approved product for use in dogs, the pharmacological features of fentanyl have been described primarily through study of the human approved fentanyl citrate formulation. These data have shown that fentanyl has a wide margin of safety where doses exceeding 200 times the analgesic dose prove to be nonfatal to dogs. Fentanyl possesses minimum effects on the cardiovascular system with no significant depression of cardiac output or effects on blood pressure at recommended doses. Although fentanyl has dose-dependent respiratory depression effects, the magnitude of these effects are minimal and plateau prior to severe respiratory depression, and are not clinically relevant to its use to control postoperative pain. Other pharmacological features include sedation, mild reductions in body temperature, and dose-dependent reduction in food intake. Drug–drug metabolism interactions have not been identified in dogs, but pharmacodynamic anesthetic sparing interactions have been reported. An advantage in the safe use of fentanyl is the ability to reverse the pharmacological effects with an opioid antagonist when the effects are no longer deemed necessary to case management or in the event of an overdose.

The short duration of action of fentanyl citrate has limited its use to perioperative injections or CRIs. To extend its use beyond the perioperative period, additional delivery technologies have been developed for human health including the fentanyl patch.

Liability, slow onset, and variability in fentanyl delivery in addition to several other disadvantages have precluded their common use in dogs. The recent approval of long-acting TFS for dogs provides a new approach for sustained delivery of fentanyl for postoperative pain management. A single, small volume of preemptive TFS administered 2–4 h prior to surgery provides opioid levels and analgesia for at least 4 days. The availability of a safe and effective approved opioid may allow further optimization of postoperative analgesia in dogs and mitigates many of the disadvantages of oral, parenteral, and patch-delivered opioids.

## ACKNOWLEDGMENT

The authors were employees or paid contributors to Nexcyon Pharmaceuticals, Inc.

## CONFLICTS OF INTEREST

The authors were employees or paid contributors to Nexcyon Pharmaceuticals, Inc.

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