JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. doi: 10.1111/jvp.12096

The safety and effectiveness of a long-acting transdermal fentanyl solution compared with oxymorphone for the control of postoperative pain in dogs: a randomized, multicentered clinical study

S. A. MARTINEZ*
M. G. WILSON†
D. D. LINTON‡
G. C. NEWBOUND‡
K. J. FREISE‡
T.-L. LIN‡ &
T. P. CLARK‡

College of Veterinary Medicine, Washington State University, Pullman, WA, USA; †Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA; ‡Nexcyon Pharmaceuticals, Inc., Madison, WI, USA

Martinez, S. A., Wilson, M. G., Linton, D. D., Newbound, G. C., Freise, K. J., Lin, T.-L., Clark, T. P. The safety and effectiveness of a long-acting transdermal fentanyl solution compared with oxymorphone for the control of postoperative pain in dogs: a randomized, multicentered clinical study. *J. vet. Pharmacol. Therap.* doi: 10.1111/jvp.12096.

A prospective, double-blinded, positive-controlled, multicenter, noninferiority study was conducted to evaluate the safety and effectiveness of transdermal fentanyl solution (TFS) compared with oxymorphone for the control of postoperative pain in dogs. Five hundred and two (502) client-owned dogs were assigned to a single dose of TFS (2.7 mg/kg) applied 2–4 h prior to surgery or oxymorphone hydrochloride (0.22 mg/kg) administered subcutaneously 2–4 h prior to surgery and q6h through 90 h. Pain was evaluated over 4 days by blinded observers using a modified Glasgow composite pain scale, and the *a priori* criteria for treatment failure was a pain score ≥8 or adverse event necessitating withdrawal. Four TFS- and eight oxymorphone-treated dogs were withdrawn due to lack of pain control. Eighteen oxymorphone-treated, but no TFS-treated dogs were withdrawn due to severe adverse events. The one-sided upper 95% confidence interval of the difference between TFS and oxymorphone treatment failure rates was −5.3%. Adverse events associated with oxymorphone were greater in number and severity compared with TFS. It was concluded that a single administration of TFS was safe and noninferior to repeated injections of oxymorphone for the control of postoperative pain over 4 days at the dose rates of both formulations used in this study.

(Paper received 6 May 2013; accepted for publication 5 November 2013)

Dr Terrence P. Clark, Nexcyon Pharmaceuticals, Inc., 644 W. Washington Ave., Madison, WI 53703, USA. E-mail: clarktp@nexcyon.com

INTRODUCTION

Opioids are generally regarded as an important part of multimodal postoperative analgesia, especially for moderate to severe pain. In human medicine, the use of opioids during and after surgery for most soft tissue and orthopedic surgeries is considered the standard of care and are included in procedure-specific treatment algorithms (Neugebauer *et al.*, 2007). In veterinary medicine, there are limited opioid options to treat moderate to severe pain in conscious, ambulatory dogs beyond the immediate postoperative period, because of inherent limitations of most opioids including poor oral bioavailability and rapid clearance (Garrett & Chandran, 1990; Pascoe, 2000; KuKanich *et al.*, 2005). As a result, extra-label opioid use is primarily limited to single or repeat parenteral injections to treat acute pain or constant rate intravenous infusions and epidural or intrathecal injections delivered during and following anesthesia. The transdermal fentanyl patch approved for use in humans has also been used extra-label in dogs, although safety, consistency and reliability issues exist (Marquardt *et al.*, 1995; Kyles *et al.*, 1996, 1998; Egger *et al.*, 1998, 2007; Robinson *et al.*, 1999; Riviere & Papich, 2001; Welch *et al.*, 2002; Gilbert *et al.*, 2003; Hofmeister & Egger, 2004; Mills *et al.*, 2004; Pettifer & Hosgood, 2004; Janssen Pharmaceutica Products, L.P., 2005; Lafuente *et al.*, 2005; Schmiedt & Bjorling, 2007; Carson *et al.*, 2010).

The recent Food and Drug Administration (FDA) approval of a transdermal fentanyl solution[a] (TFS) makes available an approved, long-acting opioid for the control of postoperative pain in dogs and potentially mitigates the disadvantages of oral, parenteral and patch delivered opioids. As a delivery method, the transdermal route has several potential strengths over oral and parenteral administration. These include noninvasive

[a]Recuvyra™ (fentanyl) transdermal solution, Nexcyon Pharmaceuticals, Inc., Madison, WI, USA.

dosing, avoidance of the gastrointestinal tract, and lack of first pass metabolism. A single, rapid drying, small volume (~50 μL/kg), topically applied dose of TFS administered prior to surgery delivers sustained therapeutic plasma fentanyl concentrations over a period of at least 4 days (Freise *et al.*, 2012c,d). Steady, continuous drug delivery avoids the potential side effects associated with repeated postdose peaks in plasma concentrations, as well as end of dose breakthrough pain associated with subanalgesic plasma levels. Additionally, single-dose administration allows for convenience and eliminates compliance concerns (Urquhart, 2000).

The study presented here is a double-blinded, positive-controlled, parallel-arm, multicenter clinical study carried out by recruiting client-owned dogs that presented for orthopedic or various types of soft-tissue surgery from 24 veterinary practices in the United States. The objective of the study was to evaluate the field safety and effectiveness of TFS when administered as a single, topical dose, 2–4 h prior to surgery compared with repeated subcutaneous (SC) injections of oxymorphone hydrochloride administered every six hours.

MATERIALS AND METHODS

Investigational and control drug

The investigational drug was transdermal fentanyl solution.[a] Dogs randomized to TFS were administered a single dose of 2.7 mg/kg (approximately 50 μL/kg) to the dorsal scapular area 2–4 h prior to surgery using the manufacturer provided syringe and applicator tip. The skin over the dorsal scapular area required no specific preparation prior to liquid application. If the hair coat allowed direct contact of the applicator tips to the skin, no specific hair clipping or preparation was necessary, except for thick-coated dogs (e.g., Siberian Huskies) where clipping the application site was necessary. To maintain blinding, the decision to clip the application site was made prior to random assignment to treatment. The dose was applied per the manufacturer's instructions as previously described (Linton *et al.*, 2012). The dog was then restrained for approximately two minutes to prevent removal by shaking or rolling, and no contact was made with the site for five minutes following application to allow full drying of the liquid and fentanyl penetration into the skin. To prevent accidental application of the liquid to humans, treatment administrators wore latex or nitrile gloves, safety glasses, and a laboratory coat while administering the drug to dogs. There were no restrictions for interaction with the application site by professional staff beyond five minutes following topical application.

Oxymorphone hydrochloride injection was the active control drug and is FDA approved for the control of postoperative pain in dogs (New Animal Drug Application [NADA] 030-535). The originally approved product is no longer manufactured, and therefore, a suitable formulation[b] approved for use in humans was utilized. To demonstrate substantial evidence of effectiveness of an investigational drug, an active control drug used must be administered at the FDA approved dose in a field study and must be approved for the species and indication for which the investigational drug is being examined (21 CFR 514.117 (b)(4)(iii) (2004); FDA-CVM, 2012). Accordingly, dogs randomized to oxymorphone were administered a subcutaneous dose of oxymorphone according to the dosing table in the FDA approved label (Branson & Gross, 2001) (Appendix 1), 2–4 h prior to intubation with additional doses at extubation and then every 6 h through 90 h post-extubation. Injectable oxymorphone has previously been demonstrated to provide postoperative analgesia in dogs when administered repeatedly every six hours (Hardie *et al.*, 1997; Kyles *et al.*, 1998; Bateman *et al.*, 2008).

Inclusion and exclusion criteria

Dogs that qualified for inclusion into the study were client-owned, at least 6 months of age, and weighed >2.7 kg. Pregnant (except for dogs undergoing ovariohysterectomy) or lactating females and males intended for breeding were not eligible for the study. Eligible surgery types included ovariohysterectomy, lateral ear resection, ear crop, cranial or caudal cruciate ligament stabilization, or laparotomy that included one of the following procedures: cystotomy, enterotomy, splenectomy, liver lobectomy or biopsy, kidney removal or biopsy, or tumor removal (including retained testes). Dogs were excluded if clinically relevant medical abnormalities conflicted with the ability of the dog to undergo surgery or other study procedures, if they had a history of seizures, or if they had severe systemic disease (i.e., American Society of Anesthesiologists (ASA) physical status classification score of P3 or greater). Dogs were also excluded if they had recently received corticosteroids or nonsteroidal anti-inflammatory drugs prior to surgery that might interfere with post-operative pain assessments. At no time, other analgesics were allowed other than transdermal fentanyl solution or oxymorphone unless pain intervention was necessary (see Pain assessment and intervention below). All owners were informed of the study procedures and risks and gave signed informed consent to include their dog in the study.

Study procedures and anesthesia

The study was conducted in compliance with the FDA Center for Veterinary Medicine good clinical practice guidance (FDA-CVM, 2001). After meeting eligibility criteria, dogs were hospitalized and randomized to treatment in blocks of two based on clinic and surgery type. The ratio of soft-tissue surgery types was restricted to a maximum of 40% ovariohysterectomies. All clinic personnel were blinded to the identity of the treatment assignments with the exception of the treatment administrator. To maintain blinding, the treatment administrator gave mock injections to all dogs randomized to TFS at the same regimen of oxymorphone injections and was not involved in any post-treatment observations.

[b]Opana® (oxymorphone hydrochloride) injection, Endo Pharmaceuticals, Chadds Ford, PA, USA.

A screening physical examination, including ophthalmoscopy and collection of blood samples, for hematology and clinical chemistry was performed for all candidate dogs. Dogs were hospitalized throughout the study from the time of meeting eligibility criteria through discharge 4 days post-surgery. In addition, for dogs assigned to TFS, a single blood sampling time for fentanyl assay was randomly assigned for collection during the 4-day duration of study, and the results are reported elsewhere (Freise *et al.*, 2012a). A presurgical physical examination was performed on the day of surgery. Throughout the study, dogs were observed according to the hospital's standard practice. A termination physical examination, including ophthalmoscopy and collection of blood samples, for hematology and clinical chemistry was conducted prior to discharge.

The anesthetic protocol was restricted in that dogs were limited to being anesthetized using combinations of the following agents according to the investigator's practice standards: (i) premedication: glycopyrrolate, acepromazine, atropine, midazolam, and/or diazepam; (ii) induction: propofol, thiopental, ketamine/diazepam, or tiletamine/zolazepam; and (iii) maintenance: isoflurane or sevoflurane in oxygen (with or without nitrous oxide). Physiological variables including capillary refill time, rectal temperature, pulse rate, and respiratory rate were monitored throughout the anesthetic period and recorded from intubation through extubation at approximately five-minute interval. Additional variables including pulse oximetry, heart rhythm via electrocardiography and blood pressure were recorded if they were monitored according to the hospital's standard procedures.

Pain assessment and intervention

Pain assessments were based on a modification (deletion of section B) of the Glasgow Composite Pain Scale (Holton *et al.*, 2001; Murrell *et al.*, 2008). Assessments were performed by a trained observer prior to treatment, on Day 0 (1-h postextubation ± 30 min, 2, 4, 6, 8, 12 h postextubation ± 1 h), Day 1 (24 h postinitial treatment ± 4 h, then 6–8 h later), Day 2 (48 h postinitial treatment ± 4 h, then 6–8 h later), Day 3 (72 h postinitial treatment ± 4 h, then 6–8 h later) and Day 4 (96 h postinitial treatment ± 4 h). The pain assessments were made by the same pain assessor for each dog. In addition, a sedation score was assigned as determined in Appendix 2. If the sedation score was ≥2 (moderate, profound, or unresponsive), then the dog was considered to be too sedated to adequately assess analgesia and the pain score assessment was not conducted at that time.

At each pain assessment time point, dogs were evaluated for the adequacy of pain control. The *a priori* criteria for the administration of pain intervention was a composite pain score ≥8 (maximum score of 20) at any time (FDA-CVM, 2007). If pain intervention was necessary, the dog was considered a treatment failure. Any dog removed from the study due to lack of pain control was treated for pain by the Investigator's standard of care and remained at the clinic for safety observations until the scheduled discharge 4 days postsurgery.

Adverse events, opioid reversal, and removal from study

An adverse event was considered to be any observation that was unfavorable and unintended and occurred after the use of the investigational or control veterinary product whether or not considered to be product related (FDA-CVM, 2001). In addition, during anesthesia, physiological variables observed during general anesthesia were considered adverse events if there was a least one excursion outside the normal anesthetic range at any five-minute monitoring interval during the entire duration of anesthesia. At the time of adverse event observation, each was scored as mild, moderate, or severe. Adverse events considered severe included those with an unusual severity, unusual frequency (e.g., repeated vomiting episodes), or a death. In addition, at the time of adverse event observation, additional observations or tests such as physical examination, complete blood count, or serum chemistry were conducted, if necessary, to assign a relationship between adverse events and the investigational or control drug. Adverse events were then classified as unknown, unrelated, possibly related, or related to investigational or control drug. Naloxone,[c] a μ-opioid receptor antagonist (Veng-Pedersen *et al.*, 1995) that is FDA approved for use in dogs (NADA 035-825), was to be administered to any dog that showed severe adverse effects consistent with opioid intoxication such as nonresponsive unconsciousness, seizure or marked abdominal breathing. The dose to be administered was 0.04 mg/kg intravenously (IV) or intramuscularly (IM) as an initial dose (Freise *et al.*, 2012b). If clinical reversal was not observed after 2–3 min, administration of naloxone at the same dose was to be repeated. Any dog requiring reversal with naloxone was considered a treatment failure but remained at the clinic until the scheduled study discharge for safety observations.

A dog could be removed at any time if the Investigator determined that an illness, injury, complication, or adverse reaction prohibited the animal from completing the study. At the time of withdrawal, a physical examination, including blood collection for hematology and serum chemistry, was completed. Any dog removed from the study was considered a treatment failure if it was removed for lack of effectiveness or safety reasons and remained at the clinic until the scheduled study discharge on Day 4 for safety assessments.

Statistical analysis

The primary variable for determining effectiveness and safety was the combined treatment failure rate due to lack of pain control (pain score ≥8) or withdrawal from the study due to adverse events or naloxone reversal, and *a priori* noninferiority margin of difference of 15% was selected based on the treatment failure rate difference between oxymorphone- and placebo-treated human beings following surgery (Gimbel *et al.*, 2005). This human study demonstrated a 32% oxymorphone-placebo difference in failure rate following orthopedic surgery.

[c]Naloxone HCl, Hospira, Inc., Lake Forest, IL, USA.

A failure rate of approximately 19% was significantly different from placebo and to be conservative in this study, the *a priori* margin of 15% was chosen. Thus, for fentanyl to be considered noninferior to oxymorphone, the one-sided upper 95% confidence interval of the difference between the TFS – oxymorphone treatment failure rates had to be no greater than the noninferiority margin of 15 percentage points (15%). The sample size was selected to achieve a power of at least 80% assuming the true fentanyl failure rate is no more than 5% points higher than this oxymorphone failure rate. A Newcombe-Wilson hybrid score method was used to calculate the confidence interval of the difference in failure rates (Newcombe, 1998). All applicable statistical assumptions of the confidence interval calculations were met.

Secondary variables included treatment failure reason, timewise pain and sedation scores, loss of body weight, and adverse events. A *post hoc* two-sided Fisher's exact test was used to test difference in treatment failure reason, loss of body weight, and adverse event incidence by treatment. For timewise pain and sedation scores, a two-sided 95% confidence intervals (CI) of the mean difference between the TFS – oxymorphone were constructed. Results that did not contain 0 were considered different (Pickel & Doksum, 2001). For these secondary variables, missing data were omitted from the estimates of the differences and confidence intervals over time. Summary statistics for other data such as age, body weight, breed and adverse events were also calculated. All statistical calculations were conducted using SAS.[d]

RESULTS

Demographics

A total of five hundred and two (502) dogs were enrolled into the study and were approximately equally divided between TFS ($N = 249$) and oxymorphone ($N = 253$). The dose of oxymorphone administered was 0.22 ± 0.079 mg/kg (mean ± SD) Animals enrolled in the study included 200 (39.8%) males and 302 (60.2%) females (Table 1A). The average age of dogs enrolled in both groups was approximately 4 years and ranged from 0.5 to 13 years (Table 1B). The average weight at the time of enrollment was approximately 25 kg and ranged from 2.7 to 59.6 kg (Table 1B). Twenty-seven point nine percent (27.9%) of dogs were crossbred and 72.1% of dogs were purebred. The 10 most common breeds were Labrador Retriever (23.9%), American Pit Bull Terrier (5.6%), Golden Retriever (5.6%), Boxer (4.8%), German Shepard Dog (4.8%), Treeing Walker Coonhound (4.4%), Rottweiler (3.4%), Dachshund (3.2%), Chihuahua (2.2%), and Siberian Husky (2.0%; Table 1C). Two point six percent (2.6% [13/502]) of dogs had the hair clipped at the application site; 3.6% (9/249) of the dogs were treated with TFS and 1.6% (4/253) were treated with oxymorphone. Dogs were equally divided between soft-tis-

[d]SAS® for Windows 9.1.3, Service Pack 4, SAS Institute Inc., Cary, NC, USA.

Table 1. Demographics of dogs enrolled in the study including gender and sexual status (A), age and body weight (B), and breed (C)

(A)

	TFS		Oxymorphone		Total	
	$N = 249$		$N = 253$		$N = 502$	
Variable	*n*	%	*n*	%	*n*	%
Gender						
Males	102	41.0	98	38.7	200	39.8
Females	147	59.0	155	61.3	302	60.2
Sex category						
Intact males	42	16.9	39	15.4	81	16.1
Castrated males	60	24.1	59	23.3	119	23.7
Intact females	60	24.1	60	23.7	120	23.9
Spayed females	87	34.9	95	37.5	182	36.3

(B)

Variable	TFS ($N = 249$)	Oxymorphone ($N = 253$)
Age (years)		
Mean	4.2	4.3
SD	3.1	3.1
Min	0.5	0.5
Max	13	13
Body weight (kg)		
Mean	24.7	25.9
SD	13.6	13.4
Median	24.5	26.1
Min	2.7	2.7
Max	56.4	59.6

(C)

	TFS		Oxymorphone		Total	
	$N = 249$		$N = 253$		$N = 502$	
Breed	*n*	%	*n*	%	*n*	%
Labrador retriever	58	23.3	62	24.5	120	23.9
Golden retriever	12	4.8	16	6.3	28	5.6
American pit bull terrier	11	4.4	17	6.7	28	5.6
Boxer	13	5.2	11	4.3	24	4.8
German shepherd dog	8	3.2	16	6.3	24	4.8
Treeing walker coonhound	9	3.6	13	5.1	22	4.4
Rottweiler	7	2.8	10	4.0	17	3.4
Dachshund	10	4.0	6	2.4	16	3.2
Crossbred/mix/no breed stated	6	2.4	9	3.6	15	3.0
Chihuahua	8	3.2	3	1.2	11	2.2
Australian cattle dog	7	2.8	3	1.2	10	2.0
Siberian husky	5	2.0	5	2.0	10	2.0
Cocker spaniel	6	2.4	3	1.2	9	1.8
Australian shepherd	8	3.2	0	0.0	8	1.6
Basset hound	4	1.6	4	1.6	8	1.6
Bichon frise	3	1.2	5	2.0	8	1.6
Border collie	2	0.8	6	2.4	8	1.6
Poodle	5	2.0	2	0.8	7	1.4
English pointer	5	2.0	1	0.4	6	1.2

(continued)

Table 1. (continued)

(C)

Breed	TFS		Oxymorphone		Total	
	N = 249		*N* = 253		*N* = 502	
	n	%	*n*	%	*n*	%
Pomeranian	5	2.0	1	0.4	6	1.2
Shih tzu	5	2.0	1	0.4	6	1.2
American bulldog	3	1.2	2	0.8	5	1.0
Shetland sheepdog	2	0.8	3	1.2	5	1.0
Doberman pinscher	3	1.2	1	0.4	4	0.8
Welsh corgi, pembroke	1	0.4	3	1.2	4	0.8
Border terrier	0	0.0	4	1.6	4	0.8
Beagle	2	0.8	1	0.4	3	0.6
Collie	2	0.8	1	0.4	3	0.6
Pug	2	0.8	1	0.4	3	0.6
West highland white terrier	2	0.8	1	0.4	3	0.6
Samoyed	1	0.4	2	0.8	3	0.6
Dalmatian	0	0.0	3	1.2	3	0.6
Miniature pinscher	0	0.0	3	1.2	3	0.6
Airedale terrier	2	0.8	0	0.0	2	0.4
Cane corso italiano	2	0.8	0	0.0	2	0.4
Great dane	2	0.8	0	0.0	2	0.4
Belgian shepherd dog	1	0.4	1	0.4	2	0.4
Brittany spaniel	1	0.4	1	0.4	2	0.4
Cavalier King Charles spaniel	1	0.4	1	0.4	2	0.4
Chow chow	1	0.4	1	0.4	2	0.4
English springer spaniel	1	0.4	1	0.4	2	0.4
German shorthaired pointer	1	0.4	1	0.4	2	0.4
Great pyrenees	1	0.4	1	0.4	2	0.4
Japanese chin	1	0.4	1	0.4	2	0.4
Lhasa apso	1	0.4	1	0.4	2	0.4
Maltese	1	0.4	1	0.4	2	0.4
Newfoundland	1	0.4	1	0.4	2	0.4
Weimaraner	1	0.4	1	0.4	2	0.4
Bullmastiff	0	0.0	2	0.8	2	0.4
English bulldog	0	0.0	2	0.8	2	0.4
Louisiana catahoula leopard dog	0	0.0	2	0.8	2	0.4
Miniature schnauzer	0	0.0	2	0.8	2	0.4
Standard schnauzer	0	0.0	2	0.8	2	0.4
Yorkshire terrier	0	0.0	2	0.8	2	0.4
American eskimo	1	0.4	0	0.0	1	0.2
Antolian shepherd	1	0.4	0	0.0	1	0.2
Bouvier des flandres	1	0.4	0	0.0	1	0.2
Cairn terrier	1	0.4	0	0.0	1	0.2
Dogue de Bordeaux	1	0.4	0	0.0	1	0.2
Dutch shepherd	1	0.4	0	0.0	1	0.2
English setter	1	0.4	0	0.0	1	0.2
Mastiff	1	0.4	0	0.0	1	0.2
Mountain cur	1	0.4	0	0.0	1	0.2
Portuguese water dog	1	0.4	0	0.0	1	0.2
Schipperke	1	0.4	0	0.0	1	0.2
Scottish terrier	1	0.4	0	0.0	1	0.2
Silky terrier	1	0.4	0	0.0	1	0.2
Smooth fox terrier	1	0.4	0	0.0	1	0.2
Standard poodle (solid & multi-colored)	1	0.4	0	0.0	1	0.2
Whippet	1	0.4	0	0.0	1	0.2
Akita	0	0.0	1	0.4	1	0.2
Bernese mountain dog	0	0.0	1	0.4	1	0.2
Bluetick coonhound	0	0.0	1	0.4	1	0.2
Chesapeake bay retriever	0	0.0	1	0.4	1	0.2
Keeshond	0	0.0	1	0.4	1	0.2
Old English sheepdog	0	0.0	1	0.4	1	0.2
Papillon	0	0.0	1	0.4	1	0.2
Pharaoh hound	0	0.0	1	0.4	1	0.2
Rhodesian ridgeback	0	0.0	1	0.4	1	0.2
Russell terrier	0	0.0	1	0.4	1	0.2

(continued)

sue (40.9%) and orthopedic surgical procedures (50.1%). Of the soft-tissue surgical procedures, the most common were ovariohysterectomy (37.6%), intra-abdominal tumor removal (16.0%), cystotomy (12.8%), liver lobectomy/biopsy (12.4%), and ear crop (9.2%). Of the orthopedic surgeries, the most common cruciate repair procedure was via tibial plateau leveling osteotomy (51.4%), followed by fabellar suture repair (39.4%) and tibial tuberosity advancement (8.8%).

Effectiveness

Pain scores were highest 2 h following extubation in both groups where values were 2.32 ± 1.77 (mean ± SD) in TFS- and 2.64 ± 1.85 in oxymorphone-treated dogs (Fig. 1). Pain scores declined throughout the study such that by 4 days post-study the mean pain scores were 0.83 ± 1.27 in TFS and

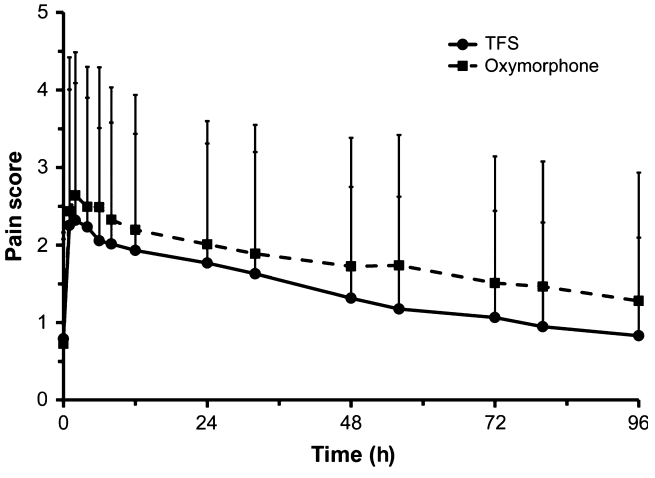

Fig. 1. Timewise Glasgow composite pain scores for transdermal fentanyl solution- and oxymorphone-treated dogs at each pain assessment time point over the 4-day study duration. Day 0 is the day of surgery. Points represent the mean and bars represent the SD.

1.28 ± 1.65 in oxymorphone-treated dogs. The 95% CI of the mean difference of TFS – oxymorphone pain scores at each pain assessment time contained 0 or was less than 0 throughout the study, suggesting that a single topical dose of TFS provides superior analgesia compared to repeated injections of oxymorphone.

Overall, there were 5 TFS- and 27 oxymorphone-treated dogs that were considered treatment failures due to lack of effectiveness or adverse events (Table 2). Twelve dogs (4 TFS, 8 oxymorphone) were withdrawn due to lack of pain control. The 4 TFS-treated dogs experiencing lack of pain control were withdrawn between 1 and 6 h postextubation with pain scores ranging from 8 to 11. The 8 oxymorphone-treated dogs were withdrawn between Day 0 at 2 hours postextubation and Day 2 with pain scores ranging from 8 to 15. No TFS-treated dogs were withdrawn due to adverse events, and none required reversal with naloxone. Eighteen oxymorphone dogs were withdrawn due to adverse events or were administered naloxone for opioid reversal (Table 3). All but one of the 18 dogs was removed were considered treatment-related. The dog that was removed was not considered as treatment-related but experienced a recurrent prolapsed rectum following surgery to reduce a prolapsed rectum (Table 3). There was no difference in the dose of oxymorphone in dogs withdrawn from the study due to lack of pain control or adverse events compared with those that remained in the study. The most common reasons oxymorphone-treated dogs in the orthopedic surgery population were withdrawn from the study were profound/persistent sedation, hypothermia, bradycardia, bradypnea, vomiting, and anorexia or some combination of these events. Nine of the 18 oxymorphone-treated dogs were reversed with naloxone. One TFS- and 1 oxymorphone-treated dog did not complete the study due to death (see the Adverse events section below).

The primary variable for determining effectiveness was a noninferiority evaluation of the TFS and oxymorphone treatment failure rates, which were 2.0% (5/249) and 10.8% (27/251), respectively. The point estimate of the difference between TFS and oxymorphone failure rates was −8.75% and the one-sided upper 95% confidence interval was −5.3%, which was not greater than 15%. Therefore, based on the treatment failure rate difference, TFS was noninferior to oxymorphone at the dose rates of both formulations used in this study'.

Table 2. Number (%) and reasons for treatment failure in transdermal fentanyl solution- and oxymorphone-treated dogs

Reason	TFS (N = 249)	Oxymorphone (N = 253)
Safety		
Adverse event	0 (0.0%)[a]	9 (3.6%)[b]
Opioid reversal	0 (0.0%)[a]	9 (3.6%)[b]
Death	1 (0.4%)	1 (0.4%)
Effectiveness		
Lack of pain control	4 (1.6%)	8 (3.2%)
Total	5 (2.0%)[a]	27 (10.7%)[b]

Within a Reason, percentages with different a, b superscripts are statistically different ($P \leq 0.05$) per a *post hoc* two-sided Fisher's exact test.

Sedation

The percentage of oxymorphone-treated dogs with sedation scores ≥2 was higher than the percentage of TFS-treated dogs at all time points (Fig. 2). At 1-h postextubation, 49% and 70% of TFS- and oxymorphone-treated dogs, respectively, had a sedation scores ≥2 and by 12 h this had diminished to 7% and 11% of dogs, respectively. No TFS-treated dogs had a sedation scores ≥2 beyond 48 h. Additionally, the 95% CI of the mean difference of TFS – oxymorphone sedation scores were less than 0 at all time points, suggesting that TFS-treated dogs experienced less sedation than oxymorphone-treated dogs.

Body weight

Over the 4 days of the study, a statistically greater number of TFS-treated dogs lost no body weight (24.3%) compared to those treated with oxymorphone (12.4%). Approximately, equal percentages of TFS- and oxymorphone-treated dogs lost up to 5% of their body weight (51% and 45%, respectively). A statistically greater proportion of oxymorphone-treated dogs lost larger percentages of body weight; 34.5% of oxymorphone-treated dogs lost between 5% and 10% body weight and 8% of oxymorphone-treated dogs lost between 10% and 15% body weight. Twenty one point nine percent (21.9%) of TFS-treated dogs lost between 5% and 10% body weight and 1.6% of TFS-treated dogs lost between 10% and 15% body weight.

Clinical pathology

The mean value for each hematology and clinical chemistry variable was within the reference range prior to treatment and at study completion (Day 4) for both treatment groups. There were no individual excursions outside the normal range that were considered causally related to fentanyl or oxymorphone treatment. There were 5 TFS-treated treated dogs that had a normal amylase at baseline that was elevated at study completion. Of the five dogs with elevated amylase, four underwent TPLO surgery and one had a cryptorchid testes removed. There were no adverse event in any of the five dogs and each completed the study.

Adverse events

Eighty-five percent (211/249) of dogs allotted to TFS and 86.1% (216/251) of dogs allotted to oxymorphone were provided external heat during surgery to support core body temperature. There were no adverse safety events related to heat application at the administration site in TFS-treated dogs. A *post hoc* statistical analysis of adverse events during anesthesia revealed two events that were significantly different between treatments during this time period (Table 4). Hypothermia

Table 3. Details on the dogs removed from the study due to adverse events or naloxone reversal. These are limited to dogs administered oxymorphone because there were no dogs removed from the study due to adverse events or naloxone reversal that were allotted to transdermal fentanyl treatment

Signalment	Surgery type	Adverse events	Withdrawal time	Naloxone reversal	Outcome
4-year-old spayed Rottweiler	TPLO	Profound sedation, hypothermia, bradycardia and bradypnea	Approximately 9 h following surgery	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
9-year-old castrated crossbred Chow	TPLO	Profound sedation, bradycardia, a decreased respiratory rate, and hypothermia	Approximately 7.5 h following surgery	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
6-year-old spayed German Shepherd mixed breed	TPLO	Bradycardia, hypothermia, and dyspnea	Approximately 9 h following surgery	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
2-year-old spayed Keeshond	TPLO	Tenesmus, colitis, nausea, vomiting, anorexia and fever	Day 1 through Day 3	No	Resolution by Day 4 and discharged to owner
5-year-old castrated German Shepherd	TPLO	Anorexia, vomiting and nausea	Day 0 through Day 3	No	Anorexia continued at Day 4 discharge and dog reported normal 1 week following discharge.
6-year-old spayed Boston Terrier	Fabellar suture	Hypothermia and bradycardia	Day 0 through Day 3	No	Resolution by Day 4 and discharged to owner
3-year-old spayed English Bulldog	TTA	Tachypnea and hypothermia	Approximately 2.5 h following surgery	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
11-year-old spayed crossbred Labrador retriever	Lateral ear resection	Ataxia, opisthotonus, clonus, panting and seizure	Day 3	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
5-year-old spayed Cocker Spaniel	Lateral ear resection	Profound sedation	Approximately 12 h following surgery	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
6-month-old intact female West Highland White terrier	OVH	Prolapsed rectum	Day 1	No	Prolapse surgically reduced by purse string; dog treated for intestinal parasites and discharged 7 days following surgery
9-month-old intact female Golden Retriever crossbred	OVH	Persistent excessive sedation, anorexia and vomiting	Approximately 18 h following surgery	No	Remained at the clinic without incident until the scheduled discharge on Day 4
3-year-old intact female Pit Bull	Liver biopsy	Hypotension and hypothermia	Intra-operative	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
6-month-old intact female Cocker Spaniel crossbred	OVH	Persistent sedation and anorexia	Day 2	No	Remained at the clinic without incident until the scheduled discharge on Day 4
7-year-old spayed Labrador retriever crossbred	Cystotomy	Sedated, depression and vomiting	Day 2	No	Remained at the clinic without incident until the scheduled discharge on Day 4
10-year-old spayed Chihuahua	Cystotomy	Persistent somnolence, vomiting and incision purulent discharge	Day 3	Yes	Enrofloxacin and amoxicillin/clavulanic acid was continued for 3 weeks following discharge where the dog had fully recovered
2-year-old spayed Bichon Frise	Cystotomy	Persistent vomiting	Day 1 through Day 2	Yes	Remained at the clinic without incident until the scheduled discharge on Day 4
4-year-old intact female Boston Terrier	OVH	Persistent vomiting and anorexia	Day 2	No	Remained at the clinic without incident until the scheduled discharge on Day 4
3-year-old intact male Beagle	Liver biopsy	Vomiting, lethargy and dehydration	Day 2	No	Remained at the clinic without incident until the scheduled discharge on Day 4

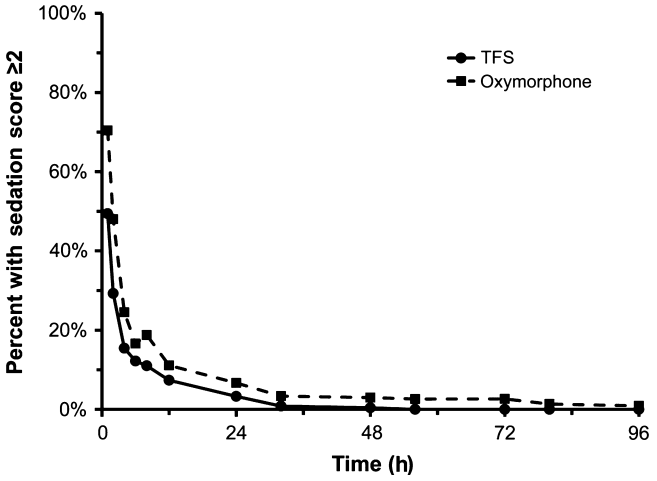

Fig. 2. The percentage of transdermal fentanyl solution- and oxymorphone-treated dogs with a sedation score of ≥2 (moderate, profound, or unresponsive) at each pain assessment time point over the 4-day study duration. Day 0 is the day of surgery.

Table 4. Number (%) of dogs with physiological adverse events during anesthesia for transdermal fentanyl solution- and oxymorphone-treated dogs

Adverse event*	TFS (N = 249)	Oxymorphone (N = 251)
Tachypnea (>20 breaths/min)	158 (63%)	151 (60%)
Bradypnea (<10 breaths/min)	116 (47%)	108 (43%)
Hypertension	37 (15%)	32 (13%)
Hypotension	32 (13%)	46 (18%)
Hypothermia (<35 °C)	23 (9.2%)[a]	71 (28%)[b]
Tachycardia (>180 beats/min)	26 (10%)[a]	8 (3.2%)[b]
Bradycardia (<50 beats/min)	9 (3.6%)	7 (2.8%)
Arrhythmia Noted	2 (0.8%)	2 (0.8%)
Pyrexia (>39.2 °C)	3 (1.2%)	1 (0.4%)
Oxygen saturation (<85%)	2 (0.8%)	3 (1.2%)

*Physiological adverse events during general anesthesia were included if there was a least one excursion outside the normal anesthetic range at any 5 min interval during the entire duration of anesthesia.
Within an Adverse Event, percentages with different a, b superscripts are statistically different ($P < 0.05$) per a *post hoc* two-sided Fisher's exact test.

affected 28% (71/251) and 9.2% (23/249) of oxymorphone- and TFS-treated dogs during anesthesia, respectively ($P < 0.05$), while tachycardia occurred in 3.2% (8/251) oxymorphone-treated dogs and 10% (26/249) of TFS-treated dogs ($P < 0.05$). Tachypnea and bradypnea were the most frequent adverse events during anesthesia, affecting approximately 60% and 45% of dogs in each group, respectively. The remaining adverse events during anesthesia were less frequent and approximately equal between groups. A single oxymorphone-treated dog was reversed with naloxone approximately 30 min into liver lobectomy/biopsy surgery due to severe hypotension and hypothermia. Fluids were also administered, and the blood pressure was immediately increased, and surgery was completed without further incident. No TFS-treated dogs were reversed with naloxone during surgery.

There were a total of 56 individual postoperative adverse events reported in 44 (17.7%) TFS-treated dogs and a total of 228 postoperative adverse events reported in 84 (33.7%) oxymorphone-treated dogs. There was only one severe adverse event in the TFS treatment group, compared with 28 severe adverse events in oxymorphone-treated dogs. All 28 severe adverse events in the oxymorphone-treated dogs occurred in the 19 dogs that were removed from the study (Table 2). Over the first 48 h postoperatively, the most frequent adverse events in TFS-treated dogs were diarrhea ranging from 0.4% to 2%, emesis ranging from 0 to 1.6%, hypothermia ranging from 1.5% to 4.4% and anorexia ranging from 0% to 0.8% (Table 5). The incidence of adverse events in oxymorphone-treated dogs was higher in some categories compared to TFS and persisted throughout the 4-day study period (Table 5). Over the 4-day study period, emesis ranged from 1.6% to 8.7% and hypothermia ranged from 1.4% to 9.5% in oxymorphone-treated dogs.

There were two deaths in this study; one each in the fentanyl- and oxymorphone-treated groups. A 13-year-old, castrated, crossbred terrier presented with 4-day history of vomiting and was allotted to fentanyl and underwent gastrotomy surgery to remove a suspected foreign body. No foreign body was identified, but some debris was noted in the caudal esophagus, possibly dog treat fragments. An increased respiratory rate on Days 1 and 2 was considered secondary to pulmonary edema and was treated with furosamide through Day 2. The dog acutely died the morning of Day 3. Necropsy and histopathological evaluation revealed moderate, suppurative pneumonia of bacterial etiology possibly secondary to vomiting and aspiration. An 11-year-old castrated crossbred Labrador retriever was allotted to oxymorphone and underwent splenectomy surgery. On Day 2, the dog was restless and vomited, collapsed and was asystolic. Cardiopulmonary resuscitation was not successful and the dog died. Necropsy revealed a large infarct in the cranial right lung lobe. Histopathology revealed changes consistent with both chronic and acute right-sided heart failure. In both cases, the deaths were judged to be unrelated to investigational or control drug treatment.

DISCUSSION

The results from this study demonstrates that a single dose of TFS applied 2–4 h prior to surgery is safe and effective for the control of pain associated with orthopedic and soft-tissue surgery in dogs and provides analgesia for 4 days. The number of treatment failures due to inadequate pain control were low in both treatment groups indicating that TFS and repeated oxymorphone injections were highly effective in controlling postoperative pain through 4 days postsurgery, a time period

Table 5. Number (%) of dogs with adverse events by study day for transdermal fentanyl solution- and oxymorphone-treated dogs. Day 0 is the day of surgery with observations beginning at the time of fentanyl or oxymorphone treatment administration through 96 h

Treatment	Adverse event	Day 0	Day 1	Day 2	Day 3	Day 4
TFS(n = 249)	Diarrhea	1 (0.4%)	5 (2.0%)	2 (0.8%)	1 (0.4%)	0 (0.0%)
	Emesis	0 (0.0%)[a]	4 (1.6%)	2 (0.8%)[a]	2 (0.8%)[a]	0 (0.0%)
	Hypothermia	4 (1.6%)[a]	11 (4.4%)[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Pyrexia	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	0 (0.0%)
	Anorexia	0 (0.0%)	2 (0.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
	Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hypersalivation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Conjunctivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Oxymorphone(n = 253)	Diarrhea	3 (1.2%)	3 (1.2%)	5 (2.0%)	4 (1.6%)	0 (0.0%)
	Emesis	10 (4.0%)[b]	11 (4.4%)	22 (8.7%)[b]	15 (6.0%)[b]	4 (1.6%)
	Hypothermia	16 (6.3%)[b]	24 (9.5%)[b]	4 (1.6%)	5 (2.0%)	4 (1.6%)
	Pyrexia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
	Anorexia	0 (0.0%)	5 (2.0%)	4 (1.6%)	2 (0.8%)	1 (0.4%)
	Constipation	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hypersalivation	5 (2.0%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
	Conjunctivitis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Death	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)

Within an Adverse Event and Day, percentages with different a, b superscripts are statistically different ($P < 0.05$) per a *post hoc* two-sided Fisher's exact test.

demonstrated to result in clinically significant postoperative pain in dogs (Clark *et al.*, 2001; Martinez *et al.*, 2001). As a primary endpoint, the failure rate over 4 days in dogs treated with a single dose of TFS was noninferior to those treated with every 6 h injections of oxymorphone through 90 h. Transdermal fentanyl solution appeared to have a safety advantage compared to oxymorphone at the doses used in this study, with fewer adverse events and adverse events of lesser severity.

A single dose of TFS provides continuous systemic fentanyl delivery over a period of days, and therefore, the control drug choice from an experimental design and regulatory perspective was critical. A placebo control was not deemed ethical because well-studied active controls were available. Oxymorphone hydrochloride injection is an FDA approved opioid for the control of postoperative pain in dogs (NADA 030-535) and was therefore chosen as an active control. Although a Pharmacokinetic/pharmacodynamic (PK/PD) relationship has not been established for oxymorphone at the doses used in this study, repeated injections at a 6-h dosing interval results in effective, long-term opioid exposure (KuKanich *et al.*, 2008) and analgesia in dogs (Hardie *et al.*, 1997; Kyles *et al.*, 1998; Bateman *et al.*, 2008). A noninferiority analysis was chosen instead of a superiority analysis (Weintraub, 2010) because it would not be likely that a full μ-agonist opioid would be superior to another opioid in the same class. However, the one-sided upper 95% confidence bound of the TFS minus oxymorphone treatment failure difference was −5.3%, indicating that on the composite endpoint of treatment failure, TFS was superior over oxymorphone. Similarly, the percentage of subjects that failed due to lack of pain control was higher in oxymorphone-treated dogs (3.2% [8/251]) than in fentanyl-treated dogs (1.6% [4/249]). This difference may be due to steady fentanyl payout with TFS compared with end of dosing interval lack of effectiveness associated with trough oxymorphone concentrations that occur with any opioid when must be repeatedly administered.

The results in this trial were comparable with a similarly designed clinical study conducted in Europe where the positive control was IM buprenorphine (20 μg/kg) administered every 6 h for 90 h instead of SC oxymorphone (Linton *et al.*, 2012). In the European study, the TFS and buprenorphine failure rates were 6.7% (15/223) and 3.6% (8/220), respectively, with a one-sided upper 95% confidence interval of the failure rate difference of 5.6%. Like the current study, the *a priori* selected margin of the difference was 15% and a single dose of TFS applied 2–4 h prior to surgery was concluded to be noninferior to repeated buprenorphine injections. Thus, TFS has been demonstrated to be safe and effective compared to both repeatedly administered injectable full and partial μ-opioid receptor agonists (e.g., oxymorphone and buprenorphine, respectively).

Furthermore, the results of this current study are consistent with the outcome reported comparing postoperative analgesia of extra-label use of the fentanyl patches to repeated oxymorphone administration in dogs (Kyles *et al.*, 1998). In that comparatively small study (n = 10 per treatment group), a single 50 μg/h fentanyl patch applied 20 h prior to ovariohysterectomy provided comparable analgesia over 24 h to IM 0.05 mg/kg oxymorphone administered presurgery and every 6 h through 18 h postsurgery. A 50 μg/h fentanyl patch had been shown in a previous study (Kyles *et al.*, 1996) in dogs to provide steady-state plasma fentanyl concentrations of 1.60 ng/mL, similar to the average plasma fentanyl concentrations of 1.32 ng/mL achieved in the present clinical trial (Freise *et al.*, 2012a). Average plasma fentanyl concentrations

of ≥0.6 ng/mL are generally considered analgesic in dogs (Hofmeister & Egger, 2004).

A marked contrast between TFS and oxymorphone treatments in this study was measures of safety. There were 18 oxymorphone-treated dogs removed from the study due to severe adverse events, nine of which required reversal by naloxone (Table 2). There were no fentanyl-treated dogs removed due to adverse events, and no fentanyl-treated dogs required reversal with naloxone. However, if fentanyl-treated dogs did need to be reversed due to adverse opioid effects, hourly IM administration of naloxone at a dose of 0.04 or 0.16 mg/kg has been demonstrated to provide sustained TFS reversal (Freise *et al.*, 2012b). Alternatively, a constant rate naloxone infusion of 1–4 μg/kg/h has been predicted to provide similar effects. The number and severity of adverse events were also much greater in oxymorphone-treated than fentanyl-treated dogs (Table 5). An explanation for the observed safety difference may be related to the peak and trough drug plasma concentrations that occur after each oxymorphone dosing compared with the steady fentanyl drug concentrations that occur following TFS administration (Freise *et al.*, 2012a,c,d).

Respiratory depression was not a reported adverse event in the TFS treatment group. Unlike in humans, spontaneous respirations are maintained independent of fentanyl concentration in dogs (Bailey *et al.*, 1987; Mathews, 2000). In a study where TFS was administered up to 5-times the recommended dose, mean respiration rates were similar to placebo at the FDA approved dose but decreased slightly in a dose-dependent manner at higher doses to a maximal decrease of approximately 30% (Savides *et al.*, 2012). The present study demonstrates that established tolerance to opioid-induced respiratory depression is not necessary prior to initiating treatment with TFS in dogs.

Along with the desired analgesic effects, sedation is an expected extension of the pharmacological effect of opioids (Gutstein & Akil, 2006). However, excessive sedation was not a key feature of either treatment in this study. At no time was the mean sedation score ≥2 even during the times near extubation where the effects of general anesthesia on sedation scores would be expected to be greatest. Comparatively, oxymorphone resulted in higher mean sedation scores at each time point compared to TFS with some individual dogs having sedation scores ≥2 for the entire 4-day study duration. This too may be the result of steady fentanyl concentrations in contrast to repeated peak oxymorphone concentrations following multiple injections.

In summary, this study demonstrates that a single, small volume of TFS administered 2–4 h prior to surgery provides noninferior efficacy with less adverse events compared with repeated injections of oxymorphone every 6 h over 4 days. It was similar to oxymorphone in behavioral measures of pain over 4 days and exhibited a greater margin of safety with regard to adverse events, sedation and body weight loss. The availability of an FDA approved, long-acting opioid could allow further optimization of postoperative analgesia in dogs.

ACKNOWLEDGMENTS

The authors wish to acknowledge the following clinical investigators for recruitment and enrollment of the clinical cases included in this study: LeeAnn Blackford, DVM, DACVS (Blackford Veterinary Surgery Referral, Knoxville, TN); Todd Gauger, DVM (Norway Veterinary Hospital, Norway, ME); Jack Gallagher, DVM, DACVS (Veterinary Surgical Referral Practice, Cary, NC); Samuel Geller, VMD (Quakertown Veterinary Clinic, Quakertown, PA); John Mauterer, DVM, DACVS (Louisiana Veterinary Referral Center, Mandeville, LA); Stephan Ladd, DVM (Hillsboro Animal Hospital, Nashville, TN); David Lukof, VMD (Harleysville Veterinary Hospital, Harleysville, PA); Andrew Pickering, DVM (Wabash Valley Animal Hospital, Terre Haute, IN); Bert Shelley, DVM, MS, DACVS (Bradford Park Veterinary Hospital, Springfield, MO); Fred Williams, DVM (South Texas Veterinary Specialist, San Antonio, TX); John T. Peacock, DVM (MedVet Memphis, Memphis, TN); John Stephan, DVM, MS, DACVS (Indianapolis Veterinary Specialist, Indianapolis, IN); Richard N. Benjamin, DVM (Berkley Dog and Cat Hospital, Berkley, CA); Scott Buzhardt, DVM (The Animal Center West, Zachary, LA); Shane Daigle, DVM (Premier Animal Hospital, Cedar Park, TX); Peter Davis, DVM (Pine Tree Veterinary Hospital, Augusta, ME); Mark Girone, DVM (PetMed, Antioch, TN); Kristy Lively, DVM (Village Veterinary Clinic & Laser Center, Farragut, TN); Mark Marks, DVM (Wakarusa Veterinary Hospital, Lawrence, KS); Wanda Pool, DVM (Deepwood Veterinary Clinic, Centreville, VA); Mike Shelton, DVM (380 West Animal Hospital, McKinney, TX); Roger L. Sifferman, DVM (Bradford Park Veterinary Hospital, Springfield, MO); Joe Wurster, DVM (Colonial Park Animal Hospital, Wichita Falls, TX).

REFERENCES

Bailey, P.L., Port, J.D., McJames, S., Reinersman, L. & Stanley, T.H. (1987) Is fentanyl an anesthetic in the dog? *Anesthesia and Analgesia*, **66**, 542–548.

Bateman, S.W., Haldane, S. & Stephens, J.A. (2008) Comparison of the analgesic efficacy of hydromorphone and oxymorphone in dogs and cats: a randomized blinded study. *Veterinary Anaesthesia and Analgesia*, **35**, 341–347.

Branson, K.R. & Gross, M.E. (2001) Opioid agonists and antagnosits. In *Veterinary Pharmacology and Therapeutics*, 8th edn. Ed Adams, H.R., pp. 268–298. Iowa State Press, Ames, IA.

Carson, H.J., Knight, L.D., Dudley, M.H. & Garg, U. (2010) A fatality involving an unusual route of fentanyl delivery: chewing and aspirating the transdermal patch. *Leg Med (Tokyo)*, **12**, 157–159.

21 CFR 514.117(b)(4)(iii) (2004). *Adequate and Well-Controlled Studies*, pp. 82–85. United States Government Printing Office, Washington, DC.

Clark, T.P, Curto, M., Huhn, J.C., Anway, S.D., Smothers, C.D. & Boy, M.G. (2001). *The Effect of Perioperative Carprofen Administration on the Alleviation of Pain Associated With Soft Tissue Surgery*. American College of Veterinary Anesthesia Annual Forum, New Orleans, LA.

Egger, C.M., Duke, T., Archer, J. & Cribb, P.H. (1998) Comparison of plasma fentanyl concentrations by using three transdermal fentanyl patch sizes in dogs. *Veterinary Surgery*, **27**, 159–166.

Egger, C.M., Glerum, L., Michelle Haag, K. & Rohrbach, B.W. (2007) Efficacy and cost-effectiveness of transdermal fentanyl patches for the relief of post-operative pain in dogs after anterior cruciate ligament and pelvic limb repair. *Veterinary Anaesthesia and Analgesia*, **34**, 200–208.

FDA-CVM, (2001) *Guidance for Industry #85; Good Clinical Practice – VICH GL9*. U.S. Department of Health and Human Services, Rockville, MD.

FDA-CVM (2007) *NADA 141–230 Freedom of Information Summary*. U.S. Department of Health and Human Services, Rockville, MD.

FDA-CVM (2012) *Guidance for Industry Active Controls in Studies to Demonstrate Effectiveness of a New Animal Drug for Use in Companion Animals Draft Guidance*. U.S. Department of Health and Human Services, Rockville, MD.

Freise, K.J., Linton, D.D., Newbound, G.C., Tudan, C. & Clark, T.P. (2012a) Population pharmacokinetics of transdermal fentanyl solution following a single dose administered prior to soft tissue and orthopedic surgery in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 65–72.

Freise, K.J., Newbound, G.C., Tudan, C. & Clark, T.P. (2012b) Naloxone reversal of an overdose of a novel, long-acting transdermal fentanyl solution in laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 45–51.

Freise, K.J., Newbound, G.C., Tudan, C. & Clark, T.P. (2012c) Pharmacokinetics and the effect of application site on a novel, long-acting transdermal fentanyl solution in healthy laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 27–33.

Freise, K.J., Savides, M.C., Riggs, K.L., Owens, J.G., Newbound, G.C. & Clark, T.P. (2012d) Pharmacokinetics and dose selection of a novel, long-acting transdermal fentanyl solution in healthy laboratory Beagles. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 3–19.

Garrett, E.R. & Chandran, V.R. (1990) Pharmacokinetics of morphine and its surrogates. X: analyses and pharmacokinetics of buprenorphine in dogs. *Biopharmaceutics & Drug Disposition*, **11**, 311–350.

Gilbert, D.B., Motzel, S.L. & Das, S.R. (2003) Postoperative pain management using fentanyl patches in dogs. *Contemporary Topics in Laboratory Animal Science*, **42**, 21–26.

Gimbel, J.S., Walker, D., Ma, T. & Ahdieh, H. (2005) Efficacy and safety of oxymorphone immediate release for the treatment of mild to moderate pain after ambulatory orthopedic surgery: results of a randomized, double-blind, placebo-controlled trial. *Archives of Physical Medicine and Rehabilitation*, **86**, 2284–2289.

Gutstein, H.B. & Akil, H. (2006) Opioid analgesics. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th edn. Eds Brunton, L.L., Lazo, J.S. & Parker, K.L., pp. 547–590. McGraw-Hill, New York.

Hardie, E., Hansen, B. & Light, G. (1997) Behavior after ovariohysterectomy in the dog: what's normal? *Applied Animal Behaviour Science*, **51**, 111–128.

Hofmeister, E.H. & Egger, C.M. (2004) Transdermal fentanyl patches in small animals. *Journal of the American Animal Hospital Association*, **40**, 468–478.

Holton, L., Reid, J., Scott, E.M., Pawson, P. & Nolan, A. (2001) Development of a behaviour-based scale to measure acute pain in dogs. *The Veterinary Record*, **148**, 525–531.

Janssen Pharmaceutica Products, L.P. (2005). *Duragesic (Fentanyl Transdermal System) Full Prescribing Information*. Janssen Pharmaceutica Products, L.P., Titusville, NJ.

KuKanich, B., Lascelles, B.D. & Papich, M.G. (2005) Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **28**, 371–376.

KuKanich, B., Schmidt, B.K., Krugner-Higby, L.A., Toerber, S. & Smith, L.J. (2008) Pharmacokinetics and behavioral effects of oxymorphone after intravenous and subcutaneous administration to healthy dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **31**, 580–583.

Kyles, A.E., Papich, M. & Hardie, E.M. (1996) Disposition of transdermally administered fentanyl in dogs. *American Journal of Veterinary Research*, **57**, 715–719.

Kyles, A.E., Hardie, E.M., Hansen, B.D. & Papich, M.G. (1998) Comparison of transdermal fentanyl and intramuscular oxymorphone on post-operative behaviour after ovariohysterectomy in dogs. *Research in Veterinary Science*, **65**, 245–251.

Lafuente, M.P., Franch, J., Durall, I., Diaz-Bertrana, M.C. & Marquez, R.M. (2005) Comparison between meloxicam and transdermally administered fentanyl for treatment of postoperative pain in dogs undergoing osteotomy of the tibia and fibula and placement of a uniplanar external distraction device. *Journal of the American Veterinary Medical Association*, **227**, 1768–1774.

Linton, D.D., Wilson, M.G., Newbound, G.C., Freise, K.J. & Clark, T.P. (2012) The effectiveness of a long-acting transdermal fentanyl solution compared to buprenorphine for the control of postoperative pain in dogs in a randomized, multicentered clinical study. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 53–64.

Marquardt, K.A., Tharratt, R.S. & Musallam, N.A. (1995) Fentanyl remaining in a transdermal system following three days of continuous use. *Annals of Pharmacotherapy*, **29**, 969–971.

Martinez, S.A., Clark, T.P., Curto, M., Huhn, J.C., Anway, S.D., Wang, C. & Boy, M.G. (2001) *The Effect of Perioperative Carprofen Administration on The Alleviation Of Pain Associated with Cruciate Surgery*. American College of Veterinary Surgeons Annual Forum, Chicago, IL.

Mathews, K.A. (2000) Pain assessment and general approach to management. *Veterinary Clinics of North America: Small Animal Practice*, **30**, 729–755, v.

Mills, P.C., Magnusson, B.M. & Cross, S.E. (2004) Investigation of *in vitro* transdermal absorption of fentanyl from patches placed on skin samples obtained from various anatomic regions of dogs. *American Journal of Veterinary Research*, **65**, 1697–1700.

Murrell, J.C., Psatha, E.P., Scott, E.M., Reid, J. & Hellebrekers, L.J. (2008) Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. *The Veterinary Record*, **162**, 403–408.

Neugebauer, E.A., Wilkinson, R.C., Kehlet, H. & Schug, S.A. (2007) PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surgical Endoscopy*, **21**, 1047–1053.

Newcombe, R.G. (1998) Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine*, **17**, 873–890.

Pascoe, P.J. (2000) Opioid analgesics. *Veterinary Clinics of North America: Small Animal Practice*, **30**, 757–772.

Pettifer, G.R. & Hosgood, G. (2004) The effect of inhalant anesthetic and body temperature on peri-anesthetic serum concentrations of transdermally administered fentanyl in dogs. *Veterinary Anaesthesia and Analgesia*, **31**, 109–120.

Pickel, P.J. & Doksum, K.A. (2001) *Mathematical Statistics: Basic Ideas and Selected Topics*. Prentice-Hall Inc., Upper Saddle River, NJ.

Riviere, J.E. & Papich, M.G. (2001) Potential and problems of developing transdermal patches for veterinary applications. *Advanced Drug Delivery Reviews*, **50**, 175–203.

Robinson, T.M., Kruse-Elliott, K.T., Markel, M.D., Pluhar, G.E., Massa, K. & Bjorling, D.E. (1999) A comparison of transdermal fentanyl versus epidural morphine for analgesia in dogs undergoing major orthopedic surgery. *Journal of the American Animal Hospital Association*, **35**, 95–100.

Savides, M.C., Pohland, R.C., Wilkie, D.A., Abbott, J.A., Newbound, G.C., Freise, K.J. & Clark, T.P. (2012) The margin of safety of a single application of transdermal fentanyl solution when administered at multiples of the therapeutic dose to laboratory dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **35** (Suppl. 2), 35–43.

Schmiedt, C.W. & Bjorling, D.E. (2007) Accidental prehension and suspected transmucosal or oral absorption of fentanyl from a transdermal patch in a dog. *Veterinary Anaesthesia and Analgesia*, **34**, 70–73.

Urquhart, J. (2000) Internal Medicine in the 21st Century: controlled drug delivery: therapeutic and pharmacological aspects. *Journal of Internal Medicine*, **248**, 357–376.

Veng-Pedersen, P., Wilhelm, J.A., Zakszewski, T.B., Osifchin, E. & Waters, S.J. (1995) Duration of opioid antagonism by nalmefene and naloxone in the dog: an integrated pharmacokinetic/pharmacodynamic comparison. *Journal of Pharmaceutical Sciences*, **84**, 1101–1106.

Weintraub, W.S. (2010) Cutting through the statistical fog: understanding and evaluating non-inferiority trials. *International Journal of Clinical Practice*, **64**, 1359–1366.

Welch, J., Wohl, J. & Wright, J. (2002) Evaluation of postoperative respiratory function by serial blood gas analysis in dogs treated with transdermal fentanyl. *Journal of Veterinary Emergency and Critical Care*, **12**, 81–87.

APPENDIX 1

Food and Drug Administration approved oxymorphone dose (NADA 030-535) used for dogs allotted to the oxymorphone treatment group (Branson & Gross, 2001)

Body weight	Amount (mg)	Dose (mg/kg)
0.9–2.7	0.75	0.83–0.28
>2.7–6.8	1	0.37–0.14
>6.8–13.6	2	0.29–0.15
>13.6–27.2	3	0.22–0.11
>27.2	4	>0.14

APPENDIX 2

Sedation score scale

0 – No Sedation Present.

1 – Slight Sedation – almost normal; able to stand easily, but appears somewhat fatigued, subdued or somnolent.

2 – Moderate Sedation – able to stand but prefers to be recumbent; sluggish; ataxic or uncoordinated.

3 – Profound Sedation – unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency.

4 – Unresponsive – in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

If the sedation score was ≥2, then the dog was considered to be too sedated to adequately assess analgesia and the pain score assessment was not conducted at that time.