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Efficacy of a micronized, nanocrystal fenofibrate formulation in treatment of hyperlipidemia in dogs

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Abstract

Background: Safe, effective, and readily available drug therapies are required for the management of hyperlipidemia and its associated complications in dogs.

Objectives: To investigate the efficacy of a micronized, nanocrystal formulation of fenofibrate (Tricor) in the treatment of hyperlipidemia in dogs.

Animals: Ten client-owned dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia. All dogs had hypertriglyceridemia at baseline; 3 dogs also had hypercholesterolemia.

Methods: Prospective dose-escalation study. Dogs were treated with fenofibrate orally once daily in up to 3 cycles of 21 days each. Fenofibrate dose was increased at the end of each cycle if hypertriglyceridemia persisted and adverse effects were not documented. Complete blood count, biochemistry, and urine protein:creatinine ratio were collected serially. Baseline (T0) parameters were compared to time of maximal reduction in serum triglyceride concentrations (T1) and reported as median (range).

Results: Triglycerides normalized in all dogs (T0 = 662 mg/dL [189-2391]; T1 = 113 mg/dL [81-132]; $P = .002$). Fenofibrate dose at T1 = 6.4 mg/kg PO q24h (range, 2.2-13.5). T1 was achieved at 3 (n = 4), 6 (n = 4), and 9 (n = 2) weeks. Serum cholesterol concentrations decreased in 9 of 10 dogs. Quiet demeanor and firm stools in 1 dog were the only reported adverse reactions. Fenofibrate administration resulted in a significant reduction in median alkaline phosphatase activity ($P = .049$).

Conclusions and Clinical Importance: Over 21 to 63 days, TriCor was effective in the management of primary and secondary hyperlipidemia in dogs.

KEYWORDS
creatine kinase, creatinine, hypercholesterolemia, hypertriglyceridemia, lipemia, nephrotic syndrome

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; BCS, body condition score; CHOL, serum cholesterol concentration; CK, creatine kinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PDH, pituitary-dependent hypercortisolism; PLN, protein-losing nephropathy; TG, serum triglyceride concentration; UPC, urine protein:creatinine ratio.

1 | INTRODUCTION

Hyperlipidemia describes an increase in serum triglyceride concentration (TG) or serum cholesterol concentration (CHOL), or both.[1] Persistent fasting hyperlipidemia is common in dogs and can be a primary or secondary disorder.[1] Primary hyperlipidemia stems from familial or inherited disorders of lipoprotein metabolism.[1-4] Secondary hyperlipidemia occurs more frequently and is associated with endocrinopathies,[5] administration of certain drugs (eg, glucocorticoids, phenobarbital),[5] cholestasis,[6] protein-losing nephropathy (PLN),[7] pancreatitis,[8-10] and obesity.[11] While hyperlipidemia is subclinical in most patients, several clinical complications have been described including some that are life-threatening.[7,12-24]

Traditionally, the first line treatment of primary hyperlipidemia is dietary fat restriction; in cases of secondary disease, treatment of the underlying cause is required.[1] Nonetheless, dietary fat restriction might not achieve normalization of hyperlipidemia in the majority of treated dogs.[25] Fibrates, or fibric acid derivatives, are a class of drugs prescribed as first line management of hyperlipidemia in people.[26,27] The mechanism of action of fibrates involves induction of lipoprotein lipase, increased hepatic fatty acid uptake and reduced hepatic TG production, increased removal of low-density lipoprotein cholesterol (LDL-C), and increase in high-density lipoprotein cholesterol (HDL-C) production.[26] These effects are mediated via peroxisome proliferator-activated receptor alpha.[26] In human patients, these drugs are efficacious and generally well tolerated; adverse effects include abdominal pain, emesis, diarrhea, elevated serum creatinine concentration, and increases in alanine aminotransferase (ALT) or creatine kinase (CK) activities.[27,28]

Limited peer-reviewed data exist on the use of fibrates in veterinary medicine. Description of gemfibrozil use is anecdotal and its efficacy in dogs is questionable with gastrointestinal adverse effects frequently encountered.[29] Bezafibrate is an effective hypolipidemic drug in dogs but it is not FDA approved for use in the United States.[30] Fenofibrate is safe and effectual as a sole therapeutic option for management of primary and secondary hyperlipidemia in dogs but the effective dose is unknown.[31]

Fenofibrate is a highly lipophilic drug with poor water solubility and oral bioavailability.[32,33] Coadministration with food is often necessary to maximize bioavailability, especially when using earlier formulations.[32,33] Bioavailability has been greatly improved with advances in drug design and therefore, the effective dose depends on the specific formulation used.[32,33] TriCor (Abbott Laboratories, Chicago, Illinois), a micronized, nanocrystal fenofibrate formulation, allows for more predictable absorption and effective treatment at lower and more precise doses when compared to generic fenofibrate, as well as reduced risk of adverse reactions.[32,33]

Given the prevalence and emerging understanding of the clinical consequences of hyperlipidemia, further investigation into potential drug therapies is required. As such, the principal aim of this study was to prospectively investigate in dogs the efficacy of the Tricor formulation of fenofibrate in the treatment of hyperlipidemia, either primary or secondary, utilizing a dose-escalation study design. The description of the effective dose for each dog and overall tolerability were considered secondary aims.

2 | MATERIALS AND METHODS

A prospective, dose escalation clinical trial was undertaken that investigated the utility of fenofibrate in the treatment of hyperlipidemia in client-owned dogs that were presented to the William R. Pritchard Veterinary Medical Teaching Hospital, University of California—Davis. The study was approved by the Institutional Animal Care and Use Committee (IACUC# 20508). Written consent was provided by the owner of each dog before enrollment in the study.

2.1 | Enrollment criteria

Dogs diagnosed with subclinical hyperlipidemia, either primary or secondary, were considered for enrollment. Participation was extended to neutered males and spayed females of all dog breeds with body weight between 3.0 and 45.0 kg. The main inclusion criterion was TG above the laboratory's reference range (TG > 133 mg/dL); concurrent hypercholesterolemia (CHOL > 353 mg/dL) could be present but was not an inclusion criterion.

Pre-enrollment diagnostic tests included complete blood count, serum biochemistry panel, urinalysis, urine protein:creatinine ratio (UPC), canine thyroid panel (ie, serum total thyroxine concentration, free thyroxine concentration, and canine thyroid-stimulating hormone concentration), and abdominal ultrasound. Specific screening for hypercortisolism was not a requirement for enrollment: testing was only pursued in cases with compatible clinical signs. All screening blood work was performed after at least 12 hours of fasting. The above diagnostic tests were used to identify secondary causes of hyperlipidemia; primary hyperlipidemia was a diagnosis of exclusion.

Patients with previously diagnosed secondary hyperlipidemia were considered for inclusion if the following criteria were met: (a) the patient's primary disease was not being treated, (b) treatment of the patient's primary disease could be reasonably postponed for the duration of the study, or (c) the patient's condition and treatment had been stable for ≥1 month before enrollment with no expected changes in therapy. Patients receiving glucocorticoid drug therapy (stable dose for ≥1 month) were also considered eligible if drug dose was not expected to change over the duration of the study. A change in glucocorticoid drug dose during the study was considered a criterion for removal from the study.

No stipulations for dietary regimen were implemented as long as the diet was unchanged within 1 month before enrollment and throughout the study; fat-restricted diets were permitted. Exclusionary criteria included any other drug therapies known to affect lipid metabolism within 1 month of enrollment, diet change within 1 month of enrollment, diabetes mellitus, and dogs with elevated ALT (>400 IU/L) or CK (>500 IU/L) activities because of the reported risk of hepatoxicity and rhabdomyolysis, respectively, in people taking fibrates.

2.2 | Study protocol

All dogs were treated with a single formulation of a micronized, nanocrystal fenofibrate (TriCor) using commercially available 48 mg or

TABLE 1 Initial dose and dose escalation regimen for fenofibrate (TriCor) as determined by body weight (kg)

	Fenofibrate, 48 mg or 145 mg tablets, orally once daily		
Body weight	**Phase 1**	**Phase 2**	**Phase 3**
3.0-12.0 kg	24 mg (2.0-8.0 mg/kg/d)	48 mg (4.0-16.0 mg/kg/d)	96 mg (8.0-32.0 mg/kg/d)
12.1-25.0 kg	48 mg (1.9-4.0 mg/kg/d)	96 mg (3.8-7.9 mg/kg/d)	145 mg (5.8-12.0 mg/kg/d)
25.1-45.0 kg	96 mg (2.1-3.8 mg/kg/d)	145 mg (3.2-5.8 mg/kg/d)	193 mg (4.3-7.7 mg/kg/d)

145 mg tablets. The initial dose and a dose escalation protocol based on body weight were determined as outlined in Table 1 (phases 1-3). Dogs were administered the initial dose for 21 days and then returned for evaluation. Fenofibrate was administered by owners once daily in the morning with food in the home environment. On the morning of recheck, fenofibrate was administered with a meatball-sized portion of the existing diet; dogs were otherwise fasted. Recheck blood and urine tests were performed within 6 hours of fenofibrate administration. If hypertriglyceridemia was not resolved and adverse effects were not documented, the dose was increased (see Table 1) and the protocol repeated with recheck in 3 weeks. Maximum duration of treatment was 63 days. During each recheck, owners were surveyed to capture any adverse effects, complete physical exams were performed, and laboratory tests were repeated as highlighted above. Considerations for drug discontinuation included (a) sustained adverse clinical signs (eg, vomiting or diarrhea), (b) ≥2-fold increase in ALT, aspartate aminotransferase, alkaline phosphatase (ALP), or gamma-glutamyl transferase activities, (c) development of hyperbilirubinemia, (d) ≥2-fold increase in CK activity, (e) a >0.3 mg/dL increase in serum creatinine concentration, or (f) any other change in any parameter that might be considered clinically significant. For each dog, each repeat diagnostic variable was individually assessed at each treatment interval.

2.3 | Diagnostic tests

Complete blood count (Advia 120, Siemens, Erlangen, Germany), biochemistry panels (Cobas c501/6000 series, Roche Diagnostics, Indianapolis, Indiana), thyroid hormone testing (Immulite, Siemens Healthcare Diagnostics, Tarrytown, New York), and urinalyses testing were performed by the clinical pathology laboratory at the William R. Pritchard Veterinary Medical Teaching Hospital, University of California—Davis. Blood was collected via jugular or lateral saphenous venipuncture. Urine samples were obtained via cystocentesis. All samples were processed on the same day of collection.

2.4 | Statistical analysis

Statistical analysis was performed using commercially available computer software (Prism9, GraphPad, San Diego, California). Categorical data are presented as counts (n) and percentages. All continuous variables are reported as medians with ranges and were analyzed with nonparametric tests. Baseline data, ie, before the initiation of fenofibrate treatment, was defined as T0. The time at which maximum reduction in TG was achieved was designated as T1. Differences in variables between T0 and T1 were compared using the Wilcoxon matched-pairs signed rank test. Categorical variables were compared using Fisher's exact test. All statistical tests were 2-sided and significance was set at $P < .05$.

3 | RESULTS

3.1 | Dogs

A total of 10 dogs were enrolled and all dogs completed the study. Median age was 9 years (range, 5-13). Three dogs were male (all castrated) and 7 dogs were female (all spayed). Breeds included mixed breed (n = 4), Miniature Schnauzer (n = 3), West Highland White Terrier (n = 1), Yorkshire Terrier (n = 1), and Havanese (n = 1). At the time of enrollment, median body weight was 7.8 kg (range, 4.1-26.5) and median body condition score (BCS) was 7/9 (range, 4-8).

Seven dogs (7/10 = 70%) were diagnosed with primary hyperlipidemia and 3 dogs (3/10 = 30%) with secondary hyperlipidemia. Causes of secondary hyperlipidemia included pituitary-dependent hypercortisolism (PDH; n = 2) and 1 dog with long-term administration of prednisone (PrednisTab, Lloyd Inc, Shenandoah, Iowa) for steroid-responsive enteropathy. Both dogs with PDH were considered to have good disease control based on the assessment of clinical signs and routine diagnostic testing: 1 dog had been maintained on an unchanged dose of trilostane (Vetoryl, Dechra, Overland Park, Kansas) since diagnosis 3 months earlier; the other dog had been undergoing treatment for 32 months and administered an unchanged dose of trilostane for 6 weeks. Prednisone treatment had been ongoing for 21 months in the dog with chronic enteropathy with an unchanged dose maintained for 5 months before enrollment.

Four dogs were being exclusively fed a kibble diet labeled as fat-restricted (18.8 g/1000 kcal; 17% metabolizable energy basis) (Royal Canin Gastrointestinal Low Fat, Royal Canin USA Inc, St. Charles, Missouri). The fat content of diets fed to the remaining dogs ranged from 26.0 to 48.9 g/1000 kcal (23.4%-43% metabolizable energy basis). All dogs had been on an unchanged diet for at least 6 weeks before enrollment and all diets were maintained throughout the study period.

Recognized comorbidities included allergic skin disease (n = 4), calcium oxalate urolithiasis (n = 2) with cystolith removal at study enrollment in both dogs, chronic enteropathy (n = 2), idiopathic epilepsy (n = 2), tracheal collapse (n = 2), asymptomatic bacteriuria (n = 1), chronic pancreatitis (n = 1), myxomatous mitral valve disease (n = 1), and urinary sphincter mechanism incompetence (n = 1). Concurrent therapeutics included oclacitinib (n = 3), ursodeoxycholic acid (n = 3), cetirizine (n = 2), levetiracetam (n = 2), S-adenosyl-L-methionine (n = 2), trilostane (n = 2), acepromazine (n = 1), cranberry extract (n = 1), cyclosporine (n = 1), diphenhydramine (n = 1), enalapril (n = 1), famotidine (n = 1), glucosamine and chondroitin (n = 1), hydrocodone (n = 1), metronidazole (n = 1), phenylpropanolamine (n = 1), pimobendan (n = 1), potassium bromide (n = 1), and prednisone (n = 1). Other than fenofibrate dose escalation, no medication changes were made throughout the study period in order to isolate the effects of fenofibrate administration.

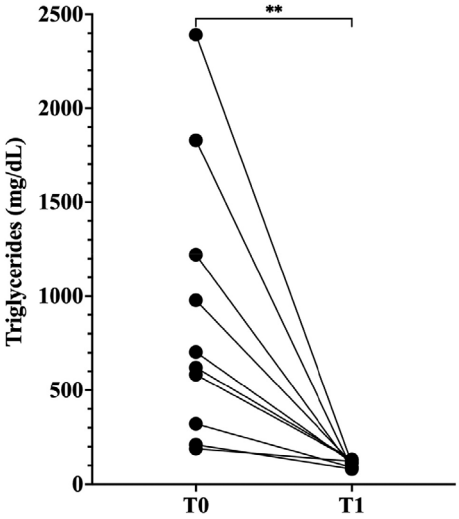

FIGURE 1 Serum triglyceride concentrations (TG) in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. TG reference range, 19-133 mg/dL. T1 defined as time at which TG were normalized. Median fenofibrate dose 6.4 mg/kg PO q24h (range, 2.2-13.5). $^{**}P = .002$

3.2 | Response to fenofibrate

All 10 dogs had hypertriglyceridemia at T0 (median 662 mg/dL, range, 189-2391). Lipemia, hypertriglyceridemia, or both were documented on a minimum of 2 occasions before enrollment. All dogs achieved TG < 500 mg/dL after phase 1 (median fenofibrate dose 3.6 mg/kg PO q24h, range, 2.2-5.9). At T1 (study completion), all dogs achieved normal TG (≤133 mg/dL). In 1 dog, normalization of TG was not achieved at 21 days (ie, after phase 1) but the owner failed to increase the dose as instructed. On day 42 recheck, TG was normal in this dog on the same starting dose of fenofibrate and thus T1 for this dog was considered day 42. Overall, T1 was achieved on day 21 in 4 dogs, day 42 in 4 dogs, and day 63 in 2 dogs. The median dose of fenofibrate required to achieve normalization of TG was 6.4 mg/kg PO q24h (range, 2.2-13.5). There was a significant reduction in TG from T0 to T1 (median 113 mg/dL at study completion, range, 81-132) ($P = .002$; Figure 1). Compared to T0, there was a median change in TG of −538 mg/dL (range, −67 to −2280) or −81% (range, −35 to −95) at T1. Complete data pertaining to dosing regimen and TG are summarized in Table 2. The proportion of dogs requiring dose escalation did not differ significantly between cases with primary vs secondary hyperlipidemia (4/7 vs 1/3; $P > .99$) nor between dogs with TG above vs below 500 mg/dL (5/7 vs 0/3; $P = .17$).

Median CHOL at T0 was 300 mg/dL (range, 172-464). Three dogs had hypercholesterolemia including 1 dog with secondary hyperlipidemia (PDH). All 3 dogs achieved normal CHOL (≤353 mg/dL) after 21, 21, and 63 days, respectively. In 1 dog, CHOL was normal at T0 but increased to 535 mg/dL at T1 (week 6). This dog also had a clinically significant increase in UPC (from 4.9 to 10.1) at the same time. There was no statistically significant change in CHOL from T0 to T1 (median 240 mg/dL at study completion, range, 168-535) ($P = .084$; Figure 2) despite a decrease in CHOL in 9 of 10 dogs. Compared to T0, there was a median change in CHOL of −17% (range, −31 to +62) at T1.

Median UPC was 2.0 (range, 0.3-9.7) at T0. Overall, there was no difference in UPC values between T0 and T1 (median 1.3 at study completion, range, 0.2-10.1; $P = .22$; Figure 3). In 8 dogs (8/10 = 80%) UPC was >0.5 at T0. Of these 8 dogs, 3 dogs had a normal UPC at T1.

TABLE 2 Changes in serum triglyceride concentrations (TG) in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia after treatment with fenofibrate separated by dose category as used in a dose-escalation protocol

Dose category	Dose (mg/kg PO q24h)	TG at start (mg/dL)	TG at end (mg/dL)	Change in TG (mg/dL)
Phase 1 (n = 10)[a]	3.6 (2.2-5.9)	662 (189-2391)	174 (81-404)	−482 (−67 to −2280)
Phase 2 (n = 5)	7.9 (5.2-11.7)	264 (216-404)	116 (83-345)	−111 (−321 to +81)
Phase 3 (n = 2)	10.7 (7.8-13.5)	266 (187-345)	110 (90-130)	−156 (−57 to −255)

Note: Dogs were treated with each dose for 21 days. Patients exited the study if/when TG was normalized. Triglyceride reference range, 19-133 mg/dL. Data are presented as median (range).

[a]One dog did not achieve normalization of TG after phase 1 (21 days); fenofibrate dose was maintained rather than increased by the owner and TG normalized on day 42.

3.3 | Adverse effects

No adverse effects were reported for dogs administered the designated dose of fenofibrate during phase 1. Adverse effects were reported in 2 of 5 dogs that proceeded to phase 2 dosing. A quiet demeanor was noted immediately after dose escalation in 1 dog that resolved after 1 week (dose 7.9 mg/kg PO q24h). A second dog also exhibited a quieter demeanor in addition to passing firm stools for the duration of the dose period (dose 11.7 mg/kg PO q24h); no hematological or biochemical adverse effects were noted in these dogs. Both of these dogs had normal TG at the conclusion of phase 2. No adverse effects were documented in the 2 dogs that progressed to phase 3 of the trial. For all dogs, there was a mild decrease in body weight between T0 and T1 (T0 median 7.8 kg, range, 4.1-26.5; T1 median 7.7 kg, range, 4.0-26.3; median change = −2%, range, −7 to +4; $P = .023$); there was no significant change in BCS (T0 median 7/9, range, 4-8; T1 median 6/9, range, 4-7; $P = .16$).

There were no significant changes in ALT ($P = .68$) or CK ($P = .38$) activities between T0 and T1 (Figures 4 and 5). One dog developed a 2.5-fold increase in ALT activity at the time of successful completion of the study after phase 2; this dog remained clinically well. Two dogs developed mildly elevated CK activities at T1 (at the conclusion of phase 3 for both dogs) without clinical signs of myopathy (1.3-fold and 1.8-fold increases); all dogs had normal CK activities at baseline. A significant decrease in ALP activity was noted between T0 and T1 ($P = .049$; Figure 6). All patients maintained normal total bilirubin concentrations (<0.2 mg/dL). No patient developed an increase in serum creatinine concentration >0.3 mg/dL. There were no significant changes in any other hematological or biochemical parameters before and after treatment with fenofibrate (data not shown).

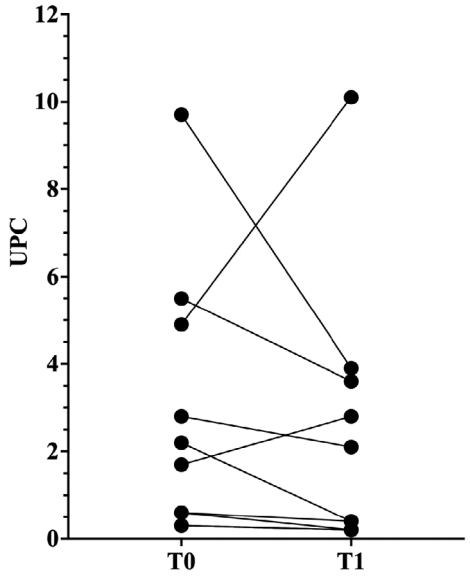

FIGURE 3 Urine protein: creatinine ratios (UPCs) in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. UPC reference range, <0.5. T1 defined as time at which serum triglyceride concentration (TG) normalized. Median fenofibrate dose 6.4 mg/kg PO q24h (range, 2.2-13.5). No difference between T0 and T1 ($P = .22$)

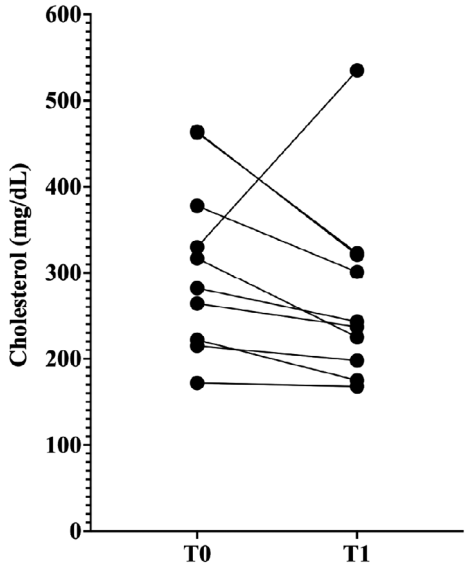

FIGURE 2 Serum cholesterol concentrations (CHOL) in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. Cholesterol reference range, 139-353 mg/dL. T1 defined as time of serum triglyceride concentration (TG) normalization. Median fenofibrate dose 6.4 mg/kg PO q24h (range, 2.2-13.5). No difference between T0 and T1 ($P = .084$)

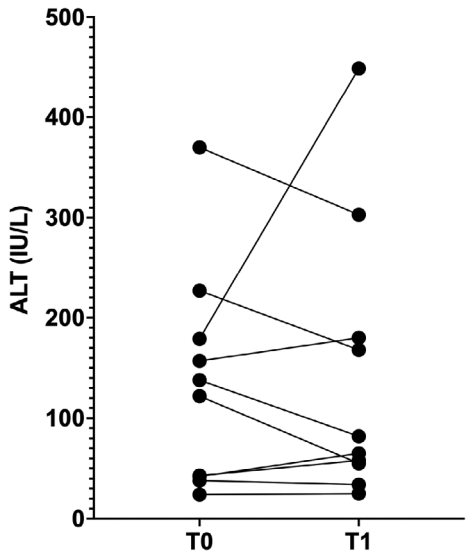

FIGURE 4 Serum alanine aminotransferase (ALT) activity in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. ALT reference range, 21-72 IU/L. T1 defined as time of serum triglyceride concentration (TG) normalization. Median fenofibrate dose 6.4 mg/kg PO q24h (range, 2.2-13.5). No difference between T0 and T1 ($P = .68$)

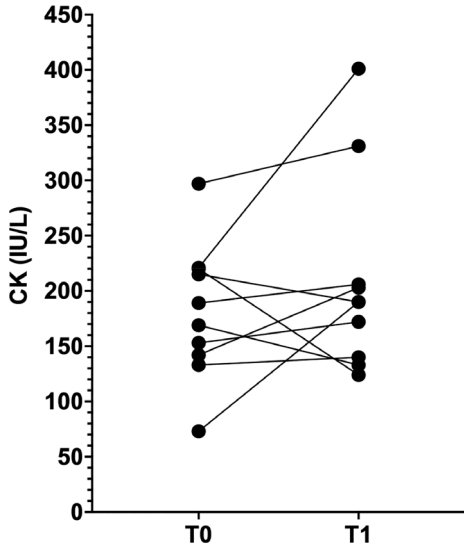

FIGURE 5 Serum creatine kinase (CK) activity in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. CK reference range, 55-257 IU/L. T1 defined as time of serum triglyceride concentration (TG) normalization. Median fenofibrate dose 6.4 mg/kg PO q24h (range 2.2-13.5). No difference between T0 and T1 ($P = .38$)

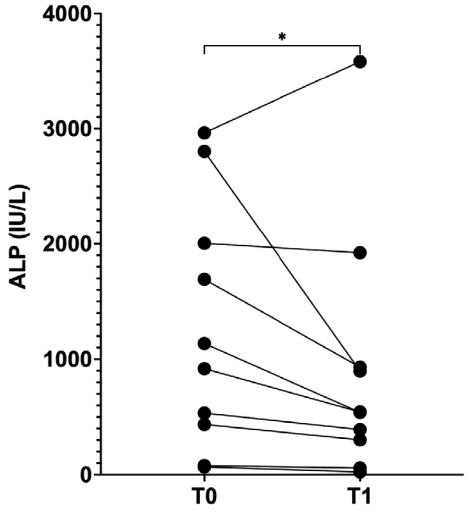

FIGURE 6 Serum alkaline phosphatase (ALP) activity in dogs with primary (n = 7) and secondary (n = 3) hyperlipidemia before (T0) and after (T1) treatment with fenofibrate during a dose-escalation study. ALP reference range, 14-91 IU/L. T1 defined as time of serum triglyceride concentration (TG) normalization. Median fenofibrate dose 6.4 mg/kg PO q24h (range, 2.2-13.5). *$P = .049$

4 | DISCUSSION

In this study, we demonstrated the efficacy of a micronized, nanocrystal formulation of fenofibrate in hyperlipidemic dogs. Using a dose-escalation protocol, we showed that normalization of TG can be achieved in dogs with primary or secondary hypertriglyceridemia on a median dose of fenofibrate of 6.4 mg/kg PO q24h (range, 2.2-13.5) in 3 to 9 weeks. Cholesterol also decreased in 9 of 10 dogs, including 3 dogs that were hypercholesterolemic at the onset of the study. Mild sustained adverse effects were reported in 1 dog (quiet demeanor and firm stools). Serum ALT and CK activities were unchanged before and after treatment; fenofibrate resulted in a significant reduction in ALP activity.

Fenofibrate was initially studied in experimental settings in which neither the drug formulation nor the proportion of dogs, if any, with abnormal baseline data were reported.[34,35] Significant reductions in TG and CHOL were achieved in 6 obese beagle dogs fed a calorically dense diet[34] and 6 healthy beagle dogs[35] after administration of fenofibrate orally once daily for 2 weeks at doses of 10 mg/kg and 100 mg/kg, respectively. More recently, fenofibrate was studied in 64 dogs with primary and secondary hyperlipidemia (formulation not reported); a fenofibrate dose of 10 mg/kg orally once daily for 30 days normalized TG and CHOL in 85.9% and 53.7% of dogs, respectively.[31]

The micronized, nanocrystal formulation of fenofibrate used in the present study resulted in a median reduction in TG of 81%. In the above-mentioned studies of dogs with primary and secondary hyperlipidemia, similar median decreases in TG of 84% (range, 68%-95%) and 88% (range, 62%-99%) were documented with bezafibrate and fenofibrate, respectively.[30,31] In people, fenofibrate has consistently been associated with substantial reductions in TG (15%-60%) with the magnitude of reduction being directly proportional to baseline TG which vary with etiology.[36-39] In contrast, we demonstrated normalization of TG in dogs with fenofibrate regardless of baseline TG. The smaller effect observed in people may reflect the role of fenofibrate in the management of cardiovascular disease where the primary emphasis is on lowering LDL-C and increasing HDL rather than achieving normalization of TG.[36-39] Other disease processes, such as diabetes mellitus, are also known to impair optimal response to fenofibrate.[39] The hypolipidemic effect of fenofibrate in dogs with naturally occurring DM has not been studied yet but we have had anecdotal success with it. We have also observed a successful reduction in serum lipids in a canine model of toxin-induced diabetes mellitus (under review). Dogs with DM were excluded from the present study due to anticipation of changes in insulin therapy that would have resulted in study exclusion.

This publication documented normalization of TG in all cases after initiation of hypolipidemic drug therapy. This is particularly relevant in light of the fact that dietary fat restriction was not implemented in 6 of 10 dogs. Therapeutic targets for management of hypertriglyceridemia in dogs have been poorly defined. However, optimal management is so important considering the range of complications that are associated with hyperlipidemia in dogs including some that are life-threatening. These complications include pancreatitis,[10,13,15] gallbladder mucocele,[12,14] vacuolar hepatopathy/increased liver enzyme activity,[16] insulin resistance,[17] proteinuria,[18-21] ocular disease,[22] seizures,[23] and atherosclerosis with hypercoagulability.[24] A reduction in TG to <500 mg/dL has historically been considered as the goal of treatment for dogs based on human guidelines for management of hypertriglyceridemia-induced pancreatitis.[40] More

recently, however, a target of <200 mg/dL was suggested in people because this range was associated with the lowest rate of pancreatitis episodes.[41] In line with this recommendation, achieving normalization of TG should be considered as a therapeutic goal in dogs as some of the complications of hyperlipidemia, as outlined above, are seen with TG elevations <500 mg/dL.

Serum cholesterol concentrations did not significantly decrease after fenofibrate treatment in this study. This result differs from the bezafibrate study in dogs in which CHOL decreased significantly including in those patients with normal CHOL at baseline.[30] Serum cholesterol concentrations also significantly decreased in the earlier publication evaluating fenofibrate.[31] The lack of significant reduction in CHOL might be a reflection of sample size both in terms of total number of cases and in terms of the number of dogs with hypercholesterolemia. However, 9 of 10 dogs in our study experienced a reduction in CHOL. The only dog that showed an increase in CHOL despite fenofibrate treatment had a progressive PLN supported by a concurrent increase in UPC. The cause of PLN in this dog was unknown and might be considered a potential adverse effect of fenofibrate treatment. It is plausible that fenofibrate does decrease CHOL in dogs without concurrent diseases. In a previous study on the effect of fenofibrate in dogs with hyperlipidemia, an increase in CHOL was documented in 5 of 64 dogs.[31] The effect of fibrate drugs on CHOL in people is variable with reported paradoxical increases in LDL-C.[26]

Fenofibrate was well tolerated as a treatment for hyperlipidemia in this cohort of dogs. However, given sample size, a definitive assessment of drug safety cannot be made on this study alone. Nausea, abdominal pain, and constipation are described in 3.2% to 4.6% of people receiving fenofibrate; these incidences do not differ significantly from placebo groups.[32] In the aforementioned studies, no adverse effects were reported with bezafibrate,[30] while self-limiting diarrhea and flatulence were reported in 3% of dogs treated with fenofibrate.[31] One dog experienced sustained adverse effects: a quiet demeanor and firm stools during phase 2 of the study. This dog successfully completed the trial while on this dose and was returned to phase 1 dose for ongoing management with resolution of these clinical signs.

Additionally, no relevant hematological or biochemical changes were reported with fenofibrate administration. Presentations associated with idiosyncratic fenofibrate hepatotoxicity in people range from hepatocellular to cholestatic to mixed patterns, and from asymptomatic presentations to acute and self-limiting disease to chronic liver injury: prevalence is reported between 0.6% and 7.5%.[32,42] One dog developed a 2.5-fold increase in ALT activity between T0 and T1: an association with fenofibrate can neither be proven nor excluded. Follow-up blood work, limited to liver values, performed 2 years after completing the study and while on the same dose of fenofibrate, showed no progression in ALT activity (499 IU/L vs 451 IU/L) and a 55% reduction in ALP activity (1922 IU/L vs 874 IU/L) with the dog remaining clinically well. No clinical features of myopathic disease were noted in any of the dogs. While myopathies are rare in people, risk of myopathy is increased when fibrates are used in combination with a statin.[27] Gemfibrozil also has a 15-fold higher risk of inducing myopathy than fenofibrate in people.[43] No changes in ALT or CK activities were found in the earlier study assessing the utility of fenofibrate in management of hyperlipidemia in dogs.[31] As discussed further below, ALT significantly decreased in dogs with hyperlipidemia treated with bezafibrate with no increases in CK activity observed.[30] The relationship between fibrate derivatives and creatinine is poorly understood. Increases in serum creatinine >50% were noted in 9.1% of people receiving a fibrate drug.[44] However, initial increases can be transient and might not affect creatinine clearance.[45,46] Furthermore, various renoprotective effects of fibrates have been described.[47,48] No clinically significant changes in serum creatinine were observed in our cohort.

A significant reduction in serum ALP activity was documented in association with successful management of hyperlipidemia in dogs. Elevations in serum ALT and ALP activities have been described in Miniature Schnauzers in association with hyperlipidemia, with the magnitude of increased activity seemingly proportional to hyperlipidemia severity.[16] These elevations are likely the result of lipid vacuolar changes as described in people.[49] Serum ALP activities were not reported in previous studies on bezafibrate or fenofibrate in dogs[30,31]; noteably, a significant reduction in ALT was reported in the bezafibrate study.[30] Conceivably, respective reductions in serum ALP and ALT activities in this and in the bezafibrate report reflect a resolving hepatic lipidosis.

There was no significant change in UPC across the study period. One dog experienced a 2-fold increase in UPC and was suspected to have progressive PLN. The decrease in UPC documented in 8 of 10 dogs must be carefully interpreted: comorbidities were present in each dog and single samples rather than pooled urine measurements might have influenced trends in each individual.[50] When monitoring proteinuria in dogs, it is also recommended that UPC must change by 80% at lower values (near 0.5) and by 35% at higher UPCs (near 12) to be considered clinically relevant.[51] The relationship between hyperlipidemia and proteinuria is important. Glomerular lipid lesions have been identified in dogs with hyperlipidemia including Miniature Schnauzers.[19,20] Proteinuria has been reported in 44% to 60% of Miniature Schnauzers with hypertriglyceridemia and does not appear to be associated with azotemia or hypoalbuminemia.[18,21] Further studies are required to explore the effect of fenofibrate treatment and resolved hyperlipidemia on changes in UPC.

Body weight decreased between T0 and T1, however, the change was minor in most dogs. One consideration is a type I error. Results may also not be biologically significant. It is noted that a similar small decrease in body weight was reported previously with fenofibrate treatment in obese dogs.[33] Eight of 10 dogs in this study had a BCS between 6 and 8/9. In rodent models of obesity, DM, and insulin resistance, fibrates have been shown to reduce body weight gain and white adipose tissue.[52,53] These effects are thought to be mediated by an increased flux of free fatty acids from the peripheral tissues to the liver with enhanced hepatic catabolism and reduction in circulating TG responsible for adipose cell hypertrophy and subsequent insulin resistance.[52,53]

Blood work reassessment was performed within 6 hours of fenofibrate dosing with the drug administered in a small volume of food. Peak levels of fenofibric acid, the active metabolite of

fenofibrate, are achieved within 6 to 8 hours of administration in people.[32] While possibly selecting for maximal response, responses to fenofibrate in this study were still marked. A defined protocol also had to be nominated to achieve standardization; timing of administration of bezafibrate or fenofibrate was not previously described preventing comparison and is a limitation of earlier studies.[30,31] Given an elimination half-life of 20 hours in people, a steady state is suspected to have been achieved within the 21-day dosing periods for all dogs ensuring sustained effect across the dosing interval.[32,54] Awareness must be given to extrapolating the dosing and recheck protocol used here when adopting the convention of fasting reassessment which may occur from 12 to >24 hours after medication administration. While the nanocrystal formulation of Tricor eliminates the requirement for administration with food in people,[54] this requires investigation in dogs and prompted administration with a meal.

Our study is limited by small sample size. As such, the data herein do not provide a precise determination of the optimal fenofibrate dose. Furthermore, when considering the requirement for dose escalation, there is a large overlap in doses across each phase of the study protocol. This could not be avoided due to the requirement for weight cut-offs and the commercially available tablet sizes for the chosen drug formulation; the dose was nominated where possible to limit inaccuracies associated with tablet splitting. The sample size limited our ability to compare the response of dogs with primary vs secondary hyperlipidemia; we did not include dogs diagnosed with diabetes mellitus due to the aforementioned reasons. Small sample size also hampered further assessment of fenofibrate on CHOL and the incidence of adverse effects, as outlined above. All of these aspects warrant further exploration.

No control population was included in this study. Variation in TG has been documented in Miniature Schnauzers with presumed breed-associated hypertriglyceridemia before and after the implementation of fat-restricted dietary therapy.[25] This variation was more pronounced before dietary therapy: while individual variations of approximately 1000 mg/dL were recorded between samples taken 1 to 2 months apart, TG were never documented to spontaneously normalize and median values did not differ between time points.[25] Additionally, the proportions of dogs experiencing increases or decreases in TG were approximately equal. While the potential for variation is yet to be described in cases of secondary hyperlipidemia, fasting hypertriglyceridemia, lipemia, or both were documented in all dogs on 2 or more occasions before enrollment. Repeated measurements of TG within dose phases and after normalization could have strengthened the study.

Other limitations apply to this study. The time to full biological effect of fenofibrate is unknown in dogs. It is possible that normalization of hyperlipidemia would have been achieved on lower doses of fenofibrate if lower doses were maintained for longer periods. This was documented inadvertently in the 1 dog when owners failed to increase the dose after starting the second phase of the study. Importantly, since all dogs had a reduction of TG < 500 mg/dL after phase 1, a reasonable clinical approach would be to maintain the phase 1 dose as described here for >3 weeks as long as obvious complications of hyperlipidemia are not developing and recheck after 6 to 9 weeks. While our study results have direct and immediate clinical utility, they could have been strengthened by lipoprotein profile analysis. In a study evaluating dietary fat restriction in the management of hyperlipidemia in Miniature Schnauzers, abnormalities in lipoprotein profiles persisted despite significant reductions in TG.[25] Finally, longer-term adverse effects were not captured with this study design.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study protocol was reviewed and approved by the IACUC at the University of California—Davis (UCD-IACUC# 20508).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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