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Lack of toxicity by medium chain triglycerides (MCT) in canines during a 90-day feeding study

Ray A. Matulka [a,*], D.V.M. Larry Thompson [b], George A. Burdock [a]

[a] Burdock Group, 801 North Orange Avenue, Suite 710, Orlando, FL 32801, United States
[b] Nestlé Purina One Checkerboard Square, St. Louis, MO 63164, United States

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ABSTRACT

Dietary fats in food are natural energy sources to animals and are included in the American Association of Feed Control Officials (AAFCO) manual as a requirement for dog food. Medium chain triglycerides are comprised of a glycerol backbone esterified to medium chain length (8–12 carbon) fatty acids (FA) and, in the context of this report, are all saturated FA. Unlike esterified long chain (>12 carbons) FA (long chain triglycerides or LCT), MCT are lower in caloric value, and are eliminated from the body more quickly than LCT. The objective of this study was to determine the safety of MCT when fed to beagles for 90 days at levels of 0%, 5%, 10%, and 15% MCT added to conventional feed. The beagles were monitored for signs of toxicity by clinical observations, body weight measurements, food consumption level, physical examinations, hematology and serum chemistry, ophthalmic examinations, and urinalysis. There were no signs of toxic effects observed in any of the animals that were related to feed, and the animal viability was 100% at the end of the study. Some animals exhibited significant increased blood urea nitrogen, potassium and cholesterol levels in the 10% and 15% MCT-fed groups. Also, in the same groups with elevated nitrogen, there were concomitant reductions in total blood protein and urine volumes. These changes in serum chemistry may be the result of protein sparing effects due to the high levels of MCT intake, and are not deemed to be pathological in nature. Animals receiving 15% MCT in feed had lower levels of food intake due to palatability issues. From the other examination parameters, there were no significant changes noted between groups receiving MCT and vehicle feed. No safety concerns were noted at any dose level, although an issue with palatability precluded identifying 15% as the highest dose level tested.

1. Introduction

Esterified fatty acids, forming molecules termed triglycerides, triacylglycerols or more commonly, fats, are a normal source of metabolizable energy for animals, and are required in dog food at a minimum level of 5% (based on the percentage of dry matter, DM) for adult maintenance and a minimum level of 8% DM for growth and reproduction (AAFCO, 2007). Fats are composed of fatty acids (FA) connected at specific points (i.e., sn positions) to a triacylglycerol backbone. There are many varieties of FA that can be esterified on the glycerol moiety. The major differences between the FA are the hydrocarbon chain length, and whether the FA is saturated or unsaturated. Saturated medium chain triglycerides (MCT) are typically classified as being composed of a mixture of six- (C6:0), eight- (C8:0), and twelve-chain (C12:0) medium chain fatty acids (MCFA), in the following concentrations: C6:0 (1–2%), C8:0 (65–75%), C10:0 (25–35%), and C12:0 (1–2%). Long chain triglycerides (LCT) generally have FA chains that are greater >12 carbons in the sn positions (FA-O-esterification) (Babayan, 1987).

MCT are composed of MCFA typically commercially derived from edible coconut and palm kernel oils that are consumed by humans and other animals. The metabolism of MCT in the canine is a process whereby lipases from the buccal cavity and pancreas release the FA's in the gastrointestinal tract where they are absorbed. Unlike long chain triglycerides (LCT), where long chain fatty acids (LCFA) form micelles and are absorbed via the thoracic lymph duct, MCFA are most often transported directly to the liver through the portal vein and do not necessarily form micelles (Bach and Babayan, 1982). Also, MCFA do not re-esterify into MCT across the intestinal mucosa. MCFA are transported into the hepatocytes through a carnitine-independent mechanism, and are metabolized into carbon dioxide, acetate, and ketones through β-oxidation, and the citric acid cycle (Bell et al., 1997; Birkhahn and Border, 1981; Schwabe et al., 1964; Wiley and Leveille, 1973).

Abbreviations: BW, body weight; FA, fatty acids; LCFA, long chain FA; LCT, long chain triglycerides; MCFA, medium chain fatty acids; MCT, medium chain triglycerides.

* Corresponding author. Tel.: +1 407 802 1400; fax: +1 407 802 1405.
E-mail address: rmatulka@burdockgroup.com (R.A. Matulka).

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The net energy value (NEV) of MCTs has been calculated at 6.80 ± 0.15 kcal/g, which is significantly less than the NEV for LCT in typical fats (9 kcal/g). This lower NEV may be a significant factor for reduced weight gain in animals that ingest MCT, compared to LCT (Ingle et al. 1999). The weight gain of rats was less when the fat was from MCT, compared to LCT in diets containing 60% of calories from fat (Bray et al., 1980). The substitution of MCT for LCT in parenteral nutrition is also aimed to increase the rate of elimination of triglycerides (TG) from the plasma (Deckelbaum et al., 1990; Richelle et al., 1994), reduce changes in plasma cholesterol and lipoprotein (Siderova et al., 1993), lower fat build-up in the liver (Baldermann et al., 1991), in addition to reducing weight gain. However, there may be effects on the health of animals that consume high levels (>60% of total caloric intake) of fats in their diet. Although balanced animal feed (with daily allowances of carbohydrates and protein) with MCT as a constituent is not known to produce toxicity. Previous studies in other species including, but not limited to rats and rabbits, have been given up to 9375 mg/kg without toxic effects (Traul et al., 2000). Our study is aimed to determine whether subchronic ingestion of 5%, 10%, and 15% MCT in the canine exhibited similar safe characteristics under similar conditions of testing.

2. Materials and methods

The study was conducted at Battelle (Columbus, OH) under the sponsorship of Nestlé Purina Global Resources, Inc.

2.1. Test article

The test article was MCT pre-formulated in adult maintenance dry food with beef tallow (vehicle feed) provided by Nestlé Purina Petcare Company. The vehicle was adult maintenance dry dog food with beef tallow added but with 0% structured lipid ingredient (Table 1). The composition of this diet provides the essential nutrients necessary for the maintenance of dogs. Three separate test articles with nominal target concentrations of 5%, 10%, and 15% of total mass of MCT were contained in (MCT replaced mass of dry feed tallow) vehicle feed. All diets were isocalorically balanced by the addition or reduction of beef tallow. Control was vehicle feed with 0% MCT. Purity, composition, and stability (for duration of the study) of test article was assessed and recorded prior to use in study.

2.2. Animals

Thirty-two male and female Beagle dogs (16 males and 16 females) from age 12 months to 6 years were received and quarantined for 7 days, and then acclimated to study environmental conditions. Animals were examined by a veterinarian to evaluate health status before release for use in the study. Procedures for animal care and housing met the current Association for Assessment and Accreditation of Laboratory Animal Care recommendations, as stated in the "Guide for Care and Use of Laboratory Animals" (NRC, 1996). All animals were housed individually under 12 h light/dark cycle, 22 °C and 45% humidity conditions. During the quarantine period, dogs were acclimated to Nestlé Purina Petcare Company vehicle control feed gradually to a three hours feeding regimen (3 h of allotted time for food consumption at the same time each day). All animals were assigned to study groups by software algorithm (Xybion Medical Systems, Version 4.2.2, Cedar Knolls, NJ), which employs a body weight (BW) stratification procedure that assures homogeneity of mean BW's across all groups.

Table 1
Typical components of the adult maintenance dry dog food utilized in this study

Parameter	Level (%)	Parameter (min)	Level
Crude protein (min)	26.0	Phosphorus	0.8%
Crude fat (min)	16.0	Selenium	0.30 mg/kg
Crude fiber (max)	3.0	Vitamin A	13,000 IU/kg
Moisture (max)	12.0	Vitamin E	100 IU/kg
Linoleic acid (min)	1.4	Glucosamine	400 ppm
Calcium (min)	1.0		

IU – international units; kg – kilogram; max – maximum; mg – milligram; min – minimum; and ppm – parts per million.

Table 2
Experimental design

Group	Nominal concentration	Number of dogs	
		Males	Females
1	15% MCT	4	4
2	10% MCT	4	4
3	5% MCT	4	4
4	Vehicle feed	4	4

2.3. Study design

All dogs received 91 consecutive days of approximately 200 g of vehicle feed with 0%, 5%, 10%, or 15% MCT for a three hour feeding regimen. Food consumption was measured by weight of remaining feed. The amount of feed given was sufficient to meet nutritional requirements of an average laboratory canine and maintain a healthy body condition. Study groups with number of animals, sex and MCT concentration given are shown in Table 2.

Potential toxic signs were evaluated by clinical observation, body weight, food consumption, physical examination, hematology, serum chemistry, and urine analysis. Clinical observations (food and water consumption, lethargy, abrasions, etc.) were conducted twice daily, at least 6 h apart, for 7 days per week. Animal body weights were measured on the day of receipt, 2 days priors to study and at weekly intervals from study Day 1 (i.e., Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and 91). Food consumption was measured by taking the difference between initial weight of the ration and after the three hour feeding regimen. Veterinary physical examination (body temperature, respiration, etc.) were made on Day 1, and during Weeks 4, 8 and 12 of the study.

Hematology parameters on the collected blood samples were: Blood smear morphology, erythrocyte count (RBC), calculated hematocrit, hemoglobin, calculated mean corpuscular hemoglobin concentration, calculated mean corpuscular hemoglobin, mean corpuscular volume, platelet count, reticulocyte count, total leukocyte count, and the absolute white blood cell differential. Blood samples were collected six days prior to the start of the study and on Days 29, 58, and 91 of the study, and were also examined for cell count and cell pathology. Serum chemistry parameters analyzed included albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total calcium, chloride, cholesterol, creatine kinase, creatinine, direct bilirubin, gamma-glutamyl transferase, calculated globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides and urea nitrogen. Urine analysis included the appearance, color, bilirubin, ketone levels, occult blood, pH, urine glucose and protein levels, urobilinogen, specific gravity, volume, and a microscopic examination of sediment. The sediment was separately evaluated for white and red blood cells, casts, epithelial cells, mucus, sperm, bacteria, yeast, amorphous sediment, and crystal formation. At the conclusion of the study, all animals were retuned to stock; no tissue samples were taken, nor were any animals terminated.

2.4. Statistical analysis

Data variances were determined for homogeneity across test groups at the 0.05 level by Bartlett's test. Tests for differences between comparison groups were made using Dunnett's test. For non-homogenous data (from Bartlett's test), test for pairwise differences between each of the comparison groups were made using Cochran and Cox's modified two-sample *t*-test. Statistical significance for each comparison was reported at the 0.05 level.

3. Results

Clinical observations included sporadic reports of abrasions and scratch wounds, but none were considered to be related to administration of MCT. There were no mortalities reported.

There were no incidences of significant group mean body weight changes from control that could be related to the test article administration. However, there were transient, sporadic, non-significant increases and decreases in body weight observed in all animal groups (data not shown).

Average food consumption for all groups was not significantly different from each other, with exception of several days at the beginning, and near the end of study. As compared to the vehicle feed group, all three MCT groups had several consecutive days of reduced food consumption at different times in the study. These periods of reduced food intake were not significant to the overall food consumption rates, but were thought to be related to palatability of MCT in feed.

Findings from physical and ophthalmic examinations were unremarkable. Incidental observations of bilateral mature cataract and corneal crystals were observed in one animal each in 15% and vehicle group, respectively. Two incidences of bilateral immature cataracts were observed (one animal in each group) in the 10% and 15% groups. None of these observations could be related to treatment.

From the clinical pathology results, there were some minor changes in hematology profiles reported; however, these were not statistically significant and were unrelated to test article administration because the findings were singly sporadic, and not dose-dependent. Contrary to the hematology results, serum chemistry revealed changes that may be related to the addition of MCT to the diet. Changes that affected both sexes included a significant increase in blood urea nitrogen and a nonsignificant increase in cholesterol in the 10% and 15% MCT-fed groups, as compared to vehicle fed animals (Table 3). An increase in serum potassium and a decrease in globulin protein levels were also observed at the 15% level, but did not follow a dose-dependent manner (Table 4). Furthermore, there were decreases in urine volumes (Table 5) with concomitant increased specific gravity observed in the 10% and 15% MCT groups (Table 6). Clinical pathology changes were determined by comparison of animals pre-study, and concurrent control animals. Note that not all observed differences in the MCT groups were statistically significant, but possible trends could be seen when compared to pre-study data and vehicle fed animals.

4. Discussion

There are several studies in the literature (Deckelbaum et al., 1990; Richelle et al., 1994) that have evaluated the physiological effects of MCT consumption; however, toxicity related to MCT has not been shown even at very high doses and despite the use of routes (e.g., intravenous) that eliminate the variabilities related to absorption (Traul et al., 2000). For example, 90-day feeding studies in rats with doses up to approximately 9.2 g/kg BW, and a 90-day administration of 0.5 ml/kg/day of intramuscular injection of MCT into the right and left thigh muscles twice per week in a rabbit model, failed to demonstrate any significant toxic results (Traul et al., 2000). Furthermore, 12,500 mg/kg/day MCT in the diet, or 4280 mg/kg intravenous injections failed to cause any maternal, or fetal toxicity, or teratogenic effects in rats (Henwood et al., 1997; Wilson et al., 1996). Lastly, while there are no known carcinogenicity studies with MCT, a two year rat study with a

Table 5
Urine volume from male and female beagle dogs treated with MCT for 90 days

Group	Urine volume (mL) Day			
	−6	29	58	91
Males				
Vehicle	114.3 ± 68.9[a]	166.5 ± 36.0	269.5 ± 140.4	363.5 ± 299.5
5% MCT	134.5 ± 25.2	131.5 ± 44.5	118.5 ± 30.1	182.0 ± 62.7
10% MCT	133.5 ± 44.6	87.5 ± 41.9*	114.5 ± 41.8	135.8 ± 99.5
15% MCT	132.0 ± 35.1	88.3 ± 27.8*	123.3 ± 86.5	117.3 ± 84.1
Females				
Vehicle	130.0 ± 100.2	147.5 ± 70.1	143.5 ± 50.3	154.0 ± 37.8
5% MCT	186.5 ± 74.5	138.8 ± 98.4	210.0 ± 122.1	133.8 ± 98.6
10% MCT	147.5 ± 39.2	127.0 ± 35.2	115.0 ± 19.2	190.0 ± 54.8
15% MCT	142.8 ± 152.5	92.3 ± 25.3	92.8 ± 23.6	69.0 ± 24.1

[a] Values are means ± standard deviation; an asterisk (*) indicates a statistically significant ($p \leqslant 0.05$) difference from the vehicle; $N = 4$ in all days.

Table 3
Serum Chemistry from male and female beagle dogs treated with MCT for 90 days

Group	Blood urea nitrogen (mg/dl) Day				Cholesterol (mg/dl) Day			
	−6	29	58	91	−6	29	58	91
Males								
Vehicle	13 ± 2[a]	13 ± 1	11 ± 2	11 ± 2	143 ± 50	163 ± 37	155 ± 40	156 ± 36
5% MCT	13 ± 2	15 ± 2	12 ± 2	13 ± 2	159 ± 23	187 ± 33	184 ± 32	182 ± 34
10% MCT	14 ± 1	16 ± 1	13 ± 2	15 ± 1*	175 ± 51	217 ± 51	223 ± 49	222 ± 49
15% MCT	15 ± 2	19 ± 2*	17 ± 1*	17 ± 3*	177 ± 12	198 ± 13	209 ± 32	222 ± 25
Females								
Vehicle	11 ± 1	13 ± 1	12 ± 1	12 ± 2	166 ± 40	190 ± 42	188 ± 46	181 ± 36
5% MCT	12 ± 1	14 ± 2	13 ± 1	14 ± 3	162 ± 14	193 ± 35	182 ± 16	181 ± 14
10% MCT	14 ± 2	16 ± 2	15 ± 1*	15 ± 2	161 ± 20	200 ± 16	218 ± 12	210 ± 14
15% MCT	14 ± 2	17 ± 3*	17 ± 1*	17 ± 1*	199 ± 30	226 ± 39	235 ± 47	253 ± 64

[a] Values are means ± standard deviation; an asterisk (*) indicates a statistically significant ($p \leqslant 0.05$) difference from the vehicle; $N = 4$ in all days.

Table 4
Serum chemistry from male and female beagle dogs treated with MCT for 90 days

Group	Globulin (g/dL) Day				Potassium (meq/l) Day			
	−6	29	58	91	−6	29	58	91
Males								
Vehicle	2.3 ± 0.3[a]	2.4 ± 0.2	2.7 ± 0.1	2.6 ± 0.2	4.6 ± 0.2	4.6 ± 0.4	4.6 ± 0.3	4.6 ± 0.3
5% MCT	2.5 ± 0.1	2.6 ± 0.4	2.7 ± 0.5	2.7 ± 0.5	4.9 ± 0.1	4.7 ± 0.4	4.6 ± 0.3	4.5 ± 0.1
10% MCT	2.4 ± 0.3	2.7 ± 1.0	2.7 ± 0.7	2.8 ± 0.9	4.6 ± 0.2	4.6 ± 0.3	4.5 ± 0.3	4.6 ± 0.2
15% MCT	2.4 ± 0.5	2.1 ± 0.1*	2.1 ± 0.3	2.2 ± 0.3	4.6 ± 0.2	4.8 ± 0.3	5.0 ± 0.4	4.8 ± 0.2
Females								
Vehicle	2.2 ± 0.2	2.4 ± 0.5	2.5 ± 0.6	2.5 ± 0.5	4.6 ± 0.2	4.4 ± 0.2	4.3 ± 0.1	4.2 ± 0.5
5% MCT	2.2 ± 0.2	2.5 ± 0.3	2.5 ± 0.3	2.6 ± 0.4	4.4 ± 0.1	4.4 ± 0.4	4.4 ± 0.2	4.3 ± 0.2
10% MCT	2.2 ± 0.3	2.5 ± 0.3	2.5 ± 0.2	2.6 ± 0.4	4.7 ± 0.3	4.7 ± 0.3	4.7 ± 0.1*	4.6 ± 0.3
15% MCT	2.0 ± 0.1	2.3 ± 0.6	2.2 ± 0.4	2.2 ± 0.4	4.6 ± 0.2	5.0 ± 0.5*	5.2 ± 0.3*	5.0 ± 0.4*

[a] Values are means ± standard deviation; an asterisk (*) indicates a statistically significant ($p \leqslant 0.05$) difference from the vehicle; $N = 4$ in all days.

Table 6
Urine parameters from male and female beagle dogs treated with MCT for 90 days

Group	Specific gravity Day			
	−6	29	58	91
Males				
Vehicle	1.043 ± 0.019[a]	1.035 ± 0.010	1.028 ± 0.011	1.024 ± 0.014
5% MCT	1.037 ± 0.011	1.043 ± 0.008	1.046 ± 0.008	1.029 ± 0.003
10% MCT	1.044 ± 0.012	1.053 ± 0.017	1.042 ± 0.010	1.036 ± 0.015
15% MCT	1.037 ± 0.005	1.036 ± 0.011	1.042 ± 0.009	1.025 ± 0.014
Females				
Vehicle	1.048 ± 0.026	1.036 ± 0.012	1.040 ± 0.015	1.027 ± 0.005
5% MCT	1.031 ± 0.006	1.034 ± 0.015	1.035 ± 0.018	1.038 ± 0.018
10% MCT	1.033 ± 0.012	1.042 ± 0.012	1.047 ± 0.011	1.031 ± 0.008
15% MCT	1.042 ± 0.018	1.045 ± 0.020	1.050 ± 0.018	1.052 ± 0.008*

[a] Values are means ± standard deviation; an asterisk (*) indicates a statistically significant ($p \leqslant 0.05$) difference from the vehicle; $N = 4$ in all days.

related lipid, tricaprylin, indicates that up to 9540 mg/kg/day is not carcinogenic, although it may cause pancreatic hyperplasia and adenomas (NTP, 1994). Therefore, there is preponderance of evidence that MCT has no demonstrable toxic effect. Similar results were found in our canine study. Clinical and physical examinations reveal no significant effects at up to 15% MCT in the diet. Our study is congruent with the findings of others, that MCT is safe.

Bloom et al. (1951) first reported that MCT were a more completely oxidized fat source than LCT. Long term MCT ingestion has been shown to reduce plasma lipids, reduce fat deposition in adipose tissue, and increase blood ketone bodies (Lavau et al., 1978; Wiley and Leveille, 1973). Although there were no toxic effects from MCT, these earlier studies may indicate that MCT can alter the body's metabolism. Contrary to these early studies of MCT metabolism, Crozier et al. (1987) reported that MCT in diets of rats reduced energy retention by 60%, and had no effect on blood insulin and glucagon levels. Furthermore, Bach and Babayan (1982) demonstrated that rats with high MCT content in their diets did not have any significant weight gain. The differences between the earlier findings of Wiley and the later findings from Crozier, may be explained by the fact that changes in fat metabolism in the early studies resulted with a diet of at least 60% MCT, with very little carbohydrate. This type of study reflects the findings of Bach and Babayan (1982) in rats, where the body weight changes were not a result of MCT in feed but rather a change in the overall metabolism from an unbalanced nutrient diet. An unbalanced nutrient diet is one that contains a large portion of the caloric intake (e.g., at least 60% MCT) for the total nutrition provided to the animals in the study is from one nutrient. This dog study provided a complete nutritive profile, although an increased consumption of beef tallow may have been consumed, in order to provide isocaloric rations between groups. This increase in beef tallow consumption may have influenced minor changes in cholesterol levels noted in this study. The blood glucose levels in this dog study were not significantly altered by MCT, thereby indicating that there were no effects on insulin or glucagon. Overall, it appears that MCT can affect metabolism and body weight; however, physiological changes would require a high level of fat as the only major source of dietary energy without significant carbohydrate intake. A diet comprised of balanced nutrients, fats, and carbohydrates as energy, did not significantly alter the physiology of the dogs in this study; there were, however, some minor changes in blood urea, potassium, and cholesterol in our canine study. Cholesterol levels tended to increase, but not significantly. Rutz et al. (2004) noted increased cholesterol levels in dogs administered MCT at up to 35% of the fat content of the diet, but the increase did not affect the well-being of the dogs. The increased serum cholesterol levels may be due to increased consumption of saturated fatty acids. In addition, there were reduced levels of urine output and total blood protein. The urine volumes measured in this study were variable, with a transient, significant decrease in urine output in the male dogs, and a nonsignificant trend to decreased urine volume in the females. Although water consumption was not significantly different from control dogs, variable water consumption may have added to this effect. Our findings do not suggest a pathological state as much as they represent changes in protein metabolism. Consumption of LCT has been known to cause nitrogen retention in animals, which is a phenomenon known as the "protein sparing effect" (Munro and Downie, 2007). The mechanism for protein sparing is thought to be caused by increased protein synthesis and a decrease in protein and amino acid catabolism (Nakano et al., 1974). Other investigators have reported increased blood urea and urine volume reduction during high levels of dietary MCT intake; however, this occurred to a lesser degree than that seen in high LCT diets. The underlying mechanism for nitrogen retention remains unclear, but Reeds et al. (1987) reported that protein sparing can be abolished by additional carbohydrate in the diet that would also increase serum glucose and insulin levels. Nakano and Ashida (1975) reported that protein sparing effect does not occur in alloxan-diabetic rats. Therefore, the probable mechanism for increased blood urea may be due to the lack of glucose and insulin signaling. In parenteral nutrition, the balance of MCT, carbohydrate, and protein may be crucial to maintain normal physiology.

Based on the findings from this 91-day MCT feeding study, there are no indications of toxicological effects in dogs fed up to 15% MCT in the diet. The minor changes in protein sparing and ancillary potassium/cholesterol did not induce any detrimental effects to the overall health of the animals. There is a palatability issue with the 15% MCT in feed and indicates a possible self-limiting effect; however, the palatability of the feed is not an indicator of toxicity. Therefore, a logical conclusion from this study is that the no-adverse-effects level (NOAEL) for the canine is 15% MCT in feed.

Conflict of interest statement

All authors have a financial relationship with the sponsor of the study, Nestle Purina.

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