

# A Report of Adverse Effects Associated With the Administration of Cannabidiol in Healthy Dogs

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## ABBREVIATIONS

CBC — cannabichromene (for Table 1)

CBD — cannabidiol

CBG — cannabigerol

CBN — cannabinol

LLOQ — lower limit of quantification

THC — delta-9-tetrahydrocannabinol

## Abstract

Cannabis-based therapies have been used for centuries for various medicinal purposes. They have recently gained recognition as an effective treatment for medical conditions in humans; and, as such, awareness is increasing among veterinarians and pet owners. However, side effects, pharmacokinetics, and efficacy in dogs are not known. The purpose of this study was to determine the tolerability of cannabidiol (CBD) by healthy dogs. We hypothesized that CBD would be tolerated in a healthy population of dogs. A group of 30 healthy Beagle dogs were randomly assigned to receive CBD in the form of microencapsulated oil beads (capsule), CBD-infused oil, or CBD-infused transdermal cream at a dose of 10 mg/kg/day or 20 mg/kg/day for 6 weeks. Complete blood counts, chemistry

panels, urinalysis, and bile acids were performed at 0, 2, 4, and 6 weeks. Elevations in serum ALP occurred in some dogs. All of the dogs in the study experienced diarrhea that was not associated with the formulation or dose of CBD that they received. CBD appeared to be well tolerated in dogs. However, a more extensive safety study is necessary to determine if there are long-term effects of CBD on the liver and an association with diarrhea.

## Introduction

Cannabis has been used as a medicinal remedy for centuries for the treatment of numerous ailments, including cancer, nausea, irritable bowel syndrome, epilepsy, amyotrophic lateral sclerosis, Parkinson's disease, dementia, glaucoma,

anxiety, depression, and sleep disorders (1–5). However, there is a paucity of published scientific reports on the safety, pharmacokinetics, or efficacy of cannabis use in human and veterinary medicine (1, 2, 6–8).

*Cannabis sativa* is a strain of cannabis plant that contains over 104 different cannabinoids including the most familiar delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (1, 2). THC is the primary psychoactive cannabinoid that is responsible for the “high” experienced with cannabis use. There is evidence that certain doses of oral THC in dogs are associated with adverse effects, (2, 9, 10). Hemp is a cannabis plant that contains less than 0.3 percent THC on a dry-weight basis but is abundant in the non-psychoactive compound CBD (1, 2). The potential medicinal value of CBD makes hemp a promising remedy for use in veterinary medicine (11–14).

To the authors’ knowledge, there are no published studies evaluating the safety and side effects of CBD in dogs. This study aimed to determine how healthy canine patients would tolerate CBD at higher doses than would be anticipated for clinical use. Since there is no established canine dosage, doses for this study were extrapolated from those reported in human clinical studies. The majority of human studies used dosages between 2–5 mg/kg per day, but some reported using up to 600 mg per day (15, 16). In this study, the dogs were administered 10 or 20 mg/kg/day.

The purpose of this study was to record any short-term effects of CBD in healthy dogs. The hypothesis was that no clinically relevant adverse events would occur; but if there were any subclinical effects, they would occur in a dose dependent manner.

## Materials and Methods

This study was approved by Colorado State University’s Institutional Animal Care and Use Committee (protocol ID: 15-5782A; approval date: February 19, 2016). A group of 31 healthy intact male research Beagle dogs were evaluated for the study. All dogs were 4–5 years old and weighed an average of 13 kg (range 9.5–16.2 kg). The dogs had physical examinations by either a board-certified neurologist or a neurology resident, and laboratory tests, including CBCs, chemistry panels, urinalyses, and pre- and postprandial bile acid assays. Conditions for exclusion from the study included comorbidity with a poor prognosis, significant abnormalities

on blood work, or current treatment with medication. Of the 31 dogs assessed, 30 met the inclusion criteria and were enrolled in the study, and 1 dog was excluded because of blood work abnormalities.

All of the dogs enrolled in the study were transported to an on-site research facility. They were either housed in a single run or shared a run with 1 other dog. The dogs were fed a maintenance diet once daily, had their runs cleaned twice daily, received CBD treatments twice daily, had a general health assessment twice daily, and had interactions with the staff for socialization and exercise once daily. All dogs received a complete physical examination by a veterinarian weekly.

The CBD for this study was formulated from hemp plants certified by a third-party company in the state of Colorado. A random number generator was used to assign each dog to 1 of 3 CBD delivery methods: Group 1 had CBD-infused transdermal cream applied to the pinnae, Group 2 received oral CBD-microencapsulated oil beads (capsule), and Group 3 received oral CBD-infused oil. Each of these groups were split into 2 subgroups of 5 dogs each. “Subgroup a” received 10 mg/kg/day of CBD, and “subgroup b” received 20 mg/kg/day of CBD. For the 6 weeks of the study, the dogs received CBD twice daily following a small meal.

At weeks 2, 4, and 6, CBCs, chemistry panels, pre- and postprandial bile acid assays, and urinalyses were run on samples collected from each dog. The results from the pre- and postprandial bile acid tests were used to determine if the effect of CBD on cytochrome P450 activity in dogs was similar to that in humans. In humans, phytocannabinoids are extensively metabolized by hepatic cytochrome P450 enzymes; but CBD is also a potent inhibitor of cytochrome P450 enzymes (16).

## Statistical analysis

Clinically significant results were recorded as binary data indicating the presence or absence of the clinical outcome. Contingency tables were constructed for each of the analyses; and the Fisher’s exact test was used to evaluate the significance of association between the formulations at each time point, and between the time points within each formulation for both doses of CBD. A *P* value of 0.05 was used to determine statistical significance. No statistics could be performed when all the subjects were in 1 group. SAS v 9.4 software (SAS Institute Inc.) was used to analyze the data.

## Results

The actual concentration of CBD in the cream, capsules, and oils was determined and compared to the concentration stated on the labels (see Table 1). All 3 formulations contained less CBD than indicated on the label. The variability was <10% for the CBD-infused transdermal cream and CBD-infused oil (6% for the CBD-infused transdermal cream, 9% for the 150 mg/mL CBD-infused oil, and 3% for the 75 mg/mL CBD-infused oil). However, there was considerable variation between the CBD concentration in the capsules and the amount stated on the label (28% for the 50 mg/capsule and 31% for the 25 mg/capsule).

Throughout the 6-week study period, gastrointestinal upset was the most frequently recorded adverse clinical sign. All of the dogs in the study developed diarrhea, and 6/30 (20%) dogs had single episodes of vomiting. The dogs that vomited were in the groups that received CBD orally in the form of capsules or oil, but it was determined that there was no correlation between the episodes of vomiting and the dose or formulation of CBD. The episodes of diarrhea were suspected to be secondary to the CBD treatments, but dietary variation, including treats, and stress from being housed in a new facility could not be ruled out as contributing factors. At the onset of diarrhea, metronidazole therapy was initiated under the direction of the laboratory animal veterinarians and with approval of the authors. All dogs responded well to treatment with metronidazole. Each dog's weight was evaluated weekly and remained stable for the duration of the study.

Erythematous pinnae was the second most common adverse clinical sign reported at week 2 and 4. A mild erythematous

reaction of the pinnae occurred in 11 dogs (36%), 9 of whom belonged to the group that received the transdermal cream; 4 of those received the 10kg/day dose and 5 of those received the 20 mg/kg/day dose. From the groups receiving the transdermal formulation, all but 1 of the dogs developed erythematous pinnae. At week 2 and week 4, it was noted that 1 dog from each group that received 10mg/kg/day of CBD orally had also developed erythematous pinnae.

Other abnormal clinical signs included ocular discharge in 10/30 dogs (33%), nasal discharge in 10/30 dogs (33%), salivary staining of the feet or ventral abdomen in 5/30 (17%), intermittent, spontaneously prolapsed glands of the nictitans in 2/30 dogs (6%), transient elevated body temperature (104.2°F) in 1/30 dogs (33%), and mild, weight-bearing lameness in 5/30 (17%) dogs. Other observations included salivation during administration of the CBD-infused oil formulations at both concentrations. The above findings were not necessarily attributed to CBD administration.

There were no clinically significant abnormalities detected on CBCs or fasting and postprandial bile acid tests for any of the dogs during the 6-week study period.

At some time during the 6 weeks, 15 dogs (50%) had transient episodes of either isosthenuria (USG <1.020), hyposthenuria (USG <1.008), and/or proteinuria (either ≥ 1+ protein with USG <1.020 or ≥ 2+ protein with USG ≥1.020). Other urinalysis parameters were considered unremarkable. There were no correlations between the urinalysis results and CBD dose, formulation, or time in the study.

The only clinically significant bloodwork abnormality detected during the 6-week study was elevation of alkaline phosphatase enzyme (ALP) activity in 11 dogs (36%). A significant elevation was defined as equal to or more than a 2-fold increase from the high end of the Colorado State University (CSU) laboratory reference range (140 IU/L). A few dogs (3/30, 10%) had clinically significant elevations in ALP after only 2 weeks of receiving 1 of the oral CBD formulations. At 4 and 6 weeks, significant increases in ALP values were detected in 1 dog that received 10 mg/kg/day of CBD

**Table 1. Calculated cannabinoid concentration of the products (transdermal cream, capsule, and oil) used in the study.**

Calculated Concentration					
CBD Dosing Formulation	Cannabidiol (CBD)	Trans-Δ9-tetrahydrocannabinol (THC)	Cannabinol (CBN)	Cannabigerol (CBG)	Cannabichromene (CBC)
100 mg/mL CBD Cream	103.0	8.12	Below LLOQ	1.92	2.28
50 mg Capsule	36.0	0.25	0.99	0.83	Below LLOQ
25 mg Capsule	17.2	0.14	0.55	0.38	Below LLOQ
150 mg/mL CBD Oil	36.0	11.6	Below LLOQ	3.11	3.48
75 mg/mL CBD Oil	77.6	4.99	Below LLOQ	1.50	1.77

from microencapsulated oil beads and CBD-infused oil, and in all but 1 of the dogs that received 20 mg/kg/day of CBD from microencapsulated oil beads and CBD-infused oil. At weeks 4 and 6, significant differences were apparent between the ALP values of the dogs given microencapsulated oil beads and CBD-infused oil formulations at 20 mg/kg/day. No animals receiving the CBD-infused transdermal cream formulation had elevations in ALP activity. (Figure 1).

## Discussion

This study is the first to assess the safety of transdermal and oral CBD use in healthy dogs. Overall, the product was well tolerated clinically. However, clinically significant adverse effects, particularly diarrhea and elevations in serum ALP levels, are noteworthy and warrant further discussion and research.

All dogs experienced mild diarrhea during the study. The overall incidence of diarrhea increased over the duration of the study, but no correlation was made between diarrhea and the formulation or dose of CBD received by the dogs. Although the diarrhea improved in most dogs once restricted diets and treatment with metronidazole were initiated, some dogs had persistent soft, formed stool. Factors that might have contributed to the prevalence of diarrhea include stress related to relocating the dogs to new housing, sharing enclosures, and diet.

Even though all the dogs were transitioned to a consistent adult maintenance dog food, they did receive various treats during socialization, enrichment, and other daily activities.

Mild diarrhea has been reported as an uncommon adverse event in 6-19% of human patients treated with CBD, but cannabis has still been used extensively for the management of inflammatory bowel disease (15, 19, 20)

A mild erythematous reaction of the pinnae occurred in 11 dogs (36%). The incidence of erythematous pinnae was greater for the dogs treated with CBD-infused transdermal cream than for those receiving the microencapsulated oil beads and CBD-infused oil formulations. For most of the dogs, this adverse reaction appeared a week after starting the application of the cream. Possible explanations for this reaction may be related to the carrier, the quantity applied, and the contact time prior to absorption.

Serum ALP values that were double the normal reference range accepted by CSU (140 IU/L) were considered to be clinically significant. The dogs that received the microencapsulated oil beads and CBD-infused oil had dose-dependent elevations of serum ALP apparent at 4 and 6 weeks. There was no evidence of short-term hepatotoxicity since fasting and postprandial bile acids remained normal for all the dogs throughout the study. However, the potential for long-term liver toxicity was not evaluated in this study. The observation of ALP elevations warrants serial monitoring of liver enzymes

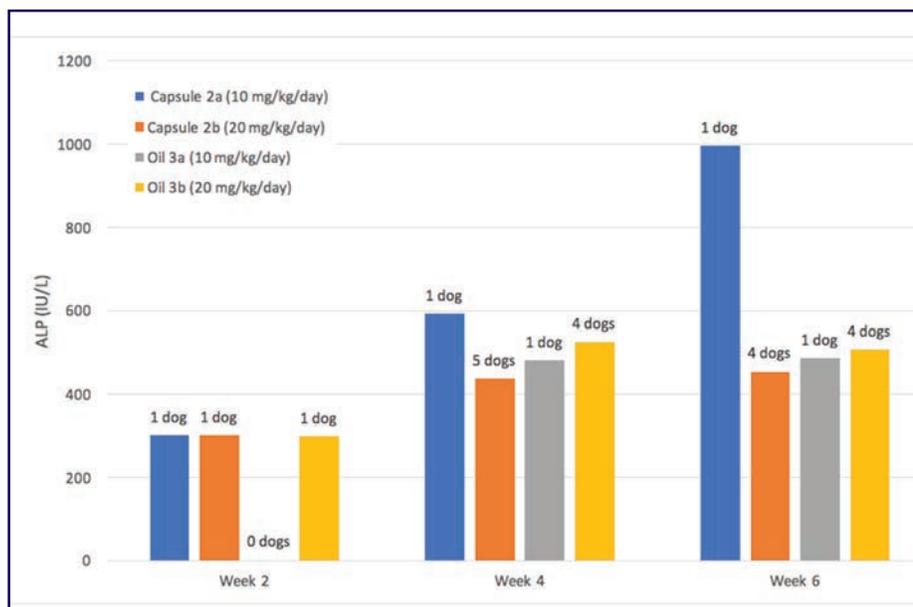


Figure 1. Number of dogs with clinically significant alkaline phosphatase (ALP) elevations during the study period.

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and bile acids for patients being treated with CBD. Subsequent studies need to consider potential drug interactions that may occur if CBD is used clinically (17, 18).

The dogs that received the capsular form of CBD had diarrhea and developed increased levels of serum ALP. It should be noted that the calculated CBD concentration in the capsules was substantially less than the reported concentration. A variance of 10% is generally considered acceptable. The 50 mg/capsules were deficient in CBD by 28%, and the 25 mg/capsule were deficient in CBD by 31%. If the concentration, and thus, the dose, had been more accurate, this might have affected, and perhaps increased, the severity of the adverse effects.

Limitations of this study include the lack of a control group and the short duration of the study period. Each dog served as its own control since all dogs were deemed healthy at the onset of the study period, but an actual control group would have helped to confirm if adverse effects were secondary to CBD versus other causes, especially with regard to the diarrhea. A lengthier study could help us understand the effects of CBD

on the canine liver and help to reveal the underlying cause of the diarrhea.

## Conclusion

Numerous potential therapeutic uses of CBD have surfaced over the last decade. An extensive safety study utilizing clinically-applicable doses is necessary to evaluate the long-term effects of CBD on the canine liver and gastrointestinal function. The results presented in this study, along with the numerous potential applications for CBD use in human medicine, has helped set the stage for veterinary clinical trials. Prospective, randomized, double-blind studies are required to investigate the effectiveness of CBD for the treatment of specific diseases and to establish doses that provide therapeutic effects.

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