THE SCIENCE BEHIND CANNABIS

Stephanie McGrath, DVM, MS, DACVIM (Neurology)

Introduction

Cannabis-based therapies have been used for centuries for various medicinal purposes. They have recently gained publicity as an effective medication for use in human medicine and, as such, awareness is increasing among veterinarians and pet owners. However, side effects, pharmacokinetics and efficacy in dogs is not known. At Colorado State University, we have successfully performed a safety and pharmacokinetic study to assess the measurability and tolerability of cannabidiol (CBD) in healthy dogs. The results of this study showed that cannabidiol seemed to be well tolerated in dogs and exposure was dose-proportional. These results provided a framework for our clinical trials in both canine osteoarthritis and canine epilepsy. The objective of our clinical trials was to compare cannabidiol with a placebo for the treatment of naturally-occurring canine osteoarthritis and epilepsy. Both studies were double blinded, placebo-controlled, randomized clinical trials using client-owned dogs with naturally occurring disease. Osteoarthritis and epilepsy are devastating to our veterinary patients and neither has an ideal treatment to date. If these current and future studies can demonstrate that dogs attain sufficient blood exposure with oral dosing and that CBD is an efficacious drug, it has the potential to improve the quality of life of this population of dogs, as well as decrease the rate of euthanasia. These talks will address past studies in veterinary medicine, ongoing studies, future directives, and practical tips for veterinarians.

Endocannabinoid System

Despite *Cannabis sativa's* long history, the endocannabinoid system (ECS) was not discovered until the 1990's. The ECS is found in almost all animals and is composed of three parts – endogenous ligands, membrane receptors, and regulatory enzymes.[1] The two most well-known receptors are CB1, primarily located in the central nervous system and CB2, predominantly associated with the immune system. Two endocannabinoids, anandamide and 2-arachidonoyl glycerol, have been well-studied and known to interact with CB1 and/or CB2 receptors, causing the release of neurotransmitters. Common regulatory enzymes include, fatty acid amide hydrolase, monoacyglcerol lipase, and cyclooxygenase-2, which are responsible for breaking down the endocannabinoids after they are released. Of the two principal phytocannabinoids, Δ^9-tetrahydrocannabinol (THC) and CBD, only THC has been shown to bind orthosterically to CB1 and CB2. Alternatively, CBD antagonizes the actions of CB1 and CB2 agonists. To date, it appears that CBD's primary actions, among others, include a non-competitive negative allosteric modulator of CB1 and CB2 receptors, an agonist of TRPV1 receptors, an inhibitor of the uptake of anandamide, a facilitator of the neurotransmission mediated by the serotonin receptor 5-HT_{1A}, and an antagonist of the G-protein-coupled receptor GPR55 and inverse agonist of GPR3, GPR6, and GPR12.[2] Through these and other mechanisms, CBD appears to exhibit beneficial properties, including hypokinetic, anticonvulsant, anti-inflammatory, anti-neoplastic, neuroprotective, and analgesic effects.

Pharmacokinetic and Safety Studies

At CSU, our research team analyzed the pharmacokinetics of orally and transdermally administered CBD in healthy dogs.[3] Thirty dogs were enrolled in the study and randomly assigned to one of six groups (n=5). Each group received a single "low" (5 mg/kg) or "high" (10 mg/kg) dose of CBD by one of three different delivery systems: oral CBD-infused oil, oral CBD capsules, or CBD-infused transdermal cream applied to the pinnae.

The study results showed that plasma CBD concentrations were measurable after a single CBD dose. It further demonstrated that at both the "low" and "high" dose of CBD, the CBD-infused oil formulation offered the highest maximal concentration (C_{max}), the longest half-life ($T_{1/2}$), the least amount of inter-individual variability, and the greatest systemic exposure (area under the curve; AUC).

For our second study focusing on the adverse effects of cannabidiol administration, 30 healthy dogs were randomly assigned to receive one of three formulations at either the "low" or "high" dose of CBD twice daily for a six-week period.[4] Every two weeks, routine bloodwork and CBD plasma levels were measured. During the study period, all dogs experienced diarrhea; the onset, severity, and duration did not correlate with the dose or formulation. No other adverse effects related to CBD were observed. The only laboratory change was an elevation in alkaline phosphatase (ALP), which occurred only in the dogs receiving the two oral formulations of CBD. Bile acids were monitored

every two weeks and no changes were noted, suggesting the liver continued to function normally. The CBD plasma levels showed similar results to the PK study, with the oil being the superior formulation of the three tested.

From these preliminary studies, we demonstrated that CBD is absorbed orally and is fairly well tolerated. However, clinical trials are required to investigate its long-term safety profile, to study its effectiveness in the treatment of specific diseases, and to establish doses that provide therapeutic effects.

Clinical Trials

The only published canine CBD epilepsy clinical trial assessed the short-term effect of CBD on seizure frequency in poorly controlled epileptic client-owned dogs.[5] Sixteen dogs successfully completed the study, nine in the treatment group and seven in the control group. The results of the study showed a significant reduction in seizure frequency for the dogs in the treatment group (89% of dogs had a reduction in seizure activity, compared to 43% in the control group). However, there was not a significant number of "responders," defined as dogs that experience at least a 50% reduction in seizure activity, with only 2 responders in each group.

The only adverse effect that was noted was an elevation in the ALP in 89% of the dogs in the treatment group. Unfortunately, bile acid tests were not performed during this study; however no clinical signs of liver dysfunction were observed.

The results of this pilot study demonstrated that although there was a significant reduction in seizure activity for the dogs receiving CBD, the number of "responders" was not significant. Therefore, it was determined that additional studies were necessary to determine whether CBD could be effective in treating canine idiopathic epilepsy.

A larger prospective, double-blinded, placebo-controlled canine epilepsy study is currently underway at CSU. The goal of this study is to enroll 60 client-owned dogs with uncontrolled idiopathic epilepsy. This study is a crossover study, in which each dog receives either placebo or CBD for 12 weeks, undergoes a four-week washout period, and then receives the opposite medication for 12 weeks. Since the study is currently underway, the results are not yet available.

Additionally, an osteoarthritis study was completed at CSU, but the results are not yet available. Twenty-four client-owned dogs suffering from chronic pain associated with osteoarthritis completed this study. It was designed as a prospective, double-blinded, placebo-controlled, crossover study in which each dog received placebo or CBD for six weeks and then the opposite medication for six weeks. The primary outcome parameters were objective gait analysis, owner assessment questionnaires, and accelerometry. The study is currently under peer review. A published randomized crossover osteoarthritis study administered 2 mg/kg of CBD oil orally or a placebo to 22 dogs for four weeks with a two-week washout period between treatments.[6] The investigators used veterinary and owner assessments as their outcome measures and concluded that CBD can help increase the comfort and activity in this subset of dogs.

Cautionary Tips

Although CBD is an enticing and perhaps promising drug, veterinarians and pet owners must be warned that right now the market is completely unregulated. Without the proper oversight, the products on the shelves and online are not always trustworthy. Unfortunately, many of the claims, including ingredients, are not accurate.[7] When looking to purchase or research specific CBD products, veterinarians and pet owners can ask for a certificate of analysis, ensure the product is produced from a hemp plant (<0.3% THC), and look for companies that support the scientific research.

References

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