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# Pharmacokinetics, efficacy, and safety of cannabidiol in dogs: an update of current knowledge

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In the last 5 years, interest has grown in using phytocannabinoids, particularly cannabidiol (CBD), in veterinary medicine to treat several pathologies, including pain, epilepsy, anxiety, nausea, anorexia, skin lesions, and even some types of cancer, among others. Indeed, due to a positive perception of CBD use, many pet owners are increasingly requesting this option to relieve their pets, and many veterinarians are exploring this possibility for their patients. Besides the widespread empiric use of CBD in pets, the research is trying to obtain proof of its efficacy and lack of adverse effects and to know its pharmacokinetics to define an appropriate posology. This review summarizes all data published so far about the canine pharmacokinetics, efficacy, and tolerability of CBD and cannabidiolic acid (CBDA). Despite a certain number of available pharmacokinetic studies, the kinetic profile of CBD has yet to be fully known, probably because of the very different experimental conditions. In terms of efficacy, most studies have tested CBD' ability to relieve osteoarthritic pain. In contrast, few studies have evaluated its role in epilepsy, behavioral disorders, and skin lesions. From obtained results, some evidence exists supporting the beneficial role of CBD. Nevertheless, the limited number of published studies and the occurrence of bias in almost all require caution in interpreting findings. From tolerability studies, CBD' side effects can be classified as mild or unremarkable. However, studies were prevalently focused on short- to medium-term treatment, while CBD is usually employed for long-term treatment. Further studies are warranted to define better whether CBD could be a valid adjunct in canine treatment.

KEYWORDS

**phytocannabinoids, cannabidiol, CBD, dog, pharmacokinetics, efficacy, tolerability**

## 1. Introduction

In the last 30 years, research has made considerable strides in studying and understanding the endocannabinoid system (ECS) and its bodily functions.

The ECS can be synthetically defined as the set of cannabinoid receptors [such as Type 1 cannabinoid receptor (CB1), Type 2 cannabinoid receptor (CB2), G protein-coupled receptor 55 and 119 (GPR55, GPR119), transient receptor potential vanilloid (TRPV) and peroxisome proliferator-activated receptor (PPAR)], endocannabinoids [compounds produced by the body that bind to cannabinoid receptors, such as anandamide (AEA) and 2-Arachidonoylglycerol (2-AG)], enzymes responsible for their synthesis and their catabolism and genes that code for these proteins. The term "endocannabinoidome" has recently been coined for this set (1). This system is of great importance for the organism's normal functioning as it underlies numerous

homeostatic functions, exerting an antioxidant, hypotensive, immunosuppressive, anti-inflammatory and pain-relieving action. Furthermore, the distribution of cannabinoid receptors in the brain also suggests a physiological role for endocannabinoids in the control of movement and perception, regulation of sleep and appetite, inhibition of learning and memory processes, regulation of emotional states (such as pleasure and aggression), neuroprotection, as well as in enhancing the action of opioids. Various observations also suggest a role of the ECS in the control of vasomotor functions and fertility, as well as of tumor cell proliferation (2).

The discovery of a pre-established endogenous cannabinoid system has led researchers to hypothesize that the active ingredients, mainly phytocannabinoids, contained in *Cannabis sativa* (both medical and industrial cultivar – this last also known as hemp), could interact with this system, producing both the therapeutic and psychotropic effects of the plant.

Cannabidiol (CBD) is an abundant non-psychoactive phytocannabinoid which has affinity on a series of receptors, including CB1, CB2, GPR55, GPR119, TRPV and PPAR. By modulating the activities of these receptors, CBD exhibits multiple therapeutic effects, including neuroprotective, antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic and anticancer properties (3).

In veterinary medicine, the use of *Cannabis* derivatives as a therapeutic approach started to be considered a few years ago. The first studies were devoted to establishing the presence of the ECS in animal species. With specific regard to the canine species, the presence of cannabinoid receptors or their ligands has been identified in skin and skin appendages of healthy dogs and dogs with atopic dermatitis (AD) (4–8), gastrointestinal tract (9, 10), peripheral and central nervous system (11–13), joints (14) and embryo (15).

Among the possible use of *Cannabis* in animals, several areas of interest have been considered, such as pain management (acute and chronic pain) (16), neurological conditions (seizures, neuroinflammation, degenerative diseases, brain tumors) (17), well-being (anxiety disorders) (18), gastrointestinal health (appetite modulation, nausea and vomiting, visceral pain/hypersensitivity, esophageal reflux, diarrhea/peristalsis) (19), dermatologic diseases (skin inflammation, wound healings, skin allergies, pruritus) (20), oncology and immune response (21).

Due to increased knowledge regarding the potential therapeutic role of *Cannabis* derivatives, especially cannabidiol (CBD), in veterinary medicine, and the recent legalization of cannabinoids in some states, more veterinarians and pet owners are exploring options for providing cannabinoid products for their patients/pets. Pet owners' and veterinarians' perceptions of CBD use are generally positive, although many veterinarians do not feel knowledgeable enough about the therapeutic and toxic effects of cannabinoid products (22, 23).

This review aims to summarize all data published so far about the pharmacokinetics, efficacy, and tolerability of *Cannabis* derivatives, specifically CBD and cannabidiolic acid (CBDA), in the canine species.

## 2. Pharmacokinetics of CBD

Cannabidiol is a high lipophilic molecule. In veterinary practice, it is generally administered orally (24). In the last few years, several pharmacokinetic studies on CBD were conducted in dogs (25–35). However, its kinetic behavior has yet to be fully elucidated.

The gastrointestinal absorption of CBD seems very low. Indeed, the only study where oral bioavailability was evaluated, it resulted lesser than 19% (36); however, it is essential to underline that the tested oral form was a capsule containing CBD as raw material. This low bioavailability, associated with a large individual variability observed in almost all conducted studies, is a challenge in identifying an appropriate dosing regimen.

Some studies have investigated the influence of CBD pharmaceutical formulation on its oral absorption in dogs; microencapsulated CBD oil beads resulted in a lower Cmax and AUC when compared with CBD-infused oil (26). Soft gel capsules containing CBD-rich hemp extract showed a significant increase in mean Cmax value, but not in that of AUC, compared to the administration of the same extract in sesame oil (33). A similar result was obtained by Wakshlag et al. (2020) comparing soft chews containing a CBD/CBDA predominant extract with the same extract diluted in an oil consisting of 75% of organic sesame oil and 25% of sunflower lecithin, while no significant difference was observed when the soft chews were compared to the extract solubilized in an oil mixture of 75:25 of organic sesame and medium-chain triglycerides (MCT) (34).

The presence of an eventual "food effect" was also hypothesized as a factor conditioning the absorption of CBD: indeed, as a lipophilic substance, CBD is thought to be more absorbable if administered with a fat meal, but in the only study that directly compared the kinetics of CBD orally administered to fed and fasted dogs, the results were not entirely conclusive. Indeed, even if the Cmax observed in fed condition was significantly higher than in fasted condition, no significant difference was observed in AUC values (30). However, in this study only 3 dogs/group were tested, and in the two groups, respectively, treated with 5 and 20 mg/kg, a greater Cmax and AUC were obtained in one fasted dog.

Cannabidiol is subject to a sizeable hepatic metabolism, witnessed by the identification of several metabolites in canine urine (37). Thus, to avoid or at least reduce the first-pass metabolism and increase its plasma concentrations, some alternative routes of CBD administration were tested, albeit without satisfactory results. In fact, following rectal administration of a suppository containing 100 mg of CBD, corresponding to a dose between 6.9–13.7 mg/kg to six dogs, the plasma concentration resulted below the lower limit of quantification (31). After application of CBD-infused transdermal cream at the dose of ~5 and ~ 10 mg/kg to dogs' pinnae, Cmax and AUCs resulted smaller than those obtained with the oral administration of CBD-infused oil and microencapsulated CBD oil beads formulations at the same doses (26). Again, intranasal (IN) administration of a formulation containing pure synthetic CBD did not show any significant difference with the oral administration of pure CBD in MCT oil when normalized for the dose, except for Tmax, which was significantly shorter following IN treatment (0.49 vs. 3.50 h for IN and oral administration, respectively) (31). Finally, oral trans-mucosal (OTM) administration was also tested, resulting in a mean plasma CBD concentrations vs. time trend almost superimposable to the oral administration (29). The possibility that salivation and subsequent swallowing could have affected the drug's transmucosal absorption cannot be ruled out (38).

In humans, two main products of CBD biotransformation were identified: a hydroxy- and a carboxy-derivate (7-OH-CBD and 7-COOH-CBD, respectively), and their eventual presence in canine

plasma following oral administration of CBD was thus investigated (27, 34, 35). Following oral administration of soft chews containing CBD/CBDA-predominant extract or the same extract in oil (dose: 1 mg/kg), the observed levels of 7-COOH-CBD was 1–2% of that observed in humans treated with a comparable dose. In the same study, the 7-OH-CBD was not detected (34). This last was observed following oral administration of CBD-purified *Cannabis* extract diluted in MCT oil, but, in any case, the carboxy-metabolite resulted produced in a greater quantity (35). The 7-OH-CBD was detected albeit intermittently in the dog's plasma even after oral treatment with a *Cannabis* herbal extract. In the same study, the 6-OH-CBD was identified up to 48 h following oral administration of CBD at 10 mg/kg (27). The more outstanding production of this latter metabolite compared to the 7-OH-CBD underlines the species/specific difference between dogs and humans in the CBD metabolism (27).

Table 1 resumes the data obtained from the pharmacokinetic studies published so far. The CBD pharmacokinetic parameters, such as terminal half-life, AUC and MRT, are sometimes quite different in average values following oral administration of oily solutions, even when normalized for the given dose. These differences can be attributable to a too small sample size, different experimental sampling times applied in the various studies and a large individual variability (i.e., breed, age and sex differences). Indeed, age may cause physiological and anatomical changes that can modify the drug pharmacokinetics due to a different water/adipose ratio of the body and a possible reduction in renal and hepatic function (39). Similarly, sex was observed to affect metabolism of some drugs (40). Also, the type of CBD used (pure or co-extracted with other phytocannabinoids) can have influenced the pharmacokinetic results. Relatively to this last issue, higher Cmax and AUC values and a shorter half-life were observed in mice when CBD was orally administered as a pure molecule compared to a full-spectrum extract (41). Likewise, della Rocca et al. (2023), comparing the mean value of the terminal half-life of pure CBD orally administered in dogs with that obtained in studies in which equal concentrations of CBD and CBDA were used, hypothesized that the absence of CBDA in their formulation may have played a role for the shorter half-life observed (29).

# 3. Clinical efficacy of CBD

## 3.1. Pain

The empiric use of *Cannabis* as an analgesic goes back more than 1,500 years. The discovery of cannabinoid receptors, the identification of endocannabinoids and their biosynthetic and degradation pathways, and the understanding of signal transduction mechanisms paved the road for scientific research in this area. It was soon recognized that one of the main physiological roles of the endocannabinoid system (ECS) is the modulation of pain (42).

An essential basis for concluding that endocannabinoids modulate pain was provided by preclinical studies, which demonstrated the presence of endocannabinoid receptors, endogenous cannabinoids and enzymatic machinery for endocannabinoid biosynthesis and degradation in peripheral and central structures devoted to pain modulation, and their antinociceptive and antihyperalgesic effects in models of transient (physiological) and inflammatory and neuropathic pain, respectively (42–47).

Endogenous cannabinoids produce antinociceptive and antihyperalgesic effects at peripheral, spinal and supraspinal levels (48). Peripherally, endocannabinoids inhibit primary afferent fibers depolarization and modulate mast cells degranulation by interacting with CB1 and CB2 receptors and other receptor types, such as TRPV1, GPR55, GPR119, and PPAR-α. These interactions lead to a decreased firing of the nociceptive fibers and a reduced release of pro-inflammatory and pro-pain mediators, followed by a reduction of the inflammatory and pain response (44, 48–50). In the spinal cord, experimental data suggest that cannabinoids increase the nociceptive threshold and reduce the wide dynamic range neurons' firing by interacting with spinal CB1 receptors. Furthermore, it appears that cannabinoids may modulate the activity of the noradrenergic and opioid spinal systems (44, 46, 48, 49). At the supraspinal level, cannabinoids could act through the activation of the descending inhibitory control and consequent modulation of the spinal cord neurons' activity. This action is probably mediated by CB1 receptors localized in several areas involved in pain control, such as periaqueductal grey matter, rostroventromedial medulla, some areas of the thalamus and amygdala, and A5 noradrenergic nucleus (44, 48, 49). It has also been hypothesized that the ECS exerts a tonic activity able to modulate the nociceptive threshold in basal conditions and hyperalgesia and that cannabinoids and opioids can mutually potentiate each other (44).

Studies conducted in animal models have paid particular attention to verifying the role of the ECS in neuropathic, cancer and osteoarthritic (OA) pain: in all cases, the "endocannabinoid machine" is present and able to modulate the excitability of nociceptors and spinal neurons (51–53).

Several preclinical studies have investigated phytocannabinoids' efficacy in animal OA pain models. Overall, data indicate that the activation of the ECS by exogenous cannabinoids proves effective in limiting joint pain both centrally and peripherally (53).

As regards the clinical efficacy of CBD in the treatment of OA pain in dogs, six scientific studies have been published so far (four of them being randomized, double-blind, placebo-controlled clinical trials, and the remaining two being a case report and a non-blinded observational study, respectively), whose study design, treatments and results are summarized in Table 2. Five studies (24, 25, 54–56) indicated that CBD significantly reduced pain and increased the activity of dogs, thus improving their quality of life. Indeed, Gamble et al. (2018) revealed a significant decrease in pain scores, as measured by the Canine Brief Pain Inventory (CBPI), and an increase in activity, as measured by the Hudson activity scale, at week 2 and 4 during CBD treatment (2 mg/kg twice daily for 4 weeks) when compared to baseline (week 0) (25). In 2019, De Álava (Cited by Coelho, 2021) described a case report of a dog with chronic osteoarthritis that was treated with CBD (1 mg/kg twice daily for 30 days): the treatment showed analgesic effect with consequent improvement of mobility and quality of life of the dog (24). Kogan et al. (2020) assessed the impact of CBD (0.3–4.12 mg/kg twice daily for 90 days) in association with the previous multimodal analgesic therapy (acupuncture, laser, nutraceuticals, polysulfated glycosaminoglycan, and/or gabapentin), and found that 30 out of 32 dogs showed pain relief and 21 out of 23 dogs could reduce or discontinue the administration of gabapentin (54). Verrico and co-workers (2020) evaluated the effect of two different CBD formulations (naked 20 and 50 mg/day, and liposomal 20 mg/day, for 4 weeks): owner assessment of animal pain by means of