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The Effects of Cannabidiol on Canine Epilepsy and Arthritis – a Case Study

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RESEARCH ARTICLE

Abstract
Cannabidiol oil (CBD) has gained notoriety in recent years due to its effectiveness as an adjuvant therapy in many pathologies.The purpose of this study is to evaluate the effects of CBD in the management of pain and the associated pathologies of epilepsy and arthritis, on a single subject, a female Labrador, 12.5 years old at the beginning of the study. The therapeutic protocol used was the administration of CBD oil, sublingually, in doses of 2.25 mg/kg/day. Hematology and biochemistry were performed at 3, 6 and 12 months. Radiology was performed before the study began and after 6 months.After the first month, a decrease in the number and severity of epilepsy crises was observed. Beginning with the first 2 weeks of CBD oil administration, the patient was already experiencing an improvement in her mobility along with general pain remittance and the amelioration of her 3rd degree lameness, quantified by the Colorado Pain Scale. After 5 months of CBD administration, with no seizures recorded, phenytoin therapy was ceased. After 8 months, phenobarbital was also excluded from the therapeutic protocol, thus making CBD an independent the rapeutic molecule. CBD appears to be a useful molecule in managing both pain and epilepsy.

Keywords: arthritis; canine; cannaidiol; epilepsy; pain management.

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INTRODUCTION

The first written pages about the anti-convulsive effects of *the Cannabis sativa* appeared in the early 1970s (Hollister, 1973). Studies have focused in particular on the effects of Δ9-THC, even if the mechanism of action was not fully known. However, to date, cannabidiol (CBD) is considered the major anti-convulsive agent. As of June 2018, the U.S. Food and Drug Administration has approved the use of the CBD drug to treat two rare and highly drug-resistant epileptic syndromes: Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) (Morano, et al. 2020). Later, the same was approved by the European Medical Agency. Recently, a review highlighted, through qualitative and meta-analyses, the effectiveness of CBD and cannabinoid derivatives in reducing the frequency and severity of seizures, also taking into account side effects (de Carvalho Reis et al., 2020). These studies demonstrated that CBD played a significant role in reducing the frequency and severity of seizures in patients with treatment-resistant epilepsy, while side effects were rare, and, more often than not, temporary. The most common side effects reported were: drowsiness, diarrhea, and fever. All of this was reversible, in the sense that the effects stopped when they stopped CBD therapy. In 2001, the first scientific evidence emerged that CBD binds and modulates receptors other than CB1Rs and CB2Rs, a discovery made by Bisogno et al. (2001). It appears that CBD binds TRPV1 (transient receptor potential vanilloid type 1), thus interacting with proteins involved in activating anadamide (an endogenous cannabinoid). These proteins seem to be involved in several neurodegenerative conditions (Cassano et al., 2020). They contribute to the

perception of heat, inflammatory reactions and the mediation of pain. CBD agonizes TRPV channels, especially the TRPV1 subtype, acts, dephosphorylates and produces a strong desensitization, which in turn produces a decrease in intracellular calcium and neuronal excitability (Boleti et al., 2022). Through this mechanism, analgesic and anti-convulsive effects are achieved (Cifelli et al., 2020). Based on the interaction between cannabinoids and calcium channel blockers, Sullivan (1999) concluded that inhibition of calcium channels is responsible for depression of synaptic transmission caused by cannabinoids. Cannabinoids also play a role in the treatment of both chronic and acute pain, both inflammatory and neuropathic in origin. Both CB1 and CB2 receptor agonists play a role in antinocioception, by either attenuating synaptic transmission or inhibiting pro-inflammatory factors, respectively (Manzanares et al., 2006). Bearing in mind, the aim of the paper is to evaluate the chronic effects of CBD oil in the treatment of pain and associated pathologies of epilepsy and osteoarthritis, on one clinical subject.

MATERIALS AND METHODS

Patient Information

Cara is a non-spayed female Labrador, 12.5 years of age at the start of the study, weighing 30 kg. Cara was diagnosed with epilepsy in 2009, aged 2, and has since been on a combined anti-epileptic therapy consisting of phenobarbital and phenytoin, dosed at 100 mg/animal/day. The frequency of the seizures prior to commencement of the CBD treatment was 3-4 seizures per month, sometimes more when she went into heat, even with the combined anti-epileptic treatment. With age, bone degradation also occurred, accompanied by lameness. Initially, the lameness was light, but over time it progressed to a third-degree lameness. At the age of 12.5 years old, the dog was also diagnosed with breast cancer. The owners chose to decline conventional treatment for the cancer, preferring more complementary alternatives due to the advancing age of the animal. The presence of all these combined pathologies, rendered the dog as the perfect candidate for CBD oil therapy.

General Clinical Exam

At the pre-administration clinical examination of the patient, the general condition of the patient was good, a lively attitude, pale-pink mucous membranes, normal temperature. The exam also revealed 3 tumors of the mammary gland, chronic otitis more severe unilaterally on the left side, lick dermatitis in the left anterior limb (granulomatous appearance) and grade III lameness.

Therapeutic Protocol

The dog received 2.25 mg/kg of a commercial, cold pressed CBD oil (Seva CBD SRL, Romania) once a day, in the evening. The product was administered sublingually, 10 minutes before her last meal of the day. This dose was chosen based on recomended doses in the literature (Potschka et al., 2022). A dose on the lower end of the scale was chosen so that the risk of side effects would be minimized and in order to be able to raise the dose if it was necessary. It was necessary, after 9 months of treatment and the onset of heat, to raise the dose to 4 mg/kg. A sublingual route of administration was chosen for a faster absorption rate.

Paraclinical Exams

The blood analyses were performed using the automatic analyzer Abacus Junior Vet 5 Diff. The analyses conducted before the administration of CBD, after 2 months, 6 months and 1 year.
Biochemical analysis was performed using the Touch UV-VIS Screen spectrophotometry analyzer (Diagnostics Hospitex, Firenze, Italy). The analyses of various parameters were performed before the administration of CBD, after 2 months, 6 months and 1 year.
The radiological examinations were performed in the Faculty of Veterinary Medicine, within USAMV Cluj-Napoca, using the Temco GRx device. X-rays were taken prior to starting CBD therapy as well as after 6 months.

Evaluation of Pain

With the help of an assessment scale of chronic pain felt in dogs, a concept developed by Colorado State University, we were able to evaluate the evolution of the dog's nociception and pain before CBD oil administration and once weekly over a period of more than a year and 5 months while maintaining the therapy. The categories scored are Psychological and Behavioral, Postural and Response to Palpation, with a possible score between 0-4 in each category. Median scores were calculated each time the test was performed (once/week).

RESULTS AND DISCUSSIONS

1-6 months of treatment

Epilepsy

During the first day of CBD administration, in the morning, a first epileptic seizure was recorded. The patient experienced a state of muscle tension, and in the end, muscle tremors. The duration of this epileptic seizure was about 15 minutes. Also on that day, in the evening, the patient started receiving 5 ml of CBD oil daily, equivalent to a concentration of 2.25 mg/kg body weight, in the evening. Previously, every morning, she was also given phenobarbital and phenytoin at a dose of 100 mg/animal, each. On the evening of the next day, another, slightly more severe epileptic seizure followed.

Two weeks later, after exactly 20 CBD oil administrations, Cara suffered a 3rd crisis. This was short-lived and much less severe compared to the previous ones.

After almost 5 months of taking CBD oil, due to the fact that epileptic seizures were no longer present, phenytoin was removed from the treatment protocol. The phenobarbital was continued daily at a dose of 100 mg/animal alongside the CBD oil at a dose of 2.25 mg/kg body weight.

For the remainder of the period leading up to the 6-month mark, the animal experienced no other epileptic seizures.

Pain

Five days before starting treatment with CBD oil, we evaluated the pain felt by the patient for the first time. Behaviorally and psychologically, she was always a cheerful and friendly dog, so throughout the study, she was ranked in this column at 0. Posturally, Cara started with a 2/3 score, because her standing position is abnormal due to the presence of the third-degree limp, her resting position being, however, comfortable. Cara's reaction to palpation of the joints was to turn her head towards the examiner's hand. When this behavior was noticed, a score of 1 was given. Initially, the average pain score was graded an average of 1.16. This average began to decline after just two weeks of CBD treatment, with an improvement in locomotor capacity that could be observed as the therapy continues (median pain score of 1).

Subsequently, after 4 weeks of administration, another decrease in the pain sensation was recorded, once again noticing a further improvement in the locomotor capacity (median pain score 0.83). The improvement of the severity of lameness clinically correlates with the resolution of degenerative processes at the bone level. The patient did not experience any further reaction to palpation of the affected joints during this period of time. The patient withstands longer walks, without noticing a decrease in locomotor capacity towards the end of the walks, being able even to run, despite the fact that she has gained weight.

6-12 months of treatment

Epilepsy

After 8 months of CBD oil administration and no further epileptic seizures recorded, phenobarbital was also removed from the therapeutic protocol as well. CBD was continued at a dose of 2.25 mg/kg body weight per day without any other anticonvulsant therapy. During the 9th month, there were 4 days when the patient did not receive CBD due to a logistics issue. Two days later, a short, mild epileptic seizure was recorded. Two weeks later, there was another epileptic crisis, very similar to the previous one in nature, and much milder than the ones observed at the beginning of the study.

Pain

In the period of 6 months to one year of CBD oil administration, the results of the pain scale remained similar to the previous period. The patient showed a very good general condition, good locomotor capacity, without response to palpation of the affected joints (median score of 0.5).

12-17 months of treatment

Epilepsy

15 months after the start of CBD oil, the patient suffered another epileptic seizure. However, this one was short-lived and easy. The owner noticed that at that time, the animal also went into heat, considering this the stimulus of the onset of the epileptic crisis.

Pain

Starting with a year and two weeks after the commencement of CBD treatment, an aggravation in the patient's posture, with an abnormal distribution of body weight and a slight decrease in locomotor capacity was observed. Also, discomfort could be observed in the resting position. As of 13 months, reactions to palpation of the affected joints by turning the head were noticed (median score of 1), and at 15 months, the dog presented a response by withdrawing the examined limb (median score of 1.33). She did not show a reaction to palpation of areas distant to the painful ones.

Hematology and Biochemistry

Hematological analysis was carried at different intervals of time. Throughout the study, at the examination of the white blood cell count, quantitative changes cannot be observed. Thus, we can say that the patient does not have a state of acute systemic inflammation. The erythrogram remains unchanged, the total number of erythrocytes and other parameters being within the physiological limits of the species. A slight thrombocytosis can be observed pre-administration of CBD that may be correlated with a vascular response or mild endothelial lesions, but was no longer seen at subsequent analyses.

Biochemical analyses (Table 1) show an increase in the enzyme Alkaline Phosphatase (ALP) in the analyses performed pre-CBD administration, at two months and at 6 months, with an improvement occurring at the analysis performed at 1 year; with the mention that, 3 months before the last analyses, phenobarbital was also eliminated from therapy. This increase can be due to both drug liver toxicity, since the hepatotoxicity of this compound is well known (Gupta, 2017), and muscle disorders associated with epileptiform seizures or the osteoarthrosis pathology. Furthermore, an increase in the specific muscle enzyme (creatine kinase) is observed prior to the commencement of CBD therapy and in the first 2 months of treatment., which can be correlated to the seizures that occurred in the first month of treatment.

Table 1. Biochemical analyses over the duration of 1 year

	Pre-admin of CBD	2 months of CBD	6 months of CBD	1 year of CBD
ALB	3,3	3,2	4,0	3,0
TP	6,7	6,3	7,0	6,5
GLU	124	102	77	129 +
ALP	236 +	253 +	545 +	168
ALT	79	88	111	62
CK	162	234 +	80	73
AMY	1575	967	585	610
BUN	9,89	10,2	11,0	12,5
CREA	0,4	0,7	0,7	0,48
Ca	9,7	9,6	10,0	9,9
Na	154	151	145	146
K	5,4	5,1	5,6	5,5
GLOB	3,4	3,1	3,2	3,5
P	3,63	4,76	5,9	5,25

Note: ALB – total albumins (2.5-4.4 g/dL), TP – total proteins (5.2-8.2 g/dL), GLU – total carbohydrates (60-110 mg/dL), ALP – alkaline phosphatase (20-212 U/L), ALT – alanine (0-88 U/L), CK – creatine phosphokinase (0-200 U/L), AMY – amylase (200-1200 U/L), BUN – blood urea nitrogen (7-25 mg/dL), CREA – creatinine (0.3-1.4 mg/dL), Ca - calcium (7.9-12 mg /dL), Na – sodium (138-160 mmol/L), K – potassium (3.5-5.8 mmol/L), GLOB – globulin (2.3-5.2 g/dL), P – phosphorus (2.9-6.6 mg/dL).

Radiology

Following the first radiological investigations performed pre-administration of CBD oil, it was possible to observe the presence of osteoarthritis of the elbow joint and spondylarthrosis (Figure 1).

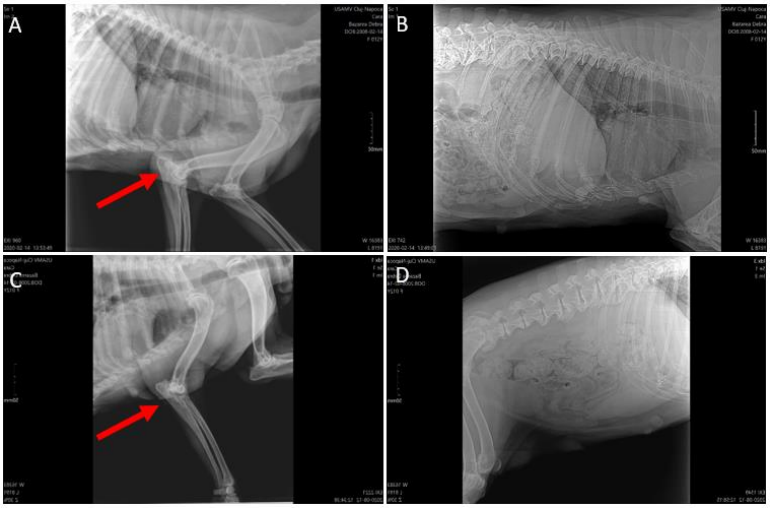

Figure 1. Radiographs of elbow and spine, before administration of CBD (1A, 1B) and after 6 months (1C, 1D). The red arrows point to the area of osteoarthritis of the elbow joints. On the second set of radiographs (1C, 1D), no further degeneration could be observed.

The presence and size of one of the breast tumors can be observed. Six months later, another radiological assessment was conducted. No new degenerative changes were observed in the bones, with the osteoarthritis and spondylarthrosis being evaluated as nonprogressive during this period. One of the inguinal breast tumors can be observed, with unchanged size during this period. This coincidental finding may be attributed to the CBD treatment, however, since it was not the focus of this study, we cannot be certain.

Studies show us that CBD oil in dogs has properties against anxiety, epileptic seizures, pain, stimulate appetite and combat nausea, help fight cancer, have myorelaxant and anti-inflammatory effects, etc. (Kaur et al., 2016).
Cara's associated pathologies of epilepsy, arthritis and cancer made her the perfect candidate for this type of treatment. However, in this study, the pathologies of epilepsy and arthritis were the most relevant. Overall, during the entire duration of the study, Cara suffered from 6 epileptic seizure in total, over 15 months. There was only one increase in the dose of CBD given, which coincided with the onset of heat, when the seizures did not seem to be as adequately controlled. In the last 9 months of the study, however, the seizures were mainly controlled by CBD alone, without other anti-epileptic drugs. This is in correlation with other studies found in the literature, McGrath et al. (2019) found that dogs in the CBD group showed a 33% reduction in the seizure frequency than those in the control group, however more research would be required on the subject for a definitive conclusion.

In humans, a positive correlation between plasma levels of 2-arachidonylglycerol and pain scores in the knee joint could be demonstrated, and also a negative correlation between joint chondropathy scores and expression of the CB2 receptor of the spinal cord (Burston et al., 2013). Clinical studies have shown that messenger RNA and CB1 and CB2 receptor proteins are expressed in the synovia of patients with osteoarthritis and rheumatoid arthritis, and that 2-arachidylglycerol and anandamide endocannabinoids were present in the synovial fluid of these patients, but not in individuals without joint symptoms. Cannabinoid receptors are expressed in the cartilages of people with osteoarthritis, in primary chondrocytes and in osteocytes of the underlying bone. The influence of cannabinoids on chondrocyte metabolism and matrix formation has been investigated in several studies. The primary chondrocytes of people with osteoarthritis treated with proinflammatory cytokines, interleukin-1β, showed fewer metalloproteinases that degrade the matrix (MMP-3 and MMP-13) when treated simultaneously with the synthetic cannabinoid WIN-55 (Li, et al., 1999). In another study, WIN-55 inhibited the activity of disintegration and metallo-proteinase with thrombospondin (Winklmayr et al., 2019).

For the evaluation of arthritis and pain sensation, the most relevant data are those collected through the Colorado Pain Scale. The improvement in the quality of locomotion throughout the study period was also observed. Research shows the intraarticular presence of cannabinoid receptors and how CBD's direct action on arthritis/arthrosis pathologies (Bryk and Starowicz, 2021). This data is also correlated with the situation of our patient, as after only two weeks a slight improvement of the grade III lameness could be observed. When we started this study, the patient was not able to run. After the first two weeks, it was possible to notice an increased walking speed, and gradually, running. Initially, when assessing the painful sensitivity of the affected joints, the patient responded by turning the head towards the examiner, a reaction that was not present in subsequent evaluations, which demonstrates a decrease in nociception. However, an overall increase in the average pain felt by the patient can be observed especially in the last months of the study. It is known that advancing age causes the accentuation of degenerative processes throughout the body, processes that CBD obviously cannot stop. It should also be borne in mind that the patient far exceeded the average life expectancy of the breed (10-12 years), Cara was 14 years old at the time of completion of the study), despite the multiple pathologies present and the toxic drug therapies maintained throughout most of her life.

Although the literature specifies a possible toxicity of CBD oil (Huestis et al, 2019), this has not been observed in our patient, with the biochemical analyses pertaining to the liver returning within the normal range after phenytoin and phenobarbital had been removed from therapy.

CONCLUSIONS

CBD therapy can be considered as a treatment in epilepsy, subject to careful monitoring. Thanks to the complementary therapy with cannabidiol, the patient recorded a total of 6 seizures of epilepsy in a one year and 5-month period, of which 3 were documented in the first month of administration of the product.
Following the administration of CBD, we were able to notice, with the help of the chronic pain scale, a decrease in the pain felt after the first two weeks of treatment and over a period of 1 year and 2 months. Also, during this period, an improvement in locomotor quality was recorded.

The dose used appears to be a favorable dose for the management of pain, arthritis and epilepsy. The patient should be kept under close monitoring and when and if epileptic crises occur, intrarectal diazepam can be administered. If the frequency and severity of seizures increase, specific therapy will be required.
Overall, in the case of the patient. CBD treatment not only helped decrease the frequency and severity of the epileptic crises, it also allowed elimination of hepato-toxic medications and management of pain.

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REFERENCES

1. Bisogno T, Hanuš L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, Moriello AS, Davis JB, Mechoulam R, Di Marzo V, Molecular targets for Cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. British Journal of Pharmacology. 2001; 134(4): 845–852.
2. Boleti AP, Frihling BE, Silva PS, Cardoso PH, de Moraes LF, Rodrigues TA, Biembengute ME, Koolen HH, Migliolo L, Biochemical aspects and therapeutic mechanisms of cannabidiol in epilepsy. Neuroscience & Biobehavioral Reviews. 2022; 132:1214–1228. Hollister LE, Cannabidiol and Cannabinol in man. Experientia. 1973; 29(7):825–826.
3. Bryk M, Starowicz K, Cannabinoid-based therapy as a future for joint degeneration. focus on the role of CB2 receptor in the arthritis progression and pain: An updated review. Pharmacological Reports. 2021; 73(3): 681–699.
4. Burston JJ, Sagar DR, Shao P, Bai M, King E, Brailsford L, Turner JM, Hathway GJ, Bennett AJ, Walsh DA, Kendall DA, Lichtman A, Chapman V, Cannabinoid CB2 receptors regulate central sensitization and pain responses associated with osteoarthritis of the knee joint. PLoS ONE. 2013; 8(11), e80440. https://doi.org/10.1371/journal.pone.0080440
5. Cassano T, Villani R, Pace L, Carbone A, Bukke VN, Orkisz S, Avolio C, Serviddio G, From cannabis sativa to cannabidiol: Promising therapeutic candidate for the treatment of neurodegenerative diseases. Frontiers in Pharmacology. 2020; 11. https://doi.org/10.3389/fphar.2020.00124
6. Cifelli P, Ruffolo G, De Felice E, Alfano V, van Vliet EA, Aronica E, Palma E, Phytocannabinoids in neurological diseases: Could they restore a physiological GABAergic transmission? International Journal of Molecular Sciences. 2020; 21(3), 723. https://doi.org/10.3390/ijms21030723
7. de Carvalho Reis R, Almeida K J, da Silva Lopes L, de Melo Mendes CM, Bor-Seng-Shu E, Efficacy and adverse event profile of Cannabidiol and medicinal cannabis for treatment-resistant epilepsy: Systematic review and meta-analysis. Epilepsy & Behavior. 2020;*102*, 106635. https://doi.org/10.1016/j.yebeh.2019.106635
8. Gupta A, Yek C, Hendler RS, Phenytoin toxicity. JAMA. 2017; 317(23): 2445.
9. Hollister LE, Cannabidiol and Cannabinol in man. Experientia. 1973; 29(7):825–826.
10. Huestis MA, Solimini R, Pichini S, Pacifici R, Carlier J, Busardò FP, Cannabidiol adverse effects and toxicity. Current Neuropharmacology. 2019; 17(10):974–989.
11. Kaur R, Ambwani S, Singh S, Endocannabinoid system: A multi-facet therapeutic target. Current Clinical Pharmacology. 2016; 11(2): 110–117.
12. Li J, Daughters RS, Bullis C, Bengiamin R, Stucky MW, Brennan J, Simone DA, The cannabinoid receptor agonist win 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. Pain. 1999; 81(1):25–33.
13. Manzanares J, Julian M, Carrascosa A, Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Current Neuropharmacology. 2006; 4(3): 239–257.
14. McGrath S, Bartner LR, Rao S, Packer RA, Gustafson DL, Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure

frequency in dogs with intractable idiopathic epilepsy. Journal of the American Veterinary Medical Association. 2019; 254(11): 1301–1308.
15. Morano A, Fanella M, Albini M, Cifelli P, Palma E, Giallonardo AT, Di Bonaventura C, Cannabinoids in the treatment of epilepsy: Current status and future prospects. Neuropsychiatric Disease and Treatment. 2020; 16:381–396.
16. Potschka H, Bhatti SFM, Tipold A, McGrath S, Cannabidiol in canine epilepsy. 2022; The Veterinary Journal, 105913. https://doi.org/10.1016/j.tvjl.2022.105913
17. Sullivan JM, Mechanisms of cannabinoid-receptor–mediated inhibition of synaptic transmission in cultured hippocampal pyramidal neurons. Journal of Neurophysiology. 1999; 82(3): 1286–1294.
18. Winklmayr M, Gaisberger M, Kittl M, Fuchs J, Ritter M, Jakab M, Dose-dependent cannabidiol-induced elevation of intracellular calcium and apoptosis in human articular chondrocytes. Journal of Orthopaedic Research. 2019; 37(12): 2540–2549.