

Study of the determination of the effective doses of two *Cannabis Sativa* molecules in pathological processes of canines in Bogota

Abstract

Studies with Cannabidiol (CBD) to reduce pain in animals have increased exponentially in recent years due to the great interest generated by the use of natural and homeopathic medicine to manage different pathologies. However, for dogs handling, the information is still limited. We've found that veterinary ethnobotanical studies carried out in Mexico City at the Faculty of Veterinary Medicine of the UNAM on the analgesic effect of CBD in animals are few and these studies are mostly carried out for use in larger animals (goats, bovines...) On the homeopathic medicine side, there is Dr. Monica Fehlmann from Switzerland, who has a homeopathy program for animals, reiki treatments, healing massages, bioresonance or acupuncture for the physical and spiritual health of pets, while the university corporation of Santa Rosa de Cabal (located in Risaralda, Colombia), ventured to carry out experimental studies with 16 dogs, using (tetrahydrocannabinol) THC as part of their treatments, she based her research on current studies that support the analgesic and antiepileptic effects of THC in critical canine conditions. Various pathologies have been studied to reduce pain, however, the ones with more supporting background are osteoarthritis, inflammation, epilepsy, seizures, behavioral problems, anxiety, neurodegenerative diseases and dermatological problems. Seizures are the most studied application of CBD in people, and it's starting to be the most studied one in dogs. Multiple investigations have shown that CBD is capable of reducing the intensity and frequency of seizures in dogs that were diagnosed with idiopathic epilepsy.

Keywords: *Cannabis Sativa*, canines, dose, cannabinol, tetrahydrocannabinol, psychoactive

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Abbreviations: THC, tetrahydrocannabinol; CBD, cannabidiol; CBN, cannabinol; THCV, tetrahydrocannabivarin; CBG, cannabigerol; CBC, cannabichromene; CB1, Cannabinoid receptor type 1; CB2, cannabinoid receptor type 2

Introduction

Cannabis is commonly known as a drug that is extracted from the *Cannabis sativa* plant. With this plant resin, leaves, stems and flowers the most widely used illegal drugs are made: marijuana, that's obtained from the crushing of the dried flowers, leaves and stems, or the hashish, that's made from the resin stored in the flowers of the plant. These hallucinogenic products produced from the plant, especially from its sprouts, in whose glandular hairs cannabinoids are synthesized and accumulate in greater proportion than in the rest of the plant, are characterized by containing THC (tetrahydrocannabinol), which later becomes the predominant psychoactive chemical compound. This compound has the famous ability to link to the CB1 receptor and produce a strong psychoactive effect.¹⁻⁵

Cannabis in its fresh state contains more than 500 different chemical compounds, including at least 113 cannabinoids besides the THC, such as cannabidiol (CBD), cannabinol (CBN), tetrahydrocannabivarin (THCV), tetrahydrocannabinol (THC), cannabigerol (CBG), and the cannabichromene (CBC). These have different effects than the ones the THC produces, these also act on the nervous system, although many cannabinoids share the same formula, the atoms within the molecule are arranged in slightly different ways and this gives individual molecules very different chemical properties.

Based on this, the analysis of other cannabinoid molecules that have a low or zero percentage of THC in their composition, have

a wide field of study because they still maintain their medicinal properties and can be used for managing different pathologies.⁶⁻¹⁵

Material and methods

What is *Cannabis Sativa*?

Cannabis Sativa is a herbaceous species of the Cannabaceae family, it is a native plant from the Himalayas in Asia. Since prehistoric times, humans have cultivated this plant due to wide uses spectrum it has, this goes from being a source of textile fiber to extract oil from its seeds, to work as a medicinal plant or hallucinogen 1, These last two forms of usage occur due to the fact that many of the varieties of *cannabis sativa* have psychoactive properties, which is why it is used to produce products with hallucinogenic characteristics.

Toxicity and adverse effects

It is complex to establish a toxic dose of the formulations based on raw Cannabis or the consumption of vegetal material due to the great variations in cannabinoid content from the different varieties of the plant 31, however the risk of intoxication will also depend on the exposure route, the purity and concentration of marijuana. The main route of intoxication in pet animals is through the ingestion of the supply of marijuana that the owner might keep on his property 32, as well as through the ingestion of cooked food (cakes, cookies, drinks, etc.) that contain the plant, in addition to this, very few cases of small animals death have been reported after Cannabis intoxication.¹⁶⁻²¹

In dogs, symptoms after ingestion of THC usually appear within 1-2 hours, the main clinical symptoms include: ataxia, incoordination, hypersalivation, depression, disorientation, hypothermia, mydriasis, bradycardia, vomiting, tremors and urinary incontinence. High toxic

doses can cause nystagmus, tachypnea, tachycardia, hyperexcitability, stupor and convulsions, the duration of symptoms varies from 1 to 3 days, with an average of 24 hours in most cases, dogs can also show hyperesthesia and excessive sensitivity to light, movement, or sounds 32.

Treatment for intoxication is fundamentally a supportive treatment, emesis can be forced if ingestion has occurred within the last 2 hours, although the antiemetic effect of THC can make vomiting difficult. The recovery time will depend on the ingested dose, although it generally occurs between the next 24-72 hours. Recently, the use of intravenous lipid therapy has been described for the treatment of cases of marijuana intoxication in dogs, the prognosis is good with complete recovery in the vast majority of cases 31.²²⁻²⁹

Molecule of interest *Cannabis Sativa*

Cannabidiol (CBD) is one of the 113 cannabinoids found in cannabis, being the main component of the plant in hemp varieties, it is not psychoactive, since it does not contain delta-9-tetrahydrocannabinol (THC) in significant quantities and is considered to have a broader scope for medical applications including epilepsy, epileptic encephalopathies such as West syndrome, multiple sclerosis, anxiety disorders, schizophrenia, nausea, anxiety, insomnia, inflammation, seizures and to inhibit growth of cancer cells. More and more people are using it to reduce pain since using CBD products does not create dependency as confirmed by the World Health Organization.

Cannabidiol is insoluble in water, but it is soluble in organic solvents, at room temperature it is a colorless crystalline solid and in strongly basic environment with the presence of oxygen, it oxidizes into a quinone, while under opposite conditions such as acid environments, it becomes cyclic forming THC.

These drugs are depressants of the nervous system and their effects on the brain are mainly due to one of their active ingredients, Tetrahydrocannabinol or THC, which is very lipophilic and is distributed in fat, liver, brain and kidney, is poorly soluble in water, but it dissolves easily in most organic solvents, specifically lipids and alcohols, quickly reaches the brain, where it accumulates and from which it is eliminated very slowly. Metabolism is mainly hepatic, with renal and fecal excretion.³⁰⁻³⁴

Pathologies

Various pathologies have been studied to reduce pain, however, the ones with the most antecedents are osteoarthritis, inflammation, epilepsy, seizures, behavioral problems, anxiety, neurodegenerative diseases and dermatological problems 2. Seizures are the most studied application of CBD in people, and it is beginning to be so in dogs since several investigations have shown that CBD is capable of reducing the intensity and frequency of seizures in dogs that are diagnosed with idiopathic epilepsy, this is due to the fact that CBD (cannabidiol) has analgesic and anti-inflammatory properties demonstrated by various studies.

Although there is no scientific data about the side effects of using CBD in dogs, there might be side effects based on how CBD affects humans. To minimize possible side effects, it is important to ensure the correct dose is given to the dog.

Results

In the use of THC for dogs as an analgesic, the dose is generally 0.2 - 0.6 mg twice a day per 10 pounds of body weight, the dose should start as a small dose and start increasing slowly and gradually

during 4 to 7 days, this is for the dose to be stable and safe for dogs, without causing side effects. It should also be taken into account that if loss of balance or sedation is observed due to the fact that the dose increased very quickly, then the dose should be decreased 10.

The lethal dose 50 (LD50) for dogs has not yet been established, however, oral doses of 3 to 9 g/kg of THC in dogs have been shown to be safe as the tested animals started recovering 24 hours after ingestion. A study called Pharmacokinetic and Safety Evaluation of Various Oral Doses of a Novel 1:20 THC:CBD Cannabis Herbal Extract in Dogs by Alan Chicoine (08/29/2020)⁶, determined the pharmacokinetics and safety of various doses of a cannabis herbal extract containing a 1:20 ratio of 19-tetrahydrocannabinol (THC): cannabidiol (CBD) in 13 healthy beagle cross dogs, the dogs were monitored for adverse events up to 48 hours post-dose, with successful results.

Discussion

THC, like CBD, are processed by the body's endocannabinoid system and serve to mimic compounds that we produce naturally: the endocannabinoids. Animals, like humans, have this endocannabinoid system with the production of CB1 receptors (responsible for brain processes) and CB2 (in the immune system and in peripheral organs), these receptors are responsible for a wide variety of physiological processes such as inflammation, anxiety, stress, mobility, learning, nausea, vomiting, appetite, emotions, aging, allergies and dermatological problems 3, so it is believed that these receptors respond to CBD / THC in a similar way as they do in humans. Regardless of the animal species involved, the laboratory diagnosis, if it can be done immediately, allows a specific treatment to be applied in each case, by confirming or reporting suspected intoxication. Laboratory tests mainly include blood tests, urine tests, such as complete blood count and biochemical analysis.

In the case of urine, the use of human drug tests to evaluate canine urine can lead to many false negatives, so its use is controversial. Gas chromatography coupled with mass spectrometry is used for diagnosis in people, but the results take several days to be obtained. Therefore, the diagnosis of CBD/THC intoxication in veterinary medicine is mainly presumptive and based on a detailed clinical history, in addition to a complete physical examination and laboratory tests.

Current Colombian legal framework

In Colombia there are still gaps in the Public Policy for Responsible Ownership of animals, such as defining, among other aspects, the responsibilities towards animals of the different entities and institutions and of the community in general. However Law 1774 of 2016, in the paragraph of article 2 recognizes animals as sentient beings, so it becomes necessary to clarify the scope of the word PET; which refers to any domesticated or domesticated animal that lives with man mainly for company and entertainment purposes and that are absolutely dependent on the human being to ensure their well-being and survival 33.

The Responsible Ownership of Animals implies the fact that whoever is called the owner or holder of a pet or production animal, assumes the responsibility of guaranteeing its basic needs, such as food, drink, shelter, recreation, freedom of movement, veterinary medical care, which goes beyond the simple fact of a purge and a health plan for vaccine-preventable diseases, that the scientific evaluation of animal welfare encompasses a series of elements that must be taken into consideration as a whole 33.

According to the Code of Ethics for the professional practice of veterinary medicine, veterinary medicine and zootechnics in

Colombia, it specifies that it is a professional responsibility and an ethical commitment to investigate, develop, produce, market and apply medicines with live or attenuated microorganisms, Biodegradable active substances without intra-species vertical or horizontal effects, or risks to public, veterinary or environmental health, duly authorized by the competent authority 34.

Conclusion

The tendency to use *Cannabis Sativa* as a treatment for ailments in animals as well as in humans has increased in recent years and these tendencies towards the use of alternative medicine are motivated by the frustration that current owners of dogs are dealing with because conventional medicine does not give them the expected results, as many modalities have little or no scientific evidence to support the efficacy of their treatments, while CBD procedures are economically viable and easily accessible alternatives.

Finding a new treatment to reduce the pain of dogs with different pathologies would not only be a benefit for these animals, but also for their owners, since currently there is no variety in the drugs used as treatment and there is a tendency to implement drugs for animals that are known for their general uses on humans, the usage of these drugs have no supportive studies that prove their effectiveness to be used in dogs. It is crucial to understand that the current situation in the country and the COVID-19 contingency have promoted the adoption and obtention of companion animals, which would also benefit from CBD treatments to reduce anxiety and behavior management.

In addition, CBD treatments provide a wide number of benefits such as neuroprotective, analgesic, anti-inflammatory, antiepileptic and anxiolytic properties, which stabilizes the pet's pathology and confidence in the owner of using molecules such as tetrahydrocannabinol (THC) due to its natural origin, opening the doors to new and various treatments that enhance the well-being of pets.

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Conflicts of interest

The manuscript was prepared and reviewed with the participation of all the authors, who declare that there is no conflict of interest that jeopardizes the validity of the results presented.

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