Pharmacokinetics, safety and efficacy of cannabidiol in dogs and cats

The market of cannabidiol (CBD) products for use in pets is expanding, and pet owners become increasingly more interested in purchasing those products as an adjunct treatment. In 2019, Lori *et al*. conducted a survey among Canadian dog owners to examine their usage and perception of CBD products (1). They predominantly purchased CBD products for treatment of pain and anxiety. The majority of dog owners reported that CBD products were equally or more productive than conventional medication for pain relief (82%) and anxiety (67%). However, owners were lacking guidance from veterinarians. Lori *et al.* also conducted a survey in the United States among veterinarians to examine their knowledge, experience and perception towards CBD (2). Only 45.5% felt comfortable to discuss CBD as treatment with their clients, which is likely due to the lack of research exploring CBD safety and efficacy in veterinary medicine.

For this literature review, Pubmed, Google Scholar and Scopus were searched for articles. Initially, the search terms “cannabidiol” OR “CBD” AND “veterinary use” were applied, leading to 61 results of which 6 were relevant (safety/efficacy). Then, literature was searched more specifically for dogs with the search terms “cannabidiol” OR “CBD” AND “canine” OR “dog”, (31 results, 6 relevant) and for cats using search terms “cannabidiol” OR “CBD” AND “feline” OR “cat” (12 results, 1 relevant). The relevant articles found during the more specific search were the same as the ones found during the more general search of “veterinary use”, even after adding more search terms such as “pain”, “epilepsy” “cancer”, “palliative care”.

Pharmacokinetics (dogs)

Recently, della Rocca and di Salvo (3) reviewed the literature concerning pharmacokinetics of Cannabis derivates, leading to a summary of the following key points that should be considered when planning to conduct a study examining CBD as potential treatment/adjunct in dogs or cats for a certain condition:

- The low bioavailability obtained after oral administration is presumably due to a first-pass effect (liver metabolism before the drug enters the systemic circulation) and the type of formulation used.
- The oil formulations guarantee a better pharmacokinetic profile (both in terms of bioavailability and half-life).
- To promote better oral absorption of the active ingredients, cannabinoids should be administered in fasted animals.
- The elimination kinetics of cannabinoids is such as to suggest administrations every 12h.

Safety/tolerability

Two studies have explicitly investigated safety of CBD use in dogs (4, 5) and cats (4). Deabold *et al.* investigated a single-dose and 12-week CBD administration in cats and dogs, assessing the pharmacokinetics and safety of CBD. The dose used was 2mg/kg twice daily and delivered as CBD infused in fish oil for cats and in soft chews for dogs. Cats were shown to have lower oral absorption kinetics and less rapid elimination of CBD, which suggests that dosing requirements might differ between cats and dogs. Cats and dogs also reacted differently to CBD regarding changes in blood count and serum chemistry parameters and showed differences in the amount and nature of adverse events (AE). While

cats were shown to have a decrease in urea nitrogen and increase in serum creatine kinase over time, no changes in serum chemistry were observed in dogs. Furthermore, cats exhibited several adverse events (1129/1344 observations) such as excessive licking, head-shaking and pacing, while dogs only exhibited very few adverse events (53/1344), mostly diarrhea and in some cases vomiting.

Vaughn *et al.* examined the safety of ten escalating doses of CBD-oil in 20 dogs (beagles) and looked at CBD-rich oil, THC-rich oil and a mixture of CBD/THC (1.5:1) oil, which was administered via oral gavage. The CBD-rich oil dose varied from 1.7 - 64.7 mg/kg. Beagles supplemented with CBD-rich oil exhibited only mild AE, which were similar in number and category (mostly gastrointestinal and constitutional) compared to placebo. The number of AE per dog in dogs supplemented with CBD-rich oil was even slightly lower compared to placebo. Since the number of gastrointestinal AEs was similar between the CBD-rich and placebo group, they might be due to the discomfort of the administration via oral gavage, oil volume and/or the MCT carrier oil rather than CBD itself. Furthermore, CBD increased alkaline phosphatase (ALP), but values were still within the normal range after the final CBD dose. The increase in ALP was also observed in two efficacy studies after CBD doses of 2 - 2.5mg/kg (6, 7). Overall, this study indicates that CBD-rich oil up to 64.7mg/kg is safe and well tolerated. However, CBD should be pure and should not be mixed with THC, as THC-rich oil and the mixture of CBD and THC showed a greater number of AE that were also more serious in nature.

Altogether, studies indicate that CBD oil supplementation is safe and well-tolerated in dogs. Only one case study found a more serious AE in a 4-year old Labrador who showed cutaneous and mucosal ulceration within 5 days of oral CBD oil administration (0.3mg/kg once daily), with no changes in diet and medication, classified as probable adverse event (8). However, no other studies reported this. For cats, more research for optimal CBD dosing is needed. Doses might need to be lower than 4mg/kg per day as changes in serum chemistry and a range of physical/behavioural AEs were reported.

Efficacy

So far, only four studies have investigated the efficacy of CBD as treatment/adjunct in dogs, with no studies undertaken in cats. Of those, three were examining CBD efficacy for osteoarthritis pain relief (6, 9, 10) and one examined its efficacy as addition to conventional therapy for epilepsy (7).

Osteoarthritic pain

The first study was performed in 2018 by Gamble *et al*., which supplemented 16 dogs with diagnosed osteoarthritis pain with 2mg/kg CBD oil every 12 hours for 4 weeks in a cross-over study. Both the veterinary and owner assessment showed a reduction in pain at week 2 and 4 and owners furthermore reported a significant increase in activity after 2 and 4 weeks, however there was no significant difference in lameness and weight-bearing as assessed by the veterinarian.

Verrico *et al*. supplemented 20 dogs with diagnosed osteoarthritis pain for 4 weeks with either liposomal CBD (20mg/day = 0.5mg/kg), or nonliposomal CBD (20 or 50mg/day = 0.5 or 1.2mg/kg) in a randomized, placebo-controlled study. The 20mg nonliposomal CBD dose had no effects, but the 50mg/d nonliposomal and 20mg/d liposomal CBD dose showed significant improvements. The veterinary assessment revealed an improvement in all quality of life scores (sitting to standing, lying to standing, walking and running) and owners

reported a decrease in pain index, which was still preserved two weeks after supplementation had stopped, compared to placebo. No adverse events were reported.

Brioschi *et al.* performed a 12-week randomized controlled trial in 21 dogs with diagnosed osteoarthritis pain, which were given a multidomal pharmacological treatment with or without 2mg/kg CBD (twice daily). Owners had to report pain intensity, pain interference and quality of life index at week 1, 2 , 4 and 12. Pain measures decreased and quality of life increased with the multidomal pharmacological treatment, but not significantly. However, the addition of CBD oil resulted in a significant decrease in pain intensity and interference and improved quality of life compared to pharmacological treatment alone. Both groups reported somnolence and mild ataxia as AE and the CBD group further reported minimal ptyalism in two out of the nine dogs.

Epilepsy

McGrath examined the efficacy of CBD in addition to existing antiepileptic treatments to reduce seizure frequency in dogs with intractable idiopathic epilepsy. For 12 weeks, 26 dogs were supplemented with CBD-infused oil (2.5mg/kg twice daily) or non-infused oil. CBD was able to significantly reduce seizure frequency compared to antiepileptic treatment only, however, the proportion of responders (i.e. >50% reduction in seizure activity) was similar in the CBD and placebo group. Plasma CBD correlated with the reduction in seizure frequency, thus the authors suggested that a higher dose might result in more responders to CBD.

Conclusion

CBD oil seems to be safe and well tolerated in dogs up to doses of 64.7mg/kg. However, low doses of CBD ranging from 0.5mg/kg to 5mg/kg per day seem to be enough to elicit beneficial effects in dogs with osteoarthritis or epilepsy. It has to be noted that most studies were performed in (hepatically) healthy dogs and a common AE was elevated ALP levels. ALP is a sensitive indicator of cholestasis in dogs, thus, CBD might cause some damage in hepatically impaired dogs and should not be prescribed until further long-term studies on the effect of CBD on liver function have been performed. For cats, more research is needed to identify the optimal CBD dose associated with less AE and to investigate if CBD oil could be used to treat arthritis and epilepsy in cats.

Overall, literature shows promising effects of CBD oil administration twice per day for pain relief in dogs with osteoarthritis, while CBD's beneficial effects on epilepsy are still preliminary. Individual pet owners have also been testing CBD for anxiety and cancer in dogs, however future research is needed to examine if CBD could also be help improve those conditions.

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