Effects of cannabidiol without delta-9-tetrahydrocannabinol on canine atopic dermatitis: A retrospective assessment of 8 cases

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Abstract

Objective

We aimed to examine the effects of cannabidiol (CBD)-containing hemp oil without delta-9-tetrahydrocannabinol (THC) as a supplemental treatment for canine atopic dermatitis (CAD), as well as its adverse effects, and effects on concurrent drug use in dogs.

Animal

In this retrospective case series, 8 dogs with CAD were diagnosed by veterinary dermatologists certified by the Japanese Society of Veterinary Dermatology.

Procedure

The medical records of dogs supplemented with CBD-containing hemp oil were evaluated with respect to signalment, physical examination, plasma C-reactive protein concentrations, pharmacologic management, the CAD Extent and Severity Index (4th iteration), and the Pruritus Visual Analog Scale.

Results

Overall, CBD, used as a supplement in combination with other drugs, was well-tolerated over a wide dose range and decreased the occurrence of pruritus in dogs with CAD when ingested twice a day.

Conclusion

This study provides the first report of supplementation with CBD without THC that was effective in controlling pruritic behavior in dogs with CAD.

Clinical relevance

Further controlled studies are required to investigate the dose range, efficacy, and safety.

Résumé

Effets du cannabidiol sans delta-9-tétrahydrocannabinol sur la dermatite atopique canine : évaluation rétrospective de huit cas

Objectif

Nous avons cherché à examiner les effets de l'huile de chanvre contenant du cannabidiol (CBD) sans delta-9-tétrahydrocannabinol (THC) en tant que traitement complémentaire de la dermatite atopique canine (CAD), ainsi que ses effets indésirables et ses effets sur les médicaments concomitants utilisés chez le chien.

Animal

Dans cette étude rétrospective de cas, huit chiens atteints de CAD ont été diagnostiqués par des dermatologues vétérinaires certifiés par la Société japonaise de dermatologie vétérinaire.

Procédure

Les dossiers médicaux des chiens supplémentés avec de l'huile de chanvre contenant du CBD ont été évalués en ce qui concerne le signalement, l'examen physique, les concentrations plasmatiques de protéine C-réactive, la gestion pharmacologique, l'indice *CAD Extent and Severity Index* (4ème itération) et le *Pruritus Visual Analog Scale*.

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Résultats

Dans l'ensemble, le CBD, utilisé comme supplément en association avec d'autres médicaments, a été bien toléré sur une large gamme de doses et a diminué l'apparition de prurit chez les chiens atteints de CAD lorsqu'il est ingéré deux fois par jour.

Conclusion

Cette étude fournit le premier rapport de supplémentation en CBD sans THC efficace pour contrôler le comportement prurigineux chez les chiens atteints de CAD.

Pertinence clinique

D'autres études contrôlées sont nécessaires pour étudier la gamme de doses, l'efficacité et l'innocuité.

(Traduit par Dr Serge Messier)

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Canine atopic dermatitis (CAD) is a chronic recurrent pruritic skin disease that is highly prevalent in veterinary dermatology practice (1). In atopic dermatitis, the immune response of the skin is enhanced, and the underlying pathogenesis involves disruption of the immune response, abnormal barrier function, and itching behavior (2).

Cannabidiol (CBD) is a non-psychoactive ingredient in cannabis plants with numerous beneficial effects on the body. Hemp-derived natural components, including CBD, are involved in regulation of the endogenous cannabinoid system and are therefore expected to improve various skin symptoms. Cannabinoid receptors (CB1 and CB2) are highly expressed in the skin of dogs with CAD compared to that of healthy dogs (3).

However, research on the use of CBD hemp oil without delta-9-tetrahydrocannabinol (THC) in dogs is limited. The present study aimed to evaluate the efficacy of THC-free CBD-containing hemp oil in the treatment of CAD. We compared the CAD Extent and Severity Index (CADESI) and quality of life [assessed by the Pruritus Visual Analog Scale (PVAS)], plasma C-reactive protein (CRP) concentrations, and clinical outcomes before and after twice-daily ingestion of THC-free CBD-containing hemp oil in 8 dogs diagnosed with atopic dermatitis by a veterinary dermatologist certified by the Japanese Society of Veterinary Dermatology (JSVD).

Eight dogs were recruited from 3 animal hospitals near Tokyo, Japan. Before treatment, each dog was diagnosed with CAD and treated according to the JSVD guidelines, and informed consent was obtained directly from all owners. The owners were free to withdraw at any time without notice.

According to the CBD manufacturer's information, all dogs were started at a dose of approximately 0.07 to 0.25 mg/kg of body weight twice daily. During the testing period, the dose was increased depending on the skin condition of each dog and the observed response at 0.125 mg/kg. The dose was increased if no apparent change was observed with the previous dose. Concomitant medications were allowed during the study period, and their doses could be maintained or reduced by the certified dermatologist on Day 0. Details of the concomitant medications are presented in Table 1.

We administered a 10% CBD-containing broad-spectrum hemp oil (Mary's Tails Hemp Extract Tincture; Mary's Nutritionals, Denver, Colorado, USA) to the 8 dogs with CAD for at least 8 wk. Each dog received oral administrations q12h for the entire study period at a dose of 0.14 to 1.43 mg/kg/d. These CBD products were certified to not contain THC.

The severity of pruritic behavior was graded using the PVAS (4). The PVAS values were determined based on medical history and the owners' evaluations. The PVAS is scored on a scale of 0 to 10, with 0 indicating a complete absence of pruritus and 10 indicating the most severe form of pruritus. The owners assessed pruritus in their dogs on Day 0 and at the end of CAD treatment. The CADESI was used to assess the severity of whole-body skin symptoms (5). The CADESI scale comprises diagnostic criteria that score the degree of 3 common clinical signs of atopic dermatitis (erythema, lichenification, and epidermal peeling/hair loss) from 0 (none) to 3 (severe) for 20 sites on the dog's body surface. Four bilateral sites were examined: the perioral areas, abdomen, perineum, and ventral aspect of the tail. A total of 16 sites were examined independently on each side, including the medial pinnae, axillae, forelimbs, hind limbs, elbow flexors, palmar metatarsals, lateral abdomen, and groin. A Board-certified dermatologist recorded scores on Day 0 and at each follow-up consultation after direct examination. We performed a clinical examination and diagnosed each dog with CAD prior to the experiment. Only dogs evaluated as clinically healthy progressed to plasma CRP assessment.

Blood samples were collected from the forelimb or hind limb veins, depending on the size of the dog, and were transferred into tubes containing 2 mL anticoagulant. Blood sample collection, blood processing, and CRP assays were performed according to the standard operating procedures of each hospital. C-reactive protein was not measured in 2 dogs before or after the testing period because owner consent for blood sampling was not obtained.

Plasma CRP concentrations were measured at the animal hospitals using a commercially available dry chemistry slide (IDEXX Catalyst CRP Test; IDEXX Laboratories, Tokyo, Japan) with a commercially available in-clinic analyzer (IDEXX) (6).

The 8 dogs represented various breeds with an average weight of 14.6 kg (range: 1.9 to 33.5 kg) and an average age of 9.0 y (range: 5 to 13 y). The characteristics [breed, age (y), and sex; FS — spayed female; MN — neutered male] of the dogs with CAD enrolled in the CBD trial are:

- Dog 1 — Toy poodle — MN (7 y);
- Dog 2 — Bichon frise — MN (9 y);
- Dog 3 — Shiba inu — FS (11 y);

Table 1. Treatments administered to dogs enrolled in the study.

Dog	CBD dose (mg/kg/d)	CBD dosing history	Concomitant medications
1	0.53 to 1.05	No effect was observed with 0.53 mg/kg for 7 d. The dose was increased to 1.05 mg/kg. A change was observed after 2 or 3 d. The dose has been constant since then.	None
2	0.43 to 1.43	No effect was observed with 0.4 mg/kg for 4 d. Dose increased to 0.57 mg/kg, no change for 4 d. Dose increased to 0.71 mg/kg, no change for 4 d. Dose increased to 1.0 mg/kg, no change for 4 d. Dose increased to 1.43 mg/kg relieved itching (PVAS: 2).	Oclacitinib 0.6 mg/kg, q12h
3	0.33	No change in dosage.	Oclacitinib 0.6 mg/kg, q12h Amoxicillin 14 mg/kg, q12h
4	0.14 to 0.42	Started at 0.14 mg/kg and titrated up to 0.42 mg/kg in 7 d. Constant dose from Day 8.	Oclacitinib 0.4 mg/kg, q12h Amoxicillin 12 mg/kg, q12h Gentamicin eye drops, q12h
5	0.2	No change in dosage.	Prednisolone 0.3 mg/kg, q48h
6	0.45 to 0.9	Started at 0.45 mg/kg, increased to 0.9 mg/kg after 7 d. Constant dose from Day 8.	Prednisolone 0.45 mg/kg, q48h
7	0.14 to 0.41	Started at 0.14 mg/kg and titrated up to 0.41 mg/kg in 7 d.	Ketoconazole 7 mg/kg, q24h Prednisolone 0.17 mg/kg, q48h
8	1.125	No change in dosage.	None

CBD — Cannabidiol; PVAS — Pruritus Visual Analog Scale.

Table 2. Pre- and post-treatment numeric rating scores and plasma CRP concentrations in a clinical trial of dogs receiving CBD for the treatment of CAD.

Dog	PVAS (Pre)	PVAS (Post)	CADESI-4 (Pre)	CADESI-4 (Post)	CRP (Pre), mg/dL	CRP (Post), mg/dL
1	6	0 (Day 44)	8	2 (Day 44)	0.6	1.2
2	4	4 (Day 124)	18	16 (Day 124)	0.3	NT
3	0	2 (Day 64)	44	47 (Day 64)	0.7	5.0 (Day 212)
4	6	2 (Day 21)	99	97 (Day 21)	1.3	1.4
5	8	2 (Day 56)	73	32 (Day 56)	> 7.0	0.3
6	8	6 (Day 16)	4	4 (Day 16)	0.4	< 0.3
7	6	3 (Day 28)	114	65 (Day 28)	NT	NT
8	6	0 (Day 147)	27	16 (Day 147)	NT	NT

CADESI-4 — Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; CAD — Canine atopic dermatitis; CBD — Cannabidiol; CRP — C-reactive protein; NT — Not tested; PVAS — Pruritus Visual Analog Scale.

- Dog 4 — Beagle — MN (12 y);
- Dog 5 — Golden retriever — FS (9 y);
- Dog 6 — Labrador retriever — MN (6 y);
- Dog 7 — French bulldog — FS — (5 y); and
- Dog 8 — Wire fox terrier — FS — (13 y).

The initial dose of CBD and subsequent increases are specified in Table 1, and changes in measured parameters are listed in Table 2.

No adverse events were reported following ingestion of the CBD oil. Improvements were noticed in each dog, as described in the following paragraphs. Due to the absence of a control group, we could not conclude whether the improvements were caused fully or in part by the CBD. The CADESI values decreased in 5 dogs, remained unchanged in 1 dog, and increased in 1 dog. The PVAS values decreased in 7 dogs but increased in 1 dog.

Although the period of improvement varied depending on the individual, a clear decrease in itching was observed after approximately 2 wk of continuous intake of CBD (Table 2). Conversely, when we observed the degree of improvement in each part of the body, there was relatively little change in the distal limbs in some cases, although the areas of lichenification in the auricular and perineal regions to the ventral side of the tail had improved (data not shown).

In the present study, improvements in pruritic behavior were observed in all dogs, which may have been related to the use of CBD. However, the lack of a control group is one of the main limitations of this study, which restricted the conclusions regarding the efficacy of CBD.

Dog 7 had improved skin symptoms that were satisfactory to the owner. However, treatment was less effective on the lichenified areas of the skin, which eventually required the use of topical steroids. Notably, the dosage of systemic prednisolone could be reduced when CBD was used with other concomitant medications. The main enzyme that metabolizes prednisolone is CYP3A4 (7). CYP3A4/2C19 inhibitors, substrates, and inducers are common drugs used in humans and animals for both acute and chronic conditions, such as hypertension, migraines, and heartburn. In a preclinical study, CBD was suggested to have CYP3A4 inhibitory effects (8). This is expected to delay

elimination of drugs metabolized by CYP3A4, thus increasing their blood concentration. Interactions between CBD and these drugs may contribute to clinical outcomes specific to the treatment for which they are indicated (9–11). Therefore, these drugs should be handled safely in recognition of both their beneficial and harmful effects (12).

When plasma CRP concentrations were compared before and after CBD use, 2 dogs had decreased concentrations, and 3 dogs had increased concentrations. One dog with a decreased concentration of CRP had an improvement in skin symptoms, whereas 1 dog had no change in clinical signs. Two dogs with increased CRP concentrations had improvements in skin symptoms, and 1 dog had worsening symptoms. Plasma CRP concentrations were measured in this small number of cases; therefore, the association between CRP concentrations and skin symptoms did not exclude concomitant medications, interval since onset, or other factors. C-reactive protein is a nonspecific inflammatory marker that modulates the acute phase response and is usually significantly elevated in infectious, immune-mediated, and neoplastic diseases (13). Only 1 study reported the relationship between CRP concentration and symptoms in dogs with CAD undergoing allergy immunotherapy for 1 y; however, CRP concentrations did not correlate with the severity of CAD symptoms (14). Due to individual differences in CRP production, it is unsuitable for one-time evaluation; however, it is useful for evaluating the course of symptoms in the same individual (13). To examine the anti-inflammatory effect of CBD, it is necessary to measure changes in various cytokines in the blood over time.

In the dogs assessed in the present study, the use of CBD in combination with current CAD treatments suggested the possibility of reducing the dose of concomitant medications while increasing their efficacy. If CBD can allow a reduction in the dosage of concomitant medications, it could also potentially reduce medical costs for pet owners. In addition, CBD should be initiated at the early stage of the disease because its use as a single agent in refractory and severe cases (not reported in this case series) did not often lead to an improvement in symptoms.

Although the sliding scale of dosing was inconsistent, establishing a dosage for atopic dermatitis is the same as that for 3 others for which we have conducted efficacy studies, namely osteoarthritis, refractory epilepsy, and anxiety/fear. In the future, the dose will be increased according to the protocol of 0.5 mg/kg q12h and reassessed after 7, 10, or 14 d (it takes several days for plasma CBD concentration to reach a steady state). The dosage should then be increased as indicated by the results (e.g., increase by 0.25 mg/kg). The correct dosage for a given patient for a particular condition would be based on the patient's endocannabinoid system density and distribution, the severity of its condition, its body surface area, and the mixture of the product being used.

In this study, we observed minimal improvement in the distal limbs when they were involved in CAD. The dogs were distracted by the affected areas and continued to lick them, which may have worsened the condition of the skin surface due to physical stimulation. Perhaps a specific mechanism, such as the number of bacteria in the skin lesions, was present, but not assessed. Therefore, additional case reports and studies to elucidate mechanisms are needed.

Although the number of cases was limited, we tested a new treatment method with the aim of examining the safety of combining a CBD supplement with therapeutic drugs, with a lack of adverse events following administration of CBD. Furthermore, there was a decrease in the frequency of concomitant medication use and an improvement in quality of life and symptoms, suggesting that a new approach using supplementary CBD could improve the quality of life for dogs as well as their owners.

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