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Pharmacokinetic Evaluation of a Cannabidiol Supplement in Horses

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Abstract

Cannabidiol (CBD) products have gained popularity among horse owners despite limited evidence regarding pharmacokinetics. The purpose of this study was to describe the pharmacokinetic profile of multiple doses of an orally administered cannabidiol product formulated specifically for horses. A randomized 2-way crossover design was used. Seven horses received 0.35 or 2.0 mg/kg CBD per os every 24h for 7 total doses, separated by a 2-week washout. Plasma CBD and delta-9-tetrahydrocannabinol (THC) were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS) daily through day 10, then on day 14 after beginning CBD administration. On the final day of CDB administration, plasma CBD and THC were quantified at multiple times. After administration of 0.35 mg/kg of CDB, the C_{max} of CBD was 6.6 ± 2.1 ng/mL while

T_{max} was 1.8 ± 1.2 h, whereas the C_{max} for THC was 0.7 ± 0.6 ng/mL with a T_{max} of 2.5 ± 1 h. After administration of 2.0 mg/kg of CBD, the C_{max} of CBD was 51 ± 14 ng/mL with a mean T_{max} of 2.4 ± 1.1 h and terminal phase half-life of 10.4 ± 6 h, whereas the C_{max} of THC was 7.5 ± 2.2 ng/mL with a T_{max} of 2.9 ± 1.1 h. Oral administration of a cannabidiol product at 0.35 mg/kg or 2.0 mg/kg once daily for 7 days was well-tolerated. Based on plasma CBD levels obtained, dose escalation trials in the horse evaluating clinical efficacy at higher mg/kg dose rates are indicated.

Highlights

- Once daily dosing of CBD at 0.35 and 2.0 mg/kg in the horse was well-tolerated but may result in plasma levels insufficient to provide clinical results.
- CBD appeared in plasma rapidly after oral administration and showed an initial rapid decline followed by a more prolonged terminal elimination phase half-life.
- Measurable THC levels are detectable in plasma with administration of this CBD product, highlighting the need to educate veterinarians and horse owners administering cannabidiol to competitive horses.

Keywords

Cannabidiol; CBD; Equine; Pharmacokinetics

1. Introduction

Cannabidiol (CBD) has steadily gained popularity in the human and veterinary medical fields as an alternative or adjunct to many established treatment modalities for a multitude of indications. In human medicine, cannabis-based products have been investigated for many conditions, most notably epilepsy [1-4], but also including multiple sclerosis-related spasticity [5], anxiety [6], mental health conditions such as schizophrenia [7, 8], elevated intraocular pressure [9, 10], and nausea and/or pain related to chemotherapy treatments [11, 12]. While cannabidiol products have been investigated for treatment of pain in rodent models, little is available on the efficacy of cannabinoids for treatment of acute and chronic pain in humans, though they are marketed for this indication in humans and animals [13-15]. In domestic animal species, CBD products have shown promise for treatment of epilepsy [16, 17], aggressive behavioral issues [18], hyperaesthesia [19], and osteoarthritis [20-22], though available objective data regarding efficacy is still scarce.

With limited research available regarding clinical efficacy of cannabidiol in domestic veterinary species, basic information regarding pharmacokinetics of cannabinoids for these species is also lacking. Pharmacokinetics of orally and/or transdermally administered cannabidiol in dogs and cats have been evaluated in recent years [21, 23-28]. Clinical use of cannabidiol products is gaining rapid popularity among horse owners with little objective evidence to support efficacy, and little published research as of this writing regarding pharmacokinetics of cannabinoids in this species [29]. Anecdotal

reports in the equine industry suggest cannabidiol products provide anti-inflammatory, analgesic, and calming effects, and these products are readily available throughout the equine community.

Investigation into the pharmacokinetics of cannabidiol products in the horse is necessary given the demand for and availability of these products and the lack of objective data supporting their use. The objective of this study was to describe the pharmacokinetics of an orally administered cannabidiol product at a low and high dose in the horse after 7 consecutive daily doses.

2. Materials and Methods

2.1 Animals

Seven healthy adult light-breed horses (4 Quarter Horses, 2 Paints and 1 Mixed Breed; 2 mares and 5 geldings) were enrolled in the study, aged 6-23 years (mean age 15 years), with body weights ranging between 497 and 600 kg. Five of seven horses were sourced from the university-owned research herd, and two were privately owned. Informed consent forms were signed by the owner for each of the privately owned horses. Subjects did not receive any other medications or supplements for a minimum of 2 weeks prior to study initiation or throughout the study period. The study protocol was approved by the Oklahoma State University Institutional Animal Care and Use Committee.

All horses were housed on pasture at the Equine Research Park of the Oklahoma State University College of Veterinary Medicine for the duration of the study period. Horses were given a minimum two-week period to acclimate to housing conditions prior to initiation of treatment groups. Daily physical examinations were performed prior to initiating and for the duration of the acclimation period; examinations were performed by trained personnel who were not blinded to treatment (CC, MI). Diet throughout the study period consisted primarily of free choice local grass pasture; twice daily, subjects were brought into individual stalls and fed ¼ pound of a standard pelleted equine diet (Purina® Impact® 12%, Purina Animal Nutrition, Arden Hills, MN); horses were not fasted at any point during the study. Horses were housed in individual stalls for a 12-hour time period during frequent pharmacokinetic sample collection on day 6; during this period, they were given free choice grass hay. Ad libitum access to fresh water was provided throughout the entire study period.

2.2 Drug administration

The study was randomized with a crossover design. Each horse was randomly assigned to one of two treatment groups: (i) 0.35 mg/kg CBD per os every 24h and (ii) 2.0 mg/kg CBD per os every 24h. Treatments were administered by one of two non-blinded operators (CC, MI), with the patient's morning pelleted diet, for 7 total doses. Horses were weighed on day 0 of each treatment round, and this weight was used to calculate the CBD dose to be administered to that horse daily for the 7-dose protocol. The CBD dose for each horse was measured by weight using a gram scale. This amounted to a volume ranging from 18-21 g of pellets for the 0.35 mg/kg dose and 101-

122 g for the 2.0 mg/kg dose. Each horse was directly observed while eating for approximately 10 minutes or until the horse's morning feeding was completely finished to ensure that the entire dose was consumed. This protocol was repeated with a 2-week washout period in-between until each horse received both treatments.

2.3 Monitoring

During both treatment group trials and throughout the washout period, horses received daily physical examinations and were monitored for evidence of colic, inappetence, and lethargy. Heart rate, respiratory rate, and temperature were recorded daily. Physical examinations and monitoring were performed by trained personnel who were not blinded to treatment (CC, MI).

2.4 CBD product

The hemp pellets used in this study were acquired from Kahm CBD (Las Vegas, NV, USA) and contained 10 mg of CBD per gram of pellets. THC present in the hemp was below the limit of quantification.

2.5 Pharmacokinetics sample collection

For analysis of CBD and THC, 6 mL of whole blood was collected into Heparinized vacutainer tubes by direct venipuncture immediately prior to drug administration, before the initial dose (day 0) and every 24 hours for 7 total doses (last dose day 6); on day 6, blood was also collected after the last medication dose at the following time points: 30

minutes, 1, 2, 4, 8, 12, and 24 hours (day 7). Blood sampling continued after discontinuation of CBD administration at 24-hour intervals on days 8, 9, 10, and 13. Protracted sampling following the final dose was performed due to the absence of published data regarding cannabidiol pharmacokinetics in the horse at the time of study design and data collection. Samples were centrifuged at 3500 g for 10 min; plasma was removed, placed in cryotubes, and stored at -80ºC until analysis. Samples were centrifuged and frozen within one hour of collection.

2.6 Assay

Plasma THC and CBD concentrations were quantified in equine heparinized plasma by a modified liquid chromatography-tandem mass spectrometry (LC-MS/MS) method previously validated [30]. Calibrants were prepared by adding appropriate concentrations of CBD and THC (Cerilliant Corporation, Round Rock, TX) in methanol to unmedicated equine plasma over a range of concentrations from 1-50 ng/ml. Experimental samples and calibrants were extracted by solid phase extraction using commercial Styre Screen THC 60 mg 3 ml columns (United Chemical Technologies, Bristol, PA), according to the manufacturer's protocol. One milliliter of plasma was mixed with 2.5 ml of cold acetonitrile that contained 10 ng of deuterated CBD and THC (Cerilliant Corporation), vortex mixed, then centrifuged. The supernatant was evaporated under nitrogen at 40° C, then redissolved in 200 µl of water before loading onto the cartridges. Cartridges were washed with 2 ml of 84:15:1 of water:acetonitrile:NH_4OH, dried under full pressure, then eluted with 1 ml of 49:49:2 of

hexane:ethyl acetate:glacial acetic acid. Samples were dried under nitrogen gas at 40° C, then redissolved in 100 µl of 0.1% formic acid in water:acetonitrile (60:40, v/v).

The high-performance liquid chromatography system included a Shimadzu DGU-20A3 degasser, LC-20ADxr pumps, SIL-20ACxr autosampler, and a CTO-20 column oven (Shimadzu Corp, Columbia, MD). Separation was accomplished with a Raptor Biphenyl column (2.7µm, 50 X 3.0mm) fitted with a Raptor Biphenyl guard cartridge (2.7µm, 5 X 3.0mm) (Restek Corp, Malvern PA). The column oven was set at 50°C, injection volume was 10µL and the autosampler was cooled at 4°C. Gradient elution was performed at a flow rate of 0.5mL/min. Initial gradient conditions were 35%A (0.1% formic acid in water (v/v)) and 65%B (0.1% formic acid in acetonitrile (v/v)). Mobile phase B increased to 75% at 2 min, then increased to 95% at 2.5 min. Mobile phase B was maintained at 95% for 1.5 min, followed by column re-equilibration to 65%B over 0.5min and hold for 0.5min. Mobile phases were directed to waste for the first 1 min. An internal and external needle rinse and wash was performed on the autosampler at the 3 min mark.

Analysis was performed on a Shimadzu LCMS-8040 with electrospray ionization in positive ionization mode using multiple reaction monitoring. During method development, tandem mass spectrometry parameters were optimized via direct infusion of individual analytes at 100ng/mL. The following transitions (*m/z)* were utilized: CBD – 315.3/193.0, 315.3/259.1; d_3 CBD – 318.3/196.3, 318.3/262.1; THC – 314.9/193.1, 314.9/123.0; d_3 THC – 318.3/196.1, 318.3/123.0. Source parameters were optimized as follows: nebulizing gas flow – 3L/min; drying gas flow – 15L/min; desolvation line

temperature – 250°C; heat block temperature – 400°C. Argon collision gas was set at 230kPa. Lab Solutions software (version 5.65) was utilized for data acquisition and data processing.

The assay conditions were also assessed for the possibility that CBD could convert to THC in equine plasma or during the extraction. One milliliter samples in triplicate of frozen-thawed equine heparinized plasma, freshly collected equine heparinized plasma, and isotonic buffer at a pH of 7.4 were all mixed with 10 ng CBD in a small volume (<5%) of methanol. These samples were then incubated for one hour at 25° C before being subjected to the SPE extraction procedure and LC/MS/MS analysis.

2.7 Pharmacokinetic analysis

Plasma CBD and THC concentration versus time curves were analyzed noncompartmentally using standard equations [31]. Maximal plasma drug concentration (C_{max}) was observed directly from the data, as was the time (T_{max}) at which that maximum concentration occurred. The apparent elimination half-life ($t_{1/2(\lambda_z)}$) was determined from the slope of the terminal phase as ($0.693/\lambda_z$) and reported as the harmonic mean and pseudo-standard deviation [32].The area under the plasma analyte concentration versus time curve (AUC_T) was calculated as the sum of trapezoids from the beginning of day six through one 24 hour dosing inverval. In order to estimate the AUC_T after the low dose of CBD, the plasma concentrations less than the limit of quantitation (<LOQ) during the dosing interval were estimated using the elimination rate determined from the high dose group and the last quantifiable plasma CBD

concentration. For estimation of the plasma THC AUC_T, the first plasma concentration within the 6th dosing interval that was <LOQ was assigned a value of ½ LOQ, and subsequent plasma concentrations were assigned a value of zero. The mean residence time (MRT) was corrected for steady state conditions [33].

3. Results

3.1 Assay performance

The assay performance was satisfactory. Cannabidiol did not spontaneously convert to THC in any of the three tested matrices: frozen-thawed heparinized equine plasma, fresh equine plasma, or buffer at pH of 7.4. Intraday accuracy for CBD analysis was 97%, 95%, and 99% at concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively. Intraday coefficient of variation (CV) was 3%, 4%, and 3% at 1.75, 7.5, and 37.5 ng/ml, respectively. Interday accuracy for CBD was 101%, 97%, and 99% for concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively. For THC, intraday accuracy was 110%, 107%, and 107% for concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively. Intraday CV for THC was 3%, 1%, and 2% for concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively. Interday accuracy for THC was 110%, 103%, and 105% for concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively. Interday CV for THC was 4%, 3%, and 2% for concentrations of 1.75, 7.5, and 37.5 ng/ml, respectively.

3.2 Pharmacokinetics

Mean +/- s.d. plasma concentrations of CBD following 7 daily oral doses at 0.35 mg/kg every 24h are shown in figure 1. Samples were lost and unable to be analyzed for one horse, therefore these values were calculated using the data from the remaining 6 horses. The mean C_{max} of CBD was 6.6 ± 2.1 ng/mL with a mean T_{max} of 1.8 ± 1.2 h (Table 1). As the samples later in the dosing interval were below the assay's LOQ, the terminal phase half-life was not estimated after administration of the low dose of CBD. Trough CBD concentrations following repeated dosing were below the lower limit of quantitation (LLOQ) for the analyzer at 24 hours following drug administration in 5/6 horses. Since few trough samples exceeded the LOQ, accumulation of CBD was not appreciated after multiple doses.

THC concentrations were quantifiable in plasma for 4/6 horses following 7 daily oral doses at 0.35 mg/kg every 24 h (Figure 1). The mean C_{max} for THC was 0.7 ± 0.6 ng/mL with a mean T_{max} of 2.5 ± 1 h (Table 1). The terminal phase half-life for THC was not estimated as plasma THC concentrations quickly dropped below the assay's LOQ. Troughs following repeated dosing were below the lower LOQ at 24 hours following drug administration in all 6 horses.

Mean ± s.d. plasma concentrations of CBD following 7 daily oral doses at 2.0 mg/kg every 24 h administered to seven horses are shown in figure 2. The mean C_{max} of CBD was 51 ± 14 ng/mL with a mean T_{max} of 2.4 ± 1.1 h and a mean terminal phase half-life of 10.4 ± 6 h. Trough CBD concentrations increased over the first few days of daily CBD

administration, but reached approximately steady state conditions after 3 days of administration (Figure 2).

Mean ± s.d. plasma concentrations of THC following 7 daily oral doses at 2.0 mg/kg every 24 h are shown in Figure 2. The mean C_{max} of THC was 7.5 ± 2.2 ng/mL with a mean T_{max} of 2.9 ± 1.1 h. Troughs following repeated dosing were below the LLOQ at 24 hours following drug administration for all horses on all days, with the exception of one horse on day 7.

3.3 Monitoring

The cannabidiol product was easily administered with feed and was well-tolerated by all horses enrolled in the study. Temperature, pulse rate, and respiratory rate remained within normal limits for all 7 horses throughout the entire cannabidiol administration period for both 0.35 mg/kg and 2.0 mg/kg CBD. No horse displayed any evidence of diarrhea or loose stool, decreased appetite, or somnolence during daily examinations throughout the study period.

4. Discussion

Similar to previous studies evaluating the pharmacokinetics of orally administered cannabidiol [21, 23-25, 29, 34], this study found that CBD appeared in the plasma fairly rapidly, with a T_{max} of approximately 2 h. Rapid absorption of CBD with oral cannabidiol dosing has been documented across species, though individual reports of the value of

the T_{max} of CBD varied with formulation [21, 24, 25, 29, 35-38]. Plasma CBD concentrations in this study also showed an initial rapid decline followed by a more prolonged terminal elimination phase half-life of approximately 10 h. This value is consistent with the elimination half-life of 10 h reported in a recently published study evaluating pharmacokinetics of cannabidiol after single doses in horses[29]. More rapid CBD elimination has been recorded in humans[39, 40], as well as in other species. Canine and feline pharmacokinetic studies of orally administered CBD products reported a shorter mean CBD elimination half-life of 1 to 4 hours [21, 23-25] with one study reporting a more prolonged value of 13.3h, similar to the present study [25].

A recently published canine study evaluated repeated oral dosing for 28 days of a CBD oil at 1, 2, 4, and 12 mg/kg. This study documented changes in pharmacokinetic variables with prolonged administration such as increases in AUC values suggestive of drug accumulation in plasma; it also established steady state plasma concentrations were reached at 2 weeks, with similar mean trough concentrations after 2 and 4 weeks of dosing[28]. While the present study is limited in its ability to establish whether a steady state was reached by lack of a complete curve after the first dose on day 0, the data presented here indicates that trough CBD concentrations increased over the first few days and then reached approximate steady state conditions after 3 days of administration. Additional studies evaluating day 0 pharmacokinetics and AUC and trough concentrations with more prolonged CBD administration are warranted to further investigate potential changes in pharmacokinetic variables with long-term administration in the horse.

The CBD and THC C_{max} values and AUC/dose increased in an approximately dose-proportional manner in the present study, as has been the case for other human and animal pharmacokinetic studies [21, 23, 25, 29, 38, 41] including the recently reported equine study[29]. An increase in C_{max} plasma concentrations of CBD and THC with increasing doses of cannabinoids that is disproportionate in comparison to the increase in mg/kg dose has also been reported in dogs, suggesting that CBD bioavailability can increase with increasing dose [21, 25]. A disproportionate increase in C_{max} in comparison to increase in mg/kg dose was not appreciated in this study, though this may have been appreciated with higher mg/kg doses or more prolonged administration.

Cannabidiol products are gaining popularity for use in equine performance horses for a number of proposed indications. As many of the available CBD products marketed to horse owners contain some quantity of THC, this should be an important point of consideration for horse owners and their veterinarians. THC levels may result in a positive drug test on a competition basis or during pre-purchase examination drug screening. Previous research has indicated that a single dose of THC may result in detectable metabolites of THC in urine or plasma for up to 8 to 12 days in humans and dogs [42-44]. The cannabidiol product evaluated here was administered at a relatively low dose and consists of a low ratio of THC:CBD. Despite this low quantity of THC administered, THC was still present in measurable quantities in plasma following the 2.0 mg/kg dose beginning at 30 minutes post-administration in 2 horses, in 6/8 horses at 1 and 2 h post-administration, in 7/8 horses at 4 h post-administration, and in 8/8 horses

at 8h post-administration; measurable plasma levels were still present in 5/8 horses 12h post-administration, and in 1/8 horses 24h post-administration. While the concentrations of THC measured here were low and therefore likely sub-therapeutic in nature, the fact that THC was measurable in plasma should be noted. Urine concentrations of CBD and THC were not evaluated in the present study. However, the recently published equine pharmacokinetic cannabidiol study reported detectable concentrations of CBD in urine up to 48 hours following 0.5 and 1.0 mg/kg dosing, and up to 72 hours following 2.0 mg/kg dosing[29]. THC levels were not measured in this study, however the detection of CBD in urine up to 72 hours following a single dose should also be noted.

Our results indicate that oral administration of a cannabidiol product at 0.35 mg/kg or 2.0 mg/kg once daily for 7 days was well-tolerated as assessed via daily physical examinations and twice daily monitoring. No incidences of diarrhea or loose stool, decreased appetite, or somnolence were recorded. It is possible that higher doses would result in clinical concerns similar to those described in other species. In dogs, examples reported include loose stool and vomiting [24, 45]. In humans, tolerability concerns reported include nausea, vomiting, decreased appetite, diarrhea, fatigue, and somnolence [3, 4, 35, 46]. Additional studies evaluating tolerability of this and other cannabidiol products at higher mg/kg dose rates and frequencies in horses are warranted. Future studies more specifically evaluating safety of cannabinoids in horses may also benefit from evaluating parameters such as pre- and post-treatment CBC and serum chemistry values, serial changes in body weight throughout the study, changes in fecal mass, and more specific subjective observation by blinded observers for effects

observed in other species such as decreased appetite, diarrhea, fatigue, and somnolence, with inclusion of a placebo treated group.

Prior to initiation of this study, information was not available in the literature regarding pharmacokinetics of orally administered cannabinoid products in the horse, despite the availability of multiple CBD products marketed for the horse. The 0.35 mg/kg dose evaluated here was based on the label dose for the product. The 2.0 mg/kg dose was chosen based on pharmacokinetic and efficacy studies performed in canine and feline patients [16, 20, 21, 24, 25, 37]. As of this writing, pharmacokinetics of orally administered cannabidiol at 0.5, 1, and 2.0 mg/kg have been evaluated in the horse when administered as a single dose [29]. Doses evaluated in that study were chosen based off of anecdotal reports from distributors of cannabinoid products for horses and dogs; C_{max} achieved with the 2.0 mg/kg dose in that study was 6.14 ± 3.52 ng/mL [29]. A recent in vitro study evaluated potential anti-inflammatory effects of CBD in the horse by assessing its effect on production of TNFα, IFNγ and IL-10 in peripheral blood mononuclear cells from older horses. In this study, a CBD concentration of 4 µg/mL was shown to significantly decrease production of these inflammatory cytokines[47]. This provides some preliminary information on a CBD concentration that suggests potential anti-inflammatory efficacy in the horse.

Although cannabinoids have been administered for treatment of a variety of clinical conditions, one that would be of particular interest for equine patients is for the treatment of pain associated with arthritis. Gamble et al. evaluated single dose

pharmacokinetics of a cannabidiol based oil in dogs and then assessed clinical efficacy in treatment of osteoarthritis using a 2.0 mg/kg dose. Single dose pharmacokinetics at this dose rate indicated a median plasma C_{max} of 102 ng/mL; clinical efficacy was appreciated when this dose was given twice daily over 4 weeks, suggesting that 102 ng/mL would be an appropriate therapeutic level for arthritis pain treatment in dogs [21]. Mean C_{max} values (5.3 ng/mL) for the 0.35 mg/kg dose evaluated in the present study were well below what have been established as therapeutic concentrations in other veterinary and human studies [1, 21], therefore a 0.35 mg/kg dose rate is unlikely to be clinically effective in the horse. The mean C_{max} (51 ng/mL) for the 2.0 mg/kg dose rate in this study was also well below therapeutic level established for osteoarthritic dogs, and well below the concentration resulting in reduction of inflammatory cytokines in vitro in the horse[21, 47]. Given that the drug in the present study was administered orally with the daily pelleted ration, loss of drug during consumption could certainly influence C_{max} values obtained. However, this risk was minimized by direct observation of each horse during dosing to ensure that each horse consumed the entire dose. Based on the relatively low plasma CBD levels obtained in this study, dose escalation trials in the horse evaluating clinical efficacy, for treatment of lameness or other indications, at higher mg/kg doses are indicated.

5. Conclusions

This study is the first to report CBD and THC concentrations after 7 daily doses of a cannabidiol product in the horse. Based on the results reported here, horses appeared to reach approximately steady state concentrations of CBD by 3 days following initiation

of multiple dose administration. Results from this study, in comparison to previous efficacy studies in other species, suggest 0.35 mg/kg dosing is unlikely to show clinical efficacy; 2.0 mg/kg dosing, while well-tolerated in this study, also may result in plasma levels insufficient to provide clinical results. Plasma levels do appear to increase in a dose-proportional manner with the dose range examined here. This information, combined with the rapid initial decline in plasma CBD levels after reaching maximum plasma concentration, indicates a need for more studies evaluating pharmacokinetics and clinical efficacy of higher and more frequent dosing of cannabidiol in the horse. Additionally, findings from this study regarding measurable THC levels in plasma highlights the need to educate veterinarians and horse owners administering cannabidiol to competitive horses.

Author Contributions

Todd Holbrook and Lara Maxwell designed the study. Megan Williams, Cara Croft, and Michelle Ientile conducted the experimental protocols. Lara Maxwell and Kacey Cilburn conducted the sample analysis. Lara Maxwell conducted the data analysis. Megan Williams, Lara Maxwell, and Kacey Cilburn drafted the manuscript. All authors revised and approved the manuscript before submission.

Ethical Statement

The protocol used in this study was approved by and conducted in accordance with guidelines provided by the Oklahoma State University Institutional Animal Care and Use Committee.

Financial Disclosure

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Declaration of interest
This work was supported by a grant from Kahm CBD,Las Vegas, NV.

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Figures

Figure 1. Mean ± SD plasma CBD and THC concentrations after the oral administration of 0.35 mg/kg CBD to six horses once per day for six days. Note that only the concentrations on the last day are depicted as concentrations were generally below the assay's limit of quantitation on the previous days.

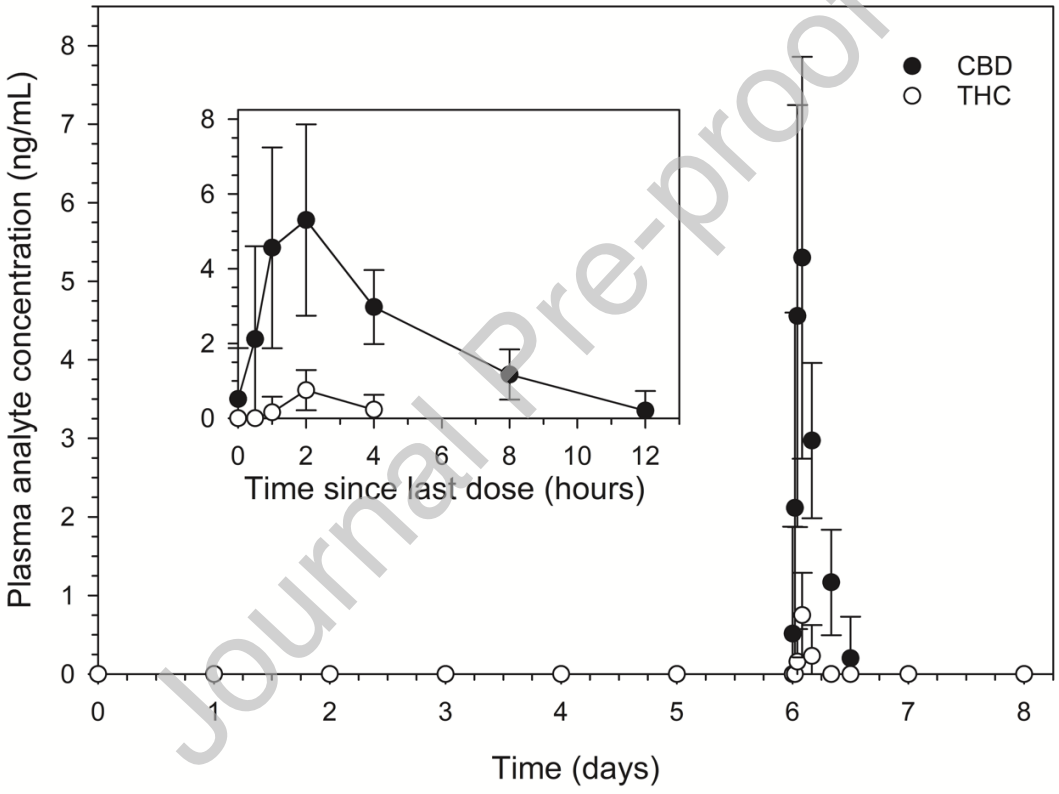
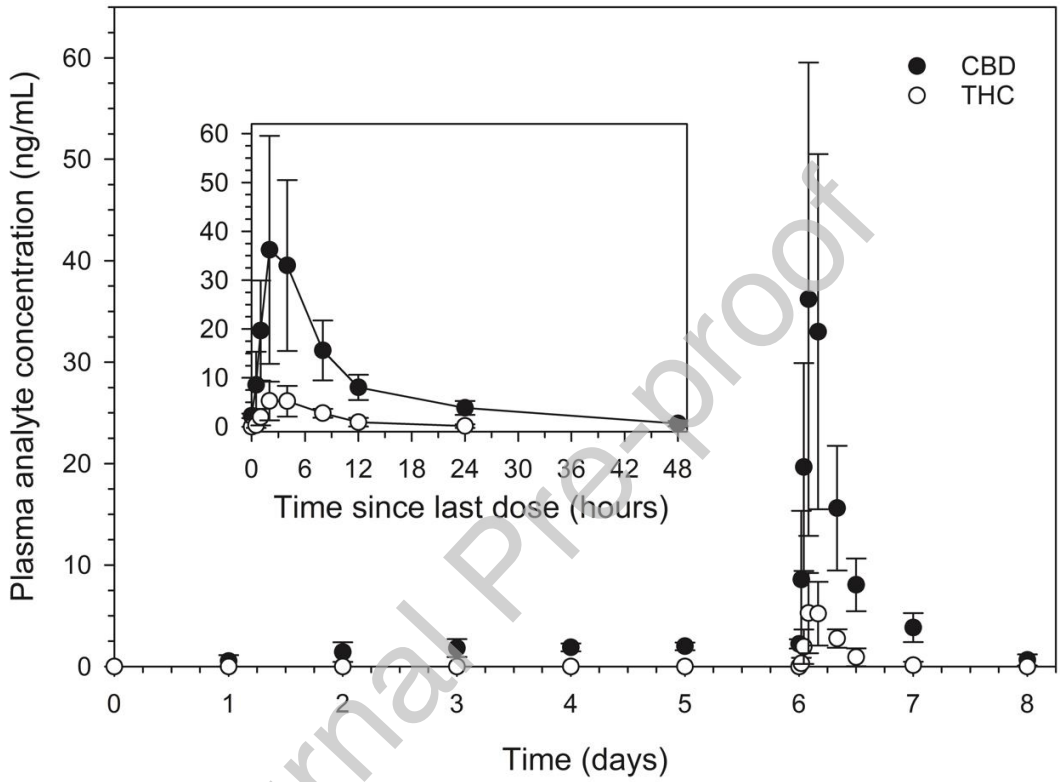


Figure 2. Mean ± SD plasma CBD and THC concentrations after the oral administration of 2 mg/kg CBD to seven horses once per day for six days.



Tables

Table 1. Pharmacokinetic parameters of CBD and THC after oral administration of 0.35 mg/kg (N=6) or 2 mg/kg (N=7) of CBD to horses.

	CDB		THC	
	0.35 mg/kg	**2 mg/kg**	**0.35 mg/kg**	**2 mg/kg**
C_{max}	6.6±2.1 (6.8, 5.7-7.3)	51±15 (44, 41-63)	0.7±0.6 (1.0, 0.2-1.2)	7.5±2.2 (7.6, 6.5-7.9)
T_{max}	1.8±1.2 (1.5, 1.0-2.0)	2.4±1.1 (2.0, 2.0-3.0)	2.5±1 (2.0, 2.0-2.5)	2.9±1.1 (2.0, 2.0-4.0)
$t_{(1/2)\lambda z}$	ND	13.3±6.9 (13.4, 8.5-15.3)	ND	ND
AUC_T	42±9 (42, 35-46)	330±72 (336, 291-353)	2.8±2.5 (3.0, 0.7-3.8)	52±20 (48, 39-54)
AUC_T/Dose	120±24 (121, 100-130)	165±36 (168, 146-177)	8±7 (8, 2-11)	26±10 (24, 20-27)
MRT_{ss}	156±11 (151, 151-152)	153±6 (151, 151-152)	ND	ND
C_{avg}	1.7±0.4 (1.8, 1.5-1).9	14±3.0 (14, 12-15)	0.1±0.1 (0.1, 0-0.2)	2.0±0.8 (2.0, 1.6-2.2)
$Vd_{area/F}$	170±56 (170, 135-212)	131±96 (115, 68-154)	ND	ND

Data are presented as mean±SD (median, lower-upper quartile). C_{max} = maximum observed plasma concentration; T_{max} = time of Cmax; $t_{(1/2)\lambda z}$ = terminal phase half-life; AUC_T= area under the plasma drug concentration-time curve during one dosing interval, AUC_T/Dose = AUC_T normalized to dose rate of CBD; MRT_{ss} = mean residence time at steady state, C_{avg} = average plasma concentration over a dosing interval; $Vd_{area/F}$ = volume of distribution/bioavailability.