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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy

Angela K. Birnbaum[1,2] | **Ashwin Karanam**[1,2] | **Susan E. Marino**[1,2] | **Christopher M. Barkley**[1,2] | **Rory P. Remmel**[1,2] | **Michaela Roslawski**[1] | **Mary Gramling-Aden**[3] | **Ilo E. Leppik**[1,2,3]

[1]Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota

[2]Center for Clinical and Cognitive Neuropharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota

[3]MINCEP Epilepsy Care, University of Minnesota Physicians, Minneapolis, Minnesota

Correspondence
Angela K. Birnbaum, Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Room 463, 717 Delaware Street, SE, Minneapolis, MN 55414.
Email: birnb002@umn.edu

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Abstract

Objective: To evaluate the pharmacokinetics of a purified oral cannabidiol (CBD) capsule administered with and without food in adults with refractory epilepsy.

Methods: Adult patients who were prescribed CBD for seizures, had localization-related intractable epilepsy with ≥4 seizures per month, and qualified for Minnesota cannabis were enrolled. A single dose of 99% pure CBD capsules was taken under both fasting (no breakfast) and fed (high fat 840-860 calorie) conditions. Blood sampling for CBD plasma concentrations was performed under each condition between 0 and 72 hours post-dose and measured by a validated liquid chormatography-mass spectometry assay. CBD pharmacokinetic profiles including maximum concentration (C_{max}), area-under-the-curve from zero to infinity ($AUC_{0-\infty}$), and time-to-maximum concentration (T_{max}) were calculated. The confidence intervals (CIs) for log-transformed C_{max} and $AUC_{0-\infty}$ ratios between fed and fasting states were calculated. Seizure and adverse events information was collected.

Results: Eight patients completed the study. On average C_{max} was 14 times and $AUC_{0-\infty}$ 4 times higher in the fed state. The 90% CI for the ratio of fed versus fast conditions for C_{max} and $AUC_{0-\infty}$ were 7.47-31.86 and 3.42-7.82, respectively. No sequence or period effect for C_{max} and $AUC_{0-\infty}$ was observed. No adverse events were reported.

Significance: Administering CBD as a capsule rather than a liquid allows for more precise determination of pharmacokinetics parameters and is more representative of CBD swallowed products. The fat content of a meal can lead to significant increases in C_{max} and $AUC_{0-\infty}$ and can account for variability in bioavailability and overall drug exposure within patients with oral products.

KEYWORDS
cannabidiol, CBD, epilepsy, food-effect, pharmacokinetics

Birnbaum and Karanam are equal first authors.

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1 | INTRODUCTION

An oral cannabidiol (CBD) liquid formulation is now approved by the US Food and Drug Administration (FDA) for use in patients with seizures associated with Lennox-Gastaut and Dravet syndromes.[1] However, due to varying US state laws, various forms of CBD, including CBD-solid formulations, are also being used in adult patients off-label. CBD has a complex pharmacokinetics profile including low bioavailability, which is attributed to high lipophilicity (log$P > 5$), poor water solubility (≤0.0126 mg/mL), and significant first-pass effect,[2–5] predominantly by cytochrome P450 (CYP) isoforms CYP3A4, CYP2C9, and CYP2C19.[2,6–9] CBD is reported to have a high apparent volume of distribution after oral dosing (V/F) ranging from 250 to 450 L/kg[1,3,10,11] and a highly variable plasma oral clearance (CL/F) ranging from 533 to 3783 L/h.[1,3,10,11] CBD half-life ($t_{1/2}$) ranges from 18 to 60 hours.[1,10–13]

Evidence exists for a large food effect with lower doses (approximately 40 mg single dose) of tetrahydrocannabinol (THC) and CBD (1:1) delivered as an oromucosal spray, resulting in a threefold higher C_{max} and fivefold higher area-under-the-concentration-time curve ($AUC_{0-\infty}$) for fed compared to fasting states.[12] A similar food effect for the currently approved FDA liquid formulation (Epidiolex) has also been reported.[11] Liquid formulations are associated with a higher possibility of inconsistent dosing, which complicates the characterization of drug pharmacokinetics.[14,15] CBD delivered orally as a capsule ensures that 100% of the dose reaches the gut, allowing for accurate characterization of CBD pharmacokinetics and allows investigation of CBD-solid formulations. Previous studies used only healthy volunteers receiving a liquid formulation and therefore the magnitude of the food effect on CBD pharmacokinetic parameters in persons with refractory epilepsy receiving antiseizure drugs has not been precisely determined. Our objective was to quantify the effect of food on the pharmacokinetic profile of purified CBD capsules in adult patients with refractory epilepsy.

Key Points

- A moderate dose of CBD administered as an oral capsule resulted in 4- and 14-fold increases in $AUC_{0-\infty}$ and C_{max}, respectively, in adult patients with epilepsy
- Steady-state concentrations from a 300 mg dose were on average 21.3 μg/mL
- Patients should be advised to take CBD with balanced meals to minimize fluctuations due to food effect

2 | METHODS

2.1 | Subjects

Persons approached for the study were adult patients (≥18 years) who had localization-related intractable epilepsy by electroencephalography (EEG) and semiology with occurrence of four or more seizures per month. To be considered for medical cannabis treatment, patients had to meet the Minnesota Cannabis Registry requirements and be a patient of University of Minnesota Physicians-MINCEP Epilepsy Care Clinic for a minimum of 6 months. To participate in this study patients needed to be able to provide informed consent, be eligible to receive CBD as part of normal clinical care, have no history of recent status epilepticus, and not be women of childbearing age who are not practicing contraception.

2.2 | Study design

The study was approved by the institutional review board at the University of Minnesota and conducted in compliance with the Minnesota Department of Health, the International Conference on Harmonization Guideline for Good Clinical Practice, and the Declaration of Helsinki. This was a two-period, two-sequence, open-label food effect study. The meals for fasting and fed conditions followed the FDA industry guidance for food effect and bioequivalence studies, with a goal of 800 calories for the fed condition.[16] In the state of Minnesota, patients are able to obtain medical cannabis from two manufacturers. Patients who were prescribed the Vireo Health Violet formulation (99% extracted and purified CBD), available as 100 mg capsules, were enrolled in the study. The Violet formulation from Vireo Health is a purified 99% CBD extract from *Cannabis sativa* in a coconut oil vehicle formulated as a soft gelatin capsule. The product is third-party tested as required by Minnesota state law. Patients in this study received Violet formulations from four different lots. Testing in a state-approved independent laboratory showed that the CBD concentration contained in each lot was within 4% of the target of 100 mg per capsule. Patients on polytherapy did not alter their medications or doses during the duration of the study. A crossover design was employed so that each patient served as their own control.

All patients continued to take their prescribed non-CBD medications as usual. Before the predose (time 0) blood draw, patients fasted overnight for at least 10 hours. For period 1, subjects were asked to take their CBD dose either in a fasting or fed state based on random assignment. Water (240 mL) was given at the time patients took their CBD dose. In the fasting state, breakfast was supplied 4 hours postdose. The fed state consisted of an overnight

TABLE 1 Participant demographics

Characteristic	Median (range) or count
Sample size	8
Age (years)	49 (27-79)
Weight (kg)	90 (66-113)
Male gender	6
Race	
Caucasian	7
African American	1
Diagnosis	
Localization-related epilepsy	5
Intractable epilepsy	3

fast, followed by a high-fat meal that consisted of a "breakfast burrito" consumed within 30 minutes of the CBD dose. This breakfast consisted of 840-860 calories, with 500-600 calories from fat. For period 2, all patients took their dose in the alternative fed/fast state depending on their period 1 assignment. Due to scheduling and patient convenience, the range of time between period 1 and 2 was approximately 2 weeks. After period 2, patients took their CBD daily with the usual pattern of food intake and returned once they reached steady-state post chronic dosing (ie, after >2 weeks on CBD) for two additional blood draws and a neuropsychological test session.

2.3 | Pharmacokinetic assessments

Blood samples were collected from an indwelling catheter or venipuncture. During both fed and fasting states, blood samples were collected predose and at 0.5, 1, 2, 2.5, 3.5, 4, 5, 6, 24, 48, and 72 hours. Blood samples for the steady-state dosing portion of the study were collected at times 1-hour and 2-hours after their morning dose. Plasma from blood samples was separated within 2 hours of blood draw by centrifugation and frozen at −80°C until analysis. Quantification of CBD in plasma was performed using a negative-ion mode electrospray-ionization liquid chromatography-tandem mass spectrometry method validated in our laboratory.[17] The lower limit of quantification was 0.05 ng/mL with 98.0%-103.3% accuracy, 2.7%-4.9% intraday, and 0.2%-3.6% interday variation.

The pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ were determined by noncompartmental methods using the NCA plugin of Phoenix 8.1 (Ceratara USA, Inc.). The slope (λz) of the terminal phase of the plasma-concentration time profile was determined by least squares minimization. The $t_{1/2}$ was estimated as $0.693/\lambda z$. $AUC_{0-\infty}$ was determined by the linear trapezoidal rule by summing the areas from zero to the time of last measured concentration and the extrapolated area. The extrapolated area was determined by dividing the last observed plasma concentration by λz.

2.4 | Neuropsychological testing, seizure counts and safety assessments

A neuropsychological battery, consisting of tests of phonemic and semantic fluency[18]; verbal working memory, maintenance, and manipulation (digit span)[19]; and psychomotor and visual information processing speed (Trails A and B and Symbol-Digit Modality Task),[20,21] was administered to characterize the effect of CBD on cognition under fasting and fed conditions. Subjects were administered the battery twice per session: first prior to dosing in both fed and fasting states to capture baseline measures, followed by a second battery 2.5 hours postdose. Seizure and adverse events were recorded daily during the study by subjects or subject caretakers as well as during the study sessions by the study coordinator.

2.5 | Statistical methods

For the quantification of the food effect, the FDA's Guidance to Industry: Statistical Approaches to Establishing Bioequivalence[22] was used. Sample size reestimation post interim analysis revealed that sample size of eight was adequate to detect a difference of at least one standard deviation with 80% power. A linear mixed-effects analysis of variance (ANOVA) model was used to calculate $AUC_{0-\infty}$ and C_{max} point estimates and the 90% confidence intervals (CIs) for the ratios of population geometric means of these parameters for fed compared to fast states. Food state (fast or fed), sequence, and period were considered as factors in the model with food state as fixed effects, and the remainder as random effects. Bioequivalence analysis was performed in the BE plugin of Phoenix 8.1 (Ceratara USA, Inc.). Absence of a food effect was indicated if the point estimates and the 90% CIs for the ratio of the geometric means for C_{max} and $AUC_{0-\infty}$, fed compared to fast states fell within the equivalence limits of 0.8 and 1.25.[16]

The effect of CBD on cognitive function was analyzed in two ways; in both cases paired two-tailed t tests assuming unequal variances were deemed appropriate due to small sample sizes. First, we compared the raw scores for each neuropsychological measure collected postdose across fed and fasting states. This analysis enabled us to directly compare performance in fed and fasting states after CBD dosing. Second, we calculated "relative change scores" for each neuropsychological measure using the formula ((postdose − predose)/predose). These scores take the form of a percentage value that reflects the magnitude of within-person, within-session, CBD-related changes in performance, enabling us

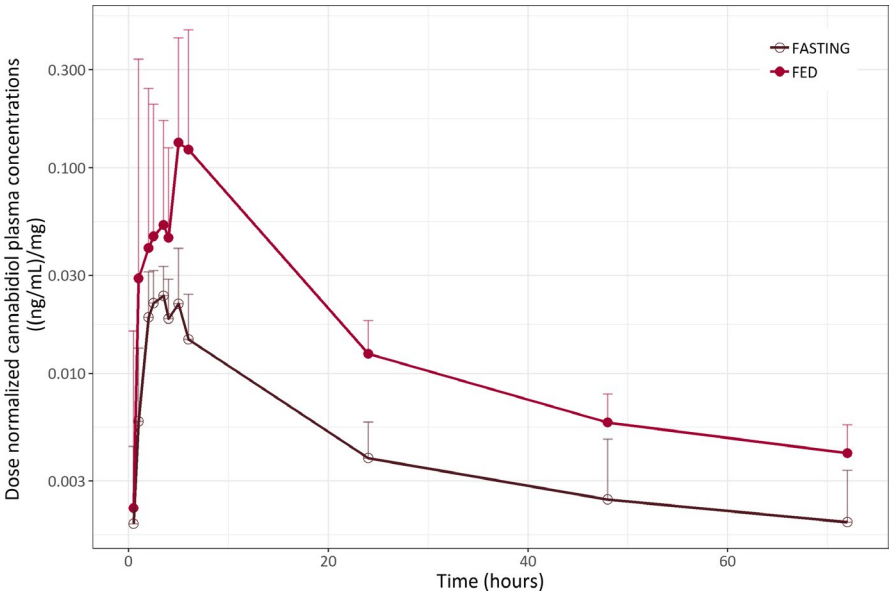

FIGURE 1 Dose-normalized plasma concentration over time profiles for cannabidiol (CBD) from fed (closed circles, red line) and fasted (open circles, dark-blue line) subjects who received a single dose of CBD. The lines represent geometric mean and error bars represent standard deviations

to quantify change while normalizing across observed differences in baseline performance that may obscure more subtle effects of CBD.

3 | RESULTS

3.1 | Subjects

Eleven subjects were enrolled into the study. Two subjects did not meet the eligibility criteria and one subject was disqualified as they were prescribed a combination product of THC plus CBD instead of a CBD-only product after enrollment. Subject demographics are described in Table 1. CBD doses were 200 mg for one subject and 300 mg for all others during the fed and fasting sessions. For the chronic dosing session, all subjects were on a 100-mg thrice daily dose of CBD. No changes in comedications were observed for any subject during the study period.

3.2 | Food effect and pharmacokinetics

The geometric mean CBD plasma-concentration time profiles under fasting and fed states are shown in Figure 1. Table 2 reports the pharmacokinetics of CBD under fed and fasting states. On average, C_{max} was 14 times and $AUC_{0-\infty}$ 4 times higher in the fed state compared to fasting. T_{max} was found to be highly variable within states with fasting state T_{max} ranging from 2 to 5 hours and 1 to 6 hours for fed state T_{max}. On average, CBD T_{max} was faster in the fed state at 2.4 hours compared to 3.2 hours in the fasting state. Half-life was found to be higher in fasting (38.9 hours) compared to fed (24.3 hours) states. Steady state concentrations post 300 mg once daily dose ranged from 4.73 to 40 ng/mL with an average of 21.33 ng/mL. The 90% CI for the ratio of fed (test) vs fast (reference) conditions for C_{max} and $AUC_{0-\infty}$ were 7.47-31.86 and 3.42-7.82, respectively, both well outside the FDA no-effect boundaries of 0.8-1.25. There was a significantly higher overall C_{max} and $AUC_{0-\infty}$ with administration of CBD with a high-fat meal ($P = 0.025$ and 0.008, respectively). No significant sequence or period effect for C_{max} and $AUC_{0-\infty}$ was observed ($P > 0.05$).

TABLE 2 Cannabidiol pharmacokinetic parameters in fed and fasting state after a single oral dose

Parameter (units)	Fasting*	Fed*
Half Life (h)	38.9 ± 19	24.3 ± 8.9
T_{max} (h)	3.2 ± 1.2	2.4 ± 2
DN C_{max} ((ng/mL)/mg)	0.03 ± 0.01	0.45 ± 0.3
DN $AUC_{0-\infty}$ ((h*ng/mL)/mg)	0.53 ± 0.26	2.57 ± 1.6
V/*F* (L/kg)	1515 ± 1024	194 ± 110
CL/*F* (L/h)	1887 ± 990	388 ± 200

*Data are presented as geometric mean ± standard deviation (SD).
Abbreviations: DN $AUC_{0-\infty}$, dose-normalized area under the curve from 0 to infinity; DN C_{max}, dose-normalized maximum concentration; CL/*F*, oral apparent clearance; T_{max}, time to maximum concentration; *V*/*F*, oral apparent volume of distribution.

3.3 | Neuropsychological testing, seizure counts, and safety assessment

Analysis of the raw neuropsychological test scores showed no significant differences for any test in the battery ($P > 0.25$). Likewise, analysis of relative change scores revealed that the magnitude of the difference between baseline and postdose performance did not differ across fed and fasting states ($P > 0.15$). There were no clinically

significant adverse events reported. Seizure frequency did not change significantly during the study in seven patients. Three individuals recorded seizure frequency during the study. Two patients had decreases in seizure frequency during the fed state and one had an increase. Only one of the two patients had a high difference in seizure frequency (decreased from an average of seven seizures per day to one during the fed state).

4 | DISCUSSION

Although CBD is FDA approved for epilepsy syndromes that are more prevalent in children, it is being used in all age groups and a number of conditions due to the availability of medical cannabis in various forms in many US states. This is the first report of the effect of food on CBD pharmacokinetics of a moderate dose in patients with adult refractory epilepsy using a 99% pure CBD capsule, rather than liquid. The concentration-time profiles showed a significant food effect for CBD in both C_{max} and $AUC_{0-\infty}$. It is possible that the variability in CBD bioavailability could lead to pharmacodynamic effects, but this study was not powered to determine this.

We observed that both C_{max} and $AUC_{0-\infty}$ crossed the equivalence limits for the fed state (test) compared to fasting (reference), thus indicating a statistically significant effect of food on CBD pharmacokinetics.[16] For C_{max}, the 90% CI was observed to be 7.47-31.86, indicating a significant increase in C_{max} when CBD is given with a high-fat meal as compared to fasting, resulting in an average 14-fold higher C_{max} (9 ng/mL in fasting vs 126 ng/mL fed). Comparatively, the study with the oral solution reports only a 4-fold higher C_{max} in fed state with a 750 mg dose (335 ng/mL in fasting vs 1628 ng/mL in fed).[11] The 90% CI for $AUC_{0-\infty}$ was estimated at 3.42-7.82, with an average fourfold higher exposure with a high-fat meal. These results are in agreement with a study conducted in healthy volunteers with a THC/CBD combination oromucosal product[12] and the oral solution[11] although we report a higher fold difference between fed and fasting states in patients with epilepsy. A significant period effect was observed in the study with the oral solution, indicating a carryover effect likely due to higher doses of 750 mg and an insufficient washout period of 10 days.[11] Our study showed no significant sequence and period effects with doses of 300 mg and a washout period of 2 weeks, indicating that no carryover effects were observed. Although consistent increases in C_{max} and $AUC_{0-\infty}$ were observed within individuals for the fed compared to fasting state, a large between-subject variability in T_{max} was also observed, with T_{max} ranging from 1 to 5 hours in both fasting and fed states, which contributes to the variability seen in Figure 1.

The exact nature of the increased bioavailability has not yet been determined; however, the chemical properties of CBD and physiological conditions are most likely responsible. A fed state can lead to longer gastric transit time and can result in increases in dissolution for highly lipophilic drugs, which in turn increases absorption and bioavailabilty.[23,24] An increased bile secretion after a high-fat meal can also increase solubility and improve absorption of highly lipophilic drugs.[25] In addition, lymph lipoproteins can increase the solubility of lyophilic drugs and increase exposure after oral dose by enhancing absorption into the lymphatic system.[25,26]

We observed a long half-life for CBD under fed (39 hours) and fasting (24 hours) states that are consistent with previous reports.[11] A shorter half-life of 5.5-6.4 hours was reported in one study using an oromucosal spray preparation[12]; however, due to the higher lower limit of quantification of their assay (0.1 ng/mL compared to 0.05 ng/mL of our assay), characterization of 20% of the AUC (terminal elimination phase) could not be determined. In addition, the amount of CBD and THC that reaches the gut from an oromucosal formulation can be more variable than a capsule that is swallowed. Oromucosal formulations are intended to be absorbed predominantly via the oral mucosa and hence bypass gut and first-pass metabolism encountered via the oral route of administration. However, the bioavailability via oromucosal formulations can vary if the drug is washed into the gut due to either the volume of the spray or errors in dosing the spray.

CBD was found to have a high V/F with an average of 194 L/kg in the fed state and 1515 L/kg in the fasting state. CBD CL/F was estimated at 388 L/h for fed and 1887 L/h for fasting. Our estimates are in agreement with literature values for CBD CL/*F* and *V*/*F*. [1,3,10–12] It is important to note that these are apparent values after an oral dose, which can explain higher values of both *V*/*F* and CL/*F* for fasting states owing to lower bioavailability. To put these values into clinical perspective, for a 300 mg total daily oral dose of CBD, the average steady-state plasma concentration would be 32.2 ng/mL for fed compared to 6.6 ng/mL for fasting. These approximated values are close to the steady state concentrations observed in the study, demonstrating the clinical importance of advising patients to take CBD consistently with food for uniform exposure. The effect of differing fat contents across meals is not known. Even with a relatively longer half-life, it might be useful to prescribe CBD twice a day to minimize fluctuations due to the difference when administered with meals of varying fat content.

Of interest, our results indicate that the differences due to administration of CBD with fatty meals could have an effect on seizure control, although our study was not powered for efficacy. This may be seizure type related, as CBD has been shown to be useful in several types of epilepsies.[27] As expected, no statistically significant differences in cognition were observed between fasting and fed, suggesting that higher exposure is not expected to lead to more or adverse neuropsychological outcomes. This finding is in accord with

those of other studies that show that acute administration of THC, but not CBD, affects learning, memory, psychomotor control, and attention.[28,29]

Our study had several limitations. (1) This study was directed at determining the effect of taking an oral capsule with or without a high-fat meal. It did not explore the effects of other diets, such as those lower in fat. (2) A standard for the metabolite 7-hydroxy-CBD, which is considered active, was not available for the assay and was not measured. (3) Our sample size for adverse effects detection was too small and the study duration too short to define what, if any, cognitive effects might occur with chronic therapy. (4) Results for this study using an oral capsule may not be generalizable to other products; however, it does provide a means for accounting for the whole dose and gives results under optimal conditions.

Administering CBD with a high-fat meal led to a marked increase in C_{max} and $AUC_{0-\infty}$. Thus, CBD should be administered with food to maximize absorption and studies of its efficacy should control for food effects. It is recognized that not all meals contain the same amount of fat and that taking CBD with a meal low in fat may not result in the same degree of increased bioavailability. Therefore, patients on a ketogenic diet may have higher and more consistent bioavailability of CBD, as the fat and caloric content of their diet is tightly controlled.

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CONFLICT OF INTERESTS

Angela K Birnbaum reports grants from the Epilepsy Foundation, National Institutes of Health, Superunus Pharmaceuticals, and Veloxis Pharmaceutics during the conduct of the study. She also has a royalty agreement for intravenous carbamazepine with Lundbeck. Susan E Marino reports grants from the Epilepsy Foundation, National Institutes of Health, Superunus Pharmaceuticals, and Veloxis Pharmaceutics during the conduct of the study. She and Rory P Remmel have a royalty agreement for intravenous topiramate with Ligand Pharmaceuticals. Ilo E Leppik reports grants from the Epilepsy Foundation, National Institutes of Health, and Superunus Pharmaceuticals during the conduct of the study. Christopher M Barkley, Michaela J Roslawski, Mary Gramling-Aden and Ashwin Karanam have no conflicts to declare. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

AKB, SEM, and IEL contributed to the conception and design of the study; AK, SEM, IEL, RPR, CMB, MGA, MR, and AKR contributed to the acquisition and analysis of data; AKB, AK, CMB, and IEL contributed to drafting the text and preparing the figures.

ORCID

Ashwin Karanam https://orcid.org/0000-0003-0654-5266

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