Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-020-00869-z

ORIGINAL RESEARCH ARTICLE

Disposition of Oral Cannabidiol-Rich Cannabis Extracts in Children with Epilepsy

George Sam Wang[1] · David W. A. Bourne[2] · Jost Klawitter[3] · Cristina Sempio[3] · Kevin Chapman[4] · Kelly Knupp[4] · Michael F. Wempe[2] · Laura Borgelt[5] · Uwe Christians[3] · Jan Leonard[1] · Kennon Heard[6] · Lalit Bajaj[1]

Abstract

Background and Objectives Despite limited evidence, cannabidiol-rich cannabis extracts have been popularly used in pediatrics. With increased use, it is critical to determine basic pharmacokinetic parameters of cannabidiol in these extracts in the pediatric population. The objective of this study was to determine the disposition of oral cannabidiol cannabis extracts and drug interactions in children with pediatric epilepsy.

Methods We conducted a prospective observational study evaluating the disposition of oral cannabidiol in children (< 18 years of age) receiving cannabidiol extracts for epilepsy. Subjects underwent serial blood draws after oral cannabidiol administration. Cannabidiol and metabolites, along with anticonvulsant concentrations were determined.

Results Twenty-nine patients had sufficient pharmacokinetic data and were included in the analysis. Mean age was 9.7 years (standard deviation 4.3) and 17 patients (59%) were male. Median peak plasma cannabidiol concentrations was 13.1 ng/mL (interquartile range 6.8–39.3 ng mL); median time to peak of 2.0 h (interquartile range 2.0–4.0 h). Mean acute elimination half-life of oral cannabidiol was 6.2 h (standard deviation 1.8 h). There was an observed half-life of degradation of 533 days noted for cannabidiol concentrations when stored for 0.6–3.1 years. There was some impact on cannabidiol pharmacokinetic parameters when cannabidiol was co-administered with zonisamide (elimination rate constant and V1) and levetiracetam (elimination rate constant).

Conclusions In pediatric patients using oral cannabidiol-rich cannabis extract for epilepsy, the time to peak concentration of plasma cannabidiol and average acute elimination half-life were shorter than those reported for adults. Co-administration of zonisamide and levetiracetam had some impact on cannabidiol pharmacokinetic parameters. There was an observed degradation of plasma cannabidiol in long-term storage.

Clinical registration ClinicalTrials.gov Identifer no. NCT02447198.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40262-020-00869-z) contains supplementary material, which is available to authorized users.

✉ George Sam Wang
George.wang@childrenscolorado.org

[1] Section of Emergency Medicine and Medical Toxicology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, 13123 E 16th Ave B251, Aurora, CO 8004, USA

[2] Department of Pharmaceutical Sciences, Center for Translational Pharmacokinetics and Pharmacogenomics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[3] iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[4] Department of Neurology and Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[5] Departments of Clinical Pharmacy and Family Medicine, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[6] Department of Emergency Medicine, University of Colorado Anschutz Medical Campus, University of Colorado Hospital, Aurora, CO, USA

Published online: 12 February 2020

Key Points

In pediatric patients receiving cannabidiol (CBD)-rich cannabis extracts, the median time to peak plasma concentrations was 2.0 h (interquartile range 2–4 h), with a median concentration of 13.1 ng/mL (interquartile range 6.8–39.3 ng/mL), and mean acute elimination half-life of 6.2 h (standard deviation 1.8 h)

We found a significant correlation between the estimated oral CBD dose and expected peak plasma concentrations, and there was some impact on CBD pharmacokinetic parameters co-administered with zonisamide and levetiracetam

We observed degradation of CBD in plasma when stored for 0.6–3.1 years

1 Introduction

There has been a large growth of the marijuana industry and the use of cannabis products for medical indications. As of 2019, there were 33 US states and Washington DC that have allowed marijuana use for various medical indications, including seizures, post-traumatic stress disorder, glaucoma, severe pain, cachexia, cancer, muscle spasms, and chronic pain [1]. In particular, the phytocannabinoid cannabidiol (CBD) has been popularly used for the treatment of refractory pediatric epilepsy. Initial evidence for the use of CBD for epilepsy and seizure disorders began in the 1970s demonstrating anticonvulsant properties in animal models [2–22]. The increased use of CBD in children started after anecdotal reports of improvements in seizures frequency in children with severe epilepsy [23–26]. In 2018, the Colorado Department of Public Health and Environment Medial Marijuana Registry reported 2785 (3.16%) patients using marijuana products for seizures, 170 (0.19%) in children aged 0–10 years [27]. Many children likely utilize this product without undergoing registration as it is not required to purchase the product in Colorado. With now over 30 states with legalized marijuana for medical use, it is likely that there will be continued growth in the use of CBD in the pediatric population.

Recently, the US Food and Drug Administration (FDA) approved a CBD pharmaceutical product for the treatment of Dravet syndrome and Lennox–Gastaut syndrome, both of which are severe epileptic encephalopathies [28]. As part of the approval process, the pharmacokinetic parameters of this product were well characterized. However, there is little rigorous scientific data for the pharmacokinetics of non-FDA-approved CBD cannabis extract products. Dosing regimens can range from once daily to several times a day, with large ranges of amount dosed. Furthermore, these products may contain different vehicles and other phytocannabinoids that could alter the pharmacokinetics of CBD. There is increasing use for other indications as well, such as autism, chronic pain, inflammatory diseases, and oncologic diagnoses [29].

There are some existing pharmacokinetic data on CBD and other cannabinoids, mostly performed in the adult population [29–33]. In adults, bioavailability in an oral form has a large range from 6 to 20% and peak concentrations can be seen at 4 h after oral administration. The half-life in adults was found to be 18–33 h following intravenous administration, and up to 2–5 days following oral dosing. Cannabidiol appears to undergo a significant first-pass metabolism leading to hydroxylated metabolites. In addition, some studies have shown CBD to be a possible inhibitor of multiple cytochrome P450 (CYP) enzymes including 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4 [34].

Despite the FDA-approved CBD product for intractable epilepsy, there will likely be continued popularity in the use of non-FDA-approved CBD extracts in the pediatric population for not only epilepsy, but also other indications. There are thousands of supplements and products unregulated by the FDA that contain CBD [35]. Most uses of these products are not substantiated nor supported by evidence-based medicine. However, the disparity between federal scheduling of marijuana and all its byproducts, including CBD, and state legalization have made rigorous scientific research of these products difficult. With increased use of CBD in the pediatric population, it is critical to determine the disposition and limited pharmacokinetic parameters of these available extracts in the pediatric population. The objective of this study was to determine the disposition of oral CBD-rich cannabis extracts in children with epilepsy. Secondary objectives were to observe other anticonvulsant concentrations while taking CBD to evaluate for possible drug interactions.

2 Patients and Methods

This was an observational prospective study evaluating the disposition of CBD in pediatric patients with epilepsy. The enrollment period was 1 October, 2015 through 31 August, 2018. Patients were recruited from our tertiary care, children's hospital outpatient neurologic clinic, and epilepsy monitoring unit. Informational flyers were advertised throughout the neurologic clinic, and prospective screening of the clinic schedule for patients listing CBD or medical marijuana as a history medication for epilepsy was performed via the electronic health record. Guardians were

informed of the study when obtaining their medical marijuana card with study contact information by the Colorado Department of Public Health and Environment; however, no patients were enrolled using this recruitment method. Additional flyer and study contact information was provided to local medical marijuana advocacy and support organizations. The Colorado Multiple Institutional Review Board approved this study.

Inclusion criteria were patients > 24 months and < 18 years of age who used orally administered CBD-rich cannabis extracts for the treatment of epilepsy, administered once or twice a day. The guardian accompanying the patient had to be at least 18 years of age. Exclusion criteria included patients without epilepsy/seizure disorder as diagnosed by a neurologist, incarceration, having known abnormalities in liver (aspartate aminotransferase, alanine aminotransferase, international normalized ratio above normal range) or kidney function (serum creatinine above normal range), known to be pregnant at the time of enrollment, taking CBD more than twice a day, or wards of the state. Guardians were required to bring laboratory verification of the cannabinoid concentrations of their CBD product (provided by the manufacturer).

Patients were scheduled for a study visit at our institutional clinical research organization inpatient unit for serial blood draws. Due to restrictions surrounding the use of marijuana products on our medical campus, patients were instructed to take their CBD as normally scheduled, which was within an hour prior to the visit and to document the time of consumption. They remained nil per os for 1 h prior and after their CBD dose. For patients 3 years of age and older, standardized meals (breakfast and lunch) allowing a low-carbohydrate, high-fat content diet based on body mass index were provided. Ketogenic meals were continued for patients on this restriction. Breakfast was provided after the 1-h blood draw, and lunch after the 4-h blood draw. Children less than 3 years of age were allowed to eat their normal diet (only two patients). For the first 16 patients enrolled, blood draws were performed at 1, 2, 4, 8, and 12 h after administration of their CBD. For the remaining patients, the last two blood draws were changed to 7 h and 10 h to improve subject recruitment and address nurse staffing. Subjects continued their scheduled and regular non-CBD medications during their stay.

Blood samples were taken to iC42 Clinical Research and Development Laboratories on the Anschutz Medical Campus to evaluate CBD and CBD metabolite concentrations, and to the Medicinal Chemistry Core Facility at the Skaggs School of Pharmacy and Pharmaceutical Sciences Building, University of Colorado, Anschutz Medical Campus to evaluate other anticonvulsant drug and metabolites. Each blood sample (~ 4 mL) was collected in a K_2EDTA blood collection tube and immediately placed onto an ice bath for a maximum of 2 h. They were centrifuged for 3 min, at 20 °C, at 1400 g. Plasma samples were equally transferred into two separate polypropylene cryovials with conical bottoms and screw-on tops, and stored at − 70 °C or below. All samples were labeled with a patient unique identifier, destination laboratory (iC42 or School of Pharmacy), and time of blood draw. Samples were delivered on dry ice quarterly for analysis. We attempted to collect urine samples; however, these results were not included because of issues with sample collection compliance and a lack of measurable concentrations in many samples.

At iC42 Clinical Research and Development, plasma samples were analyzed using a validated, fit-for-purpose, liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The assay is a modification of our previous LC-MS/MS assay for the quantification of 11 cannabinoids and metabolites in plasma [36]. Briefly, samples were extracted as previously described [36] by a one-step protein precipitation using a methanol/zinc sulfate solution including deuterated internal standards. After centrifugation, the supernatant was transferred to high-performance liquid chromatography vials. Extracts were analyzed using an online extraction LC/MS/MS approach. The high-performance liquid chromatography system (Agilent Technologies, Palo Alto, CA, USA) was interfaced with an API5000 tandem mass spectrometer (AB Sciex, Forster City, CA, USA) via a turbo-V ion source operating in positive atmospheric pressure ionization mode. Initial CBD concentrations were quantified within 2 months of the initial blood draw. Cannabidiol metabolites, 7-carboxy CBD (7-CBD-COOH) and CBD-glucuronide were quantified 0.6–3.1 years after the initial blood draw because of the delayed availability of suitable standards. In addition, CBD concentrations were re-quantified at the time of metabolite quantification. The assay had a lower limit of quantification of 500 pg/mL in blood. The inter-assay precision was within 85–115% and total imprecision, except at the lower limit of quantification, was better than 15% (Tables 1a–c of the Electronic Supplementary Material).

At the School of Pharmacy Medicinal Chemistry Core Facility, plasma samples were analyzed via LC/MS/MS methods to detect for anticonvulsants and their metabolites (when appropriate): topiramate, lamotrigine, levetiracetam, valproic acid, clobazam, felbamate, clonazepam, lacosamide, oxcarbazepine, phenobarbital, zonisamide, or rufinamide. Area under the curve (AUC) values for these co-administered drugs or their metabolites were calculated using the trapezoidal rule and used as a measure of drug exposure and potential interaction with CBD pharmacokinetics. Post-hoc parameter values were compared with these AUC values to determine a correlation.

Descriptive data were described using frequencies and percentages for categorical variables and median and interquartile range or mean and standard deviation for non-normally and normally distributed continuous variables,

respectfully. Plasma CBD vs time data were modeled with the population pharmacokinetic program Pmetrics using the NPrun module [37]. A one-compartment model with first-order absorption was used to describe the data. Covariate analysis using the PMstep module suggested that age or weight could be significant for the elimination rate constant or the apparent volume of distribution (V). Models including these covariates were explored. The PMcompare module suggested that the only significant covariate, based on minimal Akaike information criterion, was age on V. Thus, the equation $V = V0 + V1 \times$ age was included in the model. Peak concentrations and time to peak concentration were determined by inspection of the concentration vs time data.

3 Results

33 patients receiving CBD cannabis extracts for pediatric epilepsy were enrolled into the study. Twenty-nine patients had sufficient pharmacokinetic data and were included in the analysis. Ages ranged from 2.3 to 16.8 years, with a mean age of 9.7 years (standard deviation 4.3) and 17 (59%) patients were male (Table 1). The majority were Caucasian (25, 86%), followed by Latino (5, 17%) and Asian (3, 10%). All patients had at least one epilepsy diagnosis (Table 1). Other anticonvulsant medications also co-administered in these subjects included: clobazam (6), rufinamide (5), levetiracetam (5), zonisamide (3), felbamate (2), lamotrigine (2), valproic acid (1), topiramate (1), clonazepam (2), pregabalin (1), oxcarbazepine (1), lacosamide (2), phenobarbital (1), and midazolam (1).

The majority (90%) of CBD products consumed were from two brands of CBD extracts: 15 from brand A (medium-chain triglyceride oil base), 11 from brand B (safflower oil base), two brand C (medium-chain triglyceride oil base), and one brand D (almond oil base). Oral CBD dose ranged from 2.5 to 199 mg CBD, or from 0.13 to 5.0 mg/kg. Peak plasma CBD concentrations were observed between 1 and 7 h post-ingestion, median of 2.0 h (interquartile range [IQR] 2–4) (Fig. 1). The median peak concentration was 13.1 ng/mL (IQR 6.8–39.3), with a range of 2.0–112.7 ng/mL (Fig. 1). The mean acute elimination half-life of oral CBD was 6.2 h (standard deviation 1.8), ranging from 2.8 to 9.1 h (Table 2). The main CBD metabolite detected was 7-CBD-COOH, with a median concentration of 171.2 ng/mL (IQR 99.7–363.2). One other CBD metabolite, CBD-glucuronide, was also detected with a median concentration of 6.54 ng/mL (IQR 3.3–13.4).

We noted a difference in CBD concentrations when reanalyzed at the time of CBD metabolite quantification, from 0.6 and 3.1 years after initial CBD concentrations were analyzed. There was a half-life of degradation observed of 533 days (1.46 years) noted for CBD concentrations after storage. Because CBD metabolite standards were not available during the initial analysis, we do not have initial CBD metabolites for comparison. There was a significant correlation between dose per kilogram ingested and peak CBD concentrations ($R^2 = 0.48$) (Fig. 2). The correlation was worse ($R^2 = 0.383$) when the two highest dose per weight plot points were removed. When evaluating the correlation of peak CBD concentrations and dose per kilogram of subjects using two of the most common brands of CBD used, the correlation improved (only Brand A: $R^2 = 0.581$ and only Brand B: $R^2 = 0.514$). Area under the curve was calculated for the co-administered anticonvulsants and respective metabolites. There was a significant interaction with zonisamide (three patients co-administered) on the elimination rate constant and V1 of CBD, and the inactive levetiracetam (five patients co-administered) carboxylic acid metabolite on the elimination rate constant of CBD (Fig. 2a–c of the ESM). There was no other observed interactions with other anticonvulsants on CBD pharmacokinetic parameters and AUC.

Table 1 Demographic information of subjects receiving cannabidiol extracts

Mean age, years (SD)	9.7 (4.3)
Race, *n* (%)	
Caucasian	25 (86)
Latino	5 (17)
Asian	3 (10)
Other	3 (10)
Seizure diagnosis, *n*[a]	
Generalized epilepsy (non-specific)	12
Infantile spasm	6
Complex partial seizures	4
Rolandic epilepsy	2
Myoclonic epilepsy	2
Lennox–Gastaut syndrome	3
Dravet syndrome	1
Doose syndrome	1
Aicardi syndrome	1
Other neurologic diagnosis, *n*[a]	
Cerebral palsy	5
Hydro-/colpo-/microcephaly	5
Autism	4
Para-/quadriplegia	3
Chromosomal abnormalities	2
Agenesis of corpus callosum	2
Glycogen storage disease	1
Mitochondrial myopathy	1

SD standard deviation

[a]Some diagnoses may be counted more than once

4 Discussion

In pediatric patients using oral CBD-rich cannabis extract for epilepsy, the median time to peak concentration of plasma CBD of 2.0 h, and the acute elimination half-life was 6.2 h were shorter than those reported for adults (4 h and 18–33 h, respectively). There was some impact on CBD pharmacokinetic parameters co-administered with zonisamide and levetiracetam. However, we did not find evidence for interactions on CBD pharmacokinetic parameters with the remaining anticonvulsant medications amongst our small cohort. However, the lack of interactions may be due to the low dose of CBD observed in our cohort, in addition to not having enough subjects receiving any particular anticonvulsants to adequately evaluate significant drug interactions.

These initial findings help provide a basic understanding of the pharmacology of CBD-rich cannabis extracts in a pediatric population. We did find some differences in the pharmacokinetic parameters of our pediatric population compared with an FDA-approved CBD pharmaceutical product and adult pharmacokinetics [38, 39]. However, there was a notable difference in the doses used by the FDA-approved CBD product in clinical trials. Dosing was higher than what we observed in our subjects; ranging from 2.5 mg/kg twice a day to a maximum of 20 mg/kg per day [38]. The FDA-approved pharmaceutical product has a reported peak concentration occurring 2.5–5 h, with the effect of food increasing maximum concentrations five-fold and increasing bioavailability from 10% to 40–50% (increasing AUC four-fold). Thus, using edible products or a CBD extract with food may greatly impact the absorption and subsequent pharmacokinetics. The elimination half-life was reported to be 56–61 h, although this was a terminal half-life, rather than the acute half-life determined in the present study. An acute half-life maybe helpful in the setting of acute ingestion or intoxication. Finally, a half dose given twice daily would provide a lower peak concentration compared with once daily, but accumulation would be the same.

With the recent FDA approval of a CBD pharmaceutical grade product, it is unclear if patients with seizures who are currently using cannabis extracts will continue to use these products. Many factors will likely influence the use of

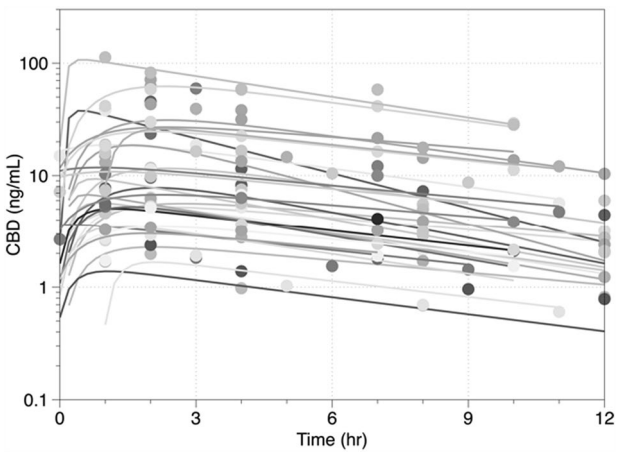

Fig. 1 Observed plasma cannabidiol (CBD) concentrations in pediatric epilepsy patients

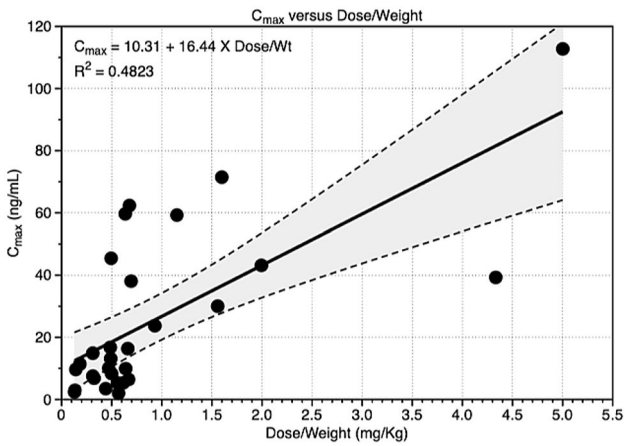

Fig. 2 Reported CBD dose (mg) per weight (Kg) and correlated peak CBD plasma concentrations (ng/ml)

Table 2 Pharmacokinetic parameter values of pediatric patients with epilepsy receiving cannabidiol-rich cannabis extracts

	C_{max} (ng/mL)	T_{max} (h)	ke (/h)	$t_{1/2}$ (h)	V_0	V_1	V/F (L)	ka (/h)
Minimum	2.0	1	0.08	2.8	0.01	0.002	188	1.00
Maximum	112.7	7	0.25	9.1	3.68	0.200	9174	7.94
Mean (SD)	–	–	–	6.2 (1.8)	–	–	–	–
Median (IQR)	13.1 (6.8–39.3)	2.0 (2–4)	0.12 (0.09–0.14)	–	0.54 (0.47–2.45)	0.026 (0.006–0.047)	2392 (773–3682)	1.29 (1.02–2.51)
CV%	105	50	35	29	92	125	79	87

C_{max} maximum concentration, *CV%* coefficient of variation, *ka* absorption rate constant, *ke* elimination rate constant, *IQR* interquartile range, *SD* standard deviation, *$t_{1/2}$* acute elimination half-life, *T_{max}* time to maximum concentration, *V0* and *V1* covariate parameters, *V/F* apparent volume of distribution after non-intravenous administration

CBD-rich cannabis extracts vs obtaining prescriptions for the FDA-approved pharmaceutical product including cost, insurance coverage, broader indications not covered with the FDA-approved product, satisfaction and efficacy with current cannabis extract product, and healthcare provider recommendations. Despite the recent availability of an FDA-approved product, there will likely be continued interest and popularity of the use of CBD cannabis extracts in both the pediatric and adult populations.

In addition to seizures, there has been significant interest in the use of CBD for other medical conditions, including autism, pain, mood disorders, movement disorders, and inflammatory diseases [40]. However, the evidence behind the use of CBD and these conditions are mostly limited preclinical animal in-vitro models, with limited and mixed results in human observational studies. There are many limitations on performing rigorous marijuana research, most of which exist because of differences between the federal and state legal status of marijuana. Universities are limited in obtaining, handling, and directing its use for research, leaving only federally approved marijuana for research, which is far different than the cannabis products being used today, including CBD [41].

Public consumption and high interest in CBD have translated into numerous CBD products that are now sold at a variety of heath, convenience, and grocery stores [35]. In addition to limited evidence, there are concerns for validity in the content and purity of products that are sold. We attempted to minimize the effects of diet on bioavailability by not allowing anything to eat or drink 1 h before or after their oral CBD dose. To minimize the variability in pharmacokinetics, the majority of products used for analysis were from one of two products and all products had laboratory verification of content determined by local laboratories. We found significance in the correlation between expected CBD peak concentration and CBD dose, which could reflect using similar products/brands, or consistency in pediatric bioavailability. Despite these findings, the FDA has released warning letters to several companies over the past 3 years warning of inaccuracies of labeled content and false claims [42]. These findings emphasize the importance of universal standards in laboratory testing to ensure the safety and quality of these products, and evidence-based research. In May 2019, the FDA held a hearing on the safety and efficacy of CBD products over concerns of over-exaggerated health claims and the number of products that are now available [43]. Any definitive decisions or ruling has yet to be concluded at the time of this publication.

There are some limitations to our data. During the time of this study, there were no approved CBD cannabis extract products available for research. While this increases the variability in the pharmacokinetic estimates, we felt it was important to perform this study on actual extracts used by the public. Because of regulations surrounding the use of cannabis products on campus, we were unable to standardize the product or dose administered. This limited our ability to evaluate full pharmacokinetic parameters. We analyzed only patients using products with laboratory verification of content. We did not find significant drug interactions with CBD extracts, but this was likely because of the low dose of CBD used, and the small number of patients enrolled and receiving limited anticonvulsants. Metabolism of CBD occurs via CYP enzymes including CYP3A4 and CYPC19, which may lead to potential drug interactions. The FDA-approved CBD product was found to have significant interactions and increases in the concentrations of clobazam, topiramate, and rufinamide, potentially increasing the concentration of clobazam and leading to increased sedation [44, 45]. Thus, continued caution should be used when these extracts are used in conjunction with other anticonvulsants. There may be interference in the metabolism of CBD with co-administration with delta9-tetrahydrocannabinol, five patients in the present study were also receiving delta9-tetrahydrocannabinol dosing that was detectable [46]. However, previous research has shown the metabolism interference to be minimal and has not shown a significant conversion of CBD into delta9-tetrahydrocannabinol [47–49]. There are additional concerns about the stability of CBD and metabolites in blood and plasma after prolonged storage. We found that when re-analyzed after a period of 1–3 years, there was a measurable degradation of CBD concentrations. Previous research demonstrated CBD to be stable up to 26 weeks at – 4 °C, and 52 weeks at – 20 °C [50]. Thus, we suggest with any future research, CBD concentrations be measured no longer than a year after storage. There are no existing data on the stability of CBD metabolites. The concentrations of CBD metabolites presented here were analyzed from 0.6 to 3.1 years after the initial sample collection when CBD metabolite standards became commercially available. Thus, we were unable to obtain CBD metabolite concentrations upon the initial blood draw. Based on our observed degradation of CBD concentrations, some degree of degradation may have occurred with the CBD metabolites during the prolonged storage. However, the LC/MS/MS approach used in our study has the advantage that 7-CBD-COOH was separated from 6α- and 6β-hydroxyl CBD, which was not the case for previously published data for the FDA-approved CBD product [51, 52]. Finally, we did not follow patients long enough to obtain other pharmacokinetic parameters such as AUC, V1, apparent clearance, and terminal elimination half-life, nor did we administer intravenous doses to determine bioavailability. These estimates would also be imprecise because of variations in dose and subjects.

5 Conclusions

In pediatric patients receiving CBD-rich cannabis extracts, we found median peak plasma concentrations within 2 h, and a mean acute elimination half-life of 6.2 h. Cannabidiol metabolites remained persistent through the 10- to 12-h study period. We found a significant correlation between the estimated oral CBD dose and expected peak plasma concentrations. There was some impact on CBD pharmacokinetic parameters co-administered with zonisamide and levetiracetam. We observed degradation of CBD in plasma when stored 0.6–3.1 years. As CBD cannabis extracts have increasing popularity for use in epilepsy and other medical indications, more rigorous research is needed to understand their pharmacology, safety and efficacy in pediatric patients.

Compliance with Ethical Standards

Funding This work was supported by the Colorado Department of Public Health and Environment Medical Marijuana Grant Program (18-103031, to George Sam Wang, David W.A. Bourne, Jost Klawitter, Cristina Sempio, Uwe Christians, Kevin Chapman, Kelly Knupp, Laura Borgelt, Michael F. Wempe, and Lalit Bajaj). George Sam Wang has received royalties from UpToDate, and is a co-investigator on grant NIH1R01DA045051-01A1 on related subjects. Laura Borgelt has received funding for research from the Colorado Department of Public Health and Environment and honoraria for providing continuing education from PharmCon, Inc. on related subjects. Kelly Knupp was a consultant for GW pharmaceuticals and participated in drug safety and monitoring board.

Conflict of interest George Sam Wang, David W. A. Bourne, Jost Klawitter, Cristina Sempio, Kevin Chapman, Kelly Knupp, Michael F. Wempe, Laura Borgelt, Uwe Christians, Jan Leonard, Kennon Heard, and Lalit Bajaj have no conflicts of interest that are directly relevant to the content of this article.

References

1. Legal medical marijuana States and DC. 2019. https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Accessed 16 Sep 2019.
2. Izquierdo I, Oshinger OA, Berardi AC. Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. Psychopharmacologia. 1973;28(1):95–102.
3. Carlini EA, Leite JR, Tennhauser M, Berardi AC. Letter: cannabidiol and cannabis sativa extract protect mice and rats against convulsive agents. J Pharm Pharmacol. 1973;25(8):664–5.
4. Consroe P, Wolkin A. Cannabidiol-antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. J Pharmacol Exp Ther. 1977;201(1):26–32.
5. Turkanis SA, Smiley KA, Borys HK, Olsen DM, Karler R. An electrophysiological analysis of the anticonvulsant action of cannabidiol on limbic seizures in conscious rats. Epilepsia. 1979;20(4):351–63.
6. Turkanis SA, Karler R. Electrophysiology properties of the cannabinoids. J Clin Pharmacol. 1981;21(S1):449S–63S.
7. Karler R, Turkanis SA. The cannabinoids as potential antiepileptics. J Clin Pharmacol. 1981;21(S1):437S–48S.
8. Consore P, Benedito MA, Leite JR, Carlini EA, Mechoulam R. Effects of cannabidiol on behavorial seizures cause by convulsant drugs or current in mice. Eur J Pharmacol. 1982;83(3–4):293–8.
9. Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther. 2010;332(2):569–77.
10. Hill TD, Cascio MG, Romano B, et al. Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. Br J Pharmacol. 2013;170(3):679–92.
11. Jones NA, Glyn SE, Aliyama S, et al. Cannabidiol exerts anticonvulsant effects in animal models of temporal lobe and partial seizures. Seizure. 2012;21(5):344–52.
12. Colasanti BK, Lindamood C 3rd, Craig CR. Effects of marihuana cannabinoids on seizure activity in cobalt-epileptic rats. Pharmacol Biochem Behav. 1982;16(4):573–8.
13. Martin AR, Consroe P, Kane VV, et al. Structure-anticonvulsant activity relationship of cannabidiol analogs. NIDA Res Monogr. 1987;79:48–58.
14. Usami N, Okuda T, Yoshia H, et al. Synthesis and pharmacological evaluation in mice of halogenated cannabidiol derivatives. Chem Pharm Bull (Tokyo). 1999;47(11):1641–5.
15. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014;3:CD009270.
16. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C. Chronic administration of cannabidiol to health volunteers and epileptic patients. Pharmacology. 1980;21(3):175–85.
17. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol. 1981;21(S1):417S–27S.
18. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J. 1985;69:14.
19. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften. 1978;65:14–9.
20. Trembly B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. In: Marijuana '90 International Conference on Cannabis and Cannabinoids; 8–11 July 1990; Kolympari; International Association for Cannabinoid Medicines, 1990;Section 2, p. 5.
21. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29(3):574–7.
22. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia. 2014;55(60):783–6.
23. CNN. Marijuana stops child's severe seizures. 2013. http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana. Accessed 1 Oct 2016.
24. The New York Times. Families see Colorado as new frontier on medical marijuana. 2013. http://www.nytimes.com/2013/12/06/us/families-see-colorado-as-new-frontier-on-medical-marijuana.html?pagewanted=all&_r=0. Accessed 1 Oct 2016.
25. NPR. Florida Bill would allow medical marijuana for child seizures. 2014. http://www.npr.org/blogs/health/2014/01/16/262481852/florida-bill-would-allow-marijuana-extract-for-child-seizures. Accessed 1 Oct 2016.
26. Huffington Post. Number of children seeking medical marijuana soars in Colorado. 2014. http://www.huffingtonpost.com/2014/02/13/medical-marijuana-children_n_4768219.html. Accessed 25 Sep 2015.
27. Colorado Department of Public Health and Environment. Medical marijuana registry program statistics. 2018. https://www.colorado.gov/pacific/sites/default/files/CHED_MMR_Monthly_Report-July-2018.pdf. Accessed 12 Jul 2019.
28. US FDA. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy.

2018. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms. Accessed 12 Jul 2019.
29. Campbell CT, Phillips MS, Manasco K. Cannabinoids in pediatrics. J Pediatr Pharmcol Ther. 2017;22(3):176–85.
30. Agurell S, Halldin M, Lingren JE, et al. Pharmacokinetics and metabolism of delta 9-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev. 1986;38:21–42.
31. Harvey DJ, Mechoulam R. Metabolites of cannabidiol identified in human urine. Xenobiotica. 1990;20:303–20.
32. Ohhsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister LE. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. Biomed Environ Mass Spectrom. 1986;13:77–83.
33. Guy GW, Whitte BA, Robson P. The medicinal uses of cannabis and cannabinoids. Cornwall: TJ International; 2004.
34. Yamori S, Oakamoto Y, Yamamoto I, Watanabe K. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP 2D6. Drug Metab Dispos. 2011;39(11):2049–56.
35. Corroon J, Kight R. Regulatory status of cannabidiol in the United States: a perspective. Cannabis Cannabinoid Res. 2018;3(1):190–4.
36. Klawitter J, Sempio C, Mörlein S, et al. An atmospheric pressure chemical ionization MS/MS assay using online extraction for the analysis of 11 cannabinoids and metabolites in human plasma and urine. Ther Drug Monit. 2017;39(5):556–64.
37. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012;34(4):467–76.
38. US FDA. Epidiolex (cannabidiol): highlights of prescribing information. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf. Accessed 12 Jul 2019.
39. Millar SA, Stone NL, Yates AS, O'Sullivan SE. A systematic review on the pharmacokinetics of cannabidiol in humans. Front Pharmacol. 2018;9:1365.
40. World Health Organization. Cannabidiol (CBD) pre-review report. 2017. https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf. Accessed 16 Sep 2019.
41. United States Department of Agriculture. Industrial hemp. 2018. https://nifa.usda.gov/industrial-hemp. Accessed 12 Jul 2019.
42. US FDA. Warning letters and test results for cannabidiol-related products. 2019. https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products. Accessed 12 Jul 2019.
43. US FDA. Scientific data and information about products containing cannabis or cannabis-derived compounds; public hearing. 2019. https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds. Accessed 12 Jul 2019.
44. Chang BS. Cannabidiol and serum antiepileptic drug levels: the ABC's of CBD with AEDs. Epilepsy Curr. 2018;18(1):33–4.
45. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015;56(8):1246–51.
46. Wang GS, Bourne DW, Klawitter J, et al. Disposition of oral delta-9 tetrahydrocannabinol (THC) in children receiving cannabis extracts for epilepsy. Clin Toxicol (Phila). 2020;58(2):124–8.
47. Karchner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral Δ9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clin Chem. 2011;57(1):66–75.
48. Nahler G, Grotenhermen F, Zuardi AW, Crippa JAS. A conversion of oral cannabidiol to delta9-tetrahydrocannabinol seems not to occur in humans. Cannabis Cannabinoid Res. 2017;2(1):81–6.
49. Nadulski T, Pragst F, Weinberg G, et al. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. Ther Drug Monit. 2005;27(6):799–810.
50. Scheidweiler KB, Schwope DM, Karchner EL, Desrosier NA, Gorelick DA, Huestis MA. In vitro stability of free and glucuronidated cannabinoids in blood and plasma following controlled smoked cannabis. Clin Chem. 2013;59(7):1108–17.
51. Taylor L, Crockett J, Tayo B, Morrison G. A phase 1, open-label, parallel-group, single-dose trial of the pharmacokinetics and safety of cannabidiol (CBD) in subjects with mild to severe hepatic impairment. J Clin Pharmacol. 2019;59(8):1110–9.
52. Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. CNS Drugs. 2018;32(11):1053–67.