The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy

NCT02815540

Protocol Version 9/28/2016

The effects of cannabidiol (CBD) on electrical and autonomic cardiac function in children with severe epilepsy

PI Name and Institutional Affiliation:
Beverly S. Wical, MD
Gillette Children's Specialty Healthcare

Co-Investigators:
- Cardiac Electrophysiologist – to be determined
- Shani Norberg, MD
- Kari Williams, MPH, CCRC
- Sam Roiko, PhD

Study Coordinator:
Heather Wendorf, MPH, CCRC

Background and Significance

Children with medically intractable epilepsy do not obtain adequate seizure control with available therapeutics. Other treatment options are needed to manage their condition. Two pediatric epilepsy syndromes where this is most evident are Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS).

Children with Dravet syndrome (DS) are affected by a severe epileptic encephalopathy. Children initially appear healthy, but then seizures emerge in the first year of life followed by a relentless course of epilepsy and cognitive impairments (1). Up to 80% of those affected by this disorder have a mutation on the SCN1A gene, which encodes for neuronal sodium channels—similar sodium channels are found in heart muscle. This severe epilepsy has a major adverse impact on health and quality of life, and carries with it a significant risk of early mortality.

Lennox Gaustaut syndrome (LGS) is a severe form of epilepsy with onset of seizures occurring between 1 and 7 years of age. Multiple disorders are associated with LGS including brain malformations, perinatal asphyxia, severe head injury, central nervous system infection, or inherited degenerative or metabolic conditions (2). LGS is characterized by multiple seizure types, and a severe epileptic encephalopathy leads to significant developmental disabilities, impaired intellectual functioning, and information processing and behavioral disturbances (2).

Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality in patients with epilepsy. Patients with DS experience one of the highest rates of SUDEP (3, 4). While mechanisms of SUDEP are complex and multifactorial, autonomic nervous system abnormalities are considered an important

contributor to mortality (5, 6). It has been reported that children with DS exhibited a significantly higher number of signs and symptoms of autonomic nervous system abnormalities than children in a control group (7). Studies of electrical and autonomic cardiac function in patients with DS demonstrated an imbalance of cardiac autonomic function toward a relative predominance of adrenergic tone compared to both healthy children and patients with other forms of epilepsy, and this finding was independent of the use of antiepileptic medications (8, 9). This suggests that dysfunction in the autonomic nervous system, or dysautonomia, is a significant factor in this condition. A number of these patients have seizures triggered by autonomic stimulation (e.g., strong emotion), and many have pronounced autonomic features (e.g., flushing of face, pallor or tachycardia) during ictal events. Modulating autonomic nervous system tone may potentially affect seizure control and risk for SUDEP.

Investigators have been unable to accurately determine the incidence of SUDEP in patients with LGS, perhaps due to variation in the etiology and definition of LGS. In addition, the literature available on LGS and autonomic nervous system dysfunction is sparse, as is the literature on LGS and cardiac function. Patients with LGS may be at an increased risk for cardiac abnormalities (10). Nei (2012) documented sinus-tachycardia, T wave inversion and ST segment depression during tonic seizures, as well as 3 to 4.8 seconds of asystole during sleep in subjects wearing a subcutaneously implanted loop recorder (10). Studies of SUDEP have identified increased risk in those with early onset and medically intractable epilepsy, neurologic abnormalities, and a need for multiple medications. Children with LGS meet all these criteria.

Available antiepileptic drugs (AEDs) have not proven to be particularly effective in offering seizure control to those with severe pediatric epileptic encephalopathies. Recently, the use of cannabidiol (CBD) has generated great interest as a novel treatment for highly refractory epilepsy such as DS or LGS. Preliminary studies suggest that CBD may be effective in treating the seizures associated with DS. Major phase III drug trials of FDA-approved orphan drug products are close to implementation or are in the initial phase of recruitment. Families are also seeking out CBD products to use on their own through state-licensed pharmacies (e.g., through the state of Minnesota or www.epilepsycolorado.org).

Thus, a significant number of children with DS and LGS will soon be enrolling in stage III clincial trials or using CBD acquired as an artisanal oil. However, a number of questions regarding the safety and efficacy of CBD for treating seizures remain unanswered since FDA approval and labeling have not yet been granted. In addition, current phase III studies do not address potential autonomic adverse effects. While information on adverse effects may be

forthcoming in the future for industry-manufactured products, the existence of state-licensed pharmacies that currently dispense CBD as an artisanal oil creates an urgency to address these questions. The purpose of this protocol is to determine whether CBD affects cardiac autonomic function, which may pose another mechanism of action for seizure reduction and prevention of SUDEP.

To date, there is no medical literature that has determined whether CBD has cardiac autonomic effects on pediatric patients using CBD for neurological disorders including epilepsy. Several previous studies only suggest that CBD may modulate cardiac autonomic effects. One preclinical study reported that CBD attenuates cardiac responses to restraint stress in rats (11). In adult humans, CBD has been shown to attenuate anxiety (12). It has also been demonstrated in healthy adult volunteers that while an acute dose of the more well-known cannabinoid delta-9-tetrahydrocannabinol (THC) increases heart rate, CBD does not, suggesting that CBD may not result in deleterious adverse effects (13). These findings indicate the importance of characterizing the cardiac autonomic effects of CBD in pediatric patients with medically refractory epilepsy. If CBD modulates cardiac autonomic effects, it may also reduce the risk of SUDEP.

Summary of Background
DS and LGS are severe forms of epilepsy that are largely unresponsive to current AEDs
SUDEP is a major cause of mortality with intractable forms of epilepsy such as DS and LGS
Dysautonomia and increased risk for cardiac abnormalities may play a role in causing SUDEP in patients with highly refractory epilepsy
Modulating autonomic nervous system tone may affect seizure control and risk for SUDEP
Cannabidiol may have an effect on the autonomic nervous system and is now being studied as a potential treatment for refractory epilepsy
Cannabidiol is being obtained from state-licensed pharmacies without having undergone study in clinical trials, and thus, has not been well-characterized
This study will determine if Cannabidiol obtained from state-licensed pharmacies has any effects on cardiac rhythm and reduction in seizures

Rationale for Conducting the Study

Although marijuana has been in use for centuries, CBD has not been well studied as an antiepileptic medication for use in children. Little is known about the autonomic effects of CBD in general, and virtually nothing is known about

the effects that CBD might have on the cardiac function of children with DS or other severe forms of epilepsy. Currently, industry sponsors are conducting studies of CBD in connection with clinical trials of their study drugs. However, similar studies of CBD when administered as an artisanal oil derived from other sources have not been reported.

We propose to study the effects of CBD on cardiac electrical function and the autonomic nervous system in children with DS and LGS, when the CBD was administered as an artisanal oil obtained through state dispensiaries or other sources. Our intent is to begin to assess potential risks and benefits of this therapy in a vulnerable patient population by characterizing the effects of CBD on EKG findings, heart rate variability and the occurrence of seizures.

Specific Aims/Study Objectives

This is a pilot study to explore the effects of cannabidiol (CBD) on autonomic cardiac function in children with DS or LGS when the CBD was administered as an artisanal oil. This will be achieved by addressing the following specific aims.

Aim #1: To determine the effects of CBD on cardiac function in 30 children with DS and LGS. This is the primary aim of the study: The effects of CBD on the cardiac function of 30 children with DS or LGS will be assessed using a 12-lead electrocardiogram (EKG), an optional signal average EKG, and a 24-hour Holter monitor. We hypothesize that there will be no alterations in ventricular repolarization and heart rate variability on the EKGs and Holter monitoring, respectively, after taking CBD for 4-8 weeks, compared to when participants were not taking CBD. *Milestone: Records from 12-lead EKG and 24-hour Holter monitor in 30 patients.*

Note: The following aims are secondary to the primary outcome and goal of assessing the effects of CBD on cardiac function.

Aim #2: To assess signs and symptoms of dysautonomia in the presence and absence of CBD. Signs and symptoms of dysautonomia include parental perception of body temperature, skin color in hands and feet, sweating, pupil size, flushing, feeding issues, heart rate, and constipation. These signs and symptoms will be collected using a previously-established dysautonomia survey. We hypothesize there will be no change in qualitative assessments of signs and symptoms of dysautonomia after taking CBD for 4-8 weeks, compared to when participants were not taking CBD. *Milestone: Completed dysautonomia surveys in 30 patients before and after CBD administration.*

Aim #3: To determine the effects of CBD on the occurrence of seizures*.* The number of seizures in children who obtain CBD will be assessed using a 7-day seizure diary (Seizure tracker). Caregivers will record the number of

seizures for a 7-day period prior to CBD administration, and repeat the seizure tracking after having received CBD for 4-8 weeks. Change in seizure numbers will be compared pre- and post-CBD administration. We hypothesize that study participants will have lower seizure counts after being on CBD compared to when weren't taking CBD. *Milestone: Completed 7-day seizure diaries in 30 patients before and after CBD administration.*

Study Design and Methodology

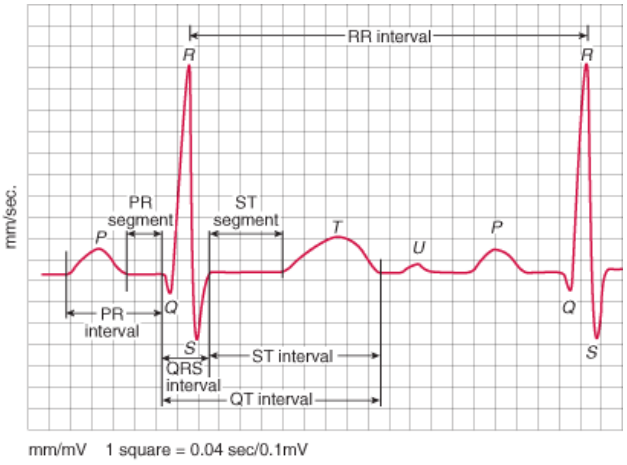
Study Design: Thirty patients with DS or LGS who are going to register to take medical cannabis (cannabidiol, or CBD) in the state of Minnesota will be offered the opportunity to participate in this study. If consent is obtained, the patient or guardian will be asked to complete a questionnaire developed for this study that documents observable signs and symptoms of dysautonomia, and to complete a seizure diary for 7 days prior to initially receiving the CBD. Each participant will also have a 12-lead electrocardiogram (EKG), an optional signal average EKG, and wear a 24-hour Holter monitor, all non-invasive measures of cardiac function, prior to being administered the CBD. The EKGs and 24-hour Holter monitor will be interpreted by a cardiac electrophysiogist and will be reviewed for heart rate variability parameters. The dysautonomia questionnaire, seizure diary and cardiac measurements will be repeated 4-8 weeks after the subject has been on a stable regimen of CBD. This time-frame is based on availability of subjects schedules and clinic visits, and it is also greater than 5 half-lives previously reported for CBD (apparent half-life, 21 hours, (15)). Steady-state levels are achieved after 5 half-lives of drug dosing, thus we expect to be at steady-state concentrations.

Subjects who are already on a stable regimen of CBD, yet plan to stop taking CBD at some point for some reason, are also eligibile to particpiate. The patient or guardian will complete the dysautonimia questionnaire and seizure diary (and research staff will be available to help with questions), and the patient will have the 12-lead EKG, an optional signal average EKG, and 24-hour Holter monitor while still on the CBD. The subjects will then come back 4-8 weeks after their last dose of CBD to have these assessments repeated while off of the CBD. Again, this time frame is based on availability of subjects schedules and clinic visits as well as being substantially greater than 5 half-lives of CBD, the standard wash-out period for pharmacological studies.

Sample Size: A power analysis was not used to determine sample size. Current sample size expectations will be 40 subjects based on the number of patients who enroll in the Minnesota state registry and who are also patients at Gillette. This available sample size will allow us to account for potential participant dropout or incomplete data so that we can achieve our target of 30

patients. This is a pilot study with a limited number of participants, and data collected will be used in a subsequent power analysis to determine the number of subjects needed in a larger study to determine statistical significance. This will be the first study of medical cannabis' effects on autonomic function in children with severe seizures, and due to the anticipated small sample size, these findings will primarily be used as pilot data to guide further characterization of CBD effects on autonomic parameters.

Methodologies: The 12-lead EKG will be used to collect information on rhythm, a detailed assessment of heart rate (RR interval), PR interval, QRS duration, QT and QTc interval, and ST segment changes in order to detect cardiac arrhythmias and other abnormalities (see graphic below). The signal average EKG will take this same information and average them during a 20 minute time period, provided our subject is able to lie still for that amount of time.



Heart rate variability (HRV) will be assessed using the 24-hour Holter ECG recordings. Both time-domain parameters (RR interval [heart rate], SDNN [standard deviation of RR intervals] and SDNN-I [the mean of standard deviation of all RR intervals for all 5 minute segments]) and frequency-domain parameters (VLF [total spectral power of all NN intervals between 0.003 and 0.04Hz], HF [total spectral power of all NN intervals between 0.15 and 0.4Hz] and LF [total spectral power of all NN intervals between 0.04 and 0.15 Hz] amplitude) will be obtained. HRV is a measure of sympathetic/parasympathetic cardiac autonomic balance, with lower HRV parameters indicating increased adrenergic tone.

Data Analysis: The number of participants (30 subjects) is small due to the limited number of patients available for enrollment into this specialized study. The study is an observational study with a cross-over design, where the patients will serve as their own controls. Primary assessments will include determination of any changes in EKG parameters and Holter heart rate variability parameters

pre- and post-treatment with CBD, as well as the percentage of items in the dysautonomia survey that changed and the number of seizures that occurred pre- and post-treatment with CBD. Appropriate data assessments will be performed to determine whether parametric or nonparametric analyses are the proper approach. Due to the small sample size and potentially highly variable or skewed data due to the complex patient population under investigation, we plan to normalize Holter heart rate variability parameters and EKG parameters and calculate change from "baseline" (off – CBD) to those collected while CBD is being administered at steady-state levels.

We also will compare reported seizure data collected from subjects who enrolled in the study prior to initiation of CBD to those who were already on CBD and then discontinued CBD use to determine if substantial differences are apparent in the two groups, since parent report may be biased. We will also confirm that EKG and Holter monitor data 4-8 weeks post-CBD (from patients who were on CBD but subsequently discontinued use) are not significantly different from baseline data acquired from patients with no previous CBD use, prior to combining all "off – CBD" as baseline values.

Study Participation

The Principal Investigator or research team members will identify subjects who have registered or plan to register with the State of Minnesota to take medical cannabis. Each participant will be in the study for approximately 2 months, and will need to visit Gillette twice. If subjects have not been on CBD, they will make one visit one week prior to starting CBD treatment and one visit after having been on CBD for 4-8 weeks. For subjects that are already on a stable regimen of CBD, yet plan to stop taking CBD at some point, their participation will last 4-8 weeks after their last dose.

Risks and Discomforts

EKG: There is no pain during an EKG; however, the EKG patches may be cold and removing the pads may make the skin red and sore. In some cases, the locations where the EKG patches are placed may need to be shaved.

24-hour Holter monitor: There is no pain during the use of a 24-hour Holter monitor; however, the patches may be cold and removing the pads may make the skin red and sore. In some cases, the locations where the patches are placed may need to be shaved.

Subject Protection

A consent form will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into

the study. The consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. The consent form will incorporate (or be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Written consent must be given by the subject and/or legal representative after the receipt of detailed information on the study and all questions have been resolved.

The Principal Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative, and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures. The Investigator or research team member will provide each subject with a copy of the signed and dated consent form.

Confidentiality

The records of this study will be kept private. Extra precautions will be taken to preserve confidentiality. All identifiable information will be replaced with a code. A list linking the code and identifiable information will be kept separate from the data. All research data and records will be stored electronically on a secure network with encryption and/or password protection to help prevent unauthorized access to personal information. All paper records will be stored in a secured area. Study participation will be recorded in the subject's medical record. Study records and samples will be kept until all data have been monitored, analyzed and published.

Data Handling and Record Keeping

It is the Principal Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation). Record retention will follow ICH E6 Section 4.9.5 and all other applicable regulations.

Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997; the US CFR Title 21 parts 50, 56, and 312) and the ethical principles that have their origin in the Declaration of Helsinki.

The Principal Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements.

Data and Safety Monitoring Plan

Data will be monitored by the Principal Investigator. All EKGs and 24-hour Holter monitors will be read by a cardiac electrophysiologist.

Clinical Implications and Dissemination

As described above, this is a pilot study with a limited number of participants and data collected will be used in a subsequent power analysis to determine the number of subjects needed in a larger study to determine statistical significance. This will be the first report of medical cannabis' effects on autonomic function in children with severe seizures, and due to the anticipated small sample size, these findings will primarily be used as pilot data to guide further characterization of CBD effects on autonomic parameters. Findings will be reported internally and at external conferences, likely the annual American Epilepsy Society meeting. Data regarding the effects of CBD on cardiac function (whether protective or detrimental) will be important for future development and use of CBD in clinical settings with patients with potential cardiac dysfunction.

Bibliography

1. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (eds) Epileptic syndromes in infancy, childhood and adolescence, 4th ed. John Libbey, London, 2005, pp 89 – 109.
2. http://www.ninds.nih.gov/disorders/lennoxgastautsyndrome/lennoxgastautsyndrome.htm, Retrieved 6.10.2015
3. Sakauchi M, Oguni H, Kato I, Osawa M, Hirose S, Kaneko S, Takahashi Y, Takayama R, Fujiwara T. Mortality in Dravet syndrome: search for risk factors in Japanese patients. Epilepsia. 2011 Apr;52 Suppl 2:50-4. doi: 10.1111/j.1528-1167.2011.03002.x. PMID: 21463280
4. Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 2011 Apr;52 Suppl 2:95-101. doi: 10.1111/j.1528-1167.2011.03012.x. PMID: 21463290
5. Jehi L. Sudden death in epilepsy, surgery, and seizure outcomes: the interface between heart and brain. Cleve Clin J Med. 2010 Jul;77 Suppl 3:S51-5. doi: 10.3949/ccjm.77.s3.09. Review. PMID: 20622077
6. Kalume F. Sudden unexpected death in Dravet syndrome: respiratory and other physiological dysfunctions. Respir Physiol Neurobiol. 2013 Nov

1;189(2):324-8. doi: 10.1016/j.resp.2013.06.026. Epub 2013 Jul 9. Review. PMID: 23850567

7. Wical, B, Wendorf H, Leighty D, Tervo M, Tervo R. Signs of Dysautonomia in Children with Dravet Syndrome. Presented at the Annual Meeting of the American Epilepsy Society, Boston, MA, Dec 2009.
8. Delogu AB, Spinelli A, Battaglia D, Dravet C, De Nisco A, Saracino A, Romagnoli C, Lanza GA, Crea F. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia. 2011 Apr;52 Suppl 2:55-8. doi: 10.1111/j.1528-1167.2011.03003.x. PMID: 21463281
9. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia. 2012 Aug;53(8):e137-40. doi: 10.1111/j.1528-1167.2012.03561.x. Epub 2012 Jun 18. PMID: 22709423
10. Ergul Y, Ekici B, Tatli B, Nisli K, Ozmen M. QT and P wave dispersion and heart rate variability in patients with Dravet syndrome. Acta Neurol Belg. 2013 Jun;113(2):161-6. doi: 10.1007/s13760-012-0140-z. Epub 2012 Oct 13. PMID: 23065439
11. Granjeiro EM, Gomes FV, Guimarães FS, Corrêa FM, Resstel LB. Effects of intracisternal administration of cannabidiol on the cardiovascular and behavioral responses to acute restraint stress. Pharmacol Biochem Behav. 2011 Oct;99(4):743-8. doi: 10.1016/j.pbb.2011.06.027. Epub 2011 Jul 12. PMID: 21771609
12. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 2011 May;36(6):1219-26. doi: 10.1038/npp.2011.6. Epub 2011 Feb 9. PMID: 21307846
13. Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, Borgwardt S, Allen P, Seal M, Langohr K, Farré M, Zuardi AW, McGuire PK. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Des. 2012;18(32):4966-79. Review. PMID: 22716148
14. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014 Mar 5;3:CD009270. doi: 10.1002/14651858.CD009270.pub3. Review. PMID: 24595491
15. Ohlsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister L. (1984). Single dose kinetics of cannabidiol in man. Cannabinoids: chemical, pharmacologic, and therapeutic aspects. S. Agurell, W. L. Dewey and R. Willette. Orlando, FL, Academic Press Inc.: 219-225. doi: 10.1016/B978-0-12-044620-9.50003-8