



Drug-Drug Interactions Between Cannabidiol and Lithium

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Abstract

Epidiolex[®] (Cannabidiol- CBD) is approved for epilepsy associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients over 2 years of age. Common side effects include somnolence and diarrhea. Recent studies have demonstrated interactions between cannabidiol and several other antiseizure medications. However, little is known regarding interactions between cannabidiol and other classes of medications. We discuss an autistic patient with LGS and significant psychiatric comorbidities who was being treated with multiple antiseizure and psychiatric medications, including lithium, when CBD was added to his medical regimen. Several weeks after initiating CBD therapy, he developed hypersomnolence, ataxia and decreased oral intake and was found to have lithium toxicity. Lithium was discontinued and his symptoms resolved. He remains on CBD and 2 other antiseizure medications, seizure-free with improved behavior. We review mechanisms of action and pharmacokinetics of CBD and discuss possible explanations for lithium toxicity in this patient.

Keywords

antiepileptic drugs, antiseizure drugs, autism, epilepsy, behavior, pediatric

Introduction

In 2018, the United States Food and Drug Administration (FDA) approved an oil-based highly purified liquid formulation of Cannabidiol (CBD) (Epidiolex[®]- Greenwich Biosciences, Inc.) for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients over 2 years of age. Unlike other approved antiseizure medications (ASMs), CBD has a unique structure and potentially novel multimodal mechanism of action and does not activate or bind directly to cannabinoid receptors CB1 or CB2 at physiologically relevant concentrations.^{1,2}

Clinical experience has demonstrated that CBD has antiseizure efficacy in LGS and Dravet Syndrome. Common side effects reported from the initial studies included somnolence and diarrhea.³⁻⁶

Since its approval by the FDA, additional studies have shown interactions between CBD and other antiseizure medications.⁷ However, little is known regarding interactions between CBD and other classes of medications.

We discuss a patient with LGS and psychiatric comorbidities treated with lithium, who, after initiating CBD, developed symptoms of hypersomnolence, ataxia and decreased oral intake and was found to have lithium toxicity.

Case Description

A 13-year-old boy with autism and LGS with a history of 2 prior epilepsy surgeries and vagus nerve stimulator (VNS) placement presented to our comprehensive epilepsy clinic to transfer care. Epilepsy onset was at 18 months, and he had a history of atonic seizures and generalized tonic-clonic seizures, along with focal seizures with loss of awareness. The etiology of his phenotype was unknown. He underwent a full corpus callosotomy at age 4, left frontal lobe resection at age 7, and VNS placement at age 11 (all at an outside institution). His parents described a semiology of staring and behavioral arrest for 2-3 minutes with oral and/or manual automatisms. These seizures were occurring several times per week. Prior antiseizure

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medication trials included rufinamide, valproic acid, levetiracetam, topiramate, oxcarbazepine, lamotrigine and lacosamide. At the time of presentation, he was taking 2 ASMs at stable doses over 4 months: Felbamate 24 mg/kg/day and Clobazam 0.5 mg/kg/day.

He met criteria for Autism Spectrum Disorder, co-morbid with severe intellectual disability and associated aggressive and self-harmful behaviors and sleep difficulties. At baseline, he was non-verbal with incontinence, though with full strength and ambulation.

He transitioned to our psychiatry service during a hospitalization several months prior to the initiation of CBD. At that prior hospitalization, he had been increasingly lethargic but also aggressive, in what was thought to be polypharmacy. During that prior admission Bupropion, Pregabalin, and Amantadine were all discontinued. He remained on a complex regimen of psychoactive medications, including Lithium 600 mg qAM, 300 mg qPM and 600 mg qhs, Perphenazine 8 mg TID, Quetiapine 200 mg twice a day and 400 mg qhs, and Trazodone 300 mg qhs. The dose of Lithium- targeted for aggression in a developmentally delayed patient- had been unchanged for over a year with stable and therapeutic lithium levels.

Upon presentation to our epilepsy clinic, we recommended a trial of CBD to improve seizure control and possibly behavior. His psychiatrist agreed to this plan of care. He started CBD at 5 mg/kg/day, divided bid. Due to potential interactions with clobazam, the clobazam dose was simultaneously decreased by 25%.

During the first 2 weeks of treatment, he did well. However, soon after his CBD dose was increased to 10 mg/kg/day as per titration schedule, he began to exhibit symptoms of lethargy, weakness, unsteadiness, and decreased oral intake, prompting an emergency department (ED) evaluation and admission to the hospital. By this point his clobazam had been decreased to 50% of the initial dose. His parents reported that soon after taking the midday doses of medications (lithium, clonidine and felbamate) he would become tired, lethargic, and off balance.

Upon evaluation in the ED, he was afebrile though somnolent. When arousable and more awake he was ataxic compared to baseline. Blood pressure, blood counts, electrolytes, liver enzyme levels, renal function tests, and clobazam levels were all unremarkable. In contrast, the lithium level was notably elevated at 2.4 mmol/L (compared to his historic baseline of 1 -1.3 mmol/L). Psychiatry and neurology were consulted. Lithium was stopped, and midday doses of clonidine and felbamate were held. He was placed NPO and on twice maintenance intravenous fluids with serial checks of lithium levels and monitoring of urine output, with a targeted goal of 1-2 ml/kg/hr. Lithium levels declined over the subsequent 48 hours, and his mental status improved. He was monitored for 3 days during which time he gradually returned to baseline and remained seizure-free. His parents reported improved behavior and requested that he remain off lithium. On the day of discharge, his lithium level was 0.6 mmol/L, and he remained on perphenazine, quetiapine, and trazodone.

Nearly one year after admission, he continues on CBD 10 mg/kg/day, half dose clobazam, home felbamate dose, and remains off lithium. Parents have not detected any seizures, and they note that his behavior is improved.

Discussion

Metabolism and Mechanism of Action of Cannabidiol

Cannabidiol has a high volume of distribution and is very lipophilic and highly protein bound.⁸ After absorption from the GI tract, CBD is metabolized in the liver, where the primary enzymes involved in its hydroxylation are those of the CYP family.⁹ In addition, CBD inhibits the function of certain CYP enzymes, which likely contributes to its pharmacologic interactions with other medications.¹⁰⁻¹²

The precise mechanisms of action by which CBD exerts its anticonvulsant effects in humans are unknown. However, it does not act via cannabinoid receptors at physiologically achievable concentrations. Recent preclinical evidence suggests multimodal mechanisms of action in which CBD reduces neuronal hyperexcitability. These mechanisms include modulation of intracellular calcium via antagonism of a G protein coupled receptor (GPR55), modulation of extracellular calcium influx via a transient receptor potential vanilloid type 1 (TRPV1) and inhibition of adenosine transport.¹³

In clinical trials, cannabidiol has been generally well tolerated. The most common adverse events included diarrhea, vomiting, fatigue, pyrexia, somnolence, poor quality sleep and transaminase elevations- all with an incidence of at least 10% greater than placebo.^{1,3-6}

Interactions With Other Anti-Seizure Medications

Cannabidiol has a bidirectional drug–drug interaction with clobazam. It inhibits cytochrome P450 (CYP)2C19 and increases levels of the nordesmethyl metabolite of clobazam, which has biologic activity.¹⁴ Conversely, clobazam increases levels of CBD's metabolite, 7-hydroxy-CBD. Adult and pediatric studies have demonstrated increased clobazam and N-desmethylclobazam (active metabolite of clobazam) in response to increasing doses of CBD.¹⁵

In an open-label study of CBD involving children and adults with refractory epilepsy, the use of concomitant ASMs was evaluated for 8 of the most commonly used agents (clobazam, lamotrigine, topiramate, rufinamide, valproic acid, levetiracetam, stiripentol, and felbamate). Most ASMs did not demonstrate significantly different serum levels in the presence of increasing CBD doses. Those that did demonstrate changes were topiramate, zonisamide, eslicarbazepine, rufinamide, and clobazam (with its active metabolite N-desmethylclobazam), all of which demonstrated higher serum levels with concomitant CBD use, either in adults or in both adults and children. Abnormal liver enzyme levels were noted in participants taking concomitant valproate.^{7,16}

Although other antiseizure medications and other medications have not been investigated, it is hypothesized that CBD

could affect serum levels of any medication which is metabolized by the enzymes that are induced or inhibited by CBD.¹⁷

Lithium

Lithium is an efficacious and FDA-approved treatment for mood disorders including mania, acute depression, and unipolar depressive disorder. However, lithium has a narrow therapeutic index. Thus, clinical monitoring along with serum concentration monitoring is imperative. Lithium is not protein bound, not metabolized, has a bioavailability of 80-100%, and is renally eliminated. Side effects associated with elevated lithium levels include vomiting, diarrhea, coarse hand tremor, sluggishness, dysarthria, hyperreflexia, and oliguria. These side effects greatly increase in frequency and severity when lithium blood levels exceed 1.5 mEq/L. Severe lithium toxicity can lead to impaired consciousness, seizures, coma, and death.¹⁸

Because lithium is renally excreted, any agent or process that impairs renal function can elevate lithium levels. Interestingly, CBD can cause elevations in serum creatinine. The mechanism of this CBD-induced renal dysfunction has not been determined. In controlled studies of healthy adults and patients with DS and LGS, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting CBD. The increase was reversible in healthy adults. However, reversibility was not assessed in the LGS and DS studies.¹ Our patient was admitted 2 weeks after starting CBD, and symptoms of lithium toxicity were noted soon after the dose was increased to 10 mg/kg/day. Though his creatinine levels were not abnormally elevated, his creatinine level did increase from 0.6 mg/dL before the institution of CBD to 0.75 mg/dL 2 weeks after CBD initiation. This represents a 25% increase. While unlikely to spike his lithium so dramatically, in part this progressed because of reduced oral intake especially of fluids. The early stages of lithium toxicity likely provoked the reduced oral intake, though he continued to receive his medications. This likely exacerbated the dramatic increase in his lithium level. At the time of discharge creatinine decreased back to 0.64 mg/dL.

Conclusions

Patients with LGS and Dravet syndrome often require multiple anti-seizure medications and may be on additional medications for comorbidities - as was our patient. Cannabidiol remains a novel and effective treatment for these refractory epilepsies, though its mechanisms of action and potential drug-drug interactions remain poorly understood. We highlight a drug-drug interaction between cannabidiol and lithium, possibly due to CBD-induced renal dysfunction, as reflected by increased creatinine levels. This article emphasizes the importance of multidisciplinary care in clinical monitoring for safety and efficacy for patients on multiple medications. As CBD becomes increasingly prescribed and available for refractory epilepsies, it is important to closely monitor patients and promptly recognize potential medication interactions.

Author Contributions

Dr. Singh, the corresponding author, participated in patient care, conceptualization, data curation, investigation, writing, reviewing, and editing. Dr. Bonthius was involved in conceptualization, review and editing. Drs. Dillon, Tatum, and Van Poppel were involved in patient care, review and editing of the manuscript.


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References

1. EPIDIOLEX® (cannabidiol) oral solution [US Prescribing Information]. Greenwich Biosciences Inc. 2018.
2. Devinsky O, Cilio MR, Cross JH, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6):791-802.
3. Devinsky O, Cross JH, Laux L, et al; Cannabidiol in Dravet syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376(21):2011-2020.
4. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016;15(4):270-278.
5. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med*. 2018;378(20):1888-1897.
6. Szaflarski JP, Bebin EM, Comi AM, et al; CBD EAP Study Group. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. *Epilepsia*. 2018;59(8):1540-1548.
7. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP; UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58(9):1586-1589.
8. Ohlsson 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(2):77-83.
9. Zendulka O, Dovrtělová G, Nosková K, et al. Cannabinoids and cytochrome p450 interactions. *Curr Drug Metab*. 2016;17(3):206-226.
10. Ibeas Bih C, Chen T, Nunn AV, Bazet M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics*. 2015;12(4):699-730.
11. Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos*. 2011;39(11):2049-2056.
12. Jiang R, Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokin*. 2013;28(4):332-338.

13. Gray RA, Whalley BJ. The proposed mechanism of action of CBD in epilepsy. *Epileptic Disorders*. 2020;22(S1):10-15.
14. Bornheim LM, Everhart ET, Li J, Correia MA. Characterization of cannabidiol-mediated cytochrome P450 inactivation. *Biochem Pharmacol*. 1993;45(6):1323-1331.
15. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol. *Epilepsia*. 2015;56(8):1246-1251.
16. Szaflarski JP, Bebin EM. Cannabis, cannabidiol, and epilepsy—from receptors to clinical response. *Epilepsy Behav*. 2014;41:277-282.
17. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav*. 2017;70(Pt B):313-318.
18. Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. *J Clin Pharmacol*, 1994;34(4):280-285.