CASE REPORT

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Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus

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Cannabidiol (CBD), a major purified nonpsychoactive component of cannabis with anticonvulsant properties, was approved by the U.S. Food and Drug Administration (FDA) in June 2018 as an adjuvant treatment for refractory epilepsy (Epidiolex; GW Pharmaceuticals). CBD is metabolized by cytochrome P450 (CYP)3A4 and CYP2C19 with a growing body of evidence suggesting it is also a potent inhibitor of these pathways. We report for the first time a significant drug-drug interaction between the purified CBD product and tacrolimus. A participant in a CBD clinical trial for epilepsy who was also receiving tacrolimus showed an approximately 3-fold increase in dose-normalized tacrolimus concentrations while receiving 2000-2900 mg/day of CBD. Our report delineates an important concern for the transplant community with the increasing legalization of cannabis and advent of an FDA-approved CBD product. Larger studies are needed to better understand the impact of this drug-drug interaction in solid organ transplant recipients.

KEYWORDS

alternative and complementary medicine, clinical research/practice, drug interaction, immunosuppressant - calcineurin inhibitor: tacrolimus, immunosuppression/immune modulation, pharmacology

1 | INTRODUCTION

Cannabinoids are a diverse group of chemicals, both naturally occurring and synthetic analogs, capable of producing a wide range of effects. The two best characterized cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are believed to be responsible for most of the pharmacologic activity. THC possesses analgesic, antispasmodic, antitremor, appetite stimulant, and antiemetic properties. THC is also responsible for the majority of the psychoactive effects. Whereas, CBD has shown beneficial anticonvulsant, antipsychotic, antioxidant, and neuroprotective properties.[1] Historically, the only pharmaceutical-grade products available and approved by the U.S. Food and Drug Administration (FDA) have been analogs of THC. In June 2018, the FDA approved the first plant-derived, purified cannabidiol prescription medication (Epidiolex, GW Pharmaceuticals) for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome.[2]

Cannabidiol is metabolized by cytochrome P450 (CYP) 3A4, CYP2C19, and UDP-glucuronosyltransferase (UGT) 1A7, UGT1A9, and UGT2B7, with a growing body of evidence suggesting it is also a potent inhibitor of these pathways.[3-6] However, the prescribing information for CBD suggests dose reductions only for substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19.[2] Calcineurin inhibitors (CNIs; eg, tacrolimus and cyclosporine) are frequently

used immunosuppressants that are substrates of CYP3A and P-glycoprotein (P-gp). Thus increased serum concentrations of CNIs are expected with concurrent use of inhibitors targeting these proteins. We report for the first time a significant drug-drug interaction between the purified CBD pharmaceutical product and tacrolimus, clinically observed in a participant in a CBD clinical trial for epilepsy.

2 | CASE REPORT

A 32-year-old woman with refractory epilepsy was receiving tacrolimus for interstitial nephritis. She was stable on tacrolimus 5 mg twice daily for a year before entry into a cannabidiol clinical trial with tacrolimus blood levels ranging from 3.9-8.4 ng/mL (mean 6.1 ng/mL) and baseline serum creatinine (Scr) of 1.2 mg/dL (Figures 1 and 2, day −365 to 0). She was initially randomized to the sesame oil placebo with no change in tacrolimus levels or Scr (Day 0 to 100). She entered into the open-label study on Day 100 and began receiving CBD, which was titrated to 20 mg/kg/day (2000 mg given in divided doses twice daily) over 10 days with improvement in seizure frequency. She began demonstrating signs of tacrolimus toxicity, with Scr of 1.92 mg/dL on Day 114 with peak Scr of 2.4 mg/dL on Day 124. Tacrolimus was empirically held at this time with improvement in Scr to 1.5 mg/dL

FIGURE 1 Tacrolimus-dose normalized trough concentration prior to study entry and during study phases [Color figure can be viewed at wileyonlinelibrary.com]
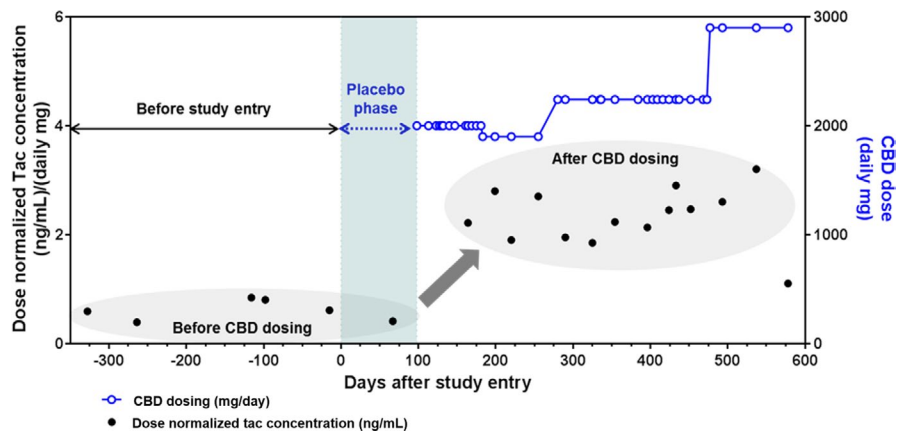

FIGURE 2 Tacrolimus daily dose including prior to study entry and during study phases [Color figure can be viewed at wileyonlinelibrary.com]
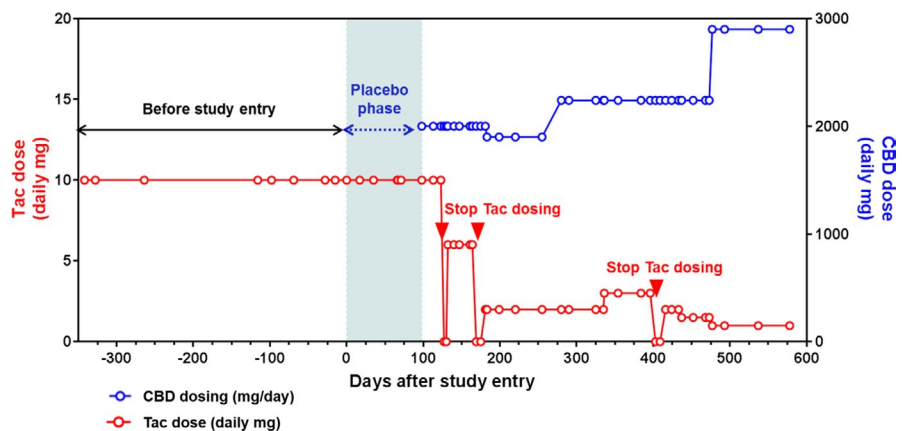
TABLE 1 Tacrolimus dosing, trough levels, and Scr in relation to CBD initiation

Study day	CBD dose	Tacrolimus dose	Tacrolimus level (ng/mL)	Scr (mg/dL)
-15	–	5 mg BID	6.1	1.2
67	Placebo	5 mg BID	4.1	0.9
114	20 mg/kg/d	5 mg BID	–	1.92
124	20 mg/kg/d	5 mg BID	–	2.4
131	20 mg/kg/d	HELD	–	1.5
164	20 mg/kg/d	3 mg BID	13.3	2.0
175	20 mg/kg/d	HELD	<1.0	1.2
255	20 mg/kg/d	1 mg BID	5.4	1.3

on Day 131. Tacrolimus was restarted at a lower dose of 3 mg twice daily on Day 133. On Day 164, the dose-normalized tacrolimus concentration was found to be increased by approximately 3-fold (Figure 1). Table 1 includes additional details regarding tacrolimus dose, levels, and Scr over this period. Beginning on Day 282, CBD was gradually increased to a maximum dose of 25 mg/kg (2900 mg/day); again, resulting in increased Scr level and a need to reduce tacrolimus dose further. Tacrolimus dose was reduced repeatedly while the patients was receiving CBD, as in Figure 2, with a last-known dose of 0.5 mg twice daily (a 10-fold reduction). To avoid changes in seizure frequency, no de-challenge of CBD was performed.

Other potential causes of the increased tacrolimus trough levels were considered. Concomitant medications were unchanged throughout treatment and included lamotrigine, rufinamide, methsuximide, gabapentin, escitalopram, quetiapine, and trazodone. There were no known changes to baseline tacrolimus administration such as formulation, relationship to food, or adherence reported by the patient and/or caregiver. Potential adverse effects were closely monitored as part of the study and diarrhea was not reported.

3 | DISCUSSION

The CNIs, particularly tacrolimus, are the backbone of most immunosuppressive regimens. Use is complicated by high pharmacokinetic and pharmacodynamic variability requiring close drug monitoring to maintain levels within the therapeutic range. Alterations in CNI exposure can be problematic in terms of both toxicity and organ rejection. Given the narrow therapeutic index, drug interactions are of particular concern. The most important factor influencing CNI disposition is change in CYP3A and/or P-gp activity.[7] Those caring for transplant patients are concerned with anecdotal reports of potential drug interactions with cannabinoids including CBD.[8] Despite the growing use of CBD products, which are typically artisanal products from state dispensaries or ordered via websites, there remains limited evidence describing the potential interaction between tacrolimus and CBD.

The overall role of cannabinoids as metabolism substrates, inducers, and inhibitors is unclear. A review summarizing the evidence for the drug interaction potential of cannabinoids has been published previously.[9] To study an investigational drug as a potential inhibitor of CYP3A, the FDA considers midazolam a sensitive index substrate. Meaning the substrate is sensitive to changes in enzyme activity with a 5-fold or more increase in area under the curve (AUC) when co-administered with a strong inhibitor.[10] Per the package labeling on in vivo assessment of drug interactions, coadministration of the CBD product with midazolam did not result in changes in the concentration of midazolam compared to midazolam alone.[2] However, in vitro data support the role of CBD as an inhibitor of CYP3A.[4,5,11] This discrepancy may be explained by several possibilities. First, CYP3A4 possesses multiple binding sites that confound the straightforward prediction of in vivo drug-drug interactions from in vitro data.[12] For example, cyclosporine (a known CYP3A4 inhibitor) inhibited in vitro CYP3A4-dependent metabolisms of nifedipine and midazolam, but did not inhibit the metabolism of terfenadine or testosterone.[13] Therefore, an inhibitory effect of CBD may vary depending on the CYP3A4 substrate such that inhibition may exist for tacrolimus but not midazolam. However, to the best of our knowledge, the CYP3A4 binding site of CBD has not yet been identified to confirm this hypothesis. Second, the CBD concentrations used in vitro are significantly higher than the serum concentrations typically reported to be achieved in vivo; as a result, concentration may not always be sufficient to inhibit CYP3A4 in the clinical setting.[9] A major limitation of this case report is we were unable to obtain CBD levels for our patient to assess the degree of CBD exposure.

Another possible mechanism for the increase in tacrolimus concentration noted is CBD inhibition of P-gp. Conflicting data have been presented. In vitro, CBD exhibits potent, concentration-dependent inhibition of the P-gp.[14] However, per the package insert, CBD is not anticipated to interact with P-gp.[2] In vivo assessment of P-gp is difficult as most probe inhibitors are not specific for a single transporter and also inhibit CYP enzymes.[10]

To our knowledge, only one case report has been published previously on clinically significant tacrolimus toxicity in the setting of a potential drug interaction with cannabis. An allogeneic hematopoietic stem cell transplant recipient experienced an increased tacrolimus trough of 45.8 ng/mL (therapeutic range at the center 8-12 ng/mL) on a dose of 1 mg twice daily after ingestion of cannabis. He then developed diarrhea, tremors, and altered mental status. Although limited details of the case are provided, the authors attribute the increased exposure to the marijuana.[15] Outside of transplantation, one small pharmacokinetic (PK) study assessed the effect of cannabinoids on the pharmacokinetics of indinavir and nelfinavir in HIV-infected individuals. Indinavir and nelfinavir are protease inhibitors that are also metabolized primarily by CYP3A4. The cannabinoid product used was marijuana cigarettes, containing 3.95% THC, but the CBD content was not stated. When compared to the subjects' baseline PK parameters, exposure to the protease inhibitor was decreased, although there was large interpatient variability. This data suggest induction, not inhibition, of CYP3A4.[16] One in vitro study using mice liver microsomes found increased CYP3A expression after repeated administration of CBD but it did not correlate with increased functional activity, as no changes in the CYP3A catalyzed metabolite, 6-keto-THC, were noted.[17]

Concern for an interaction with the pharmaceutical grade product should generate additional alarm for the variability that may result from less-regulated artisanal products. More than 60% of cannabis dispensary products have been shown to be mislabeled with respect to actual CBD content.[18] Inconsistencies in product makeup and changes in route of administration may result in variable exposure to the potentially interacting substances and in turn may increase the variability of CNI exposure. In solid organ transplant recipients, variability in CNI drug levels has been shown to negatively affect long-term outcomes.[19]

The potential for fluctuation in immunosuppression levels is supported by a brief report; 5 kidney transplant recipients on a

tacrolimus-based immunosuppressive regimen received artisanal CBD 100 mg/day with increase up to 300 mg/day from a Colorado dispensary for chronic pain. The authors note variation in levels during the first 3 weeks of CBD therapy. Tacrolimus levels decreased in two patients, increased in two patients, and remained stable in one patient. Only one patient experienced an increase in Scr attributed to the elevated trough level.[20]

Comparatively, our subject received a significantly higher dose of CBD (up to 25 mg/kg/day). As mentioned, a limitation of this report is the lack of CBD pharmacokinetic data. However, the steady-state plasma concentration of CBD achieved with the FDA-approved product at a dose of 25 mg/kg/day has been reported previously to range from 100 to 800 ng/mL (mean 450 ng/mL = 1.43 μmol/L).[6] In general, dispensary products are intended to provide lower doses, most commonly 10-20 mg/dose.[18,21] As expected, lower doses of the artisanal CBD result in lower plasma CBD levels with peak concentrations for doses ≤20 mg typically <10 ng/mL (<0.03 μmol/L) with variability depending on the administration method.[21] Based on the inhibitory constant (Ki) of 1 μmol/L, the pharmaceutical CBD product dosing is more likely to reach concentrations capable of producing inhibition.[4] This highlights the importance of assessing the dose, frequency, and route of administration/bioavailability of a particular CBD product when evaluating the drug-interaction potential.

An additional constraint of this report is the inability to discontinue CBD and assess the resulting change in tacrolimus levels. The absence of such a de-challenge limits the ability to know with perfect certainty if the change in tacrolimus levels was due to CBD alone. As is often the situation in clinical practice, we do not have extensive details on all factors known to influence tacrolimus levels such as the impact of food on bioavailability, drug-food interactions, changes in analytical assay, and patient adherence.[19] Although to the best of our knowledge, no other explanatory causes have been identified.

Our report delineates an important concern for the transplant community with the advent of an FDA-approved CBD product and increasing cannabis legalization by individual states in the United States and worldwide. As the known versus unsubstantiated risks of cannabis continue to be debated in this population, caution is warranted with a need for larger studies to better understand the potential impact of this drug interaction. Until further information is available, clinicians should be aware of the potential interaction and closely monitor tacrolimus trough levels when CBD, particularly the prescription medication (Epidiolex), is introduced.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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