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Clinical Observation

Cannabidiol Elevates Mechanistic Target of Rapamycin Inhibitor Levels in Patients With Tuberous Sclerosis Complex

Daniel Ebrahimi-Fakhari, MD [a, b], Karen D. Agricola, APRN, FNP-BC [a], Cynthia Tudor, APRN [a], Darcy Krueger, MD, PhD [a], David Neal Franz, MD [a, *]

[a] Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[b] Department of General Pediatrics, University Children's Hospital Muenster, Muenster, Germany

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ABSTRACT

Background: The mechanistic target of rapamycin inhibitors everolimus and sirolimus have activity against multiple manifestations of tuberous sclerosis complex and are approved to treat astrocytomas, angiomyolipomas, lymphangioleiomyomatosis, and epilepsy. Cannabidiol is a novel antiepileptic medication. There is lack of information regarding drug-drug interactions between mechanistic target of rapamycin inhibitors and cannabidiol in clinical practice.
Methods: We reviewed patients with tuberous sclerosis complex who were treated with a mechanistic target of rapamycin inhibitor (everolimus, sirolimus) and cannabidiol. Clinical information, mechanistic target of rapamycin inhibitor and cannabidiol dosing, concomitant antiepileptic drugs, as well as laboratory and adverse events were reviewed before and after initiation of cannabidiol.
Results: A total of 25 patients were treated with cannabidiol and a mechanistic target of rapamycin inhibitor (18 everolimus, seven sirolimus). All mechanistic target of rapamycin inhibitor levels were drawn as troughs. Levels were significantly higher in 76% patients after cannabidiol treatment ($P = 0.0003$). Median change from baseline was +9.8 ng/mL for everolimus and +5.1 ng/mL for sirolimus. Adverse events occurred in 40%, with diarrhea being the most frequent adverse event occurring in three patients. No severe adverse events occurred during the treatment period.
Conclusions: Cannabidiol resulted in increased serum levels of everolimus and/or sirolimus. Some patients experienced doubling or tripling of their mechanistic target of rapamycin inhibitor trough following the addition of cannabidiol. In some cases, this resulted in clinical toxicity, as well as laboratory abnormalities. Awareness of this interaction can lead clinicians to evaluate serum levels and other safety laboratory studies more closely, and thereby avoid potentially significant adverse effects. In patients known to be prone to mechanistic target of rapamycin inhibitor toxicity, preemptive reduction in dose may be warranted upon initiation of cannabidiol.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder resulting from mutations in genes coding for proteins hamartin (*TSC1*) or tuberin (*TSC2*).[1] Hamartin and tuberin form a dimer that works through the protein Ras homolog enhanced in brain (Rheb) to inhibit the mechanistic target of rapamycin (mTOR).[2] Patients with TSC therefore have constitutive activation of mTOR, which results in hamartomas in brain, kidney, and skin and other tissues.[3] Cortical tubers are associated with intellectual disability and epileptic seizures in 90% affected individuals.[4] Many of these patients have medically intractable epilepsy and epileptic encephalopathies, despite aggressive management. The mTOR inhibitors everolimus and sirolimus have shown activity against multiple manifestations of TSC and are approved to treat giant cell astrocytomas, angiomyolipomas, lymphangioleiomyomatosis, and refractory epilepsy.[5] mTOR inhibitors are distinctive from other therapies used in patients with TSC in

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* Communications should be addressed to: Dr. Franz; Division of Neurology; Cincinnati Children's Hospital Medical Center; MLC 2015, 3333 Burnet Avenue, Cincinnati, OH 45229-3026.
E-mail address: david.franz@cchmc.org (D.N. Franz).

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that they address the underlying pathophysiologic cause of the disorder, rather than its symptoms.

Cannabidiol is a novel anticonvulsant medication derived from marijuana and approved for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in the United States.[6-8] This drug is also approved for epilepsy associated with TSC in the European Union. Here, we report our experience at a large multidisciplinary clinic for tuberous sclerosis with the use of cannabidiol for epilepsy in patients also receiving either everolimus or sirolimus.

Methods

We retrospectively reviewed all patients with TSC who were treated with an mTOR inhibitor (everolimus, sirolimus) as well as cannabidiol at Cincinnati Children's Hospital Medical Center. All patients had a clinically defined diagnosis of TSC (2012 Consensus Diagnostic Criteria, including a positive genetic test).[9] Clinical evaluation, mTOR inhibitor dosing and levels, cannabidiol dosing, concomitant antiepileptic drugs, safety laboratory studies, and adverse events were reviewed before and after initiation of cannabidiol treatment. mTOR inhibitors were dosed as recommended and as clinically appropriate.[10] All mTOR inhibitor levels were drawn at trough times. Patients with inconsistent medication doses and noncompliance or missing data were excluded from this report. Differences between mTOR inhibitor levels before and after cannabidiol initiation were assessed using paired *t* test. A two-sided P value < 0.05 was considered statistically significant. Statistics were performed using GraphPad Prism.

Results

Twenty-five patients (seven female, 18 male) were treated with cannabidiol and an mTOR inhibitor (18 everolimus, seven sirolimus). Median age at treatment initiation was 17 years (range three to 45 years; 13 children, 12 adults). Cannabidiol was administered according to the manufacturer's recommendation, and follow-up mTOR inhibitor levels were drawn after a therapeutic dose of 5 to 20 mg/kg/day (as some patients responded to less than 10 mg/kg/day) was achieved. mTOR inhibitor levels were significantly higher in 19 of 25 (76%) patients after cannabidiol treatment (Fig) ($P = 0.0003$). Median change from baseline level was +9.8 ng/mL for everolimus and +5.1 ng/mL for sirolimus. Adverse events occurred in 10 of 25 patients (40%), with diarrhea being the most frequent adverse event in three patients (12%). Other adverse events include drowsiness, increased and severe mouth sores, increased acne, ankle swelling, sinusitis, abdominal pain, mild elevation of transaminases, and increased phenytoin level (Supplemental Table). No severe adverse events occurred during the treatment period. Relevant co-medications are depicted in the supplemental table. At the time of this report, all patients continue treatment with both mTOR inhibitor and cannabidiol.

Discussion

We found that cannabidiol frequently resulted in increased serum levels of everolimus and/or sirolimus. Some patients experienced doubling or tripling of their mTOR inhibitor trough level following the addition of cannabidiol. In some cases, this resulted in clinical toxicity, including aphthous ulcers, intercurrent infections, as well as laboratory anomalies. Of note, we reduced mTOR inhibitor dosing when increased levels were found. Fortunately, no serious adverse events were reported. Elevated serum levels were seen at an equal frequency with either everolimus or sirolimus. Our findings confirm the observations of Wiemer-Kruel et al. in a recent

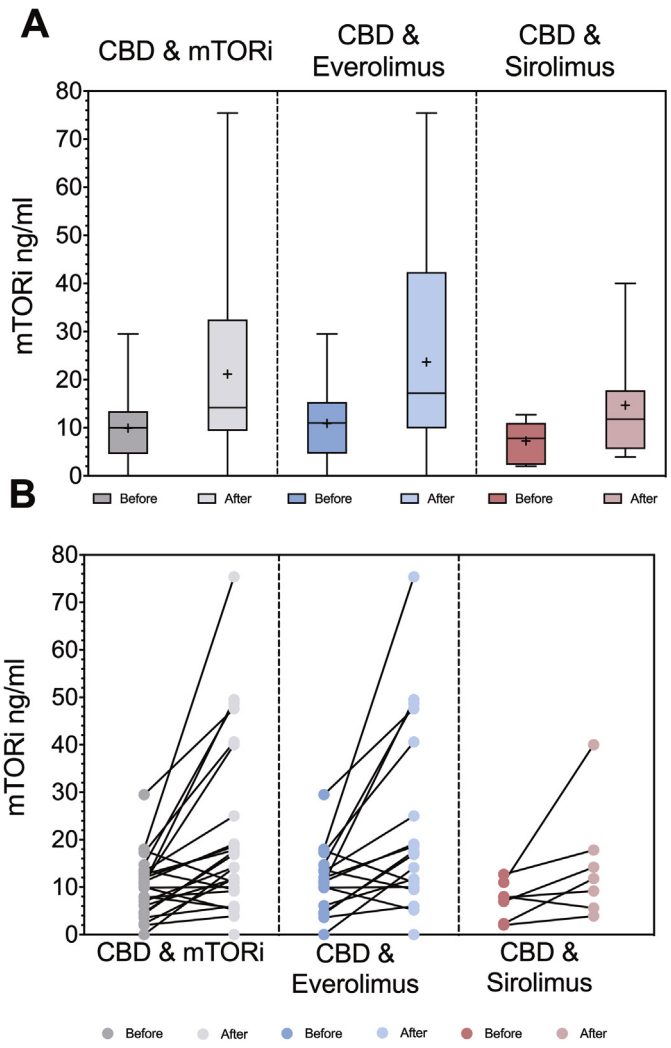

FIGURE. mTOR inhibitor levels before and after cannabidiol treatment. (A) Box plot indicating median and min/max values, + indicates mean. (B) Individual levels before and after treatment with cannabidiol. The color version of this figure is available in the online edition.

case report.[11] Awareness of this possible interaction can lead clinicians to follow serum levels and other safety laboratory studies more closely and thereby avoid potentially significant adverse effects. In patients known to be prone to mTOR inhibitor toxicity, preemptive reduction in dose may be warranted upon initiation of cannabidiol.

Concurrent use of cannabidiol and clobazam is known to result in elevation of clobazam levels.[12] Although interaction of cannabidiol with mTOR inhibitors has not been directly studied, it seems clear that it has a similar effect when used together with this class of drugs; this is perhaps not surprising given the potential of cannabidiol to inhibit the cytochrome P450 oxidase system.[13] Clobazam is a CYP3A4 inducer, and everolimus is primarily metabolized by CYP3A4.[10] Of note, in one patient in whom clobazam was added simultaneously with cannabidiol the everolimus level increased. This confounding issue should be taken into account. Clinicians should be aware of potential interaction with other antiepileptic drugs metabolized by cytochrome P450 enzyme complex, such as carbamazepine, phenytoin, and lamotrigine, as well as other classes of drugs such as oral contraceptives and antibiotics.[14,15] Interestingly, in one patient in whom oxcarbazepine was added simultaneously with cannabidiol the sirolimus level

decreased. Interaction with cytochrome P450 oxidase system might explain this observation. Elevation of mTOR inhibitor levels can be particularly significant in patients who are also receiving a ketogenic diet, as the ketogenic diet and mTOR inhibition produce similar toxicities such as lipid elevation and insulin resistance. Alternatively, this apparent inhibitory effect of cannabidiol on the metabolism of mTOR inhibitors may be useful in patients in whom therapeutic levels are difficult to achieve, as, for example, in those who have been chronically treated with enzyme inducing antiepileptic drugs. It is possible that the pairing of cannabidiol with mTOR inhibitors may represent a type of rational polytherapy, in that these agents would act against TSC-associated epilepsy through different mechanisms. Also, the use of cannabidiol would potentially allow lower doses of mTOR inhibitors to be more effective.

Conclusion

We demonstrated a significant increase in mTOR inhibitor levels after cannabidiol treatment initiation. Adverse events were reported, but no severe adverse event was seen. Clinicians should be aware of possible drug-drug interactions with everolimus or sirolimus and cannabidiol. It is reasonable to follow mTOR inhibitor safety laboratory studies closely and monitor adverse events carefully, especially during initiation of cannabidiol treatment in patients with TSC.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2019.11.017.

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