Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol

Kevin Madden, MD, Kimberson Tanco, MD, Eduardo Bruera, MD

abstract

The use of cannabidiol products in pediatric patients is becoming more frequent because of the increased ease of accessibility. This case report illustrates the potential for cannabidiol to interact with stable medication regimens. A 13-year-old girl with metastatic cancer and chronic pain presented with increased sleepiness and fatigue. She had been started on 7.5 mg of methadone by mouth twice daily 4 months earlier. Unbeknownst to her physicians, her parents had commenced her on cannabidiol and subsequently increased the dose leading up to her presentation, thinking it would result in tumor shrinkage. The initial serum methadone level was 271 ng/mL, which decreased to 125 ng/mL 14 days after discontinuing cannabidiol. The reduced serum methadone level coincided with improved sleepiness and fatigue. Cannabidiol inhibits CYP3A4 and CYP2C19, both of which are involved in the metabolism of methadone. Pediatricians should be aware of this potential interaction and inquire if their patients are receiving cannabidiol.

Cannabinoids are a group of closely related compounds, including tetrahydrocannabinol and cannabidiol, that are purported to have a variety of therapeutic effects. Tetrahydrocannabinol, under the generic names of dronabinol and nabilone, is approved by the Food and Drug Administration (FDA) only for HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting. There are, however, reports on its off-label use for cancer-related pain and spasticity and insomnia from multiple sclerosis. The FDA approved cannabidiol, in the form of Epidiolex, only for the treatment of specific seizures disorders, including Dravet syndrome and Lennox-Gastaut syndrome. There is, however, great enthusiasm in the general public and on social media about cannabidiol’s supposed therapeutic effects on anxiety, insomnia, chronic pain, inflammation, and even antineo- effects despite a lack of scientific evidence for any of these conditions. Cannabidiol products are now widely available in legalized and nonlegalized medical marijuana states via retail stores and online.

We present the case of a child with cancer-related pain who was on a stable dose of methadone and developed significant opioid-related side effects from coadministration of cannabidiol oil.

CASE DESCRIPTION

Pediatric supportive care managed a 13-year-old girl with a neuroendocrine tumor and metastatic disease of the liver, lungs, thoracic vertebrae, and scattered lesions in the cerebral cortex for pain management.

Nociceptive pain was primarily in the upper thoracic spine and neuropathic components manifested as sharp, radiating pain into the lower thoracic spine and sacrum. Her pain was well controlled on 7.5 mg of methadone by mouth twice per day with 7.5 mg of morphine by mouth every 4 hours as needed for breakthrough pain. She typically used 1 to 2 breakthrough doses of morphine a few times per week. She had been on this regimen for ~4 months, and during that time, she never exhibited any significant opioid-related side effects, including hallucinations, myoclonus, or excessive drowsiness.

On the day before admission, her family contacted the primary oncologist to report increased fatigue and sleepiness, which were markedly worse than baseline. The symptoms started 5 days earlier, and with each day, the fatigue and sleepiness worsened. There had been no recent changes to prescribed medications or dosages of prescribed medications, including opioids. Systems-review results were negative for fever, rhinorrhea, cough, neck pain, photophobia, tonic-clonic activity, staring episodes, hallucinations, altered mental status, and ill contacts. The parents were advised to bring her to the emergency department for evaluation. Computed tomography of the brain revealed “a faint area of increased attenuation that conceivably could be a small focus of hemorrhage without edema or mass effect and would not explain the current clinical symptoms.” The complete blood count and differential were normal, as were her electrolytes (sodium, potassium, and calcium), blood urea nitrogen, creatinine, aspartate aminotransferase, alanine transaminase, lipase, and amylase. Her physical examination was notable for fatigue, and her pupils were 2 mm and minimally reactive. She was alert and oriented to person, place, and time with no delirium (Cornell Assessment of Pediatric Delirium [CAPD] score of 0). Cranial nerves 2 through 12 were intact. She had normal strength with no sensory deficit, the Romberg sign was negative with no dysmetria, and her gait was normal.

When queried further, the mother revealed that she had been giving her daughter 5 mL of cannabidiol oil (25 mg/mL) by mouth 3 times per day for the last 2 months. Approximately 14 days earlier, after receiving news that the intracranial metastatic lesions were decreasing in size, she ordered a higher potency of cannabidiol oil (50 mg/mL). The mother continued to give 5 mL by mouth and increased the frequency of administration from 3 times daily to 6 times daily. The mother rationalized that the decreased size of the intracranial lesions was due to the administration of cannabidiol oil and assumed that more cannabidiol would shrink the lesions even further. She obtained her information on the antitumor properties of cannabidiol from Internet Web sites. Her mother noted that the increased fatigue started ~5 days before admission. With each subsequent day, the girl became more tired. The child was admitted for further evaluation. No changes were made to the dose of methadone on admission or during the subsequent 14 days.

Additional diagnostic studies included an EEG, which had normal results with no abnormal slowing or epileptiform discharges, and MRI of the brain showed no new intracranial metastatic lesions, cerebral hemorrhage, or infarction. There were 2 new, small parietal bone lesions with no underlying edema of the brain.

Two days after stopping cannabidiol, the first serum methadone level was 271 ng/mL, pupils were 3 mm and mildly reactive with a self-reported fatigue level of 2 out of 4, and her CAPD score was 0.

Seven days after stopping cannabidiol, the methadone level was 149 ng/mL, pupils were 3 mm and mildly reactive with a self-reported fatigue level of 2 out of 4, and her CAPD score was 0.

Fourteen days after stopping cannabidiol, the methadone level was 125 ng/mL, pupils were 3 mm and briskly reactive with a self-reported fatigue level of 1 out of 4, and her CAPD score was 0.

**DISCUSSION**

Our patient was receiving stable doses of methadone with good pain control and no significant opioid-related side effects for ~4 months. Although the initial dosing of cannabidiol appeared to be safe because there was no apparent somnolence or fatigue, the patient developed clinically significant fatigue and sleepiness that coincided with a dramatic increase in the frequency of administration of a higher-potency cannabidiol oil than she had taken in the past. Somnolence is the most common side effect of cannabidiol when used for drug-resistant seizures in Dravet syndrome. It is possible that the mother also increased the dose of methadone without alerting the medical team, as she had done with cannabidiol. If the parent is to be trusted and did not increase the dose of methadone, then possible causes for the observed clinical symptoms include cannabidiol-induced CYP isoenzyme inhibition, leading to reduced methadone clearance and the observed higher serum methadone level, a higher serum cannabidiol level, or both. Serum levels of cannabidiol were not assessed because this laboratory test is not available at our institution.

The primary step in the metabolism of methadone is N-demethylation by CYP3A4 and CYP2C19 to EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), an
inactivating metabolite. Inhibiting this enzymatic pathway would lead to increased serum methadone levels, which is what we observed in our patient. The half-life of cannabidiol oil is estimated to be 24 to 48 hours, with higher peak activity and bioavailability varying between each person, dose, and (if taken orally) timing with meals. We observed a steady decline in serum methadone concentration and improved levels of fatigue over the 14 days after cannabidiol was stopped.

Cannabidiol is both metabolized by and inhibits the cytochrome P450 enzyme pathway, specifically CYP2C19 and CYP3A4. There have been reports of cannabidiol causing significant increases in serum levels of other medications that are metabolized through this pathway, including clobazam and tacrolimus. Given that other common drugs, such as macrolide antibiotics, are metabolized through this pathway, the use of cannabidiol should garner the interest of general pediatricians as well.

The explosive increase in cannabidiol products can likely be traced to individual states passing legislation to legalize cannabidiol as well as amendments made to the 2018 Farm Bill that removed hemp (cannabis and cannabis derivatives with no more than 0.3% tetrahydrocannabinol) from the definition of marijuana in the Controlled Substances Act. Thirteen states have “low-tetrahydrocannabinol, high-cannabidiol” laws, whose primary purpose is to allow the legal use of cannabidiol by limiting the allowable concentration of tetrahydrocannabinol. To date, 33 states and the District of Columbia have approved the medicinal use of marijuana, and 11 states and the District of Columbia have legalized the recreational use of marijuana.

Cannabidiol products are commercially available to the public as capsules, edible products, sublingual concentrates, inhaled preparations, and topical lotions and balms. None of these products have been subject to the regulatory process of the FDA, and so the safety of using such products is unknown. The accuracy of the advertised concentration of cannabidiol products purchased online is widely variable, with only ~30% being labeled accurately. The FDA is attempting to answer questions about the safety and quality of products containing cannabidiol through a public FDA hearing and public docket to elicit comments and feedback. The FDA is also investigating claims that some cannabidiol products may contain contaminants, such as heavy metals or pesticides.

Our clinical experience is that parents are often reluctant to disclose their use of cannabidiol or other forms of medical marijuana. It is unclear if this is due to concern about potential or perceived legal ramifications, a concern that a physician may judge their parenting, or some other reason. What is clear, however, is that there needs to be honest, transparent, and trusting communication between pediatricians and their patients and families to ensure that our patients receive the best care possible. Education of parents through a comprehensive review of drug-drug interactions that might arise when administering cannabidiol is essential in our role as medical professionals. Offering other therapeutic modalities that may mitigate the symptoms that parents are treating with cannabidiol may also be reassuring and helpful.

CONCLUSIONS

Some of the greatest dangers of cannabidiol may lie not in its direct side effects but instead its inhibition of metabolic pathways of the liver that may cause significant drug-drug interactions. Coadministration of cannabidiol and methadone led to a marked elevation in serum methadone, most likely due to cannabidiol-induced CYP isoenzyme inhibition. Clinicians and parents should be aware of this potential drug interaction that presented as increased sleepiness and fatigue and could not be explained by disease progression or changes in medication regimen.

ABBREVIATIONS

CAPD: Cornell Assessment of Pediatric Delirium
FDA: Food and Drug Administration

REFERENCES

7. US Food and Drug Administration. Epidiolex. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_


24. US Food and Drug Administration. What you need to know (and what we’re working to find out) about products containing cannabis or cannabis-derived compounds, including CBD. 2019. Available at: https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-we-re-working-to-find-out-about-products-containing-cannabis. Accessed September 26, 2019
Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol

Kevin Madden, Kimberson Tanco and Eduardo Bruera

*Pediatrics* 2020;145;
DOI: 10.1542/peds.2019-3256 originally published online May 22, 2020;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/145/6/e20193256

References
This article cites 18 articles, 1 of which you can access for free at:
http://pediatrics.aappublications.org/content/145/6/e20193256#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Pharmacology
http://www.aappublications.org/cgi/collection/pharmacology_sub
Toxicology
http://www.aappublications.org/cgi/collection/toxicology_sub
Anesthesiology/Pain Medicine
http://www.aappublications.org/cgi/collection/anesthesiology:pain médecine_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol
Kevin Madden, Kimberson Tanco and Eduardo Bruera
Pediatrics 2020;145;
DOI: 10.1542/peds.2019-3256 originally published online May 22, 2020;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/145/6/e20193256