Anticonvulsant Effects of Cannabidiol in Dravet Syndrome

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. N Engl J Med. 2017;376(21):2011–2020.

BACKGROUND: The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. We studied cannabidiol for the treatment of drug-resistant seizures in the Dravet syndrome. METHODS: In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. RESULTS: The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% confidence interval [CI], −41.1 to −5.4; P=0.01). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group (P=0.02). The frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo (P=0.08). Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group. CONCLUSIONS: Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. (Funded by GW Pharmaceuticals; ClinicalTrials.gov number, NCT02091375).

Commentary

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are two of the chemicals found in the resin of the marijuana plant, *Cannabis sativa*. Both compounds interact with the cannabinoid receptors but produce different effects. The psychoactive component of marijuana is attributed to THC, the component that imitates the effects of the neurotransmitter anandamide, which modulates the perception of pain and helps regulate sleep and appetite. On the other hand, CBD, which shares the same chemical formula as THC and accounts for approximately 40% of cannabis extract, lacks psychoactive effects. Beneficial effects of CBD have been reported in reducing psychotic symptoms, anxiety, inflammation, nausea, and seizures.

Dravet syndrome is a severe epilepsy with many seizure types that begins in the first year of life. About 80% of affected individuals have loss-of-function mutations in their SCN1A gene. In addition to intractable seizures, affected individuals exhibit developmental delay, movement and balance abnormalities, delayed language development, sleep disorders, and disruptions of the autonomic nervous system. In 2013, a media report of the remarkable therapeutic of medical marijuana in Dravet syndrome captured global attention (http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/index.html). The patient was a 6-year-old girl who was having 300 grand mal seizures per week and had a history of cardiac arrests necessitating cardiopulmonary resuscitation on more than one occasion. After trying cannabis oil, her seizure frequency dropped to two or three per month, and she was able to walk, ride her bicycle, and feed herself. In the same year, a survey of parents of 19 children with severe childhood epilepsies, including 13 children with Dravet syndrome, explored the use of cannabidiol-enriched cannabis (1). Complete seizure freedom was reported in two subjects (11%), and a greater than 80% seizure reduction in 8 (42%). Additionally, the treatment was perceived to have resulted in improved alertness, mood, and sleep. This was followed by an open-label trial of CBD in 214 patients, 20% of whom had Dravet syndrome (2),

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which reported 36.5% median reduction in monthly motor seizures. However, safety and tolerability data for CBD use among children were still lacking.

Devinsky et al. (3) conducted a multinational, randomized, double-blind, placebo-controlled trial of CBD in Dravet syndrome. They recruited 120 children and young adults, 2 to 18 years of age, with Dravet syndrome and pharmacoresistant seizures. After a 4-week baseline phase, the subjects were randomized to either placebo or a CBD oral solution at a dose of 20 mg per kilogram of body weight per day for 14 weeks. The primary outcome measure was the change in convulsive-seizure frequency over the treatment period compared with the baseline period. The authors found that the median monthly frequency of convulsive seizures dropped from 12.4 to 5.9 in the CBD group, and from 14.9 to 14.1 in the placebo group. The adjusted median difference in seizure-frequency change between the two groups, assessed using the use of a Cochran–Mantel–Haenszel test, was −22.8 percentage points (95% confidence interval [CI], −41.1 to −5.4; $p = 0.01$). The 50% responder rate, defined as the percentage of those who experienced at least 50% reduction of convulsive seizure frequency, was 43% in the CBD group, compared with 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; $p = 0.08$). While nonconvulsive seizure frequency did not appear to differ between the two groups, the frequency of seizures of all types dropped more in the CBD group than in placebo ($p = 0.03$). Additionally, no subjects in the placebo group experienced seizure freedom, compared with 5% in the CBD group ($p = 0.08$).

The Caregiver Global Impression of Change, a seven-point scale, was used as a secondary end-point measure. In the CBD group, 62% showed improvement by at least one category on that scale compared with 34% of the placebo group ($p = 0.02$). The Quality of Life in Childhood Epilepsy scores were not significantly different between the CBD and placebo groups. Adverse events led with withdrawal from the trial of eight patients in the CBD group and one in the placebo group. In the CBD group, somnolence occurred in 36% of participants. Other adverse events that occurred more frequently in the CBD group than the placebo group included diarrhea, vomiting, fatigue, pyrexia, and liver-function test result abnormalities.

The importance of this study is that, unlike most other antiseizure medication trials, it assesses a treatment in a specific epilepsy syndrome with a known genetic basis. CBD resulted in a significant decrease of convulsive seizures and seizures of all types in Dravet syndrome, a pharmacoresistant epilepsy known to be associated with high mortality rates. It would be interesting to assess whether CBD worked best in combination with specific anticonvulsants, but not others, and whether the 5% who experienced seizure freedom have identical or different mutations of the SCN1A gene. The role of cannabinoid receptors in modulating seizure activity has been studied. For example, mutant mice that lack expression of the cannabinoid receptor type 1 (CB1) in principal forebrain neurons but not in adjacent inhibitory interneurons exhibited excessive seizures in the kainic acid model (4). Unlike the wild type, mutant mice failed to mount increased levels of anandamide in the hippocampus. Another study demonstrated that cannabinoids abolished seizures in rats using the pilocarpine model, whereas CB1 antagonism resulted in seizure exacerbation and status epilepticus (5). Why these mechanisms appear to improve seizures in Dravet syndrome, and whether the results benefit other epilepsies remain to be established.

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