Neurological Sciences (2020) 41:695–698
https://doi.org/10.1007/s10072-019-04162-1

BRIEF COMMUNICATION

The use of medical grade cannabis in Italy for drug-resistant epilepsy: a case series

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Received: 11 July 2019 / Accepted: 15 November 2019 / Published online: 27 November 2019
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Abstract

In Italy, medical grade cannabis (MGC) can be prescribed for different medical conditions, including drug-resistant epilepsy (DRE), once standard and approved therapies have failed, or caused non-tolerable side effects. Here, we present a retrospective case series report of five patients with DRE who started therapy with MGC. Authorized ISO 9001:2008 pharmacies prepared MGC according to Italian laws. Olive oil extracts (OOEs) were prepared following standard extraction protocols, and cannabinoids were measured on each OOE to check for successful extraction.After treatment with MGC, all patients reported a reduction in seizure frequency and severity, and some reported improved mood, sleep quality, and general well-being without relevant side effects. Despite the small sample size and open-label nature of the data, we show that MGC may be successfully used to treat DRE. This is especially true when considering that no valid therapeutic option exists for these patients and that MGC was extremely well tolerated.

Keywords Cannabis · Oil extract · Absence · West syndrome

Introduction

Epilepsy affects over 50 million people worldwide, and one-third of patients have drug-resistant epilepsy (DRE) [1]. Nine-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD) have received the greatest attention as potential antiepileptic agents [2].

In Italy, medical grade cannabis (MGC) can be prescribed for recommended medical conditions [3] (i.e., pain, spasticity, untreatable vomiting, appetite stimulation in anorexia, glaucoma, and Gilles de la Tourette Syndrome) or whatever condition may benefit from MGC in the opinion of the prescribing physician. Failure of approved therapies, or non-tolerable side effects, is a pre-requisite for MGC prescription [4]. No approved dose exists for MGC, leaving the decision to the physician's discretion.

As of July 2019, nine MGC variants are available in Italy (Table 1). MGC can be inhaled, ingested as an oral-non-activated (-ONA) compound [5], or can be administered orally as an olive oil extract (-OOE) [6].

Methods

This is a retrospective case series report, approved from our local ethics committee. Epilepsy syndrome and seizure types were recorded according to the International League Against Epilepsy classification [7]. Informed consents were obtained from patients. Seizure frequency was measured through patients' self-recordings using paper charts. Authorized ISO 9001:2008 pharmacies prepared MGC according to Italian laws, using standard extraction protocols [6]. Cannabinoids were measured on each OOE to check for successful extraction. MGC was administered BID orally for convenience.

Results

Case 1

Twenty-one-year-old female patient with non-specific epileptic encephalopathy, onset at 2 months of age with secondarily generalized tonic-clonic seizures (GTCs) with focal motor

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Table 1 Medical grade cannabis features

Cannabis Name	THC	CBD	Plant	Form	OOE-THC mg/ml (mg/drop)	OOE-THCA mg/ml (mg/drop)	OOE-CBD mg/ml (mg/drop)	OOE-CBDA mg/ml (mg/drop)
Bedrocan	22	< 1	Sativa	Flos	19.2 (0.6)	1.7 (0.05)	1.1 (0.03)	0.2 (0.0)
Bediol	6.5	8	Sativa	Granulate	6.2 (0.2)	0.6 (0.02)	7.5 (0.23)	1.5 (0.05)
Bedrolite	0.4	9	Sativa	Granulate	0.8 (0.03)	0.5 (0.02)	7.6 (0.24)	0.4 (0.01)
Bedrobinol	13.5	< 1	Sativa	Flos				
Bedica	14	< 1	Indica	Granulate				
Pedanios 22/1	22	< 1	Sativa	Flos				
Aurora 1/8	< 1	8	Hybrid	Granulate				
FM1	13–20	< 1	Sativa	Granulate				
FM2	5–8	7.5–12	Sativa	Granulate				

The table shows the available forms of medical grade cannabis in Italy. THC and CBD are shown in percentage in a weight/weight ratio. OOE-THC, -THCA, -CBD, and -CBDA are a mean of all measurements from all the preparations used by our five patients throughout their therapy. Measurements are not available for Bedica, Bedrobinol, Pedanios 22/1, Aurora 1/8, FM1, and FM2, as they were not prescribed to the patients of this case report

THC, tetrahydrocannabinol; *CDB*, cannabidiol; *OOE*, olive oil extract; *THCA*, THC acid; *CBDA*, CBD acid

onset characterized by aware myoclonic jerks and a frequency of 3/week (Table 2). MRI showed microcephaly, microgyria, thin brainstem, and hypoplasia of corpus callosum and thalamus. Karyotype analysis was normal. At examination, she had generalized flaccid paralysis and neurodevelopmental delay. At the age of 21, she suffered 20 seizures/month with clusters up to 7/day. Bedrolite-OOE was up-titrated to 20 drops/day (0.52 mg THC, 4.72 mg CBD) with no change in monthly seizures. She then switched to Bedrocan-OOE 30 drops/day with a successful reduction to 7 seizures/month.

Case 2

Eighteen-year-old girl with structural West syndrome and hydrocephalus (treated with ventriculoperitoneal shunt derivation), and hypsarrhythmia at EEG. Onset at 8 months of age with generalized onset epileptic spasms (20/day). At examination, she had a spastic tetraparesis, cortical blindness, and dysphagia. During childhood, seizures became GTCs (13/day). Bedrocan-OOE (20 drops/day) reduced seizures to 2/day, improved quality and duration of sleep, social interaction, and reduced spasticity.

Case 3

Fifteen-year-old girl with polymicrogyria-associated epilepsy with dysmorphic face, wide-based gait, and cognitive delay. At 16 months of age, she experienced focal impaired awareness seizures with tonic onset and secondary GTCs lasting 30 sec. Right frontal post-rolandic polymicrogyria at the MRI. EEG showed slow wave activity in the right hemisphere and epileptiform discharges over the right frontal area. Karyotype, CGH array, and mutations for MECP2, CDKL5, SCN1A, and SCN1b genes were negative. At treatment start, she had a cluster of 20 episodes/day occurring every 2 months. After 1 year of treatment with Bedrolite-OOE (30 drops/day), she had a mean of eight short-lasting GTCs clustered in 1 day every 4 months. Alertness improved, as did sleep and mood.

Case 4

Four-year-old girl with a heterozygote missense de novo mutation of *CACNA1A* pVal1393Met. Onset at the age of 4 months with aware focal tonic-onset seizures and secondary GTCs, that evolved two times a month in status epilepticus requiring urgent hospitalization. EEG showed slow waves in the central right area without epileptic activities. MRI showed a dilatation of the ventricles, cavum vergae, and moderate herniation of the cerebellar tonsils. Neurological examination highlighted a delayed neuropsychological development, broad base walking, speech impairment, head and action hand tremor, and muscle hypotonia. At MGC start, she had seven atypical absences every day. Bedrolite-OOE (20 drops/day) reduced absences to 2/day and one GTCs every 3 months with good response to rectal midazolam. Parents reported an improvement of quality and duration of sleep, no hospital emergency department visits, and a psychomotor improvement. These were not assessed using objective measures or scales.

Case 5

Twenty-five-year-old female patient with juvenile absence epilepsy. History of infantile febrile seizures, 2 GTCs/year, and a mean of 20-generalized onset typical absences every day. MRI was normal. EEG showed generalized and frequent 3–3.5 Hz spike-and-wave discharges with predominance on the anterior bilateral areas. Bedrocan-OOE (20 drops/day) reduced

Table 2 Patients seizure types, cannabis therapy, and percent seizure reduction

Case	Epilepsy type	Previous AEDs	Current AEDs	Comorbidity	Effective cannabis product	Effective dose	Baseline monthly seizure frequency	Seizure reduction	Follow-up
1	Non-specific epileptic encephalopathy	VPA (800 mg), CBZ (500 mg), LMT (75 mg), TPX (100 mg), LTC (250 mg), ZNS (200 mg)	VPA 400 mg BID ZNS 100 mg BID CBZ 250 mg BID	-Central diabetes insipidus -Congenital central hypothyroidism -Splenic hamartomas	Bedrocan-OOE	18 mg THC 1 mg CBD	20 GTCs	60%	4 months
2	West syndrome	CS (NA), PB (60 mg), VPA (800 mg), TPX (300 mg), LTC (3200 mg), KET.	TPX 150 mg BID LTC 1600 mg BID VPA 400 mg BID	Nothing to report	Bedrocan-OOE	12 mg THC 0.7 mg CBD	600 GTCs	80%	48 months
3	Polymicrogyria-associated epilepsy	VPA (400 mg), PB (60 mg), TPX (200 mg), LTC (1500 mg), CBZ (500 mg), LMT (125 mg).	LTC 750 mg BID LCS 100 mg BID TPX 100 mg BID	Nothing to report	Bedrolite-OOE	0.8 mg THC 7.2 mg CBD	10 GTCs	80%	12 months
4	Genetic epilepsy with CACNA 1a mutation	VPA (600 mg), CBZ (240 mg), CB (2,5 mg), PB (45 mg), SP (NA), ACZ (NA)	CBZ 80 mg TID VPA 200 mg TID	Patent ductus arteriosus	Bedrolite-OOE	0.5 mg THC 4.7 mg CBD	210 Abs +1.5 GTC	75%	14 months
5	Juvenile absence epilepsy	PB (NA), LTC (3000 mg), CBZ (800 mg), LMT (200 mg), TPX (200 mg), VPA (1000 mg), LCM (400 mg)	LTC 1000 mg BID TPX 200 mg BID	Ovarian cyst	Bedrocan_OOE	12 mg THC 0.7 mg CBD	600Abs + 2 GTCs/year	95%	12 months

Previous AED refers to all AEDs used in the past, current AED refers to the AED combination on the day we started cannabis

VPA, valproic acid; *CBZ*, carbamazepine; *LMT*, lamotrigine; *TPX*, topiramate; *LTC*, levetiracetam; *KET*, kethogenic diet [12]; *ZNS*, zonesamide; *CS*, corticosteroids; *PB*, phenobarital; *SP*, stiripentol; *ACZ*, acetazolamide; *LCM*, lacosamide; *CB*, clobazam; *NA*, not available; *THC*, tetrahydrocannabinol; *CDB*, cannabidiol; *OOE*, olive oil extract; *Abs*, absence; *GTC*, generalized tonic-clonic seizure; *AED*, anti-epileptic drug; *BIS*, bis in die; *TID*, ter in die

absences to 4/month during the following 6 months of follow-up. One episode of panic attack occurred during therapy.

Discussion

After treatment with MGC, all patients reported a reduction in seizure frequency and severity, and some reported improved mood, sleep quality, and general well-being without relevant side effects. Only one patient experienced one adverse event of mild intensity.

Retrospective studies in the USA showed that 272 patients with DRE, consuming variable uncontrolled artisanal cannabis, had a seizure reduction in 86% of cases, with 10% experiencing a complete clinical response and 4% an exacerbation of seizures [8].

In our cases, we observed seizure reduction with different types of MGC, but the best results were obtained with Bedrocan-OOE, that contains 22% of THC and only traces of CBD. Case 3 and 4 experienced a reduction of about 70% of seizures after Bedrolite-OOE, for which CDB doses are smaller compared with the approved dose of purified CBD for the treatment of Dravet and Lennox-Gastaut syndrome (up to 50 mg/kg/day) [9]. A reduction in glutamate excitotoxicity via the CB1 receptor is known to take place after THC administration, whereas CBD modulates intracellular calcium concentration, inhibits uptake and degradation of endocannabinoids, and shows antiapoptotic, neuroprotective, and anti-inflammatory effects [10].

It is not clear why Bedrocan was superior to Bedrolite, but it should be considered that every cannabis variant contains over 540 phytochemicals, 18 different chemical classes, and more than 100 different phytocannabinoids, creating a unique footprint for each MGC type that is not limited to THC/CBD content [11].

Our study poses some limitations. These include the small sample size, the open-label nature of the data, the limited and variable observation time, and the different types of epilepsy. Despite this, we show that MGC available in Italy, and approved preparations like OOE, may be successfully used to treat cases of DRE with an excellent safety profile.

Acknowledgments The authors are grateful to Ettore Brunello Florio and Annunziata Lombardi for their support on regulatory matters.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest for the present study.

Ethical approval This is a retrospective case series report, approved from our local ethics committee.

Statement of informed consent Informed consents were obtained from patients

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