

OPEN LABEL EVALUATION OF CANNABIDIOL IN DYSTONIC MOVEMENT DISORDERS

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Cannabidiol (CBD), a nonpsychoactive cannabinoid of Cannabis, was given to 5 patients with dystonic movement disorders in a preliminary open pilot study. Oral doses of CBD rising from 100 to 600 mg/day over a 6 week period were administered along with standard medication. Dose-related improvement in dystonia was observed in all patients and ranged from 20 to 50%. Side-effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation. In 2 patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor. CBD appears to have antidystonic and Parkinsonism-aggravating effects in humans.

As early as 1842, O'Shaughnessy reported that oral Cannabis blocked tetanic convulsions and reduced muscular spasms in his patients afflicted with epilepsy, tetanus or rabies, while in 1890 Reynolds claimed that oral Cannabis was useful in the management of "choroid and epileptoid clonic spasms." During the latter 19th century, Cannabis was commonly employed as a general antispasmodic agent, and several recent reports appear to provide some justification for this use. In 1981, Petro and Ellenberger reported that delta-9-tetrahydrocannabinol (THC), the major psychoactive cannabinoid of Cannabis, reduced spasticity of multiple sclerosis, and in 1983 Clifford reported that THC reduced tremor in a few patients with the same disease. Also, in 1980 Cunha et al. reported that cannabidiol (CBD), a major nonpsychoactive cannabinoid of Cannabis, prevented convulsions in epileptic patients who were largely refractory to standard antiepileptic drugs.

Recently, it has been mentioned that patients with idiopathic dystonia (a group of disorders characterized by abnormal movements and postures produced by prolonged spasms of muscle contractions) improved with Cannabis smoking (Marsden, 1981). In addition, findings of potent effects of cannabinoids on reserpine-induced hypokinesia in rats led to the suggestion that cannabinoids might have antidystonic properties in humans (Moss et al., 1984). In light of the above, we initiated an open trial of CBD in a patient with Meige's syndrome (blepharospasm-ommandibular dystonia) (Snider & Consroe, 1984) and a patient with levodopa-induced dystonia (Snider & Consroe, 1985). We now present the results of our preliminary open study of oral CBD in these two cases and in three additional patients with primary dystonia.

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METHODS

Five patients with dystonic movement disorders participated in our approved study (University of Arizona Human Subjects Committee and the U.S. Food and Drug Administration) after receiving informed consent. Patients No. 1, 3 and 5 were currently taking antidystonic medication but were only partially controlled by these agents. Patient No. 4 had persistent disabling generalized dystonia despite trials to reduce the dosage of his current antiparkinsonism medication. Finally, Patient No. 2 was presently taking only antihypertensive medication. The clinical characteristics of the patients are shown in Table 1.

Oral CBD (in capsules with sesame oil vehicle) was started at 100 mg/day and subsequently increased weekly by 100 mg/day to a maximum of 600 mg/day. Clinical response to treatment with CBD was assessed by using a standard dystonia movement scale, ranging from 0 to 120 (Burke et al., 1985). Patients were evaluated "live" by 1 neurologist (S.R.S.) at baseline (1 day before CBD administration), 6 weekly intervals during CBD administration, and 2 and 7 days after the cessation of CBD; examinations of patients were carried out at the same time of day. The therapeutic results were expressed as a percentage change from the baseline dystonia movement score. Patients were also videotaped according to a standard format (Burke et al., 1985), and the presence or absence of improvement to CBD therapy was assessed independently by another neurologist (R.S.). Side-effects and other subjective impressions were obtained from patients and/or their guardians who maintained a daily log of their treatment responses. Further, blood pressures and pulse rates were measured at every clinic visit, and blood counts and chemistries were evaluated at baseline and 7 days after the cessation of CBD administration.

RESULTS

Table 2 presents the results of the trial. Although there were individual differences in the response to CBD, improvement of the dystonia disability was generally dose-related with maximal improvement ranging from 20 to 50%. Two patients with associated Parkinson's signs experienced exacerbation of their hypokinesia and/or resting tremor with the higher doses of CBD. Side-effects of CBD were mild, generally variable, and were recorded or reported only occasionally during the trial. However, cardiovascular side-effects appeared to be the most consistent since a drop (10 to 20 mm Hg) in standing blood pressure (without tachycardia) was recorded in all patients.

Improvement of dystonia of each patient was confirmed by videotape assessment. Additionally in all patients, discontinuation of CBD at the end of the trial resulted in a noticeable increase of the dystonic features within 48 hours, and a return to baseline dystonic levels by 1 week after the cessation of the drug. The patients' subjective reports of improvement on CBD and exacerbation of the dystonic features following discontinuation of the drug correlated with our objective evaluations. No abnormalities of blood counts or chemistries were found in any of the patients after discontinuation of CBD.

DISCUSSION

Our findings in the above 5 cases suggest that chronic oral CBD in combination with other drugs may be useful for dystonic movement disorders. Symptomatic improve-

TABLE 1
Clinical Characteristics of Patients

Patient No.	Age	Sex	Form of Dystonia	Duration of Disease	Associated Signs	Concurrent Therapy
1	42	M	Meige's Syndrome	9 years		Trihexyphenidyl (50 mg/day) Clonazepam (2.5 mg/day) Baclofen (30 mg/day) Atenolol (50 mg/day)
2	65	F	Spasmodic Torticollis	2 years	Essential hypertension; Essential tremor	
3	31	M	Generalized Dystonia	20 years		Trihexyphenidyl (30 mg/day) Sinemet
4	40	M	Levodopa-induced Dystonia	2 years	Parkinsonian signs	(1000 mg Levodopa/day) Alprazolam (3 mg/day)
5	59	M	Generalized Dystonia	20 years	Resting tremor	Chlorpromazine (25 mg/day)

TABLE 2
Patient's Response to CBD Therapy

Patient	Baseline Dystonia Score	Maximal Improvement In Dystonia	CBD Dosage	Side-Effects	Other Features
1	29	40 %	300-400 mg/day	Hypotension Dry Mouth Lightheadedness	
2	14	35 %	400-600 mg/day	Dry Mouth Psychomotor Slowing	Essential Tremor and Hypertension Improved
3	30	35 %	500-600 mg/day	Sedation Lightheadedness	Essential Tremor Improved
4	47	50 %	100-200 mg/kg	Hypotension Orthostatic Hypotension (at 300-400 mg/day)	Exacerbation of Hypokinesia and Resting Tremor (at 300-400 mg/day)
5	42	20 %	300-500 mg/day	Orthostatic Hypotension Sedation Psychomotor Slowing	Exacerbation of Resting Tremor

ment ranging from 20–50% occurred in patients with both focal (Meige's syndrome; spasmodic torticollis) and generalized (dystonia musculorum deformans; levodopa-induced dystonia) forms of dystonia, and included both phasic and tonic components, dystonic "tremor" and postures along with pain. Although there were individual differences in the maximum response to CBD, improvement was generally dose-related. Side-effects (xerostomia, sedation, psychomotor slowing, lightheadedness and hypotension without tachycardia) of CBD were mild, and no abnormalities of blood counts or chemistries were found. The low systemic toxicity of CBD in our patients is consistent with similar findings of other studies employing acute or repeated daily administration of CBD (Cunha et al., 1980). However, CBD in higher doses exacerbated the hypokinesia and/or resting tremor of the 2 patients with coexisting Parkinsonian features. These effects were particularly marked in the patient with primary Parkinsonism (Patient No. 4); this, together with findings of a CBD increase of reserpine-induced hypokinesia in rats (Moss et al., 1984), suggests that this disease may be a contraindication to the use of CBD.

The pathophysiology of the dystonias is largely unknown but increased acetylcholine (ACH), increased or decreased dopamine (DA), and decreased gamma-aminobutyric acid (GABA) functions in the basal ganglia are postulated (Stahl & Berger, 1982; Brennan et al., 1982). In Parkinsonism, relative DA deficiency and ACH excess are well known; GABA deficiency or, alternately, GABA overactivity, may also be involved (Perry, 1983). Interestingly, CBD has been reported to affect all three of these neurotransmitters in rodents. CBD reduces ACH turnover (Revuelta et al., 1978), decreases the binding of both DA agonists and antagonists to DA receptors (Bloom, 1984), and increases GABA turnover (Revuelta et al., 1979), in the basal ganglia; it also effectively prevents tonic convulsions caused by GABA blocking drugs (Consroe et al., 1982). Although these effects may have relevance for the antidystonic and Parkinsonism-aggravating effects of CBD in our patients, the precise mode of action of CBD remains unknown.

While our findings suggest that CBD may benefit some patients with dystonia, inherent limitations of the open design and possible day-to-day fluctuations of individual patient symptoms during our trial preclude any definitive conclusions. However, our findings coupled with the often disabling clinical symptoms and lack of consistent effective pharmacological treatment (Pakkenberg & Pedersen, 1985) indicate that controlled studies with CBD are warranted to establish its efficacy in dystonic movement disorders.

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