

Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients¹

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Abstract. In phase 1 of the study, 3 mg/kg daily of cannabidiol (CBD) was given for 30 days to 8 healthy human volunteers. Another 8 volunteers received the same number of identical capsules containing glucose as placebo in a double-blind setting. Neurological and physical examinations, blood and urine analysis, ECC and EEG were performed at weekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200–300 mg daily of CBD or placebo. The drugs were administered for as long as 4½ months. Clinical and laboratory examinations, EEG and ECG were performed at 15- or 30-day intervals. Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. 4 of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in 1 patient. The clinical condition of 7 placebo patients remained unchanged whereas the condition of 1 patient clearly improved. The potential use of CBD as an antiepileptic drug and its possible potentiating effect on other antiepileptic drugs are discussed.

Anecdotal reports on the antiepileptic properties of marijuana (*Cannabis sativa*) are known since ancient times. (Li, 1974). Rosenthal

(1971) mentioned medieval Arab manuscripts in which cannabis is described as a treatment for epilepsy. During the 19th century several medical reports were published on the ameliorative effects of cannabis extracts on several forms of convulsions (O'Shaughnessy, 1842; Shaw, 1843; Reynolds, 1890).

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In spite of these promising results and its low toxicity, the use of cannabis preparations for medical purposes progressively decreased. This was due to the absence of standardized preparations, the unknown chemical composition, and the psychotropic secondary effects produced by cannabis.

Cannabidiol (CBD) is the major neutral non-psychoactive cannabinoid in most cannabis preparations. It was first isolated by Adams *et al.* in 1940 but its structure was elucidated only 23 years later (Mechoulam and Shvo, 1963). The main active component of cannabis is A'-tetrahydrocannabinol (A'-THC) which was isolated in a pure form and its structure was determined by Gaoni and Mechoulam in 1964. It is also named Δ^9 -THC. Numerous other natural cannabinoids are known today (Mechoulam, 1973; Mechoulam *et al.*, 1976).

The unraveling of the chemistry of *C. sativa* brought a new interest in its pharmacology, and quite expectedly many laboratories studied the anticonvulsant properties of its components especially since early reports had shown that some natural and synthetic cannabinoids protected rats from convulsions (Loewe and Goodman, 1947) and were of therapeutic value in epileptic children (Davis and Ramsey, 1949). More recently many reports have appeared attributing anticonvulsant properties to Δ^1 -THC and other cannabinoids, in a variety of experimental procedures (Garriott *et al.*, 1968; Sofia *et al.*, 1971; Consroe and Man, 1973; Karler *et al.*, 1973, 1974; Plotnikoff, 1976). As a rule, A'-THC was the most studied compound. Most of the results obtained confirmed the rather potent anticonvulsant property of this drug. Its possible use as an antiepileptic drug in humans has, however, been hindered by its known psychotropic effects.

Since Brazilian workers (Carlini *et al.*, 1973; Izquierdo *et al.*, 1973) first demonstrated the

anticonvulsant effects of CBD, there have been several additional reports on the effectiveness of CBD and its derivatives in protecting experimental animals from convulsions induced by various procedures (Karler *et al.*, 1973; Turkkanis *et al.*, 1974; Carlini *et al.*, 1975; Karler and Turkkanis, 1976; Consroe and Wolkin, 1977). Consroe and Wolkin (1977) demonstrated that CBD has a high protective index comparable to that of phenobarbital and a spectrum of anticonvulsant activity in rodents similar to that of phenytoin. CBD also enhances the anticonvulsant potency of both phenytoin and phenobarbital (Consroe and Wolkin, 1977; Chesher and Jackson, 1974; Chesher *et al.*, 1975).

In addition to its favorable anticonvulsant effects and absence of toxicity in animals, CBD seems to be devoid of psychotropic activity and other undesirable side effects in humans. The lack of toxicity of CBD in animals was demonstrated by intraperitoneal injection of 50 mg/kg daily for 90 days in mice, oral ingestion of 5-20 mg/kg daily for 90 days and 50 mg/kg for 27 days by rats and intravenous injection of 1,000 mg/kg in rabbits. No toxicity was observed (Cunha and Carlini, to be published). In man, oral intake of doses from 15 to 160 mg/day (Karniol *et al.*, 1974; Hollister, 1973; Carlini *et al.*, 1979), inhalation of 0.15 mg/kg (Dalton *et al.*, 1976a), and intravenous injection of 30 mg (Perez-Reyes *et al.*, 1973; Hollister, 1973) were not followed by ill effects. Chronic oral administration of 10 mg daily for 21 days did not induce any change in neurological (including EEG), clinical (including ECG), psychiatric, blood and urine examinations (Mincis *et al.*, 1973).

Another recent investigation in our laboratory (Consroe *et al.*, 1979) showed that CBD neither interferes with several psychomotor and psychological functions in humans nor potentiates alcohol effects on these functions.

The above data led us to undertake the present investigation which was performed in two phases. In phase 1, 3–6 mg/kg of CBD (roughly corresponding to 200–400 mg/subject) was administered daily to healthy human volunteers for 30 days. In phase 2, patients suffering from secondary generalized epilepsy with temporal irritative activity received 200–300 mg of the drug for periods of up to 4.5 months.

Experiment 1 (Phase 1 of Study)

Material and Methods

Subjects

16 adult volunteers (11 men and 5 women) aged 22–35 with an average weight of 65 kg were chosen from the staff of Escola Paulista de Medicina. They were in good health showing neither clinical nor laboratory evidence of cardiovascular, renal, hepatic or other impairments. The institutional review committee at Escola Paulista de Medicina previously approved the Protocol of the experiments.

On the first day of the experiment the patients were submitted to a complete medical check-up, including clinical and neurological examinations, EEG, ECG, blood tests (hematocrit, hemoglobin, leukocyte and erythrocyte counts, bilirubin, oxaloacetic and pyruvic transaminases and creatinine) and urine tests (osmolality, pH, albumin, leukocyte and erythrocyte counts, cylinders and crystals) in the Department of Medicine of the Hospital São Paulo of Escola Paulista de Medicina. On the 7th day, they returned to the hospital, signed the informed consent and were randomly divided in two groups of 8. Each group started the ingestion of identical gelatine capsules containing either glucose as placebo (control group) or CBD (experimental group). The experiment was performed on a double-blind basis and the subjects were instructed to ingest the assigned capsules, one in the morning and the second in the afternoon for 30 days. Each capsule contained an amount of CBD (or glucose) equivalent to 1.5 mg/kg, i.e. a daily dosage of 3.0 mg/

kg. 1 volunteer took 4 capsules of CBD daily (6 mg/kg) on the last 3 days of the experiment.

On the 3rd, 7th, 15th, 31st and 37th days after the beginning of drug ingestion, the subjects returned to the hospital to undergo the examinations described above.

Drug

Cannabidiol, in crystalline form (m.p. 66–67 °) was isolated from hashish of undetermined age. It was of Lebanese origin and was supplied by the Israeli Police. The isolation procedure has been described (Gaoni and Mechoulam, 1971). Part of the CBD was a gift from Makor Chemicals, P.O.B. 6570, Jerusalem.

Results

General Observations

During the entire period of the experiment, the subjects did not report any symptoms suggestive of psychotropic effect of CBD. Of the 8 volunteers receiving the placebo, 1 gave up on the 21st day of the experiment for personal reasons; a second placebo subject reported sudoresis and 'palpitations' from the 7th to the 10th day in the veins of the feet, legs and head, stating that he had to uncover his feet to feel the palpitations less in order to sleep. Clinical and laboratory examinations were normal and the symptoms subsided after the 11th day without any measures on the part of the investigators.

Of the 8 volunteers receiving CBD, 2 reported somnolence, 1 during the first week and the other throughout the entire period of the experiment. A 3rd subject, with a history of mild insomnia, reported being able to sleep better during the first week of medication.

Neurological and clinical examinations, EEG and ECG tracings, and blood and urine analyses (detailed above) were within normal limits in the 16 subjects before, during and after the experiment.

Comments

It has been suggested that Δ^1 -THC and other cannabinoids may possess therapeutic potential as antidepressive drugs in patients with cancer (Regelson et al., 1975) or in the treatment of glaucoma (Hepler and Frank, 1971), asthma (Tashkin et al., 1972), etc. For a recent review see Mechoulam and Carlini (1978). However, acute administration of 20–60 mg of Δ^1 -THC induces a marked psychic change and has peripheral effects such as an increase in heart rate (Isbell et al., 1967; Kiplinger et al., 1971; Karniol et al., 1975) which would limit its therapeutic use.

In contrast, the present experiment shows that 3 mg/kg/day of CBD administered for 30 days (1 volunteer received 6 mg/kg/day during the last 3 days of experiment) did not induce any psychic or other side effects and was well tolerated by the 8 subjects. Thus CBD does not appear to have any toxic effect in humans when administered at the above dosage over a long period. This confirms our previous data obtained in animal (Cunha and Carlini, to be published).

In our opinion these findings justified the trial of the drug in epileptic patients.

Experiment 2 (Phase 2 of Study)

Material and Methods

Subjects

15 epileptic patients, 11 women and 4 men, aged 14–49 (average 24 years), with a documented history of frequent convulsions for at least 1 year, were selected. These patients were not reacting satisfactorily to the prescribed antiepileptic drugs they were receiving (table I) in spite of special care to assure that the patients were taking them properly. The patients

were diagnosed as cases of secondary generalized epilepsy; EEG tracings revealed irritative activity with temporal projection. They had at least one generalized convulsive crisis weekly. Clinical and laboratory examinations showed no signs of renal, cardiovascular or hepatic disease. The experiment was performed in the Neurology Out-Patient Clinics of the Hospital São Paulo (8 patients) and the Hospital da Santa Cam (7 patients). Each patient was followed by the same investigator, beginning 2 weeks before first drug administration and then throughout the whole period of drug administration. In the 2 weeks before CBD or placebo administration, the number of focal and generalized convulsive crises was recorded and considered as the baseline to evaluate treatment. On the first day of the experiment, the patients were submitted to the examinations described in experiment 1. They were randomly divided into one group of 8 (control group) and another group of 7 (CBD group) and returned to the hospital for 2 more days. After 1 week each group received placebo or CBD capsules in a double-blind procedure in addition to the antiepileptic drugs they were already receiving (see table I). 1 placebo patient (Z.S.M.) was transferred to the CBD group after 1 month. Half of each group of patients was treated in each hospital. The patients were instructed to take 2 or 3 capsules daily (containing 100 mg of CBD or glucose) and to return to the hospital every week for clinical and/or laboratory examinations.

Clinical evaluation of drug treatment was made weekly using a scale with score 0–3, which took into consideration absence of convulsive crises or absence of generalization and self-reported subjective improvement (see table II). According to this criterion all patients were scored 3 during the predrug phase (baseline).

Results

General Observations

During the course of the experiment none of the 8 patients receiving CBD showed evidence of behavioral alterations which could be suggestive of a psychotropic effect. The minimum and maximum times of drug administration were 8 and 18 weeks for most patients (control

Table I. Epileptic patients, the prescribed medicines they were taking before and during the experiment, and the frequency of convulsive crises at the 2 weeks before the beginning of CBD administration (baseline)

Group	Initials	Prescribed medicine	FCC at week		GCC at week	
			2	1	2	1
Placebo	J.O.R.	Comital ^a + Tridione ^b	>10	>10	2	1
	J.S.	Comital L	2	5	3	1
	M.G.S.	Gardenal ^c + Hidantal ^d	0	2	3	2
	J.S.V.	Primidona ^e + Rivotril ^f + Gardenal	3	4	1	3
	M.L.M.	Gardenal + Rivotril + Zarontim ^g	>10	>10	1	1
	R.C.	Hidantal + Fenobarbital ^c	5	4	4	2
	M.D.M.S.	Comital L	1	1	1	1
	Z.S.M. [*]	Hidantal + Fenobarbital	>10	>10	1	2
CBD	Z.S.M. [*]	Hidantal + Fenobarbital	>10	>10	1	2
	F.R.F.	Rivotril + Tegretol ^h	>10	>10	1	2
	O.E.B.N.	Gardenal + Mysoline ^e + Rivotril	0	1	1	1
	A.A.S.	Hidantal + Gardenal	7	8	2	3
	A.S.R.	Hidantal + Fenobarbital	4	3	1	2
	N.P.	Primidona	3	5	1	1
	N.D.	Gardenal + Mysoline	>10	>10	3	4
	M.C.P.	Fenobarbital	0	1	2	1

FCC = Number of focal convulsive crises; GCC = number of generalized convulsive crises. ^aPhenytoin + mephobarbital + phenobarbital; ^btrimethadione; ^cphenobarbital; ^dphenytoin; ^eprimidone; ^fclonazepam; ^gethosuximide; ^hcarbamazepine.

* After 4 weeks on placebo crossed over to CBD.

and CBD groups). 2 of the placebo patients did not return after the end of the 4th week and 1 CBD patient after the 6th week. 1 placebo Patient (Z.S.M.) whose condition remained unaltered during 4 weeks, wanted to give up the experiment, but remained in it after crossing over to the CBD group.

4 patients under CBD and 1 receiving placebo complained of somnolence during the experiment. Another CBD patient (M.C.P.) complained of painful gastric sensations after drug ingestion at the 6th week. These symptoms disappeared after prescription of an antacid and did not return throughout the experiment.

Table II. Criteria used to evaluate clinical efficacy of cannabidiol in epileptic patients

Score	Clinical significance
0	complete improvement
1	partial improvement
2	small improvement
3	without improvement

0 = Total absence of convulsive crises and self-reported subjective improvement.

1 = Absence of generalization of crises and self-reported subjective improvement.

2 = Only self-reported subjective improvement.

3 = No reduction in crises and no self-reported improvement.

Table III. EEC analysis of epileptic patients under CBD or placebo treatment (plus other drugs; see table 2)

Group	Patient	Analysis of EEG performed at days			
		0	30	60	120
Placebo	J.O.R.	Ab	B	c	B
	J.S.	Ar*	—	—	—
	M.G.S.	Ar	—	—	—
	J.S.V.	Al**	C	B	B
	M.L.M.	Ab	B	B	—
	R.C.	Al	B	n.p.	B
	M.D.M.S.	Ar	B	B	B
	Z.S.M.	Ar	B	—	—
CBD	Z.S.M.	Ar	B	—	—
	F.R.F.	Al**	C	C	C
	O.E.B.N.	Ar**	C	C	C
	A.A.S.	Al	C	—	—
	A.S.R.	Ar	B	n.p.	B
	N.P.	Al	B	n.p.	B
	N.D.	Al	B	—	—
	M.C.P.	Ar	n.p.	B	—

A = Irritative activity with temporal projection; b = bilateral, r = right hemisphere, l = left hemisphere; B = EEG **unaltered** in relation to the first one (0 day); C = EEG improved in relation to the first one (0 day).

* Highly active with frequent generalizations; ** extremely active; n.p. = EEG not performed.

Neurological Examination and EEG

Before drug treatment 1 CBD patient (ND.) showed paresthetic walking towards the right, with spastic hypomotility of the right arm and leg, mainly of the right hand. He also presented a decrease in psychomotor functions. 2 other patients in the CBD group (A.A.S. and Z.S.M.) showed in examinations prior to the experiment some mental underdevelopment. Neurological examinations of all other patients were within normal limits.

Table III shows the results of the EEG analysis in a condensed form. Of the patients receiving CBD, 3 showed improvement in EEG pattern with signs of decrease in frequency of

crises throughout the experiment. 2 placebo patients also had improved EEG pattern (J.O.R., and J.S.V.) on one occasion, with return to their previous condition on subsequent examination.

Clinical and Laboratory Examinations

Clinical examination proved normal for all patients and the pulse, cardiac and respiratory rates remained constant during the course of the experiment. ECG tracings, blood and urine analysis (detailed in experiment 1 — materials and methods) were within normal limits. Also in all patients neither CBD nor placebo altered creatinine, bilirubin or transaminase values.

table IV. Weekly clinical evaluation of epileptic patients under CBD or placebo treatments (plus other drugs, see table I)

Patient	Drug	Clinical evaluation during treatments (as compared to baseline values) of week ¹																		Median ²
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
J.O.R.	placebo	1	3	3	3	3	3	3	3	3	3	3	3							3
J.S.	placebo	2	3	3																3
M.G.S.	placebo	3	3	3																3
J.S.V.	placebo	0	2	3	3	2	3	2	3	3	3	3	3							3
M.L.M.	placebo	1	3	3	3	3	2	3	2											3
R.C.	placebo	1	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
M.D.M.S.	placebo	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0
Z.S.M.	placebo	3	3	3	3															3
Z.S.M.	CBD 200					1	1	2	3	3	2									2
R.F.	CBD 200	0	3	0	0	1	1	0	1	1	0	0	3	1	0	1	1			1
J.E.B.N.	CBD 200	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0			0
A.A.S.	CBD 200	0	0	0	0	0	0													0
A.S.R.	CBD 200 I	0	0	1	0	0	1	1	1	0	1	1	0	1	1	0	0	0	0	0
N.P.	CBD 200	2	2	2	2	2	2	2	2	1	1	2	2	2	2	2	1			2
N.D.	CBD 200	3	3	3	3	3	3													
	300							3	3											3
M.C.P.	CBD 200	0	3	0	2	2	2													
	300							1	0	1	0	0	0							0

¹ See tables I and II.² Calculated from total weekly results.

Clinical Evaluation of Treatment

Clinical evaluation was performed weekly, scoring 0-3 points to each patient compared to its own baseline (see table II and 'methods' for details). At the end of the treatment, the median of weekly score for each patient was calculated. The results are presented in table IV. During the first week of treatment there was general improvement in almost all patients (placebo and CBD groups), but from the second week, all placebo patients with one exception (M.D.M.S.) returned to their previous clinical

state. At the end of the placebo treatment, 7 patients had a median of 3 (i.e. no improvement) whereas patient M.D.M.S. showed complete improvement (median 0). 2 placebo patients (J.S. and M.G.S.) with no improvement received the capsules for the 4th week of treatment but did not return. 3 other placebo patients (J.O.R.; J.S.V.; M.L.M.) remained under treatment for the period stated in table IV, after which it was decided to withdraw them from the experiment and to change the antiepileptic drugs they were receiving (see table I) in

an attempt to improve their condition. Patient R.C. remained in the placebo group for 18 weeks and received all known antiepileptic drugs without success. Patient Z.S.M. was on placebo for 4 weeks without improvement and was subsequently transferred to 200 mg of CBD daily for 6 weeks (without her knowledge) with a small improvement (median 2).

Of the 8 patients receiving CBD, 4 showed considerable improvement in their clinical condition (median 0). However, in 1 case (M.C.P.) this was achieved by increasing the dosage to 300 mg daily. Patient A.A.S., who showed much improvement from the first week, unfortunately moved to another city after completing 6 weeks of treatment with CBD. The 5th patient (F.R.F.) improved only partially (median 1) although he attained score 0 in clinical evaluation (no convulsive crisis and subjective improvement) in 7 out of the 16 weeks of treatment. 2 of the 3 remaining patients showed small improvement (score 2) whereas the last patient (N.D.) did not improve at all in spite of increasing CBD to 300 mg daily for the last 2 weeks of treatment.

Discussion

Treatment of epilepsy is based mainly on anticonvulsant drugs. However, even when properly administered in well-diagnosed cases, these drugs succeed in helping only about 70–75% of the epileptic patients, whereas about 30% of the patients do not benefit at all (Robb, 1975). Furthermore, all clinically effective antiepileptic drugs induce undesirable side effects at normal dosage (osteomalacia, megaloblastic anemia; gingival hyperplasia) or due to overdose (nystagmus, motor incoordination, coma and death) or to idiosyncratic reactions (Kutt and Louis, 1972).

As already stated in the introduction, many ancient reports mention the antiepileptic properties of cannabis. More recently Consroe et al. (1975) described an epileptic patient receiving phenobarbital and phenytoin without good results, who benefitted by smoking marijuana. These accounts indicate that marijuana contains chemical entities which may possess antiepileptic properties.

According to the present data, CBD may turn out to be a useful drug for the treatment of some cases of epilepsy. There is hardly any toxicity as shown in our phase 1 study; there were no changes in EEG, ECG, blood and urine analyses and neurological and clinical examinations were normal in 8 healthy volunteers receiving 3 mg/kg of CBD daily for 30 days. A similar absence of toxicity was also noted in our phase 2 study in which 8 epileptic patients received 200 or 300 mg for up to 4½ months. Furthermore, none of the 16 subjects receiving CBD showed any psychic A'-THC-type effects. The present data obtained after long-term administration also confirm previous reports showing the absence of toxicity in acute studies (Hollister, 1973; Carlini et al., 1979).

Somnolence reported by 3 healthy volunteers and 4 epileptic patients (43% of the subjects receiving the drug) was the only CBD side effect noted. A certain hypnotic effect is frequently observed with drugs which possess antiepileptic properties. We have in fact recently demonstrated that CBD does induce better sleep in human volunteers (Carlini et al., 1979). On the other hand, CBD induced a remarkable improvement (median 0) in 4 of 8 epileptic patients who remained almost free of convulsive crises during the entire period of the experiment. In a 5th patient (median 1), the crises were absent in 7 of the 16 weeks of treatment. All of these patients (as well as their relatives) reported subjective improvement. A

similar subjective effect was also reported by 2 more patients and only in 1 patient CBD failed to induce any form of clinical benefit. This is in striking contrast to the results obtained with the 8 patients receiving placebo of whom 7 showed no improvement in their clinical condition.

However, EEG results were not as consistent as the clinical evaluation. As seen in table III, clinical improvement was not always followed by positive changes in the tracings. As the International League against Epilepsy (Commission on Antiepileptic Drugs) does not consider EEG mandatory in this type of research (Penry, 1973), EEG data were not included in the overall clinical evaluation of CBD effects. It should also be emphasized that the abnormal EEGs were present from the beginning of the experiment even though all patients were receiving known antiepileptic drugs. Furthermore, phenytoin and barbiturates fail to control the EEG abnormalities of epileptics in spite of being able to abolish their behavioral convulsions; phenytoin may even increase the prominence of focal spikes (Morrel et al., 1959; Millichap, 1969).

Wall et al. (1946) have reported pharmacokinetic studies in man with ^3H -CBD injected intravenously into 5 healthy volunteers. They observed that 8% of the total initial dose (20 mg of CBD) was present in plasma 30 min after injection, to fall to 3% after 60 min. 3 days later, 33% was excreted in the feces and 16% in the urine, with 50% remaining in tissues and organs. Therefore, CBD seems to have a relatively long half-life, which favors its use as a drug in epileptics.

However, in spite of the large number of reports showing beneficial effects of cannabis and its preparations in many forms of experimental convulsions and in human epilepsy, a few reports claim the contrary. Feeney et al.

(1976) showed that Δ^1 -THC in cats induced EEG changes resembling those observed in convulsions, and Perez-Reyes and Wingfield (1974) described a similar effect of CBD in man. In neither case, however, were behavioral convulsions observed. It is interesting in this context that phenytoin may increase activity of focal spikes (Millichap, 1969). To the best of our knowledge there is only one report attributing a worsening of an epileptic convulsive crisis (grand mal) following use of marijuana smoking (Keeler and Reifler, 1967), and we do not know of any cases described for CBD. Furthermore, in none of our 8 epileptic patients did we observe deterioration of clinical symptomatology or of EEG, but rather the opposite effect was true.

The mechanism by which CBD benefitted our epileptic patients is not known. All 8 patients were also receiving known antiepileptic drugs which were by themselves, however, ineffective. One possibility is that CBD potentiated their action since enhancement by CBD of anticonvulsant activity of phenobarbital and phenytoin in animals has been demonstrated (Consroe and Wain, 1977; Chesher and Jackson, 1974; Chesher et al., 1975). In man, however, 50–500 $\mu\text{g}/\text{kg}$ CBD given in cigarette form is not able to alter plasma concentrations of secobarbital (Dalton et al., 1976b). The possibility that CBD acts *per se* should also be taken into consideration, as shown by several reports describing its direct anticonvulsant effects in animals.

In conclusion, we have found that CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal focus, who did not benefit from known antiepileptic drugs. Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans.

References

- Adams, R.; Hunt, M., and Clark, J.H.: Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. *J. Am. chem. Soc.* 62: 196-200 (1940).
- Carlini, E.A.; Leite, J.R.; Tannhauser, M., and Berardi, A.C.: Cannabidiol and *Cannabis sativa* extract protect mice and rats against convulsive agents. *J. Pharm. Pharmacol.* 25: 664-665 (1973).
- Carlini, E.A.; Masur, J., and Magalhães, C.C.P.B.: Possible hypnotic effect of cannabidiol on human beings. Preliminary study. *Ciênci Cult., S Paulo* 31: 315-322 (1979).
- Carlini, E.A.; Mechoulam, R., and Lander, N.: Anticonvulsant activity of four oxygenated cannabidiol derivatives. *Res. Commun. chem. Pathol. Pharmacol.* 12: 1-15 (1975).
- Chesher, C.B. and Jackson, D.M.: Anticonvulsant effects of cannabinoids in mice. Drug interactions within cannabinoids and cannabinoid interactions with phenytoin. *Psychopharmacology* 37: 255-264 (1974).
- Chesher, G.B.; Jackson, D.M., and Malor, R.M.: Interaction of A-9-tetrahydrocannabinol and cannabidiol with phenobarbitane in protecting mice from electrically induced convulsions. *J. Pharm. Pharmacol.* 27: 608-609 (1975).
- Consroe, P.F.; Carlini, E.A.; Zwicker, A.P., and Lacerda, L.A.: Human interaction effects of cannabidiol and alcohol. *Psychopharmacology* 66: 45-50 (1979).
- Consroe, P.F. and Man, D.P.: Effects of A-8 and A-9-tetrahydrocannabinol on experimentally induced seizures. *Life Sci.* 13: 429-439 (1973).
- Consroe, P.F. and Wolkin, A.: Cannabidiol-antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. *J. Pharmacol. exp. Ther.* 201: 26-32 (1977).
- Consroe, P.F.; Wood, G.C., and Buchsbaum, H.: Anticonvulsive nature of marihuana smoking. *J. Am. med. Ass.* 234: 306-307 (1975).
- Dalton, W.S.; Martz, R.; Lemberger, L.; Rodda, B.E., and Forney, R.B.: Influence of cannabidiol on Δ -9-tetrahydrocannabinol effects. *Clin. Pharmacol. Ther.* 19: 300-309 (1976a).
- Dalton, W.S.; Martz, R.; Rodda, B.E.; Lemberger, L., and Forney, R.B.: Influence of cannabidiol on secobarbital effects and plasma kinetics. *Clin. Pharmacol. Ther.* 20: 695-700 (1976b).
- Davis, J.P. and Ramsey, H.H.: Antiepileptic activity of marihuana active substances. Abstract. *Fed. Proc.* 8: 284 (1949).
- Feeney, D.M.; Spiker, M.D., and Weiss, G.K.: Marihuana and epilepsy: Activation of symptom by Δ -9-THC; in Cohen and Stillman, The therapeutic potential of marijuana (Plenum Press, New York 1976).
- Gaoni, Y. and Mechoulam, R.: Isolation, structure and partial synthesis of an active constituent of hashish. *J. Am. chem. Soc.* 86: 1646-1647 (1964).
- Gaoni, Y. and Mechoulam, R.: The isolation and structure of A-1-THC and other neutral cannabinoids from hashish. *J. Am. chem. Soc.* 93: 217-224 (1971).
- Garriott, J.C.; Forney, R.B.; Hughes, F.W., and Richards, A.B.: Pharmacologic properties of some cannabis related compounds. *Archs int. Pharmacodyn. Thé.* 171: 425-434 (1968).
- Hepler, R.S. and Frank, I.R.: Marihuana smoking and intraocular pressure. *J. Am. med. Ass.* 217: 1392 (1971).
- Hollister, L.E.: Cannabidiol and cannabinol in man. *Experientia* 29: 825-826 (1973).
- Isbell, H.; Gorodetzky, C.W.; Jasinski, D.; Claussen, U.; Spulak, F.V., and Korte, F.: Effects of (-)- Δ -9-tetrahydrocannabinol in man. *Psychopharmacologia* 11: 184-188 (1967).
- Izquierdo, I.; Orsingher, O.A., and Berardi, A.C.: Effect of cannabidiol and of other *Cannabis sativa* compounds on hippocampal seizure discharges. *Psychopharmacologia* 28: 95-102 (1973).
- Karler, R.; Cely, W., and Turkanis, S.A.: The anticonvulsant activity of cannabidiol and cannabinol. *Life Sci.* 13: 1527-1531 (1973).
- Karler, R.; Cely, W., and Turkanis, S.A.: Anticonvulsant of Δ -9-tetrahydrocannabinol and its 11-hydroxy and 8- α -11-dihydroxymetabolites in the frog. *Res. Commun. chem. Pathol. Pharmacol.* 9: 441-452 (1974).
- Karler, R. and Turkanis, S.A.: The antiepileptic potential of the cannabinoids; in Cohen and Stillman. The therapeutic potential of marijuana (Plenum Press, New York 1976).
- Karniol, I.G.; Shirakawa, I.; Kasinsky, N.; Pfeferman, A., and Carlini, E.A.: Cannabidiol interferes with the effects of Δ -9-tetrahydrocannabinol in man. *Eur. J. Pharmacol.* 28: 172-177 (1974).
- Karniol, I.G.; Shirakawa, I.; Takahashi, R.N.; Knobel, E., and Musty, R.E.: Effects of Δ -9-tetrahydro-

- cannabinol and cannabinol in man. *Pharmacology* **13**: 502-512 (1975).
- Keeler, M.H. and Reifler, C.B.: Grand mal convulsion subsequent to marijuana use. *Dis. nerv. Syst.* **28**: 474-475 (1967).
- Kiplinger, G.F.; Manno, J.E.; Rodda, B.E., and Forney, R.B.: Dose-response analysis of the effects of tetrahydrocannabinol in man. *Clin. Pharmacol. Ther.* **12**: 650-657 (1971).
- Kutt, H. and Louis, S.: Untoward effects of anticonvulsants. *New Engl. J. Med.* **286**: 1316-1317 (1972).
- Li, H.L.: An archeological and historical account of cannabis in China. *J. econ. Bot.* **28**: 437-448 (1974).
- Loewe, S. and Goodman, L.S.: Anticonvulsant action of marihuana-active substances. *Abstract. Fed. Proc.* **6**: 352 (1947).
- Mechoulam, R.: Marijuana. Chemistry, metabolism, pharmacology and clinical effects (Academic Press, New York 1973).
- Mechoulam, R. and Carlini, E.A.: Toward drugs derived from cannabis. *Naturwissenschaften* **65**: 174-179 (1978).
- Mechoulam, R.; McCallum, N.K., and Burstein, S.: Recent advances in the chemistry and biochemistry of cannabis. *Chem. Rev.* **76**: 75-112 (1976).
- Mechoulam, R. and Shvo, Y.: The structure of cannabidiol. *Tetrahedron* **19**: 2073-2078 (1963).
- Millichap, J.G.: Relation of laboratory evaluation to Clinical effectiveness of antiepileptic drugs. *Epilepsia* **10**: 315-328 (1969).
- Mincis, M.; Pfeferman, A.; Guimarães, R.X.; Ramos, O.L.; Zukerman, E.; Karniol, I.G. Carlini, E.A.: Administração crônica de canabidiol em seres humanos. *Revta Assoc. méd. Brasil* **19**: 185-190 (1973).
- Morrel, F.; Bradley, W., and Ptashne, M.: Effects of drugs on discharge characteristics of chronic epileptogenic lesions. *Neurology* **9**: 492-498 (1959).
- O'Shaughnessy, W.B.: On the preparations of the Indian hemp or gunjah. *Trans. med. Phys. Soc. Bombay* **8**: 421-461 (1842).
- Penry, J.K.: Principles for clinical testing of antiepileptic drugs. *Epilepsia* **14**: 451-458 (1973).
- Perez-Reyes, M.; Timmons, MC.; Davis, K.H., and Wall, M.E.: A comparison of the pharmacological activity in man of intravenously administered Δ -9-tetrahydrocannabinol, cannabinol and cannabidiol. *Experientia* **29**: 1368-1369 (1973).
- Perez-Reyes, M. and Wingfield, M.: Cannabidiol and electroencephalographic epileptic activity. *J. Am. med. Ass.* **230**: 1635 (1974).
- Plotnikoff, N.P.: New benzopyrans: anticonvulsant activities; in Cohen and Stillman, The therapeutic potential of marijuana (Plenum Press, New York 1976).
- Regelson, W.; Butler, J.R.; Schultz, J.; Kirt, T.; Peek, L., and Green, M-L.: Δ -9-THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients; in Braude and Szara, international conference on the pharmacology of cannabis (Raven Press, New York 1975).
- Reynolds, J.R.: Therapeutic uses and toxic effects of *Cannabis indica*. *Lancet* **i**: 637-638 (1890).
- Robb, P.: Focal epilepsy: the problem, prevalence, and contributing factors. *Adv. Neurol.* **8**: 11-22 (1975).
- Rosenthal, F.: The herb hashish versus medieval Muslim society (Brill, Leiden 1971).
- Shaw, J.: On the use of *Cannabis indica* in tetanus hydrophobia, and in cholera with remarks on its effects. *Madras med. J.* **5**: 74-80 (1843).
- Sofia, R.D.; Solomon, T.A., and Barry, H., III: The anticonvulsant activity of Δ -1-tetrahydrocannabinol in mice. *Abstract. Pharmacologist* **13**: 246 (1971).
- Tashkin, D.P.; Shapiro, B.J., and Frank, I.M.: Acute pulmonary physiological effects of smoked marijuana and oral Δ -9-tetrahydrocannabinol in healthy young men. *New Engl. J. Med.* **289**: 336-341 (1972).
- Turkanis, S.A.; Cely, W.; Olsen, D.M., and Karler, R.: Anticonvulsant properties of cannabidiol. *Res. Commun. chem. Pathol. Pharmacol.* **8**: 213-246 (1974).
- Wall, M.E.; Brine, D.R., and Perez-Reyes, M.: Metabolism of cannabinoids in man; in Laude and Szara, The pharmacology of marihuana (Raven Press, New York 1976).

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