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Anticonvulsant Effects of Hashish in Human Epileptics

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ABSTRACT

The possible anticonvulsant effects of a crude hashish material (containing 3.2% total cannabinoids by weight) were studied in 12 patients with idiopathic grand mal epilepsy which was not adequately controlled by phenytion therapy. After a period of eight weeks of regular phenytion therapy, the patients were divided into two equal groups. One group was maintained on hashish therapy and the other on combined hashish and phenytion therapy for another eight weeks. Both groups showed a reduction in frequency and duration of their seizures. The results of the present study are suggestive of a potential therapeutic value of hashish or its constituents in human epilepsy.

INTRODUCTION

Cannabis has been used as a medication since ancient times. Its beneficial therapeutic effects have been known throughout recorded history(Mikuriya, 1969).

Ameliorative effects of marihuana extract on "infantile convulsions" "rabies" and "tetanus" have been described since 1841 (O'Shaughnessy, 1842). Similarly, a number of the 19th century investigators pointed out the beneficial effects of marihuana preparations in controlling various spastic and seizure states (Shaw, 1943, and Reynolds, 1890).

More than 30 years ago, Davis and Ramsey (1949) stressed the value of synthetic derivatives of delta-9-tetrahydrocannabinol (delta-9-THC), the principal psychoactive constituent of cannabis, in the treatment of human epilepsy. More recently, the anticonvulsant nature of marihuana has been demonstrated in a 24 year old epileptic patient in whom marihuana smoking in conjunction with therapeutic doses of phenobarbital and diphenylhydantion was apparently necessary for controlling the seizures (Consroe **et al.**, 1975).

The anticonvulsant properties of delta - 9 - tetrahydro - cannabinol, cannabidiol (CBD), cannabinol (CBN) and dimethylheptylpyran (DMHP) derivative of delta - 9 - THC have been demonstrated in a wide variety of experimental animal species (Sofia **et al.**, 1971, Boggan **et al.**, 1973). On the other hand, there is a published case report in which marihuana smoking exacerbated grand mal convulsions in a 20 year old man. (Keeler and Reifler, 1967).

The present study is an open trial to test the possible anticonvulsant effects of crude hashish on a small group of Egyptian epileptics.

MATERIAL AND METHOD

Subjects: Tweleve subjects were selected, seven males and five females,ranging in age between 10 and 40 years. All had grand mal epilepsy of the idiopathic type with no evidence of lateralizing focal neurological deficit. They were outpatients in the "Epilepsy Clinic" attached to the Neuropsychiatry Department at Al-Hussein University Hospital. All had poorly controlled or uncontrolled recurrent seizures for at least one year prior to the study despite treatment with a variety of anticonvulsant drugs (such as phenytion, primidone, sulthiame and phenobarbital) in the recommended doses for not less than six months. All were otherwise noncomplaining as regards physical and mental health.

Drug: The crude material of hashish was analyzed for its connabinoid content by gas chromatography and was found to contain 3.2%

by weight total cannabinoids. Powdered hashish was made into capsules, each containing 300 mg of the crude material.

Procedures: Patients were interviewed and given a thorough general physical and neurological examination by two experienced neurologists (A.M. Osman and F.M. Afifi). They were then kept on phenytoin (Epanutin) capsules in doses ranging from 100 to 400 mg daily for eight weeks, with a weekly follow-up for the frequency of fits, duration of each fit, the presence of aura or sequelae, the occurrence of status epilepticus, or any drug side effects. At the end of this period, they were given oral hashish starting with one capsule (300mg) daily, and gradually increasing the daily dosage by one capsule every week, according to the patient's response, up to a maximum of 900 mg per day. At the same time, gradual withdrawal of phenytoin was accomplished over a period of one week in six patients. These patients were then maintained on hashish alone for eight weeks. The remaining six patients were kept on phenytion plus hashish for the same period of time. Patients were told they would receive an experimental drug prepared from hashish material and their agreement to participate in the study was ensured before starting. A weekly follow-up was adopted for all patients throughout this period. By the end of the eighth week period of hashish trial, all patients were kept on their original dosage of phenytoin and gradual withdrawal of hashish was accomplished over a one week period. They were then followed up for two weeks.

RESULTS

The group of patients studied showed inadequate control of their seizures during the eight week period of phenytoin therapy. Fits recurred from one to seven times a week and varied in duration from two to ten minutes. Nine patients gave a history of auras preceding each seizure in the form of unexplained fear with running (in one patient), olfactory hallucinations (in two patients), formed visual hallucinations (in two patients), formed visual hallucinations (in one patient), auditory hallucinations and vertigo (in one patient), numbness and

tingling in the extremities (in one patient), epigastric discomfort and a sensation of butterflies in the stomach (in three patients).All patients reported usual sequelae after seizures in the form of sleepiness for several hours, headache, lassitude, confusion or excitement. Status epilepticus (in the form of successive attacks of convulsions with no recovery of consciousness in between for 60–90 minutes) occurred once in two of the studied group during the whole period of study, as shown in Table I.

The six patients who have odd numbers in Table 1 were switched to hashish after gradual withdrawal of phenytoin. They showed control of their seizures in general, and complete cessation of fits was attained in four of the patients within 2 – 3 weeks after starting hashish therapy. The remaining two showed a reduction in the seizure frequency, down to 1–2 per week, and in the duration of each fit to 2–5 minutes, as shown in Tables II and IV. The other six patients who have even numbers in Table 1 were kept on combined therapy with phenytion and hashish. The results were also encouraging, as seizures were completely controlled in three of them within two weeks of combined therapy, and marked reduction in seizure frequency was achieved in the remaining three, as shown in Tables III and V.

The adverse reactions and physiological changes that were encountered during oral hashish therapy were generally very mild. A list of common cannabis symptoms was checked by each patient through an interview at the weekly follow-up, and all patients were examined for possible clinical signs of drug reactions. The results of this checklist revealed dryness of mouth and throat, as well as mild sedation and sleepiness in three patients, with hiccups, nausea and vomiting in two of them and loose stools in the third. These symptoms only occurred on increasing the dose to 900 mg and completely disappeared on reducing the dose to 600 mg. One patient developed tachycardia during the first three days of treatment, and two others noticed increased appetite. Out of the 12 patients studied, four had gum hypertrophy

TABLE I

Follow-up Findings during Phenytoin (Epanutin) Therapy

Subject No.	Age	Sex	Daily Dose in mg	Freq of fits/wk	Duration of each in min	Aura	Sequelae	Status Epilepticus
1	10	M	100	1–2	3–4	+	+	—
2	11	F	200	1–2	2–3	—	+	—
3	14	M	200	1–2	3–5	—	+	—
4	17	M	300	1–3	3–5	—	+	—
5	19	F	300	2–3	5–7	+	+	—
6	23	M	300	3–4	5–6	+	+	—
7	26	F	200	1–2	3–5	+	+	—
8	31	M	400	6–7	5–10	+	+	+
9	33	F	300	2–3	7–10	+	+	—
10	35	M	400	3–5	5–7	+	+	+
11	39	M	300	1–2	4–6	+	+	—
12	40	F	400	2–3	3–4	+	+	—

TABLE II

Follow-up Findings during Hashish Therapy

Subject No.	Daily dose in mg	Freq of fits/wk	Duration of each fit in min	Aura	Sequelae	Status Epilepticus
1	300	None	—	—	—	—
3	300	None	—	—	—	—
5	300	1 – 2	2 – 3	+	+	—
7	600	None	—	—	—	—
9	900	1 – 2	3 – 5	+	+	—
11	600	None	—	—	—	—

TABLE III

Follow-up Findings during Combined Hashish and Phenytion Therapy.

Subject No.	Daily dose in mg		Freq. of fits/wk	Duration of each fit in min	Aura	Sequelae	Status Epilepticus
	Hashish	Phenytion					
2	300	200	None	—	—	—	—
4	300	300	None	—	—	—	—
6	600	300	1 – 2	2 – 3	+	+	—
8	600	400	2 – 3	3 – 5	+	+	—
10	900	400	1 – 2	2 – 3	+	+	—
12	600	400	0 – 1	1 – 2	+	+	—

TABLE IV

A Comparison between the Response to Hashish Therapy vs. Phenytion therapy.

Subject No.	Phenytion Freq/wk	Phenytion Duration in min	Hashish Freq/wk	Hashish Duration in min
1	1 – 2	3 – 4	None	—
3	1 – 2	3 – 5	None	—
5	2 – 3	5 – 7	1 – 2	2 – 3
7	1 – 2	3 – 5	None	—
9	2 – 3	7 – 10	1 – 2	3 – 5
11	1 – 2	4 – 6	None	—

TABLE V

A Comparison between the Response to Combined Therapy with Hashish and Phenytion vs. Phenytion Therapy Alone.

Subject No.	Phenytion Freq/wk	Phenytion Duration in min	Hashish and Phenytion Freq/wk	Hashish and Phenytion Duration in min
2	1 – 2	2 – 3	None	—
4	1 – 3	3 – 5	None	—
6	3 – 4	5 – 6	1 – 2	2 – 3
8	6 – 7	5 – 10	2 – 3	3 – 5
10	3 – 5	5 – 7	1 – 2	2 – 3
12	2 – 3	3 – 4	0 – 1	1 – 2

TABLE VI

Adverse Reactions and Physiological Changes that Accompanied Hashish therapy.

	Symptoms	No. of Subjects Reporting
1	Increase in pulse rate	1
2.	Reddening of the eyes	0
3.	Dryness of the mouth and throat	3
4.	Stuffy nose	0
5.	Increased appetite	2
6.	Decreased appetite	0
7.	Sedation and sleepiness	3
8.	Insomnia	0
9.	Euphoria (feeling of well-being)	0
10.	Excitement	0
11.	Tension and anxiety	0
12.	Irritability	0
13.	Restlessness	0
14.	Tremulousness	0
15.	Muscle spasm	0
16.	Relaxation	0
17.	Nausea	2
18.	Vomiting	1
19.	Loose stools	1
20.	Hiccups	1
21.	Sweating	0
22.	Chills	0
23.	Memory impairment	0
24.	Changes in perception of time	0
25.	Changes in perception of space	0
26.	Dizziness	0
27.	Panic or fear	0

(two males and two females) and four had hirsutism (all were females), most probably due to phenytoin therapy as both symptoms were demonstrated before starting hashish administration. During the two week follow-up period after withdrawal of hashish, nine patients showed an increase in their seizure frequency amounting to 1–3 per week and in duration of each by 2–5 minutes. The remaining three patients showed little change in their seizure frequency and duration.

DISCUSSION

Reduction in the frequency and duration of seizures was demonstrated in both patient groups during the period of hashish therapy with and without phenytion therapy. The anticonvulsant effect of hashish was attained at a daily dose ranging from 300 to 900 mg of the crude plant material. A few patients tended to show dryness of mouth and throat, mild sedation, nausea, vomiting and loose stools with the higher dosage. However, these adverse reactions subsided over a 24 hour period in response to dose reduction.

As the total cannabinoid content of the tested sample of hashish was 3.2% by weight, the equivalent therapeutic daily dosage of total cannabinoids should be 9.6 to 28.8 mg. One could not tell for sure which of the cannadinoids was responsible for such anticonvulsant effect. THC and CBD are the cannabinoids most likely to occur at the highest levels in most samples of hashish. Delta–9–tetrahydrocannabinol (delta–9–THC) and cannabidiol (CBD) appear to be the most potent anticonvulsants, particularly in animal experiments (Carlini-et al., 1973, Consroe et al., 1973 and also in a few human case reports (Consroe et al., 1975).

The increase in seizure frequency and duration in most patients (9 out of 12) after withdrawal of hashish is consistent with a possible antiepileptic effect. However, one should not be over-enthusiastic in interpreting the results of the present study for a number of

reasons: (1) the limited sample of patients on whom the study was conducted; (2) the use of the crude material of hashish which contains at least four different cannabinoids (delta-9-THC, delta-8-THC, CBC and CBN); (3) the lack of determination of the probable therapeutic blood levels of cannabinoids, and (4) the data obtained emerged solely from clinical observations and reports and were not confirmed with electroencephalographic recordings. However, this study at least presents new evidence that could be added to what has already been mentioned in a great deal of literature about the possible anticonvulsant properties of cannabis and its constituents. It clearly suggests a potential therapeutic value of hashish in human epilepsy. It seems logical to proceed in the future to more specific studies on larger groups of epileptics, using pure cannabinoids in standardized dosages, and to follow them up both clinically and electroencephalographically.

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الموجـــــــز

تأثير الحشيش كعقار مضاد للتشنجات في مرضى الصرع

يتناول البحث التأثيرات المضادة للتشـــــنجات لمادة الحشيش الخام والتى تحتوى على القنبينات بنسبة ٢ر٣٪ من اجمالى الوزن فى اثنى عشر مريضا مصابا بنوبات الصرع العفوى الكبرى ، وهؤلاء لم تتم الســـيطرة

المناسبة على نوباتهم باستعمال عقار الفينيتوين . انتظم المرضى أولا فى العلاج بواسطة الفينيتوين لمدة ثمانية أسابيع ، ثم تم تقسيمهم الى مجموعتين متساويتين . عولجت المجموعة الأولى بواسطة الحشيش بينما عولجت المجموعة الثانية بواسطة الحشيش والفينيتوين مجتمعين ، لمدة ثمانية أسابيع أخرى . وقد تبين تناقص ملموس فى كل من عدد النوبات الصرعية ومدتها فى المجموعتين بعد بدء العلاج بالحشيش ، وهو ما يقترح أن لمكونات الحشيش فائدة علاجية فى مرضى الصرع .

ABSTRAIT

Effet Anticonvulsif Du Hashish Chez Les Epileptiques.

L'action anticonvulsive du hashish (contenant 3.2 % cannabinoids), a été étudiée chez 12 malades souffrant d'épilepsie idiopathique de type, grand mal, non controllés éffectivement par le phenytoin. Aprés une période de 8 semaines sous thérapie régulière au phenytoin, les malades ont été divisés en deux groupes. Le premier a été maintenu sur une thérapie de hashish, le second sur une combinaison de hashish et de phenytoin, pour 8 autres semaines. Les deux groupes ont montré une réduction significative dans la fréquence et la durée de leurs crises. Les résultats de cette étude suggèrent fortement une valeur thérapeutique possible de hashish, pour le traitement de l'épilepsie.

مستشفى قصر المعادى

للأمراض النفسية والعصبية

ت ٥٠١٠٥١ ت ٥٠٤٢٢١

موقع جميل على كورنيش النيل بالمعادى

أقسام خاصة للحالات النفسية

قسم لعلاج الإدمان . قسم خاص للأطفال

فريق متكامل من الأطباء النفسيين

والأخصائيين النفسيين والأخصائيين

الإجتماعيين والممرضات المتخصصات .

تقدم جميع أنواع الرعاية والعلاج للمرضى

الأدارة والإشراف الطبى د. محمد فؤاد أبو المجد

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عضو كلية الأطباء النفسيين الملكية