Eur Arch Psychiatry Clin Neurosci (1990) 240:1–4

European Archives of Psychiatry and Clinical Neuroscience

Delta-9-tetrahydrocannabinol Shows Antispastic and Analgesic Effects in a Single Case Double-blind Trial

M. Maurer[1], V. Henn[2], A. Dittrich[1], and A. Hofmann[3]

[1]PSIN – Psychologisches Institut für Beratung und Forschung, Jupiterstrasse 49, CH-8032 Zürich, Switzerland
[2]Neurologische Klinik und Poliklinik der Universität Zürich, Frauenklinikstrasse 26, CH-8006 Zürich, Switzerland
[3]Pharmakologisches Institut der Universität Zürich, Gloriastrasse 32, CH-8006-Zürich, Switzerland

Received June 12, 1989

Summary. A double-blind study was performed comparing 5 mg delta-9-tetrahydrocannabinol (THC) p.o., 50 mg codeine p.o., and placebo in a patient with spasticity and pain due to spinal cord injury. The three conditions were applied 18 times each in a randomized and balanced order. Delta-9-THC and codeine both had an analgesic effect in comparison with placebo. Only delta-9-THC showed a significant beneficial effect on spasticity. In the dosage of THC used no altered consciousness occurred.

Key words: Delta-9-tetrahydrocannabinol – Analgesia – Spasticity – Spinal cord injury

Introduction

In indigenous societies cannabis preparations have been used for different somatic treatments, including the therapy of muscular convulsions. The pharmacological history of cannabis has been summarized by Mechoulam (1986). Scientific research during the last few decades on therapeutic potentials of cannabinoids has concentrated especially on the antiemetic, analgesic, anticonvulsive, and intraocular pressure effects of delta-9-tetrahydrocannabinol (THC), the main active compound of hashish or marihuana (Mechoulam 1986).

The aim of this paper is to document the subjective response to delta-9-THC of a patient with spasticity and pain due to spinal cord pathology.

The review of the literature shows that there are few publications on this subject. Nearly all of them are case reports on patients with spasticity who smoked marihuana/hashish (Dunn and Davis 1974; Petro 1980; Malec et al. 1982). In general these case reports confirm the positive results published nearly 150 years ago (O'Shaughnessy 1842). Petro and Ellenberger (1981) performed a double-blind study on patients with spasticity and found a single application of THC to be effective.

In a single trial study Meinck et al. (1989) measured various electrophysiological parameters of spasticity and reported an objective as well as a subjective improvement after smoking a single marihuana cigarette.

Such single trials give valuable information about possible mechanisms of pathophysiology. However, we performed a study to evaluate the long-term subjective response. The hypothesis was that THC has a therapeutic effect on patients suffering from spasticity and pain due to central nervous pathology.

Offprint requests to: V. Henn

Methods

A patient suffering from severe paraesthesias and painful spastic paraparesis approached us inquiring about a possible therapeutic use of cannabis in his case. We started with an open trial; the second stage was double-blind, followed by maintainance therapy. All protocols were reviewed by the appropriate boards and special permission was granted by the Swiss Federal Health Agency.

Case History

Symptoms started about 1975 in a male aged 28 years, with diffuse pain in the back and a very slight and inconstant difficulty in walking. During the next two years symptoms were variable including vertigo, nausea, and paraesthesias in the extremities. The patient enrolled as a law student. He self-diagnosed his symptoms as psychosomatic. The results of a first neurological examination in July 1976 were normal. Symptoms, however, progressed, leading to a hospitalization (November 1977). An incomplete sensory deficit distal to T5 and a slightly ataxic paraspastic gait were found. The protein content of the lumbar spinal fluid was elevated to 8.5 g/l. Descending cervical myelography showed a block at the level of C6, and ascending lumbar myelography at L2.

The patient was transferred to the Department of Neurosurgery, where a 20-cm-long ependymoma was removed, which extended from C4 to T10 (*fecit* Prof. G. M. Yasargil). A cyst extended cranially to C1 and in the caudal direction to L2.

Postoperatively the patient was paraplegic and paretic in both arms. Motor strength and sensation in the arms recovered after several weeks. In the legs a pronounced spasticity developed. Control over micturition and defaecation was impaired, but not lost. After intensive physical therapy, the patient was able to stand and walk slowly on two crutches. He resumed his university studies, which he succesfully concluded. Persistent problems were painful paraesthesias and spasticity in the legs, which required constant medication with baclofen, clonazepam and carbamazepine.

Neurological Examination. At the beginning of this study (January 1985) the deficits had been stable for several years. Cranial nerves were intact. There was a sensory level of decreased sensation at T1 on both sides and virtual loss of all sensory discrimination below T5 on both sides. There was a marked spastic paraparesis of the legs with intermittent extensor spasms. Brisk elevation of the forefoot elicited sustained ankle clonus.

Psychological Evaluation. The standard German language personality test "FPI-R" (Fahrenberg et al. 1984) showed the subject to be extraverted (ST = 8) and emotionally stable (ST = 4).

Treatment. Besides regular twice-weekly physical therapy the patient received 40 mg baclofen and 1 mg clonazepam daily, which led to some relief. Further increase of the dosage was limited by decreased vigilance during the day and diminished motor control. In addition he took codeine, on average 50–100 mg twice to three times a week, when needed.

Design of the Study

During the whole course of the study the patient was treated as before at the Neurologische Klinik und Poliklinik der Universität Zürich and was furthermore seen regularly by the main authors.

In a *first phase* an open dose-finding trial was performed. In the course of 3 months the patient took THC 14 times in addition to his constant daily medication, when he otherwise would have taken codeine. The dosages were 2.5 mg three times, 5 mg 10 times, and once 10 mg THC p.o. in the form of impregnated sugar lumps.

Because of the results of this open study (see below) we felt confident enough to start the *second phase*, a double-blind study, which was performed comparing 5 mg THC p.o., 50 mg codeine p.o., and placebo in identical gelatine-capsules. The three experimental conditions were each applied 18 times during the course of 5 months. The order was randomized and balanced, i.e. the permutations of an ABC design were arranged in such a way that no substance was given twice in succession. The medication of baclofen (40 mg) and clonazepam (1 mg) remained unchanged. When he normally would have received codeine the patient took THC, codeine or placebo, usually around 9.30 p.m. The assessment schedule (see below) was filled in on the next day between 1150 and 1350 hours and sent regularly to the main authors.

In the third phase the patient received a maintenance supply of THC. He prepared written reports about actual medication every month, and was regularly seen as an outpatient.

Assessment Schedule

The effects were assessed by a questionnaire, developed together with the patient, concentrating on his most distressing symptoms. The first part of the assessment schedule asked for general information, e.g. date, time of taking the substance and filling in the questionnaire as well as reasons for taking the substance.

The second part (see Table 1) comprised relevant symptoms. A definition of subjective experience of spasticity seems more difficult from a theoretical point than in practice. The patient rated his muscle stiffness which when extensive resulted in pain similar to muscle cramps. Less stiffness resulted in more ease when trying to move the legs both while resting or when walking. The last item was concerned with the global effect of the substance taken. In addition six items from the APZ questionnaire (nos. 1, 56, 70, 107, 120, 147) were included which differentiate well between a normal waking state and an altered state of consciousness (Dittrich 1985).

Visual analogue scales of 50 mm length with the poles stated were used to assess effects.

Table 1. Main variables of the study

Variable	Poles in visual analoge scale
1. Sleep	
a) Time to fall asleep	Very short – very long
b) Frequency of awakening	Never – very often
c) Rating of sleep duration	Very short – very long
d) Recreational effect	None – excellent
2. Pain	
a) After taking the substance	None – very strong
b) When falling asleep	None – very strong
c) When awaking during the night	None – very strong
d) When getting up in the morning	None – very strong
3. Spasticity	
a) After taking the substance	None – very strong
b) When falling asleep	None – very strong
c) When awaking during the night	None – very strong
d) When getting up in the morning	None – very strong
4. Micturition during the night	Never – very often
5. Ability to concentrate	Very bad – very good
6. Mood	Very bad – very good
7. What global effect had the substance taken?	Very negative _ very positive

Statistical Analysis

As a time-dependent trend can be excluded because of the experimental design used, the three substances of the double-blind study were compared in each variable using the *t*-test for independent samples (cf. Chassan 1960; Bellak and Chassan 1964).

A result was considered clinically important when it was statistically significant ($\alpha = 0.05$, with explicit α-protection $\alpha' = \alpha/3 = 0.017$) and had a large effect size, ED ($d > 0.80$) according to Cohen (1976). In the formula for computing the ES the standard deviation for placebo were used.

Results

The results of the open study suggested that a dosage of 5 mg THC p.o. was sufficient to improve most of the symptoms as assessed with the described visual analogue scales without causing an altered state of consciousness.

The results of the double-blind study are summarized in Table 2, which shows the mean, the standard deviation and the ES *d* for each substance and the main symptoms.

As Table 2 shows, codeine and THC both improved the quality of sleep compared which placebo, without differences from each other. An analgesic effect of codeine

Table 2. Statistical comparison of delta-9-THC, codeine and placebo

Variable	THC		Codeine		Placebo		THC vs placebo (Es: *d*)		Codeine vs placebo (Es: *d*)		THC vs codeine (Es: *d*)	
	Mean	SD	Mean	SD	Mean	SD						
1. Sleep												
a) Time to fall asleep	**21.8**	6.7	25.3	9.5	27.6	8.7	NS	0.67	NS	0.26	NS	0.41
b) Freq. of awakening	**15.4**	7.2	20.4	5.2	29.5	8.3	S	1.69	S	1.09	NS	0.60
c) Sleep duration	**34.5**	7.3	30.6	9.0	21.7	7.5	S	1.70	S	1.18	NS	0.52
d) Recreational effect	**33.9**	8.7	31.6	7.9	21.1	9.0	S	1.43	S	1.17	NS	0.26
2. Pain												
a) After substance	25.6	8.9	**19.7**	6.3	34.3	7.5	S	1.13	S	1.91	NS	0.88
b) Falling asleep	12.4	8.8	**11.6**	4.0	29.4	9.6	S	1.76	S	1.85	NS	0.09
c) During the night	**9.0**	6.5	9.1	2.8	18.3	7.0	S	1.33	S.	1.32	NS	0.01
d) In the moring	**15.6**	8.2	18.3	3.6	29.7	7.5	S	1.89	S	1.53	NS	0.36
3. Spasticity												
a) After substance	**28.0**	9.7	36.1	5.7	35.9	2.9	S	2.73	NS	0.06	S	2.79
b) Falling asleep	**8.2**	5.6	25.2	8.5	29.6	9.5	S	2.25	NS	0.46	S	1.79
c) During the night	**6.0**	5.4	14.6	7.8	17.2	6.3	S	1.76	NS	0.41	S	1.35
d) In the morning	**13.3**	6.4	23.2	8.5	30.1	9.6	S	1.75	NS	0.72	S	1.03
4. Micturition	**16.1**	7.8	19.9	4.3	30.4	7.5	S	1.92	S	1.41	NS	0.51
5. Concentration	**34.9**	6.9	32.4	5.0	21.6	8.0	S	1.67	S	1.36	NS	0.31
6. Mood	**34.8**	6.9	33.2	4.2	19.4	7.2	S	2.14	S	1.91	NS	0.23
7. Global effect	35.7	6.5	33.0	3.9	20.1	8.8	S	1.76	S	1.46	NS	0.30

The mean indicating the greatest improvement is printed in bold letters
NS: not significant; S, significant; Es: *d*, effect size

and THC was shown in comparison with placebo. Only THC had an antispastic effect.

When THC or codeine had been taken, bladder control was much improved in terms of increased intervals between micturition. In retrospect the patient considers this to be an important item. The ability to concentrate on intellectual work next day and the mood were improved both by THC and codeine.

The global rating of the effect by the patient was positive for THC and codeine in comparison with placebo. No indications of the occurrence of an altered state of consciousness in the six items from the APZ questionnaire (Dittrich 1985) were found. No hangover was reported for any substance.

During the third phase the patient received a maintenance supply of THC. Motivated by a slow but sustained improvement, he undertook the effort to reduce the dosage of all medications including THC. He has learned to live with the neurological deficits and sometimes still painful paraesthesias. Subjectivly he now rates his well-being as better then at any time during treatment.

By May 1989 he had been free from all regular medications, including THC, for 1 year. The patient works part-time as a lawyer.

Discussion

The patient described above had clearly defined symptoms due to an extended spinal cord lesion. Painful paraesthesias and spasticity required sustained medication with drugs which have acute side-effects, e.g. decreased vigilance, and may lead to drug dependence.

THC was given in a dosage of 5 mg, which is well below the amount which induces altered states of consciousness.

The analgesic effects of THC corresponded with the results of Noyes et al. (1975) in a study of THC, codeine and placebo in cancer patients suffering from pain. These authors reported that THC is equivalent to codeine in its analgesic effect.

Regarding the items pain as well as sleep and mood, THC was rated in our study together with codeine as being superior to placebo. THC was the only substance to show an antispastic effect, which lasted longer than 12 h. Therefore it might be possible that not only delta-9-THC but also its metabolites, especially 11-OH-delta-9-THC, have an antispastic and analgesic effect.

On the basis of our experience we can advocate the use of THC in carefully selected patients. We hope that our and similar reports will stimulate further search on THC analogues with more specific action and without the potential for inducing altered states of consciousness.

References

Bellak L, Chassan JB (1964) An approach to the evaluation of drug effect during psychotherapy: a double-blind study of a single case. J Nerv Ment Dis 139:20–30

Chassan JB (1960) Statistical inference and the single case in clinical design. Psychiatry 23:173–184

Cohen J (1977) Statistical power analysis for the behavioral sciences. Academic Press, London

Dittrich A (1985) Aetiologie-unabhängige Strukturen veränderter Wachbewusstseinszustände. Ergebnisse empirischer Untersuchungen über Halluzinogene I. und II. Ordnung, sensorische Deprivation, hypnagoge Zustände, hypnotische Verfahren sowie Reizüberflutung. Enke, Stuttgart

Dunn M, Davis R (1974) The perceived effects of marijuana on spinal cord injured males. Paraplegia 12:175

Fahrenberg J, Hampel R, Selg H (1984) Das Freiburger Persönlichkeitsinventar FPI, 4th edn. Hogrefe, Zürich

Malec J, Harvey RF, Cayner JJ (1982) Cannabis effect on spasticity in spinal cord injury. Arch Phys Med Rehabil 63:116–118

Mechoulam R (ed) (1986) Cannabinoids as therapeutic agents. CRC Press, Boca Raton

Meinck H-M, Schönle PW, Conrad B (1989) Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. J Neurol 236:120–122

Noyes RN Jr, Brunk SF, Avery DH, Canter A (1975) The analgesic properties of delta-9-tetrahydrocannabinol. Clin Pharmacol Ther 18:84

O'Shaughnessy R (1842) On the preparation of the indian hemp or gunjah (cannabis indica): the effects on the animal system in health and their utility in the treatment of tetanus and other convulsive diseases. Trans Med Physiol Soc Bombay 8:421

Petro JP (1980) Marihuana as a therapeutic agent for muscle spasm or spasticity. Psychosomatics 21:81–85

Petro JP, Ellenberger C (1981) Treatment of human spasticity with delta-9-tetrahydrocannabinol. J Clin Pharmacol 21:413–416