Delta-9-THC in the Treatment of Spasticity Associated with Multiple Sclerosis

J. Thomas Ungerleider, MD
Therese Andyrsiak, RN
Lynn Fairbanks, PhD
George W. Ellison, MD
Lawrence W. Myers, MD

SUMMARY. Marijuana is reported to decrease spasticity in patients with multiple sclerosis. This is a double blind, placebo controlled, crossover clinical trial of delta-9-THC in 13 subjects with clinical multiple sclerosis and spasticity. Subjects received escalating doses of THC in the range of 2.5-15 mg,. five days of THC and five days of placebo in randomized order, divided by a two-day washout period. Subjective ratings of spasticity and side effects were completed and semiquantitative neurological examinations were performed. At doses greater than 7.5 mg there was significant improvement in patient ratings of spasticity compared to placebo. These positive findings in a treatment failure population suggest a role for THC in the treatment of spasticity in multiple sclerosis.

J. Thomas Ungerleider, Therese Andyrsiak, and Lynn Fairbanks are affiliated with the Department of Psychiatry at U.C.L.A. School of Medicine. George W. Ellison and Lawrence W. Myers are affiliated with the Department of Neurology at U.C.L.A. School of Medicine, 760 Westwood Plaza, Los Angeles, CA 90024.

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INTRODUCTION

The muscle spasticity which may occur in multiple sclerosis is often a significant management problem. Spasticity has been treated with some success with dantrolene (Dantrium®), baclofen (Lioreseal®) and diazepam (Valium®). However, available drugs afford only partial relief for many patients. In addition, intolerable side effects of these drugs, such as severe gastrointestinal upsets, hallucinations, drowsiness and hepatic dysfunction further complicate management.[1-4] Additional therapies are needed. Anecdotal reporting by multiple sclerosis patients of the efficacy of cannabis is common in our experience.

W. B. O'Shaughenessy in 1838 described the administration of hemp extract to treat muscle spasms associated with tetanus.[5] In 1890 Reynolds reviewed his varied experiences with the administration of cannabis, including its usefulness in the treatment of muscle spasms associated with epilepsy, chorea and nocturnal spasms.[6]

Boyde and Dagermangian evaluated the pharmacological effects of two tetrahydrocannabinols on reflex activity in the cat and found them to decrease the polysnaptic flexion and linguomandibular reflexes.[7] No effects on peripheral nerve conduction or neuromuscular transmission were found. They concluded that the site of action of these drugs was in the mesencephalon and suggested that the general class of cannabinoids may have potential in treating spasticity. Other investigators have reported similar results in female rats and mongrel dogs.[8,9] In addition, a survey of ten spinal cord injured males revealed decreased pain and spasticity with the use of marijuana.[10] Clifford found that THC improved motor coordination in two of eight multiple sclerosis patients who were seriously disabled with tremor and ataxia.[11] Petro and Ellenberger administered a single dose of delta-9-THC to nine multiple sclerosis patients. They found a reduction in spasticity which peaked at 1-1/2 hours after administration.[12] Our pilot investigation was designed to assess chronic administration of oral THC vs. placebo in the reduction of spasticity associated with multiple sclerosis and to determine an efficacious and tolerable dose level for THC.

METHODS

Subjects

Thirteen patients with clinically definite multiple sclerosis[13,14] and significant spasticity were recruited from the UCLA Multiple Sclerosis Research Clinic and Treatment Center. All patients had a documented history of intolerable side effects from the use of other drugs to control spasticity, including baclofen, dantrolene, and diazepam. Five were male and eight were female, ranging in age from 26-64 years of age (mean 48.3 years old). Eight patients used wheelchairs, four patients ambulated with a cane, and one walked unassisted. Nine patients had used marijuana one or more times prior to study admission. They all agreed to abstain from such marijuana use during the study.

Informed consent was obtained prior to study participation.

Dosing Schedule

The patients were divided into two dosing schedule groups depending on the time (day vs. night or day plus night) of their most severe spasticity. One group, of two patients, received their medication at bedtime, to relieve night time spasticity; the other group, of 11 patients, received their drug twice daily, at 10:00 a.m. and at 10:00 p.m., to relieve daytime as well as nighttime spasticity. Each group was randomly assigned in a paired double blind crossover trial (THC, placebo; placebo, THC). Patients were given drug orally for five consecutive days, were drug free for two subsequent days and then received a five day trial with the crossover drug. To assess effects of several dose levels, patients were initiated at varying doses of THC. Where there was inadequate spasticity relief at the initial dose level, and the patient had tolerated other drug effects, the patient was rerandomized and the dosage of the active drug was increased by 2.5 mg. If there was insufficient relief at the second dosage, and the patient had tolerated other drug effects, the dose was again escalated for the third and final rerandomized two week paired trial of THC and placebo. The decision to increase the dose was made by at least one of the co-investigators, based on patient reports and

clinical assessment. Of the 13 patients randomized to the study, 12 completed at least two paired trials and five of these completed three paired trials.

For the first paired trial, two patients were started at 2.5 mg. THC h.s.; three patients at 2.5 mg. THC a.m. and h.s.; four patients at 5 mg. THC a.m. and h.s.; and four patients at 7.5 mg. THC a.m. and h.s.

In the second paired trial, two patients of the 5 mg. THC group received THC doses lowered to 2.5. mg. a.m. and h.s. Both of these patients had reported excessive limb weakness which they attributed to THC. Each of the five patients in the initial 2.5 mg. THC group received doses escalated to 5 mg. (one at h.s. and four patients a.m. and h.s.); one patient was increased to 7.5 mg. THC (a.m. and h.s.), and five patients were increased to 10 mg. THC (a.m. and h.s.).

On the third paired trial, three patients received 7.5 mg. THC, one received 10 mg. THC, and one received 15 mg. THC. All of these patients were on the bid dosing regime.

Motor Function

Physician Rating Scales

The patients were examined by the neurologists prior to study drug administration and then once weekly, on the fifth day of each treatment, during the experimental period. Each examination was conducted at the same time of day, three hours after the a.m. dose for the bid group, and the morning after the h.s. dose for the once-daily group. Motor function was assessed clinically, employing an 0-3 scale (Table 1) with 0 representing the absence of impairment (normal function) in the particular area scored. The scoring criteria were delineated in advance by the examining neurologists; tests of function were performed without reference to preceding scores, to assure independence. Limb weakness tested shoulder abductors, finger extensors and abductors, hip flexors and foot dorsiflexors; scoring was done on the weakest muscle in the extremity. Limb spasticity assessment tested supinators, flexors, and extensors at the elbow, wrist and knees and abduction at the hips; scoring was done on the most spastic muscle for each extremity. Limb coordination tested finger to nose

TABLE I

CRITERIA FOR RATING MOTOR IMPAIRMENT

Limb Weakness	1 = mild weakness--full range of motion of all muscles in the extremity against partial resistance.
	2 = moderate weakness--full range of motion of all muscles in the extremity against gravity but not against resistance.
	3 = severe weakness--less than full range of motion of any muscle against gravity.
Limb Spasticity	1 = mild resistance to passive movement-overcome with gravity.
	2 = moderate resistance-overcome with some effort.
	3 = severe resistance-overcome with considerable effort.
Limb Coordination Impairment	1 = mild impairment--detected on finger to nose and/or heel to knee to shin testing.
	2 = moderate impairment--subject can perform finger to nose and/or heel to knee to shin tests only with obvious difficulty
	3 = severe impairment--subject is unable to hit the target on finger to nose testing and/or heel to knee to shin test.
Gait Impairment	1 = mild impairment--definite abnormality only on formal testing (i.e., toe walking, heel walking and tandem walking).
	2 = moderate impairment--obvious difficulty without formal testing--subject can walk one block without assistance.
	3 = severe impairment--cannot walk a block without assistance; may require assistance of cane, crutches, walker, or is unable to walk.
Reflexes	1 = hypoactive.
	2 = normal.
	3 = hyperactive.
	4 = unsustained clonus (less than 8 beats).
	5 = sustained clonus (8 or more beats).

and heel to knee to shin; special note was made of impairment due to weakness.

Evaluation of gait impairment required that the subject walk across the room rapidly on toes, on heels and in tandem: scoring was for weakness, spasticity, ataxia and apraxia. With the patient

supine, the plantar response was tested initially by gently stroking the lateral margin of the sole of the foot with the thumbnail. The first movement of the great toe was scored "flex" with movement toward the sole and "ext" with movement toward the knee. If no movement occurred, there was a repeated forceful stroke with the thumbnail; if this resulted in no movement, the stroke was repeated with the point of a key. If no movement was observed with the latter procedure, the patient was scored "neutral" in this category. Limb weakness, spasticity, coordination, gait impairment, and reflexes were scored separately for upper and lower extremities. Summary scores for each of the five areas of motor function, combining the components of the physical examination, were computed for each patient.

Patient Rating Scales

Spasticity and drug side effects were evaluated the morning following each day of study participation. Patients were asked to rate their spasticity as greatly improved, slightly improved, no effect, slightly worse, or much worse.[1-5] A side effect check list was provided for use each day for the patient to note the presence or absence of each effect listed. Additional side effect information was elicited from the patient by his daily overall rating of effects as none, barely noticeable, noticeable but tolerable, hard to live with, or unbearable. The questionnaire scores were summarized for spasticity and side effects by averaging each study day score across the five-day treatment periods for THC and placebo.

Additionally, patients were telephoned by the protocol nurse two or three times each day of study participation to insure compliance and obtain side effects and motor function information to cross-check self reports.

RESULTS

Analysis of Spasticity and Motor Function

Patient's rating for spasticity during THC administration by dose is shown in Figure 1. The level of spasticity reported by patients decreased significantly as the dose of THC increased

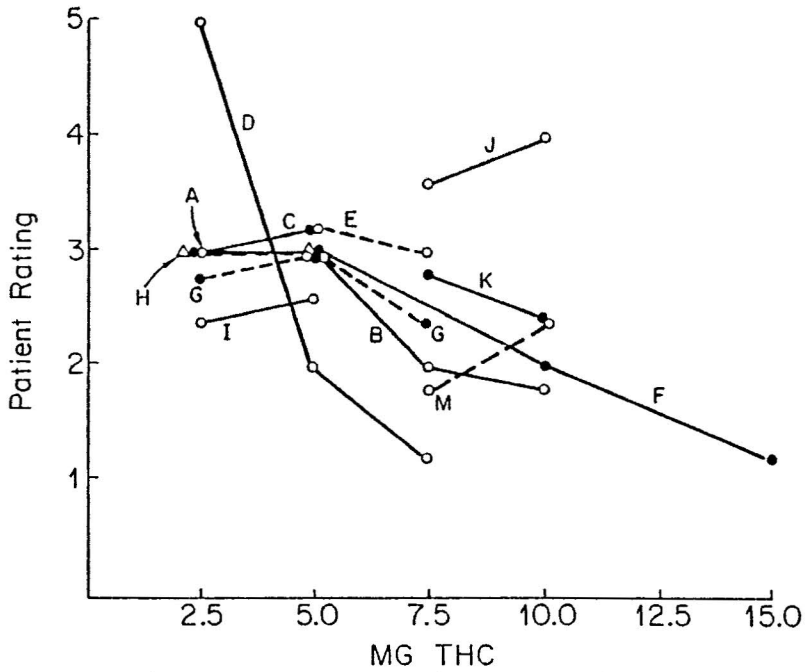

Figure 1. Individual patient ratings of spasticity (1 = greatly improved; 5 = much worse) by THC dose level.

($r = .48$ $p < 05$). Inspection of this graph indicates that, at the lower doses of THC (2.5 and 5.0 mg.), spasticity is reported to be in the "same as usual" range. Reduction in spasticity begins at 7.5 mg. and continues for most at 10 and 15 mg. Because three of the four patients who received the 10 mg. dose of THC complained of intolerable side effects, the 7.5 mg. dose was selected as the optimum dose for further analysis.

Table 2 shows the mean scores on limb weakness, limb spasticity, limb coordination, gait impairment, and reflexes, from the doctor's rating scale, for baseline, placebo, and 7.5 mg. of THC. There were no significant differences between baseline, placebo, or THC on any of the five areas of motor function, using a repeated measures analysis of variance. Lower limb scores for weakness, spasticity, coordination and reflexes were also analyzed separately, and no significant differences were found (data not shown).

TABLE 2

MULTIPLE SCLEROSIS STUDY

Dose = 7.5 mg. THC N = 8

Physician's Ratings[a]	Baseline	Placebo	THC	F	P
Limb Weakness	1.25±.74	1.33±.74	1.34±.63	0.12	0.89
Limb Spasticity	1.13±.71	1.09±.46	1.16±.62	0.11	0.90
Limb Coordination	1.93±.78	1.61±.90	1.59±1.01	1.49	0.26
Gait Impairment	2.88±.35	2.88±.35	2.88±.35	0.00	1.00
Reflexes	3.15±.24	2.99±.32	3.15±.22	1.38	0.28
Patient's Ratings					
Spasticity[b]		3.40±.73	2.23±.90	t=2.73	0.03
Side Effects[c]		1.18±.49	1.50±.44	t=1.88	0.10

(a): See Legend, Table 1. All scales except reflexes are 4 steps, 0 (normal) to 3 (severe impairment). Reflexes are 5 steps, 1 (hypoactive) to 5 (sustained clonus).

(b): Spasticity scale = 1 (less) to 5 (more).

(c): Side effects scale = 1 (none) to 5 (intolerable).

Mean values for the two-patient rating scales are also shown in Table 2. At 7.5 mg., there was a significant reduction in spasticity for THC compared to placebo, using a test for matched groups ($t = 2.73$, $p < .03$). There was also a tendency for the side effects rating to be higher in THC recipients compared to placebo ($t = 1.88$, $p = .10$).

Side Effects

Side effects were reported by all but one patient at the 7.5 mg. dose. Reported drug effects consisted of weakness, dry mouth, dizziness, relaxation, mental clouding, short-term memory impairment, and spatial-time distortions. Similar side effects were reported by five patients on placebo. At the 7.5 mg. dose there were no reports of intolerable side effects. Because two of four patients on the 10 mg. dose reported side effects as "hard to live with," the 7.5 mg. dose was selected as the highest tolerated

dose. However, it may be significant that higher doses were tolerated and effective in some individuals. As illustrated in Table 2, the mean side effect severity scores represent a difference between THC and placebo, which is not quite significant.

Four patients discontinued study participation. Reasons given for termination included perceived excessive limb weakness on previous trials for two patients and, for another two patients, anticipatory anxiety regarding possible side effects at higher THC doses. Neither of the patients in the latter group had reported intolerable side effects on lower doses.

DISCUSSION

The findings of this pilot study are consistent with previous reports of improved motor functioning of spastic patients associated with the use of marijuana or THC. Previous studies involved the evaluation of single doses. This study involved continuous administration for five days to better evaluate the clinical usefulness of THC to reduce spasticity in multiple sclerosis. We believe further investigation, with particular attention to dose, side effects, and spasticity measurement, is indicated.

The mechanism and the site of action for THC's possible antispasticity effects are unclear. Diazepam and baclofen are thought to work through the GABA-ergic system and dantrolene to work peripherally via a direct effect on the muscle. Animal studies, as mentioned, suggest a mesencephalon locus of action for THC, which may also occur in humans. THC seems to interfere with certain "second messenger" transmission systems like the prostaglandins, but this is still uncertain.

It is unclear why there is not greater spasticity reduction measured by the physician's rating in contrast to the more dramatic improvement rated by the patient. Perhaps it is the insensitivity of the techniques available to the physician to measure spasticity. Alternatively, the side effects of THC may have interfered with patient blinding. While the incidence of side effects was greater with THC than placebo, this was not statistically significant. The authors suggest greater accuracy is reflected in the patient's vs. the physician's ratings. The physician's rating is reflective of

measurement at a single point in time, while the patient's rating includes the entire 24-hour period. Because spasticity is so variable throughout the day and night, we feel it is logical to emphasize what the patient reports. There is also variance in the area of patient-reported vs. physician-rated weakness. The patients report weakness with sustained muscular action, associated with activity such as transferring, while the physician's rating addresses a briefer period of muscular action.

While the 7.5 mg. dose is required to achieve significant spasticity reduction, the concurrent emergence of unpleasant side effects sometimes at this dose, and certainly at higher doses, requires the development of improved dosing regimes. Perhaps lower doses, administered in increments of 2.5 mg over several hours would offer spasticity reduction while minimizing side effects. Use of such a dosing regimen in a further clinical trial could shed light on which psychic side effects would emerge at what dosage levels.

Several of the study patients reported intolerable side effects on THC doses less than 7.5 mg. Perhaps those patients who exhibit extreme sensitivity to the psychoactive effects of THC, even at low doses, could derive benefit from larger doses administered only at bedtime to control the spasticity which often disrupts their sleep. Several of our study patients reported improved sleep and less spasticity on awakening, with this regime. Further evaluation in this area is suggested.

It is indeed noteworthy that five patients reported side effects, such as short-term memory impairment, dizziness, dry mouth, and hunger, *while receiving placebo*. This underscores the need for placebo-controlled trials. In this type of study, using a psychoactive substance like THC, where subjective effects so often occur, one can never be sure, to what extent the subjects are truly blinded. However, the fact that five of the 13 patients experienced the same type of side effects on placebo makes it unlikely that suggestibility was the primary factor in their reported spasticity improvement.

The reported (side) effects of relaxation with THC may have contributed to its antispasticity effects as, similarly some muscle relaxants, like diazepam, have associated anxiolytic effects. This is a central phenomenon which represents some portion of the

drugs' spasmolytic effect but it is unlikely that these anti-spasticity effects are solely due to relaxation.

It is worth considering the risk-benefit ratio of THC administration. THC (and marijuana), like diazepam, are controlled substances with an "addiction potential." Dependence or addiction to oral THC is virtually unknown. Even with diazepam, however, prolonged use by multiple sclerosis patients does not necessarily lead to abuse, nor is a dependence liability an absolute contraindication to use of a drug. Tolerance could develop from the prolonged use of THC in multiple sclerosis, much as it develops to THC-produced tachycardia (but not to THC's ocular hypotensive effect); we cannot predict at this time. Most of the patients in this study did not request THC administration. Most of the patients in this study did not request THC subsequent to the study. What about longer duration of THC administration? Would tolerance develop to side effects or/and spasticity relief from THC?

NOTES

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