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Treatment of Human Spasticity with Δ^9-Tetrahydrocannabinol

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Abstract: Spasticity is a common neurologic condition in patients with multiple sclerosis, stroke, cerebral palsy or an injured spinal cord. Animal studies suggest that THC has an inhibitory effect on polysynaptic reflexes. Some spastic patients claim improvement after inhaling cannabis. We tested muscle tone, reflexes, strength and performed EMGs before and after double-blinded oral administration of either 10 or 5 mg THC or placebo. The blinded examiner correctly identified the trials in which the patients received THC in seven of nine cases. For the group, 10 mg THC significantly reduced spasticity by clinical measurement ($P < 0.01$). Quadriceps EMG interference pattern was reduced in those four patients with primarily extensor spasticity. THC was administered to eight other patients with spasticity and other CNS lesions. Responses varied, but benefit was seen in three of three patients with "tonic spasms." No benefit was noted in patients with cerebellar disease.

SEVERAL patients with multiple sclerosis reported to us that their spasticity improved after smoking marihuana. Preliminary uncontrolled observations of these patients before and after inhalation of the drug suggested to us that the improvement in spasticity was a specific effect of marihuana and not merely a result of the well-recognized euphoria or altered perception experienced by social users of the drug.

Methods

We entered nine patients with spasticity, presumably of spinal origin and related to multiple sclerosis, into a double-blinded pilot study. The blinded observer examined each patient on three separate days, before and at 1½-hour intervals after oral administration of a capsule containing either 10 mg, 5 mg, or no synthetic Δ^9-tetrahydrocannabinol (THC). Absorption of oral THC is variable, about 90 per cent, but generally slower than that of inhaled THC. Blood levels and psychologic effects peak at 3 hours after ingestion. Because blood level determination is costly and may be unreliable, we did not determine levels.

The examiner rated deep tendon reflexes, muscular resistance to stretch in the legs, and abnormal reflexes each on a scale of 0 (absent) to 4 (abnormally increased) and tabulated the total divided by the number of observations as the "spasticity score" at 1½-hour intervals. For example, if both knee jerks were 3+, both ankle jerks were 3+, and both adductor jerks were 3+, the total was 18 and the spasticity score was 18/6 = 3.0. Babinski signs were rated as 4+, their absence as 3+.

The examiner viewed the EMG interference pattern of the quadriceps muscle as the knee joint was flexed from 0° to 90° at varying velocities. The examiner also assessed walking ability, inquired about the patient's subjective response and side effects of the drug, and measured vital signs.

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Results

Three patients reported feeling "loose" and better able to walk after receiving either 5 or 10 mg THC. The changes in spasticity scores for the treated and placebo groups are illustrated in Fig. 1. Differences between the groups at 180 minutes are significant ($P < 0.01$); summed scores for the two treated groups differed significantly from summed scores of the placebo group ($P < 0.005$). The spasticity scores of four patients improved more than two standard deviations from the mean after either 5 or 10 mg THC; one patient improved after placebo. Only two of the three patients who felt improved actually did so by objective criteria. On the basis of the spasticity scores, the blinded examiner identified correctly the placebo trials in seven of the nine patients.

The EMG index of spasticity proved to be impractical in five patients—in three because resistance to stretch was too severe and in two because electrical activity was too little to record. Among the remaining four patients, the interference pattern, by visual inspection, was reduced after treatment from the pretreatment pattern at comparable velocity of stretch.

Side effects of the 5- or 10-mg oral dosage were minimal. One patient reported feeling "high" after 10 mg, and another reported a "high" after placebo. No other patients reported side effects at the relatively low doses we used.

Discussion

Our preliminary results suggest that THC or one of its synthetic derivatives warrants further study as a potential treatment for spasticity. Although many previous investigators have studied the effects of marihuana on complex motor tasks, we were not able to find previous studies of the effects of marihuana on spasticity in the medical literature. Experimental studies in animals suggest that THC has an inhibitory effect on polysynaptic reflexes mediated through the spinal cord. The results of differential sectioning of the neuraxis in cats by Dagirmangian and Boyd[1] suggest that the ability of several tetrahydrocannabinols to decrease polysynaptic flexion reflexes relates to its action in the region

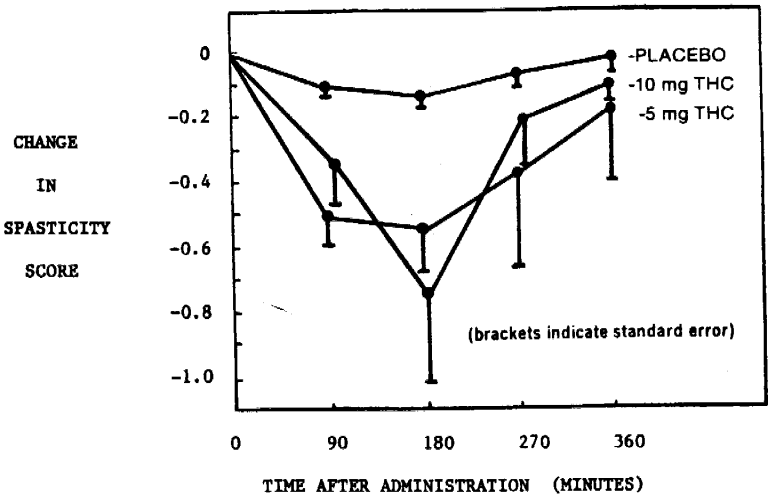

Fig. 1. Change in clinical examination scores as a function of time after dosage (N = *9 patients).*

between the mesencephalon and first cervical segment. Kayaalp et al.[2] postulate that THC has an effect on both nerve conduction and skeletal muscle contraction. Sullivan[3] and colleagues found a dose-dependent loss of reflexes and muscular weakness in dogs.

Although THC has proved to be clinically useful in the treatment of nausea induced by cancer chemotherapy and in reducing intraocular pressure in glaucoma, the results of these trials have demonstrated several disadvantages of the drug. The first is its potential for psychologic effects that limits usage in higher doses than those we employed. The second drawback to regular clinical use of the drug and of its many derivatives is the observation that many of its therapeutic effects may diminish after a relatively short period of regular usage.

References

1. Dagirmangian R, Boyd ES. Some pharmacological effects of two tetrahydrocannabinols. *J Pharmacol Exp Therap.* 1962; **135**:25-33.
2. Kayaalp SO, Kaymakcalan S, Verimer T, Ilhan M, Onur R. In vitro neuromuscular effects of Δ-9-*trans*-tetrahydrocannabinol (THC). *Arch Int Pharmacodyn.* 1974; **212**:67-75.
3. Sullivan MF, Willard DH. The beagle dog as an animal model for marihuana smoking studies. *Toxicol Appl Pharmacol.* 1978; **45**:445-462.

Discussion of the Paper

Dr. Nahas: Were the subjects that you studied naive toward marijuana, and did you observe tolerance?

Dr. Petro: All of our patients were naive to marijuana. Anecdotally, other patients claim that they have been using marijuana for periods up to 15 years for control of spasticity, but research needs to cover a larger and better controlled sample before any definitive statement would be possible. No chronic studies have been done to evaluate drug tolerance in spasticity.

Dr. Ungerleider: Did you, as blinded examiner, interview the patients and perform the tests?

Dr. Petro: I did all of the evaluations of neurologic function.

Dr. Ungerleider: Did you know that they felt *better* before you evaluated them objectively?

Dr. Petro: No; I used only objective measures, the EMG criteria and the spasticity scores.

Dr. Lindblom: Have you considered the use of patients other than those with multiple sclerosis (MS)? We studied the effect of baclofen on spasticity, and found much spontaneous variability in MS patients. In addition, some are euphoric from the disease and cannabis might add to the euphoria and confuse the results with unspecific effects. Furthermore, there are several types of spasticity, and in the case of baclofen, we found that γ-spasticity was reduced but α-spasticity was unaffected.

Dr. Petro: We had a population of MS patients that was rather large and readily accessible. Certainly, in subjects with significant cerebellar disease, marijuana (or its derivatives) would appear to be contraindicated because of relaxant effects. We examined the patient population readily available for study, which was MS patients, but as you suggest this is not the ideal group to study.

Dr. Gilbert: Poly-synaptic reflexes in the dog are very sensitive to THC. In the

morphine-dependent animal during abstinence there is an increased activity in the hind limbs. That activity can be blocked with very low doses of THC, nantradol and nabilone, before we see any other effects of the drugs (see Gilbert *et al.*, this monograph).

Dr. Dow: Could you elaborate on your conclusion that THC is not the ideal drug for spasticity?

Dr. Petro: Patients that report effects from marijuana don't like taking THC; after smoking a marijuana cigarette, they clearly have an improvement that is different from that seen from THC. As other related substances with more specific CNS effects become available, these should be studied in the treatment of spasticity.