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Cannabis and the Peripheral Nervous System*

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The possible ill-effects of cannabis on the peripheral nervous system were examined in 27 male subjects with respect to their motor and sensory nerve conduction. They were classified by their previous cannabis use into casual and heavy users. The nerve conduction studies were done after a baseline period of five days and then repeated after a three-week period during which the subjects could acquire and smoke standardized cannabis cigarettes. The casual users smoked a mean of 54·3 and the heavy users a mean of 109·5 cigarettes during the smoking period. No deterioration of peripheral nerve function could be demonstrated.

Introduction

Considerable controversy was aroused a few years ago by an article reporting 'Cerebral Atrophy in Young Cannabis Smokers' (Campbell *et al*, 1971). This report was based on findings of ventricular dilatation observed on encephalography of patients referred for investigation of mental changes supposedly due to heavy cannabis smoking. Certainly the fat-solubility of the cannabinoles does raise concern regarding their neurotoxic effects (Gill *et al*, 1970). However, the question of actual central nervous system damage is still open (*British Medical Journal*, 1973).

The possibility of toxic involvement of the peripheral nervous system has not yet been investigated. Alcohol, phenytoin (dilantin) and heroin are known to cause peripheral neuropathies after prolonged use. Even hallucinogens have recently been reported as a possible cause of minor peripheral nerve abnormality (DiBenedetto, 1973). In all of these, preclinical changes exist and are identifiable long before clinical disease is evident.

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Previous investigations in our laboratory (DiBenedetto, 1973 and 1972) have demonstrated the effectiveness of nerve condition studies in detecting the earliest changes even in the absence of overt clinical signs.

In order, therefore, to further explore the safety of chronic marijuana usage, a systematic study of possible ill effects on the peripheral nervous system seemed indicated.

Method

Subjects

Twenty-seven men between the ages of 21 and 26 years were the subjects of this study. Twelve subjects with a mean age of 23·6 years (range of 21 to 26) reported a mean duration of marijuana use of 5·3 years (range of 3 to 8 years) and a frequency of use during the past year of 11·5 ± 6·5 times per month. These subjects were designated as casual users. Fifteen subjects with a mean age of 23·2 years (range of 21 to 25 years) reported a mean marijuana use of 5·6 years (range of 3 to 9 years) and smoked 42 ± 24·5 marijuana cigarettes per month during the previous years. These subjects were designated as heavy users.

All subjects selected for the study were in good health, with no evidence of noteworthy physical or mental abnormalities as determined by appropriate clinical and laboratory examinations, which included a complete physical examination, chest X-ray study, electrocardiogram and lactic dehydrogenase, serum

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glutamic oxalacetic transaminase, total bilirubin, total protein, albumin, globulin, albumin-globulin ratio, alkaline phosphatase, uric acid, urea nitrogen, creatinine, glucose, total cholesterol, total lipids, white cell count, red cell count, haemoglobin, haematocrit, and differential count.

The study consisted of three phases: (1) a base-line period of 5 days during which time initial studies were done; (2) a 21-day period during which subjects could, using operant methodology, acquire and smoke marijuana cigarettes; and (3) a post-marijuana smoking period of 5 days' duration.

Marijuana cigarettes were obtained from the National Institute of Mental Health in a lot-standard dosage form. The cigarettes were machine-rolled to ensure maximal standardization and equivalent dosage and 'draw' characteristics. Each cigarette contained approximately 1 g of marijuana with a tetrahydro-cannabinol content of 1·8 to 2·3 per cent as assayed by the National Institute of Mental Health.

Nerve conduction studies

Initial studies consisted of sensory nerve conduction determinations of median, ulnar and sural nerves. An antidromic technique was employed. Stimulation with a rectangular pulse of 0·05–0·1 ms duration was carried out (maximal current output 300 volts) at the wrist and elbow for the upper extremity nerves and the lower half of the calf slightly lateral to midline for the sural nerve (DiBenedetto, 1970). Superficial recording electrodes were placed around the proximal and distal interphalangeal joints of the index finger and fifth finger respectively (springelectrodes) and behind the lateral malleolus (silverstrips) for the sural nerve. Interelectrode distance was 2·5–3 cm. For determination of motor nerve conduction in the median nerve, superficial disc electrodes were placed over the abductor pollicis brevis muscle and for the ulnar nerve over the abductor digiti quinti muscle. Stimulation was applied at the same areas mentioned for sensory nerve conduction studies. The peroneal nerve conduction was determined by stimulating behind the fibular head and at the ankle, recording from electrodes placed over the extensor digitorum brevis muscle. Interelectrode distance was 2 cm. A 3 cm diameter groundplate was fastened to the dorsum of the hand when the arm was tested and over the plantar surface of the foot when testing the leg. A Teca Model Te_4* was used with the frequency response set at 16 Hz to 16 kHz. Determinations were made of distal latencies and conduction velocities from elbow to wrist and knee to ankle. Responses were evaluated as to amplitude and duration. Skin temperature was measured at the wrist, fingerjoints, calf and ankle.

* Teca Corporation, White Plains, New York.

Results

The casual users smoked a mean of 54 (range 21 to 96) marijuana cigarettes and the heavy users smoked a mean of 120 (range 30 to 163) during the 21-day smoking period. Initial evaluation showed the mean values for all parameters to be well within the norm for both groups, as can be noted in Table I.

However, as to individual values some minor abnormalities were observed. Six subjects showed a decrease in the evoked median nerve sensory amplitude (less than 35 microvolts); 2 were at the border of the normal (35 microvolts). Potential duration was increased in only one subject (not accountable by temperature adjustment), who also showed a slight decrease in sensory nerve condition from elbow to wrist (less than 6 m/sec at skin temperature 32 °C). Evoked ulnar sensory nerve action potential was abnormally low in 9 subjects (less than 25 microvolts). None of the subjects showed an increase in potential duration, latency or conduction velocity. The evoked sural nerve action potential was abnormally low in 3 subjects (below 15 microvolts). No abnormality in motor nerve conduction evaluation was noted.

On repeat examination after three weeks of cannabis smoking, only one subject previously noted to have lowered median nerve sensory amplitude was still in the abnormal range; four were now at the lower border of normal. Of the nine subjects having been found to have abnormally low ulnar nerve sensory amplitude, only three still showed abnormally low values. Sural nerve testing showed two lowered responses. No previously normal amplitudes proved to be in the abnormal range after smoking. All other test values were in the normal range and showed essentially no change, when adjustments for temperature were carried out in accordance with the formula: $\gamma_2 = \gamma_1 + T \times 2$. ($\gamma_2$ is the expected nerve conduction velocity at 33 degrees centigrade; γ_1 is the actually measured conduction velocity; T is the difference in observed and standard test temperature —33 °C). The skin temperature ranged between 24–33 °C with a mean temperature of 31 °C.

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TABLE I

Sensory nerve conduction: mean values observed during initial and repeat examination, compared with established norms for our laboratory

	Group		Latency m/sec	Conduction velocity m/sec	Amplitude uV	Duration m/sec
MEDIAN	NORMAL	Mean	2·4±0·2	63± 4	55±13	1·2±0·3
		Range	2·0−3·0	60−72	45−80	1·0−2·0
	CANNABIS Before	Mean	2·4±0·4	62± 4	45±14	1·4±0·2
		Range	1·8−3·4	54−68	25−90	1·0−2·1
	CANNABIS After	Mean	2·4±0·2	62± 4	47±12	1·4±0·2
		Range	1·9−2·8	54−70	25−80	1·0−2·0
ULNAR	NORMAL	Mean	1·9±0·5	62± 4	41±14	1·2±0·2
		Range	1·5−2·7	55−73	22−75	0·9−1·6
	CANNABIS Before	Mean	2·1±0·3	61± 5	31±12	1·2±0·3
		Range	1·5−3·2	46−68	10−55	0·9−1·8
	CANNABIS After	Mean	2·1±0·2	61+ 3	32·5±11	1·3±0·3
		Range	1·7−2·9	50−69	14−55	1·0−1·8
SURAL	NORMAL	Mean	2·3±0·5		23± 3	1·3±0·3
		Range	1·4−3·2		15−36	1·2−2·0
	CANNABIS Before	Mean	2·3±0·4		22·6± 7	1·4±0·2
		Range	1·5−3·0		10−40	1·2−2·0
	CANNABIS After	Mean	2·2±0·3		23± 9	1·4±0·2
		Range	1·7−2·9		10−50	1·2−1·7

Discussion

It is unfortunate that many substances which temporarily produce alteration of nervous system function also alter the anatomy of the nervous structures if employed over long periods of time or in high degrees (Eisen *et al*, 1974). Changes may predominantly affect the Schwann cells and therefore the myelin sheath or may cause axonal deterioration. Toxins most commonly cause axonal degeneration, while nutritional, vascular and compressive elements effect their damage predominantly on the myelin. Toxins, therefore, less readily cause nerve conduction slowing. Early stages of minor axonal degeneration, especially if the onset is slowly progressive do not present with definite reduced nerve conduction times or spontaneous potentials on electromyography. The parameter most likely to be affected is the amplitude of the evoked sensory nerve action potential. Potential amplitude and duration do reflect the size of the healthy fibre population. Response amplitude lowering due to nerve conduction slowing is mostly identifiable by an increase of potential duration, while a low narrow evoked action potential suggests a reduced number of healthy nerve fibres because either of injury to the axon or degeneration secondary to disease.

Indeed, changes of this nature have been demonstrated in sub-clinical disease states such as 'non-clinical neuropathic' alcoholics (Blackstock *et al*, 1972), heroin addicts and those who frequently use LSD and amphetamines (DiBenedetto, 1973). No such effect could be related to cannabis smoking. The nine subjects who demonstrated lower evoked sensory amplitudes than expected for age and temperature had histories of previous moderate alcohol and/or hallucinogen or amphetamine abuse. The repeat examination showed no deterioration after

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TABLE II

Motor nerve conduction: results of normals, initial and repeat examinations

	Group		Latency m/sec	Conduction velocity m/sec	Amplitude uV	Duration m/sec
MEDIAN	NORMAL	Mean	2·9±0·4	56± 4		
		Range	2·2—4·0	50—65		
	CANNABIS Before	Mean	3·0±0·4	57± 4	4·9± 0·3	13·3± 1·8
		Range	2·5—4·0	52—69	0·5—13·0	9·5—17·4
	CANNABIS After	Mean	3·1±0·5	57± 2	3·9± 0·2	12·9± 1·9
		Range	2·5—4·6	53—64	1·0— 8·0	9·5—17·4
ULNAR	NORMAL	Mean	2·1±0·4	57± 4		
		Range	1·8—2·8	48—68		
	CANNABIS Before	Mean	2·3±0·4	59± 4	3·7± 0·2	12·5± 1·9
		Range	1·8—3·4	41—63	1·0— 8·0	9·8—16·0
	CANNABIS After	Mean	2·3±0·3	59± 3	3·7± 0·2	12·8± 2·0
		Range	1·9—2·9	51—66	1·0—10·0	9·8—17·0
PERONEAL	NORMAL	Mean	4·4±0·5	49± 4		
		Range	3·7—5·8	45—60		
	CANNABIS Before	Mean	4·6±0·7	48± 5	3·5± 0·2	13·0± 2·5
		Range	3·7—6·3	40—57	0·2— 7·0	11·0—20·0
	CANNABIS After	Mean	4·7±0·7	48± 3	3·6± 0·2	12·7±2·0
		Range	3·6—6·0	42—56	1·0—10·0	11·0—18·0

three weeks of heavy cannabis smoking, and indeed some had a return to normal values. Five subjects who appeared to have moderate drug histories but exhibited test values well within the norm were found to have discontinued the use of other drugs more than a year before testing. No differences as to observed mean values could be noted between the casual and the heavy smokers group. From the individual test results, seven of nine subjects noted to have low sensory amplitudes belonged to the heavy group, and the findings were also well correlated with their other drug histories (hallucinogens, amphetamines, barbiturates and in some heroin). An improvement after the three-week smoking period was also noted among subjects of this group, though it was not statistically significant. The slight improvement may have been related to the forced abstinence from other drugs and the good nutrition provided. While it is fully appreciated that nerve recovery is a slow process, it must be noted that all subjects had been at least one month off drugs. Our findings are in agreement with those previously reported in the literature (DiBenedetto, 1973). Since most heavy cannabis smokers also frequently use other drugs, investigators should be alert to the danger of assuming that any noted damage was caused by the cannabis simply on the basis that it was the substance most often used.

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