Analgesic Effect of Delta-9-Tetrahydrocannabinol

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CRUDE preparations of cannabis sativa were recommended for a variety of painful conditions toward the end of the 19th century.[1-3] As analgesics they were regarded as especially effective in conditions having a large functional or psychic contribution to the pain such as migraine, dysmenorrhea, and the pain of terminal illness. Yet they proved no match for the potent and rapid acting narcotics and eventually lost favor because their effects were milder and less predictable. In contrast to the narcotics, however, their toxicity was observed to be low, their disturbance of vegetative functions minimal, and their potential for addiction practically nonexistent. Recent identification and synthesis of delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis, has made systematic administration of the compound possible and has rewakened interest in its therapeutic potential.[4,5]

This preliminary investigation was designed to demonstrate an analgesic effect of orally administered THC in patients suffering from cancer pain. Its specific purpose was the identification of a dosage range within which the drug might relieve pain without at the same time producing disturbing toxic effects. Placebo and randomly allocated, graded doses of THC were administered to hospitalized cancer patients who volunteered for a trial of this medication.

Materials and Methods

Ten cooperative subjects, eight women and two men, were selected for participation in this study from among advanced cancer patients being followed at the University of Iowa Hospital. These patients, having a mean age of 51 years and a mean weight of 62 kg, reported continuous pain of moderate severity that was attributable to their disease. Five patients suffered from carcinoma of the breast, two from malignant lymphoma, one from carcinoma of the cervix, one from carcinoma of the colon, and one from lymphoepithelioma. Patients receiving large doses of narcotics were excluded from the study although seven had received methadone as part of their regular analgesic regimen. All were admitted to the University of Iowa Clinical Research Center where they were maintained on their usual analgesic program. Each was informed that, while on the study, he would receive varied doses of the active ingredient in marijuana. Each was further advised that doses would not be of equal strength and that the objective of the study was to determine which were the most effective in relieving pain. Informed consent was obtained in writing from all patients.

Regular analgesics were withheld after 4:00 A.M., and test medications were administered once daily at approximately

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8:30 A.M., 1 hour after eating. On successive days, placebo and 5, 10, 15, and 20 mg THC, all identical in appearance, were administered double blind in a random sequence.* A full-time registered nurse assigned to the study administered test medications and interviewed subjects hourly regarding the severity of pain and the extent of relief experienced. The categories of slight, moderate, and severe pain all represented subjective judgments on the part of the patients at the time of being interviewed. The nurse's observations, including evident or reported side effects, were recorded on a pain chart designed for that purpose.[6,7] This observer also administered an 11-item subjective effects questionnaire hourly and a side effects inventory at the end of each 6-hour observation period. The subjective effects questionnaire consisted of the following seven-point scales: sleepy–awake, energetic–fatigued, sad–happy, quiet–restless, sociable–unsociable, dreamy–clear-headed, calm–uneasy, alert–dull, worried–peaceful, time slowed–time speeded up, and trouble thinking–thinking clearly. Hourly recordings of blood pressure and heart and respiration rates were also made.

Hourly ratings of the severity of pain (0=absent, 1=mild, 2=moderate, and 3=severe) were used to arrive at hourly pain *reduction* scores. These scores were obtained by subtracting the hourly ratings from that recorded prior to the drug's administration. If, for example, severe pain was reported before the drug was given, then mild pain 3 hours afterward would be assigned a reduction score of two. Pain *relief* scores were recorded as follows: 0=none, 1=slight, 2=moderate, 3=a lot, 4=complete. The sum of hourly pain reduction or relief scores for a given 6-hour observation period (total reduction or relief scores) were used as a basis for statistical analysis. Hourly scores on the subjective effects questionnaire were assigned to the number of points a subject moved away from a predrug reference on a particular scale.

* Delta-9-tetrahydrocannabinol in capsules containing a sesame oil vehicle was obtained from the National Institute of Mental Health.

Results

Table I shows mean total pain reduction and relief scores for placebo and THC. Application of Edward's method of trend analysis of variance revealed a significant trend toward progressive relief of pain with increasing doses of the drug ($P<0.001$).[8] Since a comparison of pain relief scores between adjacent dose levels yielded no significant differences, scores for combined low dose levels (5 and 10 mg) were compared with scores for combined high dose levels (15 and 20 mg).

Here, a significant difference in the expected direction of greater pain relief with high doses of THC was demonstrated ($P<0.025$, paired observation method). Due to the small number of patients and the variability between them, further statistical analysis of these data did not seem appropriate. Mean hourly relief scores for placebo and 10, 15, and 20 mg THC are plotted in Fig. 1. They show that the analgesic effect of THC developed gradually and was prolonged. While the

TABLE I

Total Pain Reduction and Relief Scores Following Oral THC

Dose	Scores (mean ± S.E.)	
	Pain reduction	Pain relief
Placebo	0.9 ± 0.30	2.6 ± 0.61
THC, 5 mg	2.6 ± 0.53	4.7 ± 0.95
THC, 10 mg	1.4 ± 0.42	4.4 ± 0.98
THC, 15 mg	3.6 ± 0.65	5.8 ± 0.84
THC, 20 mg	4.6 ± 0.66	10.8 ± 1.19

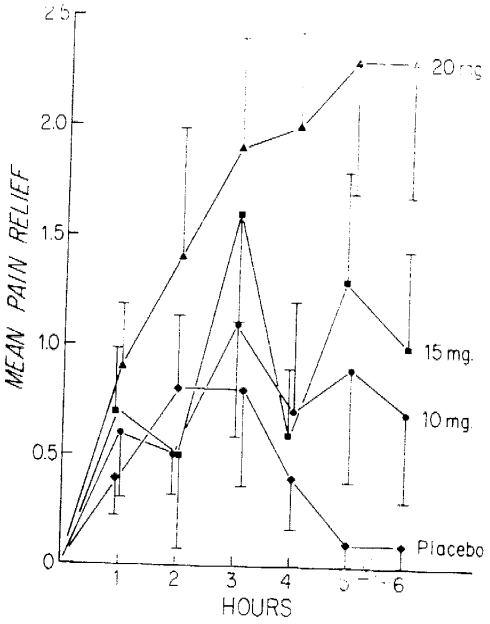

Fig. 1. Mean (± standard error) hourly pain relief in ten patients following the administration of THC.

peak effect occurred at 3 hours following 10 and 15 mg, it did not develop until 5 hours following a dose of 20 mg. A second peak observable at 5 hours after drug administration may have been the result of THC's mobilization from the gall bladder and reabsorption following food ingestion.[9] One patient with a lymphoepithelioma experienced no pain relief from THC at any dose. She differed from the others in having pain that was sharply localized, questionably related to her disease, and unresponsive to other analgesic medications. Five patients received substantial relief (total relief scores of greater than 6) from 15 mg and seven, from a dose of 20 mg.

Table II shows the frequency with which commonly experienced side effects were reported by the ten patients in this study. Patients receiving 20 mg THC were heavily sedated and even at 15 mg reported considerable drowsiness. This sedative effect was also apparent from responses on the subjective effects questionnaire. Table III shows total 6-hour change scores for three scales revealing a progressive reduction in arousal produced by the drug. Also shown in Table III is evidence of progressive mental clouding that made its appearance at 5 mg and became marked at 20 mg.

Other questionnaire scales showed no change. Euphoria was infrequently reported and was grossly evident in only two patients following the 15- and 20-mg doses. One of these was the only patient in the series giving a history of marijuana use. Several others reported minor elevations of mood when specific inquiry regarding such charges was made.

Both heart rate and blood pressure decreased following 15- and 20-mg doses of THC. The mean (± standard error) hourly decline in heart rate was 2.3± 1.93 beats per minute following 15 mg and 3.9±1.43 beats per minute following 20 mg. The mean hourly fall in blood pressure over the 6-hour observation was 11/7±1.48/1.31 mm Hg after 15 mg and 5/1±1.72/1.39 mm Hg following 20 mg. No change in respiration rate was observed.

Discussion

This preliminary trial of THC on a limited number of patients has demonstrated an analgesic effect of the drug. Attempts to establish its potency relative to standard analgesics of mild to moderate strength such as aspirin and codeine appear warranted and are currently in progress. In a dose of 20 mg, the drug is highly sedating and, consequently, of limited value for most patients. Doses of 5 and 10 mg, which showed a trend toward pain relief greater than placebo, might or might not maintain their superiority in trials involving large numbers of patients.

In the setting of this expirement, THC demonstrated sedating effects in contrast

TABLE II

Side Effects After Oral THC

Side effect	Number of patients experiencing side effects (N=10)				
	20 mg THC	15 mg THC	10 mg THC	5 mg THC	Placebo
1. Drowsiness	10	7	5	7	3
2. Slurred speech	8	8	4	4	2
3. Blurred vision	7	7	4	2	0
4. Mental clouding	6	7	4	5	2
5. Dizziness	6	4	4	2	1
6. Headache	4	3	5	5	2
7. Increased appetite	4	5	5	2	0
8. Ataxia	5	7	3	3	3
9. Dreaminess	3	6	3	4	3
10. Disconnected thought	5	1	2	2	0
11. Numbness	4	3	2	1	0
12. Euphoria	5	4	1	0	0
13. Visual hallucinations	3	0	1	0	0
14. Tinnitus	0	2	4	0	0

TABLE III

Subjective Effects After Oral THC

Effect	Mean total deviations from predrug reference points on scales				
	Placebo	5 mg THC	10 mg THC	15 mg THC	20 mg THC
Sedation					
1. sleepy–awake	+6.5	−4.4	−4.9	−6.8	−9.8
2. fatigued–energetic	+1.6	−2.1	−2.2	−6.9	−7.0
3. dull–alert	+4.9	−1.5	−3.2	−2.7	−8.7
Mental clouding					
4. dreamy–clearheaded	+0.9	−2.6	−3.6	−9.1	−11.8
5. trouble thinking–thinking clearly	+2.2	−3.3	−3.8	−6.7	−6.7

to the stimulating ones commonly associated with its social use.[10] In place of heightened perception, numbness and pain reduction occurred; in place of euphoria and enhanced sociability, a dreamy social withdrawal developed. Associated with the latter, a fall in heart rate and blood pressure occurred in contrast to the increase in pulse which is typically reported.[11] Patients in this study were exposed to little stimulation, were relatively ill, and were, for the most part, socially isolated. These circumstances may well have been determinants of the drug's depressant effects.

Finally, the preliminary data reported here suggest that an association exists between the pain reduction caused by THC

and the reduction in arousal and attention produced by this drug. On the other hand, the reduction in pain appears to be independent of the compound's euphoric and antianxiety effects. Attempts to correlate physiologic measures of arousal and psychological assessments of attention with pain relief may provide clues to an understanding of the drug's mechanism of analgesic action.[12]

Summary

A preliminary trial of oral delta-9-tetrahydrocannabinol (THC) demonstrated an analgesic effect of the drug in patients experiencing cancer pain. Placebo and 5, 10, 15, and 20 mg THC were administered double blind to ten patients. Pain relief significantly superior to placebo was demonstrated at high dose levels (15 and 20 mg). At these levels, substantial sedation and mental clouding were reported.

References

1. Grinspoon, L.: Marihuana Reconsidered. Cambridge, Harvard University Press, 1971.
2. Mijuriya, T. H.: Historical aspects of cannabis sativa in western medicine. *New Physician* 18:902 (1969).
3. Synder, S. H.: Uses of Marihuana. New York, Oxford University Press, 1971.
4. Gaoni, Y., and Mechoulam, R.: Isolation, structure and partial synthesis of an active component of hashish. *J. Amer. Chem. Soc.* 86:1646 (1964).
5. Mechoulam, R., and Gaoni, Y.: A total synthesis of delta-9-tetrahydrocannabinol, the active constituent of hashish. *J. Amer. Chem. Soc.* 87:3273 (1965).
6. Houde, R. W., Wallenstein, S. L., and Beaver, W. T.: Evaluation analgesics in patients with cancer pain. *In* International Encyclopedia of Pharmacology and Therapeutics, Section 6, Volume 1, Lasagna, L., Ed., Clinical Pharmacology. New York, Pergamon Press, 1966.
7. Keele, K. D.: The pain chart. *Lancet* 2:6 (1948).
8. Edwards, A. L.: Experimental Design in Psychological Research. New York, Rinehart, 1960, pp. 224–227.
9. Dewey, W. L., and Turk, R. F.: The excretion and metabolism of 3H-delta-9-THC in intact and bile-duct cannulated rats. *Fed. Proc.* 31:506 (1972).
10. Hill, S. Y., Goodwin, D. W., Schwin, R., and Powell, B.: Marijuana: central nervous system depressant or excitant? *Amer. J. Psychiat.* 131:313 (1974).
11. Kiplinger, G. F., Manno, J. E., Roddan, B. E., and Forney, R. B.: Dose response analysis of the effects of tetrahydrocannabinol in man. *Clin. Pharmacol. Therap.* 12:650 (1971).
12. Paton, W. D. M., and Pertwee, R. G.: The actions of cannabis in man. *In* Marijuana, Mechoulam, R., Ed. New York, Academic Press, 1973, p. 329.