The analgesic properties of delta-9-tetrahydrocannabinol and codeine

The administration of single oral doses of delta-9-tetrahydrocannabinol (THC) to patients with cancer pain demonstrated a mild analgesic effect. At a dose of 20 mg, however, THC induced side effects that would prohibit its therapeutic use including somnolence, dizziness, ataxia, and blurred vision. Alarming adverse reactions were also observed at this dose. THC, 10 mg, was well tolerated and, despite its sedative effect, may have analgesic potential.

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When tincture of hemp was introduced into Western medicine in 1839 it was claimed to be an effective analgesic.[14] Early pharmacologists recommended the drug for painful functional disorders such as dysmenorrhea, migraine, and the pain of terminal illness, and suggested that its value in these conditions might be enhanced by its sedative properties.[11] Despite the enthusiastic endorsement of a number of nineteenth century clinicians, cannabis preparations fell from favor as more potent and predictable drugs were introduced. Aspirin and the barbiturates became popular after the turn of the century, while the hypodermic syringe made rapid delivery of water-soluble opiates possible. These were naturally preferred to the weaker and slower-acting cannabis extracts.[16]

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Recent identification and synthesis of delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis, has made systemic administration of the drug possible and has reawakened interest in its therapeutic potential.[2, 10]

In a preliminary trial, reported elsewhere, the drug was given to 10 patients suffering from cancer pain, and a dosage range within which the drug might relieve pain and be safely administered was established.[13] Our investigation was undertaken to estimate the relative potency of the analgesic effects of THC and codeine and to compare their side effects.

Materials and methods

Thirty-six cooperative subjects, 26 women and 10 men, were selected for participation in this study from among advanced cancer patients at the University of Iowa Hospital. These patients (mean age, 51 years; mean weight, 639 kg) reported continuous pain of moderate severity attributable to their disease. Thirteen suffered from carcinoma of the breast, 7 from

non-Hodgkin's lymphoma, 3 from Hodgkin's disease, 2 each from carcinoma of the lung, colon, prostate, and malignant melanoma, and 1 each from carcinoma of the cervix, carcinoid, leiomyosarcoma, carcinoma of the parotid gland, and anaplastic carcinoma of unknown origin. None were receiving large doses of narcotics. All were admitted to the University of Iowa Clinical Research Center where they were maintained on their usual analgesic regimen. Each was informed that, while on the study, he would receive varying doses of codeine and of the active ingredient in marijuana. Each was further advised that test medications would not be of equal strength and that the objective of the study was to determine which were the most effective in relieving pain.

Regular analgesics were withheld after 4:00 A.M. Test medications were administered once daily at approximately 8:30 A.M., 1 hr after eating. On successive days, placebo, 10 and 20 mg of THC, and 60 and 120 mg of codeine, all identical in appearance, were administered double-blind in a random pattern.* 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.[6] The categories of slight, moderate, and severe pain 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.[7] The same observer also administered an 11-item subjective effects questionnaire hourly and a side effects inventory at the end of each 7-hour observation period. The subjective effects questionnaire consisted of the following 7-point scales: sleepy-awake, energetic-fatigued, sad-happy, quiet-restless, sociable-unsociable, dreamy-clearheaded, calm-uneasy, alert-dull, worried-peaceful, time slowed–time speeded up, and trouble thinking–thinking clearly. In addition an inventory of the psychological effects was obtained at the end of each observation period using a modified version of the Subjective Drug Effects Questionnaire developed by Waskow and associates.[17] Hourly determination of blood pressure, heart, and respiration rates was also recorded.

*Delta-9-tetrahydrocannabinol in sesame oil in capsules was obtained from the National Institutes of Mental Health.

Table I. *Mean (± SE) total pain reduction and relief scores following oral THC and codeine (N = 34)*

	Pain relief	*Pain reduction*
Placebo	6.8 ± 0.95	1.9 ± 0.44
Codeine, 60 mg	9.4 ± 1.38	3.6 ± 0.75
THC, 10 mg	9.8 ± 1.40	2.9 ± 0.62
Codeine, 120 mg	12.2 ± 1.57	4.3 ± 0.78
THC, 20 mg	12.9 ± 1.46	4.7 ± 0.65

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 hr afterward would be assigned a reduction score of 2. 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 7-hour observation period (total reduction or relief scores) was used as a basis for statistical analysis. Hourly scores on the subjective effects questionnaire were assigned to the number of points a subject moved from a pre-drug reference on a particular scale.

Using the same method of observation, a preliminary comparison of the analgesic effects of aspirin, THC, and the 2 drugs combined was undertaken in 9 of the patients who participated in the main study. Each received placebo, aspirin, 600 mg, THC, 10 mg, aspirin, 600 mg, plus THC, 10 mg, and aspirin, 600 mg, plus propoxyphene, 65 mg.

Results

Table I shows mean pain reduction and relief scores (totaled for the 7-hour observation period) for placebo, THC, and codeine obtained from 34 patients who completed the study. Scores for the low doses of THC and codeine (THC, 10 mg, and codeine, 60 mg) and for

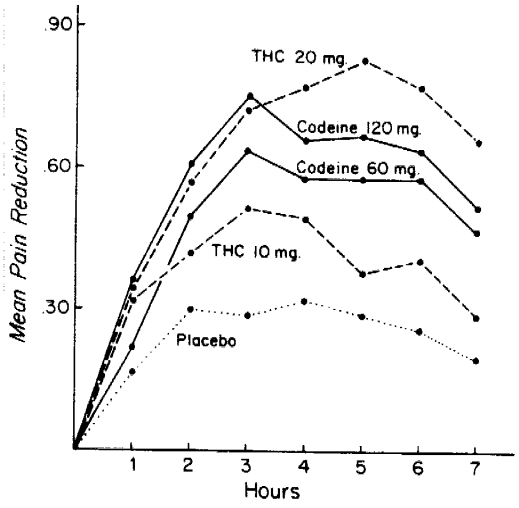

Fig. 1. Mean hourly pain reduction following THC, codeine, and placebo.

the high doses of both drugs (THC, 20 mg, and codeine, 120 mg) roughly approximated one another. The overall test for drug differences, using a multivariate analysis of variance, was significant ($p < 0.03$). Significant differences were observed between placebo and 20 mg THC and between placebo and 120 mg codeine ($p < 0.05$). Other differences did not reach significance. The number of patients who experienced substantial pain relief (total relief scores of 12 or more) after each of the test doses was as follows: 6 after placebo, 8 after codeine, 60 mg, 13 after THC, 10 mg, 16 after codeine, 120 mg, and 16 after THC, 20 mg.

The mean hourly pain reduction scores for placebo, THC, and codeine are plotted in Fig. 1. They show that the analgesic effect of THC developed gradually and was prolonged. While the peak effect of codeine occurred in 3 hr, the peak analgesic effect of 20 mg THC did not develop until 5 hr.

Table II shows the frequency with which commonly experienced side effects were reported by the 34 patients who completed the main portion of the study. Patients receiving 20 mg of THC were heavily sedated and even at 10 mg reported considerable drowsiness. Other dose-limiting side effects included dizziness, ataxia, and blurred vision. The sedative effect was also apparent from responses on the subjective effects questionnaire administered hourly. Table III shows total 7-hour change scores for 3 scales revealing a dose-related reduction in arousal produced by both THC and codeine. The reduction caused by 10 mg THC was roughly comparable to that resulting from 120 mg codeine. Also shown in Table III is evidence of mental clouding induced by high and low doses of THC. Codeine induced none of the impairment in thinking caused by THC and only minimal dreaminess.

A variety of psychological effects of THC were reported on the Subjective Drug Effects Questionnaire.[12] In addition to the effects mentioned previously, most patients acknowledged tranquilization or mood elevation in response to the drug. In contrast to the obvious sedation caused by THC, euphoria was clinically evident in only 4 patients. Depersonalization, consisting of altered perception of time, altered emotion, feeling of unreality, altered attention, sense of detachment, and loss of control, was reported in part by most patients after THC. After 20 mg, patients characteristically entered a state of dreamy immobility in the midst of which they reported a sense of unreality and disconnected thoughts together with distortions of time, space, and bodily proportions. Their responses often became sluggish and their appreciation of immediate surroundings was disrupted by lapses in orientation and recent memory. With few exceptions patients voiced dislike for these effects and expressed particular concern over the loss of control over thought and action. In contrast, the effects of 10 mg THC were relatively mild and of brief duration.

Five patients experienced adverse reactions to THC, and 2 were eliminated from the study. These reactions, one following 10 mg and 4 following 20 mg, coincided with the onset of drug effects and consisted of extreme anxiety in response to the previously mentioned loss of control. Three patients said they felt as if they were dying. Three such reactions were brief and limited to the period of the drug's psychoactivity, but in the other 2 the reactions persisted 3 to 4 days. In 2 instances depressed mood was a prominent feature and in 1, paranoid ideation.

Table IV shows mean hourly decreases in

Table II. *Number of patients reporting side effects following single oral doses of THC and codeine (N = 34)*

	THC		Codeine		
	20 mg	*10 mg*	*120 mg*	*60 mg*	*Placebo*
Gastrointestinal					
Increased appetite	7	9	5	5	3
Nausea	6	7	4	11	5
Diarrhea	5	1	1	0	2
Epigastric distress	4	4	7	2	3
Vomiting	3	1	3	1	1
Central nervous system					
Sedation	32	24	17	16	10
Mental clouding	18	11	2	3	6
Ataxia	15	10	8	4	3
Numbness	13	4	5	5	3
Disorientation	12	5	1	1	3
Disconnected thought	11	10	2	3	3
Slurred speech	11	6	2	4	3
Muscle twitching	10	8	3	5	3
Impaired memory	9	2	1	1	2
Miscellaneous					
Dry mouth	26	25	22	20	12
Dizziness	33	20	20	8	9
Blurred vision	22	14	8	4	3
Tinnitus	7	4	3	3	3
Itching	5	6	8	9	5
Frequency	4	7	5	6	3
Sweating	3	7	7	4	4
Urgency	3	1	3	5	3

heart rate and blood pressure following codeine and decreases in blood pressure following THC. The overall test for drug differences in systolic blood pressure, using a multivariate analysis of variance, was significant ($p < 0.001$), but, due to the great variability in responses, individual comparisons between drugs did not achieve a 5% level of confidence. The overall test of diastolic blood pressure differences was not significant ($p < 0.08$). No increase in heart rate was observed after THC. Comparisons of heart and respiration rate responses show no significant differences between drugs.

Table V gives mean pain reduction and relief scores for placebo, aspirin, THC, aspirin combined with THC, and aspirin combined with propoxyphene obtained from 9 patients. The scores for aspirin and THC combined were greater than those resulting from either drug alone but did not reach statistical significance.

Discussion

This trial has demonstrated an analgesic effect of THC in patients with cancer pain. The low doses of THC and codeine failed to achieve statistical significance in 34 patients. As a consequence, any estimate of the drug's potency relative to codeine might be misleading. It seems clear from the data, however, that THC is highly sedating and produces mental effects, which in a dose of 20 mg prohibit its therapeutic use. Adverse reactions to this dose occur frequently. On the other hand, 10 mg THC is well tolerated though somewhat sedating. The analgesic properties of THC appear to be mild and for that reason should be studied among patients experiencing mild pain. The preponderance of patients experiencing moderate to severe pain in this study may have been responsible for the insensitivity of our assay.

In the setting of this experiment, THC demonstrated sedating effects in contrast to the ex-

Table III. *Mean deviations from a pre-drug reference point on subjective drug effect scales following THC and codeine**

		THC		Codeine	
	Placebo	*10 mg*	*20 mg*	*60 mg*	*120 mg*
Sedation					
Awake-sleepy	4.1	8.3	17.0	4.4	8.0
Energetic-fatigued	0.9	4.3	11.3	3.3	4.1
Alert-dull	0.5	4.4	12.4	0.1	2.8
Mental clouding					
Clearheaded-dreamy	0.9	7.7	12.4	2.8	3.4
Thinking clearly–trouble thinking	−1.3	4.1	8.3	0.8	0.9
Social withdrawal					
Sociable-unsociable	1.6	1.6	5.4	1.7	2.0

*Scores represent the sum of hourly deviations over a 7-hr observation period (N = 34).

Table IV. *Mean hourly decline (± SE) in blood pressure, heart and respiration rates after the administration of THC and codeine (N = 34)*

		THC		Codeine	
	Placebo	*10 mg*	*20 mg*	*60 mg*	*120 mg*
Systolic	+1.2 ± 1.40	5.1 ± 1.36	3.4 ± 1.39	2.6 ± 1.53	4.1 ± 1.43
Diastolic	+0.1 ± 1.14	2.7 ± 1.30	2.2 ± 1.12	0.1 ± 1.09	1.3 ± 1.11
Heart rate	1.8 ± 1.23	0.6 ± 1.42	0.6 ± 1.73	4.2 ± 1.42	6.3 ± 1.91
Respiration	0.0 ± 0.43	0.7 ± 0.43	0.7 ± 0.57	1.0 ± 0.46	0.7 ± 0.65

Table V. *Mean (± SE) total pain relief and reduction scores following oral aspirin, THC, and propoxyphene (N = 9)*

	Pain relief	*Pain reduction*
Placebo	5.1 ± 1.65	2.1 ± 1.32
ASA, 600 mg	10.0 ± 3.21	3.8 ± 1.67
THC, 10 mg	10.8 ± 2.44	3.4 ± 1.09
ASA, 600 mg + PROP, 65 mg	11.7 ± 2.62	5.1 ± 1.39
ASA, 600 mg + THC, 10 mg	15.1 ± 2.85	6.6 ± 1.94

citatory ones commonly associated with its social use.[5] In place of heightened perception there was numbness and pain reduction; in place of euphoria and enhanced sociability, dreamy social withdrawal developed. Associated with the latter, no change in heart rate was observed in contrast to the increase in pulse that is usually reported.[8] The set and setting of this investigation were doubtless important determinants of THC's depressant effects. With one exception, our subjects had had no previous experience with marijuana. In th course of this study they were exposed to litt stimulation, were relatively ill, and were, fo the most part, socially isolated.

After receiving THC, several patients re ported that their pain no longer seemed a pa of their bodies; others described numb or floa ing sensations in formerly painful parts. Thes reports suggest an association between th drug's analgesic effect and drug-induced de personalization. Such detachment from,

blunting of, sensation has been described.[1, 3, 9, 15] Induction of this complex alteration of consciousness may also account for pain reduction reported after LSD.[3] If the mechanism of THC's analgesic effect differs from that of other mild analgesics such as codeine and aspirin, the drug may prove useful in combination with one or more of these drugs. Such an additive effect is suggested by the results with THC and aspirin in the preliminary comparison.

The results of this investigation on the effects of THC must be interpreted with caution in view of the important influence of the subject's experience with the drug, his expectations, and the surroundings in which he receives it. In this study single-dose administration of the drug to naive and relatively inactive inpatients was examined. No conclusions can be drawn regarding the effects of chronic administration on less severely ill outpatients. Finally, particular difficulty was experienced in evaluating the pain of patients after receiving THC. In many instances they appeared exceptionally peaceful while, at the same time, reporting little pain relief. In other instances they claimed that, though the pain was unchanged, it bothered them less. Further study of THC's analgesic effect is warranted.

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