



Title: **Delta-9-Tetrahydrocannabinol as an Antiemetic in Cancer Patients Receiving High-Dose Methotrexate**

Author: [Alfred E. Chang, M.D., et al.](#) Date: December 1979

Summary:

Download: Not yet available - check back [[get adobe acrobat \(PDF\) reader](#)]

Html: [Single Page](#)

Prospective, Randomized Evaluation

ABSTRACT: Fifteen patients with osteogenic sarcoma receiving high-dose methotrexate chemotherapy were studied in a randomized, double blind, placebo-controlled trial of oral and smoked delta-9-tetrahydrocannabinol (THC) as an antiemetic. Each patient served as his or her own control. Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo. Delta-9-tetrahydrocannabinol was significantly more effective than placebo in reducing the number of vomiting and retching episodes, degree of nausea, duration of nausea, and volume of emesis ($p < 0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured < 5.0 ng/mL, 5.0 to 10.0 ng/mL, and > 10.0 ng/mL. The incidences of nausea and vomiting were 44%, 21%, and 6%, respectively. Delta-9-tetrahydrocannabinol appears to have significant antiemetic properties when compared with placebo in patients receiving high-dose methotrexate.

(ANNALS OF INTERNAL MEDICINE. DECEMBER 1979; 91: 819-824)

Nausea and vomiting are frequent and distressing side effects of cancer chemotherapy. The severity of these symptoms contributes to the decreased ability of patients to undergo long-term chemotherapy schedules and impairs their quality of life ^(1, 2). Despite the magnitude of this problem, there have been few clinical reports ⁽³⁻¹¹⁾ investigating the effectiveness of various antiemetics in controlling the nausea and vomiting associated with chemotherapy. Conventional antiemetics, when tested, have been relatively ineffective in reducing these side effects.

Sallan and colleagues ⁽⁷⁾ were able to show that oral-delta-9-tetrahydrocannabinol (THC) had significant antiemetic properties in patients receiving various chemotherapy regimens. As in previous antiemetic studies, nausea and vomiting were assessed solely from subjective impressions based on patient interviews the day after each drug trial. The purpose of our study was to examine in a randomized, double-

[Home](#)

[Major Reports](#)

[scientific Studies](#)

[History](#)

[Opinion](#)

blind, placebo-controlled trial the efficacy of oral and smoked THC as an antiemetic. To do this we obtained both objective and subjective data during each drug trial. Serial blood samples were drawn during the course of each trial to ascertain the effective plasma concentration of THC needed to obtain an antiemetic effect.

METHODS

PATIENT POPULATION

Fifteen patients with osteogenic sarcoma treated by the Surgery Branch of the National Cancer Institute were studied. Ten were males and five, females; they ranged in age from 15 to 49 years (median, 24 years). All patients had undergone surgical removal of their primary tumor (14 amputations and one chest-wall resection) and were disease free upon entry into the study. All patients received adjuvant high-dose methotrexate therapy with leucovorin calcium rescue at 3-week intervals for a total of 18 months. Methotrexate was given at a constant dose of 250 mg/kg in each patient. Before participating in the study each patient was evaluated by a psychiatrist (D.S.) to screen out those likely to have untoward reactions to psychoactive drugs. The study was thoroughly explained to each patient and signed informed consent obtained. Each patient was told he or she would "blindly" receive either placebo or "THC, a marijuana-type compound" during the day of chemotherapy.

STUDY DESIGN

Each patient served as his or her own control. Patients accepted into the study entered Phase I and received THC three times and placebo three times during the six subsequent hospital admissions for chemotherapy infusion. The order of THC and placebo administration for these six methotrexate infusions was randomized into three paired trials of either placebo-THC or THC-placebo. At the end of three paired trials, which took approximately 5 to 6 months to complete, patients were classified as "excellent," "fair," or "nonresponders" to THC (see below) and entered Phase II. In Phase II, "excellent" responders received eight THC trials and two placebo trials during their next 10 courses of chemotherapy. The enriched sequence of THC trials was designed to assess whether repeated trials of THC resulted in continued antiemetic responses. If the patient was a "fair" responder or "non responder" to THC. The dose was increased by one third, and the patient re-entered Phase I to see if additional benefits could be obtained.

DRUG DOSE AND SCHEDULE

Delta-9-tetrahydrocannabinol capsules and cigarettes were supplied by the National Institute on Drug Abuse. The THC was suspended in sesame oil and placed in gelatin capsules. Identical-appearing placebo capsules contained only sesame oil. Placebo cigarettes were produced by multiple extractions of natural marijuana with ethanol. The active cigarettes were prepared from these placebo cigarettes by injection of THC through a

spinal needle; each weighed 900 mg and contained 1.93% THC (about 17.4 mg) (12). The odor and taste of a lit placebo cigarette were identical to those of a marijuana cigarette.

Delta-9-tetrahydrocannabinol was administered at a dose of 10 mg/m² given orally every 3 h for a total of five doses. The first dose was given at 0700 h, 2 h before the 6-h methotrexate infusion. All patients had undergone an 8-h fast before chemotherapy infusion to standardize pretreatment oral intake. In the event of a vomiting episode, the patient was given a THC cigarette for the remaining doses of that trial. Variation in the amount of smoke inhaled by each patient was minimized by using a standard inhalation technique (12). Each patient would hold the inhalation for 10 seconds, then exhale; after a 50 second wait the cycle was repeated until the whole cigarette was smoked. Most patients finished their cigarettes within 8 min. A dose modification was made only in the event of a dysphoric reaction, in which case all subsequent oral or smoked doses were decreased by one third for that patient. Placebo drug administration was handled in a similar fashion. Neither the patients nor the nursing staff was informed which drug was being administered.

PATIENT EVALUATION AND RESPONSE CRITERIA

Data collection for each trial started at 0700 h and lasted until 2400 h the day of chemotherapy. A member of the nursing staff rated the patient every hour by completing an objective questionnaire that measured number of vomiting episodes (an event producing > 30 mL of emesis), number of retching episodes, volume of emesis, degree of nausea (0 to 3 point scale: 0 = none; 1 = slightly; 2 = moderately; 3 = greatly), duration of nausea, and volume of oral intake. Similarly, once during each wakeful hour, the patient completed a subjective questionnaire rating the psychological "high" (0 to 3 point scale: 0 = none; 1 = slightly; 2 = moderately; 3 = greatly), degree of nausea, degree of comfort, and other drug side effects (questionnaire available upon request).

Four variables used to evaluate individual responses to THC and placebo were the number of vomiting and retching episodes, volume of emesis, degree of nausea, and duration of nausea. The nausea and vomiting variables on all completed paired THC trials and all placebo trials in Phase I were summed. An "excellent" response was defined as a > 80% reduction for all four nausea and vomiting variables on THC as compared to placebo. A "fair" response was defined as > 30% but < 80% reduction of at least three study variables while on THC. "No response" was defined as < 30% reduction of at least two study variables while on THC.

THC PLASMA CONCENTRATIONS

Five-milliliter aliquots of venous blood were drawn from a heparin lock placed in each patient the day of chemotherapy. Blood samples were drawn immediately before each THC or placebo dose and 1 hour later.

Within 6 h after collection in glass tubes, plasma was drawn off heparinized blood samples and subsequently stored at - 40 degrees Centigrade. Plasma samples were quantitatively analyzed for THC by Battelle Laboratories, Columbus, Ohio. The analysis was done by gas chromatography/chemical ionization-mass spectrometry ^(13, 14). Deuterium-labeled THC was used as an internal standard.

STATISTICAL ANALYSIS

Statistical analyses were restricted to Phase I of the study. The data were analyzed by three different methods. The first method, described by Koch ⁽¹⁵⁾, used only data for the first paired trial. This method tested whether the relative efficacy of THC or placebo depended on the order of administration in the first two trials, whether one drug was more effective than the other, and whether the effectiveness of both drugs changed from the first trial to the second. In the second method of analysis, for each study variable and each patient, the sum of the values of Phase-I paired trials in which THC was administered was subtracted from the sum of the Phase-I paired trials in which placebo was administered. The sign of this difference was ascertained for each patient and each variable and a sign test done. The third method of analysis consisted of a blocked Wilcoxon test for each variable in which the 15 patients determined the blocks. The data within each block consisted of the Phase-I paired trials for that patient. All significance levels correspond to two-tailed tests.

Table 1. Nausea and vomiting variables in Phase I ♥

Patient Number	Number of Paired Trials	Total and Vomiting Retching Episodes ♦		Total Volume of Emesis ♦		Total Degrees of Nausea ♦		Total Duration of Nausea ♦		Response to THC ♠
		THC	Placebo	THC	Placebo	THC	Placebo	THC	Placebo	
		numbers		milliliters		nausea points		hours		
1	2	15	23	790	2820	17	31	2.1	3.4	Fair
2	2	26	50	1000	2020	25	41	2.9	6.6	Fair
3 ♣	1	0	0	0	0	0	10	0	3.3	Excellent
4	3	0	99	0	1800	1	48	0	13.4	Excellent
5	3	4	31	195	1730	8	82	1.8	26.1	Excellent
6	1	2	21	75	690	2	21	0.3	8.6	Excellent
7 ♣	3	1	79	500	3020	5	41	0.2	10.8	Excellent
8	3	44	113	3950	4095	45	62	4.7	12.5	Fair
9	3	9	53	500	2605	5	33	0.6	3.0	Excellent
10	2	0	0	0	0	3	0	0.1	0	None
11	2	22	61	1100	1870	14	44	3.1	13.0	Fair
12	2	11	18	475	1250	12	27	0.3	5.4	Fair
13 ♣	2	0	12	0	600	2	31	0.2	5.9	Excellent
14 ♣	2	0	6	0	400	8	28	0.5	3.4	Fair

15	1	0	5	0	325	0	15	0	1.2	Excellent
		numbers			milliliters	nausea points			hours	
		THC	Placebo	THC	Placebo	THC	Placebo	THC	Placebo	
Patient Number	Number of Paired Trials	Total and Vomiting Retching Episodes ♦		Total Volume of Emesis ♦		Total Degrees of Nausea ♦		Total Duration of Nausea ♦		Response to THC ♠

♥ Sixty-four trials: 32 delta-9-tetrahydrocannabinol, 32 placebo.

♦ $p < 0.001$ (sign test and blocked Wilcoxon test).

♠ THC = delta-9-tetrahydrocannabinol

♣ No previous marijuana experience

RESULTS

Between August 1977 and September 1978, 19 patients with osteogenic sarcoma receiving high-dose methotrexate were approached for entry into the study. Fifteen patients agreed to participate. None of these patients was deemed ineligible for the study based on psychiatric evaluations. Four of the patients were inexperienced users marijuana before entering the study. The 15 patients completed a total of 97 drug trials in both Phase I and 11 58 THC and 39 placebo trials. A drug administration compliance rate of 96% was maintained throughout the study.

PHASE I

Table 1 lists the results of the 64 completed paired trials in Phase I. Each study variable represents the sum of all responses on THC trials and placebo trials completed by each patient. There was a reduction of nausea and vomiting in 14 of 15 patients. Eight of the 15 patients had an "excellent" response, specifically a > 80% reduction of all nausea and vomiting variables, while on THC. Six of the IS patients had a "fair" response to THC, namely a > 30% but < 80% reduction of at least three study variables. All four inexperienced marijuana users were "excellent" responders to THC.

Using the method of Koch (15) to analyze the first two trials, THC was found to be of statistically significant benefit for the number of vomiting and retching episodes ($p < 0.02$), degree of nausea ($p < 0.01$), duration of nausea ($p < 0.01$), and volume of emesis ($p < 0.01$). The difference for volume of oral intake approached, but did not achieve, statistical significance. For none of these variables was there any indication that response to THC and placebo changed uniformly between the first and

second trials. For the degree of nausea score, however, the relative efficacy of THC did significantly differ depending upon the order of administration ($p < 0.05$). The relative efficacy of THC in reducing the degree of nausea score was greater for Trial 1 than for Trial 2. For Trial 1 alone, THC was significantly better than placebo with regard to degree of nausea ($p < 0.01$). However, for Trial 2 the difference was not statistically significant. The results of the other two statistical tests applied were very similar to each other. With either of these tests THC was significantly better than placebo with regard to number of episodes of vomiting and retching, degree of nausea, duration of nausea, and volume of emesis ($p < 0.001$). With both tests, the differences in volume of oral intake between THC and placebo did not approach statistical significance.

Plasma concentrations from 18 THC trials along with the paired placebo trials were analyzed in 14 patients. To examine plasma concentrations each trial was divided into five 3-h time intervals beginning at each drug administration. Table 2 summarizes the plasma concentration determinations after oral and smoked THC doses. In placebo trials, where the plasma concentrations were 0 ng/mL, patients experienced nausea or vomiting, or both, in 65 of 90 time intervals, an incidence of 72%. On THC trials, plasma concentrations of < 5.0 ng/mL, 5.0 to 10.0 ng/mL, and > 10.0 ng/mL were associated with incidences of nausea or vomiting, or both, of 44%, 21%, and 6%, respectively. **The incidence of nausea and vomiting decreased with elevation of THC plasma concentrations.** It might be argued that the association of THC plasma concentrations to the incidence of nausea and vomiting is not causally related to an antiemetic effect of THC, but rather due to increased absorption of oral doses by the gastrointestinal tract in patients experiencing less nausea and vomiting from other causes. To address this issue, we examined plasma concentrations measured after smoked THC and placebo doses. Patients who vomited during the course of a trial were requested to smoke their remaining doses. The incidence of nausea and vomiting after the administration of placebo cigarettes was 96%. Smoked THC cigarettes resulting in plasma concentrations of < 5.0 , 5.0 to 10.0 and > 10.0 ng/mL were associated with incidences of nausea and vomiting of 83%, 38%, and 0%, respectively. All of the patients who smoked their THC doses were experienced cigarette smokers. **We concluded that elevations of THC plasma concentrations, achieved primarily by the inhalation route, also resulted in a reduced incidence of nausea and vomiting.**

Delta-9-Tetrahydrocannabinol (THC) Plasma Concentrations Compared to Incidence of Nausea and Vomiting

Table 2.

THC Concentration *	Time Intervals ♥	Time intervals with Nausea and Vomiting Present	Incidence of Nausea and Vomiting
------------------------	------------------	---	--

nanograms per milliliter	number	number	percentage (%)
0 ♣	90	65	72
< 5.0	43	19	41
5.0 - 10.0	29	6	21
> 10	18	1	6

♣Maximum THC concentration measured within 3 hours after each oral or smoked drug administration for 18 THC trials.

♥Three-hour time interval after each drug administration.

♠Eighteen paired placebo trials.

Table 3. Oral Versus Delta-9-Tetrahydrocannabinol (THC) Absorption

Dose Schedule	THC Blood Concentration ♥	
	Oral Doses (Number)	Smoked Doses (Number)
hour of day	nanograms per milliliter	nanograms per milliliter
0700	7.1 ± 6.9 ♠(18)	None
1000	6.4 ± 5.5 (15)	7.8 (2)
1300	4.3 ± 4.5 (15)	7.5 ± 1.8 (3)
1600	4.7 ± 6.2 (12)	7.1 ± 5.8 (6)
1900	4.5 ± 2.4 (10)	4.2 ± 3.5 (6)

♥Delta-9-tetrahydrocannabinol concentration measured 1 hr after administration of dose.

♠Mean ± 1 standard deviation

Despite a constant dose of THC given for each drug administration, absorption via the oral and inhalation routes was not uniform between patients or for individual patients. Thirty-one of 70 (44%) oral doses resulted in TI-IC plasma concentrations > 5.0 ng/mL 1 h after administration, with a range of 0 to 26.6 ng/mL. Table 3 lists the mean plasma concentrations achieved 1 h after oral and smoked doses from 18 THC trials. Oral absorption was greatest for the first two doses, with mean 1 h plasma concentrations of 7.1 and 6.4 ng/mL. Subsequent oral doses resulted in mean 1 h plasma concentrations of 4.3, 4.7, and 4.5 ng/mL. Mean 3-h plasma concentrations were consistently lower than mean 1 h values measured after oral and smoked doses. Variable absorption is suggested by the large standard deviations associated with each of the mean plasma concentrations. **The inhalation route was more reliable in achieving adequate blood concentrations:** 12 of 17 smoked doses resulted in plasma concentrations > 5 ng/mL 1 h after smoking, with a range of 0 to 13.6 ng/mL. In three of four scheduled doses, smoked THC resulted in greater mean plasma concentrations than did oral THC, with values of 7.8, 7.5, 7.1 ng/mL. There was no evidence of plasma accumulation of THC with repeated administration every 3 h.

Table 4. Subjective "High" Compared to Incidence of Nausea and Vomiting ♣

"High" ♥	Time Intervals ♠	Time Intervals with Nausea and Vomiting Present	Incidence of Nausea and Vomiting
	number	number	%
0 - 1	81	37	46
2	45	15	33
3	34	6	18

♣Thirty-two active trials.

♥0 = none; 1 = slightly; 2 = moderately; 3 = greatly

♠Three-hour lime intervals after each drug administration

Patients were asked to rate the magnitude of their psychological "high" on a 0-3 scale: 0 = none; 1 = slightly; 2 = moderately; 3 = greatly. Using time intervals similar to those employed to analyze the plasma concentrations, the patients' subjective "high" rating can be compared with the incidence of nausea or vomiting, or both. Table 4 lists the comparative results of the subjective "high" ratings with the incidence of nausea or vomiting, or both, in all THC trials of Phase I. In those time intervals in which patients rated their "highs" as 0 or 1, the incidence of nausea or vomiting was 46%. For "high" ratings of 2 and 3 the incidence of nausea or vomiting decreased to 33% and 18%, respectively. Therefore, the greater magnitude of the subjective "high" appeared to be associated with a decreased incidence of nausea or vomiting.

The subjective rating of comfort was recorded by each patient during each wakeful hour of the observation period. The patient was asked to rate comfort by choosing the following: very comfortable (2); somewhat comfortable (1); somewhat uncomfortable (-- 1); and very uncomfortable (-- 2). By summing the numerical scores associated with each response and dividing by the total number of responses, a mean comfort rating could be determined for all wakeful hours on THC and placebo trials for each patient. Figure 1 shows the mean comfort rating for all 15 patients on placebo and THC trials. All 14 patients who had a reduction of nausea and vomiting on THC also had an increase in their mean comfort rating. The one nonresponder patient had a decrease in comfort on THC compared to placebo.

[Webmaster note: Figure 1 involves more than tables and would not accurately scan into the computer with Textbridge Pro. The caption under Figure 1 states: Mean subjective comfort rating of 15 patients on placebo versus delta-9-tetrahydrocannabinol (Delta-9-THC) trials. Each line

represents one patient. All patients who had a reduction in nausea and vomiting on THC also had an increase in their mean comfort rating. The one nonresponder patient had a decrease in comfort rating on THC compared to placebo. See page 823 in the original article.]

SIDE EFFECTS

A common side effect of THC was sedation. When reviewing the patients' subjective responses during all of the trials, 12 of 15 patients rated themselves sleepier per hour on THC than on placebo. Short-lasting episodes of tachycardia in the range of 100 to 120 beats/mm and dizziness associated with orthostatic changes were occasionally noted. These episodes were well tolerated and required no specific medical intervention. Five dysphoric reactions occurred out of a total of 281 THC drug doses (2%). These reactions occurred in four patients, three of whom were experienced marijuana users. The reactions manifested themselves as short-lasting episodes (about 30 minutes) of anxiety (one patient), disorientation (one), paranoia (one), and depression (two patients). No other intervention besides reassurance of the patient was necessary to treat these adverse reactions.

OTHER OBSERVATIONS

Four "excellent" responders to THC have entered Phase II of the study. In contrast to Phase I, all four patients had only "fair" responses to repeated THC trials. Patient 4, for example, had almost complete elimination of nausea and vomiting while on THC during Phase I (see Table 1). In Phase II this patient completed an additional 12 trials (10 THC, two placebo) and had a 50% reduction in nausea and vomiting as determined by comparison of the average values of each study variable for the THC and placebo trials. Two patients entered Phase II of the study as "fair" responders to THC. These patients became nonresponders to THC despite an increased dose in accordance with the study protocol.

Five patients with resections of soft tissue sarcomas receiving monthly adjuvant doxorubicin and cyclophosphamide chemotherapy were also studied. Doxorubicin and cyclophosphamide were given at a constant dose of 70 and 700 mg/m², respectively. These patients were studied in the same manner as patients in Phase I who received high-dose methotrexate. Three of the patients have been nonresponders to THC and two, "fair" responders.

DISCUSSION

We have found that a combination of oral and smoked THC is a highly effective antiemetic compared to placebo in patients receiving high-dose methotrexate chemotherapy. This report confirms and extends earlier observations reported by Sallan and associates (7), who found oral THC

to be an effective antiemetic in patients receiving various chemotherapeutic agents (7). **In addition, it appears that the antiemetic effect of THC is associated with the THC plasma concentration after oral and smoked doses.** When compared with placebo, the incidence of nausea and vomiting was reduced to one third when THC plasma concentrations of 5.0 to 10.0 ng/mL were measured and to one tenth with THC plasma concentrations > 10.0 ng/mL. Similarly, elevations of THC plasma concentrations achieved primarily by the inhalation route were also associated with reductions in the incidence of nausea and vomiting. These data pertain only to patients receiving high-dose methotrexate at a dose of 250 mg/kg. Preliminary data indicate that the antiemetic effect of THC in patients receiving a combination of doxorubicin and cyclophosphamide may be less effective.

In our patients, as has previously been reported, oral doses administration of THC was associated with variable absorption from the gastrointestinal tract (16). Oral doses administered throughout the day resulted in a wide range of plasma concentrations between patients as well as for individual patients. Only 44% of the oral doses achieved plasma concentration > 5.0 ng/mL 1 h after drug administrations. Sallan and co-workers (7) considered inadequate drug absorption as a possible contributing factor to the lack of an antiemetic response seen in some patients. We concur, since THC plasma concentrations appeared to be causally related to an antiemetic response in our study. To avoid this problem, we switched patients to the inhalation route of drug administration when vomiting occurred. Inhaled marijuana results in the same psychological effects as orally administered THC (17). **In our patient populations, smoked THC was more reliable than oral THC in achieving therapeutic blood concentrations.** About 71% of the inhaled doses of THC resulted in plasma concentrations > 5.0 ng/mL 1 h after drug administration. Since all of our patients who smoked THC were experienced cigarette smokers, we could not determine whether nonsmokers would have absorbed inhaled doses differently. Although the inhalation method of THC administration avoids the ineffective route of oral drug administration in a nauseated or vomiting patient, it has some drawbacks in patient acceptability. Many patients complained of the adverse taste of smoked marijuana, which induced nausea and vomiting in a few instances. Also, patients who are nonsmokers may not be willing or able to smoke THC. Clearly, an alternative parenteral drug route needs to be established if THC is to have wide clinical acceptability.

In Phase II there was diminished effectiveness of THC as an antiemetic with repeated drug trials. Some reduction in THC effectiveness may be attributable to the normal variation of nausea and vomiting responses in a patient observed for multiple courses and to the fact that only THC responders were studied in Phase II. The very minimal course-to-course variation observed in Phase I for "excellent" responders would not, however, seem to account entirely for the reduced responses. McMillan and colleagues (18) have demonstrated in animals that infrequent doses of THC can result in tolerance, and this may account for our observations. Another possible factor is the development of anticipatory or conditioned

nausea and vomiting, which commonly occurs in patients receiving repeated courses of chemotherapy. Such patients, when exposed to treatment-related stimuli, become nauseated even before chemotherapy. The presence of anticipatory nausea or vomiting may make a patient more refractory to an antiemetic. Three of the six patients in Phase II developed these anticipatory responses as determined by questionnaires completed by every patient the day before each chemotherapy session. Our study was not designed to assess the ability of THC to prevent or reduce anticipatory nausea or vomiting.

The sedative effect of THC was documented in 80% of our patients. Sedation has been reported to be the commonest side effect of phenothiazine antiemetics as well (19). Moertel and Reitemeier (4) examined this side effect when comparing various phenothiazines as antiemetics. In their study, a sodium pentobarbital control was not any different from an inert placebo control in relieving nausea and vomiting induced by fluoruracil. Although the mechanism of THC's antiemetic effect is unknown, it would be unlikely to be due solely to its sedative properties.

Appetite stimulation has been reported after the smoking of marijuana (20, 21). To assess appetite, oral intake during each drug trial was measured. Oral intake on THC trials did not differ from that on placebo trials. The concomitant infusion of a chemotherapeutic drug may have precluded any appetite-enhancing actions of THC in our patient population.

Nabilone, a synthetic cannabinoid with minimal euphoriant effects capable of being administered parenterally, has been reported to have antiemetic properties in patients receiving chemotherapy (8, 9, 11). Unfortunately, additional data have indicated long-term animal toxicity that may preclude its clinical usefulness (11). At present, no available agents exist to substantially alleviate the nausea and vomiting associated with chemotherapy. Our data show that oral or smoked THC is an effective antiemetic in patients receiving high-dose methotrexate chemotherapy. The antiemetic action appears to be related to THC plasma concentrations as well as to the patient's psychological "high." A dose schedule of 10 mg/in² every 3 h for a total of five doses was associated with substantial therapeutic benefit and minimal toxicity.

Additional studies relating to THC drug tolerance, effectiveness against nausea and vomiting produced by other chemotherapy regimens, and comparisons with conventional antiemetics need to be done.

ACKNOWLEDGMENTS The authors thank the nursing staff of the National Institutes of Health Clinical Center 10 East ward for carefully collecting the clinical data; and Dr. Roger Foltz and Mr. Bruce Hidy for doing the delta-9-tetrahydrocannabinol plasma determinations.

Requests For reprints should be addressed to Alfred E. Chang, M.D.; Surgery Branch, National Cancer Institute, Building 10, Room 10N116; Bethesda, MD 20205.

Received 4 May 1979, revision accepted 29 August 1979.

REFERENCES

1. HARRIS JG. Nausea, vomiting and cancer treatment. *CA*. 1978; 28:1 94-201.
2. WHITEHEAD VM. Cancer treatment needs better antiemetics. *N Engl J Med*. 1975; 293:199-200. Letter.
3. MOERTEL CG, RETTEMEIER RJ, GAGE RP. A controlled clinical evaluation of antiemetic drugs. *JAMA*. 1963; 186:116-8.
4. MOERTEL CG, REITEMETER RJ. Controlled clinical studies of orally administered antiemetic drugs. *Gastroenterology*. 1969; 57:262-8.
5. MOERTEL CG, SCHUTT AJ, HAHN RG, OFALLON JR. Oral benzquinamide in the treatment of nausea and vomiting. *Clin Pharmacol Ther*. 1975; 18:554-7.
6. PLOTKIN DA, PLOTKIN D, OKUN R. Haloperidol in the treatment of nausea and vomiting due to cytotoxic drug administration. *Curr Ther Res Gun Exp*. 1973; 15:599-602.
7. SALLAN SE, ZINBERO NE, FREI E III. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med*. 1975; 293:795-7.
8. HERMAN TS, JONES SE, DEAN J, et al. Nabilone: a potent antiemetic cannabinol with minimal euphoria. *Biomedicine [Express]* 1977; 27:331-4.
9. NAGY CM, FURNES BE, EINHORN LH, BOND WH. Nabilone antiemetic crossover study in cancer chemotherapy patients. *Proc Am Assoc Cancer Res-Am Soc Clin Oncol*. 1978; 19:30. Abstract.
10. ISRAEL L, RODARY C. Treatment of nausea and vomiting related to anticancerous multiple combination chemotherapy: results of two controlled studies. *J Int Med Res*. 1978; 6:235-40.
11. HERMAN TS, EINHORN LH, JONES SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med*. 1979; 300:1295-7.
12. STILLMAN R, GALANTER M, LEMBERGEJS L, Fox 5, WEINGARTNER H, WYATT RJ. Tetrahydrocannabinol (THC): metabolism and subjective effects. *Life Sci* 1976; 19:569-76.

13. ETRICH R, FOLTZ RL. Quantitation of delta-9-tetrahydrocannabinol in body fluids by gas chromatography/chemical ionization-mass spectrometry: cannabinoid assays in humans. *Natl Inst Drug Abuse Monogr.* 1976; 7:88-95.
14. FOLTZ RL, CLARKE PA, HIDY BJ, LIN DCK, GRAFFEO AP, PETERSON BA. Quantitation of delta 9-tetrahydrocannabinol and 11-Nor-delta-9-tetrahydrocannabinol-9-carboxylic acid in body fluids by GC/CI-MS. In: VINSON JA, ed. *Cannabinoid Analysis in Physiological Fluids.* Washington, D.C.: ACS; 1979; 59-72. (ACS symposium Series 98).
15. KOCH GG. The use of non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics.* 1972; 28:577-84.
16. PEREZ-REYES M, LIPTON MA, TIMMONS MC, WALL ME, BRINE DR, DAVIS KR. Pharmacology of orally administered delta-9-tetrahydrocannabinol. *Clin Pharmacol Ther.* 1973; 14:48-55.
17. LEMBERGER L, WEISS JL, WATANABE AM, GALANTER IM, WYATT RJ, CAROON PV. Delta-9-tetrahydrocannabinol temporal correlation of the psychologic effects and blood levels after various routes of administration *N Engl J Med.* 1972;286:685-S.
18. McMILLAN DE, DEWEY WL, HARRIS LS. Characteristics of tetrahydrocannabinol tolerance. *Ann NY Acad Sci.* 1971; 91:83-99.
19. CLARKE RSJ, DUNDEE JW. Side effects of antiemetics: results of a class experiment. *Eur J Pharmacol.* 1971;14:291-300.
20. HOLLISTER LE. Hunger and appetite after single doses of marijuana, alcohol, and dextroamphetamine. *Clin Pharmacol Ther.* 1971; 12:44-9.
21. REGELSON W, BUTLER JR. SHULTZ J, KIRK T, PECK L, GREEN ML. Delta-9-tetrahydrocannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: BRAUDE MC, SZARA S, eds. *The Pharmacology of Marijuana.* New York: Raven Press: 1975:763.

Authors

ALFRED E. CHANG, M.D.; DAVID J. SHILING, M.D.; RICHARD C. STILLMAN, M.D.; NELSON H. GOLDBERG, M.D.; CLAUDIA A. SEIPP, R.N.; IVAN BAROFSKY, Ph.D.; RICHARD M. SIMON, Ph.D.; and STEVEN A. ROSENBERG, M.D., Ph.D.; Bethesda, Maryland

From the Surgery and Biometric Research Branches. Division of Cancer Treatment, National Cancer Institute; the Laboratory of Clinical

Psychopharmacology and Unit on Geriatric Psychiatry, Division of Special Mental Health Research, National Institute of Mental Health; and the Division of Research, National Institute on Drug Abuse; National Institutes of Health; Bethesda, Maryland.