Delta-9-Tetrahydrocannabinol as an Antiemetic for Patients Receiving Cancer Chemotherapy

A Comparison with Prochlorperazine and a Placebo

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The antiemetic activity and side-effects of delta-9-tetrahydrocannabinol (THC) were evaluated in 116 patients (median age 61 years) receiving combined 5-fluorouracil and semustine (methyl CCNU) therapy for gastrointestinal carcinoma. In a double-blind study, patients were randomized to receive THC, 15 mg orally three times a day, prochlorperazine, 10 mg orally three times a day, or placebo. The THC had superior antiemetic activity in comparison to placebo, but it showed no advantage over prochlorperazine. Central nervous system side-effects, however, were significantly more frequent and more severe with THC. With the dosage and schedule we used, and in our patient population of largely elderly adults, THC therapy resulted in an overall more unpleasant treatment experience than that noted with prochlorperazine or placebo. Although THC may have a role in preventing nausea and vomiting associated with cancer chemotherapy, this role must be more clearly defined before THC can be recommended for general use.

CHEMOTHERAPY-INDUCED nausea and vomiting are a major problem both for the cancer patient and the chemotherapist. This problem is occasionally so great that the patient may voluntarily withdraw from a beneficial chemotherapy program. In addition to the effect of chemotherapy, the physician must contend with various emotional and mental factors that may augment the nausea and vomiting experienced by these patients.

Although the 1979 *Physicians' Desk Reference* lists 33 marketed antinauseants, very few have proved valuable against the nausea and vomiting induced by chemotherapeutic agents. Only the phenothiazines have shown consistent effectiveness in controlled clinical trials, but the magnitude of their effectiveness is usually inadequate to ensure the comfort of patients treated with cytotoxic drugs having strong emetic side-effects (1-3). The need for more effective antiemetic treatment under these circumstances is grossly apparent.

Cannabis sativa, the plant from which marijuana is derived, has been used for medicinal purposes over 5000 years (4). Cannabis is a collective term used to describe all the biologically active products, including marijuana, derived from this ubiquitous plant. Nahas (5), in his comprehensive review of marijuana, notes that the use of cannabis has been continually marked with controversy as evidenced in ancient India where the Brahmans tried in vain to restrict the use of cannabis to religious purposes, whereas the commoners prized it as an inebriant. The prospect of the possible value of cannabis derivatives as antiemetic agents has been raised because of anecdotal reports from younger cancer patients that smoking marijuana seemed to ameliorate the nausea and vomiting induced by cancer chemotherapy.

The active principle of marijuana, which is thought to be responsible for its psychoactive and other physiologic properties, is delta-9-tetrahydrocannabinol (THC) (6). Oral THC has been shown to cause the same physiologic effects as smoking marijuana (7, 8). In 1975, Sallan, Zinberg, and Frei (9) reported significant antiemetic activity of oral THC in comparison to placebo in a study of 20 evaluable patients receiving cancer chemotherapy with a variety of agents. This study, however, was limited in scope because it primarily involved young patients (median age, 29 years), several of whom were known marijuana users, and it did not involve a control group treated with a standard antiemetic of known effectiveness. Our study was undertaken to expand observations of THC as an antiemetic agent using a larger population of patients within the more typical cancer age groups and to compare the antiemetic effects and side-effects of THC with those of prochlorperazine, which is probably the most commonly marketed agent for prophylaxis of nausea and vomiting induced by chemotherapy.

Materials and Methods

All patients were selected for study while undergoing their initial chemotherapy exposure to combined 5-fluorouracil and semustine (methyl CCNU) either as a two-drug combination or in three-drug combinations with vincristine, doxorubicin (adriamycin), razoxane (ICRF 159), or triazinate. Patients selected for study were at least 21 years old with either unresectable gastrointestinal cancer or were participants in gastrointestinal cancer surgical adjuvant programs. All were ambulatory outpatients. A pretreatment oral intake of at least 1500 calories daily was required, and patients could not have been experiencing nausea or vomiting before entry into the study. Any patient taking psychotherapeutic agents or other antiemetics was excluded from study. A past history of drug dependence or a significant psychological disturbance was also grounds for exclusion. No patient was known to be a user of marijuana. 5-fluorouracil was given intravenously for 5 consecutive days at dosages of from 300 to 350 mg/m^2 of body surface area per day,

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Table 1. Patient Characteristics According to Antiemetic Study Drug

Characteristic	Drug		
	Placebo	Prochlorperazine	THC*
	← no. →		
Sex: male/female	27/10	21/20	22/16
Age; *yrs*			
21–39	2	3	3
40–49	4	4	2
50–59	15	10	14
60–69	10	17	10
70+	6	7	9
Primary neoplasm			
Colorectal	27	29	28
Gastric	8	11	7
Liver	2	1	2
Miscellaneous	0	0	1
Gastric surgery	1	4	5
Hepatic metastasis	18	17	20
Chemotherapy regimen†			
5-FU + semustine	13	10	9
5-FU + semustine + VCR	9	11	5
5-FU + semustine + TZT	2	1	8
5-FU + semustine + razoxane	8	9	7
5-FU + semustine + doxorubicin	5	10	9
Performance status (ECOG score‡)			
0	8	14	10
1	21	23	19
2	7	2	9
3	1	2	0

* THC = delta-9-tetrahydrocannabinol.
† 5-FU = 5-fluorouracil; VCR = vincristine; TZT = triazinate.
‡ Eastern Cooperative Oncology Group score: 0: fully active, to 4: totally disabled.

and semustine was given orally on Day 1 at dosages from 110 to 175 mg/m^2. Study observations were carried out only on the first 4 d of treatment. Thus, patients were exposed to a strong emetic stimulus (semustine plus 5-fluorouracil) on Day 1 and a weaker stimulus (5-fluorouracil alone) on Days 2 to 4. Patients were studied only during their first course of chemotherapy.

After they had signed an informed-consent form, patients were randomized to receive prochlorperazine, 10 mg; THC, 15 mg; or placebo (lactose). Patients were told that THC was the active principal of marijuana. The dosage of THC was chosen to duplicate that previously used by Sallan and colleagues (9). Patient treatment assignments were determined by sequential entry on a list of antiemetic treatments arranged in random order and identified only by code number. Each antiemetic drug or placebo was prepared in identical opaque gelatin capsules. The drugs were dispensed in individual packets identified only by code number. On Day 1, the initial dose of antiemetic was given 2 h before the initiation of chemotherapy. Subsequent doses were then given 2 h and 8 h after the initiation of chemotherapeutic treatment. On the remaining 3 study days, the antiemetic agents were given three times daily, ½ h before each regular meal. Patients were seen by a physician each day. They were first allowed to volunteer information on the occurrence of such problems as nausea, vomiting, sedation, incoordination, "highs," or any other side-effects by a general question regarding their well-being. They were then specifically queried regarding the occurrence of these problems during the preceding 24-h period. For the purposes of this study, a "high" was defined as a euphoric, dreamy, floating type of feeling. Our definition of a coordination problem was rather broad and encompassed any abnormality that upset the smooth, synchronous, relation between mind and body necessary for the normal functioning of the person.

The occurrence of nausea and vomiting was noted each day in the following manner: no nausea or vomiting; nausea mentioned only on questioning; nausea a significant symptom; vomiting only once during the preceding 24-h period; or vomiting two or more times. On Day 1 the number of times a patient vomited was recorded. On Days 2 to 4, any patient who vomited more than two times was judged a treatment failure and withdrawn from study. Sedation, coordination problems, or "highs" were specifically recorded each day as were any other side-effects mentioned by the patients.

Results

One hundred seventeen patients were randomized to receive either THC, prochlorperazine, or placebo. One patient was disqualified from study after inadvertently taking another antiemetic agent on Day 1. Thus, 116 patients were evaluable for study purposes. Patient and treatment characteristics are displayed in Table 1 according to treatment assignment. The three treatment arms appeared to be reasonably homogeneous. The majority of patients were in their sixth and seventh decades of life, with a median age of 61 years.

A comparison of the antiemetic effectiveness of these agents on Day 1 is shown in Table 2. The results of Day 1 are analyzed separately because the strong emetic stimulus, semustine, was administered on this day in contradistinction to Days 2 to 4 when only the weak emetic stimulus, 5-fluorouracil, was given. On Day 1 a significantly higher percentage of placebo patients experienced some nausea and vomiting than patients in the other two study groups ($P=0.05$, chi-square test). The antiemetic effect of THC was almost identical with that of prochlorperazine. The comparative effectiveness of the three study drugs on Days 2 to 4 is also shown in Table 2. Note that 18 patients were dropped from the study after Day 1 because of intolerable central nervous system toxicity or excessive vomiting. Ten of these patients had been assigned to THC, five to prochlorperazine, and three to placebo. Although the percentage of patients experiencing no nausea or vomiting on Days 2 to 4 was higher for the prochlorperazine group, this was not statistically significant

Table 2. Occurrence of Nausea and Vomiting in the Three Groups

	Placebo	Prochlorperazine	THC*
	← % →		
Day 1 (strong emetic stimulus)†	37 patients	41 patients	38 patients
None	19	42	42
Nausea only	16	2	5
Nausea and vomiting	65	56	53
Days 2–4 (weak emetic stimulus)‡	34 patients	36 patients	28 patients
None	53	72	57
Nausea only	29	14	21
Vomiting	18	14	21

* THC = delta-9-tetrahydrocannabinol.
† Chi square (4) = 9.547; $P = 0.049$.
‡ Recorded only for the 1 day when severity was greatest. Chi square (4) = 3.653; $P = 0.455$.

Table 3. Rate of Occurrence and Severity of Side-Effects in the Three Groups

Side-Effect*	Placebo (37 Patients)	Prochlorperazine (41 Patients)	THC† (38 Patients)
	← % →		
Sedation‡			
None	54	29	24
On questioning	30	41	26
Volunteered	16	27	45
Intolerable	0	2	5
Coordination problems§			
None	81	90	29
On questioning	14	10	24
Volunteered	3	0	16
Intolerable	3	0	32
"High"‖			
None	100	88	42
On questioning	0	7	24
Volunteered	0	5	34

* Determined on the one day out of the 4-d period when side-effects were most severe.
† THC = delta-9-tetrahydrocannabinol. Complete data obtained on 36 of 38 patients for sedation, on 37 of 38 for coordination problems, and on 36 of 38 for "high".
‡ Chi square (4) = 13.933; $P = 0.0075$.
§ Chi square (4) = 45.253; $P < 0.0001$.
‖ Chi square (4) = 40.079; $P < 0.0001$.

($P=0.22$, chi-square test). There was no suggestion of antiemetic effect for THC during this latter part of the study period.

In addition to testing antiemetic effectiveness, the study was designed to compare the toxicities of the three study drugs. Table 3 shows the highest degree of sedation experienced by those in the three study groups during the entire 4-d observation period. The three treatment groups had significantly different distributions of maximum sedation scores ($P=0.007$, chi-square test) with those in the THC group experiencing a much higher degree of sedation than those in the other two groups.

The severity of coordination problems experienced by the study participants during the study period also is shown in Table 3. There were significantly different distributions of maximum incoordination scores among the three treatment groups ($P < 0.0001$), again with the overwhelming majority of these problems occurring in the THC group. The degree of "high" experienced among the study participants during the study period is shown in Table 3. Again, the three treatment groups had significantly different distributions of maximum scores ($P < 0.0001$). Of those experiencing a marked "high" feeling, the overwhelming majority had received THC.

Fourteen patients refused to continue on study because of intolerable central nervous system side-effects. One of these patients was treated with placebo, one with prochlorperazine, and 12 with THC. This latter group represents 32% of the 38 patients assigned to THC. The specified THC side-effects documented in those patients who found continued treatment intolerable are listed in Table 4. Most of these patients had a multiplicity of debilitating side-effects.

Table 5 relates the occurrence of all disabling side-effects, either related to antiemetic therapy or chemotherapy, according to antiemetic study drug assignment. For this table antiemetic side-effects were considered disabling if they required the patient to discontinue study participation. Chemotherapy side-effects were considered disabling if the patient had repeated nausea and vomiting on any one day of the treatment program. From an overall standpoint patients treated with THC had a more disagreeable therapeutic experience than those treated with prochlorperazine or even with placebo.

A number of study factors that might have affected the antiemetic results and toxicity seen in our trial were analyzed using chi-square tests of independence. These factors included sex, age group, primary tumor, pretreatment disability, the presence of hepatic metastasis, liver function tests (alkaline phosphatase, serum glutamic-oxaloacetic transaminase), and the specific chemotherapy regimen to which the patient was assigned. The only positive associations noted were between sex and "highs" and between liver metastasis and coordination problems. There was a significant ($P=0.02$) association between sex and occurrence of "highs," with women experiencing relatively more "highs" than men. Overall, women tended to have more toxicity, including sedation and coordination problems, than men. In our study age did not appear to have any significant effect on THC toxicity, but only eight patients (7%) were less than 40 years old so that a very meaningful difference easily could have been missed. Liver metastasis did show some association with coordination problems. However, analysis of the alkaline phosphatase and serum glutamic oxaloacetic transaminase values did not confirm this. When doing 32 tests of association, obtaining small P values in one or two tests would not be unlikely when, in fact, no real associations exist. Thus, the association between liver metastasis and incoordination seems spurious. Using a similar analysis technique we attempted to correlate the occurrence of central nervous system side-effects with antiemetic effect, but we could not find any significant relation. Specifically, we could not confirm the findings of Sallan and associates (9) that the occurrence of a "high" implied that the patient would have a superior antiemetic result.

Pharmacologic Studies

As an addendum to this study nine patients receiving 5-fluorouracil-semustine treatment for various gastrointestinal neoplasms received known THC as an antiemetic, and serial blood samples were drawn to study the plasma levels of THC. The analysis was done by Battelle

Table 4. Nature of Side-Effects in 12 Patients Who Considered THC Therapy Intolerable

Toxic Effect	Number of Patients
Ataxia	7
Hypotension	3
Visual hallucinations	2
Blurred vision	2
Muddled thinking	2
Paresthesias (face and extremities)	2
Depression, anxiety, nightmares, amnesia, fainting, slurred speech, fecal incontinence	1 each

Table 5. Occurrence of Disabling Side-Effects of Chemotherapy or Antiemetic Agent According to Study Drug*

Condition	Placebo (*N* = 37)		PCP (*N* = 41)		THC (*N* = 38)	
	no.	(%)	*no.*	(%)	*no.*	(%)
CNS side-effects	1	(3)	1	(2)	12	(32)
Repeated vomiting	20	(54)	18	(44)	17	(45)
Total disabled	20	(54)	19	(46)	24	(63)

* PCP = prochlorperazine; THC = delta-9-tetrahydrocannabinol.

Laboratories of Columbus, Ohio, using a gas-chromatographic/chemical ionization-mass spectrophotometry technique (10). These patients were assessed after a 15 mg-dosage of THC given 2 h before the initiation of chemotherapy. The results are summarized in Table 6. Peak levels in this group of patients ranged from 2.7 to 6.3 ng/mL (median, 4.0 ng/mL), and the time of occurrence of peak levels after THC administration ranged from 1 to 6 h (median, 1 h). A similar wide variability is shown in absorption and disappearance rates. Only one patient (Patient 5) vomited, and this patient had one of the highest THC serum levels. The mean peak level for patients experiencing central nervous system side-effects was 4.2 ng/mL and for those with no side-effects, 4.9 ng/mL. In this small group of patients no correlation could be established between THC serum levels and either side-effects or antiemetic effects.

Subtotal gastrectomy appeared to have no consistent effect on rate of absorption of THC. A single patient (Patient 1) had hepatic metastasis with severe impairment of liver function and deep jaundice. Plasma levels of this patient are illustrated in Figure 1A. Absorption of THC was very delayed and elevation of plasma levels prolonged after a single 15-mg dose in contradistinction to the other two patients with liver metastasis but with no impairment of liver function (Patients 2 and 3).

Plasma THC levels were also measured in three patients without hepatic metastasis receiving THC in the same dosage and schedule as those patients in our controlled study (Figure 1B). Peak plasma levels also varied markedly in these patients, but the time of peak levels after drug administration and the patterns of disappearance were similar. For each of these patients there was a delay in absorption rate after the second dose compared to that after the first dose, and peak levels were lower in two of three patients. In Patient 8 the peak level was reduced strikingly from 5.5 ng/mL to 2.1 ng/mL. Plasma levels in these three patients measured 24 h after administration of their first THC dose failed to reveal detectable THC.

Discussion

Under the specific conditions of our study, THC did show evidence of antiemetic activity. However, the antiemetic effectiveness was certainly not superior to that of a standard phenothiazine antiemetic, prochlorperazine. In addition, the occurrence of significant toxicity, often intolerable, would make such treatment unattractive if equally effective, but less toxic, agents were available.

Nahas (5), in his review of the clinical pharmacology of cannabis, cites a number of factors that are important in interpreting the results of clinical studies with this agent. These factors include dosage of active drug, route of intake (ingestion or inhalation), previous experience of the subject with the drug, frequency of intake, development of tolerance, individual genetic characteristics regulating hepatic and pulmonary enzyme induction by delta-9-THC and the formation of other active metabolites, intake of other drugs that stimulate or inhibit this enzyme induction, mood of the subject, and the setting in which the drug is taken. Obviously, control of all of these variables would be next to impossible in any clinical study.

Two other antiemetic trials comparing THC and placebo in a relatively small number of patients have suggested a strong antiemetic effect of THC with very tolerable toxicity (9, 11). Because of the basic differences in study design, making meaningful comparisons of the results obtained in these two studies and ours would be impossible. However, some aspects of these studies should be scrutinized closely to provide pertinent directions for further trials of THC aimed at defining its role as an antiemetic.

The median age of patients in these two studies (29.5 and 24 years) was much less than that in our own study (61 years). Because of the relatively young population comprised by these two studies, it is not surprising that many of the patients had admitted to previous use of marijuana. The factors of age and previous marijuana experience could affect the results of these studies through not only differences in social acceptability and expectations of treatment but also differences in the meta-

Table 6. Pharmacologic Studies of Delta-9-Tetrahydrocannabinol (THC)

Patient	Primary Tumor	Liver Metastasis	THC Side-Effects	Peak THC Serum Levels		Comments
				ng/mL	*time, h*	
1	Gallbladder	Yes	+	3.6	6	Deep jaundice
2	Stomach	Yes	+	3.7	2	No gastric surgery Normal liver function
3	Colon	Yes	0	4.0	1	Normal liver function
4	Stomach	No	0	2.7	4	Subtotal gastrectomy
5	Stomach	No	+	5.0	1	Subtotal gastrectomy
6	Colon	No	+	4.0	2	
7	Colon	No	0	6.3	1	
8	Stomach	No	+	5.5	1	Subtotal gastrectomy
9	Colon	No	+	3.3	1	

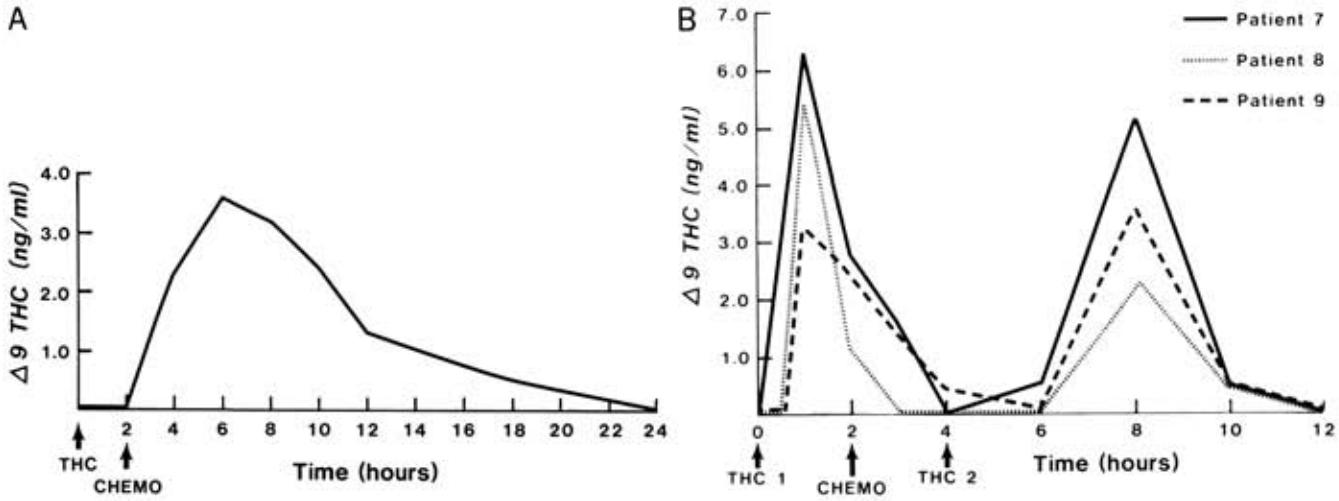

Figure 1A. Plasma levels of delta-9-tetrahydrocannabinol (*THC*) after a single 15-mg dose in a patient with adenocarcinoma of the gallbladder and severe impairment of liver function (direct bilirubin, CHEMO=chemotherapy, 15 mg/dL). **B.** Plasma levels of delta-9-THC in three patients with gastrointestinal malignancies who received two doses of 15 mg at a 4-h interval.

bolic handling of THC. Previous marijuana use may influence the subsequent catabolism through an enzyme induction mechanism (5). The formation of certain psychoactive catabolites by this mechanism may be needed for the mood alterations observed with THC. This pathway could explain the lack of any notable mood change with the first marijuana experience in contradistinction to that noted with its subsequent use. In addition, a depersonalization reaction could be entirely acceptable or even desired by a person with previous marijuana experience whereas this same reaction could be devastating to an older person. Because malignant tumors have a relatively higher frequency in older persons, it is important that an antiemetic effective against chemotherapy-induced nausea and vomiting be well tolerated in this age group.

These various studies suggest also that dose level may be an important consideration in THC trials. In the study by Sallan and associates (9), 13 of 16 patients receiving THC at a dose of 15 mg three times a day experienced a "high" defined as easy laughing, elation, heightened awareness, aberration of fine motor coordination, and minimal distortion of their activities. These effects were described as relatively mild, with none necessitating discontinuation of the study. However, two of 16 patients receiving a higher dose, 20 mg three times a day, had more marked toxicity consisting of visual distortions. In Chang and colleagues' study of 15 patients with osteogenic sarcoma receiving high-dose methotrexate therapy, treatment consisted of oral THC at a dosage of 10 mg/m^2 of body surface area every 3 h for a total of five doses, a much higher dosage than given in either our study or that of Sallan and colleagues. The commonest side-effects were sedation, occasional cardiovascular problems manifest as dizziness, orthostatic hypotension, and five dysphoric reactions consisting of anxiety (one instance), disorientation (one), paranoia (one), and depression (two). These reactions were transient, and only reassurance was needed for their treatment.

Noyes, Brunk, and Avery (12) studied the analgesic properties of oral THC in a group of 34 advanced cancer patients (median age, 51). Single oral doses of 10 and 20 mg were administered and the analgesic effectiveness and toxicities evaluated. Prominent central nervous system side-effects were frequently noted in the patients given the 20-mg dose. Those receiving the 10-mg dose had a lower incidence of these problems. That approximately 20% of patients in this particular study experienced nausea or vomiting or both at the 20-mg dosage level was notable. Most patients voiced a particular dislike for the toxicity related to the 20-mg dose. The authors concluded that THC was highly sedating and produced many mental side-effects, which in a single 20-mg dose prohibited its therapeutic use. The effects of a 10-mg dose of THC were relatively mild and of shorter duration. The characteristics of the study by Noyes and colleagues, including an older age group of advanced cancer patients, paralleled our investigation somewhat more closely than the other two trials mentioned previously. The toxicity spectrum in the analgesic study likewise reflected that noted in our investigative trial.

In addition to age and dosage, the setting of the study could be of major importance. Our study was conducted on an outpatient basis. An outpatient experiencing perceptive or thinking difficulties might experience much more anxiety than an inpatient, who is in much closer contact with the hospital and its personnel and would perhaps feel less threatened. However, an acceptable antiemetic should be suitable for outpatient usage also.

There is a distinct possibility that different chemotherapeutic agents may induce nausea and vomiting through different physiologic pathways, thus rendering an antiemetic that is beneficial for one drug completely ineffective against another. Several chemotherapeutic agents were used in the reported THC antiemetic studies. The finding by Chang and colleagues that patients receiving cyclophosphamide and doxorubicin seemed more refractory to the antiemetic effects of THC than those receiving methotrexate may lend credence to this concept.

Another factor that might influence the effectiveness of THC therapy is the ability of the patient to absorb the

drug. It is possible that our particular population of gastrointestinal cancer patients could have had impaired absorption of THC reflected by the lower peak plasma levels in comparison with the study of Chang and associates. They believed that antiemetic effectiveness increased with peak plasma levels of 5.0 ng/mL or higher. Only 26% of the oral THC doses in our pharmacologic study achieved this level, compared with 44% of the oral doses and 71% of the inhaled doses in Chang and colleagues' osteogenic sarcoma patients. We were unable to confirm an association between antiemetic effectiveness and a particular plasma level of THC in the relatively small population of nine patients on whom pharmacologic data was obtained. However, many of the THC patients in the controlled study apparently absorbed sufficient amounts of THC to render them toxic.

Based on the data of Chang and associates one might argue that the inhalation route would be the most efficacious method to utilize THC. However, the preparation of standardized THC cigarettes is quite tedious, and many patients would find this route unacceptable. Smoking the substance we know as marijuana (a combination of over 300 chemical agents, some inherently carcinogenic) would not be an acceptable substitute for THC either. Interestingly, the actual smoking of THC caused nausea and vomiting in some of the patients as reported by Chang and colleagues.

Before THC can be recommended for general use as an antiemetic, several critical areas need to be clarified. The recent experience with the synthetic cannabinoid, nabilone, illustrates the need for documenting the effects of chronic THC therapy (13). Although early trials with nabilone indicate antiemetic activity, chronic administration of this drug to animals has shown serious central nervous system toxicity. Optimum therapeutic but safe dosage levels that would be amenable to outpatient use must be worked out for older patients. More needs to be learned about the absorption and metabolism of THC and other cannabinoids. The toxicity and potential therapeutic value of these metabolites should be studied also. According to available data, a more uniformly absorbed cannabinoid would be most beneficial. The question of whether extended use of THC may cause tolerance to its antiemetic properties needs exploration also. In addition, the drug should be tested against various therapeutic combinations to see which may be amenable to its antiemetic effects. Future antiemetic testing of THC or other cannabinoids to compare their efficacy against standard agents must continue to utilize patients who have not been classified as failures on the more standard antiemetics. Only then can a true comparative picture of the antiemetic efficacy of the cannabinoids be obtained.

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