PERSPECTIVE

Delta-9-Tetrahydrocannabinol in Cancer Chemotherapy: Research Problems and Issues

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A critical review of the literature assessing the antiemetic efficacy of delta-9-tetrahydrocannabinol (THC) in patients receiving cancer chemotherapy showed considerable inconsistency in results. The equivocal nature of these results partly reflects the difficulty of doing research on antiemetic therapies, but also can be attributed to differences in the adequacy and nature of the research designs, procedures, and assessment instruments that have been used. Several factors were also identified that are seldom studied but may be important in determining whether THC will be effective: patient variables, such as chemotherapy regimen and age; pharmacologic variables, such as drug tolerance, dose, schedule, toxicity, route of administration, and drug interactions; and environmental variables associated with administration setting. The need to differentiate pharmacologically induced from conditioned nausea and vomiting was also pointed out. We believe that THC does have antiemetic efficacy, but the lack of controlled research does not allow precise knowledge of its true effectiveness and toxicity. Well-controlled trials are needed to help answer some of these questions.

CHEMOTHERAPY has been established as a useful therapy for many kinds of cancer (1). Together with surgery and radiation therapy, chemotherapy has been responsible for increasing life expectancy and hope of cure for many patients with cancer. The appeal of this therapy has been attenuated, however, by several side effects, one of the commonest being severe nausea and vomiting (2, 3). Unfortunately, the use of standard antiemetics, such as the phenothiazines, has not been sufficient in controlling these side effects (4, 5). This failure has resulted in many patients refusing to continue their chemotherapy treatments, and a reduced quality of life for those who do continue chemotherapy. An urgent plea for a more effective antiemetic treatment to supplement cancer chemotherapy has been voiced by oncologists (6), oncology nurses (7), as well as by patients with cancer (8).

Whereas traditional antiemetic agents have not been effective in most patients receiving chemotherapy, anecdotal reports of the effectiveness of marijuana in alleviating chemotherapy-induced nausea and vomiting suggested its potential usefulness as an antiemetic therapy. Subsequent clinical research has provided much information on the antiemetic effectiveness of delta-9-tetrahydrocannabinol (THC), the active ingredient in marijuana; 17 studies testing its effectiveness have been completed to date (9-25) (Table 1). Controlled studies have compared the antiemetic effectiveness of THC to that of several other treatments, including a placebo (9, 10, 12, 13, 17, 19, 20), prochlorperazine (11, 12, 17, 18, 20, 21, 25), metoclopramide (11, 14, 24), haloperidol (22), and thiethylperazine (14).

Unfortunately, the results of the studies assessing the antiemetic efficacy of THC have not yielded a clear conclusion. Ten studies have reported THC to be superior to another antiemetic drug or placebo (9-11, 13, 15-18, 21, 23). These studies have reported success rates (percent of patients responding to THC therapy) ranging from 59% (18) to 93% (10). Conversely, seven studies have reported that THC is either ineffective or no better than other antiemetic agents (12, 14, 19, 20, 24, 25). In general, when THC has been found to be only equivalent to other antiemetics, its use has been discouraged due to the presence of untoward side effects. Regrettably, variations in research design, patient populations, and pharmacologic variables make it difficult to compare studies that claim THC efficacy with others that report no antiemetic benefit. Moreover, even in studies that have reported THC effectiveness, it is not possible to isolate the specific variables that predict THC efficacy. Thus, despite the burgeoning literature on the antiemetic effectiveness of THC, many questions regarding the use of this controversial drug remain.

The equivocal nature of these studies can be partially understood by considering three limiting factors in the development of this research area. First, although THC can now be obtained rather easily, previous research was hindered by political and legal deterrents to the acquisition of the drug (26, 27). Second, antiemetic research in general is a very young endeavor, with only six studies reported before 1976 (28). Thus, it is not surprising that many investigations in this area are intended as preliminary pilot investigations rather than as rigorously designed experiments. Finally, research on antiemetic therapy for patients on chemotherapy is a very difficult endeavor. Antiemetic treatment is only one component of a very complex patient care system. Moreover, because antiemetic treatment is secondary in importance to the treatment of the disease, it is often not possible to allow the needs of the antiemetic study design to take precedence over other factors in determining how the patient is treated. Consequently, and not surprisingly, this research has not been conclusive and needs further refinement.

Poster and his colleagues (29) recently reviewed the

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results of many of the THC studies. We focus on the methodologic difficulties that have limited many of the previous studies and critical variables that may influence the antiemetic effectiveness of THC. Increased attention to these issues will strengthen future THC antiemetic research and help to resolve much of the ambiguity and controversy that now surrounds the use of THC as an antiemetic agent in patients receiving cancer chemotherapy.

Methodologic Considerations

Much of the research that has investigated the effectiveness of THC as an antiemetic therapy is flawed by methodologic problems that fall into one of two categories: problems related to experimental design, and problems with the definition and measurement of antiemetic "efficacy."

ANALYSIS OF ANTIEMETIC STUDY DESIGNS

The randomized, "double-blind," crossover design has been the most frequently used design in THC antiemetic research (9-11, 13-15, 17-19, 21, 22, 25). This design includes three components, which are recognized as methodologic strengths. Both the randomization and the double-blind components protect against threats to internal validity, to ensure that the alteration of the independent variable caused change in the dependent variable. The crossover component can increase the power of an experimental test (the probability of detecting true differences between differing treatments).

Randomization: Randomization is attained when only chance determines the order in which treatments are received (crossover designs) or the treatment group to which a subject is assigned (between-subject designs). Randomization helps to preserve the internal validity of a study. In a randomized crossover design, two procedures should be followed to control for the order in which the drugs are given. First, the sequence of treatment courses should be counterbalanced. For example, in a three-session study comparing THC and prochlorperazine, the presentation of treatments might be varied as follows: THC-prochlorperazine-THC, THC-prochlorperazine-prochlorperazine, prochlorperazine-THC-prochlorperazine, prochlorperazine-THC-THC, with each order being given to an equal number of patients. Second, each patient should receive more than one crossover (that is, THC-prochlorperazine-THC rather than THC-prochlorperazine). In a randomized non-crossover design, patients are often matched on important clinical variables (such as chemotherapy regimen) before the random assignment to treatment groups (that is, to THC or prochlorperazine). Matching helps to assure that the groups are equivalent on these variables before manipulation of the independent variable. Although some investigators (24) have matched subjects on one or more variables, other investigators apparently have not (12, 20).

Double-Blind Studies: The "double-blind" design is a method of investigation in which neither the patient nor the investigator know which pharmacologic agent, if any, the patient is receiving. This design is generally accepted as the preferred research method in drug trials because it controls for experimenter bias and for the effects due to patient expectation. However, the double-blind design can produce some problems, especially when THC is involved. Studies of THC using a double-blind design can be difficult to administer in a clinical setting. For example, Ungerleider and associates (25) reported that the uncertainty of patients who did not know which drug they were receiving was so threatening that one third of the patients refused to continue in the study. These patients generally indicated that they "would rather take a known, though ineffective, antiemetic [prochlorperazine] than not to be told which drug they were being given." Some patients, after having read the potential side effects of THC on the consent form, begin to experience these side effects even when given prochlorperazine. Also, the double-blind design is often transparent: Both patients and nurses are able to correctly determine which drug is being administered (30). Finally, although a true (that is, nontransparent) double-blind study adds rigor to the identification of the pharmacologic effects of a drug by eliminating any effects due to expectancy or other "nonspecific" factors, it does not directly address the clinical effectiveness of a drug because nonblind procedures are generally used in a treatment setting. For example, it is possible that even if THC were shown to have considerable antiemetic efficacy, some people would refuse to take it in a clinic situation.

Two researchers (16, 23) have chosen to use a procedure that is not randomized or double-blind, arguing that it is difficult to keep patients "blinded" when using THC because the effects of THC are markedly different from those of a placebo pill or any antiemetic agents previously taken. In these studies, only patients who previously had had severe nausea and vomiting refractory to even the most aggressive, standard antiemetic treatments were selected. In this way, carefully screened patients served as their own control without having received a standard antiemetic trial within the actual study. Although this method represents a pragmatic clinical decision, it presents difficulties for the interpretation of results because it does not control for expectation or suggestion effects. That is, patients who respond to THC therapy might be responding to the enthusiasm of the primary caregiver. This design could be strengthened considerably by including self-report measures of expectancy, which could subsequently be partialed out of the outcome data, and a baseline period to verify the stable nature of the nausea and vomiting problem. After a stable baseline had been established, the treament (that is, THC) should then be applied. If a change occurs, the withdrawal of the treatment after symptoms have stabilized and a return to baseline provides evidence for treatment efficacy. This A-B-A (no treatment, treatment, no treatment) design is accepted in clinical research (31).

Crossover Design: In a crossover (within-subjects) design, each patient receives every drug being studied, "crossing over" from one drug to the next in a predetermined order. The strength of the crossover design is that the patient can serve as his or her own control, which

Table 1. Studies Assessing Antiemetic Efficacy of Delta-9-Tetrahydrocannabinol (THC) with Cancer Chemotherapy Patients*

Investigators, Reference, Year	Study Design (Number of Patients)	Dose and Schedule	Dependent Measures	
			Subjective	Objective
Sallan et al. (9) 1975	Randomized, double-blind crossover (n = 20)	THC, 10 mg/m² bsa every 4 h × 3, versus placebo	Patient: nausea, vomiting, food intake	NR
Chang et al. (10) 1979	Randomized, double-blind crossover (n = 15)	THC, 10 mg/m² bsa every 3 h × 5, versus placebo	Patient: nausea, side effects, "high" Nurse: nausea	Blood samples, n vomiting episodes, n retching episodes
Ekert et al. (11) 1979	Randomized, double-blind crossover (n = 33)	THC, 10 mg/m² bsa every 4 h × 4, versus metoclopramide, 5-10 mg; versus prochlorperazine, 5-10 mg	Patient: nausea, vomiting, side effects, "high"	NR
Frytak et al. (12) 1979	Randomized, double-blind crossover (n = 116)	THC, 15 mg every 4 h × 3, versus prochlorperazine, 10 mg; versus placebo	Patient: nausea, vomiting, side effects, "high"	NR
Kluin-Neleman et al. (13) 1979	Randomized, double-blind crossover (n = 11)	THC, 10 mg/m² bsa every 4 h × 3, versus placebo	Patient: nausea, vomiting, side effects	Blood sample
Colls et al. (14) 1980	Randomized, double-blind crossover (n = 35)	THC, 12 mg/m² bsa every 4 h × 3; versus thiethylperazine, 6 mg/m² bsa; versus metoclopramide, 15 mg/m² bsa	Patient: nausea, vomiting, side effects	n vomiting episodes
Garb et al. (15) 1980	Randomized, double-blind crossover (n = 47)	THC, 10 mg, and prochlorperazine, 10 mg four times daily, versus placebo and prochlorperazine, 10 mg	NR	n vomiting episodes
Lucas and Laszlo (16) 1980	Single group, before/after (n = 53)	THC, 5 and 15 mg/m² bsa every 4 h × 9	Patient: nausea, vomiting	NR
Orr et al. (17) 1980	Randomized, double-blind crossover (n = 55)	THC, 7 mg/m² bsa every 4 h × 4; versus prochlorperazine, 12 mg/m² bsa; versus placebo	Patient: nausea, food intake	n vomiting episodes
Sallan et al. (18) 1980	Randomized, double-blind crossover (n = 84)	THC, 10 mg/m² bsa every 4 h × 3; versus prochlorperazine, 10 mg/m² bsa	Patient: nausea, vomiting, food intake, "high"	NR
Chang et al. (19) 1981	Randomized, double-blind crossover (n = 8)	THC, 10 mg/m² bsa every 3 h × 5; versus placebo	Patient: nausea, side effects, comfort Nurse: duration of nausea	n retching episodes, n vomiting episodes, volume of emesis, volume of oral intake, blood samples
Levitt et al. (20) 1981	Randomized, noncrossover (n = 120)	THC, 5, 10, and 15 mg every 4 h × 4; versus prochlorperazine, 10 mg; versus placebo; versus no treatment	Patient: nausea, side effects	Heart rate, blood pressure, intraocular pressure, vital capacity, temperature
McCabe et al. (21) 1981	Randomized, double-blind crossover (n = 36)	THC, 15 mg every 4 h × 6; versus prochlorperazine, 10 mg	Patient: nausea, vomiting, side effects, "high"	n vomiting episodes
Neidhart et al. (22) 1981	Randomized, double-blind crossover (n = 52)	THC, 10 mg every 4 h × 8; versus haloperidol, 2 mg	Patient: nausea, vomiting, side effects	n vomiting episodes, time before first drinking or eating
Sweet et al. (23) 1981	Single group, before/after (n = 25)	THC, 5 mg/m² bsa every 8 h × 6	Patient: nausea, vomiting, side effects, expectation	NR
Gralla et al. (24) 1982	Randomized, double-blind (n = 27)	THC, 10 mg/m² bsa every 3 h × 5; versus metoclopramide, 2 mg/kg body weight	Patient: side effects	n vomiting episodes
Ungerleider et al. (25) 1982	Randomized double-blind crossover (n = 214)	THC, every 4 h: bsa < 1.4 m² = 7.5 mg, 1.4 m² < bsa < 1.8 m² = 10 mg, 1.8 m² < bsa = 12.5 mg; versus prochlorperazine, 10 mg	Patient: nausea, vomiting, side effects, anxiety, mood, expectation, concentration	NR

* bsa = Body surface area, NR = not reported.
† Mean age.

Table 1. (Continued)

Chemotherapy Regimen	Median Age	Previous Marijuna Use	Setting	Outcome
	yrs			
Not controlled	29.5	Yes	NR	THC superior to placebo
Methotrexate	24	Yes	Inpatients	THC superior to placebo
Not controlled	11	NR	NR	THC superior to both metoclopramide and prochlorperazine
5-Fluorouracil and semustine	61	No	Outpatients	THC equivalent to prochlorperazine, both superior to placebo
Mechlorethamine, vincristine, procarbazine, prednisone (MOPP)	32	NR	Inpatients	THC superior to placebo
Not controlled	NR	NR	NR	THC equivalent to both thiethylperazine and metoclopramide
Not controlled	Not controlled		NR	THC/prochlorperazine superior to placebo/ prochlorperazine
Not controlled	NR	NR	Both inpatients and outpatients	72% response rate to THC
Not controlled	46†	NR	NR	THC superior to both prochlorperazine and placebo
Not controlled	32.5†	Yes	NR	THC superior to prochlorperazine
Doxorubicin and cyclophosphamide	41	Yes	Inpatients	THC no better than placebo
Not controlled	55.7†	NR	Outpatients	THC, 15 mg, superior as antiemetic; prochlorperazine superior as antinauseant
Not controlled	48	NR	NR	THC superior to prochlorperazine
Cisplatin, mechlorethamine, doxorubicin	41	NR	Outpatients	THC equivalent to haloperidol
Not controlled	51.5	NR	Outpatients	72% partial response to THC; 8% complete response to THC
Cisplatin	NR	NR	NR	Metoclopramide superior to THC
Not controlled	NR	Yes	Mostly outpatients (83%)	THC equivalent to prochlorperazine

minimizes error variance due to individual differences and allows for efficient use of subjects (32). Unfortunately, however, in two of the studies of THC using a crossover design (17, 18), patients known to be refractory to conventional antiemetic therapies (such as prochlorperazine) were selected as subjects and given both THC and prochlorperazine. Because it was known a priori that these patients would not respond to prochlorperazine, this comparison was biased, and thus the internal validity of the experiment severely compromised.

An important axiom of experimental design is that only one independent variable should be altered at a time, so that it is possible to identify which variable caused which effects. In one study (15), THC was administered together with prochlorperazine and compared with the combination of prochlorperazine and placebo. The difficulty with the design used in this study is that any difference observed between the two groups may have been due to a single agent (THC or prochlorperazine) or to the interaction of two agents. The effects of THC alone cannot be determined.

Between-Subjects Design: The non-crossover (between-subjects) design has also been used to evaluate THC efficacy (12, 20, 24). The between-subjects design is one in which each subject is tested under only one level of each independent variable. One of the advantages of a between-subjects design is that, because subjects in any one condition receive only one treatment, a researcher does not have to be concerned with extraneous effects that can be troublesome for within-subjects designs. Thus, order effects (those due to the order in which the treatments are given) and residual effects (those due to the influence on a subject of an early treatment when a later treatment is given) are avoided. However, because the between-subjects design results in more error variance due to individual differences, it is less sensitive in detecting differences due to drug treatments; effects due to individual differences may mask treatment effects. Moreover, the between-subjects design requires more subjects to provide a test of equivalent power.

Recommended Design: Several different designs have been used to study the antiemetic efficacy of THC. The crossover design is preferred because it is more powerful statistically and requires fewer subjects than does the between-subjects (non-crossover) design. Randomization of the order of treatments is an essential component for the crossover design. Finally, to control for nonspecific factors such as expectancy effects, the use of either a double-blind procedure or the assessment of physician, nurse, and patient expectations is recommended.

ASSESSMENT OF ANTIEMETIC EFFICACY

The assessment of the antiemetic effectiveness of THC is contingent on the reliable and valid measurement of nausea and vomiting. In the effort to obtain valid and reliable measures, investigators have used both objective and subjective methods.

The objective measurement of vomiting would seem to be relatively direct. Researchers typically have recorded the number and duration of emetic episodes and the volume of the emesis. Several problems with this assessment procedure, however, must be considered. First, vomiting is a two-stage behavior, which consists of retching followed by expulsion (33). The objective measurement of emesis would require the differentiation of these two stages. Second, when a patient vomits continuously over a given period of time, it is difficult to reliably determine the frequency of individual episodes for that period; some investigators may count each as a separate episode. Third, because the side effects occurring after chemotherapy often last for 24 to 48 hours, it is very difficult to obtain an accurate tally of the number of emetic episodes. Although some ingenious researchers have circumvented this problem with inpatients by using time-lapse videocassette recordings (34), this procedure is costly and its use is limited to inpatients. Fourth, emetic volume depends on each patient's consumption before chemotherapy treatment. Thus, an increase in the volume of emesis does not necessarily reflect a more severe problem. Controlling food and fluid intake during the trial will avoid this difficulty (35), but may not be possible for all patients. Finally, clinical research experience has indicated that the collection and measurement of vomitus often meets with resistance from both the medical and research staff and from patients, which may affect the accuracy of the reported measurements.

The assessment of nausea presents even more difficulties for researchers studying THC. Because there is no animal model for nausea, and because the experience of nausea is a subjective phenomenon, its assessment has relied almost entirely on reports by the patient. One group of researchers has tried to avoid this difficulty by collecting objective correlates of nausea, such as pulse rate, blood pressure, and vital capacity (20). Behavioral researchers have also collected correlates of nausea such as muscle tension, pulse rate, and blood pressure (36, 37). In general, these measures have paralleled patient report measures of nausea, suggesting a relation between these different variables, although there have been exceptions (20). An additional correlate of nausea has been used by Cotanch (38), who measured caloric intake after chemotherapy. However, these objective measures are difficult to interpret because each is influenced by many other physiologic factors, which may or may not be related to nausea. They can be, at best, only indirect measures of nausea. Nonetheless, this attempt to obtain convergent evidence is worthy of attention in future trials.

Clearly, the patient report is currently the most critical index of nausea. To measure patient-reported nausea, most researchers have composed their own questionnaires. A good illustration of a typical nausea questionnaire is that used by Ungerleider and colleagues (25) in which patients were asked to rate their nausea on a 6-point scale: 0 = no nausea; 1 = mild nausea; 2 = moderate nausea; 3 = severe nausea without vomiting or retching; 4 = no episodes of vomiting but retching (dry heaves); 5 = one episode of vomiting; 6 = multiple episodes of vomiting. The extent to which these numeric scales are valid or reliable is unknown.

As an alternative form of patient report, Redd and

Andrykowski (39) have suggested the use of a visual analogue scale to measure patients' subjective experience of nausea. Severity of nausea is indicated by placing a mark along a 10-cm line labeled "no nausea" at one end and "nausea as bad as it could be" at the other. Similar visual analogue assessment techniques have been used to assess patient reports of pain (40) and seem to produce more reliable data that are less influenced by response sets than are traditional numeric rating scales (40, 41).

Unfortunately, none of the scales developed to measure nausea have yet been adequately validated or widely adopted, and it is likely to be some time before a validated scale is available. Thus, due to the subjective nature of the experience of nausea, its measurement will remain an extremely challenging task for researchers.

For the present, the use of individually designed nausea scales is necessary and appropriate. However, given the fact that neither the reliability nor validity of these scales has been determined, greater confidence could be placed in the outcome of a study if two or more nausea indices converge to suggest the same result. One example is the procedure followed by Chang and his coworkers (10, 19) of having both the patient and an observer rate nausea and vomiting. Measurement of the physiologic correlates of nausea is also recommended.

Variables Affecting Antiemetic Efficacy

In addition to improvements in design and assessment features, future research can be strengthened by controlling for factors that may influence the efficacy of THC as an antiemetic therapy, including patient variables, pharmacologic variables, setting variables, and the differentiation of pharmacologically induced from conditioned nausea and vomiting.

PATIENT VARIABLES

The antiemetic efficacy of THC may be influenced by chemotherapy regimen and the age of the patient.

Type of Chemotherapy Regimen: Most clinical trial studies of THC have used heterogeneous patient populations with various tumor types and different chemotherapy regimens. Because different antineoplastic drugs and combinations of drugs have different emetic potential, it is likely that THC may be effective with some drug regimens but not with others. The few studies that have controlled chemotherapy regimen support this reasoning. For example, Chang and associates found THC to be effective against methotrexate-induced emesis (10), but not against doxorubicin- and cyclophosphamide-induced emesis (19). Conversely, Orr and colleagues (17) reported that the antiemetic effect of THC appeared to be more beneficial for cyclophosphamide, 5-fluorouracil, and doxorubicin than for mechlorethamine and the nitrosureas. Lucas and Laszlo (16) suggested that the emesis caused by cisplatin and other cisplatin-containing regimens may not be alleviated by THC. Overall, these studies suggest that the antiemetic properties of THC may be effective only against specific chemotherapy agents or combinations, but not against others. Unfortunately, they disagree on the specific agents and combinations. Part of this confusion, in turn, may be due to the confounding of the other patient, pharmacologic, or setting variables.

Age of the Patient: Delta-9-tetrahydrocannabinol may be differentially effective in younger versus older patients. Although no study has focused directly on a comparison of younger and older patients, studies reporting the most promising results have used younger patients (9, 10, 18). In the three studies cited above, the median ages of patients were 29.5, 24, and 32.5 years respectively. Furthermore, Frytak and coworkers (12) have reported that THC may be contraindicated for many elderly patients because of its central nervous system toxicity. These authors have suggested that the depersonalization reaction, which can be experienced during a THC or marijuana "high," may be entirely acceptable or even desired by a younger person, but that for the older patient this experience can be emotionally devastating. Further, the dose and schedule given to older patients may be an important factor in their development of depersonalization reaction. In general, the data suggest that a patient's attitude toward THC and its side effects may have an important role in the extent to which the drug is tolerated and effective. If THC is a potentially effective antiemetic agent, it may be worthwhile to increase older patients' acceptance of and positive expectancies toward THC, and thereby increase its use and effectiveness in elderly populations.

More data are needed however to determine whether THC antiemetic therapy is indeed more effective with younger than older patients. If so, physiologic, psychologic, or social reasons for this age-related difference should be identified. If social factors alone are responsible, perhaps a brief educational intervention will allay the fear older patients may have about THC therapy and will allow them to be better served by this treatment.

PHARMACOLOGIC VARIABLES

The clinical effectiveness of THC as an antiemetic therapy may depend on pharmacologic variables such as drug tolerance; drug dose, schedule, and toxicity; route of administration; and drug interactions.

Drug Tolerance: The influence of prior marijuana use on the antiemetic potential of THC remains controversial. Hepatic microsomal enzymes metabolize THC and other cannabinoids (42). In heavy marijuana users, THC-induced enzyme induction, which might contribute to enhanced THC or other drug metabolism, has been found (43). Although some clinical data (9, 25) suggest that prior marijuana use has no influence on the current antiemetic or psychologic effect of THC, no confirmatory pharmacologic data have been presented. Chang and associates (10) have addressed the question of drug tolerance over a prolonged drug-exposure period. In patients who achieved at least an 80% reduction in nausea and vomiting, further treatment with an additional eight THC treatments resulted in continued, but somewhat diminished, antiemetic response. Although such clinical data are consistent with drug tolerance, the mechanism of tolerance was not investigated.

Dose, Schedule, and Toxicity Variables: Some of the variability in the literature on THC may be due to differ-

ences in drug dosage and scheduling. The antiemetic benefit resulting from THC appears to be associated with the patient's subjective report of a "high" (9), which is usually but not always achieved from a single dose of 10 mg/m^2 body surface area. The most frequent treatment schedule used has been 10 mg/m^2 body surface area every 3 hours beginning 2 hours before chemotherapy and continuing for at least five doses (10, 19, 24). Sallan and colleagues (9) reported that scheduling THC doses at 4-hour intervals resulted in a loss of a "high" and increased nausea and vomiting for some patients. They suggested a schedule that provides for more frequent drug administration. However, in their subsequent study (18), they continued to treat at 4-hour intervals. Lucas and Laszlo (16) found schedules of lower doses (5 mg/m^2 body surface area) every 4 hours beginning 8 to 12 hours before chemotherapy to be effective. Toxicity reported with the doses and schedules mentioned above are generally minor and transient and include somnolence, xerostomia, and self-limiting tachycardia. Increased doses to 15 mg/m^2 body surface area have yielded a proportionally higher incidence and severity of toxicity (16), including severe somnolence or psychologic reactions such as fear, anxiety, intense visual hallucinations, and severe distortions of time. Frytak and colleagues (12) administered 15 mg to patients regardless of body size and reported dysphoric reactions in 5 of 116 treated patients but otherwise acceptable toxicity.

Although the antiemetic effectiveness and toxicity of THC are functions of dosage level and frequency of administration, this relation occurs only if the THC is adequately absorbed into the bloodstream. In fact, Sallan and coworkers (9) attributed inadequate drug absorption as a contributing factor in those patients who did not have an antiemetic response. As a result, Chang and associates (10) have suggested that plasma THC concentrations be measured and compared with THC effectiveness and toxicity. Their original findings suggested a dose-response relation in that progressively higher 1-hour plasma concentrations of THC were associated with a decreased incidence of nausea and vomiting. Frytak and colleagues (12) did not find a correlation between THC serum levels and either side effects or antiemetic effects, but this result is based on a small group (nine patients) added post hoc to their study. In a second study by Chang and associates (19), the effectiveness of THC was limited, but efficacy was more pronounced with increased 1-hour concentrations of serum THC. Future studies must determine the critical issues of optimal dose and schedule of administration. Further, because serum THC concentration rather than dosage level may be the important variable, future studies should compare both measures with THC effectiveness.

Route of Administration: Usually, THC is administered orally. Although preferred by patients, this route has two major problems. First, considerable individual variation in oral absorption exists, ranging from 8% to 24% of the measured administered dose (44-46). Second, orally administered THC is sometimes vomited before it has been fully absorbed. These two factors probably account for much of the inconsistency in THC effectiveness reported in the literature.

Because of the problems with orally administered THC, inhalation has been recommended as a route of administration. Inhalation provides a more predictable and rapid route of absorption: about half of the dose is absorbed within 15 minutes of drug administration (44, 46, 47). Chang and colleagues (10) also found that inhalation, as compared with oral administration, produced a more constant antiemetic effect and plasma concentration at 1 hour after administration. However, problems are also encountered with the inhalation route, including smoke-induced nausea and vomiting, especially in nonsmokers, an unpleasant residual taste, and pulmonary changes that occur with any smoke. Further development of alternative drug administration routes (such as nasal, intramuscular, rectal) is warranted.

Drug Interactions: Because most patients with cancer are receiving multiple drugs, many of which bind to microsomes, evidence of drug interactions with possible enhancement of toxicity or metabolism should be sought. Riggs and coworkers (48) found little change in the metabolism of doxorubicin and cyclophosphamide in patients treated with THC. Benowitz and Jones (42) found minor changes in antipyrine, pentobarbital, and ethanol metabolism in patients taking THC, but attributed these changes to the increased plasma volume induced by THC rather than drug interactions or drug-induced microsomal inhibition. Unfortunately, few data exist and more information is needed.

SETTING VARIABLES

In addition to patient and pharmacologic characteristics, whether THC is administered in an inpatient or outpatient setting may have major importance in determining its antiemetic efficacy. Although no direct comparison of the use of THC with inpatients as opposed to outpatients has been carried out, differing reports of toxicity have come from studies using inpatients (12) and outpatients (16). Although it is not clear what factors account for this finding, inpatients generally are willing to tolerate more side effects than are outpatients.

Andrysiak and associates (49) and Seipp and colleagues (30) have suggested that the primary caregiver's attitude is critical in determining the patient's acceptance of and, hence, benefit from THC therapy. Because the use of marijuana and THC is socially controversial, it might be valuable to assess the attitude of the caregiver and its association with patient response. Further, as indicated earlier with respect to older patients, it might be useful to provide patients with additional information about THC, its medical use, and its side effects before therapy.

DIFFERENTIATION OF TYPE OF NAUSEA AND VOMITING

Most of the research reviewed in this paper has been concerned with pharmacologic nausea and vomiting, effects due to the pharmacologic properties of the antineoplastic agents and usually beginning 2 to 3 hours after chemotherapy injections and continuing for as long as 24

hours (2). However, many patients receiving cancer chemotherapy also develop conditioned nausea and vomiting. Conditioned or learned nausea usually occurs after several courses of chemotherapy when a patient begins to associate various environmental stimuli (such as the chemotherapy nurse, the hospital, or clinic) with their responses to chemotherapy. These stimuli become capable of eliciting responses such as nausea, vomiting, and high levels of anxiety. In about 15% of conditioned patients, anticipatory nausea results in anticipatory vomiting (50). Conditioned nausea and vomiting can occur before, during, or after an individual chemotherapy session (37) and can make a patient more refractory to an antiemetic therapy. Nausea and vomiting occurring after chemotherapy probably often represent a combination of both conditioned and pharmacologically caused side effects, with the differentiation of the two being difficult if not impossible. Nausea and vomiting occurring before the chemotherapy treatment, often referred to as anticipatory nausea and vomiting, are the clearest examples of conditioned responses. Chang and colleagues (10) have reported that THC is not effective against anticipatory nausea and vomiting, and Kutz and coworkers (51) have even suggested that THC itself may become a conditioned stimulus. However, Lucas and Laszlo (16) have suggested that if THC is given beginning 12 or more hours before administration of chemotherapy, when anticipatory nausea and vomiting are generally present, THC might be effective in reducing this type of nausea and vomiting. Clearly, additional research is needed in this area.

Conclusion

Delta-9-tetrahydrocannabinol is becoming a popular antiemetic therapy for patients receiving cancer chemotherapy. Studies of the antiemetic efficacy of THC have compared it to that of standard phenothiazines as well as to that of newer agents (such as metoclopramide) with conflicting and confusing results. Although these results are partially due to unavoidable difficulties in conducting research on antiemetic therapy with patients on chemotherapy, our review suggests that much of the inconsistency is due also to differences in the nature and adequacy of the study designs and methods. Moreover, many variables that might be important in determining the effectiveness of THC, and therefore also in explaining the conflicting data, have not been adequately analyzed. These factors include patient variables such as chemotherapy regimen and age; pharmacologic variables such as drug tolerance, dose, schedule, toxicity, route of administration, and drug interactions; and setting variables such as administration on inpatient and outpatient basis and the attitude of the primary caregivers toward THC. Additional research is needed to assess the effectiveness of THC in reducing nausea and vomiting that are conditioned. Only through such carefully designed and well-controlled research can the antiemetic efficacy of THC be identified, its limits defined, and its effectiveness relative to other treatments established.

Appendix: Regulatory Climate

Societal pressures within and outside the United States have contributed to strict control of THC for legal use as an antiemetic agent; THC is considered a schedule I drug, a drug for which there is "no recognized medical use." The drug is controlled by the Psychotropic International Convention, to which the United States is a signatory. Therefore, THC is regulated under the Food and Drug Administration (FDA) as a research substance requiring an approved protocol for use.

Despite these restrictions, THC is available to the scientific community through two major mechanisms. The first is through the National Cancer Institute (NCI), Investigation Drug Branch (IDB) of the Division of Cancer Treatment (DCT). The NCI has filed a protocol with the FDA that registers THC as a Group C chemotherapy agent. The drug is available to hospital pharmacies that have registered and have been approved by the IDB and the Drug Enforcement Administration to handle group C drugs. Physicians are required to file FDA form 1573 for IDB approval to prescribe THC.

Alternatively, individual states, usually under the sponsorship of its Department of Health, can file a research protocol for THC use. This research must be supervised by an FDA-approved, state-appointed review board. At the time of this writing (January 1983), about 16 states have applied for and received FDA approval to dispense THC. Physicians wishing to prescribe THC under state protocols must file FDA form 1573. The FDA then approves the physician's request allowing THC to be prescribed as an antiemetic therapy.

Currently, a New Drug Application is pending with the FDA from Unimed, Inc. (Sommerville, New Jersey) that would allow THC to be marketed as a Schedule II drug. Approval is expected by the summer of 1983 (Tocus EC, Federal Drug Administration, personal communication, January 1983; Abraham D, National Cancer Institute, personal communication, January 1983).

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