Δ^9-Tetrahydrocannabinol for Refractory Vomiting Induced by Cancer Chemotherapy

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• **Fifty-three patients receiving antineoplastic chemotherapy who had experienced severe nausea and vomiting refractory to standard antiemetic agents were treated with Δ^9-tetrahydrocannabinol (THC). These patients were given THC 8 to 12 hours before, during, and for 24 hours after chemotherapy. Ten patients (19%) had no further nausea and vomiting; 28 (53%) had at least a 50% reduction of nausea and vomiting compared to previous courses with the same agents. No appreciable reduction of nausea and vomiting was seen in 15 patients (28%). Toxic reactions were generally mild, with only four patients experiencing reactions that necessitated stopping THC therapy. We suggest that, since THC is a useful antiemetic agent in patients having refractory chemotherapy-induced vomiting, existing restrictions prohibiting its therapeutic use should promptly be eased.**

(*JAMA* 243:1241-1243, 1980)

AGGRESSIVE programs of chemotherapy that are intended to improve the quality and duration of life for cancer patients often pose serious problems to the comfort of patients and limit their willingness to accept repeated courses of therapy. Frequently, the most bothersome side effects are chemotherapy-induced nausea and vomiting, and occasionally they seem even worse than the disease itself. Phenothiazines and other conventional antiemetics are only moderately effective in suppressing nausea and vomiting. Furthermore, drugs such as phenothiazines are themselves associated with many adverse reactions, particularly in the CNS.[1,2]

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Although nausea and vomiting following chemotherapy administration can be controlled by conventional antiemetic agents in many cancer patients, there remain a large number who could benefit from an alternative antiemetic. The reports by Sallan et al[3] and Regelson and associates,[4] plus the unscheduled observations of youthful patients, have demonstrated that marijuana or its most active constituent, Δ^9-tetrahydrocannabinol (THC), lessened or prevented the nausea and vomiting associated with chemotherapy.

The purpose of this study was to determine whether orally administered THC was an effective and practical antiemetic for the control of chemotherapy-induced nausea and vomiting in patients who were unresponsive to conventional antiemetics.

SUBJECTS AND METHODS

Adult patients receiving cancer chemotherapy who had persistent severe nausea and vomiting in spite of the aggressive use of standard antiemetics were eligible for this study unless excluded by brain metastasis, concomitant brain or spinal irradiation, angina pectoris, or allergy to THC or sesame oil.

Patients refrained from ingestion of any psychoactive drugs (alcohol, antidepressants, sedatives, tranquilizers, and other antiemetics) while receiving THC. Standard antiemetic therapy is defined as drug therapy beginning ten to 12 hours before the first dose of chemotherapy, continuing at a fixed dosage interval throughout the course of chemotherapy, and supplemented by additional doses of antiemetics as needed to obtain maximally tolerated doses. An example of this would be prochlorperazine, 10 mg orally every six hours, starting at midnight the night before chemotherapy and continuing throughout the course of chemotherapy, supplemented by 10-mg intramuscular injections.

All of the usual studies done to monitor the effects of chemotherapy were carried out; no special laboratory tests were needed to monitor the effects of THC administration. The initial studies were limited to patients on our cancer research ward; later, patients on other hospital wards and then outpatients were included.

Two dosage schedules were used. The initial schedule was 15 mg/sq m orally every six hours, starting one hour before chemotherapy administration and continuing every six hours for four doses. In those patients who received chemotherapy over several days, THC administration was continued during the entire course, with four doses given after chemotherapy was discontinued. The first nine patients were treated with this program; all experienced either severe somnolence or an acute psychologic reaction. Because of the side effects and the episodes of nausea and vomiting, which occurred about one to two hours before the next THC dose, the dosage scheduled was modified. Δ^9-Tetrahydrocannabinol was given orally at doses of 5 mg/sq m every four hours, starting eight to 12 hours before chemotherapy administration and continuing for 24 hours after chemotherapy was discontinued. The THC was dissolved in sesame oil

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and formulated in liquid-filled capsules containing 2.5, 5, and 10 mg of THC (supplied by the National Institute of Drug Abuse).

Patients' responses were evaluated by first taking a history of past nausea and vomiting and antiemetic therapy so that a comparison could be made in each patient who received subsequent chemotherapy with THC. The investigators observed each patient during the course of chemotherapy and reviewed nurses' notes, food intake, and other history taken from the patient and his family (for outpatients). Subjective data were obtained from the patient, his family, the physician, and other personnel in contact with the patient; mainly, these dealt with the subjective comparison of chemotherapy-induced nausea and vomiting with and without THC.

Definitions of responses were based on a comparison of chemotherapy courses with and without THC. Complete response to THC was defined as no nausea and vomiting, partial response as at least a 50% reduction in nausea and vomiting, and no response as less than a 50% reduction of nausea and vomiting, compared with chemotherapy given in conjunction with standard antiemetics. Each patient gave written, informed consent to therapy with THC. Among other explanations, the consent form stated that THC was an active compound found in marijuana that might cause a "high" and that would preclude driving a car or working with machinery.

RESULTS

The 57 patients eligible for this study were admitted between Feb 19, 1978, and June 15, 1979. Fifty-three patients were studied for antiemetic response; four patients given only one dose were not evaluative for therapeutic response. In three of these latter patients, acute reactions developed after their first dose of THC, and they refused to take the drug again. One outpatient did not like the way she felt and discontinued the drug treatment herself.

These 57 patients had a variety of types of cancer: lung cancer (11), Hodgkin's disease (9), breast cancer (6), leukemia (4), testicular carcinoma (4), melanoma (4), brain tumors (3), ovarian carcinomas (3), cervical carcinomas (2), renal cell carcinomas (2), lymphomas (2), sarcomas (2), multiple myeloma (1), endometrial carcinoma (1), thyroid carcinoma (1), and choriocarcinoma (1). One patient had an extremely severe vasculitis that could be controlled only with moderately large doses of cyclophosphamide that caused severe nausea and vomiting. These patients were treated with 20 different combination chemotherapy regimens, one of which is described in the following case report:

A 23-year-old man whose condition was diagnosed as stage IVB Hodgkin's disease received three courses of chemotherapy consisting of doxorubicin hydrochloride (Adriamycin), 90 mg intramuscularly, vinblastine sulfate, 15 mg intramuscularly, and lomustine, 15 mg orally, all on day 1. During each course of chemotherapy, the patient experienced severe nausea and vomiting that were uncontrolled by high doses (25 mg every four hours rectally) of prochlorperazine. He vomited every ten to 15 minutes for 14 hours and was nauseated for an additional ten hours. Because of the severe vomiting, the patient became severely dehydrated and had to remain in the hospital for two to three days after each course of chemotherapy; he was unable to work for one week following each course of chemotherapy. Eight hours before his fourth course of chemotherapy, administration of THC, 10 mg every four hours orally, was begun. He experienced no nausea, vomiting, or other side effects and was able to return home after receiving chemotherapy and was even able to return to work. This experience was repeated in five subsequent courses.

The Table summarizes the results of the study. Fifty-three patients received 115 courses of chemotherapy with THC. Ten patients (19%) had no nausea and vomiting; 28 patients (53%) had partial responses. No appreciable reduction of nausea and vomiting was seen in 15 patients (28%). Patients who had a complete or partial response usually received THC with each subsequent course of chemotherapy. In fact, several patients refused further chemotherapy unless they were also given THC. Twenty courses of THC were administered to the 15 patients who derived no response; three nonresponders requested a dose increase in the second course, and this subsequently resulted in a partial or complete response. Thus, these patients were judged to be overall partial responders. Two other patients, one with a complete and one with a partial response during the first course, did not take THC before their second course of chemotherapy and had severe nausea and vomiting. During the subsequent courses, they complied with the protocol and had no further nausea and vomiting.

Responses in 53 Patients Given Chemotherapy and Δ^9-Tetrahydrocannabinol

Response	No. (%) of Patients (N=53)	No. (%) of Courses (N=111)
Complete	10 (19)	33 (30)
Partial	28 (53)	58 (52)
None	15 (28)	20 (18)

All patients who entered the study were evaluated for toxic reactions, which were mild except in the nine patients who received 15 mg/sq m of THC. Of these nine, three had severe psychological reactions manifested as fear, anxiety, intense visual hallucinations, and severe distortions of time. These reactions resolved within three hours when no further THC was given. The other six patients were bedridden because of somnolence and postural hypotension; all of them noticed an extremely dry mouth. Patients who received 5 mg/sq m of THC had no serious side effects, but 15 complained of being more sleepy than usual and 30 complained of a dry mouth. All outpatients were able to carry on their usual activities except those restricted by the constraints of the study.

All 38 patients achieving a complete or partial response stated that they felt somewhat "high," characterized as temporary mood changes, usually laughing, heightened awareness, elation, mild distortions of time, and mild, though pleasant, visual or auditory hallucinations. Three of the patients who had no response stated that they felt "high" until they received their chemotherapy (cisplatin) and then felt normal. No patients experienced any delayed effects, hangovers, or other sequelae that we could attribute to the drug.

COMMENT

The problem of chemotherapy-induced nausea and vomiting is extremely important in the management of the cancer patient. In pointing to advances in the prognosis for patients having certain types of cancer (eg, leukemia, lymphomas, testicular cancer), considerable recognition has been given to the advent of innovative and increasingly aggressive uses of drug combinations. However,

oncologists also recognize the critical importance of supportive care with blood components, prophylactic antibiotics, and aggressive treatment of infections, particularly during periods of high risk of complications. As chemotherapy programs have become more intense and, in many instances, more effective, the problem of nausea and vomiting has also become progressively worse.

The results of this study clearly demonstrate that THC is an effective antiemetic agent in cancer patients receiving chemotherapy. These patients, who had previously experienced severe nausea and vomiting due to their chemotherapy, received little, if any, relief from standard antiemetics. Even though ours was not a randomized study—randomized studies with THC being difficult to keep "blinded"—each patient served as his own control. Each patient had been carefully screened before entering the study to unequivocally demonstrate refractoriness to adequate courses of antiemetic therapy. In some cases, patients who had not received adequate standard antiemetic therapy had their nausea and vomiting well controlled when therapy for these conditions was upgraded with maximally tolerated doses of phenothiazines. Therefore, the results of the use of THC are particularly impressive when one considers that eligible patients were restricted to those in whom aggressive standard therapy had failed and whose lives were made miserable by chemotherapy.

While the numbers in each of the treatment groups are small, we have the impression that nausea and vomiting caused by certain drugs may not be equally susceptible to THC. For example, of the 15 patients who failed to receive relief of nausea and vomiting with THC, seven were receiving cisplatin in combination with other agents—an observation that emphasizes the refractory nature of nausea and vomiting related to this agent.[5] Six patients who received cisplatin doses of more than 120 mg had neither complete nor partial responses with THC, while of those who received less than 120 mg, six had partial responses and one had no response.

All eight of the nonresponders receiving combination chemotherapy other than cisplatin-containing regimens reported that they did not experience any "high." This suggests that they either did not receive enough drug or failed to absorb it completely. Δ^9-Tetrahydrocannabinol is erratically absorbed from the gastrointestinal tract, and dosage individualization may be necessary to control these patients.[6]

It is most disturbing to consider the current difficulty of gaining access to THC and the near-term prospects of its becoming available for use by practicing oncologists. Our own efforts to obtain THC for this study required 18 months. Although the process may have been streamlined since, this drug is still restricted for research purposes and there is no way to provide patients (or their physicians) with this medication unless they are enrolled in an approved protocol. Indeed, this study remains open so that our own patients might have access to this medication.

Difficulties that we experienced with the use of this drug should be mentioned because they illustrate the problem of technology transfer, which is being impeded largely by the regulations of federal agencies. Up to now, the drug has been licensed under Schedule I, which is reserved for substances with high abuse potential that are not known to have medicinal value and that may be handled only by approved researchers. Although it makes no scientific sense at this juncture not to allow physicians licensed to prescribe narcotics to prescribe THC, the problems with its availability seem to be partly political, with governmental agencies who have been devoted to showing the lack of benefit of marijuana now being petitioned to license its use for medicinal purposes. Recent conferences on the subject, sponsored by the National Cancer Institute and attended by representatives of the Food and Drug Administration and the National Institute of Drug Abuse, may serve as a stimulus to recognition of the therapeutic importance of THC.

Curiously, the absence of a pharmaceutical company with an interest in marketing this Schedule I drug may also be an impediment to resolution of some of these issues. There are other promising cannabinoids being developed by pharmaceutical companies[7] that may eventually be licensed as Schedule II drugs; some of these ultimately may be as good or better than THC. Unfortunately, a recent update on nabilone, a potentially very important synthetic cannabinoid that, in a prospectively randomized study, greatly alleviated nausea and vomiting produced by a curative chemotherapy program for testicular cancer, states that the drug has been withdrawn for reasons of unexplained deaths in long-term animal administration.[8] In the meantime, there is no suitable substitute for managing this debilitating complication of cancer chemotherapy.

This project was supported in part by grant CA 11265 from the National Cancer Institute. We are grateful to our colleagues who referred their patients to us, particularly Drs Berry, Creasman, Fay, Moore, Odom, Paulson, Rosse, Rundles, Seigler, Silberman, and Tallos. The nurses on Jordan Ward made detailed clinical observations. Connie Fennema helped prepare the manuscript.

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