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ANTIEMETIC EFFECT OF DELTA-9-TETRAHYDROCANNABINOL IN PATIENTS RECEIVING CANCER CHEMOTHERAPY

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Abstract Anecdotal accounts suggested that smoking marihuana decreases the nausea and vomiting associated with cancer chemotherapeutic agents. Oral delta-9-tetrahydrocannabinol was compared with placebo in a controlled, randomized, "double-blind" experiment. All patients were receiving chemotherapeutic drugs known to cause nausea and vomiting of central origin. Each patient was to serve as his own control to determine whether tetrahydrocannabinol had an antiemetic effect. Twenty-two patients entered the study, 20 of whom were evaluable. For all patients

an antiemetic effect was observed in 14 of 20 tetrahydrocannabinol courses and in none of 22 placebo courses. For patients completing the study, response occurred in 12 of 15 courses of tetrahydrocannabinol and in none of 14 courses of placebo ($P < 0.001$). No patient vomited while experiencing a subjective "high." Oral tetrahydrocannabinol has antiemetic properties and is significantly better than a placebo in reducing vomiting caused by chemotherapeutic agents. (*N Engl J Med* 293:795-797, 1975)

NAUSEA and vomiting of central origin occur after the administration of a variety of cancer chemotherapeutic agents and frequently constitute the major morbidity associated with such treatment. Control with classic antiemetics is incomplete and variable.

Anecdotal accounts from patients suggested that smoking marihuana before receiving intravenous anti-tumor drugs resulted in diminution of nausea and vomiting, and, in contradistinction to the usual post-therapeutic anorexia, some were able to take food shortly after therapy. Effects of marihuana on nausea and vomiting in human beings deserve to be reported. It has been demonstrated that oral delta-9-tetrahydrocannabinol (THC) causes the same physiologic effects as smoking marihuana.^{1,2}

The purpose of this study was to determine the effects of orally administered THC on nausea and vomiting in patients receiving cancer chemotherapy.

PATIENTS, MATERIALS AND METHODS

Twenty-two patients known to have a variety of neoplasms were enrolled in the study. Ten males and 12 females ranging in age from 18 to 76 years (median of 29.5) participated. Twenty patients had previously received cancer chemotherapeutic agents known to cause nausea and vomiting (adriamycin, 5-azacytidine, nitrogen mustard, imidazole carboxamide, procarbazine, high-dose cyclophosphamide or high-dose methotrexate, or combinations thereof). Twenty of the 22 were known to be refractory to conventional antiemetics. The other two patients had never been treated with chemotherapy before entering the study. Pregnant women and patients with a past history of emotional instability or untoward reactions to psychoactive drugs were not eligible.

The study was thoroughly explained to the patients. They were told that they would receive a placebo or a "marihuana-like drug for the purpose of controlling nausea and vomiting." Subjects agreed not to smoke marihuana during the course of the study.

THC was supplied by the National Institute on Drug Abuse. The drug was suspended in 0.12 ml of sesame oil and supplied in gelatin capsules. Identical-appearing placebo capsules contained only sesame oil. Initially, THC dosage was 15 mg given every four hours for three doses. Because of some variability in responses, the dose was changed to 10 mg per square meter body-surface area per dose. Nineteen patients received 15-mg doses, and three 20-mg doses.

A randomized, "double-blind," crossover experiment was employed, each patient being used as his own control. Optimally,

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patients received three one-day courses of drug (either THC or placebo). Each course consisted of three doses of drug, the first taken two hours before and the other two and six hours after chemotherapy. Patients were randomized to receive courses in one of four sequences: THC-placebo-THC; THC-placebo-placebo; placebo-THC-placebo; or placebo-THC-THC.

Nausea, vomiting, and food intake were assessed by the patient on the day after treatment through the use of self-administered questionnaires.* In addition, the patient, nurses, and other personnel in contact with the patient were interviewed by one of us (S.E.S.), who also reviewed the questionnaires and nurses' notes.

RESULTS

Definitions of responses are based upon a comparison of THC and placebo courses.

Complete response to THC means that there was no vomiting in patients for whom the same antitumor drugs caused unequivocal moderate to severe vomiting after placebo. Conversely, a complete response to placebo theoretically is possible, but never occurred.

Partial response to THC means that there was at least a 50 per cent reduction in vomiting as compared to placebo after the same chemotherapy. Included in this group are the patients whose vomiting, which occurred shortly after chemotherapy during a placebo course, was delayed until escape from control of THC. These patients attained a "high" that wore off before the next dose, or after the last dose of THC, and during this time vomiting "broke through." A partial response to placebo is also a theoretical possibility but never occurred.

No response to the THC means that there was either no decrease or less than a 50 per cent reduction in vomiting as compared with placebo after the same antitumor drugs. No response to placebo means that the patients vomited after chemotherapy as often or more often than after THC.

Absence of vomiting after both THC and placebo makes the response unevaluable because there was neither demonstrable emetic effect of chemotherapy nor antiemetic effect of THC or placebo. One patient who had no prior chemotherapy before entering the study was excluded from analysis for this reason.

Eleven patients completed three courses of treatment, two completed two courses, and nine completed one course.

One of the 11 never vomited and was excluded from evaluation as noted above. The remaining 10 patients received 30 courses of drug, but a single course was excluded from analysis because the dose of cancer chemotherapeutic agent was reduced by 50 per cent. Therefore, 29 courses were evaluated: 14 placebo and 15 THC. All courses of placebo resulted in no response. Of the THC courses, there were five complete responses, seven partial responses, and three no responses. The therapeutic response derived from the THC was independent of the sequence of THC or placebo courses administered. Accepting complete and partial responses as positive responses,

questionnaire available on request.

the difference between THC and placebo is highly significant (chi-square with Yates's correction $P < 0.001$).

Of the two patients who completed two courses in the study, one died of disease, and the other decided to smoke marijuana, thus becoming ineligible to continue. Both these patients had no response after placebo; after THC, both had partial responses.

Nine patients received one course of treatment. Six had placebo only, and five of them vomited after chemotherapy. The patient who did not vomit after placebo had no prior chemotherapy. His response to placebo, therefore, is unevaluable because of the impossibility of differentiating an antiemetic effect of placebo from the emetic effect of chemotherapy. Of the six, two voluntarily withdrew from the study because they did not want to risk another placebo course, one had chemotherapy discontinued, one died of disease, and two are still in the study. Three had THC only. Of these, two vomited and left the study, and the third went off study because of THC toxicity.

In summary, 20 courses of THC were administered, resulting in five complete responses, nine partial responses, three no responses, and three unevaluable responses. Twenty-two courses of placebo resulted in no complete responses, no partial responses, 16 no responses, and six unevaluable responses.

Side Effects

Of 16 patients receiving THC, 13 (81 per cent) experienced a "high." This effect was characterized by mood changes, which varied and consisted of one or more of the following: easy laughing; elation; heightened awareness; mild aberrations of fine motor co-ordination; and minimal distortion of their activities and interactions with others. There were no hangovers or delayed effects.

The next most common side effect was somnolence. For one third of the patients, somnolence curtailed activities for two to six hours, but the patients were easily aroused. Another third had somnolence which did not curtail activities; the remainder experienced nosomnolence.

Toxicity characterized by paranoid ideation, apprehension, fear, panic, and frightening visual hallucinations has been reported after single THC doses of 35 mg.² Only two of our patients (9 per cent) experienced THC toxicity both after three doses of 20 mg. One had visual distortion lasting for a few seconds, and the other reported visual hallucinations of 10 minutes' duration and depression for several hours.

DISCUSSION

The results of this placebo-controlled "double-blind" study demonstrate that THC has antiemetic effects.

The study was designed to compare THC with placebo. It was not designed to evaluate placebo effect. No comparisons were made between placebo and absence of placebo, or between placebo and retrospective emesis control. If a placebo effect exists in this clinical and investigative setting, THC cannot be evaluated.

No patient vomited while experiencing a subjective

"high." No "highs" were reported after placebo. In some patients, the "high" wore off before the next THC dose, and during this interval, nausea and vomiting frequently occurred. After this study, patients taking THC received **their** next dose as soon as the "high" began wearing off. Preliminary results indicate that this dose-scheduling adjustment sustains the antiemetic effect of THC.

Variability in gastrointestinal absorption of orally administered THC between, but not within, individual **subjects has been reported.**² Three of our patients (19 per cent) reported the absence of a "high" after THC. The lack of THC effect ("high" and antiemesis) in at least some patients may be related to failure of absorption. Some patients who did not attain a "high" after the initial dose were able to do so with subsequent doses. This effect may be analogous to the experience of Weil et al.³ with smoked marihuana: failure to respond to an initial dose of marihuana, and then response to subsequent doses. This phenomenon may also be related to induction of hepatic **microsomal enzymes necessary** for drug metabolism as suggested by Lemberger et al.⁴

Patients became "high" 20 to 60 minutes after ingestion of drug. The duration of the "high" varied from one to five hours, but was **usually** two to three hours, suggesting that the rigid four-hourly schedule between doses was probably too long for some patients, and possibly explaining some partial responses. When dosage was based on body-surface area, less variability in onset and duration of effects was noted.

Time of onset, duration of effect, and intensity of "high" were unrelated to previous marihuana use. Six patients admitted prior use of marihuana, but only one was considered more than an occasional user (defined here as smoking less than once a week).

It has been demonstrated that orally administered THC results in the same physiologic effects as inhaled marihuana.^{1,2} The previous studies showing inhaled marihuana to be more potent than oral THC¹ were probably in error because the THC was delivered in poorly absorbed vehicles.² Inhalation appears to be more suitable for patients with suboptimal gastrointestinal absorption.

Hollister has shown that the effects of smoked THC clearly resemble those of marihuana.⁵ We have made preliminary observations comparing the antiemetic effect of **smoked marihuana and oral** THC. The marihuana belonged to individual patients and, therefore, was neither qualitatively nor quantitatively controlled. For most pa-

tients, both smoked and oral routes had identical effects. Theoretically, smoking might be the preferable route since it may result in less variability of absorption than the gastrointestinal route. Moreover, smoking provides greater opportunity for individual patient control by permitting the patient to regulate and maintain the "high."

THC has been reported to have a biphasic clinical effect, with initial stimulation and elation followed by sleepiness and tranquility.⁶ With other antiemetics, such as the phenothiazine derivatives, sedative effect seems to parallel antiemetic effect.⁷ Although somnolence occurred in about two thirds of our patients, in the dosage used, THC prevented or reduced vomiting in most patients without appreciable curtailment of activities.

Appetite stimulation follows the smoking of marihuana.⁸ Four of our patients reported food intake "more than usual" after chemotherapy **when taking** THC. No patient reported this effect after placebo.

These data demonstrate that THC is an effective antiemetic for patients receiving cancer chemotherapy. Failure of response in 19 per cent of patients receiving THC perhaps is explicable on the basis of pharmacologic factors. THC can be used safely in the dosage of 10 mg per square meter per dose every four hours for at least three doses. Lack of effectiveness for some patients might be correctable by shortening the interval between doses to maintain a "high." The safety of such a dose-schedule adjustment is still to be determined.

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