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Recent Clinical Experience With Dronabinol[1]

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PLASSE, T. F., R. W. GORTER, S. H. KRASNOW, M. LANE, K. V. SHEPARD AND R. G. WADLEIGH. *Recent clinical experience with dronabinol.* PHARMACOL BIOCHEM BEHAV **40**(3) 695–700, 1991.—Dronabinol, Δ-9-tetrahydrocannabinol in sesame oil, has been used for several years as an antiemetic for patients receiving cancer chemotherapy. In combination studies with prochlorperazine, enhancement of efficacy, as measured by duration of episodes of nausea and vomiting and by severity of nausea, has been found. The incidence of psychotropic effects from dronabinol appears to be decreased by concomitant administration of prochlorperazine. In open pilot studies, dronabinol caused weight gain in seven of ten patients with symptomatic HIV infection. In both HIV and cancer patients, dronabinol improved appetite at a dose which was well tolerated for chronic administration.

Dronabinol Cannabinoids THC Antiemetics Palliative care Supportive care AIDS Cancer chemotherapy

DRONABINOL (Marinol®, Roxane Laboratories, Columbus, OH) is Δ-9-tetrahydrocannabinol (Δ-9-THC) formulated in sesame oil. It was approved in the U.S. in 1986 for treatment of cancer chemotherapy-induced nausea and vomiting refractory to other agents. It is supplied in 2.5, 5 and 10 mg capsules for oral administration. Marijuana had been noted anecdotally to relieve nausea in patients receiving cancer chemotherapy. Following the isolation and characterization of Δ-9-THC as the major active component of marijuana by Mechoulam and colleagues (9), a technique for producing synthetic material was developed (22). Several clinical studies with Δ-9-THC have demonstrated its antiemetic efficacy (15, 19, 28).

Cancer patients consider nausea and vomiting the most serious adverse effects they experience (5). Many drugs are used to control these symptoms, but none, when used alone, is entirely satisfactory. Even with the new 5-HT_3 antagonists being tested now as antiemetics, about half of patients undergoing cancer chemotherapy still suffer from nausea and vomiting (3, 6, 13). Thus there is still a need for multiple agents to treat these side effects.

Dronabinol has proven to be an extremely safe drug. While side effects are common, especially sedation and psychotropic symptoms, they are usually mild to moderate (14, 20, 21, 24). Furthermore, they resolve rapidly, usually within hours after discontinuation of therapy. We have no reports of persistent or fatal side effects due to dronabinol.

Drug diversion, a major consideration of regulatory agencies, has not been reported with dronabinol. The abuse potential of the medication appears to be much less than that of many other controlled substances. While psychological dependence has been noted in healthy individuals, physical dependence is uncommon and generally occurs only after prolonged administration of high doses (12). In addition, in the patient population for which dronabinol is prescribed, substance abuse is rare. The negative conditioning associated with chemotherapy administration (25) seems to far outweigh the euphoria some patients experience, making abuse even less likely.

The goal of therapy is to enhance overall quality of life. Therefore, we would like to minimize side effects of the antiemetic regimen when possible. From the results of several studies (4, 7, 8, 15, 17, 18, 26, 28), we have done a retrospective analysis of side effects and efficacy of dronabinol as a function of dose. As shown in Table 1, drowsiness and other nonpsychotropic symptoms are as common in patients receiving ≤ 7 mg/m^2 as in those receiving >7 mg/m^2. Drowsiness and sedation are often related to other concomitant medications and the stress of disease and therapy together. However, the incidence of dysphoric effects was only 12% in the low-dose group as compared to 28% in the high-dose group.

Table 2 shows a metaanalysis of response to treatment as a function of dronabinol dose. While the incidence of dysphoric effects was reduced in the low-dose group, efficacy was not. Thus it appears that use of a relatively low dose of dronabinol can minimize side effects while maintaining therapeutic benefit. Several new studies have been conducted over the past several years. The following discussion reviews several of these studies:

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TABLE 1

DOSE RELATIONSHIP TO DRONABINOL SIDE EFFECTS

	Dronabinol Used as an Antiemetic Metaanalysis of 454 Patients	
	≤7 mg/m²	>7 mg/m²
	Percent of Patients	
No side effects	23	13
Nondysphoric effects (drowsiness, dizziness, etc.)	65	58
Dysphoric effects	12	28

use of dronabinol in combination as an antiemetic, and use of dronabinol as an appetite stimulant in cancer and HIV-infected patients.

DRONABINOL AND PROCHLORPERAZINE IN COMBINATION FOR TREATMENT OF CANCER CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Previous studies have suggested that combining dronabinol with a phenothiazine may improve efficacy while decreasing the adverse effects of each drug (1, 10, 14). To further evaluate the efficacy of the combination versus each individual drug, dronabinol and prochlorperazine were tested alone and in combination in a double-blind, parallel group, multicenter study (16). Patients received cancer chemotherapy other than high-dose cisplatin. They were randomized to receive either (A) dronabinol 10 mg q.i.d. plus placebo; (B) prochlorperazine 10 mg q.i.d. plus placebo; or (C) dronabinol and prochlorperazine, each 10 mg q.i.d. Antiemetic treatment was begun 24 hours prior to chemotherapy and continued for 24 hours after the last dose.

A total of 62 patients were randomized to the three groups: 21 each in the dronabinol and prochlorperazine single agent groups and 20 in the combination group. Groups were similar with regard to age, sex, body surface area, tumor type, emetogenicity and duration of chemotherapy. The most common tumor types were breast (24 patients), lymphoma (17 patients) and lung cancers (8 patients). For evaluation of patient characteristics, disposition and side effects, Chi-square and Fisher's Exact Test analyses were used. Wilcoxon's Rank Test was used to compare medians in efficacy analyses. Differences between groups were considered significant if the two-tailed p value was ≤ 0.05.

Side effects, which were generally mild, occurred in 76% of patients receiving dronabinol alone, 33% of those receiving prochlorperazine alone, and 55% of those receiving the combination. The most common side effects were neurologic, including sedation. Dysphoric effects were most common in the dronabinol only group (8 patients). None of the patients in the prochlorperazine group and only three patients in the combination group experienced dysphoric effects. It thus appears that the dysphoric effect of dronabinol is counteracted to some extent by prochlorperazine.

TABLE 2

DOSE RELATIONSHIP TO DRONABINOL EFFICACY

	Dronabinol Used as an Antiemetic Metaanalysis of 750 Courses of Therapy	
	≤7 mg/m²	>7 mg/m²
	Percent of Patients	
Complete response	36	33
Partial response	32	31
Poor response	32	36

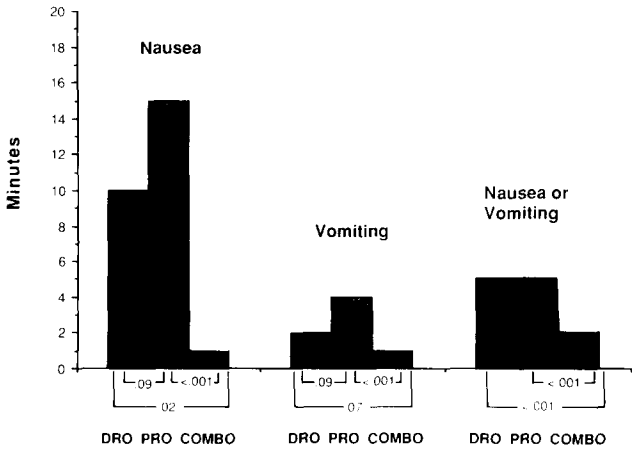

FIG. 1. Dronabinol/prochlorperazine combination antiemetic study: Median duration per episode of nausea, vomiting, and nausea or vomiting.

There was a trend to decreased incidence of nausea and vomiting in the combination group, as compared to the single agent groups: 53% of patients in the combination group, 59% in the dronabinol group and 70% of those in the prochlorperazine group experienced nausea or vomiting. As shown in Fig. 1, there was a highly significant decrease in median duration per episode of nausea and vomiting in patients receiving the combination as compared to either agent alone. In addition, there was a trend toward decreased duration in the dronabinol group as compared to the prochlorperazine group.

Severity of nausea was measured on a visual analog scale. This is a card with a 100 mm line. At one end it says "no nausea" and at the other "severe nausea." The patient marks the scale to show the relative intensity of the parameter being measured, and the line segment is measured. As shown in Fig. 2, the median severity of nausea was far lower for patients on the combination regimen than for those receiving either single agent.

Phenothiazines are thought to act as antiemetics by blocking dopamine receptors in the chemoreceptor trigger zone (27). The antiemetic mechanism of action of dronabinol is not known. In animal studies, however, Δ-9-tetrahydrocannabinol has concentration-dependent effects on both 5-hydroxytryptamine and norepinephrine (11). In rats, cannabinoid receptors, found in significant

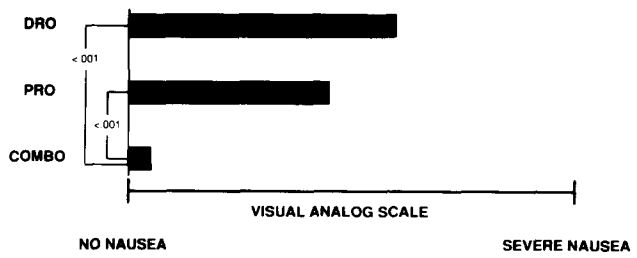

FIG. 2. Dronabinol/prochlorperazine combination antiemetic study: Median severity of nausea.

TABLE 3

PATIENT CHARACTERISTICS: DRONABINOL IN CANCER PATIENTS

	Treatment Group				
	2.5 mg q.d.	2.5 mg b.i.d.	5 mg q.d.	5 mg b.i.d.	All
Number of patients	8	9	19	6	42
Sex					
Male	8	6	13	6	33
Female	0	3	6	0	9
Body surface area, M^2	1.7	1.6	1.7	1.8	1.7
Median					
Range	1.6–1.9	1.4–1.9	1.3–1.9	1.5–2.0	1.3–2.0
Karnofsky performance status					
Median	90	70	80	80	80
Range	70–100	70–90	70–100	60–100	60–100
Previous THC exposure	0	1	2	1	4
Primary tumors					
Lung	5*	1	8*	1	15
Prostate	1*	0	6*	3	10
Colon	2	2	0	1	5
Melanoma	1	1	1	0	3
Other†	0	5	5	1	11

*One patient in each of the 2.5 mg q.d. and 5 mg q.d. groups had a double primary, lung and prostate.

†2.5 mg b.i.d.: endometrial, renal (2), leukemia, vocal cords; 5 mg q.d.: breast (2), endometrial, unknown primary (2); 5 mg b.i.d.: esophagus.

concentrations in the cerebral cortex and cerebellum, apparently mediate decreases in cyclic AMP levels (2). Clinically, the side effects of prochlorperazine and dronabinol are quite different. By combining two drugs with different side effect profiles and probably different modes of action, better antiemetic efficacy was achieved than with treatment with either agent alone. In addition, the antipsychotic effect of prochlorperazine may have decreased the incidence and severity of psychotropic effects of dronabinol.

In summary, fewer patients receiving dronabinol than receiving prochlorperazine experienced nausea or vomiting. These differences were similar to those in previously published studies (14, 19, 21, 24). In those studies, the composite percentage of patients with any nausea or vomiting was 51% for those receiving dronabinol and 83% for those receiving prochlorperazine. Dronabinol was more effective than prochlorperazine in decreasing the duration of episodes of nausea and of vomiting. Combining the two drugs reduced the side effects, especially dysphoric symptoms. The combination was more effective than either agent alone in controlling chemotherapy-induced nausea and vomiting.

DRONABINOL FOR APPETITE STIMULATION IN CANCER PATIENTS

We have conducted two multicenter, open, dose-ranging studies on the effect of dronabinol as an appetite stimulant in cancer patients. These studies were undertaken based on anecdotal reports from cancer patients and others smoking marijuana. In addition, an earlier study by Regelson et al. (23) demonstrated improvement in appetite and weight gain in cancer patients given dronabinol.

Patients on the first study were treated for three weeks, after a one-day baseline evaluation. Use of chemotherapy was not allowed. On the second study, patients were observed for three days without medication and then treated for six weeks. Patients on the second study could be receiving chemotherapy. If they were, the baseline was taken immediately before chemotherapy; patients could receive one course of chemotherapy during the study period. Treatment was with 2.5 mg q.d., 2.5 mg b.i.d., 5 mg q.d. or 5 mg b.i.d.

A total of 42 patients were treated on these studies; patient characteristics are shown in Table 3. The number of patients in each group was not balanced; the largest group was that of patients receiving 5 mg q.d. Karnofsky performance status was good for all patients. Only four patients noted prior exposure to THC, either as a pharmaceutical or as marijuana. The most common tumor types were lung (15), prostate (10) and colon (5) cancers. Statistical tests were the same as those used in the antiemetic study described above.

Patients were considered evaluable if they received at least three weeks of therapy. Therefore, patients on the first study had to complete the entire course of therapy; patients on the second had to complete only half to be considered evaluable. About half the patients terminated the study early. Ten patients (24%) terminated because of side effects. The lowest rates of termination for side effects were in the 2.5 mg q.d. and b.i.d. groups, only one patient in each group. The side effects most commonly associated with discontinuation of therapy were dizziness, memory or mood changes. Most patients discontinuing therapy had more than one side effect related to medication.

Many of the side effects reported may have been related to underlying disease or concomitant medications rather than to dronabinol. The most common side effects were weakness and fatigue, dizziness, drowsiness, and memory or concentration difficulties. Psychotropic effects were noted by none of the patients in the 2.5 mg q.d. group, four in the 2.5 mg b.i.d., eight in the 5 mg q.d., and two in the 5 mg b.i.d. group.

Patients treated with 5 mg q.d. on the initial study received their dose before breakfast. Those treated on the second study received their dose before dinner. Four of ten patients in the first but only two of nine patients in the second study dropped out because of side effects. It appears that a morning dose, on an

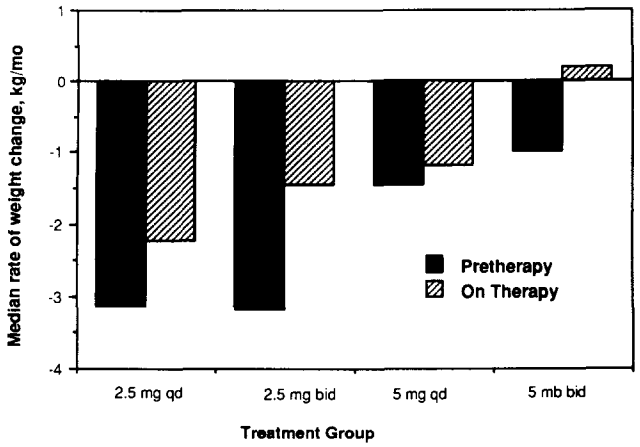

FIG. 3. Dronabinol for appetite stimulation in cancer patients: Rate of weight change.

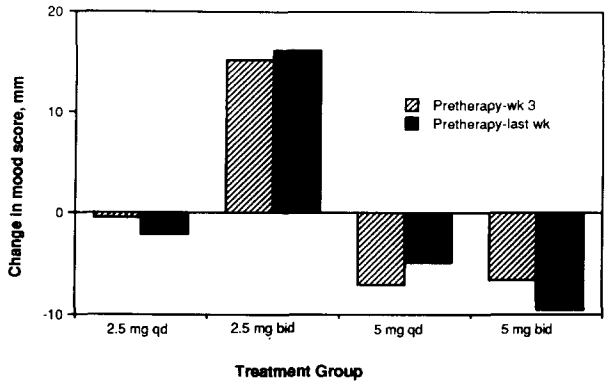

FIG. 5. Dronabinol for appetite stimulation in cancer patients: Mood changes.

empty stomach, may cause more severe side effects than a dose taken later in the day, after eating. Whether this is due to differences in absorption or to circadian pharmacologic effects is not known.

Weight change on treatment was compared to change during the 60 days prior to starting study medication. Overall, no group gained a significant amount of weight while on study, though some individual patients did actually gain weight. However, there was a reduction in the rate of weight loss in all groups. The median rates of weight loss before and on therapy are shown in Fig. 3. The reduction in the rate of weight loss was significant for the 2.5 mg q.d. and 5 mg q.d. groups ($p<0.05$).

Appetite and mood were evaluated with visual analog scales. For appetite, cards were completed before each meal; for mood, cards were completed each day before lunch. The defining terms for appetite were "Extremely Hungry" and "Not Hungry at All." For mood, the defining terms were "Very Cheerful" and "Extremely Depressed." The median changes in appetite scores from baseline to week 3 and the end of the study are shown in Fig. 4. There was a trend toward an increase in appetite scores at the end of the study ($p=0.08$, compared to baseline) for the 2.5 mg b.i.d. group. Comparing the 2.5 mg b.i.d. group to the others, the difference was significant against the 2.5 mg q.d. and 5 mg q.d. groups ($p<0.05$). Given the small sample size and variations among patients, we feel this difference, which represents a 47% increase over baseline, is clinically meaningful.

Figure 5 shows the effect of dronabinol on mood visual analog scores. The changes in the mood visual analog scores showed a similar pattern: an increase for the 2.5 mg b.i.d. group. While the differences between baseline, week 3 and end of study were not statistically significant, the differences between the 2.5 mg b.i.d. group and the 2.5 mg q.d. and 5 mg b.i.d. groups were of borderline significance ($p=0.06$ and 0.05, respectively).

Several conclusions can be derived from these pilot studies. At a dose of 2.5 mg b.i.d., dronabinol was well tolerated by most patients. The rate of weight loss decreased at all dose levels; there was no clear dose-effect relationship. Dronabinol at 2.5 mg b.i.d. both stimulated appetite and improved mood.

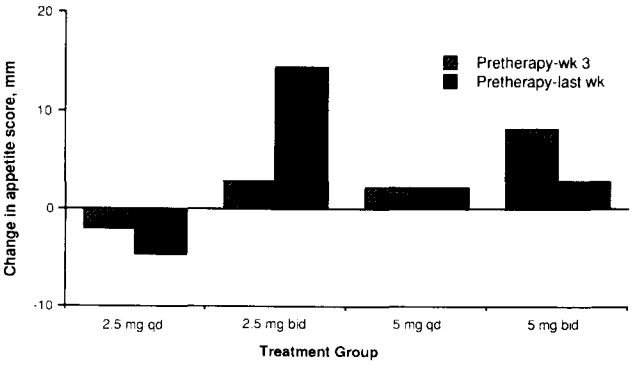

FIG. 4. Dronabinol for appetite stimulation in cancer patients: Appetite changes.

DRONABINOL FOR APPETITE STIMULATION IN PATIENTS WITH SYMPTOMATIC HIV INFECTION

Dr. Robert Gorter of San Francisco General Hospital has treated ten symptomatic HIV patients with dronabinol. This was done both to stimulate appetite per se and to relieve nausea from

TABLE 4

PATIENT CHARACTERISTICS: DRONABINOL IN AIDS PATIENTS

Number of Patients	10
Age, years	
Median	36
Range	30–53
Time from HIV diagnosis, years	
Median	1.9
Range	0.6–4.2
Number of patients with	
Orocutaneous fungal infections	8
Herpetic infections	7
Pneumocystis carinii pneumonia	5
Kaposi's sarcoma	2
CNS manifestations of HIV	2
Other HIV-related problems (one patient each)	
CNS toxoplasmosis	
Cytomegalovirus colitis	
Mycobacterium avium intracellular	
Pulmonary tuberculosis	

antiviral chemotherapy. Table 4 shows patient characteristics for the ten patients. The patients studied were all homosexual males; one had a history of intravenous drug abuse as well. The infectious complications they had represent the spectrum of those usually seen in a symptomatic HIV-infected population. Patient characteristics are shown in Table 4.

Most of the patients had received or were on antiviral therapy, primarily zidovudine (azidothymidine). Two had previously received and one was receiving megestrol acetate as well.

Patients received dronabinol, usually at a dose of 2.5 mg, for one to five months; most were continuing on treatment at the time of this analysis. Frequency of dosing varied; patients were instructed to take medication t.i.d. as needed; many took it somewhat less often.

Initially, patients were losing a median of 0.93 kg/month. On therapy, they gained 0.54 kg/month. The median difference on versus pretherapy was 1.92 kg/month ($p = 0.01$, Wilcoxon signed-rank test). Seven of the patients actually gained weight on dronabinol; two of the others lost less weight while on dronabinol. Patients tolerated a low daily dose over a period of months. They were able to adjust the dose to avoid side effects yet retain therapeutic efficacy. Formal dose-ranging studies are currently under way.

SUMMARY

Dronabinol has now been marketed in the U.S. for four years. It has an extremely good safety profile. While side effects occur fairly often, they are usually mild and resolve quickly and without sequelae on discontinuation of treatment.

Drug diversion and inappropriate prescribing of dronabinol have not been reported. In fact, physicians and patients often seem reluctant to use the medication because it is a cannabinoid. However, dronabinol appears at least as safe as many other antiemetics and much safer than many other controlled substances.

A number of randomized, placebo-controlled studies have demonstrated good antiemetic efficacy of dronabinol, both alone and in combination. In open appetite studies for both cancer and symptomatic HIV infection, doses which are tolerable for chronic administration have been effective in stabilizing or improving weight, and enhancing appetite.

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