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Suppression of Cancer Chemotherapy-Induced Vomiting in the Cat by Nabilone, a Synthetic Cannabinoid[1] (40465)

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Marijuana and its major active derivative Δ9-tetrahydrocannabinol have been credited with the ability to suppress the vomiting encountered in patients undergoing cancer chemotherapy (1). More recently, the same antiemetic property has been attributed to nabilone, a crystalline synthetic cannabinoid with psychotropic activity (2, 3). Antiemetic effectiveness is difficult to determine in man owing to the large subjective factor in nausea and vomiting and because the extent of vomiting has not been definitively established in each of the diverse chemotherapeutic regimens being employed clinically. The purpose of the present work was to measure in cats the antiemetic activity of nabilone against certain well established emetic agents and some representative anticancer drugs.

Materials and methods. Eighty-five healthy adult cats were used in this study. A jugular venous catheter was implanted with sterile precautions into each cat at least three days prior to drug testing. Animals scheduled to receive apomorphine were provided additionally with an intracranial cannula placed stereotaxically in the right lateral cerebral ventricle (4). Vomiting induced by the injection of apomorphine (0.25 mg in 0.25 ml H_2O) served in itself as functional confirmation of proper cerebroventricular cannulation.

In addition to apomorphine HCl (Mallinckrodt) given intracerebroventricularly, nicotine salicylate (Fisher) and the digitalis glycoside deslanoside (Cedilanid-D, Sandoz) were given intravenously to evoke vomiting responses representative of the classic drug types. The chemotherapeutic drugs we employed to produce emetic reactions as occur in cancer clinics were 1,3-*bis*-(2-chlorethyl)-1-nitrosourea (BCNU), mechlorethamine (HN2), and *cis*-diamminedichloroplatinum II (*cis*-Pt) made available by the Norris Cotton Cancer Center. These drugs were in every case administered as a single dose by slow injection through an indwelling intravenous catheter in the unrestrained awake cat. Solutions were prepared according to package directions with slight modification when necessary to reduce total dose volume.

Nabilone, *dl*-3-(1,1-dimethylheptyl)-6,6ab 7, 8, 10, 10a alphahexahydro-1-hydroxy-6,6-dimethyl-9H dibenzo [b,d] pyran-9-one, was obtained in powder form from Eli Lilly and Co. The substance was initially dissolved at the concentration of 1 mg/ml in 50% ethanol and 50% Emulphor (GAF EL-620) to make a stock solution. This was diluted tenfold in water for iv injection. Prochlorperazine (Smith, Kline and French), was used from commercial ampoules for comparison of its antiemetic effectiveness with that of nabilone. The nabilone solution vehicle, i.e. 5% ethanol and 5% Emulphor, was given as the non-drug pretreatment to all cats in which control tests of emetic drug activity were performed.

The emetic response was scored and analyzed as an all-or-none event. Hence, neither severity nor repetition of vomiting was taken into account in evaluating emetic or antiemetic effectiveness. Response latency was measured as the time interval between injection of the emetic agent and the first emetic episode. An 8-hour observation limit was set for scoring a negative control effect or a suppressed response after antiemetic pretreatment. This latency cut-off was chosen because other pathophysiological mechanisms, unrelated to the primary emetic stimulus, could result in vomiting as a late effect. Further explanation is given below.

Results. Behavioral effects of nabilone. Intravenous injection of 25–200 μg/kg nabilone

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produced effects which appeared in 2–5 min, became fully developed soon thereafter and lasted from 12 to 24 hr. The effects consisted of mild ataxia and display of pleasure at 25 μg/kg (4 cats), more severe ataxia and hyperstartle responses at 50 μg/kg (8 cats) and severe locomotor disturbance, catatonic behavior, mixed excitement and depression and vocalization at 100 μg/kg (21 cats). All of these signs were compressed and intensified at 200 μg/kg of nabilone. Frank hypothermia was observed in one cat that received 500 μg/kg.

Nabilone vs. apomorphine, deslanoside and nicotine. Apomorphine, 0.25 mg intraventricularly, regularly produces one or two bouts of vomiting within 1.5–5 min after injection followed by rapid recovery. By contrast, intravenous deslanoside (0.12–0.16 mg/kg) evokes emesis reliably within one hour after injection but vomiting usually continues sporadically for many hours or even days thereafter. The antagonistic effect of nabilone on these emetic drug stimuli is shown in Fig. 1. The antiemetic ED50 was approximately 75 and 150 μg/kg *vs* apomorphine and deslanoside, respectively. It should be noted that the doses of nabilone which afforded the greatest protection against apomorphine- and deslanoside-induced vomiting were also those which evoked pronounced behavioral disturbance. Thus, as a compromise between antiemetic effectiveness and severity of side effects, the intravenous dose of 100 μg/kg nabilone was employed as the standard pretreatment within 1–2 hr for all subsequent tests of emetic antagonism.

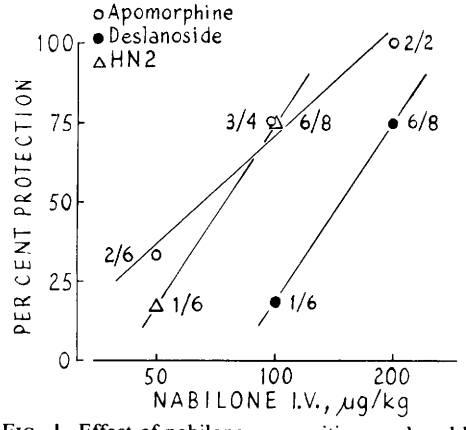

FIG. 1. Effect of nabilone on vomiting produced by apomorphine (0.25 mg/ml icv), deslanoside (0.12–0.16 mg/kg, iv) and HN2 (5 mg/kg, iv). HN2 is mechlorethamine. Nabilone was given 1–2 hr prior to the emetic challenge. Points show number of animals protected/number of animals tested.

Nicotine was used as an emetic stimulus by two modes of intravenous administration, either by bolus injection of 20–50 μg/kg or by infusion of 50–100 μg/min up to the emetic threshold. Emesis was evoked in 19 tests on five cats. Following pretreatment with nabilone, vomiting occurred in response to nicotine in all of 8 tests with an increase in emetic threshold resulting in one instance. Thus, unlike the situation for apomorphine and deslanoside, no evidence was obtained for antagonism of nicotine-induced vomiting by nabilone.

Nabilone vs. anticancer agents. The vomiting response to sufficient doses of anticancer drugs occurs in two distinct stages. The early stage of vomiting, occurring within 8 hours after injection, is considered to be a direct neuroexcitatory effect and was of primary interest to us as pertains to clinical practice. The large doses required to obtain consistent early vomiting were usually lethal after a phase of protracted late vomiting which resulted from generalized systemic toxicity of the anticancer drugs. Therefore, the cats were, except where indicated, routinely sacrificed no later than 8 hr after the emetic test drug injection.

Observations on the emetic activity of the cancer chemotherapeutic agents and the suppressant effect of nabilone are summarized in Table I. The results were evaluated statistically with the Chi Square test. All differences

TABLE I. EFFECT OF PRETREATMENT WITH NABILONE (100 μg/kg) ON THE EARLY VOMITING INDUCED BY CANCER CHEMOTHERAPEUTIC AGENTS. ALL DRUGS WERE ADMINISTERED INTRAVENOUSLY IN CATS.

Anti-cancer drug	Dose mg/kg	Nonpretreated		Nabilone pretreated[a]	
		No. Trials	No. Vomited	No. Trials	No. Vomited
BCNU	10	13	5	10	0
	20	9	6	4	0
HN2	5	5	5	8	2
cis-Pt	5	2	2	—	—
	10	6	5	11	2

[a] All differences between non-pretreated and pretreated groups were significant at the 0.05 level as determined by the Chi Square test.

between control and antiemetic trials were significant at the probability level of .05 or less.

BCNU. At 10 mg/kg iv, which was sublethal, BCNU elicited vomiting in 5 of 13 trials. Even the lethal dose of 20 mg/kg produced vomiting in only 6 of 9 animals. However, the mean latency to vomiting was reduced from 130 min at 10 mg/kg to 80 min at 20 mg/kg BCNU. Following pretreatment with nabilone, not a single instance of vomiting resulted from injection of BCNU at either test level in 14 trials.

HN2. At the lethal dose level of 5 mg/kg iv, HN2 produced vomiting in all of 5 cats with an average latency of 16 min. Pretreatment with nabilone reduced the incidence of vomiting after HN2 to 2 in 8 trials (see Fig. 1). Moreover, the average latency to emesis was prolonged to 209 min in the responding animals.

cis-Pt. The lethal dose of 5 mg/kg iv *cis*-Pt caused vomiting in both of two cats with a long average latency of 4 hr. At 10 mg/kg iv, the average latency of emesis was reduced to 2 hr in 5 responders out of six cats tested. Following pretreatment with nabilone, only 2 of 11 animals vomited in response to 10 mg/kg *cis*-Pt at an average emetic latency greater than 3 hr.

Thus nabilone afforded a significant degree of protection against vomiting evoked by all of the anticancer drugs employed in this study.

Comparison of prochlorperazine and nabilone against HN2. Groups of four cats were pretreated with prochlorperazine at 1 and 4 mg/kg iv and challenged after one hour with 5 mg/kg iv HN2, already established as a consistent emetic dose. The results are given in Table II. In no case was protection against vomiting afforded by prochlorperazine even though the drug produced locomotor disturbance. Thus, it is evident that the antiemetic activity of nabilone is not simply the result of nonspecific neurological impairment.

Discussion. Nature of the emetic stimuli. According to Wang and Borison (5) the vomiting center in the reticular formation of the medulla oblongata is not directly responsive to chemical emetic stimuli. Hence vomiting from every cause must be initiated at one or more receptor site(s), whether located inside or outside of the neuraxis, from which the provocative signal(s) are then transmitted via the appropriate afferent neural pathway(s) to the vomiting center. The chemoreceptor trigger zone (CTZ) for emesis, situated in the area postrema on the lateral margins of the IVth ventricle, has been implicated in many vomiting responses resulting from both pharmacological and pathophysiological stimuli. In particular, the primary responses to apomorphine and digitalis (deslanoside) are mediated exclusively by the CTZ, even though they operate through different macromolecular receptors (6). For example, apomorphine-induced vomiting is blocked by dopamine receptor antagonists which do not interfere with deslanoside-induced emesis; yet ablation of the CTZ abolishes both emetic responses without interrupting other afferent inputs for vomiting (5). The reflex mechanisms of vomiting induced by nicotine and the anticancer drugs are more complex but they likely involve a component of action at the CTZ (7, 8).

TABLE II. EFFECT OF PRETREATMENT WITH INTRAVENOUS PROCHLORPERAZINE ON THE EARLY VOMITING INDUCED BY HN2 (5 mg/kg, iv) IN CATS.

Prochlorperazine pretreatment dose mg/kg	Response to HN2	
	No. trials	No. vomited
None	5	5
1.0	4	4
4.0	4	4

Spectrum of emetic antagonism by nabilone. The results show that, in the cat, nabilone blocks vomiting initiated by apomorphine, deslanoside, and all of the anticancer drugs tested herein but it does not antagonize the emetic effect of nicotine. Thus, the spectrum of emetic blockade by nabilone does not conform to the chemosensitivity of any known pharmacological or morphological receptor type. In this connection, other work in this laboratory has demonstrated that naloxone, an opiate antagonist, is capable of reversing the blocking action of nabilone against apomorphine- and deslanoside-induced vomiting (9).

Probable locus of antiemetic action. Two factors apply to the definition of a locus of drug action, namely pharmacological selectivity and anatomical site. Among the available antiemetic drugs, the narcotics stand out as having the widest spectrum of action (6).

Since narcotic blockade of vomiting encompasses neural inputs of diverse origins, the opiate action is best assigned to a point of convergence in the reflex pathway, most advantageously at the vomiting center itself. In contrast, the phenothiazine drugs as represented by prochlorperazine have a more restricted sphere of antiemetic action expressed against dopaminergic agonists such as apomorphine (10). A solitary action of nabilone at the CTZ could not explain its antiemetic effectiveness against the anti-cancer drugs which are known to involve other inputs to the vomiting center. On the other hand, the spectrum of antiemetic activity of nabilone does not appear to match that of the narcotics though some overlap is evident.

Quite recently, Shannon *et al.* (11) reported on their inability to demonstrate an antiemetic effect of Δ9-tetrahydrocannabinol against apomorphine infused intravenously in dogs. Reconciliation of that report with the present work on nabilone in cats is not feasible owing to differences in experimental conditions, drug forms and species employed. Furthermore, those investigators made no mention of the behavioral influence of cannabinoid treatment in the dogs.

Two clues suggest that nabilone may act on the forebrain to suppress vomiting from various causes. First, the behavioral concomitants of emetic blockade observed clinically and in the laboratory indicate that psychomotor disturbance engendered by nabilone is a correlate of antiemetic effectiveness. Second, it has been shown that the vomiting evoked by HN2 involves long pathways from the abdominal viscera through the forebrain (8). Antagonism of the depressant actions of nabilone by naloxone suggests that "endogenous opiates" may be a link in the descending suppressant influence of the cannabinoid from the forebrain upon the vomiting center against selected inputs for emesis.

Summary and conclusion. Nabilone, a synthetic cannabinoid, has been shown to have a unique spectrum of antiemetic activity in the cat. Doses of nabilone (25–100 μg/kg) required to suppress emesis induced by apomorphine, deslanoside and the anticancer drugs BCNU, HN2 and *cis*-Pt produced behavioral disturbances concomitantly. Vomiting evoked by nicotine was not blocked by nabilone. It is suggested that the emetic suppressant action of nabilone is effected in the forebrain in association with its psychotropic influence to cause an inhibition of the vomiting control mechanism in the medulla oblongata through descending connections. We conclude that the results with nabilone in an appropriate animal model confirm the clinical finding that the cannabinoids provide therapeutic benefit against the severe vomiting of cancer chemotherapy.

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