

Antiemetic efficacy of smoked marijuana

Subjective and behavioral effects on nausea induced by syrup of ipecac

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Received 30 October 2000; received in revised form 13 February 2001; accepted 19 February 2001

Abstract

Although the public debate about the legalization of marijuana has continued for as long as 25 years, few controlled studies have been conducted to assess its potential medical benefits. The present study examined the antiemetic effect of smoked marijuana cigarettes (8.4 and 16.9 mg Δ^9 -tetrahydrocannabinol [THC]) compared to a highly potent antiemetic drug, ondansetron (8 mg) in 13 healthy volunteers. Nausea and emesis were induced by syrup of ipecac. Marijuana significantly reduced ratings of “queasiness” and slightly reduced the incidence of vomiting compared to placebo. Ondansetron completely eliminated the emetic effects of ipecac. These findings support and extend previous results, indicating that smoked marijuana reduces feelings of nausea and also reduces emesis in this model. However, its effects are very modest relative to ondansetron, and the psychoactive effects of marijuana are likely to limit its clinical usefulness in the general population. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Ipecac; Marijuana; Nausea; Ondansetron; Smoking; Subjective effects

1. Introduction

Marijuana is believed to have potential for a variety of therapeutic applications, including the relief of nausea associated with chemotherapy (Ko and Woods, 1999; Vinciguerra et al., 1988). Indeed, the primary constituent of marijuana, Δ^9 -tetrahydrocannabinol (THC), is approved by the Food and Drug Administration (FDA) for oral administration as an antiemetic for cancer patients undergoing chemotherapy. However, few studies have examined the antiemetic effects of smoked, whole plant marijuana. Smoked marijuana may have several benefits over oral Δ^9 -THC as a therapeutic agent. First, marijuana has a more rapid onset of effect than orally administered Δ^9 -THC. This provides the patient with more rapid relief from the symptoms, and it may also make it easier for the patient to control the dose. Secondly, the smoked route is associated with higher peak concentrations of drug, which may be beneficial to manage acute bouts of nausea.

Thirdly, it is possible that other constituents in the whole plant material may contribute to the therapeutic effects or reduce some of the less desirable effects of pure Δ^9 -THC (Ohlsson et al., 1980). Finally, although smoking is likely to be an unacceptable route of administration for some patients, it may be of particular value to other patients, such as those who have difficulty with taking medications by mouth.

It is not clear how Δ^9 -THC produces its antiemetic effects. Emesis is thought to be controlled by a cluster of neurons in the medulla oblongata, which receives afferent input from various central and peripheral pathways, depending upon the location of the emetogenic stimulus (Leslie et al., 1990; Naylor and Rudd, 1994). Three neuropharmacological pathways to the emetic center have been elucidated (Takeda et al., 1993). The first pathway involves the release of serotonin (5-HT₃) from enterochromaffin cells of the gastrointestinal tract. This release stimulates transmission via the splenic nerve to the emetic center (Costall and Naylor, 1992; Cubeddu, 1992; Takeda et al., 1993), and it is the mechanism through which cancer chemotherapeutic drugs such as cisplatin are believed to induce nausea. Another pathway for emetic effects is through histaminergic and cholinergic systems originating in the vestibular laby-

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rinth (Takeda et al., 1993). The last pathway originates in the area postrema in the fourth ventricle, which is thought to contain the “chemotrigger zone” that mediates emesis induced by dopamine (D_2) agonists such as apomorphine (Takeda et al., 1993). Given that emesis can be induced via separate neuropharmacological mechanisms, the efficacy of an antiemetic drug may be dependent upon the particular pathway it affects. For example, ondansetron, which is a 5-HT₃ antagonist, has been shown to be more effective than D_2 antagonists at reducing cisplatin-induced emesis (Naylor and Rudd, 1994). Although clinical studies have shown that oral Δ^9 -THC is a safe and effective treatment of nausea and vomiting in individuals receiving cancer chemotherapy (Lane et al., 1991; Lewitt, 1986; Ungerleider et al., 1982; Vincent et al., 1983), the mechanism by which Δ^9 -THC produces its antiemetic effects is not known. There have been no direct comparisons of the antiemetic efficacy of marijuana or Δ^9 -THC and 5-HT₃ antagonists, nor has there been systematic investigation of the effectiveness of Δ^9 -THC or marijuana in reducing emesis induced by different pathways. The purpose of the present study was to examine whether smoked marijuana reduces emesis induced by syrup of ipecac. Ipecac, like cisplatin, acts by releasing serotonin in the gastrointestinal tract.

2. Materials and methods

2.1. Subject recruitment and screening

Thirteen volunteers (nine men and four women) aged 18–26 were recruited from the university and surrounding community via newspaper advertisement and posters. Subjects were accepted without regard to race or ethnic origin, as long as they were fluent in English and had a minimum of a high school education. Volunteers who passed an initial structured telephone interview completed a health questionnaire detailing their medical and current lifetime recreational drug use, a marijuana use questionnaire, and a psychiatric symptom checklist (Derogatis, 1983). A psychiatric social worker evaluated the completed questionnaires and conducted a structured psychiatric interview to rule out candidates with any major psychiatric disorder defined by the DSM-IV Axis 1 criteria (American Psychiatric Association, 1994). Inclusion criteria relating to marijuana use were (i) use of marijuana for at least 1 year, (ii) use of marijuana at least 10 times in their lifetime and (iii) use of marijuana within the past 2 months. There was no limit on the quantity of marijuana use, but subjects who met criteria for Abuse or Dependence were not accepted. Candidates with a history of drug or alcohol abuse or dependence, or with a history of cannabis-induced disorders (DSM-IV criteria) were excluded. Screening also included a physical examination and an electrocardiogram. Candidates were excluded if they had a history of (i) cardiovascular disease, including high or low blood pressure, (ii) asthma or other pulmonary disease

or (iii) liver disease. Women were excluded if they were or expressed intent to become pregnant and pregnancy tests were performed prior to inclusion in the study.

2.2. Design

Subjects participated in a within-subjects study consisting of four laboratory sessions. On each session, subjects received a capsule containing ondansetron or placebo, and a cigarette containing active marijuana (moderate dose or a low dose) or placebo marijuana, followed by syrup of ipecac. The four treatment conditions were (1) ondansetron and placebo marijuana, (2) placebo capsule and a moderate dose marijuana cigarette, (3) placebo capsule and placebo marijuana cigarette, (4) placebo capsule and a low dose marijuana cigarette. The drugs were administered in a randomized order under double-blind conditions, and sessions were conducted with a minimum of 48 h between them.

2.3. Drugs

Ondansetron (GlaxoWellcome; 8 mg, 5-HT₃ antagonist) was placed in opaque gelatin capsules and filled with dextrose. The placebo capsules only contained dextrose. Active and placebo marijuana cigarettes were obtained from the National Institute on Drug Abuse (NIDA). Each active cigarette contained 800-mg marijuana with a Δ^9 -THC content of $2.11 \pm 0.06\%$ (w/w). In the moderate dose condition, subjects smoked an active marijuana cigarette containing 16.9 mg Δ^9 -THC. The cigarette was administered in two half cigarettes. In the low dose condition, subjects smoked half of an active cigarette and half of a placebo cigarette, resulting in a dose of 8.4 mg Δ^9 -THC. In the placebo condition, subjects smoked two halves of a placebo cigarette. The active marijuana cigarettes also contained 0.30% cannabinal and 0.05% cannabidiol. Syrup of ipecac, a serotonin agonist that induces nausea (5 ml unit doses; University of Chicago pharmacy), was administered to the subjects mixed with 20 ml of Ora-Sweet Syrup vehicle, Paddock Laboratories. This is the smallest effective dose of ipecac that has been used in research with humans (Goldenberg et al., 1976). It is important to note that syrup of ipecac can be confused with ipecac extract, which can be very toxic.

2.4. Laboratory environment

This study was conducted in the recreational laboratory environment in the Human Behavioral Pharmacology Laboratory (HBPL), Department of Psychiatry, University of Chicago. The recreational environment consists of three rooms each furnished to resemble a living room. The rooms have an incandescent lighting, couches and upholstered chairs, casual tables with magazines and board games, posters on the walls, televisions and VCRs with a choice of movies. Subjects were tested individually. When not

completing questionnaires, they were encouraged to engage in recreational activities of their choice, but they were not allowed to work or study.

3. Procedure

Prior to participation, subjects signed a written consent form describing the details of the procedures. Subjects were informed that the cigarettes might contain marijuana or placebo plant material and that the capsule might contain one of several drugs including stimulant/appetite suppressant, sedative/tranquilizer, antihistamine, emetic, cannabinoid, antiemetic or placebo. They were told that the purpose of the study was to investigate the effects of drugs on mood and behavior. Subjects agreed to refrain from recreational drug use for 24 h prior to and 12 h following test sessions. Subjects were informed that they would be dropped from the study if extracurricular drug use was detected in urine screens.

Each experimental session was conducted between 08:45 and 15:30 h. Upon arrival for each session, subjects provided a urine sample for drug and pregnancy screening (women only), and blood alcohol level was estimated by breath alcohol level (BAL) using an Alco-Sensor III handheld breathalyzer (Intoximeters, St. Louis, MO). At 09:00 h, vital signs (e.g., diastolic/systolic blood pressure and heart rate) were recorded. Subjects completed a series of baseline mood and drug effect questionnaires. At 09:15 h, subjects ingested a capsule containing either ondansetron or placebo, and consumed a light breakfast. Two hours later, 15 min before taking ipecac, subjects smoked two half cigarettes (active or placebo marijuana) using the paced smoking procedure. In this procedure, the cigarette is placed in a hollow cigarette holder. Upon lighting the cigarette, the subject is instructed to (i) draw smoke into his or her mouth for 5 s, slowly and consistently, (ii) inhale room air to completely fill the lungs, (iii) hold for 10 s and (iiii) exhale. This process was repeated 45 s later, until both halves of the cigarette were finished. Consequently, the duration of each “puff” was 15 s, and one “puff” was taken every minute until the cigarette was completely smoked. Subjects smoked for approximately 10 min, and the number of “puffs” taken for each subject was recorded. Immediately after smoking, subjects completed the subjective effects questionnaires (see below), and their vital signs were measured. Five minutes after finishing the last puff from a cigarette, subjects ingested the syrup of ipecac in a volume of 25 ml. Then, subjects completed a visual analog scale rating their level of nausea and subjective state (see below) every 10 min for the next 60 min, and again 90, 120, 150, 180 and 240 min later. Vital signs (heart rate and blood pressure) were taken after 20, 40, 60, 120, 180 and 240 min. A small lunch was provided after 120 min. Subjects were discharged at 15:15 h, 240 min after the beginning of the session. After completing the four sessions, subjects attended a debriefing

session in which questions were answered and they were paid for their participation.

3.1. Dependent measures

Subjective effects of marijuana were assessed with the Addiction Research Center Inventory (ARCI; Martin et al., 1971) and the Visual Analog Mood Scale (VAS; Folstein and Luria, 1973). The ARCI consists of 53 true–false questions with six empirically derived scales, all sensitive to the effects of several drug classes: M (marijuana scale), A (amphetamine-like: stimulants effects), BG (benzedrine group: energy and intellectual efficiency), MBG (morphine–benzedrine group: euphoric effects), LSD (lysergic acid diethylamide: dysphoric effects, somatic complaints and PCAG (pentobarbital–chlorpromazine–alcohol group: sedative effects). The VAS test assessed current drug effects and consisted of 11 adjectives and visual analog scale (queasy, nauseated, feel drug, stimulated, anxious, elated, interested, content, drowsy, sedated, hungry). These questions were presented on a 100-mm line with the extremes “feel not at all” to “feel extremely.” Nausea and queasiness are referred to in the text as a subjective state. Both the ARCI and the VAS test were evaluated using questionnaires administered via computer. Blood pressure and heart rate were assessed using a Dinamapp vital signs monitor Model 1846 (Criticon, Tampa, FL). The technician conducting the session, who was blind to the drug conditions, also recorded each time a subject vomited.

3.2. Data analysis

The subjective ratings and physiological measures were analyzed with two-way repeated measure ANOVAs (drug and time) and one-way ANOVAs. The post-hoc comparisons were made using least significant difference (LSD) tests. The episodes of emesis were analyzed using chi-square test. The significance level for all statistical tests was set at $P < .05$.

4. Results

4.1. Subject demographics

Table 1 shows the demographic characteristics of the subjects participating in the study. Thirteen subjects, nine males and four females, completed the study and provided usable data. Their mean age was 21.3 ± 2.4 years and their mean weight was 80.7 ± 14.5 kg. Eleven subjects were Caucasian and two were African American. They reported a mean weekly consumption of 6.5 ± 4.5 alcoholic drinks, 8.7 ± 7.4 caffeinated drinks and 4.8 ± 7.1 nicotine cigarettes. All of the subjects also reported smoking at least half a marijuana cigarette per week.

Table 1
Demographic characteristics for the 13 subjects participating in the study

Subject demographic and drug use summary (<i>N</i> =13)	
<i>Age (years)</i>	
Range	18–26
Mean ± S.D.	21.3 ± 2.4
Weight (lb: mean ± S.D.)	169.5 ± 30.4
<i>Sex (n)</i>	
Male	9
Female	4
<i>Race/ethnicity</i>	
Caucasian	11
African American	2
<i>Education (n)</i>	
Partial college	9
College degree	2
Advanced degree	1
Full-time student (<i>n</i>)	7
<i>Current drug use</i>	
Alcohol (mean ± S.D.; drinks/week)	6.5 ± 4.5
Caffeine (mean ± S.D.; drinks/week)	8.7 ± 7.4
Cigarettes (<i>n</i> > 2.5 cigarettes/day)	6
Marijuana (<i>n</i> > 0.5 cigarettes/week)	13
<i>Lifetime drug use</i>	
Stimulants (<i>n</i> : ever used)	5
Tranquilizers (<i>n</i> : ever used)	1
Hallucinogens (<i>n</i> : ever used)	11
Opiates (<i>n</i> : ever used)	3
Marijuana	
Used 10–50 times (<i>n</i>)	1
Used >50 times (<i>n</i>)	12
Inhalants (<i>n</i> : ever used)	4

Data for age, weight, alcohol and caffeine are presented as mean ± S.E.M. and the remainder as frequency.

The significant main effects and interactions from the analysis of each dependent measure are presented in Table 2.

4.2. Effects of ipecac

Ipecac produced the expected effects of nausea and vomiting (Ilett et al., 1977) when subjects were pretreated with placebo (i.e., seven subjects vomited and six subjects reported feelings of nausea).

4.3. Vital signs

Marijuana significantly increased heart rate and diastolic blood pressure (Fig. 1 and Table 2). The post-hoc test revealed that at both doses tested (8.4 and 16.9 mg), marijuana elevated heart rate beginning 5 min after smoking, lasting for 40 min at the lower dose ($P < .02$), and almost 240 min for the moderate dose ($P < .05$). Ondansetron had no effect on heart rate. Both the moderate doses of marijuana and ondansetron increased diastolic blood pressure. The moder-

Table 2
Significant *F* values for main effects and interactions

Measure	Drug [<i>F</i> (3,21)]	Hour [<i>F</i> (7,21)]	Interaction [<i>F</i> (1,21)]
<i>Vital signs</i>			
Heart rate	13.9***	9.8***	4.25***
Systolic	NS	NS	NS
Diastolic	NS	3.5**	3.5**
	Drug [<i>F</i> (3,36)]	Hour [<i>F</i> (12,36)]	Interaction [<i>F</i> (1,36)]
<i>ARCI</i>			
Nausea	4.18**	2.71**	NS
Queasiness	NS	3.46**	1.54*
<i>VAS</i>			
Feel drug	23.3***	13.4***	3.4***
Stimulated	11.7***	3.14***	2.9***
Anxious	3.75*	NS	NS
Elated	4.7**	4.06***	1.75**
Sedated	3.5*	2.2**	NS
Interested	NS	NS	NS
Drowsy	NS	NS	NS
Content	NS	NS	NS
Hungry	NS	2.7**	NS

Significant *F* values and for the main effects and interactions of marijuana (8.4 and 16.9 mg) and ondansetron (8 mg) and hour (time within session). All significant effects were due to marijuana vs. placebo comparisons. Significant elevations over vehicle levels are denoted by an asterisk. NS refers to nonsignificant. * $P < .05$. ** $P < .01$. *** $P < .001$.

ate dose of marijuana, but not the lower dose, increased the diastolic pressure 40 min after smoking ($P < .01$). Ondansetron increased diastolic blood pressure 20 min after smoking

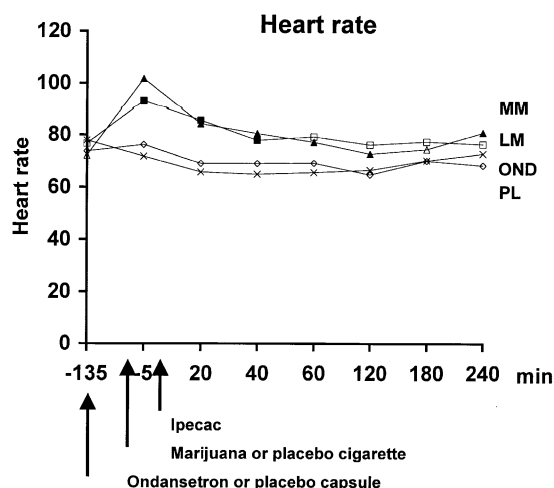


Fig. 1. Effects of marijuana and ondansetron on heart rate (mean beats per minute). At time point -135, subjects ingested a capsule containing either ondansetron or placebo and, at time point -15 min, they smoked either marijuana or placebo cigarettes. At time point 0, subjects ingested the syrup of ipecac. Significant elevations over the placebo levels ($P < .05$) are denoted with a filled symbol. The results are presented as mean ± S.E.M. MM = moderate dose of marijuana, LM = lower dose of marijuana, OND = ondansetron, PL = placebo.

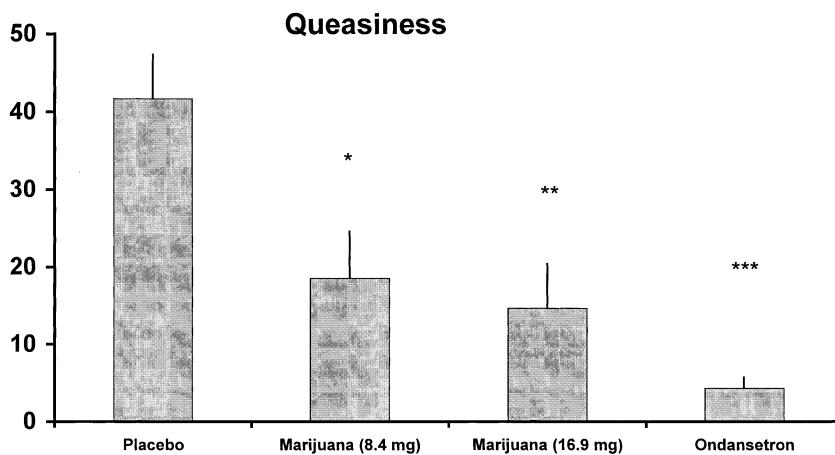


Fig. 2. Effects of marijuana and ondansetron on peak ratings of queasiness. The low and moderate doses of marijuana and ondansetron suppressed queasiness compared to the placebo condition. The results are presented as mean \pm S.E.M. Significant elevations over placebo levels are denoted by an asterisk, * $P < .05$, ** $P < .01$, *** $P < .001$.

($P < .002$). Neither marijuana nor ondansetron had any effect on systolic blood pressure.

4.4. Self report and behavioral measures

The lower dose of marijuana reduced queasiness at the 40 min time point ($P < .008$, Table 2). Ondansetron sup-

pressed queasiness at the 20, 40, 90 and 120 min after ipecac administration. The maximum ratings of queasiness were also analyzed for the three drug conditions using a one-way ANOVA. This analysis (Fig. 2) revealed that both the low ($P < .04$) and the moderate doses ($P < .01$) of marijuana as well as ondansetron ($P < .001$) suppressed queasiness compared to placebo.

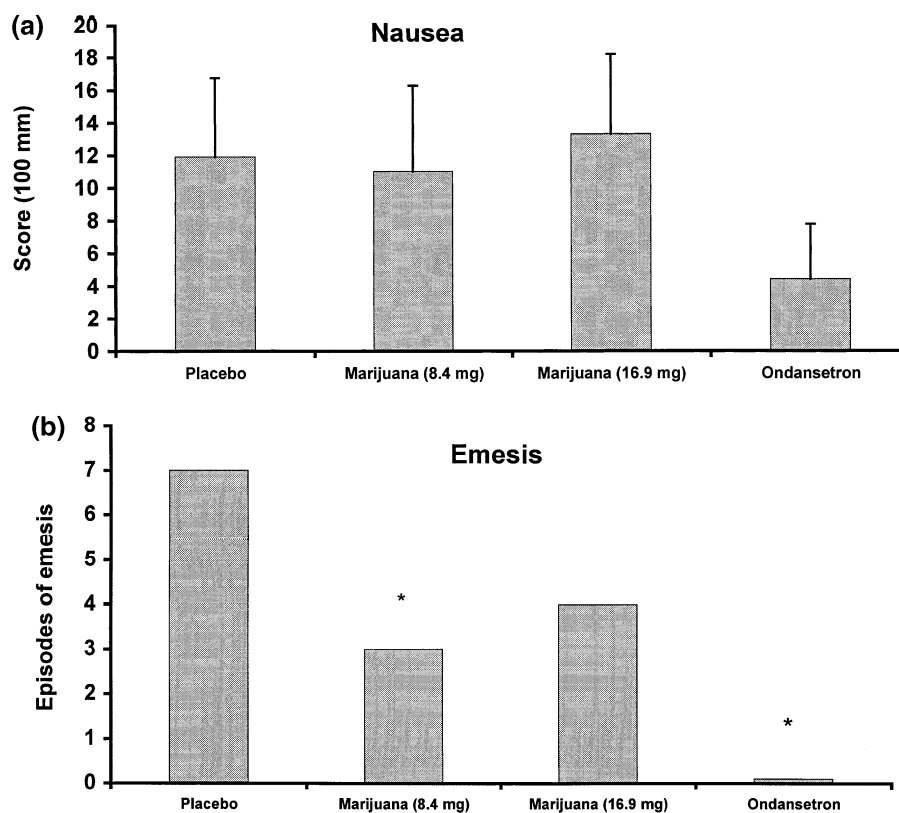


Fig. 3. (a) Effects of marijuana and ondansetron on ratings of feeling nauseous. Marijuana had no significant effect on nausea, whereas ondansetron reduced nausea. The results are presented as mean \pm S.E.M. (b) Effects of marijuana and ondansetron on the episodes of vomiting. The lower dose of marijuana and ondansetron suppressed the episodes of vomiting compared to the placebo condition. The results are presented as mean frequency. Significant elevations over vehicle levels are denoted by an asterisk, * $P < .05$, ** $P < .01$, *** $P < .001$.

Marijuana and ondansetron had inconsistent effects on ratings of nausea and the incidence of emesis (Fig. 3a,b and Table 2). The post-hoc tests revealed that the higher dose of marijuana significantly reduced nausea at 20 min, whereas ondansetron reduced nausea 90 min after ipecac ($P < .003$). The episodes of vomiting were analyzed using a chi-square test, which showed that the lower dose of marijuana did suppress the episodes of vomiting compared to the placebo condition ($\chi^2 = 4.95$, $P < .03$), but the moderate dose of marijuana did not (Fig. 3b). Ondansetron ($\chi^2 = 15.2$, $P < .001$) completely suppressed vomiting.

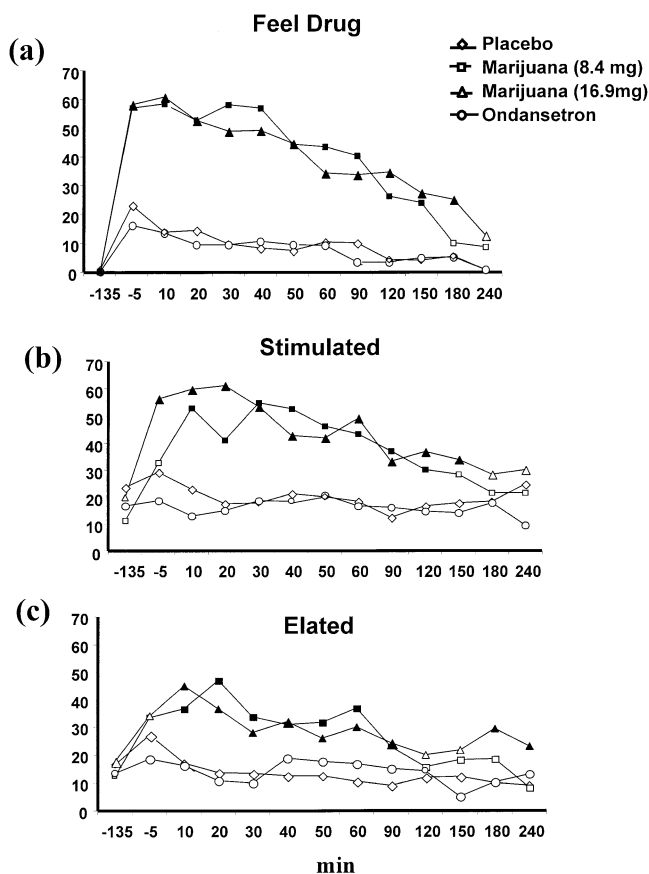


Fig. 4. (a) Effects of marijuana and ondansetron on ratings of "feeling the drug." See Fig. 1 for explanation of figure. Significant elevations over the placebo levels are denoted with a filled symbol. The results are presented as mean. MM=moderate dose of marijuana, LM=lower dose of marijuana, OND=ondansetron, PL=placebo. (b) Effects of marijuana and ondansetron on ratings of "feeling stimulated." Both doses of marijuana significantly increased the scores for feeling stimulated. The results are presented as mean. See Fig. 1 for explanation of figure. MM=moderate dose of marijuana, LM=lower dose of marijuana, OND=ondansetron, PL=placebo. (c) Effects of marijuana and ondansetron on ratings of elation. See Fig. 1 for explanation of figure. The results are presented as mean. MM=moderate dose of marijuana, LM=lower dose of marijuana, OND=ondansetron, PL=placebo. Ondansetron or a placebo capsule were administered at -135 min, marijuana or placebo cigarettes were administered at -5 min and Ipecac was administered at 0 min. The symbols shown in the figures are: Marijuana 8.4 mg (squares); Marijuana 16.9 mg (triangles); Ondansetron (circles); Placebo (diamonds).

Marijuana produced its prototypic effects on mood and subjective state. It significantly increased ratings of "feel drug," "feel stimulated," "feel anxious," "feel elated" and "feel sedated" relative to placebo (Table 2, Fig. 4a–c). Both the low and high doses of marijuana increased the ratings of "feeling a drug effect" 5 min after smoking (8.4 and 18.6 mg, $P < .001$). The effect of the lower dose of marijuana lasted until the 150-min time point, whereas with the moderate dose the effect lasted through most of the session. Ondansetron had no significant effect on any measure of mood or subjective state. Fig. 4b and Table 2 show that both doses of marijuana significantly increased scores for feeling stimulated. After both doses of marijuana, the effects began within 5–10 min of smoking ($P < .00004$) and lasted about 2 h ($P < .03$). Ondansetron decreased the ratings of feeling stimulation at the last time point of the session ($P < .03$).

Fig. 4c and Table 2 show the effect of marijuana on elation. On ratings of "feeling elated," both doses of marijuana significantly increased scores compared to placebo, beginning 10 min after smoking ($P < .002$) and lasting until the 90-min time point ($P < .03$) for the low dose and almost through the end of the session for the moderate dose ($P < .04$). Ondansetron had no significant effect on elation. On ratings of "feeling anxious," the lower dose of marijuana (10 ± 6) had no effect, but the moderate dose (17 ± 7) significantly increased ratings of feeling anxious almost throughout the session ($P < .04$) compared to placebo (5 ± 3). Ondansetron (6 ± 4) had no effect on anxiety. Finally, both doses of marijuana increased sedation beginning 5 min after smoking ($P < .04$) compared to placebo (mean 7 ± 4). This sedative effect lasted for about 40 min at the low dose ($P < .04$, mean 14 ± 6) and almost throughout the session at the moderate dose ($P < .04$, mean 18 ± 7). Ondansetron had no significant effect on sedation (mean 7 ± 3).

5. Discussion

The present study showed that smoked marijuana reduced subjective ratings of queasiness and also the objective measures of vomiting. Both doses of marijuana were effective at reducing the feelings of "queasiness" after intake of syrup of ipecac compared to the placebo condition, and the lower dose of marijuana also reduced vomiting. However, relative to the effects of ondansetron on emesis and on ratings of queasiness and nausea, the effects of marijuana were very modest. Ondansetron completely blocked subjective ratings of nausea, and no subjects vomited in this condition. Marijuana also produced the predicted classic effects on mood and subjective state. It increased ratings of "feel drug," and it increased ratings of stimulation, anxiety, elation and sedation compared to the placebo condition. In contrast, ondansetron produced no changes in subjective state. Our findings support previous

studies indicating that smoked marijuana (cannabis) may, like oral Δ^9 -THC, be an effective antiemetic and may be of benefit for certain patients with severe nausea or emesis (Vinciguerra et al., 1988).

Although an antiemetic effect of smoked marijuana was obtained in this study, the magnitude of the effect was very modest, especially when compared to the potent drug, ondansetron. There are several reasons for the relatively small effect. First, the dose of the marijuana was relatively low, and may not have been large enough to overcome the robust emetic effect of the syrup of ipecac. It is possible that higher doses of marijuana would have produced more effective relief of the nausea. Secondly, the interval between smoking marijuana and the intake of ipecac could have been too short. The peak subjective reports of “feeling” the marijuana appeared approximately 5 min after smoking, and the peak of feeling nausea appeared approximately after 20–30 min after the intake of ipecac. Thus, the peak emetic effects of ipecac occurred about 45 min after smoking, at the time the subjective ratings of feeling the effects of the marijuana already had begun to decline. It is possible that more robust antiemetic effects would be observed at the time of the peak of marijuana’s effect.

The results of this study suggest that there may be dissociations between the subjective experience of nausea or queasiness and the overt emetic response (i.e., vomiting). The lower dose of marijuana decreased the number of times subjects vomited, without decreasing feelings of nausea. The moderate dose of marijuana condition reduced subjective feelings of queasiness without decreasing the frequency of vomiting. This type of dissociation between subjective feelings of nausea and the physiological symptoms of nausea has been reported previously. Andre et al. (1996) compared the effects of tilted and vertical stripes in an optokinetic drum on motion sickness, and found that although gastric activity was higher for the tilted stripes condition than for vertical stripes subjects reported no difference in their feelings of nausea. This result supports our finding that the subjective experience does not always correspond with the physiological responses. However, this dissociation does not explain why the low dose of marijuana reduced vomiting, whereas the higher dose did not. It will be interesting in future studies to determine whether the effects of marijuana or Δ^9 -THC truly are dissociable on these two measures of antiemetic effects.

In the present study, ondansetron completely blocked both the subjective and physiological emetic effects of ipecac, whereas it produced no effect on the subjective ratings, including feel drug, stimulation, elation or sedation. In many respects, this makes the drug an ideal therapeutic agent to control nausea and vomiting in patients. Although a number of other drugs alleviate nausea, including antihistamines, dopamine antagonists, steroids, benzodiazepines, serotonin antagonists and anticholinergics, these classes of drugs produce a number of other, unwanted effects on patients’ mood or physiology (Leslie et al., 1990). Thus,

our study confirms earlier studies and extensive clinical experience showing that ondansetron is a reliable antiemetic (Naylor and Rudd, 1994).

In this study, we used syrup of ipecac to induce emesis. Syrup of ipecac is an effective emetic used commonly for emptying of gastric contents, especially after accidental poisonings (Holdclaw and Nykamp, 1992). It is thought to act primarily through peripheral and central 5-HT₃ pathways (Minton, 1994) and, accordingly, emesis induced with ipecac can be profoundly suppressed by ondansetron, a 5-HT₃ antagonist. Prior studies have shown that syrup of ipecac, at doses of 15 or 30 ml given with approximately 200-ml water, reliably cause emesis (Ilett et al., 1977). In the present study, the dose of ipecac was low to minimize discomfort to the subjects, and because the feeling of nausea (rather than the incidence of emesis) was our primary variable of interest. Our findings agree with previous studies showing that a 5-ml dose of syrup of ipecac is sufficient to produce nausea in most subjects, while it produced vomiting in only 7 of 13 subjects (Goldenberg et al., 1976).

The present study had a number of limitations. First, the subjects in the study were healthy normal volunteers and their nausea was acute and brief. It is difficult to determine whether patients with prolonged chemotherapy or other illnesses would respond similarly. Secondly, the subjects were exposed to a single, low to moderate dose of marijuana. If the dose had been higher or if the subjects had been able to smoke repeatedly, and under their own control, more robust effects might have been observed. Thirdly, we only used one agent to induce nausea. In further studies, it may be of interest to examine the effects of marijuana or Δ^9 -THC on nausea induced by other methods.

Few studies have been conducted to assess the clinical efficacy of smoked marijuana, and those that exist have been done with a small number of patients (Vinciguerra et al., 1988). This line of research raises a wide variety of issues and social concerns. Ultimately, however, empirical data are needed regarding the medical uses of marijuana and cannabinoids, concerning both their efficacy and their safety, and these can only be determined in carefully controlled studies. This class of drugs is likely to receive increasing attention as a source of therapeutic agents, because of the rapid growth in basic research on cannabinoid receptor mechanisms. It seems likely that different cannabinoids will have different effects, and research into the physiological effects of both synthetic and plant-derived cannabinoids is needed. There is a need for more clinical trials of cannabinoid drugs to determine efficacy and manage clinical symptoms. New drugs will provide patients with a choice of drugs and delivery modes. The psychological effects of cannabinoids, including changes in anxiety and sedation, which can either facilitate or impede medical benefits, should be evaluated in clinical trials. To many patients, the mood altering subjective effects of cannabinoids are likely to be undesirable. However, in selected

populations, the sedation or increased feelings of well being may be a benefit to medically ill patients. More research is also needed on the role of individual differences in these psychological effects in the medical utility of the drugs.

It should also be noted that marijuana is not a harmless drug. Smoking marijuana regularly over a longer period of time has been shown to harm both tissue and organs. For example, it has been reported that habitual marijuana smokers have abnormal airway appearance and impairment of the immune effector cells of the lung (Baldwin et al., 1997; Gong et al., 1987; Sherman et al., 1991). Future research may consider investigating methods of delivering cannabinoids by inhalation without smoking to avoid these harmful effects. It has also been shown that certain subpopulations may be at risk for developing dependence on cannabinoids, including adolescents with conduct disorder and adults with certain psychiatric disorders (Brooks et al., 1998).

In conclusion, the effects of smoked marijuana on emesis were mild. Marijuana had a modest effect on nausea, queasiness and emesis in this model of nausea induced by syrup of ipecac. The comparison drug, ondansetron, totally eliminated both the subjective feelings of nausea and the emesis. These findings confirm clinical reports that smoked marijuana can reduce nausea, but relative to the potent effects of ondansetron and because of its psychoactivity, its usefulness in the clinical setting is likely to be limited.

Acknowledgments

This study was supported by DAO3157 and F32 DA05868 and the Swedish Foundation for International Cooperation in Research and Higher Education (STINT). We thank Paul Meyer for his contribution to early phases of the study and Dr. Stephen Wachtel for helpful comments in preparing the manuscript.

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