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Ethanol increases plasma Δ^9 -tetrahydrocannabinol (THC) levels and subjective effects after marihuana smoking in human volunteers

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Abstract

Marihuana and alcohol are often used together, yet little is known about why they are combined. Male volunteers were assigned to one marihuana treatment group (placebo, low or moderate dose Δ^9 -tetrahydrocannabinol (THC)) and, on three separate study days, they also drank a different dose of ethanol (placebo, 0.35 or 0.7 g/kg). Plasma THC levels and changes in subjective mood states were recorded for 90 min after smoking. For many of the drug combinations, when subjects consumed ethanol they detected marihuana effects more quickly, reported more episodes of euphoria and had higher plasma THC levels than when they consumed placebo ethanol. These data suggest that ethanol may increase the absorption of THC resulting in an increase in the positive subjective mood effects of smoked marihuana and contributing to the popularity of this drug combination. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Ethanol; Plasma Δ^9 -tetrahydrocannabinol (THC) levels; Polydrug abuse; Marihuana; Human subjects

1. Introduction

Polydrug use has increased over the last two decades with marihuana and alcohol being a popular combination (Grupp, 1972; Stein et al., 1983; Norton and Colliver, 1987). The use of marihuana by young adults is still high as 11.4, 21.8 and 11.5% of 12–17, 18–25 and 26–34 year olds, respectively reported using marihuana in the last year (Substance Abuse and Mental Health Services Administration, 1996). With the recent change in some state laws in the US allowing the use of oral Δ^9 -tetrahydrocannabinol (THC) for medical reasons, and the widespread use of alcoholic beverages, the incidence of using these two together may actually increase. Over the past 11 years, we have been tracking

the reasons for using various drugs given by our subjects who participate in drug challenge studies by having them fill out a polydrug use questionnaire. About 70% of the 97 subjects queried reported that ‘to get a better high’ was the most important reason for combining alcohol and marihuana and 23–25% reported that they used the second drug to enhance the effects of the first drug (S. Lukas, pers. commun.).

Alcohol and marihuana combinations impair performance on various tasks more than those of either drug separately, but it is unclear why alcohol/marihuana combinations are so popular. Potentiation of intoxicating effects have been reported with smoked marihuana (Chait and Perry, 1994), and cognitive, perceptual and motor function tests are impaired more when ethanol is combined with oral THC (Chesher et al., 1976, 1977; Bird et al., 1979; Belgrave et al., 1979a). One explanation may be that alcohol potentiates marihuana’s effects on mood, producing a greater ‘high’ (Manno et al., 1971; Hollister, 1976). Even though pharmacodynamic interactions between marihuana and alcohol have been well documented (Benowitz and Jones, 1977;

Abbreviations: THC, Δ^9 -tetrahydrocannabinol.

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Consroe et al., 1979; Belgrave et al., 1979b; Perez-Reyes et al., 1988b; Lukas et al., 1992), the mechanism by which alcohol potentiates the behavioral effects of marihuana is unknown. The principal psychoactive component of marihuana, THC, has a high lipid-solubility and is rapidly transported from the bloodstream to the central nervous system. Thus, estimates of such interactions using plasma THC levels alone may be difficult because tissue or organ levels may still be substantial even as blood levels approach zero (Hunt and Jones, 1980).

One possible mechanism of this alcohol/marihuana interaction is that these drugs may alter the pharmacokinetic profile of each other. Several studies have focused on the effects of marihuana smoking on ethanol kinetics, and the majority of laboratories have found that blood ethanol levels are reduced after marihuana smoking (Benowitz and Jones, 1977; Consroe et al., 1979; Lukas et al., 1992), although one study found that the levels did not change (Belgrave et al., 1979a).

Fewer studies have been directed at exploring the reverse order of drug administration — the effects of ethanol on plasma THC levels. Although Perez-Reyes et al. (1988b) reported that plasma THC levels were increased (but not significantly) by ethanol, we decided to re-analyze the data from our earlier ethanol/marihuana study in which we reported only on the effects of marihuana smoking on plasma ethanol levels (Lukas et al., 1992). The aim of the present study was to analyze the plasma THC level data as a function of ethanol dose. Since ethanol causes peripheral vasodilation (Altura and Altura, 1982), we hypothesized that it would increase the absorption of THC in subjects who smoked marihuana with a concomitant increase in positive or good subjective mood effects.

2. Methods

2.1. Subjects

All procedures and consents were approved by the

McLean Hospital Institutional Review Board. Informed consent was obtained from 22 healthy male Caucasian volunteers; the demographic profile of the subjects is depicted in Table 1. Subjects reported using marihuana (1.5–2 joints per week) and alcohol (4–8 beers per week) on an occasional basis. None of the variables, including drug use history and current use patterns of licit and illicit drugs, differed significantly among the three treatment groups. Subjects were recruited via newspaper advertisements and passed a rigorous physical and mental status examination performed by a physician. In addition, they were required to have hemogram and blood chemistry values that were within the normal range for their age. All urine screens for licit and illicit drug use had to be negative. Further, subjects with past or current histories of psychiatric disorders, drug or alcohol abuse or dependence (DSM-III criteria), or positive family histories for alcoholism (using criteria established by Schuckit, 1985) were excluded from participation. Tobacco smokers were included only if they smoked less than $\frac{1}{2}$ pack per day and were told not to smoke in the 2 h interval before drinking at the laboratory. The study was designed to assess the effects of three different ethanol doses (conditions) on three different doses of marihuana (groups) under randomized, double-blind conditions. Subjects were randomly divided into one of three groups and always smoked the same dose marihuana cigarettes (placebo, low or moderate) during each of their three visits to the laboratory. However, they drank a different dose of ethanol at each visit. Fifteen of the subjects were the same as those who participated in our earlier study (Lukas et al., 1992); seven subjects were added to increase the power for detecting differences in the plasma THC data.

2.2. Marihuana cigarettes

Research grade marihuana cigarettes having a mean weight of 850 ± 39.5 mg and moisture content of 10% were obtained from Research Triangle Institute (Research Triangle Park, NC) via the National Institute on

Table 1
Demographic profile of subjects by treatment group (mean $\pm$ S.E.M.)

	Placebo	Low dose marihuana	Moderate dose marihuana
Age (years)	25.17 $\pm$ 1.01	26.33 $\pm$ 2.55	22.33 $\pm$ 0.42
Height (cm)	176.17 $\pm$ 2.71	176.97 $\pm$ 2.20	175.83 $\pm$ 1.05
Weight (kg)	74.69 $\pm$ 2.99	75.25 $\pm$ 4.26	67.86 $\pm$ 2.18
BMI ^a	24.12 $\pm$ 0.89	24.12 $\pm$ 1.45	21.98 $\pm$ 0.60
<i>Drug use frequency</i>			
Marihuana (joints per week)	1.63 $\pm$ 0.52	1.54 $\pm$ 0.25	1.96 $\pm$ 0.41
Alcohol (beers per week)	7.67 $\pm$ 1.54	8.17 $\pm$ 2.56	4.25 $\pm$ 1.56
Cocaine (lifetime)	6.42 $\pm$ 2.25	6.58 $\pm$ 1.88	8.58 $\pm$ 2.62

^a BMI = wt. (lbs) $\times$ 704.5 (height (in.))².

Drug Abuse (Rockville, MD) and stored frozen until 24 h before the study. The THC potencies included, 0.004% (placebo) ($n = 8$ subjects); 1.26% (low dose) ($n = 8$ subjects) and 2.53% (moderate dose) ($n = 6$ subjects). Cigarettes were thawed overnight in an airtight container with a small amount of concentrated saline solution. This procedure raised the moisture content to about 14% as recommended by the Research Triangle Institute. Placebo and marihuana cigarettes were attached to a custom-designed trap bottle located outside of the experimental chamber (Lukas et al., 1994). A flexible plastic tube was attached to the vented side of the bottle and was passed through the chamber wall. A standard cigarette-holder mouthpiece was attached to the distal end of the tubing and was supported by a flexible metal arm so that the subject was free to leave his left hand (the right one was semi-restrained for blood withdrawal) on the joystick device while smoking. The smoke was cooled and filtered by routing it through cold water contained within the trap bottle.

Specific instructions for smoking the cigarette were recorded verbally on magnetic tape and played for the subject as follows, 'inhale' for 3 s, 'hold' your breath for 5 s and then 'exhale'. This sequence was repeated every 30 s until only 10 mm of the cigarette remained, but subjects had to finish the cigarette within 10 min. Since the burning characteristics of placebo cigarettes differed from active cigarettes, the coached smoking procedure (2 puffs per min) resulted in the subjects finishing the placebo cigarettes in 2.5–3.75 min and the active cigarettes in 5.1–6.0 min.

2.3. Ethanol drinks

During each of the three visits subjects drank a different dose of ethanol in random order (placebo, low, or moderate). Each drink consisted of chilled orange juice and vodka (86 proof) in a total volume of 350 ml. Ethanol and placebo solutions were delivered using a peristaltic pump device, which provided a constant flow of beverage to the subjects which they consumed via a long tube and mouthpiece. For all three doses (placebo, low and moderate), a 10-ml reservoir located between the pump and the mouthpiece was filled with 3 ml of vodka (i.e. 'primer'). The smell and taste of this solution is an effective placebo control, as the small amount of vodka in the placebo solution does not produce any measurable plasma ethanol levels (Lukas et al., 1986, 1989). The ethanol doses used included placebo (just the 'primer'), low dose (0.35 g/kg) and moderate dose (0.7 g/kg).

2.4. Procedure

Subjects fasted overnight (including no caffeinated beverages after midnight) and reported to the labora-

tory at 09:00 h. After having passed a rapid urine test for illicit drugs (Triage™) including opiates, THC, cocaine, amphetamines, barbiturates, benzodiazepines and phencyclidine and a breath test for alcohol (Alco-Sensor IV, Intoximeter), subjects were escorted to an electrically-shielded, sound- and light-attenuated double-walled chamber (IAC, Bronx, NY). The chamber was equipped with a wired intercom and one-way glass window for maintaining auditory and visual contact with the subjects. After a 30 min baseline period, subjects drank one of the three doses of alcohol using a standardized drinking procedure; this was done to reduce the variability in absorption. The peristaltic pump (which delivered 23 ml/min) was turned on for 3 min then off for 1 min; this cycle was repeated until the beverage was consumed (in 18 min). Then 12 min after the drink was finished, subjects smoked a marihuana cigarette and were instructed to keep their eyes closed and relax in the chair while blood samples, physiologic activity and subjective reports were collected for the remainder of the study.

2.5. Subjective measures

The latency to and duration of good or euphoric, bad or dysphoric effects, as well as the latency to and duration of ethanol and marihuana effects were reported continuously via an instrumental joystick device (Lukas et al., 1986; Lukas, 1993; Lukas et al., 1993). This device is a computer style joystick, the output of which was sent to a polygraph with a timer circuit to permit matching the behavioral data with the other events such as drug taking. Movement of the joystick in a forward direction signaled detection of ethanol effects only while movement to the left signified detection of marihuana effects only. A backward movement signaled detection of both drugs simultaneously. Subjects released the joystick when all effects disappeared. Two buttons located on the handle of the joystick were used by the subjects to report episodes of intense good feelings (euphoria) and intense bad feelings (dysphoria). The operation of the buttons was independent so subjects *could* report both effects simultaneously.

2.6. Blood sampling

Continuous blood samples were collected for subsequent analysis of plasma alcohol and THC levels. The needle of a 183 cm Kowarski-Cormed Thromboresistant Blood Withdrawal Butterfly Needle and Tubing Set (DAKMED Inc., Buffalo, NY) was inserted into the subject's antecubital vein and kept patent with a slow infusion of 0.9% NaCl. The distal end of the tubing (dead space = 2.5 ml) was attached to a 10 ml syringe mounted on a withdrawal syringe pump and adjusted to withdraw blood at a rate of 1.0 ml/min;

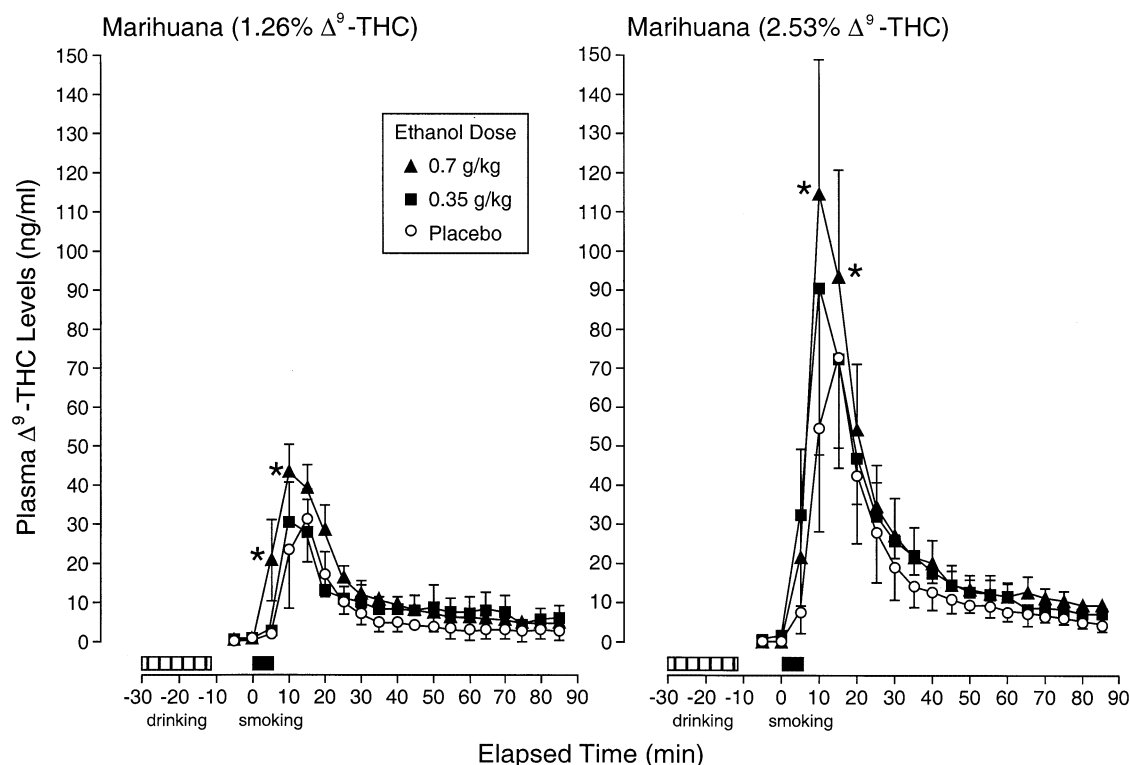


Fig. 1. Ethanol effects on plasma THC levels (mean $\pm$ S.E.M.) after both 1.26% THC (left side) and 2.53% THC (right side) doses of marihuana. Ethanol was consumed from -30 to -12 min and the marihuana cigarette was smoked from 0 to 8 min on the elapsed time scale. * denotes significance at $P < 0.05$, moderate dose ethanol versus placebo.

syringes were changed every 5 min. Blood samples were immediately centrifuged and the plasma samples frozen for subsequent THC analysis via a radioimmunoassay procedure (National Institute on Drug Abuse/Research Triangle Institute) or ethanol determination via head space gas chromatography (see Lukas et al., 1992 for details).

2.7. Data analysis

Due to the unique and rapidly changing pharmacokinetic profile of smoked marihuana, analysis of the THC data was performed on two separate phases. The ascending phase lasted from the onset of smoking to the onset of the descending phase while the descending phase lasted until the end of the study. The ascending phase was determined by calculating the slope of the THC level curve from baseline (zero) to peak THC levels (Tallarida and Murray, 1987). Data points from later sampling times were added until the goodness of fit to a linear model became nonsignificant; this occurred when data from the $+20$ min time point was added. The descending phase consisted of the remaining data points.

The effect of ethanol dose (placebo, 0.35 or 0.7 g/kg ethanol), area under the curve (combined THC levels at 5, 10 and 15 min post smoking) and marihuana group (placebo, low vs. moderate dose) on plasma THC levels were assessed using 3×3 repeated measures univariate

analysis of variance (ANOVA; SPSS, version 6.1). When repeated measures ANOVA indicated significant main effects or interactions, independent post-hoc comparisons were conducted using paired sample t -tests. On all comparisons, significance was determined at the $P = 0.05$ level. Due to the occasional catheter problems, complete sets of blood samples were collected from only five to six subjects in each group. One subject was eliminated from the moderate dose marihuana group because he felt too intoxicated from the alcohol to continue and decided not to smoke the marihuana cigarette.

3. Results

3.1. THC levels

THC levels were not detected in the plasma of any of the subjects who smoked placebo marihuana (data not shown). Fig. 1 depicts the effects of ethanol on plasma THC levels after subjects smoked either the low (left) or the moderate (right) dose marihuana cigarette. An analysis of the ascending phase data ($t = 0-15$ min) revealed an ethanol main effect ($F(2,3) = 8.19$, $P < 0.02$); post hoc paired sample t -test revealed that these increases in plasma THC levels were significant for the placebo versus moderate dose ethanol condition ($t(8) = -2.52$, $P < 0.04$). Further, compared with placebo, the latency to the

peak plasma THC levels occurred 5 min sooner in the moderate dose ethanol condition ($t(4) = -4.00$, $P < 0.02$). An analysis of the descending phase ($t = 20$ –120 min) of the plasma THC level curve revealed no significant differences among the three ethanol conditions.

3.2. Subjective effects

The joystick device provided an immediate and constant measure of subjective effects. The left panel of Fig. 2 shows that the latency to detect marihuana effects was reduced by ethanol pretreatment ($F(2,7) = 7.468$, $P < 0.018$). Paired sample *t*-tests revealed that moderate dose ethanol pretreatment reduced the latency to detect marihuana effects in the moderate dose marihuana group ($t(5) = -3.85$, $P < 0.012$, moderate vs. low ethanol; $t(5) = -9.55$, $P < 0.001$, moderate vs. placebo ethanol). The number of euphoric events (Fig. 2, middle) was increased by the low dose of ethanol ($F(4,34) = 2.618$, $P < 0.050$). Subsequent analyses revealed that compared with placebo ethanol, the moderate dose ethanol condition increased the number of euphoric events in the placebo and low dose marihuana groups ($t(7) = 2.49$, $P < 0.042$; $t(7) = 3.43$, $P < 0.011$). However, in the moderate dose marihuana group, low dose ethanol pretreatment resulted in more euphoric events ($t(5) = -4.19$, $P < 0.009$, low vs. moderate; $t(5) = 3.48$, $P < 0.018$, low vs. placebo). There also were no reports of dysphoria or bad effects by the subjects, and the latency to euphoria was shorter after ethanol. Fig. 2 (right panel) also shows that the duration of euphoria after both drugs was increased by ethanol pretreatment, and this interaction was statistically sig-

nificant ($F(2,38) = 5.39$, $P < 0.009$). Specifically, moderate dose ethanol pretreatment produced a longer duration of euphoria in the low dose marihuana group ($t(7) = 2.88$, $P < 0.024$, moderate vs. placebo). In the moderate dose marihuana group, ethanol pretreatment increased the duration of the euphoric events ($t(5) = -3.85$, $P < 0.012$, low vs. moderate ethanol; $t(5) = 5.79$, $P < 0.002$, low vs. placebo ethanol). These changes in subjective mood state all occurred within the same time interval during which plasma THC levels were elevated (0–15 min post onset of smoking); however, detection and euphoria episodes persisted up to 30–40 min post smoking onset.

4. Discussion

We reported earlier that marihuana smoking actually slows the absorption of ethanol, and as a result, reduces ethanol's psychoactive effects (Lukas et al., 1992). The present study considered the reverse relationship and provides a pharmacological and pharmacokinetic explanation for why individuals use ethanol/marihuana combinations. In the present study, plasma THC levels were significantly increased when subjects had first consumed ethanol. The reason why significant increases in THC levels were detected in the present study while others did not (Perez-Reyes et al., 1988b) is most likely due to the fact that ethanol may only affect the early ascending limb of the plasma THC curve that occurs immediately after smoking. Ethanol appears to have no effect in the descending limb of the THC plasma/time curve. Significant changes were not observed when the entire plasma THC curve was analyzed. However, as

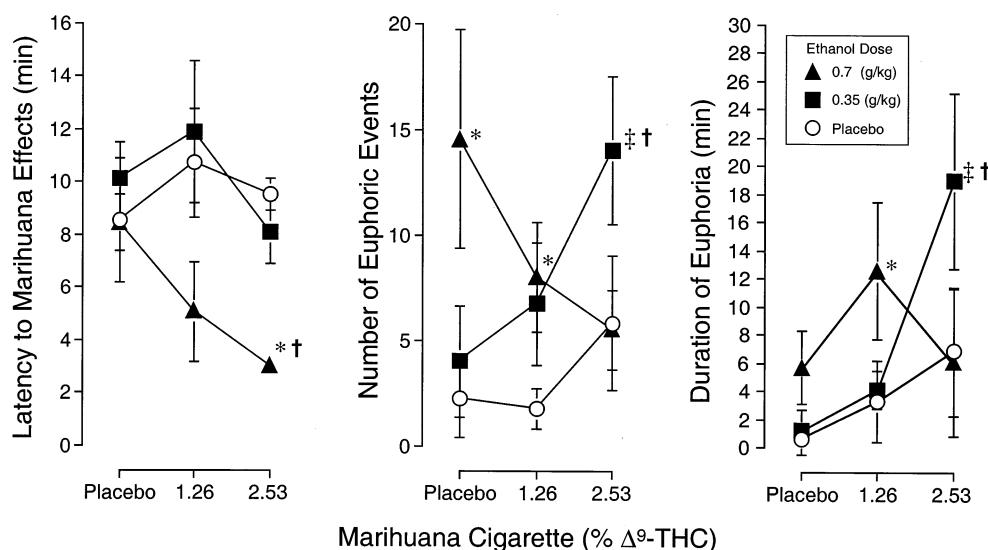


Fig. 2. Ethanol-induced changes (mean $\pm$ S.E.M.) in latency to detect, number of euphoric events and duration of euphoria after smoking either placebo, low dose (1.26% THC) or moderate dose (2.53% THC) marihuana cigarettes. * denotes significance at $P < 0.05$, moderate dose ethanol versus placebo. † denotes significance at $P < 0.05$, moderate dose versus low dose ethanol. ‡ denotes significance at $P < 0.05$, low dose versus placebo ethanol; details of the comparisons are provided in Section 3. Data were collected during the first 15 min after smoking onset.

the early absorption phase is most often associated with changes in mood state (Lukas et al., 1994, 1995), attention to the first 15 min of the plasma data after smoking is justified.

Inspection of the individual data revealed that nearly all subjects experienced higher plasma THC levels when ethanol was consumed. There are two possible explanations for this finding. The first is that ethanol-induced changes in vascular smooth muscle (Altura and Altura, 1982) may have increased the absorption of THC during each inhalation. Acute administration of ethanol lowers blood pressure and causes peripheral vasodilation (Nakano and Kessinger, 1972; Altura et al., 1979; Friedman et al., 1979), and regardless of the route of administration, ethanol also dilates precapillary sphincters, arterioles and muscular venules in a dose-dependent manner (Altura, 1978; Altura et al., 1979; Altura, 1981). Further, norepinephrine-, epinephrine-, angiotensin-, serotonin-, vasopressin- and prostaglandin-induced vasoconstriction are blocked by ethanol (Nakano and Kessinger, 1972; Altura et al., 1979; Friedman et al., 1979). Although the precise mechanism of this effect is unknown, it is suspected to be due to ethanol-induced interference with the translocation of Ca^{2+} across vascular membranes (Altura and Altura, 1982). Thus, dilation of the pulmonary microcirculation would permit more THC to traverse the alveolar sac/capillary membrane with each inhalation.

The second possible explanation for these findings is that alcohol may have altered marihuana smoking topography or the depth of inhalation during smoking. There is a report of such an effect on tobacco smoking topography (Griffiths et al., 1976), and so a standardized smoking procedure was used in the present study to minimize the variance. While there was some variance in the time it took to smoke the cigarette and the number of puffs each subject took, there were no systematic differences related to ethanol dose, yet the placebo marihuana cigarettes did burn faster than the two active doses. If ethanol had increased the depth of inhalation (which was not measured in this study), then the cigarettes would most likely have burned more quickly, and the subjects would have used fewer puffs to reach the 10 mm line. Nevertheless, a greater depth of inhalation per puff could result in higher plasma THC levels and increased subjective effects — an effect that may very well occur in real world scenarios of polydrug use.

Regardless of the mechanism involved, increased plasma THC levels very likely contributed to the more rapid appearance of marihuana subjective effects and the more euphoric or good effects that were observed in the present study. Thus, the desire for a more intense and pleasurable 'high' may explain why marihuana and ethanol combinations are so popular. Alternatively, as marihuana use is often opportunistic (e.g. someone else

brings it to parties), these results also provide some insight as to how individuals might first experience pleasurable subjective mood effects of this combination if they drink alcohol first and then smoke marihuana.

While the above pharmacologic explanations of the results are plausible in a controlled laboratory setting, there may be an alternative explanation for this interaction in the natural setting. While not measured in the present study, marihuana's antiemetic effects may reduce any ethanol-induced nausea, thus attenuating some of the negative effects of drinking, which would contribute to an increased use of the two drugs. However, the results of our ongoing survey did not reveal that subjects combined the two to avoid negative effects (S. Lukas, personal communication).

Although there has been some controversy over whether marihuana-induced subjective effects directly parallel plasma THC levels (c.f. Hollister et al., 1981; Barnett et al., 1982; Perez-Reyes et al., 1988a; Lukas et al., 1995), we have shown earlier that the use of a continuously available joystick device permits the subjects to report detection of effects the moment they are perceived (Lukas et al., 1995). Thus, a more rapid increase in plasma THC levels, especially during the initial minutes after smoking may increase the positive subjective mood effects of smoked marihuana in these subjects. However, the effects of ethanol on marihuana-induced subjective mood states were not linear. It appeared as if an optimal combination for increasing positive mood effects was either a moderate dose of ethanol alone or a combination of moderate dose marihuana and low dose ethanol (Fig. 2, middle panel). In fact, the number of euphoric events actually decreased when the moderate dose of both drugs was combined (Fig. 2, middle panel), suggesting that moderate doses of both drugs may not be as reinforcing as combining lower doses.

The impact of these results may be limited to the subject population studied, self-identified polydrug users. Subjects in the present study used alcohol and marihuana on an occasional basis only, and so the results may not be generalizable to individuals who only use one drug at a time or to individuals who are dependent on alcohol and/or cannabis. The second limitation is inherent in the controlled smoking procedure. If the subjects had been allowed to smoke marihuana cigarettes under *ad libitum* conditions, then we might have gained a better insight to the mechanism of the observed increase in plasma THC levels and enhanced subjective effects. The third limitation is in the interpretation of the mechanism of observed interaction. While smoking rates were coached, the depth of each inhalation could not be quantified and so this could explain why plasma THC levels were higher after ethanol.

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