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ORIGINAL INVESTIGATION

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Separate and combined effects of marijuana and alcohol on mood, equilibrium and simulated driving

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Abstract *Rationale:* Marijuana and alcohol, when used separately and in combination, contribute to automobile accidents and failed sobriety tests of standing balance. However, the extent to which the drugs have additive effects on both of these measures is unknown. *Objectives:* This study was designed to compare directly the separate and combined effects of marijuana and alcohol on simulated emergency braking and dynamic posturography. *Methods:* Twelve healthy subjects who regularly used both marijuana and alcohol completed nine test sessions in a counterbalanced within-subject design. Subjects drank a beverage (0, 0.25, or 0.5 g/kg alcohol) then smoked a cigarette (0, 1.75, or 3.33% THC). Testing began 2 min after smoking and was conducted within the ascending limb of the blood alcohol curve. *Results:* The 0.5 g/kg alcohol dose significantly increased brake latency without affecting body sway. In contrast, the 3.3% THC dose increased body sway but did not affect brake latency. There were no additive drug effects on mood or behavior. *Conclusions:* Although field sobriety tests are often used to determine driving impairment, these results suggest that impaired balance following marijuana use may not coincide with slowed reaction time. Conversely, braking impairment from low doses of alcohol may not be revealed by tests of balance.

Keywords Marijuana · Alcohol · Equilibrium · Automobile driving · Psychomotor performance · Humans

Introduction

Many marijuana users simultaneously use other drugs. Alcohol is the drug most frequently paired with marijuana (Earleywine and Newcomb 1997). Compared to their use of alcohol alone, combined use of marijuana and alcohol by college students has been more associated with increased substance use problems (Shillington and Clapp 2001). As alcohol is also the drug most commonly associated with vehicular crashes (Lowenstein and Koziol-McLain 2001), marijuana-alcohol combinations may represent an increased danger to a driver. Several behavioral tests of marijuana-alcohol combinations have shown that although the individual effects of marijuana on performance may be minimal, the combined effects of tetrahydrocannabinol (THC) and alcohol on performance are additive (Chesher et al. 1976, 1977; Belgrave et al. 1979; Perez-Reyes et al. 1988;Chait and Perry 1994). As with the effects of alcohol alone, these additive effects may be more prominent in the ascending limb of the blood alcohol curve; in one study, THC began counteracting the effects of alcohol 100 minutes after drinking began (Chesher et al. 1977).

Previous studies in our laboratory have shown that the effects of alcohol on both body sway and a simulated driving emergency braking task are robust and reproducible in a dose-dependent manner (Liguori et al. 1999; Liguori and Robinson 2001). In addition, the effects of high-potency marijuana (3.95% Δ-9 THC) on these measures were found to be comparable to effects at a breath alcohol concentration (BrAC) of 0.05% (Liguori et al. 1998). If THC and alcohol have additive effects, the combined effects of moderate doses of these drugs should produce impairment similar to that from BrACs above 0.08%. Other researchers have reported driving impairment from the combination of low doses of THC and alcohol that had no or modest impairing effects when given by themselves (Robbe 1998; Ramaekers et al. 2000; Lamers and Ramaekers 2001). In one of these studies, combinations of THC and a BrAC of 0.04% produced driving impairments equivalent to impairments from BrACs of 0.09–0.14% (Ramaekers et al. 2000).

The purpose of this study was to determine if alcohol-induced impairment of body sway and simulated emergency braking would be significantly increased by mari-

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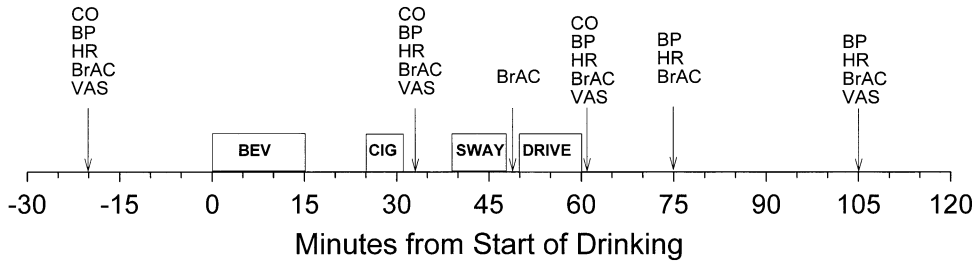

Fig. 1 Timeline of experimental procedures. *CO* Carbon monoxide measurement, *BP* blood pressure measurement, *HR* heart rate measurement, *BrAC* breath alcohol concentration measurement, *VAS* administration of visual analog scales, *BEV* beverage consumption, *CIG* period of cigarette smoking, *SWAY* dynamic posturography measurement, *DRIVE* simulated driving

juana. We postulated that marijuana in combination with alcohol would produce greater impairment of both measures than alcohol alone. The study was designed to measure behavior within the ascending limb of the blood alcohol curve, when performance impairments are most likely (Nicholson et al. 1992). We also postulated that the subjective "high" from marijuana in combination with alcohol would exceed that of marijuana alone.

Materials and methods

Subjects

Twelve subjects (four female, eight male; one African-American, 11 Caucasian) between the ages of 21 and 45 years were recruited via newspaper advertisements and initially screened by telephone interview. For inclusion in the study, subjects were required to report: possession of a current driver's license, body mass index (BMI) <30, use of marijuana between 2 and 21 of the past 30 days, not trying to stop or reduce caffeine, alcohol use, or caloric intake; no present use of prescription, over-the-counter, or illicit psychoactive medications, and no significant medical illness in the past 6 months. All subjects completed the Alcohol Use Disorders Identification Test (AUDIT) to screen for problem drinking (maximum allowable score=10; Saunders et al. 1993). So that present results could be compared with those of future sleep-related studies in our laboratory, subjects were also required to report time-in-bed between 7 and 9 h nightly, less than 2 h of variation in bedtime, sleep pattern devoid of naps, and no rotating shift work. Female subjects were excluded if they were pregnant, planning to become pregnant, or breast-feeding. Subjects who met all these criteria then met with a physician who conducted a physical examination and clinical interview to screen for medical conditions contraindicated for marijuana or alcohol use, past or current Axis I psychiatric disorder (DSM-IV criteria), and history of alcohol or non-nicotine drug abuse or dependence in the past year.

The mean (±SD) age of the subjects was 24±3 years, their mean body weight was 74±16 kg, and the mean BMI of the group was 24±4. Subjects reported smoking marijuana an average of 10 of the 30 days before giving informed consent (range 2–19 days) and average consumption of 12 standard alcohol drinks per week (range 4–24). Seven subjects (three female, four male) were current smokers of tobacco cigarettes (mean eight cigarettes per day, range 1–20 cigarettes). Two women reported use of oral contraceptives.

General procedure

The experimental protocol was approved by the Institutional Review Board of Wake Forest University School of Medicine. Subjects completed one practice session and nine test sessions. During practice sessions, subjects completed all tasks and forms without receiving drug. Subjects were transported to and from the laboratory by taxi service for all test sessions. Test sessions began between 1215 and 1745 hours and were separated by a mean of 7 days (range 2–28 days). Participants were instructed to abstain from marijuana for 48 h, alcohol and caffeine for 12 h, food for 4 h, and tobacco cigarettes for 1 h before each test session.

Upon arrival in the laboratory, subjects provided a urine sample that was used for qualitative illicit drug content analysis [Triage panel plus TCA (tricyclic antidepressants); Biosite, San Diego, Calif., USA] and, in women, pregnancy testing (QuickVue; Quidel Corp., San Diego, Calif., USA). After heart rate, blood pressure, BrAC, and carbon monoxide (CO) level were measured, subjects completed a field sobriety test (standing balance with eyes closed, walk-and-turn, one-legged balance, finger-to-nose, and alphabet recitation) and visual analog scales (see below).

In each test session, subjects received a different pairing of alcohol dose (0, 0.25, and 0.5 g/kg) and Δ-9 THC dose (0, 1.75%, and 3.33%). A test battery was scheduled to coincide with both the ascending limb of the blood alcohol curve and peak THC absorption (see Fig. 1). Subjects drank the beverage within 15 min, rested for 10 min, then smoked a single cigarette within 6 min. Testing began 2 min later and typically concluded 65 min after drinking began. Subjects then rested for 2 h 45 min, during which they were provided a lunch and, in tobacco smokers, ad libitum access to their cigarettes. BP, HR, and BrAC were measured at 30-min intervals to monitor subject safety. At the end of the rest period, subjects were required to complete a field sobriety test with no evidence of impairment before being taken home by taxi service.

Alcohol administration

Each active alcohol dose (0.25 or 0.5 g/kg) was prepared as a combination of diet tonic water and alcohol (95% w/v) for a total volume of 795 ml. Placebo beverages consisted of 795 ml of diet tonic water. During each test session, the 795 ml beverage was divided into three 265 ml drinks, and 4 ml of lime juice was added to each drink. To provide olfactory and taste cues, 1 ml of alcohol was added to each of the three drinks during placebo sessions. Subjects received a beverage at 5-min intervals. Drinking was monitored so that the three drinks were consumed at an even pace over a 15-min period.

Marijuana administration

Marijuana was administered in cigarettes prepared and supplied by the National Institute on Drug Abuse. The cigarettes averaged 85 mm in length and 25 mm in circumference and contained 0.003%, 1.75%, or 3.33% THC. Cigarettes were stored in airtight containers in a freezer and humidified overnight before test sessions. Each subject smoked the cigarette according to a uniform puffing procedure slightly modified from that previously reported (Higgins and Stitzer 1986). The following cycle was repeated through ten inhalations and exhalations: inhale for 7 s with ad libitum puff volume (Block et al. 1998), retain smoke in lungs for 7 s, exhale, inhale 30 s after prior inhalation ended.

Order of dosing

The present study was initially designed to study active alcohol doses of 0.5 and 0.8 g/kg with THC. Because the first two subjects vomited during one of the 0.8 g/kg sessions, the alcohol dosing parameters were changed to those described above. The order of the nine alcohol-THC dose pairings was randomized and double-blind with the exception of the last three sessions in these two subjects, who needed to complete an extra two or three sessions. The dose schedule for these particular sessions included the THC doses in random order always paired with 0.25 g/kg alcohol. Before the extra sessions, the two subjects were told that the only procedural change was a decrease in the maximum possible alcohol dose.

Test battery

The test battery consisted of equilibrium testing followed by simulated driving. Physiological measures and visual analog scales were completed before and after the test battery.

Physiological measures

Hand-held meters were used to measure BrAC (Breathalyzer; Intoxilizers, Inc., Lenexa, Kan., USA) and carbon monoxide (CO; Vitalograph; Vitalograph Inc., Lenexa, Kan., USA). Blood pressure and heart rate were measured with a digital wrist monitor (Omron Healthcare Inc., Vernon Hills, Ill., USA). Measurements were taken 20 min before alcohol administration (pre-drug) and at up to five time points after drinking began as shown in Fig. 1. Post-drug measures were as follows: CO at 2 and 30 min post-smoking, BrAC at 33, 49, 61, 75, and 105 min after the start of drinking, blood pressure and heart rate at 33, 61, 75, and 105 min after the start of drinking.

Visual analog scales

Visual analog scales were completed following pre-drug physiological measures and 33, 61, and 105 min after the start of drinking (see Fig. 1). Each VAS consisted of a question below which a 100-mm line indicated a range of responses from "not at all" to "extremely". Subjects answered by drawing an intersecting line through the 100-mm line. Scale items asked if subjects felt anxious, clear-headed, confused, drunk, energetic, high, impaired, relaxed, sluggish, and stoned (Azorlosa et al. 1992; Liguori et al. 1998). Six additional post-drug visual analog scales, administered after the test battery, asked subjects to rate the taste, harshness, draw, and potency of that day's cigarette, as well as the taste and potency of that day's beverage.

Equilibrium

The computerized sensory organization test (EquiTest, Neurocom International Inc., Clackamas, Ore., USA) has been previously described in detail (Nashner and Peters 1990; Liguori et al. 1998). Subjects faced a surrounding wall while standing on a dual force-plate supported by strain gauges. Across six conditions, vision (eyes open or closed), the platform (stable or "sway-referenced"), and the visual surround (stable or "sway-referenced") were manipulated. When the platform or visual surround was sway-referenced, its movements exactly matched any anterior-posterior swaying by the subject.

Each condition included three 20-s trials. For each trial, a score ranging from 0 to 100 was derived from the ratio of each subject's anteroposterior sway to the normal limit of anteroposterior sway supported by the EquiTest. The three trial scores within a condition were then averaged to produce a condition score. A composite score of general equilibrium was derived as a weighted mean of the condition scores.

Simulated driving

The AGC Mobile Operations Simulator (AMOS) model SV5000LE (Time Warner Interactive, Milpitas, Calif., USA) is a chamber with five video monitors (63 cm diagonal) arranged in a semicircle around a driver's seat. Each monitor is approximately 65 cm from the driver's eyes. Beneath the third (center) monitor is a steering wheel mechanism with ignition and gearshift. During the driving simulation, subjects saw an open stretch of highway on the center monitor and a mountainous horizon on the other four monitors. Subjects were instructed to start the car and drive on the highway, accelerating to 55 miles per hour (mph) as quickly as possible. Subjects maintained a speed between 55 and 60 mph. At a random distance (mean 1.3 miles, range 0.4–2.2 miles), a yellow barrier fence suddenly appeared on the center monitor in the direct path of the vehicle. Subjects were instructed to brake as quickly as possible to stop the vehicle and avoid hitting the fence. The latency to press the brake pedal (brake latency) following the appearance of the fence was averaged across five trials.

Data analysis

Statistical significance was defined as $P<0.05$. Because preliminary analyses revealed no interactions of gender and dose condition on any dependent variable, data from men and women were combined in subsequent analyses. All physiological and VAS data were entered into two-way repeated measures analyses of variance with dose condition (placebo, 0.25 g/kg alcohol, 0.5 g/kg alcohol, 1.75% THC, 3.33% THC and the four active dose combinations of alcohol and THC) and time factor (pre-drug and post-drug time points as shown in Fig. 1 and described above). Post-hoc Tukey pairwise comparisons were used to interpret significant interactions. Equilibrium and driving data were entered into one-way repeated measures analyses of variance with dose condition factor. Significant results of these analyses were analyzed initially with Bonferroni *t*-tests to identify which doses differed from placebo. Bonferroni *t*-tests were then used to compare the effects of any doses that differed from placebo. The phrases "marijuana alone" or "alcohol alone" refer to conditions when an active dose of that drug was given with a placebo dose of the converse drug. Unless noted, all reported *F* values are from significant condition-time interactions.

Results

Verification of abstinence from marijuana

One male subject had positive THC levels during each visit (mean±SD level=376±205 ηg/ml) that were suggestive of recent marijuana use. Because behavioral data analyses with or without his data produced similar results, his data were included in analyses. Across all other samples >50 ηg/ml (n=23 of 99 possible sessions), the mean (±SD) THC level was 108±60 ηg/ml.

Physiological measures

BrAC

BrAC with the placebo beverage was 0.004% for all subjects at all time points. The time-course BrAC curves differed between the two alcohol doses [$F(40,438)=96.0$, $P<0.001$]. As shown in Fig. 2, mean BrAC with the 0.5 g/kg dose administered alone ascended from 0.051%

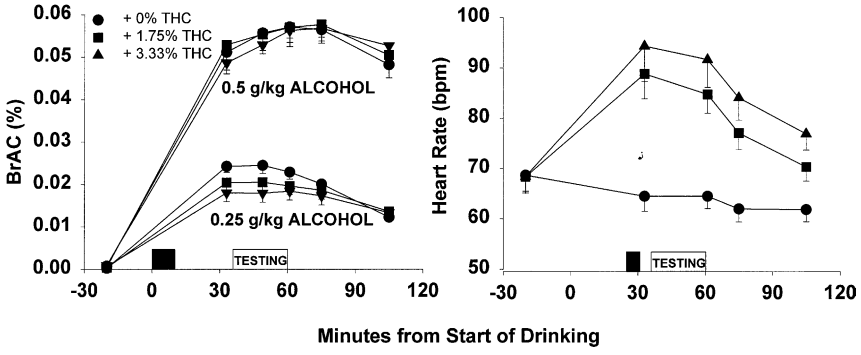

Fig. 2 Breath alcohol concentration following active doses of alcohol-marijuana combinations (*left panel*) and heart rate following THC administered alone (*right panel*). Data points illustrate mean of 12 subjects. Error bars: 1 SEM. *Black bar*: drinking period (*left panel*) and smoking period (*right panel*). *TESTING* physiological measurement, VAS, dynamic posturography, and simulated driving tasks

immediately before testing to 0.057% immediately after testing (P=0.005). In contrast, mean BrAC with the 0.25 g/kg dose administered alone rose to 0.024% before testing and did not significantly differ from that value through the end of testing. BrAC with both alcohol doses significantly descended from peak values when the third post-drug VAS was administered 105 min after the start of drinking (P<0.001). Marijuana did not significantly affect BrAC with either alcohol dose.

CO and blood pressure

These measures were not significantly affected by marijuana, alcohol, or any marijuana-alcohol combination.

Heart rate

Heart rate with both THC doses peaked 2 min post-smoking [F(32,350)=8.2, P<0.001]. With both THC doses, heart rates did not decline from peak values until 15 min after testing (P<0.03; see Fig. 2). Within any time point, the effects of the two THC doses on heart rate did not significantly differ. There were no significant effects of alcohol alone on heart rate, and alcohol did not significantly alter the effects of THC on heart rate.

Visual analog scales: mood

Unless noted, significant results (see Fig. 3) are based on condition-time interactions [F(24,264)=1.9, P<0.006] and reported P values are from post-hoc tests.

Relative to placebo, the 0.5 g/kg alcohol dose increased ratings of drunk, high, and impaired both before and immediately after testing (P=0.039). On the clear-headed scale, ratings with 0.5 g/kg were significantly lower than those with placebo only at 45 min post-testing (P=0.02). Relative to placebo, the THC doses comparably increased ratings of high, impaired, and stoned through 45 min post-testing (P<0.02). Ratings of high were significantly greater with marijuana alone than with alcohol alone (P<0.05). Immediately before testing, 3.3% THC also increased ratings of anxious [F(24,263)=3.0, P<0.001] and confused, and decreased ratings of clear-headed (P=0.001). The increased anxiety produced by 3.3% THC 45 min after testing was restored to placebo levels when 3.3% THC was combined with 0.25 g/kg alcohol (P=0.027; data not shown). The addition of alcohol did not significantly alter any other THC effects.

Occasionally a dose combination, compared to placebo, produced significant effects not seen with either dose alone at that time point. Immediately before testing, the combination of 0.5 g/kg alcohol and 1.75% THC decreased ratings of clear-headed and increased ratings of confused (P=0.028). Immediately after testing, ratings of confused were significantly increased by the combination of 0.5 g/kg alcohol and 3.3% THC (P<0.001). At 45 min after testing, the combination of 0.25 g/kg alcohol with either THC dose significantly reduced ratings of clear-headed (P=0.024; data not shown) and the combination of 0.5 g/kg alcohol with either THC dose significantly increased ratings of drunk (P=0.011).

Visual analog scales: beverage and cigarette ratings

All significant results are based on F(8,88)=2.6, P=0.012, and reported P values are from post-hoc tests.

The 0.5 g/kg alcohol dose significantly increased ratings of beverage potency (mean±SEM increase from placebo scores=+38±11; P<0.001). There were no significant effects of alcohol dose on ratings of beverage taste. The effects of combinations of alcohol and marijuana on beverage ratings were not significantly different from the effects of alcohol alone.

The 1.75% THC dose increased ratings of cigarette taste only when given with 0.25 g/kg (+27±11 versus placebo cigarettes; P=0.022). The 3.3% THC dose increased ratings of cigarette taste only when given with 0.5 g/kg alcohol (+27±10; P=0.025). Increased ratings of cigarette potency with 1.75% THC alone (+43±5; P<0.001) and 3.3% THC alone (+55±7; P<0.001) did not significantly differ from each other. The effects of combinations of marijuana and alcohol were not significantly different from the effects of marijuana alone. Rat-

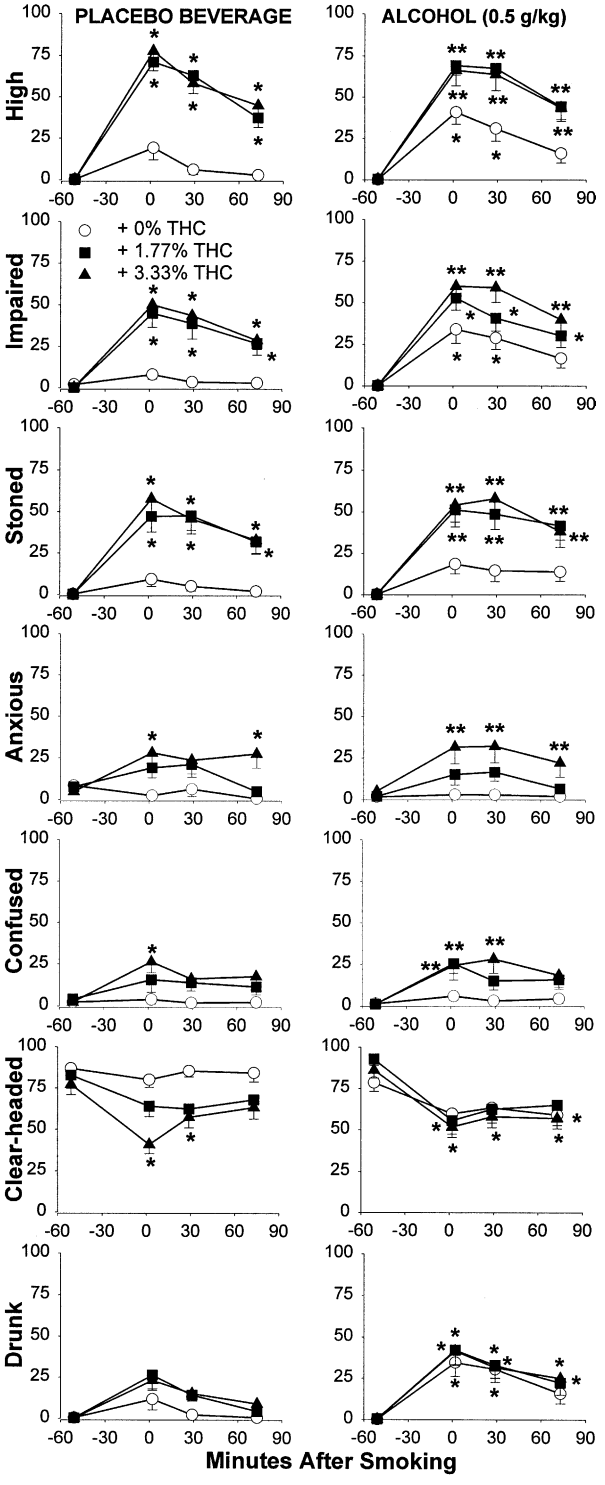

Fig. 3 Time course of subjective effects following alcohol-marijuana combinations. Data points illustrate mean of 12 subjects. Error bars: 1 SEM. *Significantly different from placebo (*open circles*, *left panel*) at that time point; **Significantly different from both placebo and 0.5 g/kg alcohol (*open circles*, *right panel*) at that time point

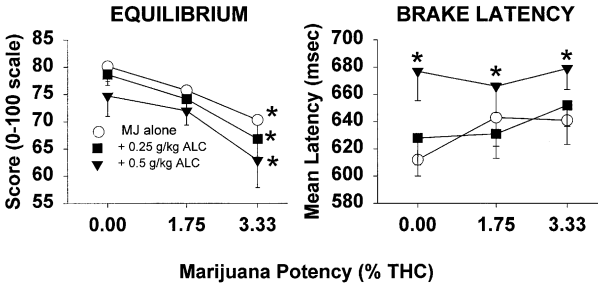

Fig. 4 Composite equilibrium scores (*left panel*) and mean brake latency (*right panel*) following alcohol and marijuana. Error bars: 1 SEM. *Significantly different from placebo

ings of cigarette harshness or draw did not differ with respect to dose condition.

Body sway

The 3.3% THC dose administered alone or with either alcohol dose significantly decreased composite equilibrium scores [$F(8,88)=5.2$, $P<0.001$] (see Fig. 4). Alcohol administered alone did not significantly affect equilibrium scores. The effects of combinations of marijuana and alcohol were not significantly different from the effects of marijuana alone.

Brake latency

Marijuana administered alone did not significantly affect brake latency. The 0.5 g/kg alcohol dose administered alone or with either active marijuana dose significantly increased brake latency [$F(8,88)=3.0$, $P=0.005$] (see Fig. 4). The effects of combinations of alcohol and marijuana were not significantly different from the effects of alcohol alone.

Discussion

In the present study, there were no significant additive effects of alcohol and marijuana on brake latency or body sway. Alcohol significantly slowed brake latency, but the effects of marijuana in combination with alcohol were no greater than the effects of alcohol alone. This finding is consistent with those of post-accident surveys, suggesting that alcohol may play a greater role than other drugs in traffic collisions. In one survey of injured drivers, marijuana, in the absence of alcohol, was not associated with crash responsibility (Lowenstein and Koziol-McLain 2001). In another survey, drivers responsible for a crash were significantly more likely to be alcohol-positive than alcohol-negative, but the difference in prevalence of drug-positive and drug-negative drivers was not significant (Timby et al. 1998).

The inability of marijuana to potentiate alcohol-induced driving impairment in the present study may

have been due to the selection of reaction time as the key dependent variable. Several studies have found additive or multiplicative marijuana and alcohol effects on other aspects of actual driving performance, including visual search (Lamers and Ramaekers 2001), road tracking (Robbe 1998; Ramaekers et al. 2000), and car handling (Hansteen et al. 1976). In contrast, marijuana did not significantly alter alcohol-induced slowing of reaction time in one of these studies (Hansteen et al. 1976), and additive effects were modest in another (Lamers and Ramaekers 2001). Similarly, measures of tracking, perception, and vigilance have typically been more sensitive than reaction time to THC impairment when THC alone is administered (see Moskowitz 1985 for review). In contrast to the robust and repeatable impairment of reaction speed observed with alcohol, extra distractions and dependent measures other than reaction time may be necessary to illustrate driving impairment from marijuana.

Another factor that may have contributed to the absence of significant marijuana effects on the simulated driving task is increased caution under the influence of THC. In on-road studies that quantified lane position and speed, THC-intoxicated drivers maintained a longer distance from the car in front of them and drove slower through obstacle courses (Robbe and O'Hanlon 1993). Marijuana has slowed reaction time on tasks during simulated driving that are of secondary importance to vehicle operation (Moskowitz et al. 1976; Smiley et al. 1981), suggesting that distraction may be a key factor in marijuana-related collisions. However, effects of THC on direct emergency responding appear to be dependent on whether subjects have some warning or other knowledge of when that response is needed. If, as in the present study, there is some degree of expectation, THC-intoxicated drivers will probably perceive their own impairment, slow down, and appropriately focus attention (Smiley 1998). The present findings suggest that impairing effects of moderate breath alcohol levels on emergency braking override any self-awareness and attentiveness that may accompany concurrent THC use.

Although pretreatment with alcohol increased positive ratings of cigarette taste, there was no evidence of pharmacodynamic interactions between alcohol and marijuana on the subjective effects scales. Both drugs separately increased ratings of high and impaired, but the subjective effects of the drug combinations were no greater than the strongest of the two drug effects when given alone. For example, marijuana alone produced greater ratings of high than alcohol alone, but the addition of alcohol to marijuana did not increase the reported high beyond that of marijuana alone. Conversely, the addition of marijuana to 0.5 g/kg alcohol did not increase ratings of drunk beyond those observed with alcohol alone. Marijuana also did not significantly affect breath alcohol concentrations, and alcohol did not significantly affect THC-induced heart rate increases. Although plasma levels were not taken in the present study, our results differ from those of studies in which marijuana smoking slowed absorption and subjective effects of alcohol while alcohol increased plasma THC levels and subjective effects of marijuana (Lukas et al. 1992; Lukas and Orozco 2001). The difference in results is surprising given that prior potentiation of marijuana-induced euphoria occurred within the first 15 min after smoking and drinking were completed (Lukas and Orozco 2001).

When administered separately, marijuana and alcohol produced contrasting behavioral effects. A marijuana cigarette with 3.33% THC significantly impaired body sway but not brake latency. This finding is consistent with our prior research, although reaction time was previously slowed to a marginally significant degree ($P<0.1$) with a 3.95% THC dose (Liguori et al. 1998). Conversely, an alcohol dose that produced mean BrACs in the 0.05–0.06% range significantly impaired brake latency but not body sway. The effects of alcohol in the driving simulator are consistent with prior evidence of impairment of driving-related skills below 0.06% BrAC (Moskowitz and Fiorentino 2000). However, the lack of corresponding body sway impairment lends support to recommendations for toxicologic testing in addition to standard sobriety testing (Brookoff et al. 1994). Similar results were found in a prior study when 43% of reckless cocaine-intoxicated drivers passed standard sobriety tests (Brookoff et al. 1994). Our data suggest that following alcohol or marijuana doses that do not cause gross motor impairment, impaired balance may not always coincide with slowed reactions while driving.

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