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BRIEF COMMUNICATION

Acute and Residual Effects of Marijuana: Profiles of Plasma THC Levels, Physiological, Subjective, and Performance Measures

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HEISHMAN, S. J., M. A. HUESTIS, J. E. HENNINGFIELD AND E. J. CONE. *Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective, and performance measures.* PHARMACOL BIOCHEM BEHAV **37**(3) 561–565, 1990.—Three experienced marijuana smokers participated in four 2-day experimental sessions in which they smoked either 0, 1, or 2 marijuana cigarettes containing 2.57% Δ^9-tetrahydrocannabinol (THC) at two different times on the first day. A battery of physiological, subjective, and performance measures was repeated throughout day 1 to assess acute effects and on day 2 to measure any residual effects of marijuana. Blood samples were also repeatedly collected to examine the relationship between plasma levels and pharmacological effects of THC. Acutely, marijuana increased heart rate and subjective ratings of drug effects and slightly impaired performance on a circular lights task in all subjects. Performance was also impaired (decreased accuracy and increased response time) on serial addition/subtraction and digit recall tasks on day 1 in two subjects. On day 2, tachycardia and subjective effects of marijuana were not observed. Performance remained impaired on the arithmetic and recall tasks on day 2, although the decrements were not as large as those observed on day 1. In general, plasma THC levels covaried with the other measures. These preliminary results suggest that marijuana can adversely affect complex human performance up to 24 hours after smoking.

Marijuana Plasma THC levels Residual effects Physiological effects Subjective effects Human performance Cognitive tasks Psychomotor tasks

IT is estimated that 12 million Americans currently use marijuana (18). This widespread use presents an important public health issue of marijuana's short- and long-term effects on human performance. It is of public health and scientific interest to determine whether the performance of a person who operates machinery or a car the day after smoking marijuana is likely to be impaired.

Recent research has documented that moderate doses of smoked marijuana can impair human performance for 2 to 8 hours, especially on tasks requiring divided attention or cognitive ability (1, 9, 10, 13). However, few studies have investigated residual effects of marijuana lasting longer than 8 hours. Perhaps the most widely cited study concerning the residual effects of marijuana on human performance reported that experienced aircraft pilots were impaired in attempting a landing maneuver on a flight simulator 24 hours after smoking a single marijuana cigarette compared to baseline performance before smoking (19). Interpretation of the data from this study was hindered by the lack of a placebo control condition. Chait *et al.* (3) reported minimal evidence for residual effects of marijuana 9 hours after smoking two 2.9% THC cigarettes the previous evening. Other studies, which demonstrated acute performance impairment, reported no residual impairment at 16–23 hours after smoked marijuana (1) or oral cannabis (14,15) administration.

The present study was an initial attempt to examine acute and residual effects of smoked marijuana on a battery of physiological, subjective, and cognitive and psychomotor performance measures. Blood samples were obtained concurrently to assess the relationship between plasma THC levels and the pharmacological effects of marijuana. We attempted to simulate the course of marijuana

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use in a social setting by having subjects smoke at two different times during the day, separated by several hours. The assessment battery was administered and blood samples were collected repeatedly during the day of marijuana dosing and the following day.

METHOD

Subjects

Participants were three healthy male volunteers, ranging in age from 27 to 29. Each subject is identified by two letters randomly selected from the alphabet. Before participation, subjects were medically and psychiatrically screened. All subjects reported current use of tobacco and marijuana; average marijuana use was 4.7 joints per month. After admission to the research unit, subjects were required to be drug-free for a minimum of 3 days before beginning the study. Subjects provided written informed consent and were paid for their participation.

Procedure

Subjects lived on the residential unit of the Addiction Research Center and participated in four experimental conditions, each of which spanned 2 days. The first day involved marijuana dosing and assessment of acute effects; measurements on day 2 assessed residual effects. Each condition was separated by the time required for each subject to test negative for urinary cannabinoids by immunoassay (20 ng/ml cutoff). This period averaged 1 week for two subjects and 2 weeks for the third. Each condition involved subjects smoking two marijuana cigarettes at 0900 and two more cigarettes at 1300 on day 1; the two cigarettes at each time were separated by a 10-min interval. Machine-rolled NIDA marijuana cigarettes contained either 0 (P) or 2.57% (A) THC and were smoked under double-blind conditions according to a paced procedure (8). The four drug conditions were: 1) 0900: PP, 1300: PP; 2) 0900: AP, 1300: PP; 3) 0900: AP; 1300: AP; and 4) 0900: AA, 1300: AA. The order in which cigarettes were smoked at each time was fixed as indicated, but the order of drug conditions was randomized for each subject. One subject completed only two conditions (2 and 3) because his participation was stopped following the 0900 dosing of the two active cigarettes due to extreme intoxication.

At 0830 on day 1, a predrug blood sample was collected and a battery of physiological, subjective, and performance measures was completed. Subjects smoked the first two marijuana cigarettes from 0900 to about 0920 and the second two cigarettes from 1300 to 1320. The battery of subjective and performance measures was repeated on day 1 at 0930, 1000, 1100, 1230, 1330, 1400, and 1600. Physiological measures and a blood sample were taken at these same times and at 0945, 1200, 1345, and 1500. On day 2, the complete battery of measures was administered and a blood sample was collected at 0800, 1000, 1200, 1400, and 1600.

Performance and Subjective Measures

Prior to the first experimental condition, subjects practiced the cognitive and psychomotor tasks until their performance was stable. Cognitive performance was assessed using four tasks selected from a computerized performance assessment battery (PAB): two-letter search, logical reasoning, digit recall, and serial addition/subtraction (16,17). For each task, number of attempted trials, percent correct trials, and mean response time per trial were recorded. Psychomotor performance was assessed using a circular lights task, which utilized a Wayne Computerized Saccadic Fixator (Model 287; Wayne Engineering; Northfield, IL). Subjects faced a wall-mounted panel consisting of 33 button-lights arranged in three concentric circles. Subjects pressed the buttons in response to the random illumination of only the 16 lights on the outer circle (72-cm diameter). The score was the number of responses during a 1-min session. Subjects were instructed to perform all tasks as rapidly and accurately as possible; they were paid 1 cent per correct response on each task.

Subjective measures included six visual analog scales (VAS) that appeared individually on the video monitor. Subjects rated the following items from 0 (not at all) to 100 (extremely): drug high, drug liking, impaired performance, clear-headed, stoned, and relaxed.

Physiological Measures and Plasma Δ^9-THC Analysis

Blood pressure, heart rate, and oral temperature were measured using an automated monitor (IVAC Model 4000). Blood samples were withdrawn through an intravenous catheter placed in a forearm vein, which remained in place for the duration of each 2-day condition. Plasma was analyzed for Δ^9-THC by radioimmunoassay (7). The precision of the assay at 5.0 ng/ml Δ^9-THC was 10.9% and 12.2% within and between runs, respectively.

RESULTS

Performance Measures

Figure 1 shows percent correct trials for each drug condition on the serial addition/subtraction and digit recall tasks for two subjects, PB and NU. Marijuana had little effect on HV's PAB performance. Compared to predrug baseline, marijuana decreased accuracy on both tasks on day 1. Effects were typically opposite in direction from those of condition 1 (placebo), generally dose-related within subjects, and especially evident in conditions 3 and 4. On day 2, performance decrements in serial addition/subtraction had generally returned to predrug levels. In contrast, digit recall accuracy remained below predrug and placebo levels on day 2, although the decreases were less than those on day 1. Mean response time was increased in serial addition/subtraction on day 1 in conditions 2 and 4, which persisted on day 2. Marijuana had no effect on number of attempted trials in either task.

Performance on the other PAB tasks was not consistently affected. Marijuana decreased percent correct trials in logical reasoning during conditions 2 (HV) and 4 (PB); these decrements in accuracy were accompanied by increased response times. Increased response times were also observed on the two-letter search task in conditions 3 or 4, but these did not typically covary with a change in accuracy. On day 2, performance was not impaired on either task. Marijuana produced slight decreases in number of responses on the circular lights task in conditions 3 and 4. Maximal effects generally occurred immediately after smoking, and decrements were not observed on day 2.

Subjective and Physiological Measures

All subjects reported increased VAS ratings of drug high, stoned, drug liking, and impaired. Increases peaked immediately after smoking and generally declined gradually over the morning or afternoon. Average increases in ratings of drug high from predrug baseline for the 0930 and 1330 measurements, respectively, were: condition 1 (0,0); condition 2 (75,43); condition 3 (80,82); and condition 4 (95,85). One day 2, no subjective measure in any condition was different from day 1 predrug baseline.

Marijuana increased heart rate in all subjects on day 1. Maximal increases were observed immediately after smoking and had nearly returned to baseline levels by 1600 on day 1 in all

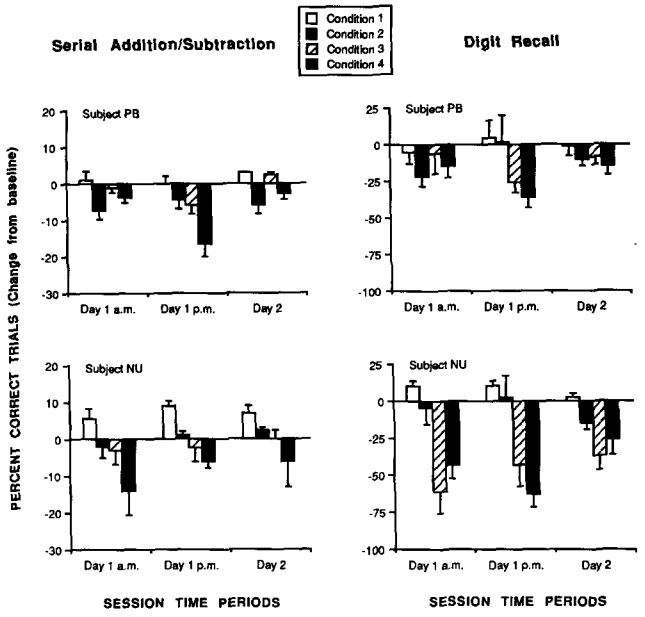

FIG. 1. Effect of marijuana on percent correct trials on serial addition/subtraction task (left column) and digit recall task (right column) for Subject PB (top panel) and Subject NU (bottom panel). Each graph shows data from the four drug conditions (see text for description) as the mean difference ±1 S.E.M. from day 1 predrug baseline for the three morning postsmoking assessments (Day 1 a.m.: 0930, 1000, 1100); the three afternoon postsmoking assessments (Day 1 p.m.: 1330, 1400, 1600); and the five Day 2 assessments (0800, 1000, 1200, 1400, 1600). The absence of a data column for a specific drug condition indicates that the mean change from baseline = 0; absence of error bars indicates S.E.M. = 0.

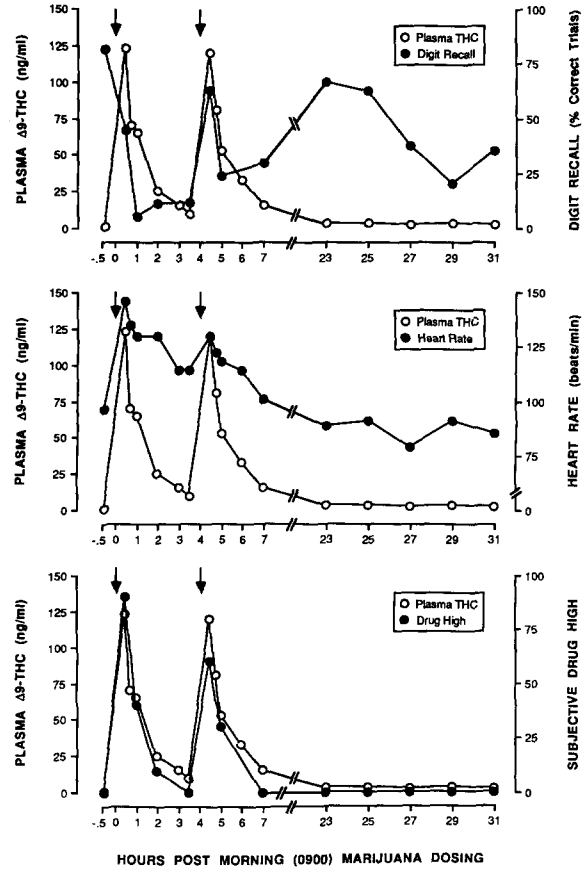

FIG. 2. Temporal relationship between plasma THC concentration and percent correct trials on digit recall task (top panel), heart rate (middle panel), and subjective rating of drug high (bottom panel) for Subject NU in drug condition 3. Arrows indicate time of administration of one active and one placebo marijuana cigarette in the morning (0900) and afternoon (1300) on day 1.

conditions. Compared to predrug baseline, no change in heart rate was observed on day 2. Blood pressure and temperature were not systematically affected by marijuana on either day 1 or 2.

Plasma Δ^9-THC

Table 1 shows plasma THC concentrations for each subject over the course of each active drug condition. Peak plasma levels were obtained immediately after smoking in all conditions, which gradually declined over the morning or afternoon. By day 2, levels had decreased below 10 ng/ml, ranging from 1.2 to 6.3 ng/ml. In condition 3, similar peak plasma levels occurred after the morning and afternoon dosing for all subjects. In condition 4, PB also achieved similar morning and afternoon peak plasma levels; however, NU had a more than two-fold increase following the afternoon dosing (342.2 ng/ml) compared to the morning (119.4 ng/ml). These high levels achieved by NU were also reflected in the day 2 levels. Figure 2 shows the temporal relationship between plasma THC levels and the pharmacological effects of marijuana for NU in drug condition 3. Plasma THC levels, tachycardia, and subjective drug high peaked immediately after the morning and afternoon dosing and declined over similar times. Maximal impairment on the digit recall task occurred about 30 min after peak plasma concentration.

DISCUSSION

Although only three subjects were tested, it appeared that the repeated dosing design was effective in demonstrating acute and residual effects of smoked marijuana. Acutely, marijuana produced tachycardia and increased subjective ratings of drug effect in all subjects. Performance was impaired on two cognitive tasks in two subjects and slightly impaired on a psychomotor task in all subjects. On the day after smoking marijuana, heart rate and subjective measures had returned to predrug baseline levels, whereas performance on the cognitive tasks remained somewhat impaired. In general, plasma THC levels covaried temporally with pharmacological effects. These data indicated that performance decrements from smoking two or four marijuana cigarettes may be evident for as long as 24–31 hours.

With one notable exception (19), the majority of studies investigating residual effects of marijuana have reported little if any decrements in performance 9–23 hours after marijuana or cannabis administration (1, 3, 14, 15). In this study, accuracy on the digit recall task remained impaired in two subjects for all active drug conditions the day after smoking marijuana (Fig. 1). Decreased accuracy in serial addition/subtraction on day 2 was not as consistently observed. However, the increased response time observed on day 1 for serial addition/subtraction remained increased on day 2 above predrug baseline or at levels comparable to those on day 1.

Acutely, marijuana impaired performance in two of three subjects on serial addition/subtraction and digit recall. Accuracy

TABLE 1

PLASMA Δ^9-THC LEVELS (ng/ml) FOR INDIVIDUAL SUBJECTS IN EACH DRUG CONDITION

	Subject PB			Subject NU			Subject HV	
Time of Day	Cond. 2	Cond. 3	Cond. 4	Cond. 2	Cond. 3	Cond. 4	Cond. 2	Cond. 3
Day 1								
0900—smoking								
0930	52.0	85.4	140.1	82.7	123.3	119.4	38.5	—*
0945	46.8	73.4	97.6	49.4	69.8	91.9	36.6	23.6
1000	39.4	59.4	70.9	39.4	64.8	90.3	24.5	21.4
1100	28.0	33.2	34.4	22.2	25.3	46.7	13.7	9.9
1200	17.7	19.4	19.9	12.9	16.0	33.9	7.5	4.6
1230	12.1	13.4	15.8	8.8	9.5	27.8	4.9	4.2
1300—Smoking								
1330	—*	75.8	128.4	8.2	119.7	342.2	3.9	40.3
1345	10.4	67.9	104.8	7.4	80.2	160.0	4.2	28.9
1400	7.9	46.0	67.4	5.8	53.1	120.7	3.5	24.7
1500	6.5	29.6	36.4	5.5	33.2	67.1	3.3	11.0
1600	6.5	25.0	22.8	5.0	15.6	44.0	3.4	6.7
Day 2								
0800	3.1	4.7	4.3	2.2	3.7	6.3	1.5	1.5
1000	2.8	3.1	3.6	2.0	3.4	6.0	1.2	1.6
1200	2.9	3.0	3.5	2.5	3.0	4.8	1.1	1.5
1400	3.5	3.0	3.4	2.5	3.2	5.2	1.9	1.4
1600	2.8	2.8	3.2	2.2	2.8	4.9	1.6	1.4

*Blood sample was not obtained.

was decreased and mean response time per trial was increased, especially in condition 4 (four active cigarettes). These findings are consistent with past research documenting marijuana's acute impairment of memory and mathematic abilities (9, 11, 15). Marijuana also slightly decreased circular lights responding, which has been reported by some (6), but not all investigators (8). Consistent impairment was not observed on the two-letter search or logical reasoning tasks. The acute effect of marijuana on heart rate and subjective drug effects was consistent with that documented in past studies (8, 9, 13). The maximal tachycardiac response following the afternoon dosing in conditions 3 and 4 was generally less than that of the morning dosing, probably reflecting the development of acute tolerance (2,5). Peak plasma THC levels were similar or higher following the afternoon dosing, compared to the morning, whereas subjective ratings of drug high and stoned were similar in magnitude after both administrations. There were no measureable effects on day 2 on either heart rate or subjective reports in any drug condition. This agrees with other studies investigating the residual physiological and subjective effects of smoked marijuana (3,19) or oral cannabis resin (14,15).

Although the data from the present study are limited and should be considered preliminary, some observations can be made concerning the temporal relationship between plasma THC levels and pharmacological effects. Comparing the three subjects in condition 3, task performance of HV was least impaired and his plasma THC levels were also the lowest. Conversely, the extreme impairment observed in NU on the digit recall task in conditions 3 and 4 (Fig. 1) was associated with some of the highest plasma THC concentrations. Additionally, the residual performance impairment of NU in digit recall was associated with the highest plasma levels on day 2 (4–6 ng/ml). There was close temporal correspondence between his plasma levels and subjective effects and tachycardia (Fig. 2). In contrast, there was a lag time of about 30 min between peak THC levels and maximal performance impairment. This is consistent with past research reporting a 30–60 minute delay between peak plasma levels and other pharmacological effects of smoked marijuana (4, 5, 12). This delay likely represents the time required for disposition of THC to neuronal substrates. After complete distribution, a linear relationship between plasma THC levels and subjective high (4, 5, 12) and tachycardia (5) has been reported.

In summary, these results provided preliminary evidence that smoking two or four marijuana cigarettes produced residual impairment on two cognitive tasks; other cognitive tasks and a psychomotor task were not affected the day after smoking. The design of two smoking periods in one day separated by several hours may have contributed to the measurement of residual effects. Previous studies reporting no residual effects of marijuana utilized either acute administration (1, 14, 15) or repeated administration separated by a relatively short interval (3). It will be necessary to replicate and extend these findings using more subjects and other measures to determine more precisely the nature and magnitude of residual effects of marijuana on human performance.

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