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The Pharmacologic Effects of Daily Marijuana Smoking in Humans

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PEREZ-REYES, M., W. R. WHITE, S. A. McDONALD, R. E. HICKS, A. R. JEFFCOAT AND C. E. COOK. *The pharmacologic effects of daily marijuana smoking in humans.* PHARMACOL BIOCHEM BEHAV **40**(3) 691–694, 1991.—Six healthy male, paid volunteers smoked one NIDA cigarette containing 1.0% THC each day for 13 consecutive days. They were tested before and after the period of drug administration by the following procedure: the subjects smoked one NIDA marijuana cigarette containing 1.0% THC followed 15 minutes later by the intravenous infusion of 52 μg/min of deuterated THC for 50 minutes. The THC plasma concentrations, ratings of "high" and heart rate effects produced by the combined drug administration were measured, and absolute bioavailability of smoked THC was calculated on Days 1 and 22. Statistical analyses indicate that the only significant changes induced by daily marijuana exposure were in cardioacceleration.

Daily marijuana smoking Subjective effects Heart rate effects THC plasma levels THC infusion Humans

TOLERANCE to the pharmacologic effects of Δ-9-tetrahydrocannabinol (THC) has been demonstrated consistently in all animal species investigated (5) except humans. This tolerance is characterized by rapid development, large magnitude, and persistence (13).

In contrast, development of tolerance to the effects of THC in humans is not readily demonstrable. For example, there were no differences between frequent (493 ± 190.7 times per year) and infrequent (3.0 ± 1.0) smokers of marijuana regarding the magnitude of "high" and heart rate acceleration in response to intravenous challenge doses of THC (22). This observation has been confirmed in studies in which the challenge THC dose was administered via marijuana smoke inhalation. Comparisons were made between naive and experienced marijuana users (4,14) or between frequent and infrequent marijuana users (3). These independent observations indicate that tolerance to the effects of THC does not occur in response to usual patterns of marijuana smoking.

Nevertheless, evidence of tolerance to THC, in particular to its cardioacceleratory effects, has been found in controlled laboratory investigations by independent groups of investigators [for review see (10)]. With one exception (6), reported studies were conducted with hospitalized subjects. In these studies, the potency of the marijuana ranged from 1.5 to 2.0% THC; dosage ranged from 4 to 26 cigarettes per day; and the duration of daily smoking ranged from 16 to 94 days (1, 8, 16, 23). In one study, THC was administered orally in an escalating divided-dose schedule until a total of 210 mg/day was reached. This dosage was sustained for an 11–16-day period (11).

The degrees of daily exposure to THC in hospitalized subjects represent worst-case scenarios and do not resemble real life circumstances. Thus it is unlikely that any but the heaviest marijuana users smoke as many "joints" per day, or ingest equivalent amounts of marijuana, to correspond with the levels of exposure to THC used in these studies. Moreover, confinement on a research ward for extended periods of time is completely divorced from everyday life circumstances, detracting further from the clinical value of the results of these studies.

Therefore, demonstration is needed regarding whether or not daily exposure to more realistic doses of THC (under conditions that closely resemble real life circumstances) induces pharmacologic tolerance. To accomplish this objective, nonhospitalized volunteers smoked (in their customary fashion) a 1.03% marijuana cigarette daily for 13 days. The subjective and heart rate effects produced by the combined administration of smoked marijuana and intravenously infused deuterated THC were measured before and after the period of daily marijuana smoking. Infusion of deuterated THC was used to obtain information about the bioavailability of smoked marijuana.

METHOD

Subjects

Six healthy male, paid volunteers who had previously used marijuana daily for extended periods participated in the study. Subject characteristics were age, 27.8 ± 1.3 years; weight,

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84.3 ± 2.6 kg; height, 181.1 ± 2.3 cm, and current marijuana use (i.e., over the previous six months), 4.0 ± 1.4 times per month. Subjects contracted to abstain from the use of marijuana and other illicit drugs for two weeks before the initiation of the study and throughout its duration. To assure compliance with the drug abstinence restrictions, urine samples were obtained on the first day and at frequent intervals thereafter. These samples were analyzed by EMIT techniques. The volunteers were informed of the purpose, procedures and potential risks of the study. All signed a consent form approved by the Committee on the Protection of the Rights of Human Subjects of the University of North Carolina at Chapel Hill.

Marijuana Cigarette Preparation

National Institute on Drug Abuse (NIDA) cigarettes were prepared by the Research Triangle Institute (RTI) from a combination of active and placebo plant material in order to obtain a 1% THC content. The average mass of the plant material was 876 mg, i.e., the average THC content was 8.8 mg per cigarette.

Intravenous THC Preparation

Ten milligrams of 5′,5′,5′-trideutero-Δ-9-THC (deuterated THC, d_3-THC), obtained from NIDA, was dissolved in absolute ethanol (0.5 ml) and then microsuspended in 50 ml of 25% sodium-free human serum albumin. To assure sterility and particle size, the preparation was filtered through a 0.22-μm micropore membrane (21). The theoretical concentration of this preparation was 200 μg/ml of THC. After filtration, the concentration was 113 μg/ml, as analyzed by gas chromatography. This preparation was intravenously infused at a rate of 0.46 ml/minute (i.e., 52 μg of THC per minute) for 50 minutes. Therefore, the total dose of deuterated THC infused on each occasion was 2.6 mg.

Experimental Timetable

Day 1. The subjects were instructed to smoke one NIDA marijuana cigarette (1.0% THC) in their customary fashion. At the end of the period allowed for smoking (15 minutes), the volunteers were intravenously infused at the rate of 52 μg/minute with deuterated THC for 50 minutes. Deuterated THC was infused to allow determination of the absolute bioavailability of smoked THC. The use of deuterated THC allowed differentiation of infused THC from smoked THC. The pharmacokinetic analyses of these studies will be reported elsewhere.

Days 1–8. For pharmacokinetic analyses, subjects collected the total urine excreted daily. Blood samples were obtained on Days 1–3.

Days 9–21. The volunteers smoked one NIDA cigarette containing 1.03% THC marijuana in the laboratory each day. This dosage regimen was designed to produce minimal and transient effects that would allow the volunteers to continue their customary daily activities with minimal disruption, while affording the possible development of enzyme induction and tolerance.

Day 22. Subjects were tested as on Day 1.

Day 22–29. Biological specimens were collected as on Days 1–8.

Experimental Variables

Amount of marijuana smoked. To determine how much of the marijuana cigarette each subject smoked on Days 1 and 22, the weight of the butt was subtracted from the original weight of the cigarette.

Subjective rating of "high." The subjects were asked to rate their perceived magnitude of marijuana "high" at frequent intervals during the experiment. For these ratings, the subjects were instructed to use a scale of 0 to 100, with 0 representing no drug effects and 100 representing the "highest" they had ever been after using marijuana. Every time a rating was made, the subjects were given their previous rating to use for comparison. This technique allowed the subjects to rate themselves as experiencing more, less, or the same effects as those rated in the previous time interval.

Cardiovascular effects. The most consistent and pronounced effect of THC on the cardiovascular system is acceleration of heart rate. This effect parallels changes in the subjective rating of "high" over time in a dose-response manner (18). Heart rate was measured with EKG electrodes placed on the chest. After obtaining baseline data, heart rate was recorded continuously during the period of drug administration and at frequent intervals thereafter.

THC plasma concentrations. Blood samples for the determination of both deuterated and nondeuterated THC were drawn at appropriate intervals for 48 hours. Plasma was analyzed by capillary GC/MS (electron impact mode) of the trimethylsilyl ether derivative after a solid-phase extraction. Nonadeutero-THC (d_9-THC) was used as the internal standard.

Bioavailability of smoked THC. The bioavailability of THC from marijuana cigarette smoking was calculated by comparison with the bioavailability of intravenously infused deuterated THC. Because different doses were administered by each route, the following equation was used (12):

$$\text{Bioavailability} = \frac{\text{AUC (0–48 h) smoked}}{\text{AUC (0–48 h) IV}} * \frac{\text{IV dose}}{\text{Smoked dose}} \times 100$$

Statistical analyses. For each dependent variable, a time-response analysis was performed. Orthogonal polynomial regressions were performed on the Time factor in an analysis of variance model in which Subject, Day and Time were completely crossed (2). Reliability coefficients were obtained from each analysis using intraclass correlation procedures (9). Analyses were also done on area under the (time-response) curve, time to peak, and peak response.

RESULTS

Amount of Marijuana Smoked

Cigarettes were uniformly smoked over a 15-minute interval. The mass of the cigarettes smoked on Day 1 was 852 ± 16 mg and on Day 22 was 825 ± 5 mg. Subtraction of the weight of the remaining butt indicated that the amount of marijuana smoked was 689 ± 35 mg and 711 ± 35 mg on Days 1 and 22, respectively. The difference between means is not statistically significant.

THC Plasma Concentrations

On the test Days 1 and 22, nondeuterated THC (i.e., THC derived from marijuana smoking) reached maximal concentrations rapidly and then progressively declined. Deuterated THC (i.e., THC derived from intravenous infusion) reached maximal values more slowly and then progressively declined (Fig. 1). The combined smoke inhalation of marijuana and intravenous infusion of deuterated THC resulted in drug plasma concentrations that are not significantly different between Days 1 and 22. Intersubject means ($r_i = .80$, $p<0.01$) and time-response patterns ($r_i =$

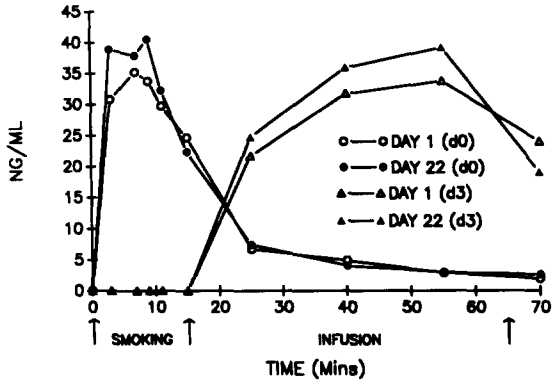

FIG. 1. Mean plasma concentrations of total THC for smoked marijuana and infused deuterated (d_3-) THC on Days 1 and 22. One marijuana cigarette was smoked from 0 to 15 minutes and was followed by intravenous infusion from 15 to 65 minutes, as indicated by the arrows.

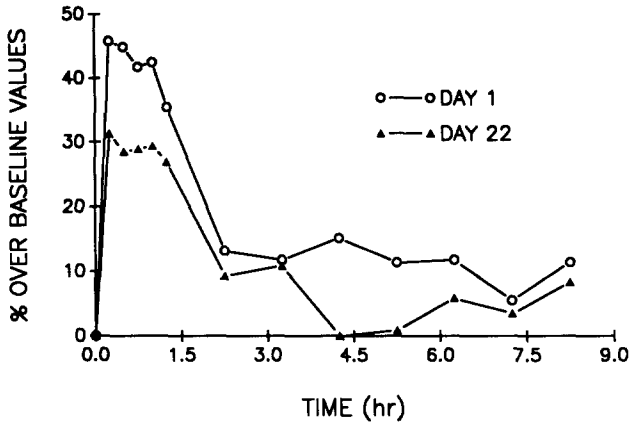

FIG. 3. Mean heart rate acceleration from the combination of smoked marijuana and infused d_3-THC on Days 1 and 22.

.80, $p<0.01$) for both days are highly reliable, i.e., interindividual differences in plasma concentrations were stable across days.

Bioavailability of Smoked THC

The bioavailability of THC derived from marijuana cigarette smoking on Day 1 was 14.4±4% (range 1.4–23.3%). On Day 22, mean bioavailability was 13.5±5% (range 3.2–34.5%). Mean bioavailibility is not significantly altered by daily exposure to marijuana.

Subjective Effects

The magnitude of subjective ratings of "high" over time in response to the combined smoke inhalation of marijuana and intravenous infusion of deuterated THC are shown in Fig. 2. These ratings are not significantly different between Days 1 and 22. Intersubject means ($r_i = .89$, $p<0.01$) and time-response patterns ($r_i = .63$, $p<0.01$) for both days are highly reliable, indicating that interindividual differences in subjective ratings were stable across days.

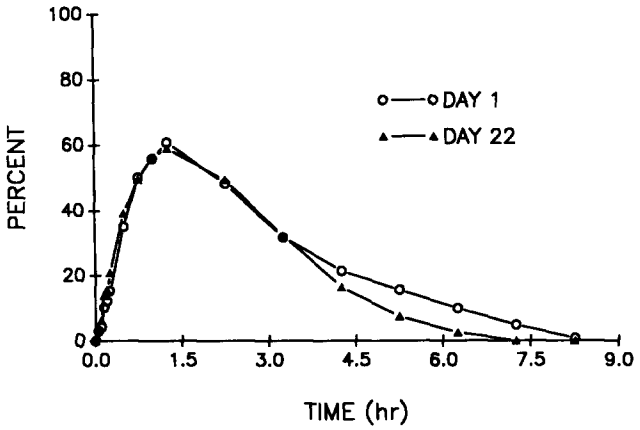

FIG. 2. Mean ratings of "high" from the combination of smoked marijuana and infused d_3-THC on Days 1 and 22.

Heart Rate Effects

The magnitude of the heart rate acceleration over time in response to the combined smoke inhalation of marijuana and intravenous infusion of deuterated THC is shown in Fig. 3. The dependent measure analyzed was the proportion of baseline (predrug) heart rate for each postdrug heart rate measurement. Baseline heart rate is highly reliable across subjects on Days 1 and 22 ($r_i = .65$, $p<0.01$). Heart rate shows a trend towards more acceleration on Day 1 than on Day 22, $F(1,5) = 4.3$, $p<0.09$. The time-response patterns are reliable across days ($r_i = 0.43$, $p<0.01$), and are significantly greater on Day 1 than Day 22, $F(1,5) = 8.12$, $p<0.04$, indicating that heart rate accelerated less rapidly on Day 22.

Analyses were also completed on the time to peak, peak value, and area under the time-response curve (AUC) for each dependent variable. However, the differences between Days 1 and 22 for these variables are not significant.

DISCUSSION

Studies of the effects of daily marijuana smoking are important to assess the consequences of habitual rates of consumption under conditions that approach real life circumstances. Therefore, these studies should ideally be conducted in nonhospitalized volunteers, who are allowed to conduct their daily activities with minimal interference. These objectives were accomplished in the present study by selection of a daily dose of marijuana that produced modest and transient subjective effects, but was representative of habitual use patterns. Thus, although some marijuana users smoke marijuana many times a day and others smoke the drug occasionally (a few times per year), the great majority smoke the drug once a day or less.

The potency of street marijuana has increased progressively for 15 years, i.e., the average THC content of confiscated marijuana (loose plant material) was 0.36% in 1974, but had risen to 3.54% in 1990 (7). In light of this information, it could appear that exposure to the 1.0% marijuana used in this study was low and unrepresentative of current levels of exposure. This is not necessarily the case, however, as marijuana is predominantly used in social situations in which "reefers" are shared between two or more individuals. In contrast, the volunteers in this study smoked the majority of each marijuana cigarette. Hence, they inhaled a total dose of THC comparable to that inhaled when

cigarettes of commonly available marijuana are shared.

Plasma analyses indicate that the concentrations of deuterated and nondeuterated THC were similar before and after daily marijuana smoking. This finding suggests that no changes in the metabolic disposition of the drug occurred in the experimental paradigm used.

Study design permitted direct estimation of the bioavailability of THC derived from marijuana cigarette smoking, information not previously available. Exposure to daily marijuana smoking did not alter the bioavailability of smoked THC. Wide individual variations were found, which confirms the observation of large individual variability of the manner in which marijuana cigarettes are customarily smoked (17).

Marijuana is smoked because of the pleasant psychologic effects induced. The finding that daily marijuana smoking produced no changes in the magnitude of marijuana "high" is important because it suggests no tolerance to this psychologic effect. Therefore, as long as marijuana is not used more than once daily, it appears that there is no need to escalate the dose to obtain the same degree of "high."

Acceleration of the heart rate is a consistent effect of THC. In this study, a trend toward diminished cardioacceleration and a significant decrease in the heart rate acceleration time-response pattern were found to occur after the period of daily marijuana smoking. Taken together, these observations suggest that tolerance to the heart rate-accelerating effects of THC develops in response to modest daily doses of the drug. A similar result has been found in a study using nonhospitalized subjects, in which one cigarette containing 1.4% THC was smoked daily for 21 consecutive days (6). Another study (20) indicates that tolerance to the heart rate-accelerating effects of THC occurs rapidly. When two marijuana cigarettes containing 1.0% THC were smoked within a two-hour interval, the percent heart rate acceleration in response to the first cigarette was significantly greater than that observed to occur after the second cigarette. It is noteworthy that this two-dose study demonstrated cardioacceleratory tachyphylaxis without acute tolerance to the subjective effects of THC.

That tolerance to the heart rate-accelerating effects of THC develops more readily than tolerance to its subjective effects is not understood. Nonetheless, it is possible to speculate that the relative complexity of the neuronal circuits involved in each of these effects may be responsible for the observed differences. Awareness of marijuana "high" consists of diversely perceived somatic, affective, sensory, and cognitive changes. Obviously, these effects involve complex neuronal circuits, e.g., the cortex, basal ganglia, limbic system, hypothalamus, etc. In contrast, heart rate is controlled by the vasomotor centers primarily located in the hypothalamus and the medulla oblongata, i.e., much less complex neuronal circuitry. Therefore, tolerance to cardioacceleration may occur more readily as fewer neuronal circuits are involved.

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