

Blood Cannabinoids. I. Absorption of THC and Formation of 11-OH-THC and THCCOOH During and After Smoking Marijuana*

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Abstract

Δ^9 -Tetrahydrocannabinol (THC), the primary psychoactive constituent of marijuana, is rapidly transferred from lungs to blood during smoking. Oxidative metabolism of THC yields the active metabolite, 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC), and the inactive metabolite, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH). Characterization of THC's absorption phase is important because of the rapidity with which THC penetrates the central nervous system to produce psychoactive effects. This study incorporated a highly automated procedure to sample blood and to capture rapid drug level changes during and following smoking. Human subjects smoked one marijuana cigarette (placebo, 1.75%, or 3.55% THC) once a week according to a randomized, crossover, double-blind Latin square design. Samples were analyzed by GC/MS for THC, 11-OH-THC, and THCCOOH. THC levels increased rapidly, peaked prior to the end of smoking, and quickly dissipated. Mean peak 11-OH-THC levels were substantially lower than THC levels and occurred immediately after the end of smoking. THCCOOH levels increased slowly and plateaued for an extended period. The mean peak time for THCCOOH was 113 min and a correspondingly longer time course of detection was observed. This study provides the first complete pharmacokinetic profile of the absorption of THC and appearance of metabolites during marijuana smoking. These findings have implications for understanding the mechanisms underlying the performance-impairing effects of marijuana, as well as for aiding forensic interpretation of cannabinoid blood levels.

Introduction

Smoked drugs, including marijuana, cocaine, methamphetamine, and phencyclidine, offer unique challenges to pharmacokinetic and pharmacodynamic investigations. It is likely that smoked drugs are highly abused, in part, because of the speed of delivery of drug to the brain (1). Δ^9 -Tetrahydrocannabinol (THC), the primary psychoactive component of marijuana, is rapidly absorbed from the lungs and quickly distributed throughout the body. Few studies have attempted to measure THC or metabolite

concentrations during marijuana smoking because of the rapidity of the absorption process. Peak THC concentrations occur during smoking and are missed if sampling begins after this time. During this critical phase, active and inactive metabolites of THC are formed and make their first appearance in blood. Characterization of the absorption phase of THC has been impeded by the need for fast sequential blood sampling during the critical smoking period and the necessity of sensitive analytical methods.

Little is known of the formation of THC metabolites during marijuana smoking. Microsomal hydroxylation of THC was shown to produce the active metabolite, 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC), believed by early investigators to be the true active analyte (2). However, this theory was later disputed because of the lack of immediate effects following intravenous administration of 11-OH-THC (3). 11-OH-THC concentrations have been reported to be low following marijuana smoking, with metabolite levels attaining less than 10% of THC concentrations (4). Further oxidation of active 11-OH-THC produces the inactive metabolite, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH) (5). THCCOOH levels gradually increase and surpass concurrent THC levels shortly after completion of smoking, because of the precipitous drop in THC levels during this period. The time course of detection of THCCOOH is much longer than that of either of the active analytes. This extended detection time was shown to be caused by the slow release and subsequent metabolism of THC from tissue stores (6).

The absorption and distribution of THC and formation of 11-OH-THC and THCCOOH in blood during and after marijuana smoking were studied in a controlled clinical setting. Six subjects smoked a single marijuana cigarette during each test session. Sequential blood samples were collected during smoking by using a continuous withdrawal pump. Gas chromatography/mass spectrometry (GC/MS) was used for determination of plasma drug analyte concentrations. THC, 11-OH-THC, and THCCOOH concentrations were evaluated in relation to time of drug exposure.

Methods

Subjects

Six healthy male volunteers with a history of marijuana use resided on a closed research ward of the Addiction Research Center, National Institute on Drug Abuse, for 4–6 weeks. Subjects' ages

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ranged from 29 to 36 years with a mean of 31.3 years. Mean height and weight were 1.74 m (range of 1.65 to 1.84 m) and 77.6 kg (range of 64.8 to 93.4 kg), respectively. First marijuana use occurred between the ages of 13 to 16 years with a mean of 14.5 years. Prior drug use within the past 30 days included nicotine, ethanol, heroin, marijuana, cocaine, and barbiturate use. Subjects reported smoking an average of 2.3 marijuana cigarettes per week with a range of exposure from 0.4 to 7.9 cigarettes per week. Subjects provided informed consent and were paid for their participation. Medical histories, physical examinations, and electrocardiograms were obtained prior to testing. Additional evaluation criteria included blood chemistry and hematology screens, Shipley Institute Living Scale and SCL-90 Mood Scale evaluations, descriptions of current and prior drug use, and absence of active disease. Urine drug testing for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, methadone, opiates, phencyclidine, and marijuana metabolites was performed prior to admission and during residence to ensure lack of exposure to unauthorized drugs during the study.

Dose and route of administration

Marijuana cigarettes were obtained from the Research Technology Branch, National Institute on Drug Abuse. Subjects smoked a single marijuana cigarette (placebo, 1.75% THC, or 3.55% THC) according to a computer-signaled paced smoking procedure on each of three test days. Cigarettes weighed an average of 900 mg, yielding THC doses of approximately 15.8 and 33.8 mg for the low and high doses. The smoking protocol consisted of a 2-s inhalation, a 10-s hold period, and a 72-s exhalation and rest period. A total of eight puffs were inhaled in 11.2 min. Doses were administered according to a randomized, double blind, Latin square design at weekly intervals.

Collection, preparation, and analysis of plasma samples

The Dakmed Ambulatory Withdrawal Pump Model ML6-5S3R (Dakmed, Inc.) was used for rapid blood sampling and integrated blood collections from 1 h prior to 3 h post drug administration. Blood was collected through 4-ft Dakmed silanized tubing via a 19-gauge butterfly needle inserted in a nondominant

Table I. Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette

Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject B</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.0
0.017*	20.0	1.2	0.0	17.0	0.0	0.0
0.033*	38.0	2.8	0.0	54.0	0.0	0.0
0.050*	66.0	5.4	0.0	84.0	0.9	0.0
0.067*	52.0	2.2	0.0	106.0	1.6	0.5
0.083*	86.0	6.4	0.0	82.0	1.4	0.8
0.100*	108.0	7.8	0.7	116.0	2.2	1.4
0.117*	102.0	8.6	1.1	120.0	2.2	1.6
0.134*	98.0	7.8	1.5	122.0	2.4	2.2
0.150*	108.0	10.4	2.2	112.0	3.4	2.8
0.167*	88.0	7.8	2.6	140.0	4.0	3.2
0.200	90.0	5.6	3.7	126.0	4.0	4.8
0.250	56.0	6.4	5.1	78.0	3.4	7.8
0.300	36.0	4.0	7.0	64.0	3.6	11.0
0.375	28.0	2.4	8.0	44.0	4.1	14.0
0.542	16.0	1.6	8.2	18.0	2.8	18.0
0.792	13.0	1.8	10.0	14.0	2.8	22.0
1.210	7.4	1.6	12.0	5.8	1.8	26.0
1.710	2.6	1.0	12.0	8.0	2.4	26.0
2.210	2.2	0.8	12.0	2.6	1.7	26.0
2.500	1.8	0.5	10.0	3.6	2.1	26.0
3.000	1.4	0.0	14.0	2.2	1.4	24.0
4.0	1.2	0.0	16.0	1.4	0.8	23.0
6.0	0.6	0.0	13.0	0.8	0.0	15.0
12.0	0.0	0.0	10.0	0.6	0.0	17.0
24.0	0.0	0.0	5.6	0.0	0.0	9.0
27.0	0.0	0.0	4.4	0.0	0.0	11.0
30.0	0.0	0.0	3.4	0.0	0.0	7.4
36.0	0.0	0.0	3.1	0.0	0.0	5.6
48.0	0.0	0.0	3.3	0.0	0.0	5.0
54.0	0.0	0.0	1.9	0.0	0.0	4.0
60.0	0.0	0.0	1.1	0.0	0.0	3.6
72.0	0.0	0.0	1.8	0.0	0.0	3.2
168.0	0.0	0.0	0.0	0.0	0.0	0.8

*Smoking period
†No value reported

Table I (continued). Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette

Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject C</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.0
0.017*	3.8	0.0	0.0	11.0	0.0	0.0
0.033*	8.6	0.0	0.0	32.0	0.0	0.0
0.050*	19.0	0.0	0.0	64.0	0.0	0.0
0.067*	28.0	0.0	0.0	97.0	1.6	1.2
0.083*	44.0	0.0	0.0	110.0	2.1	2.2
0.100*	40.0	0.0	0.0	116.0	3.5	4.8
0.117*	45.0	0.0	0.0	122.0	4.3	7.1
0.134*	46.0	0.0	2.5	120.0	4.3	10.0
0.150*	50.0	0.0	3.8	126.0	6.6	13.0
0.167*	46.0	0.0	4.9	116.0	5.9	17.0
0.200	41.0	4.0	9.1	116.0	5.4	23.0
0.250	29.0	4.1	13.0	88.0	6.2	33.0
0.300	21.0	5.0	17.0	66.0	4.2	37.0
0.375	15.0	5.5	20.0	45.0	5.5	50.0
0.542	8.0	4.2	22.0	25.0	3.7	57.0
0.792	3.3	3.4	24.0	14.0	3.2	43.0
1.210	2.9	3.5	21.0	7.1	2.5	39.0
1.710	2.8	2.3	20.0	6.2	1.8	35.0
2.210	1.8	2.2	18.0	6.0	1.6	35.0
2.500	1.3	0.0	16.0	4.7	1.1	30.0
3.000	0.9	0.0	13.0	3.7	0.6	30.0
4.0	0.7	0.0	13.0	1.9	1.0	28.0
6.0	0.0	0.0	7.8	0.9	0.5	12.0
12.0	0.0	0.0	4.2	0.7	0.0	8.4
24.0	0.0	0.0	3.8	0.0	0.0	8.8
27.0	0.0	0.0	3.0	0.0	0.0	8.6
30.0	0.0	0.0	2.0	0.0	0.0	5.8
36.0	0.0	0.0	2.0	0.0	0.0	5.0
48.0	0.0	0.0	1.4	0.0	0.0	5.6
54.0	0.0	0.0	0.0	0.0	0.0	3.2
60.0	0.0	0.0	0.0	0.0	0.0	2.6
72.0	0.0	0.0	0.0	0.0	0.0	2.1
168.0	0.0	0.0	0.0	0.0	0.0	0.0

*Smoking period
†No value reported

forearm vein. Subjects received 5000 units of sodium heparin prior to drug administration to prevent blood clotting in the tubing. All subjects' clotting times had returned to normal within 4 h after heparin administration.

The pump was calibrated for collection of 5-mL blood samples in 1, 5, or 25 min. Samples were obtained in the hour prior to smoking with the pump operated in the slow mode (0.2 mL/min). During and immediately after smoking (from 0 to 20 min), the pump was operated in the fast mode (5 mL/min) for rapid blood sampling. This permitted the collection of 10 samples spaced at 1-min intervals from the beginning to the end of marijuana smoking. Thereafter, samples were collected at increasingly spaced intervals, yielding a total of 34 plasma samples taken over a 7-day period from the initiation of smoking. From 20 to 60 min, the medium pump speed provided integrated 5-mL samples over 5-min collection periods. Samples from 1 to 3 h after smoking were collected in the slow mode (0.2 mL/min) in 25-min collection periods. Additional samples were collected over the next three

days through an angiocatheter in the forearm vein in the dominant arm. A final sample was collected just prior to the next study day at 168 h.

Blood samples were collected on ice in 7-mL sodium EDTA Vacutainer® tubes. Samples were centrifuged and the plasma removed for storage in silanized glass tubes at -30°C until the time of analysis. Plasma THC levels were determined by negative chemical ionization GC/MS by a previously published method (7). The limits of detection (LOD) for THC, 11-OH-THC, and THCCOOH in plasma were 0.5 ng/mL for a 0.5-mL sample. For THC, 11-OH-THC, and THCCOOH analysis 26 blind quality control specimens were used. Quantitative results were within 15% of targeted values for THC and THCCOOH and within 20% of targeted values for 11-OH-THC samples. Coefficients of variation for repetitive analyses were as follows: THC; 16.9% (5 ng/mL) and 17.7% (20 ng/mL); 11-OH-THC; 19.3% (2.5 ng/mL), 15.8% (5 ng/mL), and 11.8% (10 ng/mL); and THCCOOH; 8.9% (10 ng/mL) and 5.5% (50 ng/mL).

Table I (continued). Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette

Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject E</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.0
0.017*	3.4	0.0	0.0	25.0	0.0	0.0
0.033*	14.0	0.0	0.0	45.0	0.0	0.0
0.050*	24.0	0.0	0.0	56.0	1.4	0.0
0.067*	38.0	0.0	0.0	56.0	2.2	1.1
0.083*	38.0	0.0	0.5	52.0	2.7	1.8
0.100*	50.0	0.0	0.9	54.0	2.6	3.0
0.117*	50.0	1.6	1.3	65.0	3.6	4.2
0.134*	56.0	1.4	1.9	66.0	3.2	5.4
0.150*	64.0	1.2	2.7	76.0	3.2	7.2
0.167*	56.0	1.2	3.4	60.0	3.6	8.8
0.200	54.0	3.3	4.5	52.0	3.8	11.0
0.250	38.0	2.7	6.9	32.0	3.8	14.0
0.300	38.0	1.1	9.0	26.0	3.8	17.0
0.375	24.0	1.5	10.0	18.0	3.4	18.0
0.542	13.0	1.4	11.0	10.0	3.2	18.0
0.792	7.6	0.0	13.0	8.6	2.2	21.0
1.210	5.4	0.0	12.0	5.4	2.2	22.0
1.710	3.4	0.0	12.0	3.4	1.6	22.0
2.210	2.0	0.0	12.0	2.6	1.0	19.0
2.500	1.8	0.0	15.0	2.0	0.0	18.0
3.000	1.0	0.0	9.9	2.0	0.0	†
4.0	0.6	0.0	9.4	1.1	0.0	12.0
6.0	0.0	0.0	6.5	0.7	0.0	9.4
12.0	2.6	0.0	5.7	0.0	0.0	13.0
24.0	0.0	0.0	4.5	0.0	0.0	5.0
27.0	0.0	0.0	2.5	0.0	0.0	5.0
30.0	0.0	0.0	2.0	0.0	0.0	4.8
36.0	0.0	0.0	1.9	0.0	0.0	4.2
48.0	0.0	0.0	1.5	0.0	0.0	3.4
54.0	0.0	0.0	1.1	0.0	0.0	3.8
60.0	0.0	0.0	1.1	0.0	0.0	2.3
72.0	0.0	0.0	0.9	0.0	0.0	2.0
168.0	0.0	0.0	0.0	0.0	0.0	0.5

*Smoking period
†No value reported

Table I (continued). Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette

Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject F</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.0
0.017*	1.0	0.0	0.0	1.8	0.0	0.0
0.033*	9.4	0.0	0.0	30.0	0.0	0.0
0.050*	22.0	0.0	0.0	63.0	1.0	0.0
0.067*	35.0	0.5	0.0	98.0	1.4	0.0
0.083*	74.0	1.3	0.6	134.0	1.6	0.6
0.100*	104.0	2.2	0.8	214.0	2.6	1.0
0.117*	89.0	2.8	1.5	256.0	4.2	2.0
0.134*	112.0	3.8	2.2	220.0	4.6	3.4
0.150*	112.0	5.4	3.0	260.0	6.4	4.8
0.167*	129.0	5.5	3.8	262.0	6.6	7.0
0.200	103.0	6.8	5.6	218.0	8.0	11.0
0.250	83.0	7.1	7.8	162.0	9.2	16.0
0.300	63.0	5.9	9.8	121.0	8.4	22.0
0.375	38.0	6.0	12.0	74.0	7.6	26.0
0.542	26.0	3.3	14.0	42.0	4.4	31.0
0.792	12.0	2.6	15.0	21.0	4.0	31.0
1.210	9.0	1.8	14.0	11.0	3.1	33.0
1.710	5.3	1.4	10.0	9.4	2.3	32.0
2.210	3.5	0.9	9.8	8.1	1.8	27.0
2.500	2.3	0.8	9.2	5.6	2.0	29.0
3.000	2.3	0.7	13.0	3.1	1.3	28.0
4.0	1.3	0.5	12.0	2.5	1.4	28.0
6.0	0.7	0.0	7.8	1.0	0.0	19.0
12.0	0.0	0.0	7.0	0.5	0.5	24.0
24.0	0.0	0.0	6.2	0.0	0.0	20.0
27.0	0.0	0.0	4.4	0.7	0.6	15.0
30.0	0.0	0.0	3.0	0.0	0.0	14.0
36.0	0.0	0.0	4.4	0.0	0.0	11.0
48.0	0.0	0.0	1.4	0.0	0.0	14.0
54.0	0.0	0.0	2.0	0.0	0.0	8.4
60.0	0.0	0.0	1.7	0.0	0.0	14.0
72.0	0.0	0.0	1.8	0.0	0.0	11.0
168.0	0.0	0.0	0.0	0.0	0.0	2.2

*Smoking period
†No value reported

Results

Individual plasma levels of THC, 11-OH-THC, and THCCOOH for the six subjects during and following smoking of a single marijuana cigarette (1.75 or 3.55% THC) are shown in Table I. The primary psychoactive constituent of marijuana, THC, appeared rapidly in blood during smoking. THC was detected in the first sample obtained immediately after the first marijuana puff. Plasma levels of THC ranged from 0 to 20.0 ng/mL with a mean of 7.0 ng/mL (Table II) and from 1.8 to 37.0 ng/mL with a mean of 18.1 ng/mL following the first inhalation of a low or high dose marijuana cigarette, respectively. Levels continued to increase rapidly and peaked at 8.4 min (4.8–10.2), prior to initiation of the last puff sequence at 9.8 min. Peak levels ranged from 50.0 to 129.0 ng/mL with a mean peak drug level of 84.3 ng/mL and from 76.0 to 267.0 ng/mL with a mean of 162.2 ng/mL for the 1.75 and 3.55% THC marijuana cigarettes, respectively (Figure 1a). THC decreased rapidly after the peak. Concentrations at 15 min post smoking of the low and high doses were 52.3 and 94.8 ng/mL, respectively. THC

levels of 17.3 and 29.7 ng/mL were noted after approximately 30 min. Within 2 h, levels of THC were at or below 5 ng/mL but remained detectable for up to 12 h after smoking. The time of detection of THC (GC/MS LOD = 0.5 ng/mL) varied from 3 to 12 h after the low dose and from 6 to 27 h after the high dose marijuana cigarette. The area under the curve for the mean data from 0 to 168 h was 36.5 and 72.2 ng-h/mL, respectively, for the low and high dose conditions, demonstrating a dose-response relationship.

The active metabolite, 11-OH-THC, was detectable in the plasma of only one subject after the first marijuana cigarette puff but was observed in three subjects by the second puff. 11-OH-THC levels were approximately 6–10% of the concurrent THC concentrations for up to 45 min after the start of smoking. However, after this timepoint, [11-OH-THC]/[THC] ratios began to gradually increase because of the more rapid decline of THC levels. Peak 11-OH-THC levels were noted 13.5 min (9.0–22.8) after the start of smoking. Mean peak levels of 6.7 (range 3.3 to 10.4 ng/mL) and 7.5 ng/mL (range 3.8 to 16 ng/mL) were measured following smoking of one marijuana cigarette (1.75% or 3.55%

Table I (continued). Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette						
Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject G</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.0
0.017*	0.0	0.0	0.0	17.0	0.0	0.0
0.033*	30.0	0.0	0.0	64.0	0.0	0.0
0.050*	34.0	0.8	0.0	130.0	1.2	0.7
0.067*	38.0	1.8	0.7	174.0	3.4	1.4
0.083*	49.0	1.8	1.4	210.0	6.6	2.6
0.100*	56.0	2.4	2.0	267.0	7.9	4.8
0.117*	61.0	2.7	2.9	247.0	10.0	7.2
0.134*	77.0	2.9	3.8	260.0	11.0	11.0
0.150*	73.0	3.5	5.1	261.0	12.0	17.0
0.167*	78.0	4.4	5.6	231.0	14.0	24.0
0.200	69.0	3.6	8.1	193.0	14.0	34.0
0.250	56.0	5.7	10.0	155.0	16.0	42.0
0.300	35.0	5.4	12.0	145.0	13.0	54.0
0.375	25.0	5.4	15.0	70.0	16.0	68.0
0.542	15.0	4.9	17.0	51.0	11.0	78.0
0.792	7.8	3.8	20.0	26.0	9.4	86.0
1.210	5.8	2.6	21.0	17.0	7.4	94.0
1.710	3.0	2.2	20.0	11.0	5.8	96.0
2.210	2.3	1.8	21.0	7.2	3.4	101.0
2.500	1.7	1.4	23.0	4.2	3.6	82.0
3.000	1.0	1.4	21.0	3.0	3.2	98.0
4.0	0.0	1.0	19.0	2.0	1.4	84.0
6.0	0.0	0.7	14.0	0.6	0.0	64.0
12.0	0.0	0.7	10.0	0.0	0.0	38.0
24.0	0.0	0.0	7.7	0.0	0.0	27.0
27.0	0.0	0.0	5.1	0.0	0.0	30.0
30.0	0.0	0.0	4.2	0.0	0.0	19.0
36.0	0.0	0.0	3.1	0.0	0.0	17.0
48.0	0.0	0.0	2.8	0.0	0.0	12.0
54.0	0.0	0.0	1.2	0.0	0.0	7.2
60.0	0.0	0.0	1.0	0.0	0.0	8.0
72.0	0.0	0.0	1.1	0.0	0.0	5.2
168.0	0.0	0.0	0.0	0.0	0.0	0.7

*Smoking period
†No value reported

Table I (continued). Plasma THC, 11-OH-THC, and THCCOOH Concentrations (ng/mL) During and After Smoking a Single Marijuana Cigarette						
Time (h)	1.75% THC			3.55% THC		
	THC	11-OH-THC	THC-COOH	THC	11-OH-THC	THC-COOH
<i>Subject H</i>						
-0.500	0.0	0.0	0.0	0.0	0.0	0.9
0.017*	14.0	0.0	1.1	37.0	0.0	1.0
0.033*	36.0	1.0	1.1	63.0	0.0	1.3
0.050*	42.0	1.1	1.3	70.0	0.0	1.8
0.067*	55.0	2.2	1.6	85.0	0.0	2.8
0.083*	61.0	2.8	2.2	102.0	1.3	4.1
0.100*	68.0	5.6	4.6	83.0	1.4	5.9
0.117*	70.0	5.8	3.1	82.0	3.7	8.2
0.134*	77.0	5.5	6.6	80.0	3.2	11.0
0.150*	67.0	5.7	8.1	77.0	4.0	13.0
0.167*	71.0	7.4	8.3	74.0	3.8	17.0
0.200	74.0	6.7	11.0	56.0	5.6	20.0
0.250	52.0	8.4	17.0	54.0	4.8	21.0
0.300	42.0	5.8	21.0	41.0	4.8	35.0
0.375	35.0	5.7	24.0	42.0	3.9	42.0
0.542	26.0	5.4	32.0	32.0	4.0	62.0
0.792	13.0	3.8	42.0	18.0	3.8	64.0
1.210	9.0	2.5	44.0	12.0	3.2	71.0
1.710	4.5	2.4	50.0	10.0	3.6	85.0
2.210	4.0	1.8	43.0	6.0	3.5	80.0
2.500	2.6	1.8	49.0	4.6	2.4	76.0
3.000	0.8	2.2	41.0	3.8	2.4	73.0
4.0	1.0	0.9	54.0	1.9	1.7	58.0
6.0	0.0	0.5	28.0	0.9	1.2	42.0
12.0	0.7	0.0	16.0	0.5	1.0	26.0
24.0	0.0	0.0	9.0	0.0	1.0	11.0
27.0	0.0	0.0	5.8	0.0	0.0	8.8
30.0	0.0	0.0	5.0	0.0	0.0	7.6
36.0	0.0	0.0	5.1	0.0	0.0	8.3
48.0	0.0	0.0	5.1	0.0	0.0	3.9
54.0	0.0	0.0	2.9	0.0	0.0	2.8
60.0	0.0	0.0	2.4	0.0	0.0	2.1
72.0	0.0	0.0	2.0	0.0	0.0	1.9
168.0	0.0	0.0	0.9	0.0	0.0	1.8

*Smoking period
†No value reported

Table II. Mean Plasma Concentrations and Mean Times of Appearance and Disappearance of Cannabinoids During and After Smoking Marijuana

Dose (% THC)	Analyte	Peak concentration (ng/mL)	Time to peak concentration* (h)	Detection time† (h)	Concentration after first puff (ng/mL)
1.75	THC	84.3 (50–129)	0.14 (0.10–0.17)	7.2 (3–12)	7.0 (0–20)
3.55	THC	162.2 (76–267)	0.14 (0.08–0.17)	12.5 (6–27)	18.1 (1.8–37.0)
1.75	11-OH-THC	6.7 (3.3–10.4)	0.25 (0.15–0.38)	4.5 (0.54–12)	0.2 (0–1.2)
3.55	11-OH-THC	7.5 (3.8–16.0)	0.20 (0.15–0.25)	11.2 (2.2–27)	Not detected
1.75	THCCOOH	24.5 (15–54)	2.43 (0.8–4.0)	84.0 (48–168)	0.2 (0–1.1)
3.55	THCCOOH	54.0 (22–101)	1.35 (0.54–2.21)	152.0 (72–168)	0.2 (0–1.0)

*Time to peak concentration is expressed as mean time interval (h) from beginning of smoking to appearance of peak concentration.
†Detection time (h) is expressed as mean time interval (h) from beginning of smoking to time of last detectable drug concentration (> 0.5 ng/mL).

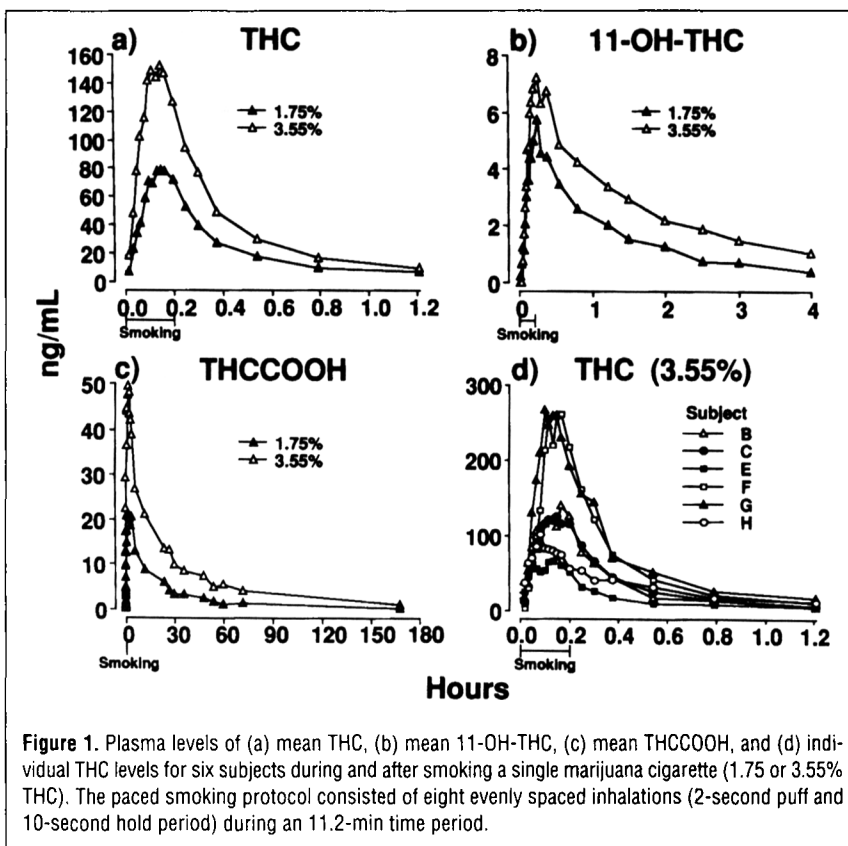


Figure 1. Plasma levels of (a) mean THC, (b) mean 11-OH-THC, (c) mean THCCOOH, and (d) individual THC levels for six subjects during and after smoking a single marijuana cigarette (1.75 or 3.55% THC). The paced smoking protocol consisted of eight evenly spaced inhalations (2-second puff and 10-second hold period) during an 11.2-min time period.

THC), respectively (Figure 1b). The areas under the curves from 0 to 168 h were 7.0 and 14.7 ng-h/mL for the low and high doses, respectively. 11-OH-THC levels decreased gradually with mean detection periods of 4.5 h and 11.2 h after the two doses. In most, but not all cases, the 11-OH-THC concentrations dissipated earlier than concurrent THC levels.

THCCOOH concentrations in plasma increased slowly and plateaued for an extended period of time. This inactive metabolite was detected in only one subject after the first cigarette puff and was not detectable in all subjects' plasma until 8 min after the start of marijuana smoking. Peak levels were consistently lower than peak THC levels but were higher than 11-OH-THC peak concentrations. Because of the plateau effect, time to peak levels varied from 32 to 240 min, but absolute differences in plasma concentrations during this time were minimal. Peak THCCOOH concentrations were 24.5 ng/mL (range of 15 to 54 ng/mL) and 54.0 ng/mL (range of 22 to 101 ng/mL) after the low and high dose marijuana

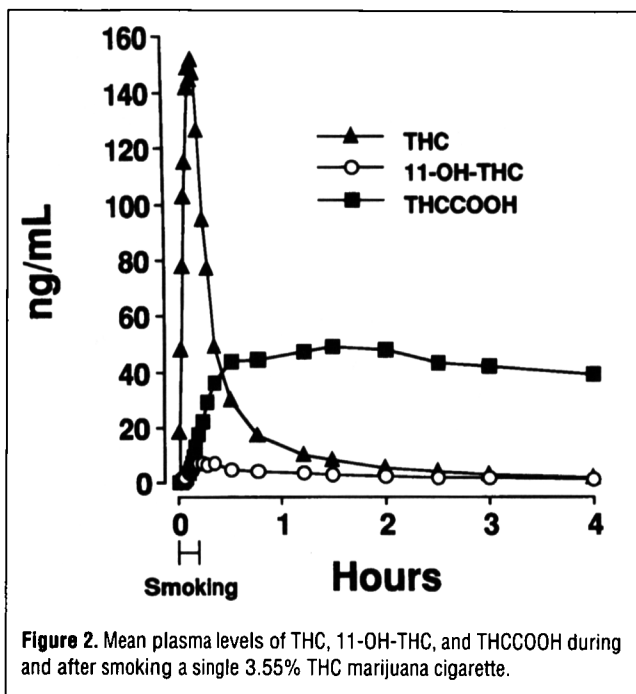
cigarettes, respectively (Figure 1c). The area under the curves reflected a dose-response relationship with areas of 401.4 and 1146.5 ng-h/mL. Following smoking of a 1.75% THC marijuana cigarette, THCCOOH was detected from 48 to 168 h, with a mean of 84 h. Detection times ranged from 72 to 168 h with a mean of 152 h following smoking of the 3.55% THC marijuana cigarette.

Overall, mean peak THC levels were approximately three times greater than mean peak THCCOOH levels and 20 times greater than 11-OH-THC concentrations (Figure 2). Times to peak concentrations of THC and 11-OH-THC were rapid, with short time courses of detection. A different profile and time course of detection for THCCOOH was evident. THC levels fell steadily while THCCOOH levels were increasing. THCCOOH levels reached a plateau within the first hour and remained elevated for 2–4 h, after which they slowly declined to the level of sensitivity of the assay (LOD = 0.5 ng/mL) over a period of 168 h.

Discussion

Integration of physiologic, behavioral, and biochemical effects with simultaneously obtained drug levels is important to our understanding of the pharmacodynamic effects of abused drugs. Description of the absorption of THC and formation of metabolites provides insight into the reasons for onset and duration of marijuana's effects. Effects of marijuana and other smoked drugs must be evaluated in terms of concurrent drug levels because of the inability to deliver a specified dose by the smoking route. Characterization of the time course of detection of THC and metabolites under controlled clinical conditions provides needed information to investigators of marijuana's behavioral effects and to forensic scientists who must interpret cannabinoid blood levels.

THC was detected in plasma immediately after the first inhalation of marijuana smoke, attesting to the efficient absorption of THC from the lungs. THC levels rose rapidly and peaked prior to the end of smoking. Collection of blood samples during this rapidly changing phase was facilitated through the use of a continuous blood withdrawal device for collection of sequential



blood samples. Perez-Reyes et al. (8,9) first noted that peak THC concentrations occurred during smoking but could not discount the possibility that the observed peaks were caused by artifacts of the sampling process. The methodology used in the current study eliminated the possibility of sampling artifacts and clearly established that peak THC levels were achieved while smoking. Mean peak THC levels of 84.3 and 162.2 ng/mL were observed after smoking a single marijuana cigarette (1.75 or 3.55% THC). These are in general agreement with reported peak THC levels of 94.3, 107.4, and 155.1 ng/mL after smoking a single 1.32, 1.97, or 2.54% THC marijuana cigarette, respectively (8). In another study (9), THC measurements during smoking of a 1% THC marijuana cigarette yielded a mean peak concentration in male subjects of approximately 120 ng/mL. Ohlsson et al. (10) reported a 77-ng/mL mean peak THC level 3 min after smoking. The marijuana cigarettes in this latter study contained approximately 13 mg of THC (approximately 2% THC).

Forensic scientists are frequently requested to estimate the time of marijuana exposure based upon individual cannabinoid blood level determinations. Establishment of a meaningful threshold concentration or range of THC concentrations that are likely to be found at specified times after smoking would facilitate interpretation. In the present study, plasma THC ranges of 8–50 ng/mL, 3–20 ng/mL, 1–8 ng/mL, and 0–2.5 ng/mL were observed at 0.5, 1, 2, and 4 h after smoking, respectively. These data are in general agreement with other reports of THC plasma levels after smoking (8–13). Unfortunately, these ranges are broad and overlapping, thus reducing their applicability for interpretation of blood level data. Also, other reported data do not fit these ranges. THC ranges of 36 to 177 ng/mL after 30 min and 14 to 69 ng/mL after 60 min were reported following the smoking of two marijuana cigarettes containing a total of 150 µg/kg of THC (14). Their findings suggested that a plasma THC threshold greater than 2–3 ng/mL was the best indicator of recent marijuana use, i.e., within the previous 6 h. Data from the present study supports use of a 2–3 ng/mL THC threshold as an indicator of recent marijuana exposure. THC levels at 6 h post smoking

ranged from 0.0 to 0.7 ng/mL and from 0.6 to 1.0 ng/mL following the smoking of the low and high dose marijuana cigarettes, respectively. However, it is evident that additional studies are needed to determine the efficacy of a THC threshold to predict time of use under different exposure conditions, e.g., higher doses, ingestion of marijuana, and chronic usage.

The establishment of detection times of THC in blood also may be useful in interpretation of forensic samples. In the present study, THC was detected in the plasma of six subjects by GC/MS (LOD = 0.5 ng/mL) for 3 to 12 h and 6 to 27 h after the low and high dose marijuana cigarettes, respectively. Mean detection times were 7.2 and 12.5 h. A mean detection time of 4.8 h (range of 3.5 to 5.5 h) was reported by McBurney et al. (14) with subjects who smoked two marijuana cigarettes containing a total of 150 µg/kg THC (GC/MS LOD = 0.8 ng/mL THC). In another study (15), a detection time of 13 days was reported for deuterated THC in the blood of chronic marijuana users who smoked four deuterium-labeled THC cigarettes (GC/MS LOD = 0.02 ng/mL for THC). This latter study demonstrated that THC is excreted at low levels for an extended period of time, likely as a result of release of drug from deep tissue storage compartments, i.e., fat tissue. The terminal half-life of THC was determined to be approximately 4.1 days.

Few studies have included 11-OH-THC measurements in marijuana smoking experiments. McBurney et al. (14) reported peak 11-OH-THC levels of 7.4 to 40.7 ng/mL (mean of 18.9 ng/mL) 50 min after smoking and found a mean detection time of 8 h (GC/MS LOD = 0.8 ng/mL). Quantitative levels were based on external rather than internal standardization techniques. These levels were higher than those reported in other studies following the smoking route (4) and possibly could be explained by differences in recovery efficiency. In the present study, peak 11-OH-THC levels of 6.7 and 7.5 ng/mL were observed after smoking a low or high dose cigarette. Immediately after smoking, the [11-OH-THC]/[THC] plasma ratio was low but increased over time because of a more gradual decrease in 11-OH-THC concentration. Mean detection times of 4.5 and 11.2 h after the low and high doses were slightly shorter than corresponding THC detection periods. Longer detection times for 11-OH-THC could possibly occur if marijuana were ingested rather than smoked. Substantially greater amounts of 11-OH-THC have been reported to be produced following marijuana ingestion (4).

THCCOOH levels in plasma gradually increased after marijuana smoking and peaked between 0.54 and 4 h (mean of 1.9 h). The current findings are in agreement with previously reported time to peak concentrations of THCCOOH, which ranged from 0.7 to 3.5 h (mean of 1.6 h) (14). In contrast, time to peak THCCOOH levels have been reported as early as 0.3 h after the start of marijuana smoking (8). Other suggestions for interpretation of blood THCCOOH levels have been made. It has been proposed that approximately equal amounts of THCCOOH and THC in blood are indicative of recent drug exposure (16). In the present study, THCCOOH and THC concentrations were nearly equal at 0.5 h after smoking (range of 0.3 to 0.8 h) because of simultaneous increases in THCCOOH and decreases in THC. Similar findings were reported by Perez-Reyes et al. (8); however, McBurney et al. (14) reported generally higher THC levels than THCCOOH levels for approximately 2 h after smoking (range of 0.4 to 4 h).

Wide interindividual variations were noted in plasma THC levels despite a paced smoking protocol to control dose. These variations diminish the usefulness of ranges of THC concentrations in the prediction of time of marijuana exposure based on

single blood THC determinations. Other approaches to forensic interpretation of THC and metabolite levels such as use of threshold limits or metabolite/parent ratios may prove more fruitful for the estimation of time of marijuana exposure.

The smoking route provides an efficient and rapid means of drug delivery to the brain. This study demonstrated for the first time that THC was present in blood after the first puff of marijuana smoke and peaked soon thereafter. Increased awareness is needed regarding the risks of even minimal exposure to smoked marijuana.

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