

Urinary Elimination of 11-Nor-9-Carboxy- Δ^9 -tetrahydrocannabinol in Cannabis Users During Continuously Monitored Abstinence*

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Abstract

The time course of 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH) elimination in urine was characterized in 60 cannabis users during 24 h monitored abstinence on a closed research unit for up to 30 days. Six thousand, one hundred fifty-eight individual urine specimens were screened by immunoassay with values ≥ 50 ng/mL classified as positive. Urine specimens were confirmed for THCCOOH by gas chromatography–mass spectrometry following base hydrolysis and liquid–liquid or solid-phase extraction. In 60%, the maximum creatinine normalized concentration occurred in the first urine specimen; in 40%, peaks occurred as long as 2.9 days after admission. Data were divided into three groups, 0–50, 51–150, and > 150 ng/mg, based on the creatinine corrected initial THCCOOH concentration. There were statistically significant correlations between groups and number of days until first negative and last positive urine specimens; mean number of days were 0.6 and 4.3, 3.2 and 9.7, and 4.7 and 15.4 days, respectively, for the three groups. These data provide guidelines for interpreting urine cannabinoid test results and suggest appropriate detection windows for differentiating new cannabis use from residual drug excretion.

Introduction

Cannabis continues to be the most widely used illicit drug in the United States and in many countries around the world (1), and is the most commonly detected drug of abuse in workplace urine drug tests (2). Δ^9 -Tetrahydrocannabinol (THC), the major psychoactive component of cannabis, is rapidly metabolized to the inactive metabolite 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH), conjugated with

glucuronic acid, and excreted in urine. Fifteen to 20% of a THC dose is eliminated as acidic urinary metabolites (3).

An important issue for drug-testing programs is the ability to distinguish recent cannabis use from residual drug excretion. Exceptionally long detection times have been reported for cannabinoid metabolites in the urine of frequent drug users during abstinence (4–8). During the terminal elimination phase, an individual may produce consecutive specimens that test positive, negative, and positive again over time. This makes interpretation of cannabinoid urine drug test results difficult if it is necessary to determine whether positive results are indicative of new drug use or reflective of previous cannabis exposure. Detection time is dependent on pharmacological factors (e.g., drug dose, route of administration, state of hydration, and rates of metabolism and excretion) and chemical factors (e.g., assay sensitivity, specificity, and accuracy). Ellis et al. (9) reported that in one case, it took up to 77 days of abstinence for one individual to produce 10 consecutive negative urine specimens with a 20 ng/mL cutoff.

Hawks (10) first proposed adjusting urinary cannabinoid concentrations to account for urine dilution. This is achieved by normalizing cannabinoid concentrations in nanograms per milliliter to urinary creatinine concentrations reported in milligrams per deciliter or moles per liter. Manno et al. (11) suggested that new use was indicated if the ratio of the creatinine normalized THCCOOH concentration (ng/mg) of a later specimen to an earlier specimen was at least 1.5. Huestis and Cone (12) tested this hypothesis in an experiment with controlled THC dosing, collection of all individual urine voids, and residence of participants on a secure research unit throughout the study. These investigators demonstrated that the most accurate differentiation between new cannabis use and residual cannabinoid excretion occurred if this ratio was greater than 0.5. The prediction model required a minimum of 24 h between specimens and provided false-negative and false-positive rates for different cutoffs to permit drug-testing administrators to select the most appropriate cutoff based on the goals of the program.

* Presented in part at the 2008 American Academy of Forensic Sciences meeting, Washington, D.C.

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The aim for the present study was to determine the time course of urinary THCCOOH excretion under monitored abstinence, to better understand patterns of residual cannabinoid excretion and to improve predictions of new cannabis use from urine cannabinoid tests. Participants included daily and non-daily cannabis smokers.

Materials and Methods

Subjects

Healthy cannabis users, aged 18–45 years, were invited to reside on the secure clinical research unit of the National Institute on Drug Abuse (NIDA) Intramural Research Program, National Institutes of Health during 24 h monitored cannabis abstinence. Participants self-reported cannabis dependence or abuse, and had a positive urine cannabinoid test (50 ng/mL) that supported a history of cannabis exposure. The NIDA Institutional Review Board approved the study. All participants provided written informed consent and were financially compensated for time and inconvenience. Before inclusion, each participant underwent thorough medical (physical exam, ECG, blood and urine chemistries) and psychological evaluations, including past and recent drug use history. All subjects in this study were required to have normal serum creatinine (0.6–1.2 mg/dL) and have no history or symptoms of renal disease in order to participate. Thus, any changes that occurred in urine creatinine were the result of changes in hydration rather than altered kidney function and/or diet. Twenty-four hour medical surveillance prevented access to unauthorized licit or illicit drugs. In addition, random urine drug tests for amphetamines, cannabinoids, cocaine, opiates, and phencyclidine were performed. All individual urine voids were collected ad libitum for up to 30 days.

Specimen collection and analysis

Each urine void was collected in a polypropylene container and refrigerated immediately after urination. Specimen volume was measured, and aliquots of the urine were frozen at -20°C on the day of collection. Urine specimens were analyzed for THCCOOH at LabOne, Salt Lake City, NV; Navy Drug Screening Laboratory, Jacksonville, FL; and Forensic Toxicology Drug Testing Laboratory, Tripler Army Medical Center, HI. Specimens were thawed just prior to analysis and subjected to only a single freeze-thaw cycle. After careful mixing, specimens were screened by immunoassay with values ≥ 50 ng/mL classified as positive for cannabinoids. For confirmatory analyses and quantification, an alkaline hydrolysis was followed by liquid–liquid or solid-phase extraction and THCCOOH quantification by gas chromatography–mass spectrometry (GC–MS) with a 2.5 ng/mL limit of quantification (13–17). A modified Jaffe method on an automated clinical analyzer was used to obtain urine creatinine concentrations (18). Cannabinoid GC–MS concentrations (ng/mL) were normalized to the urine creatinine concentration (mg/mL) to account for the state of hydration and to reduce variability. The final normalized units were expressed as

nanograms per milligram of creatinine.

Statistics

Data were analyzed to assess which independent variables were predictive of each dependent variable. Independent variables included normalized THCCOOH concentration in the first specimen, average number of joints smoked per day, number of days used during the last 14 days, days since last use, years of use, body mass index (BMI), sex, age, and age at first use. Group was an additional independent variable established by assigning participants to one of three groups according to creatinine normalized THCCOOH concentrations in the first specimen collected as follows: 0–50 ng/mg; 51–150 ng/mg; and > 150 ng/mg. Dependent variables included day of first negative urine specimen (< 50 ng/mL); last day for a positive urine specimen (≥ 50 ng/mL); detection rate (number of positive specimens in a day/total number of specimens collected during that day multiplied by 100); last day with a detection rate greater than 50%; number of days between first negative and last positive specimen; maximum, median, and mean concentrations between first negative and last positive specimen; and log transformed values for maximum, median, and mean concentrations between first negative and last positive specimens. For each dependent variable, a frequency histogram and scatter plot were created to assess whether data were normally distributed. None of the non-log transformed dependent variables were found to be normally distributed. However, because of the robustness of the F-test in the stepwise regression, the SAS[®] (SAS Institute, Cary, NC) STEPWISE procedure was used to identify those subsets of independent variables that best predict each dependent variable. Only the main effect of each independent variable, without interaction terms, was used in the stepwise regression analysis.

Correlations between group and mean values of several dependent variables were graphed and linear correlation coefficients determined (Microsoft Office Excel 2003, SP1). Variables investigated included mean number of days before the first negative urine test, mean number of days until the last positive urine test, number of days between first negative and last positive urine test, number of specimens between first negative and last positive urine test, C_{max} THCCOOH/creatinine between first negative and last positive urine test, and mean detection rate for each day after the first negative urine test.

Results

Sixty cannabis users (50 African Americans, 5 Caucasians, 3 Hispanics, 1 mixed race, and 1 American Indian), who self-reported daily to weekly cannabis smoking, participated in this residential study of urinary cannabinoid excretion (Table I). Forty-six males and 14 females with a mean age of 26.9 ± 6.4 years, smoked an average of 9.4 ± 9.7 joints per week using 10.6 ± 4.3 days of the last 14. Subjects began using cannabis at a mean of 15.6 ± 3.2 years and had smoked the drug for a mean of 11.2 ± 6.4 years.

Table I. Demographic Characteristics and Self Report of Cannabis Users

	Subject	Age (years)	Sex	Race	Weight (pounds)	Height (inches)	Joints/Week	Days Used in Last 14 Days	Age of First Use	Years Used
1	A	23	M	AA*	186	68	2	4	15	8
2	B	42	M	AA	147	69	10	10	17	25
3	C	22	M	AA	185	66	12	14	13	9
4	D	21	M	AA	168	69	8	14	9	12
5	E	42	M	AA	145	70	3	7	18	24
6	F	23	M	AA	200	76	6	14	13	10
7	G	30	M	AA	145	68	1	9	19	11
8	H	25	M	AA	200	70	11	11	17	8
9	I	29	M	AA	185	68	10	14	12	17
10	J	34	M	AA	190	73	4	3	17	17
11	K	24	M	AA	245	75	16	14	n/a [#]	n/a
12	L	21	M	AA	155	74	n/a	1	10	11
13	M	21	M	AA	170	68	18	13	14	7
14	N	21	M	AA	135	69	23	14	13	8
15	O	37	M	AA	130	68	4	13	13	24
16	P	21	M	AA	135	68	n/a	14	n/a	n/a
17	Q	29	M	AA	145	64	6	8	25	4
18	R	21	M	AA	208	73	6	14	15	6
19	S	33	M	AA	170	67	3	14	23	10
20	T	29	M	AA	195	67	6	14	20	9
21	U	24	M	AA	250	74	4	10	14	10
22	V	22	M	AA	150	69	6	6	15	7
23	W	26	M	AA	200	72	12	12	13	13
24	X	25	M	AA	150	67	12	14	12	13
25	Y	22	M	AA	195	73	6	14	18	4
26	Z	30	M	AA	195	74	60	14	14	16
27	AA	42	M	AA	170	64	0	0	14	28
28	BB	42	M	AA	162	70	4	5	17	25
29	CC	35	M	AA	160	74	3	5	18	17
30	DD	32	M	AA	140	66	9	14	15	17
31	EE	26	M	AA	245	75	n/a	n/a	n/a	n/a
32	FF	38	M	AA	239	74	6	7	16	22
33	GG	33	M	AA	175	74	8	14	13	20
34	HH	22	M	AA	200	68	n/a	n/a	15	7
35	II	22	M	AA	160	73	13	13	13	9
36	JJ	25	M	AA	140	68	3	8	16	9
37	KK	22	M	AA	160	68	11	14	17	5
38	LL	23	M	AI [†]	145	74	12	14	18	5
39	MM	28	M	C [‡]	155	71	3	0	13	15
40	NN	28	M	C	140	64	3	10	13	15
41	OO	24	M	C	150	69	2	9	14	10
42	PP	21	M	C	180	72	8	6	19	2
43	QQ	23	M	C	140	67	4	14	19	4
44	RR	25	M	H [§]	130	65	1	10	15	10
45	SS	24	M	H	174	72	6	10	18	6
46	TT	21	M	Mixed	160	70	1	1	15	6
47	UU	31	F	AA	165	68	1	6	23	8
48	VV	21	F	AA	200	67	30	14	9	12
49	WW	22	F	AA	125	60	15	14	14	8
50	XX	30	F	AA	130	63	5	10	18	12
51	YY	21	F	AA	150	68	9	14	14	7
52	ZZ	26	F	AA	147	61	6	14	17	9

* African-American.

† American Indian.

‡ Caucasian.

§ Hispanic.

Data not available.

Table I. (continued) Demographic Characteristics and Self Report of Cannabis Users

Subject	Age (years)	Sex	Race	Weight (pounds)	Height (inches)	Joints/Week	Days Used in Last 14 Days	Age of First Use	Years Used	
53	AAA	23	F	AA*	220	63	24	14	15	8
54	BBB	23	F	AA	198	66	12	14	20	3
55	CCC	23	F	AA	240	63	6	14	18	5
56	DDD	38	F	AA	130	68	n/a [†]	n/a	n/a	n/a
57	EEE	22	F	AA	219	68	9	8	17	5
58	FFF	20	F	AA	135	66	15	14	12	8
59	GGG	20	F	AA	110	63	30	14	16	4
60	HHH	38	F	H [‡]	160	65	7	14	16	22
	Mean =	26.9			170.6	68.8	9.4	10.6	15.6	11.2
	SD =	6.4			33.8	3.8	9.7	4.3	3.2	6.4

* African-American.
[†] Data not available.
[‡] Hispanic.

Table II. Urine Cannabinoid Data Separated Into Three Groups (0–50, 51–150, and > 150 ng/mg) Based on Creatinine-Normalized THCCOOH Concentration in the First Urine Specimen at Admission*

Subject	THCCOOH/ Creatinine in 1st Specimen (ng/mg)	Time of 1st Negative Specimen (days)	Time of Last Positive Specimen (days)	Length of Observation (days)	# Urine Specimens	Days Between 1st Negative and Last Positive Specimen	# Specimens Between 1st Negative and Last Positive Urine Specimen	C _{max} (ng/mg) Between 1st Negative and Last Positive Specimen
0 to 50 ng/mg								
A	47.3	1.7	4.3	4.8	47	4	31	32.4
B	30.1	0.3	1.5	6.9	71	2	14	15.7
C	34.6	1.6	3.8	4.4	30	3	17	16.5
E	9.8	0.0	2.2	5.1	26	3	10	9.8
H	46.8	1.4	1.2	2.8	18	1	0	— [‡]
L	27.8	0.3	0.0	29.9	109	1	0	— [‡]
AA	11.6	0.0	0.7	5.8	43	1	3	25.5
BB	1.8	0.0	— [†]	2.9	19	— [†]	— [†]	— [†]
DD	0.0	0.0	— [†]	9.5	60	— [†]	— [†]	— [†]
EE	40.4	1.4	3.3	16.3	73	3	9	42.1
GG	15.7	0.3	2.4	11.8	103	3	16	14.3
LL	24.8	0.1	21.8	21.8	87	22	86	30.2
MM	32.1	0.0	— [†]	0.6	3	— [†]	— [†]	— [†]
OO	29.5	1.2	5.6	5.7	37	5	30	27.0
RR	34.4	0.9	3.8	3.8	31	4	24	24.7
TT	15.5	0.0	— [†]	1.7	15	— [†]	— [†]	— [†]
ZZ	43.4	2.2	8.6	29.5	181	7	34	22.0
DDD	5.1	0.0	— [†]	20.6	211	— [†]	— [†]	— [†]
FFF	0.0	0.0	— [†]	12.0	7	— [†]	— [†]	— [†]
Mean ± SD	23.7 ± 15.9	0.6 ± 0.8	4.6 ± 5.6	10.3 ± 9.1	61.6 ± 56.8	4.5 ± 5.5	21.1 ± 22.6	23.6 ± 9.3
51 to 150 ng/mg								
D	133.5	0.5	4.3	4.5	59	5	49	79.0
F	101.0	1.0	3.1	2.2	18	3	27	132.2
G	70.2	— [§]	1.8	1.8	11	— [§]	— [§]	— [§]

* Urine specimens were collected from cannabis users under continuous medical surveillance during cannabis abstinence for up to 30 days.
[†] No urine specimens screened positive at 50 ng/mL.
[‡] No urine specimens between first negative and last positive.
[§] No urine specimens screened negative at 50 ng/mL.

Table II. (continued) Urine Cannabinoid Data Separated Into Three Groups (0–50, 51–150, and > 150 ng/mg) Based on Creatinine-Normalized THCCOOH Concentration in the First Urine Specimen at Admission*

Subject	THCCOOH/ Creatinine in 1st Specimen (ng/mg)	Time of 1st Negative Specimen (days)	Time of Last Positive Specimen (days)	Length of Observation (days)	# Urine Specimens	Days Between 1st Negative and Last Positive Specimen	# Specimens Between 1st Negative and Last Positive Urine Specimen	C _{max} (ng/mg) Between 1st Negative and Last Positive Specimen
J	74.6	1.3	11.6	26.3	204	11	89	44.1
K	120.8	7.9	8.3	9.6	55	2	4	8.4
N	90.6	0.9	3.3	5.8	66	4	18	56.7
R	142.2	7.8	10.1	20.8	94	4	11	15.6
S	96.0	2.4	3.7	20.4	117	2	8	11.5
V	62.6	2.9	8.9	22.4	94	7	22	26.4
W	78.9	2.8	2.6	29.0	166	1	0	— [‡]
Y	83.7	6.7	16.0	29.2	109	11	37	112.7
CC	114.9	1.2	3.8	13.5	129	3	25	55.8
FF	61.9	2.2	25.3	25.7	194	24	164	38.8
HH	101.4	— [§]	11.0	11.0	7	— [§]	— [§]	— [§]
JJ	96.1	— [§]	11.0	11.0	8	— [§]	— [§]	— [§]
NN	120.7	3.7	12.1	18.6	164	10	77	71.6
QQ	110.0	1.2	10.7	24.6	174	10	78	83.0
WW	110.2	8.3	20.9	30.4	111	13	42	19.9
XX	92.3	0.0	17.0	27.9	264	17	139	55.9
CCC	71.0	1.7	5.0	29.3	164	4	18	44.4
HHH	109.2	5.7	13.3	22.6	126	9	47	51.4
Mean ± SD	97.2 ± 22.6	3.2 ± 2.8	9.7 ± 6.4	18.4 ± 9.7	111.1 ± 70.9	7.8 ± 6.0	47.5 ± 46.0	53.4 ± 34.5
> 150 ng/mg								
I	364.6	0.8	12.7	12.7	107	13	87	126.9
M	155.1	1.4	6.0	7.3	69	5	36	52.3
O	171.7	1.6	3.6	11.0	86	3	17	43.3
P	279.1	— [§]	8.2	8.2	48	— [§]	— [§]	— [§]
Q	158.4	0.8	3.6	5.7	68	4	34	129.4
T	681.9	2.5	29.8	29.8	249	28	221	194.3
U	190.5	15.2	29.3	29.7	198	15	96	19.6
X	171.8	5.8	14.7	29.6	127	10	36	23.2
Z	248.5	4.9	6.3	29.7	125	3	5	11.0
II	425.2	— [§]	11.0	11.0	7	— [§]	— [§]	— [§]
KK	315.3	— [§]	11.0	11.0	6	— [§]	— [§]	— [§]
PP	155.7	1.2	6.7	6.7	72	6	57	77.4
SS	181.3	3.0	8.8	28.5	123	6	24	53.2
UU	333.5	5.6	18.9	20.8	125	14	76	158.2
VV	176.8	3.7	27.3	27.3	122	25	99	51.0
YY	668.1	6.1	29.2	29.7	229	24	174	141.3
AAA	323.3	2.1	28.5	28.5	335	27	287	288.7
BBB	286.9	16.1	29.8	29.8	300	14	119	77.0
EEE	341.4	— [§]	12.0	12.0	8	— [§]	— [§]	— [§]
GGG	1165.9	— [§]	11.0	11.0	7	— [§]	— [§]	— [§]
Mean ± SD	339.8 ± 247.3	4.7 ± 4.8	15.4 ± 9.8	19.0 ± 9.9	120.6 ± 96.9	13.1 ± 9.0	91.2 ± 80.7	96.4 ± 76.7
* Urine specimens were collected from cannabis users under continuous medical surveillance during cannabis abstinence for up to 30 days.								
† No urine specimens screened positive at 50 ng/mL.								
‡ No urine specimens between first negative and last positive.								
§ No urine specimens screened negative at 50 ng/mL.								

Table II includes detection times of first negative and last positive specimen based on the 50 ng/mL immunoassay screen, the number of days participants abstained from cannabis use and resided on the closed research unit, total number of urine specimens collected and number of days, number of speci-

mens, and THCCOOH C_{max} between first negative and last positive urine specimen for each participant. Data were separated into three groups based on the creatinine-normalized THCCOOH concentration of the first urine specimen collected on admission, 0–50 (*N* = 19 subjects), 51–150 (*N* = 21 subjects),

and > 150 ng/mg ($N = 20$ subjects). Correlation coefficients were determined for the mean interval to the first day with a negative specimen (Figure 1A), mean interval to the last day with a positive specimen (Figure 1B), number of days between first negative and last positive specimen (Figure 1C), number of specimens between first negative and last positive specimen (Figure 1D), and maximum normalized THCCOOH concentration between first negative and last positive specimen (Figure 1E).

Mean \pm standard deviation (SD), median, and range of concentrations for the three groups are presented in Table II. Group was significantly correlated to the day of the first negative urine specimen ($p = 0.0021$), mean concentration between first negative and last positive urine specimen ($p = 0.0202$), and the day of the last positive urine specimen ($p = 0.0003$). Mean detection rates on the day of the first negative specimen were 57.6, 73.4, and 79.8%, respectively.

In 60% of all participants, the maximum normalized THCCOOH concentration occurred in the first urine specimen collected during monitored abstinence. In the other 40%, peak

concentration occurred as long as 2.9 days after admittance.

Mean detection rates based on the 50-ng/mL screening results were calculated daily for up to 28 days after the day of the first negative test (Figure 2). By eight days, all specimens screened negative in the 0–50 ng/mg group. Detection rates declined more slowly in the 51–150 ng/mg group, and in the > 150 ng/mg group, mean detection rates remained between 60 and 100% for 28 days after the first negative urine test. Normalized THCCOOH concentration (ng/mg) in the first specimen also was significantly correlated ($p = 0.0001$) to the last day with a detection rate $\geq 50\%$ and to the number of days ($p = 0.0002$) between the first negative and last positive specimen.

Figure 3 shows mean urinary creatinine normalized cannabinoid excretion over time for the 0–50, 51–150, and > 150 ng/mg groups. The mean creatinine-corrected urine concentration for each subject for each day was determined, and the mean for each group for each day was calculated. Concentrations decreased rapidly during the first three days of monitored abstinence followed by a more gradual reduction over the course of the residential stay.

The average number of joints smoked per day was significantly correlated ($p = 0.0383$) to the log transformed maximum concentration between the first negative and last positive specimens. BMI was significantly correlated ($p = 0.0489$) to the day of the last positive specimen.

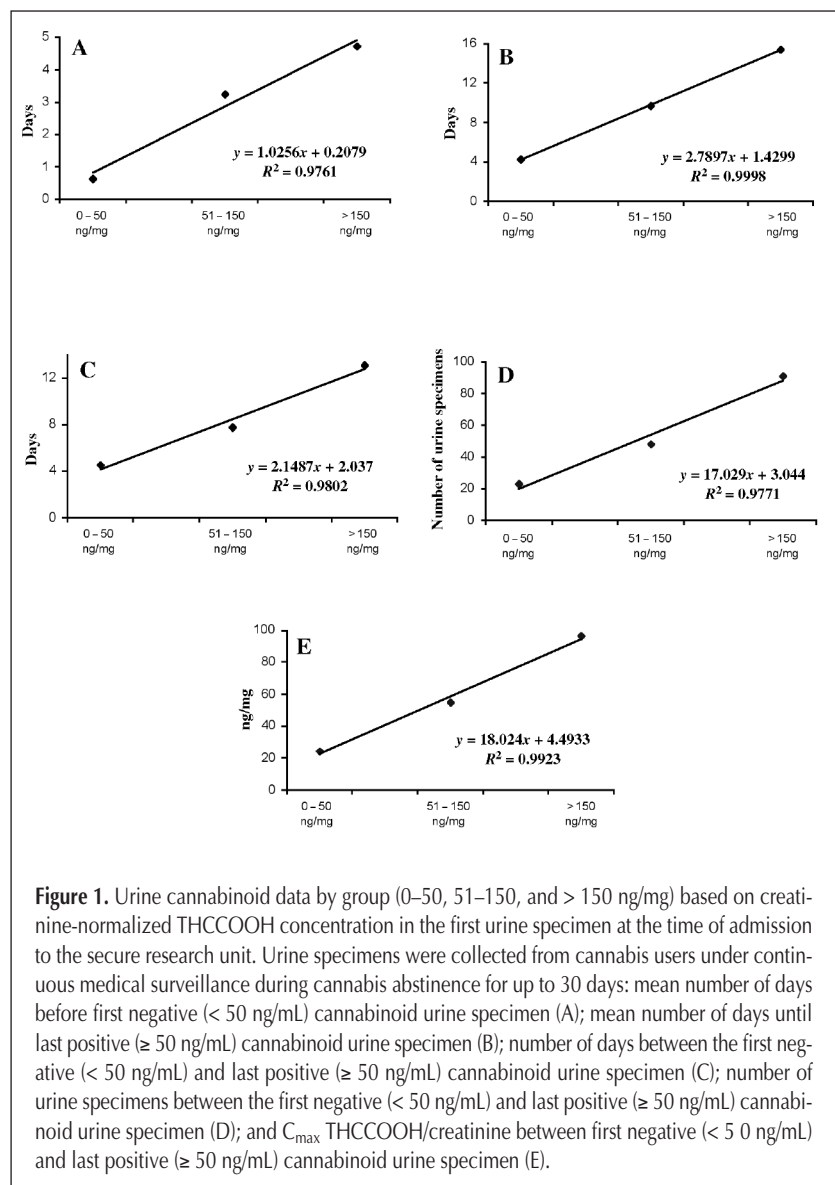


Figure 1. Urine cannabinoid data by group (0–50, 51–150, and > 150 ng/mg) based on creatinine-normalized THCCOOH concentration in the first urine specimen at the time of admission to the secure research unit. Urine specimens were collected from cannabis users under continuous medical surveillance during cannabis abstinence for up to 30 days: mean number of days before first negative (< 50 ng/mL) cannabinoid urine specimen (A); mean number of days until last positive (≥ 50 ng/mL) cannabinoid urine specimen (B); number of days between the first negative (< 50 ng/mL) and last positive (≥ 50 ng/mL) cannabinoid urine specimen (C); number of urine specimens between the first negative (< 50 ng/mL) and last positive (≥ 50 ng/mL) cannabinoid urine specimen (D); and C_{\max} THCCOOH/creatinine between first negative (< 50 ng/mL) and last positive (≥ 50 ng/mL) cannabinoid urine specimen (E).

Discussion

The aim of the present research was to characterize the time course of THCCOOH elimination in urine following variable cannabis exposure to provide data for improved interpretation of urine cannabinoid tests. Cannabinoid metabolites have been detected in the urine of frequent cannabis users for prolonged periods during abstinence (4–8). During the terminal elimination phase, alternate positive and negative urine test results may occur in consecutive specimens. This makes it problematic to determine whether positive results are indicative of new drug use or reflective of previous cannabis exposure. Complicating this issue is the fact that there are few studies in which participants are continuously monitored during abstinence to ensure that no illicit drug use has occurred. This study was unique in that it was conducted on a closed research unit with subjects under continuous medical surveillance during cannabis abstinence for up to 30 days.

Maximum THCCOOH/creatinine concentrations occurred in the first urine specimen collected during monitored abstinence in most

participants, but in 40%, peak concentration occurred up to three days after admission. BMI was significantly correlated with the day of the last positive specimen (i.e., the greater the BMI, the longer the interval until the last positive specimen was produced). BMI is a surrogate measure of body adiposity. THC distributes into fat tissue due to its lipophilicity and creates a depot of THC in the body after frequent cannabis use. During abstinence, the slow release of THC back into the blood

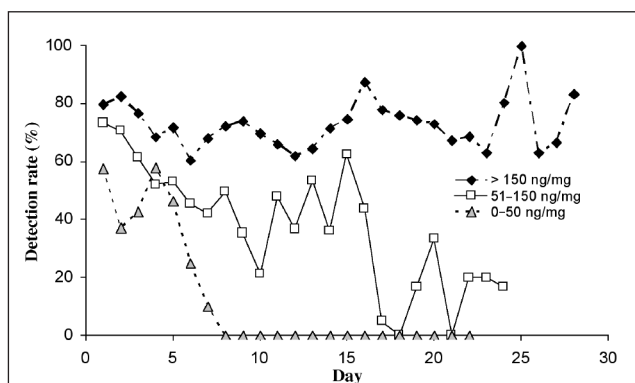


Figure 2. Mean detection rate each day after the first negative (< 50 ng/mL) cannabinoid urine specimen. Cannabis users were separated into three groups (0–50, 51–150, and > 150 ng/mg) according to creatinine-normalized THCCOOH concentrations in the first specimen collected at admission. Mean detection rate (number of positive specimens in a day/total number of specimens collected that day multiplied by 100) for the three groups was determined each day after the first negative specimen.

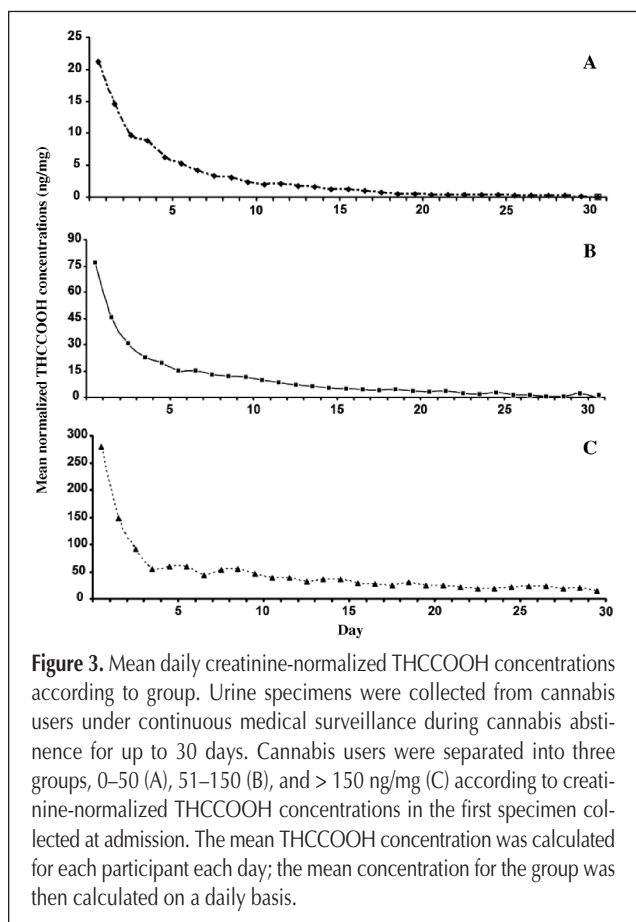


Figure 3. Mean daily creatinine-normalized THCCOOH concentrations according to group. Urine specimens were collected from cannabis users under continuous medical surveillance during cannabis abstinence for up to 30 days. Cannabis users were separated into three groups, 0–50 (A), 51–150 (B), and > 150 ng/mg (C) according to creatinine-normalized THCCOOH concentrations in the first specimen collected at admission. The mean THCCOOH concentration was calculated for each participant each day; the mean concentration for the group was then calculated on a daily basis.

is the rate-limiting step in the drug's excretion (19). Thus, the significant correlation between BMI and time until last positive urine cannabinoid test. During abstinence, the release of THC from adipose tissue into the blood is highly variable, possibly based on differences in activity, diet, enzymatic activity, and other undetermined factors. This release causes fluctuations in blood concentrations that in turn lead to variability in urinary cannabinoid concentrations. Thus, the many poorly studied factors that affect redistribution of THC from adipose tissue, and excretion into urine can result in significant intra-subject variability of creatinine normalized urinary THCCOOH concentrations.

The higher the creatinine-corrected THCCOOH concentration of the first specimen, the longer the mean interval for the first negative and last positive urine specimen. Intervals prior to the first negative urine specimen ranged from 0–16 days after admission; the range for the last positive specimen was 0–30 days. The creatinine corrected THCCOOH concentration was positively associated with the number of days, number of specimens, and C_{max} for specimens collected between the first negative and last positive urine tests. Detection rates also were positively associated with the normalized THCCOOH concentration of the first specimen. In the group with initial normalized THCCOOH concentrations > 150 ng/mg ($N = 20$ subjects), 13 had positive specimens on the last day of observation that averaged 19 days. For 4 of these subjects, this last day of observation represented the 30th day of monitored drug cessation. Mean peak THCCOOH/creatinine concentrations of 96.4 ± 76.7 ng/mg occurred between the first negative and last positive urine specimen, demonstrating the long and slow elimination of THC from the body. For the group with initial normalized THCCOOH concentrations of 0–50 ng/mg ($N = 19$ subjects), only 2 had positive specimens on the last day of observation that averaged approximately 10 days. Mean peak THCCOOH/creatinine concentration between the first negative and last positive specimen was approximately the same as the group's mean concentration at admission, approximately 23 ng/mg. Despite this initial low cannabinoid concentration, the last positive urine cannabinoid test occurred on average 4.6 days later. Thus, the initial normalized THCCOOH concentration is an important factor in determining the time course of urinary cannabinoid excretion. Regardless of the initial concentration, a rapid decrease was seen during the first three days of monitored abstinence, followed by a more gradual decrease in concentration during subsequent days.

These urinary cannabinoid excretion data collected under controlled monitored conditions from 60 cannabis users are of value for establishing expected windows of drug detection for the first negative and last positive cannabinoid tests. Furthermore, maximum creatinine-normalized THCCOOH concentrations that should be expected in later urine specimens are suggested, also helping to differentiate new cannabis use from residual drug excretion. Also, the detection rate data provide insight into the probability of obtaining a positive or negative result on each day after the first negative specimen.

If the THCCOOH concentration of a specimen collected in a drug-testing program is normalized to its urine creatinine concentration and classified into one of the three described

groups, expected detection times for first negative and last positive tests, highest expected THCCOOH/creatinine concentration of a later urine specimen, and expected detection rates for each day after the first negative urine specimen can be estimated from the appropriate group in Table II.

Conclusions

This study monitored cannabis users on a closed research unit under continuous medical surveillance during cannabis abstinence for up to 30 days. The greater the creatinine corrected initial THCCOOH concentration, the greater the interval until the first negative and last positive specimens, the greater the window of drug detection, and the higher the detection rate of positive specimens. Cannabis users who present with an initial normalized THCCOOH concentration > 150 ng/mg can be expected to have detection rates between 60 and 100% for 28 days after the first negative urine test. These data increase our understanding of THCCOOH urinary elimination and provide guidelines for the interpretation of urine cannabinoid test results. They also suggest appropriate detection windows for differentiating new cannabis use from residual drug excretion based on creatinine normalized THCCOOH urine data.

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