Δ^9-Tetrahydrocannabinol, 11-Hydroxy-Δ^9-Tetrahydrocannabinol and 11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol in Human Plasma After Controlled Oral Administration of Cannabinoids

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Abstract: A clinical study to investigate the pharmacokinetics and pharmacodynamics of oral tetrahydrocannabinol was performed. This randomized, double-blind, placebo-controlled, within-subject, inpatient study compared the effects of THC-containing hemp oils in liquid and capsule form to dronabinol (synthetic THC) in doses used for appetite stimulation. The National Institute on Drug Abuse Institutional Review Board approved the protocol and each participant provided informed consent. Detection times and concentrations of THC, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) in plasma were determined by gas chromatography-mass spectrometry [limits of quantification (LOQ) = 0.5, 0.5, and 1.0 ng/mL, respectively] after oral THC administration. Six volunteers ingested liquid hemp oil (0.39 and 14.8 mg THC/d), hemp oil in capsules (0.47 mg THC/d), dronabinol capsules (7.5 mg THC/d), and placebo. Plasma specimens were collected during and after each dosing condition. THC and 11-OH-THC concentrations were low and never exceeded 6.1 ng/mL. Analytes were detectable 1.5 hour after initiating dosing with the 7.5 mg THC/d regimen and 4.5 hour after starting the 14.8 mg THC/d sessions. THCCOOH was detected 1.5 hour after the first dose, except for the 0.47 mg THC/d session, which required 4.5 hour for concentrations to reach the LOQ. THCCOOH concentrations peaked at 3.1 ng/mL during dosing with the low-dose hemp oils. Plasma THC and 11-OH-THC concentrations were negative for all participants at all doses within 15.5 hours after the last THC dose. Plasma THCCOOH persisted for at least 39.5 hours after the end of dosing and at much higher concentrations (up to 43.0 ng/mL).

This study demonstrated that subjects who used high THC content hemp oil (347 μg/mL) as a dietary supplement had THC and metabolites in plasma in quantities comparable to those of patients using dronabinol for appetite stimulation. There was a significant correlation between body mass index and C_{max} and body mass index and number of specimens positive for THC and 11-OH-THC.

Key Words: oral administration, tetrahydrocannabinol, cannabinoids, plasma, GC/MS, hemp oil

(*Ther Drug Monit* 2006;28:545–551)

The clinical study of orally administered cannabinoids has gained importance due to the availability of therapeutic cannabinoid preparations, Marinol [dronabinol, synthetic delta-9-tetrahydrocannabinol (THC)] and Sativex (a whole plant cannabis extract). Dronabinol is approved to treat anorexia associated with AIDS and refractory nausea and vomiting in patients undergoing chemotherapy.[1] Sativex was recently approved by Health Canada as a treatment for the relief of neuropathic pain in multiple sclerosis. The United States National Academy of Sciences, Institute of Medicine has called for clinical trials to test the effectiveness of cannabinoids in pain relief, spasticity, movement disorders and for other indications, and to improve medication delivery systems.[2] Studies have shown that orally administered cannabinoids provide effective relief from cancer pain,[3–5] and clinical trials have shown that treatment with Sativex improves sleep quality and relieves pain and inflammation in patients suffering from rheumatoid arthritis.[6] Several phase 2 trials of patients with multiple sclerosis demonstrated that treatment with oral cannabinoids resulted in significant improvement in bladder dysfunction and spasticity.[7–9] Likewise, oral cannabinoids have proven effective in reducing chronic neuropathic pain in randomized controlled trials.[10,11]

In recent years, the number of hemp products containing THC has increased substantially. Many are advertised as nutritional supplements with high concentrations of essential amino and fatty acids. Hemp oil is

Received for publication February 27, 2006; accepted April 20, 2006.
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Supported by the Intramural Research Program of the National Institutes of Health, National Institute on Drug Abuse.
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produced from cannabis seed and is an ingredient in a variety of commercially available food and nutritional supplements. THC content in hemp oil is dependent upon the effectiveness of seed cleaning and oil filtration processes. Hemp oil samples of greater than 300 and 3500 μg THC/g were previously available in the US and Europe, respectively.[12] Currently, hemp oil THC concentrations from US manufacturers are low, reflecting mandated reduction in the amount of THC in hemp products.

There are other important factors that contribute to THC concentrations in blood. Dose, route of administration, vehicle, and physiological factors such as absorption, metabolism, and excretion rates are important determinants as well. Perez-Reyes[13] described the efficacy of 5 different vehicles for the oral administration of THC via gelatin capsules. Glycocholate and sesame oil improved the bioavailability of oral THC; however, there was considerable variability in peak concentrations and rates of absorption, even when drug was administered in the same vehicle. Oral THC bioavailability was estimated to be 10% to 20% by Wall et al.[14] Participants received either 15 mg (women) or 20 mg (men) THC in sesame oil. A percentage of the THC was radiolabeled; however, at that time, differentiation of labeled THC and metabolites was not possible. Thus, THC concentrations were overestimated. Possibly a more accurate assessment of oral bioavailability utilizing gas chromatography/mass spectrometry (GC/MS) to quantify THC in plasma was reported by Ohlsson.[15] He estimated 6% bioavailability after a 20 mg THC dose in a cookie. Slow rates of absorption and low THC concentrations were observed. Low oral THC bioavailability may be due to poor absorption, degradation by stomach acid, and/or biotransformation to metabolites during first passage through the liver.

THC is the major psychoactive component of cannabis, the most widely used illicit drug in the world.[16] Oral THC has been shown to be reinforcing[17,18] and thus, has abuse potential. The historically low incidence of oral THC abuse is attributed to the relatively infrequent use of the drug for medicinal purposes, limiting its availability. With renewed interest in cannabis-based therapeutics, oral THC will be more readily available and a concomitant increase in abuse of oral THC has been predicted.[17]

The behavioral and physiological effects of cannabis adversely affect academic, work, and driving performance. Cross-sectional studies have revealed significant associations between cannabis use and a range of measures of educational attainment including lower grade point average, less satisfaction with school, negative attitudes towards school, and increased rates of absenteeism.[19] THC also has been shown to impair cognition, psychomotor function, and driving performance in a dose-related manner.[20] There is evidence that recent use of cannabis increases the risk for motor vehicle accidents compared with drug-free drivers, particularly with heavy use.[20] Likewise, early cannabis use predicts diminished income, even when users maintain a consistently light level of use.[21]

In view of these adverse effects of cannabis, it has become necessary to screen for its illicit use. Urine drug screening is routinely performed for cannabis in occupational, military, and judicial settings. Therapeutic cannabinoid and hemp oil use could produce positive drug screening tests and impact drug detection programs. As we previously reported, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) concentrations exceeded urinary cutoffs for cannabinoids in participants ingesting multiple doses of 0.39 and 0.47 mg THC/d in hemp oil.[22] This was consistent with the results of Leson et al[12] who found that 1 of 3 participants ingesting a daily dose of 0.6 mg THC in hemp oil tested positive for THCCOOH in urine by immunoassay at a cutoff concentration of 50 ng/mL. Bosy and Cole[23] reported urine cannabinoid results after daily oral hemp oil use for 7 days. Positive specimens occurred by the third day after a moderate daily dose, 0.54 mg THC in hemp oil, and on the first day after a high-dose of 1.76 mg THC with a 50 ng/mL cutoff.

Detection and quantification of urinary cannabinoids remains an important forensic toxicology tool for documenting cannabinoid exposure. However, urine drug concentration data do not provide adequate answers to demanding clinical and forensic questions. These are more readily answered with quantitative plasma data.[24] Generally, plasma or whole-blood concentrations of cannabinoids are required for the evaluation of driving under the influence of drugs, overdose, and postmortem assessments.

Although there are several pharmacokinetic studies of THC and its metabolites in plasma or urine after smoked cannabis,[25–30] few studies have investigated their disposition in plasma after oral administration.[13–15,31] The objectives of this study were to determine plasma profiles of THC, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), and THCCOOH after controlled ingestion of natural cannabinoids in hemp oil and synthetic THC (dronabinol) and to relate these concentrations to ongoing physiological and subjective effects.

MATERIALS AND METHODS

Participants

Six healthy participants with a history of cannabis use resided in the secure clinical research unit of the National Institute on Drug Abuse (NIDA) Intramural Research Program, National Institutes of Health while participating in a protocol designed to characterize the pharmacokinetics and pharmacodynamics of oral THC. The NIDA Institutional Review Board approved the study. All participants provided written informed consent, were under continuous medical supervision, and were financially compensated for their time and inconvenience. Subject characteristics and drug use histories were previously described.[22]

Before admission, each participant underwent thorough medical (physical exam, ECG, blood, and urine chemistries) and psychologic evaluations, including past

and recent drug use history. Participants were not dosed until urine cannabinoid concentrations were below 10 ng/mL by fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, IL). Twenty-four hour medical surveillance on a closed, secure residential unit prevented access to unauthorized licit or illicit drugs. In addition, random weekly urine drug tests for amphetamines, cannabinoids, cocaine, opiates, and phencyclidine were performed.

Drug Administration

This protocol was a randomized, double-blind, double-dummy, placebo-controlled, within-subject study. Double dummy refers to the fact that liquid oil and capsules were administered at each time point, although at most, only one of the dosage forms contained active cannabinoids. Neither research personnel nor participants were aware of drug content, thus the term double-blind. Each subject participated in 5 dosing conditions, each entailing supervised administration of 15 mL (1 tablespoon) hemp oil and 2 capsules 3 times per day with meals for 5 consecutive days. Subjects freely selected food choices without restriction from the clinical research unit menus. After 5 consecutive dosing days, there was a 10-day washout period. Individuals resided on the secure clinical unit for 10 to 13 weeks.

Dosing conditions were randomized and assigned by the IRP's pharmacy. The 5 oral dosing conditions were as follows: (1) placebo oil and placebo capsules; (2) low-dose hemp oil and placebo capsules; (3) high-dose hemp oil and placebo capsules; (4) placebo oil and low-dose capsules; and (5) placebo oil and high-dose (dronabinol) capsules. Dronabinol and hemp oil capsules were contained within larger capsules to maintain double-blind conditions.

Hemp oils were assayed by GC-MS to accurately determine the concentration of THC. Flax oil was administered as the placebo. Low-dose hemp oil contained 9 μg THC/g of hemp oil for a total daily dose of 0.39 mg THC. Low-dose hemp oil administered in capsules contained 92 μg THC/g of hemp oil for a total dose of 0.47 mg THC/d. A total daily dose of 14.8 mg THC was achieved with the high-dose hemp oil (concentration 347 μg THC/g hemp oil). Dronabinol (synthetic THC in sesame oil), 2.5 mg THC per capsule, was administered as a positive control with a daily total dose of 7.5 mg. For safety reasons, only 2 doses (5.0 mg THC) were administered on the first dosing day of the session. Doses administered reflected concentrations of THC in commercially available hemp oil at the time of study design.

Timeline

Drug or placebo was administered at 0800, 1300, and 1730 for 5 consecutive days for each of the 5 dosing conditions. Six milliliter whole-blood specimens (75 per subject over the 10 wk study) were collected before and up to 10 days after dosing.

Blood pressure, heart rate, and respiratory rate were taken at the following times: day 1 at 0730, 0930, 1430, and 1900; days 2 to 5 at 1430; and day 6 at 0930. Nine-item 100-mm visual-analog scales (VAS) anchored with "not at all" at zero and "extremely" at 100 were administered when vital signs were taken. These items included "good," "bad," "like," "high," "stoned," "impaired/tired," "confused," "clear headed," and "relaxed/energetic." Participants were asked to evaluate the way they felt at the time the VAS was administered.

Clinical Specimen Analysis

Blood was collected on ice, centrifuged, and plasma removed within 2 hour; specimens were stored at −20°C until analysis. A previously published procedure for the simultaneous extraction and quantification of THC, 11-OH-THC, and THCCOOH was employed.[24] *Escherichia coli* β-glucuronidase hydrolysis cleaved glucuronic acid moieties to capture total cannabinoid concentrations.[32,33] One milliliter of plasma was combined with 1.0 mL of 0.1 M potassium phosphate buffer and 250 μL of a 20,000 units/mL solution of β-glucuronidase in the same buffer. Samples were placed in a 37°C water bath and incubated for 16 hours. After cooling, 1.0 mL of cold acetonitrile was added, specimens were centrifuged, and supernatants decanted into clean tubes. Two milliliters of 2 N sodium acetate buffer was added and the tubes were centrifuged. SPE columns (Condition CleanScreen ZSTHC020, United Chemical Technologies, Bristol, PA) were conditioned with sequential addition and elution of 1.0 mL of primary elution solvent (methylene chloride: 2-propanol: concentrated ammonium hydroxide, 80:20:2 by volume), 3.0 mL methanol, 3 mL of deionized water, and 2.0 mL 2 N sodium acetate buffer. Supernatants were decanted onto conditioned SPE columns. Columns were washed by the sequential addition and elution of 2.0 mL deionized water and 1.25 mL 0.2 N hydrochloric acid and dried under vacuum. Analytes were eluted by the addition of 2.5 mL primary elution solvent and 2.5 mL of a secondary elution solvent of hexane: ethyl acetate (80:20 by volume). The combined eluates were dried under a stream of nitrogen at 40°C. Extracted residues were reconstituted with 20 μL acetonitrile, centrifuged for 5 minutes, and transferred to autosampler vials. 20 μL of BSTFA containing 1% TMCS was added, and vials were heated at 80°C for 45 minutes. The trimethylsilyl derivatives (2 μL) were injected on the GC-MS system. GC-MS analysis was performed on an Agilent 6890 gas chromatograph interfaced with an Agilent 5973 mass-selective detector. Separation of analytes was achieved with a HP-5MS (30 m × 0.25 mm ID, 0.25 μm film thickness) column with helium as carrier gas. The initial column temperature of 120°C was held for 0.5 min, followed by a 15°C/min increase to 300°C. The MS was operated in the positive chemical ionization mode and selective ion monitoring was used with a dwell time of 100 ms/ion. One ion for each analyte was monitored: [$^2H_3$]-THC, *m/z* 390; THC, *m/z* 387; [$^2H_3$]-11-OH-THC, *m/z* 462; 11-OH-THC, *m/z* 459; [$^2H_3$]-THCCOOH, *m/z* 492; and THCCOOH, *m/z* 489. Limits of quantification were 0.5, 0.5, and 1.0 ng/mL

of plasma for THC, 11-OH-THC, and THCCOOH, respectively.

Statistical Analysis

Plasma THC, 11-OH-THC, and THCCOOH concentrations were compared between the 7.5 and 14.8 mg THC/d dosing sessions with analysis of variance (ANOVA) and Wilcoxon Signed Ranks Test for Areas Under the Curve. Correlations of body mass index (BMI) and C_{max} and for the number of specimens positive for THC and 11-OH-THC were analyzed by Spearman's rank correlation coefficient.

RESULTS

There were no specimens (N = 180) with THC or 11-OH-THC plasma concentrations greater than the limit of quantification (0.5 ng/mL) during or after the 0.39 or 0.47 mg THC/d doses (Table 1). THC and 11-OH-THC were detected 1.5 hour after initiating dosing with dronabinol and 4.5 hour after starting the 14.8 mg THC/d sessions. These analytes were detected in about 35% of plasma specimens (N = 60) collected during the first 12 hours of dosing at the LOQ of 0.5 ng/mL. Both were measurable in approximately half the specimens (N = 12) 1.5 hour after the last dose (107 h after the first cannabinoid doses) after the high-dose sessions. All participants had at least 1 positive THC specimen and 5 of 6 had at least one positive 11-OH-THC plasma specimen.

THCCOOH was found in higher concentrations and in more participants' plasma than either of the other analytes. Nearly all specimens had measurable THCCOOH. THCCOOH was detectable 1.5 hour after initiating all dosing regimens, except for the 0.47 mg THC/d sessions, which required 4.5 hour. THCCOOH concentrations generally increased over the 5 days of dosing and peaked with the specimens obtained 1.5 hour after the last of 15 doses. Mean plasma concentrations of THCCOOH were significantly greater during and after the 7.5 as compared with the 14.8 mg THC/d doses ($P \leq 0.01$). Areas under the curve for the 3 cannabinoids were not significantly different for the 2 high-doses.

The maximum plasma concentrations (C_{max}) of THC and 11-OH-THC were 6.1 and 5.6 ng/mL, respectively (Table 2). These concentrations were achieved in Participant N during the 14.8 mg THC/d hemp oil sessions. There were significant positive correlations between participant BMI and THC C_{max} ($r = 0.886$, $P \leq 0.05$) and 11-OH-THC C_{max} ($r = 0.829$, $P \leq 0.05$). The C_{max} for THCCOOH during and after the 2 low THC doses was 3.1 ng/mL, occurring 4.5 hour after dosing was initiated. THCCOOH C_{max} ranged from 10.6 to 43.0 ng/mL during and after the 2 high THC doses. THCCOOH C_{max} concentrations after the 7.5 mg THC/d dronabinol dose were greater than those after the 14.8 mg THC/d hemp oil dose in 5 of 6 cases. Times of maximum cannabinoid concentrations (T_{max}) varied widely within doses and between subjects.

TABLE 1. Mean Plasma Concentrations (ng/mL ± Standard Deviation) of THC, 11-OH-THC, and THCCOOH*

Time After First Dose (h)	Dose (mg THC/d) 0.39	0.47	7.5	14.8
THC				
1.5	0.0	0.0	0.5 ± 0.9	0.0
4.5	0.0	0.0	0.4 ± 0.5	0.3 ± 0.5
6.5	0.0	0.0	0.9 ± 1.5	1.0 ± 1.5
9.0	0.0	0.0	0.6 ± 0.7	0.5 ± 0.7
11.5	0.0	0.0	0.1 ± 0.3	1.1 ± 1.2
23.5	0.0	0.0	0.0	0.0
47.5	0.0	0.0	0.0	0.0
71.5	0.0	0.0	0.0	0.0
95.5	0.0	0.0	0.0	1.0 ± 2.7
107.0	0.0	0.0	1.1 ± 1.3	1.2 ± 0.8
121.0	0.0	0.0	0.0	0.0
130.5	0.0	0.0	0.0	0.0
145.0	0.0	0.0	0.0	0.0
154.5	0.0	0.0	0.0	0.0
11-OH-THC				
1.5	0.0	0.0	0.7 ± 1.0	0.0
4.5	0.0	0.0	0.5 ± 0.6	0.1 ± 0.2
6.5	0.0	0.0	0.6 ± 1.0	0.3 ± 0.5
9.0	0.0	0.0	0.6 ± 0.7	1.4 ± 2.2
11.5	0.0	0.0	0.5 ± 0.6	0.5 ± 0.7
23.5	0.0	0.0	0.0	0.0
47.5	0.0	0.0	0.0	0.0
71.5	0.0	0.0	0.0	0.0
95.5	0.0	0.0	0.1 ± 0.3	0.0
107.0	0.0	0.0	1.3 ± 1.1	0.3 ± 0.3
121.0	0.0	0.0	0.0	0.0
130.5	0.0	0.0	0.0	0.0
145.0	0.0	0.0	0.0	0.0
154.5	0.0	0.0	0.0	0.0
THCCOOH				
1.5	0.2 ± 0.6	0.0	2.3 ± 2.7	1.6 ± 2.0
4.5	0.5 ± 1.3	0.2 ± 0.6	5.3 ± 4.5	2.5 ± 1.4
6.5	0.7 ± 1.1	0.2 ± 0.6	7.3 ± 7.3	5.7 ± 2.4
9.0	0.2 ± 0.9	0.6 ± 0.9	10.6 ± 5.9	6.4 ± 2.6
11.5	0.7 ± 1.1	0.7 ± 1.2	10.6 ± 8.8	7.6 ± 4.1
23.5	0.7 ± 1.1	0.5 ± 0.7	6.2 ± 5.5	7.0 ± 3.7
47.5	0.6 ± 0.9	0.9 ± 1.0	9.2 ± 4.0	7.9 ± 3.0
71.5	0.7 ± 1.1	0.7 ± 1.0	11.9 ± 6.0	8.3 ± 3.1
95.5	0.3 ± 0.7	1.0 ± 1.1	13.8 ± 7.3	9.9 ± 2.7
107.0	0.7 ± 1.1	1.1 ± 1.2	19.8 ± 12.3	11.1 ± 0.9
121.0	0.5 ± 0.8	0.5 ± 0.8	10.7 ± 6.1	9.5 ± 3.5
130.5	0.3 ± 0.8	0.4 ± 0.6	7.4 ± 2.3	6.1 ± 2.5
145.0	0.3 ± 0.6	0.2 ± 0.5	5.3 ± 2.6	4.4 ± 3.6
154.5	0.0	0.0	4.4 ± 2.2	4.4 ± 3.1

*Mean ± SD plasma concentrations (N = 6) of THC, 11-OH-THC, and THCCOOH were determined after the first dose of a 5-day dosing session with 0.39, 0.47, 7.5, and 14.8 mg THC/d. The last dose occurred 105.5 hours after the first dose. Limits of quantification were 0.5, 0.5, and 1.0 ng/mL of plasma for THC, 11-OH-THC, and THCCOOH, respectively. For specimens with concentrations below the LOQ, a value of 0 was used in calculating means.

The detection rate for THC and 11-OH-THC was 0 for the low-dose THC sessions and ranged from 10.0% to 25.9% during and up to 49 hours after the 2 high-dose sessions (Table 3). Detection rates for THCCOOH were 20.0% to 27.8% for the low-dose THC sessions but were much greater for the 2 high-dose THC regimens, ranging from 92.6% to 100%. The number of specimens positive for THCCOOH during and after the 0.39 and 0.47 mg THC/d regimens varied widely, ranging from 0 to 23, out of a possible 28 per participant.

TABLE 2. C_{max}* and T_{max}† of Cannabinoid Analytes

		Dose (mg THC/d)							
		0.39		0.47		7.5		14.8	
Subject	BMI‡	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}
THC									
A	27.0	0.0	—	0.0	—	1.0	107	1.7	9
G	17.8	0.0	—	0.0	—	0.6	107	1.0	107
H	24.6	0.0	—	0.0	—	0.8	9	1.5	11.5
L	20.2	0.0	—	0.0	—	1.6	107	0.7	9
N	33.2	0.0	—	0.0	—	3.8	6.5	6.1	95.5
P	26.1	0.0	—	0.0	—	1.0	9	1.8	107
11-OH-THC									
A	27.0	0.0	—	0.0	—	2.0	107	1.5	9
G	17.8	0.0	—	0.0	—	0.0	—	0.0	—
H	24.6	0.0	—	0.0	—	1.3	107	1.7	11.5
L	20.2	0.0	—	0.0	—	2.1	107	0.6	107
N	33.2	0.0	—	0.0	—	2.6	107	5.6	9
P	26.1	0.0	—	0.0	—	1.6	1.5	0.9	6.5
THCCOOH									
A	27.0	0.0	—	2.6	11.0	43.0	107	15.0	11.5
G	17.8	1.1	121	1.8	95.5	13.4	107	11.1	107
H	24.6	0.0	—	0.0	—	13.9	107	11.0	107
L	20.2	3.1	4.5	2.5	107	24.5	107	15.2	121
N	33.2	2.6	23.5	1.3	47.5	10.6	107	11.6	95.5
P	26.1	0.0	—	0.0	—	13.4	107	12.1	107

*Maximum THC, 11-OH-THC, and THCCOOH plasma concentrations (ng/mL) for 6 subjects were determined during and after 5 day dosing sessions with 0.39, 0.47, 7.5, and 14.8 mg THC/d.

†Time (h) after the first dose for maximum plasma concentrations (C_{max}) were determined for THC, 11-OH-THC, and THCCOOH for 6 subjects during and after 5 day dosing sessions with 0.39, 0.47, 7.5, and 14.8 mg THC/d.

‡Body mass index—below 18.5 is considered underweight, 18.5–24.9 is normal, 25.0–29.9 is overweight, and 30.0 and above is considered obese.

Participant N had 9 of 15 specimens positive for THC and 6 of 18 positive for 11-OH-THC during dosing with the high potency oil and capsules (Fig. 1), considerably more than any other subject. Participants A, H, P, L, and O had 11, 8, 8, 5, and 0 of 36 positive specimens, respectively. This correlates significantly with subjects' BMI, ie, the greater the BMI, the greater the number of positive THC or 11-OH-THC specimens ($r = 0.986$, $P \leq 0.001$; $r = 0.928$, $P \leq 0.01$, respectively).

After the last THC dose, the maximum analyte detection time varied by analyte and dosing session. THC and 11-OH-THC were detected only in specimens obtained 1.5 hour after the last 7.5 and 14.8 mg THC/d doses. Specimens were not collected between 1.5 and 15.5 hours after the last dose due to restriction in the total amount of blood that could be collected. It is possible that analytes could have been detected during this interval. THCCOOH was detected (> 1.0 ng/mL) up to 39.5 hours after the final low-doses of THC in 2 of 6 participants. THCCOOH was still detectable in all participants 49 hours after the final administration of the high-dose oil or capsules.

Ratios of THC/11-OH-THC, THC/THCCOOH, and 11-OH-THC/THCCOOH varied with time and dosing regimen. Ratios of THC/11-OH-THC ranged from 0.34 to 4.00. Ratios of THC/THCCOOH and 11-OH-THC/THCCOOH were 0.29 or less.

TABLE 3. Detection Rates* of Analytes in Plasma (%) During Cannabinoid Dosing (N = 54) and within 49 hours After the Last Dose (N = 30)

Dose	THC		11-OH-THC		THCCOOH	
(mg THC/day)	During	After	During	After	During	After
0.39	0.0	0.0	0.0	0.0	27.8	20.0
0.47	0.0	0.0	0.0	0.0	27.8	26.7
7.5	20.4	13.3	25.9	13.3	92.6	100
14.8	24.1	16.7	16.7	10.0	92.6	100

*The percentage of positive specimens from 6 subjects with analyte concentrations greater than the limit of quantification were determined for THC, 11-OH-THC, and THCCOOH during 5 day dosing sessions with 0.39, 0.47, 7.5, and 14.8 mg THC/d and for 49 hour after the completion of dosing.

Blood pressure, heart rate, and respiratory rate remained relatively unchanged during and after the various dosing conditions. Likewise, there was little change in the 9-item VAS scores among the different dosing conditions for each participant.

DISCUSSION

When hemp oil is ingested as a dietary supplement, THC and its metabolites are detected in plasma in quantities comparable to those observed when a low-dose of dronabinol is administered for appetite stimulation. In the present study, concentrations of THC and 11-OH-THC were similar during the 7.5 mg THC/d dronabinol and 14.8 mg THC/d hemp oil doses, never exceeding 6.1 ng/mL. No specimens had measurable THC or 11-OH-THC during or after the 0.39 or 0.47 mg THC/d dosing sessions. The lower dose regimens are reflective

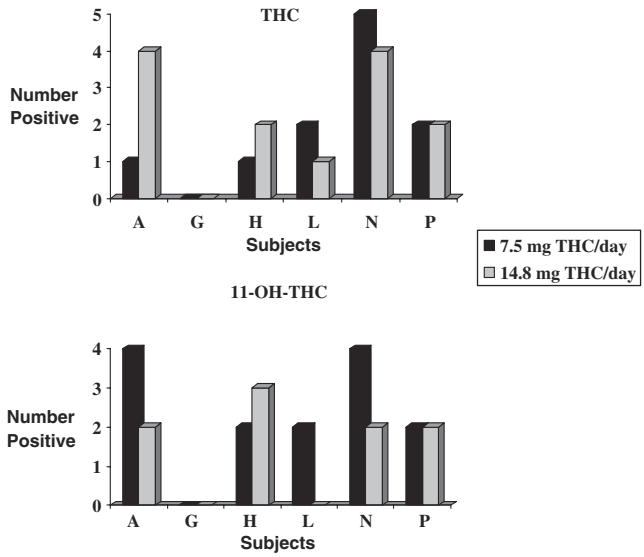

FIGURE 1. Number of plasma specimens (N = 9) for either 7.5 or 14.8 mg THC/d with THC or 11-OH-THC concentrations above the limit of quantification (0.5 ng/mL) for each subject during 5 days of dosing.

of THC concentrations in hemp oil currently produced by US manufacturers, indicating that consumption of these hemp oils according to manufacturer's instructions should not lead to positive THC or 11-OH-THC plasma tests. Furthermore, because whole-blood cannabinoid concentrations are approximately 50% of plasma concentrations, whole-blood cannabinoid tests, such as those utilized for driving under the influence of drugs evaluations, should also not be positive under these conditions.

The maximum concentrations of THC and 11-OH-THC were seen in the 14.8 mg THC/d hemp oil sessions and occurred in the participant with the greatest BMI. There was a significant correlation between BMI and C_{max} for both THC and 11-OH-THC. Likewise, there was a significant correlation between BMI and number of specimens positive for these analytes. THC is widely distributed, particularly to adipose tissues, a long-term storage site.[34] The positive correlations between BMI and THC and 11-OH-THC suggest that concomitant with deposition in fatty tissue, there is release of THC and metabolites into the plasma proportional to that which has been deposited in fat. Indeed, it has been shown that the rate-limiting step for THC elimination is the slow release to plasma of THC sequestered in tissues.[35] This process could have a differential effect on plasma concentrations dependent upon BMI and upon the frequency of cannabinoid use, because those participants with higher fat content could have a larger body burden of cannabinoids. All participants began dosing sessions at the same baseline level of circulating cannabinoids, ie, hemp oil or dronabinol was not administered until urine concentrations were below 10 ng/mL by fluorescence polarization immunoassay. But the release of cannabinoids to plasma would be more substantial for participants with greater amounts stored in adipose tissue, ie, those with greater BMI. Because cannabinoid concentrations in plasma were low, this augmented release of residual THC from fat to plasma in obese participants may have been sufficient to raise low analyte concentrations above the LOQ.

Mean THCCOOH concentrations during and after the 7.5 mg THC/d dronabinol sessions were significantly greater than those from the 14.8 mg/d hemp oil sessions ($P \leq 0.01$). This could have been due to better bioavailability of THC in sesame oil and/or greater degradation of hemp oil by gastric acid relative to the dronabinol capsules. THC in dronabinol may have been protected somewhat from degradation by being contained within another capsule, whereas hemp oil was administered as a liquid. This would result in more THC delivered to the portal circulation from the capsules, and subsequently greater formation of the carboxylated metabolite by cytochrome P450 enzymes. A difference in mean analyte concentrations between the 2 dosing regimens was not evident for THC or 11-OH-THC.

Detection rates were similar for THCCOOH during and after the 7.5 mg THC/d and high potency hemp oil sessions, ranging from 92.6% to 100%. THCCOOH was detectable in all participants 49 hours after the final administration of the high-dose oil or capsules and could be detected up to 39.5 hours after the final administration of the low-dose sessions.

Administration of oral THC in hemp oil (up to 14.8 mg/d) or in dronabinol capsules (up to 7.5 mg/d) produced maximum plasma concentrations of THC and 11-OH-THC in the 6 ng/mL range, but resulted in no measurable pharmacodynamic effect. It must be remembered that these doses were divided into 3 doses with meals each day. There was no significant change in vital signs or VAS scores of subjective measures after individual doses of up to 5 mg. These results are consistent with those described by Ohlsson et al, who demonstrated no significant pharmacodynamic effects after 5 mg oral THC in a cookie.[15] However, after 20 mg THC in the same vehicle, the authors reported significant intoxication in participants.

The last decade has seen an expanding global market for food products and nutritional supplements derived from or containing cannabinoids such as hemp oil. Similarly, the number of therapeutic applications of cannabinoids has grown. Ingestion of these products may result in positive drug tests.[36–38] This has led to questions about the validity of drug tests intended to deter drug use in treatment, workplace, criminal justice, and military programs. The impact of increased medicinal use of cannabinoids on the evaluation of driving under the influence of drugs, in cases of drug overdose, and in postmortem analyses has yet to be determined.

CONCLUSIONS

This study demonstrated that in subjects using hemp oil with a high THC content (347 μg/g) as a dietary supplement, THC and its metabolites were detectable in plasma in quantities comparable to those in patients using dronabinol for appetite stimulation. Concentrations of THC and 11-OH-THC were low and peaked at a maximum of 6.1 ng/mL. There were no specimens with concentrations of these analytes greater than the limit of quantification during or after the low-doses. No pharmacodynamic effects were observed with any dosage regimen. THCCOOH was detectable during all dosing sessions within 5 hours of the first dose and was found in higher concentrations and in more participants' plasma specimens than either of the other analytes. Nearly all specimens had measurable THCCOOH. There was a significant correlation between BMI and the number of specimens positive for THC and 11-OH-THC and between BMI and C_{max} for both analytes, possibly indicating greater deposition in adipose tissue and release to plasma of THC and metabolites in obese individuals. These controlled drug administration data should assist in the interpretation of plasma cannabinoid results and provide clinicians with valuable information for future pharmacological studies.

ACKNOWLEDGMENT

The authors acknowledge Bonnie Ladaga for her assistance with statistical analysis.

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