Oral Fluid Cannabinoids in Chronic Cannabis Smokers during Oral Δ⁹-Tetrahydrocannabinol Therapy and Smoked Cannabis Challenge

Dayong Lee,1 Ryan Vandrey,2 Damodara R. Mendu,1 Sebastien Anizan,1 Garry Milman,1 Jeannie A. Murray,2 Allan J. Barnes,1 and Marilyn A. Huestis1*

BACKGROUND: Oral Δ⁹-tetrahydrocannabinol (THC) is effective for attenuating cannabis withdrawal and may benefit treatment of cannabis use disorders. Oral fluid (OF) cannabinoid testing, increasing in forensic and workplace settings, could be valuable for monitoring during cannabis treatment.

METHODS: Eleven cannabis smokers resided on a closed research unit for 51 days and received daily 0, 30, 60, and 120 mg of oral THC in divided doses for 5 days. There was a 5-puff smoked cannabis challenge on the fifth day. Each medication session was separated by 9 days of ad libitum cannabis smoking. OF was collected the evening before and throughout oral THC sessions and analyzed by 2-dimensional GC-MS for THC, cannabidiol (CBD), cannabinol (CBN), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH).

RESULTS: During all oral THC administrations, THC OF concentrations decreased to ≤78.2, 33.2, and 1.4 μg/L by 24, 48, and 72 h, respectively. CBN also decreased over time, with concentrations 10-fold lower than THC, with none detected beyond 69 h. CBD and 11-OH-THC were rarely detected, only within 19 and 1.6 h after smoking, respectively. THCCOOH OF concentrations were dose dependent and increased over time during 120-mg THC dosing. After cannabis smoking, THC, CBN, and THCCOOH concentrations showed a significant effect and decreased significantly over time.

CONCLUSIONS: Oral THC dosing significantly affected OFTHCCOOH but minimally contributed to THC OF concentrations; prior ad libitum smoking was the primary source of THC, CBD, and CBN. Higher cannabinoid concentrations following active oral THC administrations vs placebo suggest a compensatory effect of THC tolerance on smoking topography.

Oral synthetic Δ⁹-tetrahydrocannabinol (THC)³ (dronabinol, Marinol®) is approved by the US Food and Drug Administration as a treatment for AIDS-related anorexia and chemotherapy-induced emesis (1). Oral THC also showed limited efficacy in treating multiple sclerosis–related pain (2), spasticity (3), glaucoma (4), and cancer pain (5). Oral THC also reliably and dose dependently attenuated craving and cannabis withdrawal during abstinence from daily cannabis smoking (6–10), suggesting potential efficacy as an adjunct therapy in the treatment of cannabis dependence.

Objective monitoring of cannabis relapse and medication compliance is critical during treatment of cannabis use disorders. Clinical use of urine toxicology testing to differentiate oral THC medication compliance from smoked cannabis has been difficult (11). Oral fluid (OF) is a biological matrix for cannabinoid testing with multiple advantages for drug-testing programs (12). Understanding cannabinoid OF disposition following controlled oral and smoked cannabinoid ingestion is essential for guiding the development of OF as a test matrix for clinical use in substance abuse treatment settings and could also assist with interpreting results in investigations of driving under the influence of drugs (13–14) and drug testing in the workplace (15–16). Two prior studies have evaluated OF cannabinoid testing following oral THC administration. In the first study, THC decreased and 11-nor-9-carboxy-THC (THCCOOH) increased during administration of 37 doses (20 mg each) of oral THC with...
increasing frequency over 8 days (17). In the second study, THC OF concentrations significantly decreased over time after single 5- and 15-mg oral THC doses (18). THCCOOH OF concentrations were dose dependent (greater after 15- than 5-mg oral THC and placebo doses), indicating that oral THC contributed to THCCOOH OF concentrations, but THCCOOH changes over time were significantly confounded by THCCOOH baseline concentrations from previously self-administered smoked cannabis and low THC doses (18).

THC is the primary analyte in OF after cannabis smoking/inhalation, with initial concentrations often much higher than those in blood owing to extensive oral cavity contamination from THC-laden smoke (19–20). After a single smoked cannabis cigarette, OF THC detection windows can reach 72 h (19, 21–24). We recently reported a median OF THC detection window of 24 h, with occasional positives for up to 28 days in chronic cannabis smokers during ≤33 days of abstinence (25).

Oral THC doses and frequency of administration vary according to treatment goals. The recommended initial oral THC dose for appetite stimulation is 2.5–5 mg/day and for antiemesis 20–30 mg/m2 (1); higher doses of 30–120 mg/day were effective in treating cannabis withdrawal in habitual cannabis smokers (8, 10, 26–27), although relapse rates were not affected (7, 27). Thus, OF cannabinoid disposition after different oral THC dosing regimens is of particular interest in evaluating THC and THCCOOH OF concentrations to monitor compliance and relapse in cannabis smokers during oral THC pharmacotherapy.

Finding relationships between cannabinoid OF concentrations and clinical outcomes could further expand the applicability of OF testing. Cannabis-related pharmacological conditions may change cannabis smoking topography, which, in turn, could affect cannabinoid OF concentrations. There is evidence that tolerance development in chronic cannabis smokers may lead to higher THC concentrations in initial OF samples (19, 22, 28). Therefore, in this study we examined OF THC, THCCOOH, cannabinol (CBN), and cannabidiol (CBD) disposition during daily administration of 0, 30, 60, and 120 mg oral THC for 5 days and following a single smoked cannabis challenge on the last day of each medication session. We characterized time courses, last detection times with different cutoff criteria, and oral THC dose effects on OF cannabinoids after smoked cannabis intake. Each medication session was preceded by periods of supervised ad libitum cannabis smoking, enabling us to evaluate OF cannabinoid elimination profiles after multiple smoked doses. Lastly, we investigated whether oral THC dosing impacted OF cannabinoid concentrations after programmed exposure to smoked cannabis following 4.5 days of monitored abstinence from smoking.

Materials and Methods

PARTICIPANTS

Cannabis smokers, at least 18 years old, were recruited via newspaper advertisements and flyers distributed in the Baltimore area. Inclusion criteria were self-reported cannabis smoking on ≥25 days per month during the past 3 months, negative urine immunoassay test for drugs other than cannabinoids, negative breath alcohol test, negative urine pregnancy test on admission, reported ≥2 cannabis withdrawal symptoms of at least moderate severity in prior periods of abstinence, an eighth grade or higher level of education, and demonstrated literacy. Participants were excluded if they received psychoactive medication, met clinical criteria for Axis I psychiatric disorders [Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)] other than cannabis or nicotine dependence, were seeking treatment for cannabis-related problems or using cannabis for medical purposes, or had donated blood within 6 weeks of admission. Participants also were required to have no history of seizure, severe head trauma, dementia, or other condition associated with significant cognitive impairment; heart attack or major cardiac event in the prior 6 months; abnormal electrocardiogram; or allergy to sesame oil (dronabinol capsule ingredient). The Johns Hopkins Medicine Institutional Review Board approved the study and participants provided written informed consent.

STUDY DESIGN

Participants resided on the closed Johns Hopkins Bayview Behavioral Pharmacology Research Unit for 51 days. This within-subject crossover study examined dose-dependent clinical outcomes to assess oral THC’s tolerability and efficacy for cannabis dependence treatment (8). In the present report, OF cannabinoid disposition during short-term oral THC maintenance and following smoked cannabis administration was characterized. Days 1–4 of the study served as a baseline, during which participants became acclimated to the research unit and received training on study procedures and neurocognitive tasks; ad libitum cannabis smoking was allowed from 12:00 to 23:00 each day. Four 5-day oral THC sessions (days 5–9, 19–23, 33–37, and 47–51) followed during which oral synthetic THC was administered at 9:00, 14:00, and 19:00 each day. Participants received, in a counterbalanced order, 1 of 4 doses of oral THC: 30 mg/day [10 mg 3 times a day (tid)], 60 mg/day [20 mg tid], 120 mg/day [40 mg tid], or placebo (0 mg tid). Cannabis smoking was prohibited except...
on the fifth day (days 9, 23, 37, and 51) when participants were administered 5 controlled puffs of smoked cannabis at approximately 11:30. The paced puff procedure consisted of 5-s inhalation, 10-s breath holding, and 40-s inter puff interval. Each oral THC session was separated by 9 days of ad libitum cannabis smoking between 12:00 and 23:00 h daily (days 10–18, 24–32, and 38–46). Cannabis cigarettes for baseline, 3 ad libitum cannabis smoking sessions, and the smoked cannabis challenges were obtained from the National Institute on Drug Abuse; mean (SD) cannabis cigarette weight was 0.9 (0.07) g and contained 5.9% (0.3%) THC, 0.36% (0.04%) CBN, and 0.01% (0.00%) CBD, yielding approximately 53.1, 3.2, and 0.1 mg per cigarette, respectively.

**OF sample collection and analysis**

Eleven and 12 OF samples were collected on the first and last days of each oral THC session, respectively, from 9:00 to 22:00. On the second, third, and fourth days, 3 OF samples were collected at 9:00, 19:00, and 22:00. Of 32 OF samples obtained in each oral THC session, 10 were collected after paced smoking of a cannabis cigarette on the last day. The OF collection schedule is illustrated in Fig. 1. OF was collected with the Quantisal™ device (Immunalysis); an absorptive pad was placed into a plastic tube containing 3 mL of PBS buffer. The tube was refrigerated for at least 24 h before decanting into a Nunc® cryotube and storage at −20 °C until analysis.

THC, CBD, CBN, 11-hydroxy-THC (11-OH-THC), and THCCOOH in OF were quantified according to a modified version of our previously published method (29). Minor changes improved method productivity: (a) positive pressure was used in place of vacuum for more efficient elution and evaporation of the washing solvent residue; (b) 0.4 mL hexane was added to the solid-phase extraction column before loading the first elution solvent to reduce a chromatographic interference with THCCOOH that occurred after many sample injections but was resolved with the addition of hexane; (c) gas chromatography column configuration for neutral cannabinoid analysis was changed to a DB-1MS (Agilent Technologies) as the primary column and ZB-50 (Phenomenex) as the secondary column, following our plasma method (30); (d) limits of quantification (LOQ) for 11-OH-THC and THCCOOH were increased to 1 μg/L and 15 ng/L from 0.5 μg/L and 7.5 ng/L, respectively; and (e) low and medium QC concentrations for THCCOOH were increased to 75 and 120 ng/L, respectively. The LOQs remained the same at 0.5 μg/L for CBD and THC and 1 μg/L for CBN. The modified method’s performance was comparable to that of the original method with 0.8–6.6 %CV (n = 5 per each QC level) intra assay imprecision, 1.8–11.8 %CV (n = 10 per QC; 6 assays) inter assay imprecision, 47.0%–101.6% extraction efficiency of day 0 and day 3 analytes, and 92.2%–107.2% (n = 15 per QC level) analyte recovery.

**Data analysis**

IBM SPSS Statistics version 20 and Microsoft Excel 2007 were used for statistical evaluation. Cannabinoid concentrations were nonnormally distributed, as determined by the Kolmogorov–Smirnov test and Normal Q–Q plot. Accordingly, the effects of time (Δtime calculated from actual collection and last smoking times), dose, and baseline concentrations (if applicable) on cannabinoid concentrations post-dose were evaluated with generalized linear mixed models after log transformation of the data and multiple comparisons adjusted with sequential Bonferroni correction. Values below the LOQ were considered as one-tenth the LOQ for all statistical analyses. Results with 2-tailed P < 0.05 were considered significant.
Eleven chronic cannabis smokers (ages 25–52 years; 1 female) completed the 51-day study, each providing 132 OF samples at 22:00 the evening before and throughout each oral THC session (Fig. 1). Seven OF samples and participant P’s OF samples during the 60-mg oral THC session were not included in data analysis due to missed collections or loss during extraction. Owing to study design complexity, OF was collected at scheduled time points rather than relative time points from last smoking. Baseline OF collections for oral THC sessions occurred at 22:00, 1 h before the end of ad libitum smoking. Thus, times were calculated with respect to last smoking occurring at/before 22:00 for baseline samples and 23:00 for samples during oral THC sessions. Time variation among participants since last smoking for each collection time is described in Table 1 in the Data Supplement that accompanies the online version of this report athttp://www.clinchem.org/content/vol59/issue12. Actual times were used for statistical and pharmacokinetic analyses, but theoretical times were included in the figures and text for clarity. Participants’ demographics and cannabis-smoking history are provided in Table 1.

### Table 1. Demographics and self-reported cannabis use history of 11 chronic, frequent cannabis smokers.

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*aInformation from the screening assessments collected at a mean of 23 (range 4–49) days prior to study admission.

*bAccording to criteria specified by the DSM-IV.

*cCalculated from the total number of times used in past 30 days.

*dAA, African American.

## Results

Eleven chronic cannabis smokers (ages 25–52 years; 1 female) completed the 51-day study, each providing 132 OF samples at 22:00 the evening before and throughout each oral THC session (Fig. 1). Seven OF samples and participant P’s OF samples during the 60-mg oral THC session were not included in data analysis due to missed collections or loss during extraction. Owing to study design complexity, OF was collected at scheduled time points rather than relative time points from last smoking. Baseline OF collections for oral THC sessions occurred at 22:00, 1 h before the end of ad libitum smoking. Thus, times were calculated with respect to last smoking occurring at/before 22:00 for baseline samples and 23:00 for samples during oral THC sessions. Time variation among participants since last smoking for each collection time is described in Table 1 in the Data Supplement that accompanies the online version of this report at http://www.clinchem.org/content/vol59/issue12. Actual times were used for statistical and pharmacokinetic analyses, but theoretical times were included in the figures and text for clarity. Participants’ demographics and cannabis-smoking history are provided in Table 1.

### OF CANNABINOIDS DURING 5-DAY ORAL THC ADMINISTRATION

On the last ad libitum smoking day before each medication session, participants smoked median (range) 20 (1–40) cannabis cigarettes, with no significant differences ($P = 0.759$; 1-way ANOVA) among 0-, 30-, 60-, and 120-mg oral THC sessions. Oral THC minimally contributed to THC OF concentrations. THC OF concentrations significantly covaried with baseline concentrations ($F_{1936} = 156.12, P < 0.001$) and decreased over time ($F_{1936} = 2149.04, P < 0.001$), with changes not significantly affected by oral THC dose ($F_{1936} = 1.26, P = 0.289$). Maximum concentrations primarily occurred at baseline, with medians of 92.8–320 $\mu$g/L for the 4 oral THC sessions, collected at a median of 0.7–2.4 h postsmoking. Likewise, during all (active and placebo) oral THC sessions, concentrations decreased to $78.2 \mu$g/L (medians 4.4–6.7 $\mu$g/L; 73%–100% positive), $33.2 \mu$g/L ($<$LOQ–0.9 $\mu$g/L; 45%–64% positive), and $1.4 \mu$g/L ($<$LOQ; 9%–27% positive) by 24, 48, and 72 h after the end of smoking, respectively (Fig. 2). Two participants in the placebo session and 2 in the 120-mg session were still THC positive, with concentrations of 0.5–1.1 $\mu$g/L in the last OF samples collected approximately 109 h postsmoking.

CBN similarly decreased over time ($F_{1936} = 527.72, P < 0.001$) and was significantly dependent on baseline concentrations ($F_{1936} = 139.07, P < 0.001$) but not oral THC dosage ($F_{1936} = 0.45, P = 0.714$). CBN also was generally highest at baseline, with concentrations 10-fold lower than THC (medians 14.4–22.0 $\mu$g/L), decreasing to $\leq 7.6 \mu$g/L (10%–36% posi-
positive) by 24 h postsmoking (Fig. 2). No participant was positive for CBN beyond 69 h. Only 3% of OF samples were positive for CBD, with most positive results at baseline. After oral THC administrations, CBD concentrations never exceeded 2.5ng/L and no participant was CBD positive beyond 19 h after smoking.

In contrast, OF THCCOOH significantly depended on oral THC dose ($F_{3936} = 23.94$, $P < 0.001$) and baseline concentrations ($F_{1936} = 74.97$, $P < 0.001$) after controlling for time (Fig. 2). Unlike parent cannabinoids, THCCOOH concentrations did not change over time after 30 ($F_{1237} = 0.36$; $P = 0.549$) and 60 ($F_{1217} = 2.42$; $P = 0.122$) mg oral THC, but significantly decreased after placebo ($F_{1239} = 38.79$; $P < 0.001$). THCCOOH in all 3 sessions covaried with baseline concentrations ($P$ values <0.001). However, after 120 mg oral THC, OF THCCOOH trended higher over time ($F_{1237} = 2.96$; $P = 0.086$) and baseline effect was no longer significant ($P = 0.119$), suggesting an increased contribution of oral THC to THCCOOH concentrations. Ninety-three percent of OF samples were THCCOOH positive, with 73%–100% of participants positive 109 h postsmoking at the last collection time of the 4 oral THC sessions. Even with daily 120-mg oral THC dosing, THCCOOH never exceeded 1274 ng/L.

Cannabinoid last detection times during oral THC sessions were evaluated with 7 different cannabinoid cutoffs (Table 2). Delta times were calculated with respect to the last ad libitum smoking time before oral THC dosing. THCCOOH/THC $\leq 4$ng/g and THC $\geq 2$ng/L + CBD $\geq 0.5$ng/L generally limited detection windows to 24 h postsmoking, whereas most participants were positive for 109 h, with a THCCOOH cutoff of $\geq 20$ ng/L. The other cutoffs, including THC $\geq 2$ng/L with and without THCCOOH and CBN generally were positive for up to 72h.

**OF CANNABINOIDS AFTER SMOKED CANNABIS CHALLENGE**

On the last (fifth) day of each oral THC session, participants inhaled 5 puffs of cannabis, with controlled inhalation, hold, and interpuff intervals. Cannabinoid concentration changes for 10.5 h after smoked cannabis are illustrated in Fig. 3, with pharmacokinetic characteristics listed in Table 3. As expected, THC ($F_{1431} = 409.24$; $P < 0.001$), CBN ($F_{1431} = 355.06$; $P < 0.001$), and THCCOOH ($F_{1411} = 23.39$; $P < 0.001$) significantly decreased over time after smoking. Interestingly,
not just THCCOOH ($F_{441} = 5.46; P < 0.001$), but also THC ($F_{443} = 3.06; P = 0.028$) and CBN ($F_{443} = 3.45; P = 0.017$) showed significant oral THC dose effects. Compared to placebo, THC concentrations after smoked cannabis challenge were significantly higher ($r = 0.347; P = 0.004$) in the 30-mg oral THC session and showed an increasing trend ($r = 0.228; P = 0.061$) in the 120-mg oral THC session. CBN also tended to be higher after 30 and 120 mg oral THC compared to placebo ($r = 0.299, P = 0.007; r = 0.299, P = 0.005$, respectively) and showed an increasing trend after 60 mg oral THC ($r = 0.171, P = 0.089$). THCCOOH showed significant dose-dependent increases compared to placebo after smoked cannabis challenge ($r \geq 0.132, P \leq 0.005$). Time and oral THC dose effects on CBN were not evaluated owing to low CBN detection rates (6%).

11-OH-THC (1.3–8.3 μg/L) was detected in only 11 OF samples (0.8%) throughout the study within 0.0–1.6 h postsmoking, when THC concentrations were high (379–13518 μg/L).

**Discussion**

Five days of 30-, 60-, and 120-mg oral THC doses per day led to more evident dose-dependent increases in THCCOOH OF concentrations than after single 5- and 15-mg oral THC doses (18). THCCOOH OF concentrations appeared to achieve plateaus within 109 h during 30- and 60-mg oral THC daily administrations, leading to nonsignificant changes over time. However, 120 mg oral THC/day dosing increased OF THCCOOH over time, possibly because of THC drug bioavailability exceeding its elimination rate. The detection rate of another metabolite, 11-OH-THC, was low (0.8%); an analytically more sensitive quantification method is needed to fully evaluate OF 11-OH-THC disposition.

THC, CBN, and CBD elimination profiles in OF also were observed during 109 h of cannabinoid abstinence (placebo oral THC session) and during multiple oral THC administrations. THC, CBN, and CBD OF concentrations decreased over time with no significant differences between placebo and active doses; the results point to the previous ad libitum smoking as the primary source because oral THC minimally affected parent cannabinoid concentrations in OF. As we and others showed (19, 21, 23–25, 31), the rapid decline from high THC OF concentrations within a few hours after smoking was followed by a slower elimination that could last several days in chronic cannabis smokers; similarly, in the present study, up to 13 518 μg/L OF THC decreased to 11.3 μg/L within 24 h of smoking abstinence. Only 9%–27% of participants were THC positive, with concentrations ≤1.4 μg/L by 72 h, the others being negative at this time point. Four samples contained 0.5–1.1 μg/L THC 109 h postsmoking. CBN’s detection window was up to 69 h, much longer than the ≤24 h observed in our previous research (19). This difference presumably reflected the CBN concentrations in the cigarettes smoked (0.36% vs 0.21%), although 70%–82% of participants in the current...
study were negative by 24 h. On the other hand, CBD (0.01% vs 0.25%) was rarely detected in the current OF samples, whereas concentrations and detection rates were similar to CBN in the previous research (19). These results confirm that different cannabis plant strains can alter OF cannabinoid detection rates. Additionally, daily oral THC dosing and/or frequent cannabis smoking during the 9-day ad libitum smoking periods before medication sessions further lengthened cannabinoid detection windows (Table 2) compared to prior findings during extended cannabis abstinence and with the same cutoff criteria (25).

After 4.5 days of 0-, 30-, 60-, or 120-mg oral THC dosing, participants smoked 5 puffs of a cannabis cigarette according to a paced procedure. THC and CBN OF concentrations after smoked cannabis correlated with preceding oral THC dose. Because parent OF cannabinoids are directly related to the extent of oral mucosal contamination from cannabis smoke, the results suggest that the oral THC dose may have influenced participants’ smoking behavior. Controlled cannabis/THC administration studies documented that (a) individuals titrate their dose during cannabis smoking (32–33), (b) tolerance to subjective intoxication developed after multiple oral THC doses (34–36), and (c) tolerance to THC influenced effects of smoked cannabis (27, 35). We hypothesize that participants developed dose-related tolerance to the subjective effects of cannabis during oral THC dosing and consequently changed their smoking topography to achieve the desired “high” of smoked cannabis. Thus, tolerance developed during active oral THC and/or diminished during placebo dosing may have affected THC and CBN OF concentrations but not subjective effects after smoked cannabis (8) because participants titrated their smoked dose to achieve comparable drug effects.

In the present study, we dictated inhalation and breath-hold times and interpuff interval; however, inhalation volume was not controlled. Variable inhalation volume could have produced significant differences in plasma THC concentrations and subsequent subjective effects (37). A similar study design but with an ad libitum smoking challenge might corroborate our hypothesis that THC and CBN OF concentrations could increase with tolerance to smoked cannabis intoxication. On the other hand, dose titration did not appear sufficient to overcome tolerance to drug-induced physiological effects; our participants still ex-
hibited attenuation of cannabis-induced increased heart rate after 60 and 120 mg oral THC (8). Heishman et al. also found that titrating smoked cannabis with different THC potencies led to no significant dose effects on subjective responses but heart rate and neurocognitive performance were dose dependent (33). As expected, the OF THCCOOH increase after smoked cannabis was smaller than that for THC and CBN, but dose effects on OF THCCOOH were highly significant.

We confirmed previous research showing that OF THC, CBD, and CBN could be used to identify relapses to cannabis smoking during oral THC pharmacotherapy for cannabis dependence. These parent cannabinoid concentrations continued to decrease over time during up to 120 mg/day oral THC administration. Thus, sudden increases in OF parent cannabinoid concentrations indicate relapse to smoked cannabis. Additionally, incorporating OF THCCOOH, CBD, CBN, and THC cutoffs may shorten cannabis detection windows to identify recent smoked intake. THCCOOH OF concentrations were dose dependent during 30, 60, and 120 mg oral THC administrations for 5 days, but time-dependent increase occurred only with a 120-mg dose. Lastly, we characterized dose effects of oral THC on OF cannabinoid disposition after smoked cannabis. OF THC, CBN, and THCCOOH concentrations after the smoked cannabis challenge significantly varied depending on the preceding oral THC doses, indicating

Table 3. Median (range) OF cannabinoid pharmacokinetic parameters (n = 11) following the 5-puff smoked cannabis challenge for approximately 10.5 h on the fifth day of the oral THC medication sessions (0, 30, 60, or 120 mg per day).

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<td>THC Cmax, µg/L</td>
<td>&lt;LOQ (&lt;LOQ–1.1)</td>
<td>&lt;LOQ (&lt;LOQ)</td>
<td>&lt;LOQ (&lt;LOQ)</td>
<td>&lt;LOQ (&lt;LOQ–0.6)</td>
</tr>
<tr>
<td>Cmax, µg/L</td>
<td>43.6 (1.6–9330)</td>
<td>75.2 (13.8–12829)</td>
<td>174.8 (20.0–1514)</td>
<td>111.5 (13.3–5973)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.5 (0.4–0.8)</td>
<td>0.4 (0.2–0.8)</td>
<td>0.4 (0.0–0.6)</td>
<td>0.5 (0.2–0.8)</td>
</tr>
<tr>
<td>Clast, µg/L</td>
<td>1.0 (0.5–24.3)</td>
<td>0.9 (0.7–20.6)</td>
<td>1.7 (0.5–5.7)</td>
<td>0.8 (0.5–10.1)</td>
</tr>
<tr>
<td>Tlast, h</td>
<td>7.7 (1.3–10.8)</td>
<td>10.3 (3.6–10.8)</td>
<td>9.2 (2.3–10.7)</td>
<td>8.9 (5.6–10.8)</td>
</tr>
<tr>
<td>THCCOOH Cmax, µg/L</td>
<td>55.7 (&lt;LOQ–91.8)c</td>
<td>97.4 (40.1–191.0)</td>
<td>170.9 (32.2–359.7)</td>
<td>224.9 (&lt;LOQ–354.2)</td>
</tr>
<tr>
<td>Cmax, µg/L</td>
<td>92.1 (25.6–209.5)</td>
<td>171.8 (75.0–1431)</td>
<td>248.3 (43.7–1183)</td>
<td>472.1 (88.3–1137)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.7 (0.4–5.9)</td>
<td>1.4 (0.2–9.1)</td>
<td>1.2 (0.0–10.7)</td>
<td>4.4 (0.2–9.2)</td>
</tr>
<tr>
<td>Clast, µg/L</td>
<td>33.7 (15.6–67.2)</td>
<td>89.9 (22.7–163.1)</td>
<td>141.4 (19.6–804.3)</td>
<td>214.7 (16.1–619.4)</td>
</tr>
<tr>
<td>Tlast, h</td>
<td>10.7 (2.6–10.8)</td>
<td>10.6 (10.3–10.8)</td>
<td>10.6 (8.9–10.8)</td>
<td>10.7 (10.0–10.8)</td>
</tr>
<tr>
<td>CBN Cmax, µg/L</td>
<td>7.2 (2.4–399.9)</td>
<td>16.0 (1.7–400.9)</td>
<td>16.2 (3.6–135.0)</td>
<td>36.9 (1.3–352.0)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.5 (0.4–0.8)</td>
<td>0.4 (0.2–0.8)</td>
<td>0.4 (0.0–0.6)</td>
<td>0.5 (0.2–0.8)</td>
</tr>
<tr>
<td>Clast, µg/L</td>
<td>1.3 (1.1–5.8)</td>
<td>2.3 (1.1–13.3)</td>
<td>1.7 (1.0–4.0)</td>
<td>1.4 (1.2–5.0)</td>
</tr>
<tr>
<td>Tlast, h</td>
<td>1.3 (0.5–10.7)</td>
<td>1.4 (0.4–10.7)</td>
<td>1.6 (0.8–5.9)</td>
<td>3.5 (0.8–10.6)</td>
</tr>
<tr>
<td>CBD Cmax, µg/L</td>
<td>23.7c</td>
<td>3.8 (0.5–40.8)c</td>
<td>1.7 (0.8–3.5)c</td>
<td>2.5 (1.0–14.0)c</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.5</td>
<td>0.3 (0.3–0.5)</td>
<td>0.4 (0.0–0.6)</td>
<td>0.5 (0.2–0.6)</td>
</tr>
<tr>
<td>Clast, µg/L</td>
<td>0.7</td>
<td>1.2 (0.5–3.8)</td>
<td>0.9 (0.7–2.4)</td>
<td>1.8 (1.0–9.7)</td>
</tr>
<tr>
<td>Tlast, h</td>
<td>4.3</td>
<td>0.3 (0.3–4.2)</td>
<td>0.5 (0.0–0.7)</td>
<td>0.5 (0.2–1.1)</td>
</tr>
</tbody>
</table>

*Thc<sub>base</sub>, baseline OF concentration for smoked cannabis challenge approximately 109 h after the last ad libitum smoking; C<sub>max</sub>, maximum concentration; T<sub>max</sub>, time of C<sub>max</sub>; C<sub>last</sub>, last sample concentration at ≧LOQ (0.5 µg/L for THC and CBD, 15 ng/L for THCCOOH, and 1 µg/L for CBN); T<sub>last</sub>, time of C<sub>last</sub>.

*Thc<sub>base</sub>, baseline OF concentration for smoked cannabis challenge approximately 109 h after the last ad libitum smoking; C<sub>max</sub>, maximum concentration; T<sub>max</sub>, time of C<sub>max</sub>; C<sub>last</sub>, last sample concentration at ≧LOQ (0.5 µg/L for THC and CBD, 15 ng/L for THCCOOH, and 1 µg/L for CBN); T<sub>last</sub>, time of C<sub>last</sub>.

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possible relationships among OF cannabinoid concentrations, smoking behavior, and tolerance to oral THC effects. These results suggest that OF cannabinoid testing could be a promising research and monitoring tool in the development and management of oral THC pharmacotherapy.

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Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

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