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Predictive model accuracy in estimating last Δ^9 -tetrahydrocannabinol (THC) intake from plasma and whole blood cannabinoid concentrations in chronic, daily cannabis smokers administered subchronic oral THC*

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Abstract

Background—Determining time since last cannabis/ Δ^9 -tetrahydrocannabinol (THC) exposure is important in clinical, workplace, and forensic settings. Mathematical models calculating time of last exposure from whole blood concentrations typically employ a theoretical 0.5 whole blood-to-plasma (WB/P) ratio. No studies previously evaluated predictive models utilizing empirically-derived WB/P ratios, or whole blood cannabinoid pharmacokinetics after subchronic THC dosing.

Methods—Ten male chronic, daily cannabis smokers received escalating around-the-clock oral THC (40–120 mg daily) for 8 days. Cannabinoids were quantified in whole blood and plasma by two-dimensional gas chromatography-mass spectrometry.

Results—Maximum whole blood THC occurred 3.0 h after the first oral THC dose and 103.5 h (4.3 days) during multiple THC dosing. Median WB/P ratios were THC 0.63 (n=196), 11-hydroxy-THC 0.60 (n=189), and 11-nor-9-carboxy-THC (THCCOOH) 0.55 (n=200). Predictive models utilizing these WB/P ratios accurately estimated last cannabis exposure in 96% and 100% of specimens collected within 1–5 h after a single oral THC dose and throughout multiple dosing, respectively. Models were only 60% and 12.5% accurate 12.5 and 22.5 h after the last THC dose, respectively.

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Contributors: Authors Huestis, Goodwin, Schwilke and Gorelick designed the study and wrote the protocol. Authors Huestis, Gorelick, Goodwin, Schwilke, Karschner and Schwoppe managed collection of data and data management. Author Karschner undertook the statistical analysis and wrote the first draft. All authors contributed to and have approved the final manuscript.

Author Disclosures

Conflict of Interest: None of the authors has any conflicts of interest to disclose.

Conclusions—Predictive models estimating time since last cannabis intake from whole blood and plasma cannabinoid concentrations were inaccurate during abstinence, but highly accurate during active THC dosing. THC redistribution from large cannabinoid body stores and high circulating THCCOOH concentrations create different pharmacokinetic profiles than those in less than daily cannabis smokers that were used to derive the models. Thus, the models do not accurately predict time of last THC intake in individuals consuming THC daily.

Keywords

Δ^9 -tetrahydrocannabinol; chronic; cannabis; predictive models; cannabinoids; marijuana

1. INTRODUCTION

Knowledge of the time interval since last cannabis use is important in clinical, forensic, and workplace contexts. If there is suspicion of driving under the influence of cannabis or cannabis intake prior to an occupational accident, blood, plasma or serum samples are collected to determine cannabinoid concentrations. Concentrations of Δ^9 -tetrahydrocannabinol (THC) and its acid metabolite, 11-nor-9-carboxy-THC (THCCOOH), provide insight into the time of last THC consumption. Models for estimating time of last cannabis/THC intake were developed in the author's laboratory based on plasma data collected after controlled smoked cannabis administration (Huestis et al., 2005; 2006; 1992), while accident investigations and postmortem analyses are primarily conducted on whole blood. Thus, implementation of predictive models, and interpretation of cannabinoid concentrations in general, requires accurate whole blood (WB) to plasma (P) ratios to enable application of plasma-derived models to whole blood data. Previous studies of predictive models utilized the generally accepted WB/P ratio of 0.5. We are not aware of any previous model evaluations that employed empirically derived WB/P ratios. This may be due, in part, to the fact that few controlled drug administration studies simultaneously analyze both whole blood and plasma specimens.

Another limitation of existing predictive models based on plasma data, whether validated with oral (Huestis et al., 2006) or multiple smoked cannabinoid administration (Huestis et al., 2005), is that they were developed in less than daily cannabis smokers. Therefore, the models' application was recommended only for specimens from occasional or less than daily cannabis smokers. This was due to limited knowledge of cannabinoid elimination in chronic, daily cannabis smokers, and how residual THC and THCCOOH concentrations in this population might affect predictions. We recently documented measureable THC in whole blood (Karschner et al., 2009a) and plasma (Karschner et al., 2009b) for at least 7 days after cannabis cessation in chronic, daily smokers who consumed up to 10 joints/blunts per day for up to 22 years.

A study of spontaneous and antagonist-elicited cannabis withdrawal in chronic, daily cannabis smokers (Gorelick et al., 2011) provided an opportunity to characterize whole blood THC, 11-hydroxy-THC (11-OH-THC), and THCCOOH pharmacokinetics and WB/P cannabinoid ratios in simultaneously collected specimens. Specimens were collected for 19.5 h of abstinence from previously self-administered smoked cannabis, after a single 20-mg oral THC dose, during administration of up to 120 mg oral THC per day for eight days, and for 22.5 h after the last oral THC dose. Now, for the first time, data are available to test the accuracy of predictive models in individuals who had a large THC body burden from previously self-administered chronic, daily cannabis smoking, and who received subchronic around-the-clock oral THC while abstaining from smoked cannabis. Furthermore, for the first time predictive models utilized empirically-derived WB/P cannabinoid ratios.

2. METHODS

2.1. Participants

Inclusion criteria for participants included ages 18–45 years, cannabis use history for 1 year, daily smoking (on average) for 3 months, and cannabinoid-positive urine specimen within 30 days prior to enrollment. Participants with a history of clinically significant medical or psychiatric disease, clinically significant illness within 2 weeks of study initiation, current DSM-IV axis I disorder (other than cannabis, caffeine or nicotine dependence, or simple phobia), current physical dependence (other than for cannabis, nicotine or caffeine), or clinically significant adverse event associated with cannabis intoxication or withdrawal were excluded. Additional exclusion criteria included IQ <85, consumption of 6 alcoholic drinks/day 4 times/week, blood donation within 30 days, sesame oil allergy, or interest in drug treatment.

Eligible participants provided written informed consent to a protocol approved by the Institutional Review Boards of the National Institute on Drug Abuse, University of Maryland Baltimore, and Maryland Department of Health and Mental Hygiene.

2.2. Study Design

20 mg oral synthetic THC (Marinol®; Unimed Pharmaceuticals, Marietta, GA) was administered as an escalating dose: twice on Day 1 (the day after admission to a closed research unit) and every 3.5–8 h thereafter for a total of 8 days (40–120 mg/day) to standardize THC tolerance (Supplemental Table 1¹). Dosing began at 1500 on Day 1, 17.5–21 h after admission (time 0), with the last of 37 doses administered at 0930 on day 8 (162.5 h). Dosing frequency, rather than dose amount, was increased to minimize adverse events reported after higher single oral doses (Haney et al., 1999; Jones and Benowitz, 1976).

Whole blood (3 mL) was collected in sodium heparin at study admission, twice before and every hour for 5 h after the first dose to evaluate single dose THC pharmacokinetics (Supplemental Table 1²). Daily blood collections occurred at approximately 2200 during continuous oral THC dosing. Blood specimens also were collected before and at 2.5, 10.5, 12.5 and 22.5 h after the final oral THC dose. Whole blood for plasma (7 mL) was collected on ice and plasma separated within 2 h. Plasma specimens were collected twice before and every 30 min for 5 h after the first dose, at 1000, 2000, and 2200 daily during around-the-clock dosing and at multiple time points up to 22.5 h following the last dose (Supplemental Table 1³). Specimens were stored at 4°C and analyzed within 2 weeks.

2.3. Specimen Analysis

Whole blood and plasma cannabinoids were solid phase extracted (SPE) and analyzed by two-dimensional gas chromatography mass spectrometry (2D-GCMS) according to previously validated procedures (Lowe et al., 2007; Schwilke et al., 2009b). Briefly, 1 mL whole blood was mixed with 3 mL cold acetonitrile (stored at –20°C) to precipitate proteins. Samples were centrifuged, decanted into 5 mL sodium acetate buffer, mixed and added to 10 mL ZSTHC020 SPE columns (United Chemical Technologies; Bristol, PA, USA). Columns were washed with 3 mL deionized water and 2 mL 0.1 N HCl/acetonitrile (70:30) and dried under vacuum for 15 min. THC, 11-OH-THC and THCCOOH were eluted from SPE columns with 5 mL hexane/ethyl acetate (80:20) and dried under nitrogen. Extracts were derivatized with 25 µL N,O-bis(trimethylsilyl)trifluoroacetamide and 1%

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trimethylchlorosilane at 70°C for 30 min, injected splitless and analyzed in selected ion monitoring mode with 2D-GCMS with cryofocusing. Split calibration curves provided quantification through multiple orders of magnitude, THC 0.25-25, 25-100 ng/mL, 11-OH-THC 0.25-10, 10-75 ng/mL and THCCOOH 0.25-25, 25-100 ng/mL. Inter- and intra-assay imprecision were 14.0% and analytical recovery/bias was 85.0-113%.

2.4. Statistical Analyses

Body mass index (BMI) was calculated as weight (kg)/height (m)². Statistical analyses were performed with SPSS, version 12.0 (SPSS, Inc., Chicago, IL). Because Shapiro-Wilk analyses indicated non-normality, nonparametric Wilcoxon Sign Rank and chi-squared tests were employed for statistical comparisons. Linear regression analysis was employed to evaluate the relationship between model accuracy and increasing abstinence time. Two-tailed $P < 0.05$ was considered statistically significant. Area under the curve (AUC) from 0 to 5.0 h (AUC_{0-5.0 h}) and from 0 to 185.0 h (AUC_{0-185.0 h}) was determined by linear trapezoidal non-compartmental analysis (WinNonlin; Pharsight Corp., Mountain View, CA). Median concentration maximum ($C_{\max}$) and time to $C_{\max}$ ($T_{\max}$) were assessed by determining the $C_{\max}$ and $T_{\max}$ for each participant and then calculating the median $C_{\max}$ and $T_{\max}$ for the group. Similarly, median peak 11-OH-THC/THC and THCCOOH/THC ratios were calculated by determining the maximum ratio for each participant and calculating the median of maximum ratios.

Mathematical equations for estimating time of last cannabis/THC exposure were previously published (Supplemental Table 2⁴; Huestis et al., 2005; 2006; 1992). Times of last use estimates were calculated from THC concentrations (model I) and THCCOOH/THC ratios (model II).

Models I and II were evaluated with empirically determined median WB/P ratio data. As recommended previously (Huestis et al., 2005; 2006), the most accurate results are achieved by combining 95% CI from models I and II. 95% CI for time of last use were determined for each model and the lowest and highest CI utilized. Elapsed times after dosing were compared to the combined CI to determine model accuracy and estimation error. Accuracy (%) was calculated by (number of correct estimates/total number of estimates) $\times$ 100. Over- or underestimates were calculated by the absolute value of the mean calculated error from the CI (actual time-calculated time). Overestimates occurred when actual times were less than the CI lower limit and underestimates occurred when actual times were greater than the CI upper limit.

3. RESULTS

Ten adult males last smoking cannabis within 24 h of admission completed the study (see Table 1 for participant characteristics). Median (range) whole blood cannabinoid concentrations on admission from previously self-administered smoked cannabis were 3.0 ng/mL (1.4-20.3), 1.7 ng/mL (0.8-7.3), and 31.0 ng/mL (12.8-86.9) for THC, 11-OH-THC, and THCCOOH, respectively (Table 1, Figure 1). 12.5 h later, THC and 11-OH-THC concentrations decreased to 2.3 (0.9-5.9) and 0.6 (0.5-3.5) ng/mL, respectively, while THCCOOH concentrations were 27.2 ng/mL (11.2-89.3). 19.5 h after admission, at the time of the first 20-mg oral THC dose, median THC, 11-OH-THC and THCCOOH whole blood concentrations were 2.3 (1.1-6.1), 0.7 (not detected [ND]-2.4), and 16.0 (7.0-47.2) ng/mL. 11-OH-THC ($P=0.008$) and THCCOOH ($P=0.005$) concentrations significantly decreased from admission to 19.5 h, while THC concentrations did not ($P=0.051$). Median percent

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decreases during this time were 20.1% for THC, 72.8% for 11-OH-THC and 47.2% for THCCOOH. Percent decreases did not vary by self-reported cannabis smoked per day.

After a single 20-mg oral THC dose (Figure 1), median $C_{\max}$ occurred at 3 h and were 6.4, 3.4, and 36.6 ng/mL for THC, 11-OH-THC, and THCCOOH, respectively (Table 2). THC ($P=0.007$), 11-OH-THC ($P=0.009$), and THCCOOH ($P=0.007$) concentrations significantly increased between 1 and 2 h following the first oral THC dose. THC ($P=0.005$) and 11-OH-THC ($P=0.022$) concentrations significantly decreased between 3 and 5 h, while THCCOOH concentrations did not ($P=0.059$).

During multiple THC dosing up to 120 mg/day, median whole blood $C_{\max}$ were 16.3 ng/mL at 103.5 h (day 5), 9.8 ng/mL at 103.5 h (day 5), and 120.7 ng/mL at 163.8 h (day 8) after the first dose for THC, 11-OH-THC (Figure 1c), and THCCOOH (Figure 1d), respectively (Table 2). THC concentrations significantly increased between days 2 and 3 ($P=0.047$), when THC dose increased from 80 to 100 mg/day. THCCOOH concentrations also significantly increased when dose escalated from 80 (day 2) to 100 mg/day (day 3) ($P=0.037$).

After the final THC dose, peak whole blood concentrations occurred 2.5 h post-dose for all analytes and then generally decreased until discharge. Whole blood (plasma) maximum THC concentrations were 11.5 (17.8), 6.5 (9.1), 7.2 (7.6), and 5.2 (5.2) at 2.5, 10.5, 12.5, and 22.5 h after the last oral THC dose, respectively. Median concentrations at 22.5 h after the last oral THC dose were 2.5 (1.5-5.2), 1.2 (0.6-4.4), and 85.1 (17.1-191.5) ng/mL for THC, 11-OH-THC and THCCOOH, respectively. Median percent decreases from the final dose (162.5 h) to the last specimen at 185 h were 54.7% for THC, 76.1% for 11-OH-THC and 22.7% for THCCOOH.

3.1. Whole blood metabolite/parent ratios

Whole blood 11-OH-THC/THC ratios significantly decreased ($P=0.017$) between admission and time of first THC dose (Figure 2). After the initial 20-mg dose, 11-OH-THC/THC ratios significantly increased at 2 h ($P=0.028$) and continued to rise until the final oral THC dose at 162.5 h. 11-OH-THC/THC ratios declined following the last oral THC dose. Median peak 11-OH-THC/THC ratios were 1.4 (0.7-1.9) at 162.5 h (Day 8) after the first THC dose. THCCOOH/THC ratios were highly variable during the pre-dose period, gradually increased during repeated dosing, and peaked at the last time point (185 h). Median peak THCCOOH/THC ratios were 36.3 (10.7-119.7) at 173.0 h (Day 8).

3.2. Whole blood/plasma ratios

Median whole blood/plasma (WB/P) ratios on admission ($n = 10$) were 0.61 (0.56-0.74) THC, 0.63 (0.52-0.76) 11-OH-THC, and 0.59 (0.47-0.84) THCCOOH. Inter-individual ratios showed a 30.6% coefficient of variation (CV) for THC, 26.6% for 11-OH-THC, and 24.2% for THCCOOH across all individuals and time points. There were significant differences among participants' WB/P ratios for all analytes ($P<0.001$). Intra-individual ratio CVs ranged from 6.4-59.1, 4.7-56.5, and 4.4-39.3% for THC, 11-OH-THC, and THCCOOH, respectively. Intra-subject paired comparisons revealed THC WB/P ratios were significantly greater than 11-OH-THC ($P<0.001$) and THCCOOH ratios ($P<0.001$), and 11-OH-THC WB/P ratios were significantly higher than THCCOOH ratios ($P<0.001$). Analyte WB/P ratios did not significantly differ ($P>0.05$) during the initial smoked cannabis abstinence, 1-5 h post first oral THC dose, during multiple THC dosing, and after the last THC dose. When combined across all participants and time points, median WB/P ratios were 0.63 (0.3-1.7) THC ($n=196$), 0.60 (0.1-1.3) 11-OH-THC ($n=189$), and 0.55 (0.2-1.5) THCCOOH ($n=200$).

3.3. Predictive models of last THC exposure

Predictive accuracy (Figure 3) based on plasma concentrations was only 10.0% 0.5 h after the first THC dose, with overestimations from 0.1-0.6 h (Figure 4); whole blood was not collected at this time. Over- (Figure 4c) and underestimates (Figure 4a-c) outside 95% CI are displayed in Figure 4. Models were 98.8% accurate 1-5 h after a single THC dose utilizing plasma concentrations, 90.0% with an assumed WB/P ratio of 0.5 (Huestis et al., 2005; 2006), and 96.0% with the empirically-derived median WB/P ratios determined in the present study (0.63 and 0.55 for THC and THCCOOH, respectively). During 37 multiple THC doses, the estimated time of last intake was within the 95% CI 96.6% of the time with plasma concentrations and 100% with both WB/P ratios. Model accuracy significantly decreased ($P=0.018$; $R^2=0.965$) with increasing abstinence time. Accuracy was 100% for plasma and both WB/P ratios 2.5 h after the last dose (Figure 3), decreasing to 20% (underestimates 1.2-14.9 h) for plasma and 12.5% (underestimates 2.2-17.9 h) for both WB/P ratios 22.5 h after the final dose.

4. DISCUSSION

To the best of our knowledge, this is the first study to evaluate the accuracy of estimation models for time since last THC intake utilizing empirically derived (rather than theoretical) WB/P ratios in individuals administered subchronic oral THC. In addition, this is the first study to evaluate the time course of cannabinoid disposition in whole blood and plasma during around-the-clock oral THC dosing and initiation of abstinence in such a population. The models overestimated time of last exposure at the first time point (0.5 h) after a single oral THC dose by as much as 0.6 h (Figure 4a). Although this represents a clear overestimation error in the predictive model, the absolute error may not be as critical for interpreting results in a criminal or occupational case. Residual THCCOOH concentrations from previously smoked cannabis were 4.2 to 13.8-fold higher than residual THC concentrations at this time. We hypothesize that residual THC and THCCOOH concentrations following chronic cannabis smoking combined with THC just beginning to be absorbed from the first administered oral dose resulted in overestimations of time of last use. This differs from the case with cannabis smoking, where cannabinoid absorption after smoking is much more rapid than after oral administration, resulting in immediate concentration increases to much higher C_{max} . One to 5 h after the first oral THC dose, residual THC was a minor contributor to total THC, yielding high accuracy for predictive models with plasma concentrations (98.8%). For predictive models with blood concentrations, utilizing the empirically derived WB/P ratios (0.63/0.55) improved accuracy compared to the previously suggested theoretical ratio (0.5/0.5): 96.0% vs. 90.0%, respectively. Additionally, model accuracy was high during 37 multiple THC doses using plasma (96.6%) and whole blood concentrations with both WB/P ratios (100%).

The models underestimated time of last THC intake in 80% of cases 22.5 h after the last oral THC dose, based on plasma or whole blood concentrations and both WB/P ratios. At this time, there was little cannabinoid contribution from the final THC dose; rather, the primary contributor to total THC was suspected to be residual drug from the body burden of previously self-administered smoked cannabis prior to study entry and the previous 37 controlled oral THC administrations. Evaluating the models with theoretical cannabinoid concentrations revealed that plasma THC concentrations must be 0.35 ng/mL (model I: 95% CI 22.5 h) or plasma THCCOOH/THC concentrations 83.6 (model II: 95% CI 22.5 h) for models to accurately estimate time of last THC dose. Both are highly unlikely within 24 h of abstinence initiation in this cohort due to THC accumulation in the tissues. As recently reported, we observed cannabinoid release into blood for many days after last use in chronic, daily cannabis smokers (Karschner et al., 2009a; 2009b). Therefore, as previously recommended (Huestis et al., 1992), these predictive models are not appropriate for

predicting last cannabis intake in chronic, daily cannabis smokers, as others also suggested (Skopp and Potsch, 2008; Toennes et al., 2008). Although we do not recommend the use of predictive models in this population, this study demonstrates that the models had a high degree of predictive accuracy during subchronic oral THC dosing in recently abstinent chronic, daily cannabis smokers, and may be appropriate for individuals prescribed oral THC for medical reasons.

Maximum cannabinoid concentrations for all analytes after multiple THC doses were almost three-fold higher than following a single 20-mg oral THC dose. When daily THC doses increased from 100 to 120 mg/day on day 5, THC and 11-OH-THC concentrations decreased. As proposed by Schwilke et al. (2009c), repeated oral THC dosing in daily cannabis smokers may induce gastrointestinal THC metabolism, resulting in lower concentrations later in the dosing regimen. Although these individuals were chronic, daily cannabis smokers at the time of study initiation and hepatic metabolism was expected to be at steady state, oral ingestion was uncommon, suggesting that gastrointestinal metabolism might be inducible with chronic oral THC exposure.

This study has several limitations. Cannabis is typically used by the smoked route both recreationally and medically, but oral cannabis and THC are prescribed medically around the world (Gorter RW, 2005; Hagenbach et al., 2006; Lynch et al., 2006; Smith, 2010) and also sometimes taken recreationally (André C, 2006; Chaudry HR, 1991). Aside from decreased bioavailability, delayed peak cannabinoid concentrations, and greater 11-OH-THC concentrations via the oral route, both oral and smoked THC routes of administration have comparable pharmacokinetic parameters after a few hours. Thus, our findings, derived from subchronic oral THC administration, would be generally applicable to smoked cannabis. A second limitation was the small sample size, which limits statistical power. A third limitation was the presence of residual cannabinoid concentrations (whole blood THC at admission 1.4 ng/mL) from prior self-administered smoked cannabis before the first oral THC dose, which obscured the accuracy of the predictive models at the earliest (0.5 h) time point. However, this was unavoidable, given that chronic, daily cannabis smokers were needed to achieve the scientific objectives of the primary study, viz., to evaluate antagonist-elicited and spontaneous cannabis withdrawal (Gorelick et al., 2011). However, this is also an advantage, as this design provided the first opportunity to test the accuracy of the predictive models after subchronic oral THC dosing in recently abstinent chronic, daily cannabis smokers. A further advantage was specimen analysis within 2 weeks of collection following storage at 4°C, rather than after extended frozen storage. Schwilke et al. (2009a) examined cannabinoid stability in fortified whole blood specimens and found that cannabinoids were stable at 4°C for two weeks in fortified specimens, but decreased >20% when stored at -20°C for the same period.

5. Conclusions

An accurate predictive model to determine the time of last exposure to cannabis or THC is important in clinical, workplace, and forensic contexts, although the degree of accuracy needed may vary with the context. For example, in a drug abuse treatment setting, a positive test may trigger significant consequences, regardless of the time of last exposure, whereas accuracy to within minutes may be important in the context of an accident or crime. These data reaffirm our recent research (Karschner et al., 2009a; 2009b) documenting that low concentrations of THC in whole blood and plasma do not necessarily indicate recent THC exposure. Although plasma and whole blood concentrations and WB/P data predicted time of last THC exposure with acceptable accuracy after single and during multiple oral THC doses, the models were inaccurate during extended abstinence due to residual THC and THCCOOH concentrations. These data document under controlled conditions that predictive

models for the estimation of time of last THC exposure are not applicable to individuals consuming oral THC on a daily basis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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After two 20-mg oral THC doses (a and b) and after multiple 20-mg oral THC doses over 8 days (last dose at 162.5 h) (c and d). Arrows in panels c and d indicate when 80 mg (4x/day), 100 mg (5x/day) and 120 mg (6x/day) were administered. The final dose was administered at 162.5 h.

Figure 1. Median (n=10) whole blood Δ^9 -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) concentrations.

Arrows indicate when 80 mg (4x/day), 100 mg (5x/day) and 120 mg (6x/day) were administered. The final dose was administered at 162.5 h.

Figure 2.

Median (n=10) 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) to THC ratios and 11-nor-9-carboxy-THC (THCCOOH) to THC ratios in whole blood after multiple 20-mg oral THC doses across 8 days.

^aPredictions were based on combined models I (based on THC concentrations) and II (based on THCCOOH/THC ratios) and 95% confidence intervals (CI) as described in text. Specimens were collected after a single 20-mg oral THC dose (0.5-5 h), during multiple doses (7-162.5 h after the first dose), and for 22.5 h after the last oral THC dose. Total specimen numbers at each time point are noted above each bar. Specimens with THC and THCCOOH ≥ 0.25 ng/mL were included. 0.5/0.5 and 0.63/0.55 refer to whole blood to plasma (WB/P) ratios for THC and THCCOOH, respectively, were either the assumed ratio of 0.5 as previously recommended (Huestis et al., 2005; Huestis et al., 2006), or the empirically determined ratios obtained in this study. Specimens were refrigerated and analyzed within 2 weeks of collection.

Figure 3. Predictive model accuracy (%) in estimating last THC exposure in 10 male recently abstinent chronic, daily cannabis smokers administered subchronic oral THC^a.

^aPredictions were based on combined models I (based on THC concentrations) and II (based on THCCOOH/THC ratios) and 95% confidence intervals (CI) as described in text. Specimens were collected after a single 20-mg oral THC dose (0.5-5 h), during multiple doses (7-162.5 h after the first dose), and for 22.5 h after the last oral THC dose. Total specimen numbers at each time point are noted above each bar. Specimens with THC and THCCOOH ≥ 0.25 ng/mL were included. 0.5/0.5 and 0.63/0.55 refer to whole blood to plasma (WB/P) ratios for THC and THCCOOH, respectively, were either the assumed ratio

of 0.5 as previously recommended (Huestis et al., 2005; Huestis et al., 2006), or the empirically determined ratios obtained in this study. Specimens were refrigerated and analyzed within 2 weeks of collection. Overestimates are demonstrated with positive inaccuracy data and underestimates with negative inaccuracy data

Figure 4.

Predictions outside of 95% CI (in hours) utilizing plasma cannabinoid concentrations or whole blood to plasma (WB/P) ratios from 10 male recently abstinent chronic, daily cannabis smokers administered subchronic oral THC*. Left y-axis corresponds to filled circles (●) and the right y-axis corresponds to open circles (○).

Table 1

Demographic and self-reported substance use characteristics for 10 adult male chronic daily cannabis smokers at time of study screening

Participant	Age (y)	Race ^a	BMI ^b (kg/m ²)	Cannabis smoking frequency (joints/day)	Lifetime cannabis use (y)	Age of first cannabis use (y)	Other drug use (in prior year) ^c	At admission (ng/mL)		
								THC	11-OH-THC	THCCOOH
A	20	AA	17.8	6	2	16	T, A	4.3	2.0	39.9
B	32	AA	29.8	3	4	14	T, A	20.3	7.3	86.9
C	26	AA	25.1	24	8	13	T, A, Amp	3.0	1.0	12.8
D	18	AA	23.7	3	4	14	T, A, O	3.0	0.9	24.9
E	23	AA	21.1	6	12	13	T, A	3.7	1.7	30.0
F	21	Multiple	22.9	1	2	17	T, A, Coc, B, H	1.4	0.8	17.6
G	25	W	30.6	3	8	14	T, A	3.0	1.8	35.2
H	27	AA	28.7	9	15	11	T, A, Coc	2.4	NA	31.9
I	25	AA	30.5	2	10	12	T, A, O, Amp	7.1	3.5	57.0
J	22	AA	29.7	3	10	12	T, A	2.2	1.2	28.9
Mean	23.9		26	6	7.5	13.6		5.0	2.2	36.5
SD	4		4.5	6.7	4.4	1.8		5.6	2.1	21.5
Median	24		26.9	3	8	13.5		3.0	1.7	31.0

^a A, African American; W, White

^b Body mass index

^c T, tobacco; A, alcohol; Amp, amphetamines; O, opiates; Coc, cocaine; B, benzodiazepines; H, hallucinogens

^d NA, not available due to analytical error

Whole blood pharmacokinetics for Δ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) in 10 adult, males^a after a single oral 20-mg THC dose and 37 multiple 20-mg oral THC doses up to 120 mg/day.

Table 2

	Single 20-mg THC dose			Multiple 20-mg THC doses		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
THC C _{max} , ng/mL	8.7 ± 4.8	6.4	4.1 - 17.5	22.4 ± 16.1	16.3	7.5 - 51.9
THC T _{max} , h	3.0 ± 0.9	3.0	2.0 - 4.0	101 ± 26.6	104	55.0 - 152
THC AUC, h · ng/L	24.4 ± 7.2	24.8	13.2 - 35.4	1780.7 ± 957.6	1430	698 - 3317
11-OH-THC C _{max}	4.0 ± 2.1	3.4	1.8 - 7.8	11.0 ± 5.4	9.8	3.9 - 20.9
11-OH-THC T _{max}	2.8 ± 0.9	3.0	2.0 - 5.0	106 ± 21.2	104	79.0 - 152
11-OH-THC AUC	11.9 ± 5.6	10.0	6.4 - 20.2	1077 ± 503	1040	438 - 2094
THCCOOH C _{max}	38.4 ± 15.9	36.6	19.7 - 68.7	142.2 ± 63.5	120.7	60.2 - 253.0
THCCOOH T _{max}	3.1 ± 1.0	3.0	2.0 - 5.0	144.0 ± 40.3	163.8	79.0 - 185
THCCOOH AUC	147 ± 61.1	134	74.1 - 261	15,985 ± 6701	14,220	8,107 - 25,256

^aParticipants were chronic, daily cannabis smokers with the last smoked dose within 24 h of the first 20 mg oral THC dose.